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## Review

## Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis

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## SUMMARY

**Background:** Antibiotics are amongst the most commonly used drugs in children. In addition to inducing antibiotic resistance, antibiotic exposure has been associated with adverse long-term health outcomes.

**Methods:** A systematic search using PRISMA guidelines to identify original studies reporting associations between antibiotic exposure and adverse long-term health outcomes in children. Overall pooled estimates of the odds ratios (ORs) were obtained using random-effects models.

**Results:** We identified 160 observational studies investigating 21 outcomes in 22,103,129 children. Antibiotic exposure was associated with an increased risk of atopic dermatitis (OR 1.40, 95% confidence interval (CI) 1.30–1.52,  $p < 0.01$ ), allergic symptoms (OR 1.93, 95%CI 1.66–2.26,  $p < 0.01$ ), food allergies (OR 1.35, 95%CI 1.20–1.52,  $p < 0.01$ ), allergic rhinoconjunctivitis (OR 1.66, 95%CI 1.51–1.83,  $p < 0.01$ ), wheezing (OR 1.81, 95%CI 1.65–1.97,  $p < 0.01$ ), asthma (OR 1.96, 95%CI 1.76–2.17,  $p < 0.01$ ), increased weight gain or overweight (OR 1.18, 95%CI 1.11–1.26,  $p < 0.01$ ), obesity (OR 1.21, 95%CI 1.05–1.40,  $p < 0.01$ ), juvenile idiopathic arthritis (OR 1.74, 95%CI 1.21–2.52,  $p < 0.01$ ), psoriasis (OR 1.75, 95%CI 1.44–2.11,  $p < 0.01$ ), autism spectrum disorders (OR 1.19, 95%CI 1.04–1.36,  $p = 0.01$ ) and neurodevelopment disorders (OR 1.29, 95%CI 1.09–1.53,  $p < 0.01$ ). Dose-response effects and stronger effects with broad-spectrum antibiotic were often reported. Antibiotic exposure was not associated with an altered risk of allergic sensitisation, infantile colic, abdominal pain, inflammatory bowel disease, celiac disease, type 1 diabetes, fluorosis, and attention deficit hyperactivity disorder.

**Conclusion:** Although a causal association cannot be determined from these studies, the results support the meticulous application of sound antibiotic stewardship to avoid potential adverse long-term health outcomes.

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## Introduction

Antibiotics belong to the greatest discoveries in medicine and amongst the most life-saving medical interventions. Their efficacy and presumed safety have led to their widespread use, which sometimes is irrational or even inappropriate.<sup>1–3</sup> In infants and children, antibiotics are amongst the most commonly used drugs. In many settings, more than two-thirds of children receive

antibiotics before reaching the age of two years and, on average, more than half of all children receive at least one antibiotic each year with the highest rate in the second year of life.<sup>4,5</sup>

The reduction in the incidence of infectious diseases in many countries over the last few decades has been paralleled by a dramatic rise in the prevalence of immune-mediated diseases, including allergic diseases, inflammatory bowel diseases (IBD), rheumatological diseases and diabetes mellitus.<sup>6–8</sup> The 'hygiene hypothesis' proposes that decreased microbial exposure explains the rise in immune-mediated diseases.<sup>9</sup> It is likely that the overuse of antibiotics contributes to this.<sup>10</sup>

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In this systematic review and meta-analysis, we summarise studies that have investigated the association between antibiotic exposure and adverse long-term health outcomes in children.

## Systematic review methods

To identify original studies investigating the association between antibiotic exposure and adverse long-term health outcomes in children and adolescents (less than 18 years of age) MEDLINE (1946 to present) was searched in April 2021 using the Ovid interface with the search terms detailed in the supplementary data. Exclusion criteria were studies in which: (i) the effect of prenatal antibiotics was investigated; (ii) the timing of antibiotic exposure was not specified; (iii) antibiotic exposure occurred after the onset of the adverse health outcome and (iv) included preterm infants without adjusting values for prematurity. References of retrieved articles were hand-searched for additional publications. The following variables were extracted from the included studies: author, country, publication year, study design, cohort size, time of antibiotic exposure, specification of antibiotic treatment, age at outcome measure, number of cases, outcome definition and key findings. Review Manager (version 5.3) was used for the calculation of the odds ratios and the meta-analyses. If studies evaluated several time points, only the latest was included in the meta-analysis. Diversity in study design and reporting, which might result in selection and reporting bias, precluded quality evaluation according to the PRISMA guidelines. The ROBINS-1 tool was used to assess risk of bias.<sup>11</sup>

## Systematic review results

Our search identified 23,225 studies. Of these, 150 fulfilled the inclusion criteria.<sup>12–161</sup> An additional 10 relevant studies were identified by hand searching of references.<sup>162–171</sup> The selection of studies is summarised in Fig. 1. The 160 studies included in this review investigated 21 outcomes in 22,103,129 children; 159 were observational studies (23 registry-based studies, 69 cohort studies, 34 cross-sectional studies, 11 case-control studies, and 22 retrospective studies) and one was a secondary analysis of data from a randomised control trial;<sup>45</sup> 145 of the studies were done in industrialised countries. The number of participants in each study ranged from 50 to 9,400,000 (median 3944, mean 138,146). Exposure to antibiotics was captured through registries, medical and prescription records or parent questionnaires; studies included any course of antibiotic received, antibiotic exposure during an early-life period (e.g. first week, months or first years of life) or during a certain time before diagnosis. Outcomes were defined by validated questionnaires, diagnostic codes, parent-reported symptoms, or diagnosis, or clinical or laboratory evaluation. The results of these studies are summarised in Table 1. In addition to the overall antibiotic exposure, 17 studies investigated the effect of the number of antibiotic courses received, 17 studies compared the effect of different types of antibiotics and 41 studies both. The risk of bias summary of studies included in the review can be found in Supplementary Table 2.

### Atopic dermatitis

Forty studies in 1,602,639 children (183,244 cases with one study not reporting number of cases) investigated the association between antibiotic exposure and the risk of developing atopic dermatitis, evaluated by the International Study of Allergy and Asthma in Childhood (ISAAC) questionnaire, international classification of disease (ICD) codes, parent-reported symptoms or physician's diagnosis, the Criteria by the American Academy

of Dermatology, Hanifin and Rajka criteria or William's criteria (Table 1).<sup>32,37,40,43,48–51,53,62,79,80,82,93,96,98,103,105,114,120,123,129,135,150,153–155,157,161,162,172–181</sup> Of the 40 studies, 38 (95%) investigated the effect of antibiotic exposure in the first five years of life (36 (90%) in the first two years of life).<sup>32,37,40,43,48–51,53,62,79,80,82,93,96,98,103,105,114,120,123,129,135,150,153,157,161,162,172–181</sup> Overall, 26 (65%) studies reported a significantly increased incidence of atopic dermatitis in children who were exposed to antibiotics<sup>37,40,48–51,53,62,82,93,96,103,120,123,129,150,153,157,161,172,173,175,176,179–181</sup>; However, in two studies the incidence atopic dermatitis was higher only if exposed to two or more courses of antibiotics.<sup>123,180</sup> In contrast, two studies (5%) reported a decreased incidence in children who were exposed to antibiotics.<sup>40,51</sup> Five studies reported that the risk of atopic dermatitis increased with the number of antibiotic courses.<sup>32,93,103,123,176</sup> One study, however, did not find an association between the number of antibiotic courses and the risk of atopic dermatitis.<sup>182</sup> Four studies compared the effect of different antibiotic classes.<sup>123,157,172,182</sup> One study reported that the risk of atopic dermatitis increased after exposure to cephalosporins and macrolides, but not after exposure to penicillins<sup>123</sup>; one study after amoxicillin but not penicillin, amoxicillin/clavulanic acid, macrolides or cephalosporins,<sup>182</sup> one study after macrolides<sup>157</sup> and the last study reported an increased risk in girls after exposure to cephalosporins but a decreased risk after exposure to macrolides.<sup>172</sup>

Of the 40 studies, 32 (80%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 1).<sup>32,37,40,43,48,49,51,53,62,79,80,82,93,96,103,105,114,120,123,135,153,154,157,161,162,172–174,176,178,180,181</sup> Of the 309,828 children exposed to antibiotics 51,543 (17%) developed atopic dermatitis compared to 105,587 (14%) of 766,331 children not exposed to antibiotics. The overall odds ratio (OR) for developing atopic dermatitis after antibiotic exposure was 1.40, 95% confidence interval (CI) 1.30 to 1.52,  $p < 0.01$  (Fig. 2).

### Allergic sensitisation

Twenty-three studies in 34,806 children (8952 cases) investigated the association between antibiotic exposure and the risk of developing allergic sensitisation diagnosed by skin prick test or serum immunoglobulin (Ig) E levels (Table 1).<sup>24,40,43,49,60,70,79,80,82,87,93,105,116,126,135,153,175–178,181,183,184</sup> Of the studies, 21 (91%) investigated the effect of antibiotic exposure in the first five years of life (18 (78%) in the first two years of life).<sup>24,40,43,49,60,70,79,80,82,93,105,116,126,135,153,175–178,181,183</sup> Four (17%) reported a significant increased incidence of allergic sensitisation in children who were exposed to antibiotics.<sup>87,116,181,183</sup> In contrast, one study (4%) reported a decreased incidence of allergic sensitisation in children who were exposed to antibiotics.<sup>40</sup> The one study which investigated if the risk of allergic sensitisation correlated with the number of antibiotic courses found no association.<sup>176</sup>

Of the 23 studies, 18 (78%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 2).<sup>24,40,43,49,70,79,80,82,87,93,105,116,135,153,176,178,181,183</sup> Of the 12,502 children exposed to antibiotics 2582 (21%) developed allergic sensitisation compared to 3642 (22%) of the 16,731 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing allergic sensitisation (OR 1.11, 95%CI 0.98–1.26,  $p = 0.05$ ) (Fig. 2).

### Food allergies

Fifteen studies investigated the association between antibiotic exposure and the risk of developing food allergies

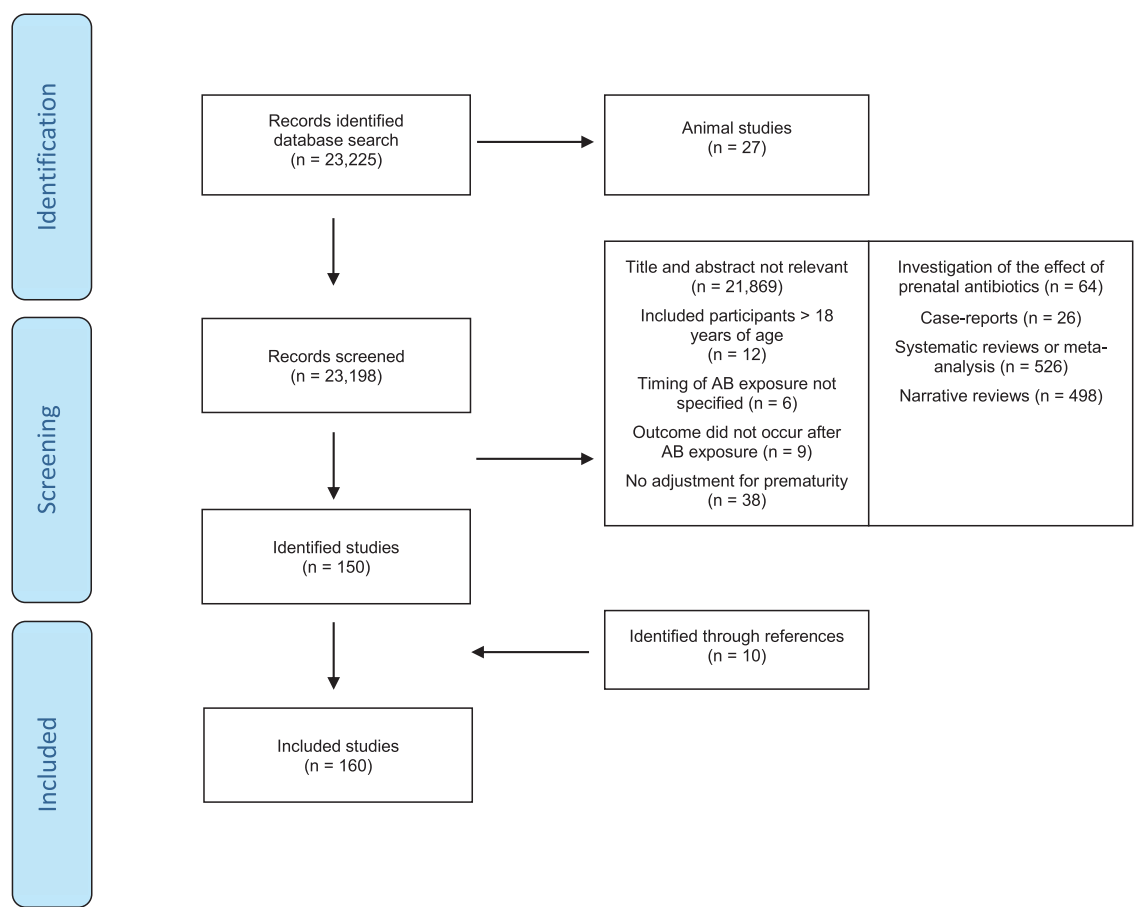
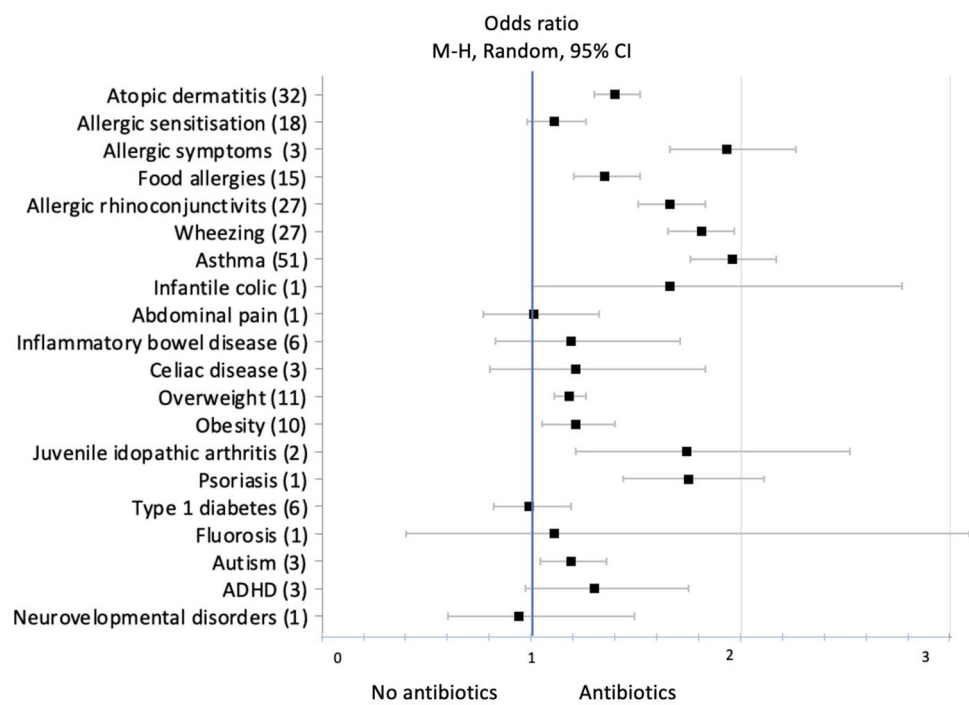


Fig. 1. Selection of studies.



CI – confidence interval      H-M – Mantel-Haenszel

Fig. 2. Comparison of incidence of adverse health outcomes in children exposed and not exposed to antibiotics (number of studies in brackets).

**Table 1**Summary of studies investigating the effect of antibiotic exposure on health outcomes in children. See Ref. [240](#)

| Author<br>Country<br>Publication year       | Study type<br>(Level of evidence)         | No of cases;<br>cohort size<br><br>No of cases in<br>children with<br>antibiotics; no<br>of children with<br>antibiotics<br><br>No of cases in<br>children<br>without<br>antibiotics; no<br>of children<br>without<br>antibiotics | Time of<br>antibiotic<br>exposure<br>(age unless<br>otherwise<br>specified)<br><br>Antibiotic<br>specified<br><br>Evaluation<br>of antibiotic<br>exposure | Age at<br>outcome<br>measure | Outcome<br>definition                                | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Factors adjusted for                                                                                                          |
|---------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>Atopic dermatitis</b>                    |                                           |                                                                                                                                                                                                                                   |                                                                                                                                                           |                              |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                               |
| Aversa et al. <sup>172</sup><br>USA<br>2021 | Multicentre prospective cohort study (2b) | 297; 14,572<br><br>231; 10,220<br>66; 4,352                                                                                                                                                                                       | < 2 y<br><br>Yes<br><br>Medical records                                                                                                                   | 6–11 y                       | ICD-9 and ICD-10 codes                               | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aHR 1.47 (95%CI 1.12–1.94), p&lt;0.01</b><br><br>Girls<br>• penicillins: HR 1.27 (95%CI 0.87–1.87), p=0.22<br>• cephalosporins: <b>HR 1.69 (95%CI 1.14–2.52), p=0.01</b><br>• macrolides: <b>HR 0.59 (95%CI 0.37–0.92), p=0.02</b><br>• sulfonamides: HR 0.98 (95%CI 0.49–1.96), p=0.95<br><br>Boys<br>• penicillins: HR 1.40 (95%CI 0.96–2.03), p=0.08<br>• cephalosporins: HR 1.29 (95%CI 0.90–1.84), p=0.17<br>• macrolides: HR 0.83 (95%CI 0.57–1.19), p=0.30<br>• sulfonamides: HR 1.37 (95%CI 0.75–2.51), p=0.30 | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode             |
| Zou et al. <sup>161</sup><br>China<br>2020  | Multicentre cross-sectional study (3b)    | 2,752; 12,667<br><br>772; 3,049<br>1,980; 9,618                                                                                                                                                                                   | < 1 y<br><br>No<br><br>Parent questionnaire                                                                                                               | 4–6 y                        | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.17 (95%CI 1.05–1.31), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure |

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Table 1 (continued)

|                              |                                             |                 |                      |         |                                                      |                                                                                                                                      |                                                                                                                                                                  |
|------------------------------|---------------------------------------------|-----------------|----------------------|---------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Levin et al. <sup>82</sup>   | Multicentre prospective cohort study (2b)   | 301; 1,185      | < 1 y                | 12–36 m | Criteria by American Academy of Dermatology          | Exposure to AB in first y of life associated with increased risk in urban cohort.                                                    |                                                                                                                                                                  |
| South-Africa                 |                                             | 182; 654        | No                   |         |                                                      | • <b>OR 1.33 (95%CI 1.02–1.74), p=0.03*</b>                                                                                          |                                                                                                                                                                  |
| 2020                         |                                             | 8; 398          | Parent questionnaire |         |                                                      | Exposure to AB in first y of life not associated with increased risk in rural cohort.                                                |                                                                                                                                                                  |
|                              |                                             | 7; 347          |                      |         |                                                      | • <b>OR 1.03 (95%CI 0.12–8.54), p=0.98*</b>                                                                                          |                                                                                                                                                                  |
| Rutter et al. <sup>120</sup> | Multicentre cross-sectional study (3b)      | 15,152; 120,799 | < 1 y                | 6–7 y   | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.                                                                    | Sex, maternal education and smoking; medication use, open fire cooking                                                                                           |
| UK                           |                                             | 13,108*; 97,631 | No                   |         |                                                      | • <b>aOR 1.41 (95%CI 1.34–1.48), p=nr</b>                                                                                            |                                                                                                                                                                  |
| 2019                         |                                             | 2,044*; 23,168  | Parent questionnaire |         |                                                      |                                                                                                                                      |                                                                                                                                                                  |
| Metzler et al. <sup>93</sup> | Multicentre prospective cohort study (2b)   | 275; 1,019      | < 1 y                | < 6 y   | Parent-reported physician's diagnosis                | Exposure to AB in first y of life associated with increased risk.                                                                    | Sex, family history of atopy, number of siblings, living area, smoking and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure |
| Switzerland                  |                                             | 154; 419        | No                   |         |                                                      | • <b>aOR 1.91 (95%CI 1.36–2.67), p&lt;0.05</b>                                                                                       |                                                                                                                                                                  |
| 2019                         |                                             | 121; 600        | Parent questionnaire |         |                                                      | • 1 AB course: aOR 1.60 (95%CI nr), p=nr<br>• 2 AB courses: aOR 2.06 (95%CI nr), p=nr<br>• ≥ 3 AB courses: aOR 7.25 (95%CI nr), p=nr |                                                                                                                                                                  |
| Gao et al. <sup>51</sup>     | Single-centre prospective cohort study (2b) | 226; 903        | < 1 y                | 12 m    | Parent-reported atopic dermatitis symptoms           | Exposure to AB in first y of life associated with decreased risk.                                                                    | Sex, family history of atopy, antibiotic use during pregnancy, season of birth, egg and milk consumption                                                         |
| China                        |                                             | 26; 184         | No                   |         |                                                      | • <b>aOR 0.44 (95%CI 0.28–0.70), p&lt;0.01</b>                                                                                       |                                                                                                                                                                  |
| 2019                         |                                             | 200; 719        | Parent questionnaire |         |                                                      |                                                                                                                                      |                                                                                                                                                                  |
| Ho et al. <sup>62</sup>      | Multicentre cross-sectional study (3b)      | 2,625; 23,908   | < 1 y                | 6–8 y   | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.                                                                    | Sex, number of siblings, number of LRTIs, duration of breastfeeding, timing of solid food introduction, pet and home dampness-related exposure                   |
| Taiwan                       |                                             | 562; 3,691      | No                   |         |                                                      | • <b>aOR 1.37 (95%CI 1.22–1.53), p&lt;0.01</b>                                                                                       |                                                                                                                                                                  |
| 2019                         |                                             | 2,063; 20,217   | Parent questionnaire |         |                                                      |                                                                                                                                      |                                                                                                                                                                  |

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Table 1 (continued)

|                                       |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
|---------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------|------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Norbäck et al. <sup>103</sup>         | Multicentre retrospective cohort study (2b) | 9,573; 39,782<br>7,497; 29,303<br>2,076; 10,479                                    | < 1 y<br>No<br>Parent questionnaire  | 3–6 y            | Parent-reported physician's diagnosis                                     | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.20 (95%CI 1.11–1.30), p&lt;0.01</b><br>• 1 AB course: <b>aOR 1.15 (95%CI 1.07–1.24), p&lt;0.01</b><br>• > 1 AB courses: <b>aOR 1.45 (95%CI 1.36–1.56), p&lt;0.01</b>                               | Living area, temperature in each city, time spend outdoors, air pollution                                                                                        |
| China                                 |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2019                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| Oosterloo et al. <sup>105</sup>       | Multicentre prospective cohort study (2b)   | 156; 436<br>57; 151<br>99; 285                                                     | < 1 w<br>No<br>Parent questionnaire  | 0–1 y            | Parent-reported atopic dermatitis symptoms                                | Exposure to AB in first w of life not associated with increased risk.<br>• aOR 1.09 (95%CI 0.70–1.70), p=0.70                                                                                                                                                                      | Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking |
| Netherlands                           |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2018                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| Mitre et al. <sup>96</sup>            | Multicentre retrospective cohort study (2b) | 112,608; 792,130<br>21,638; 131,708<br>90,970; 660,422                             | < 6 m<br>No<br>Registry              | 1–6 y            | ICD-9-CM codes                                                            | Exposure to AB in first 6 m of life associated with increased risk.<br>• <b>aHR 1.18 (95%CI 1.16–1.19), p=nr</b>                                                                                                                                                                   | Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use                                                                                   |
| USA                                   |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2018                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| Singh et al. <sup>129</sup>           | Multicentre cross-sectional study (3b)      | 1,249; 44,928<br>nr; nr<br>nr; nr                                                  | < 1 y<br>No<br>Parent questionnaire  | 6–7 y            | Questionnaire for atopic dermatitis symptoms (ISAAC)                      | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 1.80 (95%CI 1.60–2.00), p&lt;0.01</b>                                                                                                                                                                 |                                                                                                                                                                  |
| India                                 |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2018                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| Yamamoto-Hanada et al. <sup>157</sup> | Multicentre prospective cohort study (2b)   | 194; 902<br>107; 436<br>87; 466                                                    | < 2 y<br>Yes<br>Parent questionnaire | 5 y              | Questionnaire for atopic dermatitis symptoms (ISAAC) plus medical records | Exposure to AB in first 2 y of life associated with increased risk.<br>• <b>aOR 1.40 (95%CI 1.01–1.94), p=0.04</b><br>• penicillins: aOR 1.41 (95%CI 0.82–2.43), p=0.22<br>• cephem: aOR 1.37 (95%CI 0.94–1.99), p=0.10<br>• macrolides: <b>aOR 1.58 (95%CI 1.07–2.33), p=0.02</b> | Sex, maternal age, BMI education and history of atopy; parity, smoking during pregnancy, gestational age, delivery mode, number of LRTIs, day care               |
| Japan                                 |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2017                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| Park et al. <sup>174</sup>            | Multicentre cross-sectional study (3b)      | 1,424; 4,003<br>607; 1585*<br>817; 2418*<br>981; 4,112<br>288; 1090*<br>693; 3022* | < 1 y<br>No<br>Parent questionnaire  | 6–7 y<br>12–13 y | Questionnaire for atopic dermatitis symptoms (ISAAC)                      | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 1.09 (95%CI 0.88–1.39), p=0.70<br>Exposure to AB in first y of life not associated with increased risk.<br>• aOR 1.04 (95%CI 0.86–1.34), p=0.70                                                     | Age, sex, family history of atopy, living area, atopy                                                                                                            |
| Korea                                 |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |
| 2016                                  |                                             |                                                                                    |                                      |                  |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                  |

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Table 1 (continued)

|                                       |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
|---------------------------------------|---------------------------------------------|-----------------------------------------------|-------------------------------------|--------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Taylor-Robinson et al. <sup>173</sup> | Multicentre prospective cohort study (2b)   | 3,489; 12,917<br>1,909; 5,678<br>1,580; 7,239 | < 1 y<br>No<br>Registry             | 5 y                | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.28 (95%CI 1.16-1.42), p&lt;0.01</b>                                                                                                                                                                                                                   | Sex, ethnicity, maternal age, BMI, education and history of atopy; maternal smoking and alcohol consumption during pregnancy; day care, number of siblings, birth weight, delivery mode, breastfeeding, timing of solid food and cow's milk introduction, smoke and grime exposure          |
| UK                                    |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
| 2016                                  |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
| Loo et al. <sup>175</sup>             | Multicentre prospective cohort study (2b)   | 43; 792<br>nr; nr<br>nr; nr                   | < 6 m<br>No<br>Parent questionnaire | 6 m-1 y<br>1-1.5 y | Parents-reported physician's diagnosis               | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• <b>aOR 3.19 (95%CI 0.72-14.11), p=0.13</b><br><br>Exposure to AB in first 6 m of life associated with increased risk.<br><br>• <b>aOR 3.11 (95%CI 1.10-8.76), p=0.03</b>                                                                                 | Sex, sibling history of atopy, living area, age of child at outcome                                                                                                                                                                                                                         |
| Singapore                             |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
| 2015                                  |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
| Hoskin-Parr et al. <sup>176</sup>     | Single-centre prospective cohort study (2b) | 994; 5,780<br>494*; 2,659<br>500*; 3,121      | < 2 y<br>No<br>Parent questionnaire | 7.5 y (mean)       | Parents-reported physician's diagnosis               | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aOR 1.20 (95%CI 1.02-1.41), p=nr</b><br><br>• 1 AB course: aOR 1.05 (95%CI 0.85-1.29), p=nr<br>• 2 AB courses: aOR 1.23 (95%CI 1.00-1.51), p=nr<br>• 3 AB courses: aOR 1.17 (95%CI 0.93-1.47), p=nr<br>• ≥ 4 AB courses: aOR 1.41 (95%CI 1.14-1.74), p=nr | Age, sex, maternal age and education; parental marital status, home ownership status, difficulty in paying for food, smoking and disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure |
| UK                                    |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |
| 2013                                  |                                             |                                               |                                     |                    |                                                      |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                             |

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Table 1 (continued)

|                               |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
|-------------------------------|---------------------------------------------|----------------------------------------------|-------------------------------------|------------|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wang et al. <sup>150</sup>    | Multicentre prospective cohort study (2b)   | 19,015; 263,620<br>nr; 15,663<br>nr; 247,957 | < 1 y<br>Yes<br>Medical records     | 2-6 y      | ICD-9-CM codes                                       | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aHR 1.61 (95%CI 1.53-1.70), p&lt;0.05</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                                                                                                        | Living area, socioeconomic status, healthcare use                                                                                                                                                                      |
| Taiwan                        |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| 2013                          |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| Sandini et al. <sup>177</sup> | Single-centre prospective cohort study (2b) | 270; 925<br>nr; nr<br>nr; nr                 | < 6 m<br>No<br>Parent questionnaire | 2 y<br>5 y | William's criteria                                   | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 1.18 (95%CI 0.77-1.81), p=0.44<br><br>Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 1.20 (95%CI 0.79-1.81), p=0.39                                                                                                                                                                                                   |                                                                                                                                                                                                                        |
| Finland                       |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| 2011                          |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| Schmitt et al. <sup>123</sup> | Multicentre prospective cohort study (2b)   | 44; 370<br>24; 155<br>20; 215                | < 1 y<br>Yes<br>Registry            | 2 y        | ICD-10 codes plus prescription records               | Exposure to AB in first y of life associated with increased risk, significant only for ≥ 2 AB courses.<br><br>• OR 1.79 (95%CI 0.95-3.37), p=0.07*<br><br>• 1 AB course: RR 1.45 (95%CI 0.76-2.75), p=nr<br>• ≥ 2 AB courses: <b>RR 2.11 (95%CI 1.05-4.22), p=nr</b><br><br>• penicillins: RR 0.88 (95%CI 0.37-2.12), p=nr<br>• cephalosporins: <b>RR 1.93 (95%CI 1.07-3.49), p=nr</b><br>• macrolides: <b>RR 2.15 (95%CI 1.18-3.91), p=nr</b> |                                                                                                                                                                                                                        |
| Germany                       |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| 2010                          |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| Su et al. <sup>135</sup>      | Single-centre prospective cohort study (2b) | 134; 424<br>49; 136<br>85; 288               | < 9 m<br>No<br>Parent questionnaire | 1-5 y      | Parent-reported physician's diagnosis                | Exposure to AB in first 9 m of life not associated with increased risk.<br><br>• OR 1.35 (95%CI 0.87-2.07), p=0.18*                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                        |
| USA                           |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| 2010                          |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| Dom et al. <sup>40</sup>      | Multicentre prospective cohort study (2b)   | 243; 670<br>192; 564<br>51; 106              | < 4 y<br>No<br>Parent questionnaire | < 4 y      | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first 4 y of life associated with decreased risk.<br><br>• <b>OR 0.56 (95%CI 0.37-0.85), p&lt;0.01*</b><br><br>Exposure to AB in first y of life not associated with decreased risk.<br>• aOR 0.61 (95%CI 0.36-1.01), p=0.05<br><br>Exposure to AB in second to fourth y of life with decreased risk.<br><br>• <b>aOR 0.11 (95%CI 0.05-0.23), p&lt;0.01</b>                                                                  | Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking and pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure |
| Belgium                       |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |
| 2010                          |                                             |                                              |                                     |            |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                        |

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Table 1 (continued)

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| Mai et al. <sup>178</sup>          | Single-centre prospective cohort study (2b)          | 663; 3,306  | < 1 y                | 4 y   | Questionnaire for atopic dermatitis symptoms (BAMSE based on ISAAC) | Exposure to AB in first y of life associated with increased risk.     | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding           |
| Sweden                             |                                                      | 318; 1,420  | No                   |       |                                                                     | • <b>aOR 1.30 (95%CI 1.10-1.50), p=nr</b>                             |                                                                                                     |
| 2010                               |                                                      | 523; 3,306  | Parent questionnaire | 8 y   |                                                                     | Exposure to AB in first y of life associated with increased risk.     |                                                                                                     |
|                                    |                                                      | 255; 1,420  |                      |       |                                                                     | • <b>aOR 1.30 (95%CI 1.10-1.60), p=nr</b>                             |                                                                                                     |
|                                    |                                                      | 268; 1,886  |                      |       |                                                                     |                                                                       |                                                                                                     |
| Garcia-Marcos et al. <sup>53</sup> | Multicentre retrospective case-control study (3b)    | 922; 13,325 | < 1 y                | 6–7 y | Questionnaire for atopic dermatitis symptoms (ISAAC)                | Exposure to AB in first y of life associated with increased risk.     | Age, sex, number of siblings, living area, maternal education and smoking; pet and traffic exposure |
| Spain                              |                                                      | 589; 6,831  | No                   |       |                                                                     | • <b>aOR 1.66 (95%CI 1.43-1.92), p&lt;0.01</b>                        |                                                                                                     |
| 2010                               |                                                      | 333; 6,494  | Parent questionnaire |       |                                                                     |                                                                       |                                                                                                     |
| Karimi et al. <sup>162</sup>       | Multicentre cross-sectional study (3b)               | 90; 1,476   | < 1 y                | 6–7 y | Questionnaire for atopic dermatitis symptoms (ISAAC)                | Exposure to AB in first y of life not associated with increased risk. |                                                                                                     |
| Iran                               |                                                      | 63; 952*    | No                   |       |                                                                     | • <b>OR 1.30 (95%CI 0.79-2.13), p=0.20</b>                            |                                                                                                     |
| 2009                               |                                                      | 27; 524*    | nr                   |       |                                                                     |                                                                       |                                                                                                     |
| Foljaki et al. <sup>50</sup>       | Multicentre retrospective cross-sectional study (3b) | nr; 193,412 | < 1 y                | 6–7 y | Questionnaire for atopic dermatitis symptoms (ISAAC)                | Exposure to AB in first y of life associated with increased risk.     | Sex, language, living area, income                                                                  |
| Sweden                             |                                                      | nr; 135,775 | No                   |       |                                                                     | • <b>aOR 1.58 (95%CI 1.33-1.51), p=nr</b>                             |                                                                                                     |
| 2009                               |                                                      | nr; 57,637  | Parent questionnaire |       |                                                                     |                                                                       |                                                                                                     |

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Table 1 (continued)

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|----------------------------------------------------|-----------------------------------------------------|----------------------------------------|--------------------------------------|---------------|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wickens et al. <sup>153</sup>                      | Multicentre prospective cohort study (2b)           | 398; 1,064<br>52*; 148<br>346*; 916    | < 3 m<br>No<br>Parent questionnaire  | 15 m          | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first 3 m of life not associated with increased risk.<br><br>• aOR 0.84 (95%CI 0.57-1.22), p=0.35                                             | Number of LRTIs                                                                                                                                                                                            |
| New Zealand                                        |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| 2008                                               |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
|                                                    |                                                     | 305; 1,011                             | < 15 m                               | 4 y           |                                                      | Exposure to AB in first 15 m of life associated with increased risk.<br><br>• aOR 1.75 (95% CI, 1.03-2.96), p=0.04                                              |                                                                                                                                                                                                            |
|                                                    |                                                     | 242*; 722<br>63*; 289                  |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| Kusel et al. <sup>80</sup>                         | Multicentre prospective cohort study (2b)           | 62; 198<br>37*; 107<br>25*; 91         | < 1 y<br>Yes<br>Parent questionnaire | 0-5 y         | Hanifin and Rajka criteria                           | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.50 (95%CI 0.70-3.30), p=nr<br><br>Results according to antibiotic class nr | Sex, day care, number of GP visits, pet exposure                                                                                                                                                           |
| Australia                                          |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| 2008                                               |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| Kummeling et al. <sup>79</sup>                     | Multicentre prospective cohort study (2b)           | 817; 2,462<br>145; 489<br>672; 1,973   | < 6 m<br>No<br>Parent questionnaire  | < 2 y         | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first 6 m not associated with increased risk.<br><br>• aOR 0.94 (95%CI 0.75-1.18), p=nr                                                       | Sex, family history of atopy, day care, number of siblings, delivery mode, vaccination status, fever, breastfeeding, pet and smoke exposure                                                                |
| Netherlands                                        |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| 2007                                               |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| Mullooly et al. <sup>98</sup>                      | Single-centre retrospective case-control study (3b) | 58; 844<br>nr; nr<br>nr; nr            | < 2 y<br>No<br>Medical records       | 10.3 y (mean) | Parent-reported physician's diagnosis                | Exposure to AB in first 2 y of life not associated with increased risk.<br><br>• aOR 1.03 (95%CI 0.96-1.10), p=nr                                               | Sex, ethnicity, maternal age, birth weight, age of child at time of outcome, breastfeeding, household smoking                                                                                              |
| USA                                                |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| 2007                                               |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| Floistrup et al. <sup>49</sup>                     | Multicentre cross-sectional study (3b)              | 520; 4,606<br>126*; 788<br>394*; 3,818 | < 1 y<br>No<br>Parent questionnaire  | 7-11 y        | Parent-reported physician's diagnosis                | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.63 (95%CI 1.22-2.17), p=nr                                                     | Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure |
| Netherlands, Austria, Germany, Sweden, Switzerland |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |
| 2006                                               |                                                     |                                        |                                      |               |                                                      |                                                                                                                                                                 |                                                                                                                                                                                                            |

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Table 1 (continued)

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|--------------------------------|-----------------------------------------------------|--------------------------------------------------------|-------------------------------------|------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Purvis et al. <sup>114</sup>   | Multicentric, prospective case-control study (3b)   | 87; 550<br>57; 369<br>30; 181                          | < 1 y<br>No<br>Parent questionnaire | 3.5–4 y                | Questionnaire for atopic dermatitis symptoms (ISAAC) plus serum IgE (environmental allergens) | Exposure to AB in first y of life not associated with increased risk.<br><br>• OR 1.18 (95%CI, 0.61–2.26), p=0.62                                                                                                                                                                                                                          |                                                                                                                                              |
| New Zealand<br>2005            |                                                     |                                                        |                                     |                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |
| Cohet et al. <sup>37</sup>     | Single-centre retrospective case-control study (3b) | 1,549; 3,927<br>1,130; 2,684<br>419; 1,243             | < 1 y<br>No<br>Parent questionnaire | 6–7 y                  | Questionnaire for atopic dermatitis symptoms (ISAAC)                                          | Exposure to AB in first y of life associated with increased risk.<br><br>• OR 1.40 (95%CI 1.21–1.62), p=nr                                                                                                                                                                                                                                 |                                                                                                                                              |
| New Zealand<br>2004            |                                                     |                                                        |                                     |                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |
| Celedon et al. <sup>32</sup>   | Multicentre prospective cohort study (2b)           | 22; 448<br>16; 302<br>6; 146                           | < 1 y<br>No<br>Parent questionnaire | 5 y                    | Parent-reported physician's diagnosis                                                         | Exposure to AB in first y of life not associated with increased risk.<br><br>• 1 AB course: aOR 0.90 (95%CI 0.30–3.40), p=nr<br>• ≥ 2 AB courses: aOR 1.10 (95%CI 0.40–3.10), p=nr                                                                                                                                                         | Sex, family history of atopy, income                                                                                                         |
| USA<br>2002                    |                                                     |                                                        |                                     |                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |
| Bohme et al. <sup>180</sup>    | Multicentre prospective cohort study (2b)           | 952; 3,786<br>≥ 2 AB courses: 450; 1,586<br>502; 2,200 | 1–2 y<br>No<br>Parent questionnaire | 2 y                    | Questionnaire for atopic dermatitis symptoms (BAMSE)                                          | Exposure to ≥ 2 AB courses in first 2 y of life associated with increased risk.<br><br>• aRP 1.29 (95%CI 1.07–1.56), p=nr                                                                                                                                                                                                                  | Sex, maternal age and smoking; family history of atopy, parental education, gestational age, age of child at outcome, breastfeeding duration |
| Sweden<br>2002                 |                                                     |                                                        |                                     |                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |
| McKeever et al. <sup>182</sup> | Single-centre prospective cohort study (2b)         | 3,580; 19,133<br>nr; 12,497<br>nr; 6,636               | < 1 y<br>Yes<br>Medical records     | < 11 y<br>2.2 y (mean) | Oxford Medical Information System (OXMIS), ICD-8 or Read codes                                | Exposure to AB in first y of life associated with increased risk.<br><br>• 1 AB course: aHR 1.22 (95%CI 1.12–1.34), p=nr<br>• 2 AB courses: aHR 1.21 (95%CI 1.09–1.35), p=nr<br>• 3 AB courses: aHR 1.22 (95%CI 1.08–1.38), p=nr<br>• 4 AB courses: aHR 1.11 (95%CI 0.95–1.28), p=nr<br>• > 4 AB courses: aHR 1.01 (95%CI 0.88–1.17), p=nr | Number of GP visits                                                                                                                          |
| UK<br>2002                     |                                                     |                                                        |                                     |                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |

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Table 1 (continued)

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|----------------------------------|------------------------------------------------------|-------------|----------------------|--------|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
|                                  |                                                      |             |                      |        |                                                      | <ul style="list-style-type: none"> <li>• penicillin: aHR 1.07 (95%CI 0.97–1.18), p=nr</li> <li>• amoxicillin: <b>aHR 1.09 (95%CI 1.01–1.17), p=nr</b></li> <li>• amoxicillin/clavulanic acid: aHR 1.16 (95%CI 0.98–1.38), p=nr</li> <li>• cephalosporins: aHR 0.90 (95%CI 0.80–1.02), p=nr</li> <li>• macrolides: aHR 0.96 (95%CI 0.89–1.04), p=nr</li> </ul> |                                                                                                         |
| Wjst et al. <sup>155</sup>       | Multicentre cross-sectional study (3b)               | 768; 2,512  | < 5–14 y             | 5–14 y | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB between the fifth and fourteenth y of life not associated with increased risk.                                                                                                                                                                                                                                                                 | Age, sex, family history of atopy, season, parental education                                           |
| Germany                          |                                                      | nr; 2,025   | No                   |        |                                                      | • aOR 1.30 (95%CI 0.80–2.20), p=0.27                                                                                                                                                                                                                                                                                                                          |                                                                                                         |
| 2001                             |                                                      | nr; 487     | Medical records      |        |                                                      |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |
| Droste et al. <sup>43</sup>      | Multicentre retrospective cross-sectional study (3b) | 233; 1,180  | < 1 y                | 7–8 y  | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk in high-risk children.                                                                                                                                                                                                                                                                       | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure |
| Belgium                          |                                                      | 85; 375     | No                   |        |                                                      | • <b>aOR 1.30 (95%CI 1.00–1.80), p=0.05</b>                                                                                                                                                                                                                                                                                                                   |                                                                                                         |
| 2000                             |                                                      | 148; 805    | Parent questionnaire |        |                                                      |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |
| Von Mutius et al. <sup>181</sup> | Single-centre cross-sectional study (3b)             | 812; 5,006  | < 3 y                | 5–7 y  | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first 3 y of life associated with increased risk.                                                                                                                                                                                                                                                                                           |                                                                                                         |
| Germany                          |                                                      | 673; 3,904  | No                   |        |                                                      | • <b>OR 1.44 (95%CI 1.19–1.76), p&lt;0.01*</b>                                                                                                                                                                                                                                                                                                                |                                                                                                         |
| 1999                             |                                                      | 139; 1,102  | Medical records      | 9–11 y |                                                      | Exposure to AB in first 3 y of life associated with increased risk.                                                                                                                                                                                                                                                                                           |                                                                                                         |
|                                  |                                                      | 865; 5,267  |                      |        |                                                      | • <b>OR 1.42 (95%CI 1.18–1.70), p&lt;0.01*</b>                                                                                                                                                                                                                                                                                                                |                                                                                                         |
|                                  |                                                      | 701; 4,006  |                      |        |                                                      |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |
|                                  |                                                      | 164; 1,261  |                      |        |                                                      |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |
| Wickens et al. <sup>154</sup>    | Multicentre retrospective cross-sectional study (3b) | 125; 447    | < 10 y               | 5–10 y | Questionnaire for atopic dermatitis symptoms (ISAAC) | Exposure to AB in first 10 y of life not associated with increased risk.                                                                                                                                                                                                                                                                                      | Age, sex, ethnicity, family history of atopy, household size, parental smoking                          |
| New Zealand                      |                                                      | 98; 334     | No                   |        |                                                      | • aOR 1.23 (95%CI 0.71–2.13), p=nr                                                                                                                                                                                                                                                                                                                            |                                                                                                         |
| 1999                             |                                                      | 27; 113     | Parent questionnaire |        |                                                      |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                         |
| Farooqi et al. <sup>48</sup>     | Single-centre retrospective cohort study (2b)        | 367; 1,855  | < 2 y                | 6–12 y | Physician's diagnosis                                | Exposure to AB in first 2 y of life associated with increased risk.                                                                                                                                                                                                                                                                                           |                                                                                                         |
| UK                               |                                                      | 287*; 1,237 | Yes                  |        |                                                      | • <b>OR 2.04 (95%CI 1.53–2.73), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                 |                                                                                                         |
| 1998                             |                                                      | 80*; 618    | Medical records      |        |                                                      | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                      |                                                                                                         |

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Table 1 (continued)

| Allergic sensitisation          |                                           |            |                      |         |                                                    |                                                                                       |                                                                                                                                                                  |
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| Levin et al. <sup>82</sup>      | Multicentre prospective cohort study (2b) | 107; 1,185 | < 1 y                | 12–36 m | SPT (food and inhalant allergens)                  | Exposure to AB in first y of life not associated with increased risk.                 |                                                                                                                                                                  |
| South-Africa                    |                                           | 64; 654    | No                   |         |                                                    | • OR 1.23 (95%CI 0.82–1.85), p=0.31*                                                  |                                                                                                                                                                  |
| 2020                            |                                           | 11; 398    | Parent questionnaire |         |                                                    | Exposure to AB in first y of life not associated with increased risk in rural cohort. |                                                                                                                                                                  |
|                                 |                                           | 11; 347    |                      |         |                                                    | • OR 3.52 (95%CI 0.20–60.65), p=0.39*                                                 |                                                                                                                                                                  |
|                                 |                                           | 0; 51      |                      |         |                                                    |                                                                                       |                                                                                                                                                                  |
| Metzler et al. <sup>93</sup>    | Multicentre prospective cohort study (2b) | 388; 1,019 | < 1 y                | < 6 y   | Serum IgE (seasonal, perennial and food allergens) | Exposure to AB in first y of life not associated with increased risk.                 | Sex, family history of atopy, number of siblings, living area, smoking and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure |
| Switzerland                     |                                           | 167; 419   | No                   |         |                                                    | • aOR 1.06 (95%CI 0.70–1.60), p=nr                                                    |                                                                                                                                                                  |
| 2019                            |                                           | 221; 600   | Parent questionnaire |         |                                                    |                                                                                       |                                                                                                                                                                  |
| Oosterloo et al. <sup>105</sup> | Multicentre prospective cohort study (2b) | 18; 205    | < 1 w                | 0–1 y   | Serum IgE (food and inhalant allergens)            | Exposure to AB in first w of life not associated with increased risk.                 | Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking |
| Netherlands                     |                                           | 9; 77      | No                   |         |                                                    | • aOR 3.26 (95%CI 0.95–11.13), p=0.06                                                 |                                                                                                                                                                  |
| 2018                            |                                           | 9; 128     | Parent questionnaire |         |                                                    |                                                                                       |                                                                                                                                                                  |
| Batool et al. <sup>183</sup>    | Multicentre prospective cohort study (2b) | 141; 576   | < 1 y                | 1 y     | SPT (food and inhalant allergens)                  | Exposure to AB in first y of life associated with increased risk.                     |                                                                                                                                                                  |
| Canada                          |                                           | 63; 205    | No                   |         |                                                    | • OR 1.67 (95%CI 1.13–2.46), p<0.01*                                                  |                                                                                                                                                                  |
| 2016                            |                                           | 78; 371    | Parent questionnaire |         |                                                    |                                                                                       |                                                                                                                                                                  |
| Azad et al. <sup>24</sup>       | Multicentre prospective cohort study (2b) | 12; 166    | < 3 m                | 1 y     | SPT (food allergens)                               | Exposure to AB in first 3 m of life not associated with increased risk.               |                                                                                                                                                                  |
| Canada                          |                                           | 6; 78      | No                   |         |                                                    | • OR 1.14 (95%CI 0.35–3.69), p=0.83*                                                  |                                                                                                                                                                  |
| 2015                            |                                           | 6; 88      | Medical records      |         |                                                    |                                                                                       |                                                                                                                                                                  |
|                                 |                                           | 12; 166    | < 1 y                |         |                                                    | Exposure to AB in first y of life not associated with increased risk.                 |                                                                                                                                                                  |
|                                 |                                           | 9; 105     | No                   |         |                                                    | • OR 1.81 (95%CI 0.47–6.97), p=0.39*                                                  |                                                                                                                                                                  |
|                                 |                                           | 3; 61      | Medical records      |         |                                                    |                                                                                       |                                                                                                                                                                  |

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Table 1 (continued)

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|------------------------------------------------------------|------------------------------------------------------|------------------------------------------|----------------------------------------|-----------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Loo et al. <sup>175</sup><br>Singapore<br>2015             | Multicentre<br>prospective<br>cohort study<br>(2b)   | 94; 696<br>nr; nr<br>nr; nr              | < 6 m<br>No<br>Parent<br>questionnaire | 1.5 y           | SPT (food and<br>inhalant<br>allergens) | Exposure to AB in first 6 m of life not associated with<br>increased risk.<br><br>• aOR 11.44 (95%CI 0.50-260.29), p=0.13                                                                                                                                                                                                                 | Sex, living area, family<br>history of atopy, age of<br>child at time of outcome                                                                                                                                                                                                                                                                              |
| Semic-<br>Jusufagic et<br>al. <sup>126</sup><br>UK<br>2014 | Multicentre<br>prospective<br>cohort study<br>(2b)   | 209; 800<br>nr; 564<br>nr; 236           | < 1 y<br>No<br>Parent<br>questionnaire | 1-11 y          | SPT (food and<br>inhalant<br>allergens) | Exposure to AB in first y of life not associated with<br>increased risk.<br><br>• HR 1.02 (95%CI 0.60-1.78), p=0.92                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                               |
| Hoskin-Parr<br>et al. <sup>176</sup><br>UK<br>2013         | Single-centre<br>prospective<br>cohort study<br>(2b) | 830; 5,780<br>386*; 2,659<br>444*; 3,121 | < 2 y<br>No<br>Parent<br>questionnaire | 7.5 y<br>(mean) | SPT (inhalant<br>allergens)             | Exposure to AB in first 2 y of life not associated with<br>increased risk.<br><br>• aOR 1.02 (95%CI 0.85-1.22), p=nr<br><br>• 1 AB course: aOR 1.00 (95%CI 0.80-1.25), p=nr<br>• 2 AB courses: aOR 1.10 (95%CI 0.89-1.39), p=nr<br>• 3 AB courses: aOR 0.96 (95%CI 0.74-1.24), p=nr<br>• ≥ 4 AB courses: aOR 1.00 (95%CI 0.79-1.27), p=nr | Age, sex, maternal age<br>and education; parental<br>marital status, home<br>ownership status,<br>degree of difficulty in<br>paying for food, smoking<br>during pregnancy,<br>disinfectant use during<br>pregnancy, gestational<br>age, birth weight,<br>delivery mode, age of<br>child at outcome,<br>breastfeeding, time<br>spend outdoors, pet<br>exposure |

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Table 1 (continued)

|                               |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |
|-------------------------------|---------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risnes et al. <sup>116</sup>  | Multicentre prospective cohort study (2b)   | 151; 1,401<br>71*; 464<br>80*; 937                                               | < 6 m<br>No<br>Parent questionnaire | 6 y        | SPT (food and inhalant allergens)              | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• aOR 1.59 (95% CI, 1.10-2.28), p=nr                                                                                                                              | Maternal age, family history of atopy, number of LRTIs                                                                                                                                                                 |
| USA<br>2011                   |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |
| Sandini et al. <sup>177</sup> | Single-centre prospective cohort study (2b) | 271; 916<br>nr; nr<br>nr; nr<br>367; 889<br>nr; nr<br>nr; nr                     | < 6 m<br>No<br>Parent questionnaire | 2 y<br>5 y | SPT or serum IgE (food and inhalant allergens) | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 1.22 (95%CI 0.79-1.88), p=0.37<br><br>Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 0.82 (95%CI 0.54-1.25), p=0.35 |                                                                                                                                                                                                                        |
| Finland<br>2011               |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |
| Dom et al. <sup>40</sup>      | Multicentre prospective cohort study (2b)   | 160; 450<br>121; 384<br>39; 66                                                   | < 4 y<br>No<br>Parent questionnaire | < 4 y      | Serum IgE (food and inhalant allergens)        | Exposure to AB before first 4 y of life associated with decreased risk.<br><br>• OR 0.32 (95%CI 0.19-0.54), p<0.01*                                                                                                                          | Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking and pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure |
| Belgium<br>2010               |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |
| Mai et al. <sup>178</sup>     | Single-centre prospective cohort study (2b) | 579; 3,306<br>244; 1,420<br>335; 1,886<br>828; 3,306<br>358; 1,420<br>470; 1,886 | < 1 y<br>No<br>Parent questionnaire | 4 y<br>8 y | Serum IgE (food and inhalant allergens)        | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 0.90 (95%CI 0.70-1.10), p=nr<br><br>Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.00 (95%CI 0.80-1.20), p=nr       | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding                                                                                                                              |
| Sweden<br>2010                |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |
| Su et al. <sup>135</sup>      | Single-centre prospective cohort study (2b) | 202; 398<br>65; 136<br>137; 262                                                  | < 9 m<br>No<br>Parent questionnaire | 1-5 y      | Serum IgE (food and inhalant allergens)        | Exposure to AB in first 9 m of life not associated with increased risk.<br><br>• OR 0.84 (95%CI 0.55-1.26), p=0.39*                                                                                                                          |                                                                                                                                                                                                                        |
| USA<br>2010                   |                                             |                                                                                  |                                     |            |                                                |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                        |

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Table 1 (continued)

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|-----------------------------------------------------------------------|------------------------------------------------------|-------------------------------------|-----------------------------------------|---------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kusel et al. <sup>80</sup><br>Australia<br>2008                       | Multicentre<br>prospective<br>cohort study<br>(2b)   | 67; 198<br>36*; 107<br>31*; 91      | < 1 y<br>Yes<br>Parent<br>questionnaire | 0-5 y   | SPT plus serum<br>IgE (food and<br>inhalant<br>allergens) | Exposure to AB in first y of life not associated with<br>increased risk.<br>• aOR 1.00 (95%CI 0.50-2.10), p=nr<br>Results according to antibiotic class nr | Sex, day care, number<br>of GP visits, pet<br>exposure                                                                                                        |
| Wickens et<br>al. <sup>153</sup><br>New Zealand<br>2008               | Multicentre<br>prospective<br>cohort study<br>(2b)   | 249; 1,064<br>44*; 148<br>205*; 916 | < 3 m<br>No<br>Parent<br>questionnaire  | 15 m    | SPT (food and<br>inhalant<br>allergens)                   | Exposure to AB before 3 m of life not associated with<br>increased risk.<br>• aOR 1.36 (95% CI, 0.91-2.05), p=0.14                                         | Number of LRTIs                                                                                                                                               |
| Harris et al. <sup>60</sup><br>UK<br>2007                             | Single-centre<br>prospective<br>cohort study<br>(2b) | 104; 490<br>27; nr<br>77; nr        | < 5 y<br>No<br>Medical<br>records       | 8 y     | SPT (inhalant<br>allergens)                               | Exposure to AB in first 5 y of life not associated with<br>increased risk.<br>• aOR 1.00 (95%CI 0.97-1.03), p=0.86                                         | Family history of atopy,<br>birth order, smoke<br>exposure                                                                                                    |
| Majkowska-<br>Wojciechowska<br>et al. <sup>87</sup><br>Poland<br>2007 | Multicentre<br>prospective<br>cohort study<br>(2b)   | 128; 201<br>8*; 10<br>120*; 191     | nr<br>No<br>Parent<br>questionnaire     | 12-16 y | SPT                                                       | Early-life exposure to AB associated with increased risk.<br>• <b>OR 2.12 (95%CI 1.16-3.85), p=0.02</b>                                                    |                                                                                                                                                               |
| Kummeling<br>et al. <sup>79</sup><br>Netherlands<br>2007              | Multicentre<br>prospective<br>cohort study<br>(2b)   | 223; 2,462<br>44; 489<br>179; 1,973 | < 6 m<br>No<br>Parent<br>questionnaire  | 2 y     | Serum IgE (food<br>and inhalant<br>allergens)             | Exposure to AB in first 6 m of life not associated with<br>increased risk.<br>• aOR 1.32 (95%CI 0.86-2.02), p=nr                                           | Sex, family history of<br>atopy, day care, number<br>of siblings, delivery<br>mode, vaccination<br>status, fever,<br>breastfeeding, pet and<br>smoke exposure |

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Table 1 (continued)

|                                                    |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
|----------------------------------------------------|-------------------------------------------|--------------------------------------------|-------------------------------------|---------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Floistrup et al. <sup>49</sup>                     | Multicentre cross-sectional study (3b)    | 1,487; 4,606<br>264*; 788<br>1,223*; 3,818 | < 1 y<br>No<br>Parent questionnaire | 7–11 y              | Serum IgE (food and inhalant allergens) | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 0.91 (95%CI 0.60–1.37), p=nr                                                                                                                            | Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, parental smoking, pet exposure |
| Netherlands, Austria, Germany, Sweden, Switzerland |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| 2006                                               |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| Johnson et al. <sup>70</sup>                       | Multicentre prospective cohort study (2b) | 157; 448<br>83*; 221<br>74*; 227           | < 6 m<br>No<br>Medical records      | 6–7 y               | Clinical evaluation plus SPT            | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• aOR 1.48 (95%CI 0.94–2.34), p=0.09                                                                                                                        | Family history of atopy, number of LRTIs, duration of breastfeeding, pet exposure                                                                                                                         |
| USA                                                |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| 2005                                               |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| Wjst et al. <sup>155</sup>                         | Multicentre cross-sectional study (3b)    | 1,944; 2,512<br>nr; 2,025<br>nr; 487       | < 5–14 y<br>No<br>Medical records   | 5–14 y              | SPT (food and inhalant allergens)       | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 0.90 (95%CI 0.60–1.40), p=0.71                                                                                                                          | Age, sex, family history of atopy, season, parental education                                                                                                                                             |
| Germany                                            |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| 2001                                               |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| Droste et al. <sup>43</sup>                        | Multicentre cross-sectional study (3b)    | 130; 660<br>45; 210<br>85; 450             | < 1 y<br>No<br>Parent questionnaire | 7–8 y               | SPT (inhalant allergens)                | Exposure to AB in first y of life not associated with increased risk in high-risk children.<br><br>• aOR 1.10 (95%CI 0.70–1.70), p=0.10                                                                                                    | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure                                                                                                   |
| Belgium                                            |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| 2000                                               |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| Von Mutius et al. <sup>181</sup>                   | Single-centre cross-sectional study (3b)  | 222; 5,006<br>168; 3,904<br>54; 1,102      | < 3 y<br>No<br>Medical records      | 5–7 y<br><br>9–11 y | Serum IgE (inhalant allergens) plus SPT | Exposure to AB in first 3 y of life not associated with increased risk.<br><br>• OR 0.87 (95%CI 0.64–1.19), p=0.40*<br><br>Exposure to AB in first 3 y of life associated with increased risk.<br><br>• OR 1.20 (95%CI 1.02–1.43), p=0.03* |                                                                                                                                                                                                           |
| Germany                                            |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |
| 1999                                               |                                           |                                            |                                     |                     |                                         |                                                                                                                                                                                                                                            |                                                                                                                                                                                                           |

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Table 1 (continued)

| Food allergies               |                                           |               |                      |         |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                |
|------------------------------|-------------------------------------------|---------------|----------------------|---------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aversa et al. <sup>172</sup> | Multicentre prospective cohort study (2b) | 261; 14,572   | < 2 y                | 6–11 y  | ICD-9 and ICD-10 codes                                                                          | Exposure to AB in first 2 y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                     | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode,                                                             |
| USA                          |                                           | 201; 10,220   | Yes                  |         |                                                                                                 | • aHR 1.33 (95%CI 0.99–1.77), p=0.05                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                |
| 2021                         |                                           | 60; 4,352     | Medical records      |         |                                                                                                 | Girls<br>• penicillins: HR 0.74 (95%CI 0.47–1.15), p=0.18<br>• cephalosporins: <b>HR 2.73 (95%CI 1.74–4.28), p&lt;0.01</b><br>• macrolides: HR 1.00 (95%CI 0.62–1.59), p=0.99<br>• sulfonamides: HR 1.27 (95%CI 0.65–2.49), p=0.49<br><br>Boys<br>• penicillins: HR 1.06 (95%CI 0.73–1.53), p=0.77<br>• cephalosporins: <b>HR 1.96 (95%CI 1.39–2.76), p&lt;0.01</b><br>• macrolides: HR 0.99 (95%CI 0.69–1.41), p=0.94<br>• sulfonamides: HR 0.67 (95%CI 0.31–1.43), p=0.30 |                                                                                                                                                                                |
| Zou et al. <sup>161</sup>    | Multicentre cross-sectional study (3b)    | 1,938; 12,667 | < 1 y                | 4–6 y   | Questionnaire for allergic symptoms (ISAAC)                                                     | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                           | Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure                                                  |
| China                        |                                           | 560; 3,049    | No                   |         |                                                                                                 | • aOR 1.29 (95%CI 1.13–1.46), p<0.01                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                |
| 2020                         |                                           | 1,378; 9,618  | Parent questionnaire |         |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                |
| Levin et al. <sup>82</sup>   | Multicentre prospective cohort study (2b) | 27; 1,185     | < 1 y                | 12–36 m | Questionnaire for allergic symptoms (based on ISAAC)                                            | Exposure to AB in first y of life not associated with increased risk in urban cohort.                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                |
| South-Africa                 |                                           | 18; 654       | No                   |         |                                                                                                 | • OR 1.64 (95%CI 0.73–3.68), p=0.23*                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                |
| 2020                         |                                           | 9; 531        | Parent questionnaire |         |                                                                                                 | Exposure to AB in first y of life not associated with increased risk in rural cohort.                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                |
|                              |                                           | 2; 398        |                      |         |                                                                                                 | • OR 0.75 (95%CI 0.04–15.75), p=0.19*                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                |
|                              |                                           | 2; 347        |                      |         |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                |
|                              |                                           | 0; 51         |                      |         |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                |
| Metzler et al. <sup>93</sup> | Multicentre prospective cohort study (2b) | 75; 1,019     | < 1 y                | < 6 y   | Questionnaire for allergic symptoms (based on ISAAC) plus parent-reported physician's diagnosis | Exposure to AB in first y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                       | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, pet exposure during pregnancy, delivery mode, duration of breastfeeding, pet exposure |
| Switzerland                  |                                           | 37; 419       | No                   |         |                                                                                                 | • aOR 1.47 (95%CI 0.73–2.98), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| 2019                         |                                           | 38; 600       | Parent questionnaire |         |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                |

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Table 1 (continued)

|                             |                                             |                                                       |                                                   |       |                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                           |
|-----------------------------|---------------------------------------------|-------------------------------------------------------|---------------------------------------------------|-------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gao et al. <sup>51</sup>    | Single-centre prospective cohort study (2b) | 200; 903<br>43; 201<br>157; 702                       | < 1 y<br>No<br>Parent questionnaire               | 12 m  | Parent-reported                                                        | Exposure to AB in first y of life not associated with increased risk.<br><br>• OR 0.94 (95%CI 0.65–1.38), p=0.77*                                                                                                                                                                                                                                                                                  | Sex, family history of atopy, antibiotic use during pregnancy, season of birth, egg and milk consumption                                                  |
| Li et al. <sup>185</sup>    | Multicentre prospective cohort study (2b)   | 14,812; 1,001,294<br>9,193; 500,647<br>5,619; 500,647 | < 1 y<br>No<br>Registry                           | < 4 y | ICD-9-CM codes                                                         | Exposure to AB in first y of life associated with increased risk.<br><br>• aHR 1.40 (95%CI 1.34–1.45), p=nr                                                                                                                                                                                                                                                                                        | Day care, living area, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission, State Children's Health Insurance Program, atopy |
| Mitre et al. <sup>96</sup>  | Multicentre retrospective cohort study (2b) | 24,514; 792,130<br>4,753; 131,708<br>19,761; 660,422  | < 6 m<br>No<br>Registry                           | 1–6 y | ICD-9-CM codes                                                         | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• aHR 1.14 (95%CI 1.10–1.18), p=nr                                                                                                                                                                                                                                                                                      | Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use                                                                            |
| Hirsch et al. <sup>61</sup> | Multicentre case-control study (3b)         | 484; 2,904<br>210; 1,074<br>274; 1,830                | >1–2 m before diagnosis<br>Yes<br>Medical records | < 7 y | Cow's milk allergy ICD-9 codes plus medical or prescription records    | Exposure to AB until 2 m before diagnosis associated with increased risk.<br><br>• aOR 1.58 (95%CI 1.24–2.02), p=nr<br><br>• ≤ 2 AB courses: aOR 1.49 (95%CI 1.15–1.96), p=nr<br>• ≥ 3 AB courses: aOR 1.78 (95%CI 1.28–2.48), p=nr<br><br>• penicillins: aOR 1.58 (95%CI 1.24–2.02), p=nr<br>• cephalosporins: aOR 1.40 (95%CI 1.02–1.93), p=nr<br>• macrolides: aOR 1.68 (95%CI 1.19–2.37), p=nr | Ethnicity, healthcare use                                                                                                                                 |
|                             |                                             | 598; 3,588<br>445; 2,496<br>153; 1,092                |                                                   |       | Non-milk food allergy ICD-9 codes plus medical or prescription records | Exposure to AB until 2 m before diagnosis associated with increased risk.<br><br>• aOR 1.49 (95%CI 1.18–1.87), p=nr<br><br>• ≤ 2 AB courses: aOR 1.38 (95%CI 1.08–1.77), p=nr<br>• ≥ 3 AB courses: aOR 1.65 (95%CI 1.27–2.14), p=nr<br>• penicillins: aOR 1.29 (95%CI 1.04–1.59), p=nr<br>• cephalosporins: aOR 1.57 (95%CI 1.29–1.93), p=nr<br>• macrolides: aOR 1.58 (95%CI 1.28–1.96), p=nr     |                                                                                                                                                           |

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Table 1 (continued)

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|-------------------------------------|----------------------------------------------------|--------------------------------------------|-------------------------------------------|---------|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Batool et al. <sup>183</sup>        | Multicentre prospective cohort study (2b)          | 143; 818<br>62; 285<br>81; 533             | < 1 y<br>No<br>Parent questionnaire       | 1 y     | Parent-reported food allergies or SPT                   | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.55 (95%CI 1.07-2.24), p=0.02*</b>                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                |
| Canada                              |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| 2016                                |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| Love et al. <sup>163</sup>          | Multicentre retrospective case-control study (3b)  | 1,504; 7,499<br>722; 3,324<br>782; 4,175   | < 1 y<br>Yes<br>Prescription records      | 0-3 y   | ICD-9-CM codes                                          | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.21 (95%CI 1.06-1.39), p&lt;0.01</b><br><br>• penicillins: <b>aOR 1.19 (95%CI 1.04-1.36), p=0.01</b><br>• cephalosporins: <b>aOR 1.50 (95%CI 1.27-1.77), p&lt;0.01</b><br>• macrolides: <b>aOR 1.36 (95%CI 1.13-1.63), p&lt;0.01</b><br>• sulfonamides: <b>aOR 1.54 (95%CI 1.19-2.01), p&lt;0.01</b>                                                              | Maternal age and smoking, pre-pregnancy diabetes, living area, smoking during pregnancy, gestational age, delivery mode, atopy, breastfeeding, |
| USA                                 |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| 2016                                |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| Metsälä et al. <sup>91</sup>        | Multicentre case-control study (3b)                | 533; 15,672<br>162*; 3,292<br>371*; 12,380 | < 1 m before diagnosis<br>Yes<br>Registry | 1 m-8 y | Cow's milk allergy ICD-10 codes plus SPT plus serum IgE | Exposure to AB within 1 m before diagnosis associated with increased risk.<br><br>• <b>aOR 1.71 (95%CI 1.59-1.84), p=nr</b><br><br>• penicillin: <b>aOR 1.97 (95%CI 1.50-2.58), p=nr</b><br>• amoxicillin: <b>aOR 1.39 (95%CI 1.29-1.51), p=nr</b><br>• cephalosporins: <b>aOR 2.43 (95%CI 2.14-2.77), p=nr</b><br>• macrolides: <b>aOR 1.65 (95%CI 1.49-1.82), p=nr</b><br>• trimethoprim/sulfamethoxazole: <b>aOR 1.60 (95%CI 1.27-2.02), p=nr</b> | Maternal age, parity, maternal smoking during pregnancy, birth weight, delivery mode                                                           |
| Finland                             |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| 2013                                |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| Dowhower Karpa et al. <sup>42</sup> | Single-centre retrospective case-control study (4) | 99; 291<br>16; 40<br>83; 251               | < 1 m<br>No<br>Medical                    | 0-18 y  | ICD-9-CM codes plus serum IgE or SPT or physician's     | Early exposure to AB not associated with increased risk.<br><br>• <b>OR 1.35 (95%CI 0.68-2.68), p=0.39</b>                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                |
| USA                                 |                                                    |                                            |                                           |         |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |

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Table 1 (continued)

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|-------------------------------------|-----------------------------------------------|------------------------------------------|-------------------------------------|------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Raciborski et al. <sup>115</sup>    | Multicentre retrospective cohort study (2b)   | 307; 1,330<br>211; 820<br>96; 510        | < 1 y<br>No<br>Parent questionnaire | 6-8 y      | Questionnaire for allergic symptoms (ISAAC)                | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.49 (95%CI 1.14-1.96), p&lt;0.01*</b><br><br>• 1 AB course: OR 1.23 (95%CI nr), p=0.22<br>• 2-3 AB courses: OR 1.30 (95%CI nr), p=0.18<br>• > 3 AB courses: <b>OR 1.52 (95%CI nr), p=0.05</b> |                                                                                                                                                 |
| Poland                              |                                               | 307; 1,321<br>273; 1,145<br>34; 176      | 1-3 y<br>No<br>Parent questionnaire |            |                                                            | Exposure to AB in first to third y of life not associated with increased risk.<br><br>• OR 1.31 (95%CI 0.88-1.95), p=0.19<br><br>• 1-2 AB courses: OR 1.12 (95%CI nr), p=0.62<br>• 3-4 AB courses: OR 1.32 (95%CI nr), p=0.23<br>• > 4 AB courses: OR 1.32 (95%CI nr), p=0.24   |                                                                                                                                                 |
| Mai et al. <sup>178</sup>           | Single-centre prospective cohort study (2b)   | 354; 3,306<br>181; 1,420<br>173; 1,886   | < 1 y<br>No<br>Parent questionnaire | 4 y<br>8 y | Questionnaire for allergic symptoms (BAMSE based on ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.40 (95%CI 1.10-1.70), p=nr</b>                                                                                                                                                              | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding,                                                      |
| Sweden                              |                                               | 436; 3,306<br>206; 1,420<br>230; 1,886   |                                     |            |                                                            | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.20 (95%CI 0.90-1.40), p=nr                                                                                                                                                                 |                                                                                                                                                 |
| Eggesbo et al. <sup>46</sup>        | Single-centre retrospective cohort study (2b) | 32; 2,759<br>12; 963<br>20; 1,796        | < 6 m<br>No<br>Parent questionnaire | 2.5 y      | Parent-reported immediate reaction plus serum IgE          | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• aOR 1.50 (95% CI, 0.60-3.70), p=0.40                                                                                                                                                           | Maternal age, education and smoking; number of siblings, restricted growth in pregnancy, pregnancy complications, gestational age, birth weight |
| Norway                              |                                               |                                          |                                     |            |                                                            |                                                                                                                                                                                                                                                                                 |                                                                                                                                                 |
| 2003                                |                                               |                                          |                                     |            |                                                            |                                                                                                                                                                                                                                                                                 |                                                                                                                                                 |
| <b>Allergic rhinoconjunctivitis</b> |                                               |                                          |                                     |            |                                                            |                                                                                                                                                                                                                                                                                 |                                                                                                                                                 |
| Aversa et al. <sup>172</sup>        | Multicentre prospective cohort study (2b)     | 971; 14,572<br>760; 10,220<br>211; 4,352 | < 2 y<br>Yes<br>Medical records     | 6-11 y     | ICD-9 and ICD-10 codes                                     | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aHR 1.36 (95%CI 1.17-1.59), p&lt;0.01</b>                                                                                                                                                       | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode,                              |
| USA                                 |                                               |                                          |                                     |            |                                                            |                                                                                                                                                                                                                                                                                 |                                                                                                                                                 |
| 2021                                |                                               |                                          |                                     |            |                                                            |                                                                                                                                                                                                                                                                                 |                                                                                                                                                 |

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Table 1 (continued)

|                                    |                                              |               |                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                   |
|------------------------------------|----------------------------------------------|---------------|----------------------|---------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                              |               |                      |         |                                                               | Girls<br>• penicillins: HR 1.15 (95%CI 0.91–1.46), p=0.25<br>• cephalosporins: <b>HR 1.83 (95%CI 1.46–2.30), p&lt;0.01</b><br>• macrolides: HR 1.11 (95%CI 0.88–1.40), p=0.36<br>• sulfonamides: HR 1.16 (95%CI 0.81–1.66), p=0.41<br><br>Boys<br>• penicillins: HR 1.16 (95%CI 0.95–1.41), p=0.15<br>• cephalosporins: <b>HR 1.29 (95%CI 1.07–1.55), p&lt;0.01</b><br>• macrolides: <b>HR 1.39 (95%CI 1.16–1.66), p&lt;0.01</b><br>• sulfonamides: HR 1.10 (95%CI 0.80–1.52), p=0.56 |                                                                                                                                                                                                   |
| Zou et al. <sup>161</sup>          | Multicentre cross-sectional study (3b)       | 1,579; 12,667 | < 1 y                | 4–6 y   | Questionnaire for allergic rhinitis symptoms (ISAAC)          | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                     | Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure                                                                     |
| China                              |                                              | 479; 3,049    | No                   |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                   |
| 2020                               |                                              | 1,100; 9,618  | Parent questionnaire |         |                                                               | <b>• aOR 1.23 (95%CI 1.07–1.41), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                   |
| Levin et al. <sup>82</sup>         | Multicentre prospective cohort study (2b)    | 295; 1,185    | < 1 y                | 12–36 m | Questionnaire for allergic rhinitis symptoms (based on ISAAC) | Exposure to AB in first y of life associated with increased risk in urban cohort.                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                   |
| South-Africa                       |                                              | 187; 654      | No                   |         |                                                               | <b>• OR 1.57 (95%CI 1.20–2.06), p&lt;0.01*</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                   |
| 2020                               |                                              | 108; 531      | Parent questionnaire |         |                                                               | Exposure to AB in first y of life not associated with increased risk in rural cohort.                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                   |
|                                    |                                              | 13; 398       |                      |         |                                                               | <b>• OR 1.79 (95%CI 0.23–14.07), p=0.58*</b>                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                   |
|                                    |                                              | 12; 347       |                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                   |
|                                    |                                              | 1; 51         |                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                   |
| Chinratanapit et al. <sup>35</sup> | Multicentre cross-sectional study (3b)       | 462; 3,074    | < 1 y                | 6–7 y   | Questionnaire for allergic rhinitis symptoms (ISAAC)          | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                     | Age, sex, family history of atopy, number of siblings, migration, birth weight, BMI, medication use, parental smoking, diet, pet, farm animal, air pollution, cooking fuels, and traffic exposure |
| Thailand                           |                                              | 237; 1,138    | No                   |         |                                                               | <b>• OR 2.00 (95%CI 1.64–2.44), p&lt;0.01*</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                   |
| 2019                               |                                              | 225; 1,936    | Parent questionnaire |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                   |
| Ni et al. <sup>102</sup>           | Single-centre retrospective cohort study (4) | 233; 2,398    | < 1 y                | 1–10 y  | ICD-9 and ICD-10 codes                                        | Exposure to AB in first y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                 | Age, sex, ethnicity, socioeconomic status, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission                                                                       |
| USA                                |                                              | 130*; 1,060   | Yes                  |         |                                                               | <b>• aOR 1.41 (95%CI 0.48–4.14), p=0.53</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                   |
| 2019                               |                                              | 103*; 1,338   | Medical records      |         |                                                               | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                   |
|                                    |                                              | 215; 2,398    | < 10 y               |         |                                                               | Exposure to AB in first 10 y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                   |
|                                    |                                              | 198*; 1,755   | Yes                  |         |                                                               | <b>• aOR 2.43 (95%CI 1.43–4.11), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                   |
|                                    |                                              | 17*; 643      | Medical records      |         |                                                               | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                   |

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Table 1 (continued)

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|-------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Norbäck et al. <sup>103</sup> | Multicentre retrospective cohort study (2b) | 3,463; 39,782<br>3,000; 29,303<br>463; 10,479                                                                         | < 1 y<br>No<br>Parent questionnaire | 3–6 y | Parent-reported physician's diagnosis                                                           | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.77 (95%CI 1.54–2.03), p&lt;0.01</b><br>• 1 AB course: <b>aOR 1.19 (95%CI 1.06–1.34), p&lt;0.01</b><br>• > 1 AB courses: <b>aOR 1.51 (95%CI 1.36–1.68), p&lt;0.01</b> | Living area, time spend outdoors, air pollution, temperature in each city                                                                                               |
| China                         |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |
| 2019                          |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |
| Metzler et al. <sup>93</sup>  | Multicentre prospective cohort study (2b)   | 59; 1,019<br>21; 419<br>38; 600                                                                                       | < 1 y<br>No<br>Parent questionnaire | < 6 y | Questionnaire for allergic symptoms (based on ISAAC) plus parent-reported physician's diagnosis | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 0.70 (95%CI 0.33–1.51), p=nr                                                                                                                                          | Sex, family history of atopy, number of siblings, living area, smoking during and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure |
| Switzerland                   |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |
| 2019                          |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |
| Mitre et al. <sup>96</sup>    | Multicentre retrospective cohort study (2b) | 24,585; 792,130<br>5,047; 131,708<br>19,538; 660,422<br>248,232;<br>792,130<br>52,135; 131,708<br>196,097;<br>660,422 | < 6 m<br>No<br>Registry             | 1–6 y | Allergic conjunctivitis ICD-9-CM codes<br>Allergic rhinitis ICD-9-CM codes                      | Exposure to AB in first 6 m of life associated with increased risk.<br>• <b>aHR 1.42 (95%CI 1.34–1.50), p=nr</b><br>Exposure to AB in first 6 m of life associated with increased risk.<br>• <b>aHR 1.75 (95%CI 1.72–1.78), p=nr</b>                 | Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use                                                                                          |
| USA                           |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |
| 2018                          |                                             |                                                                                                                       |                                     |       |                                                                                                 |                                                                                                                                                                                                                                                      |                                                                                                                                                                         |

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Table 1 (continued)

|                                       |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
|---------------------------------------|-------------------------------------------|----------------------------------------------|--------------------------------------|-------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Singh et al. <sup>129</sup>           | Multicentre cross-sectional study (3b)    | 1,753; 44,928<br>nr; nr<br>nr; nr            | < 1 y<br>No<br>Parent questionnaire  | 6-7 y | Questionnaire for allergic rhinoconjunctivitis symptoms (ISAAC)           | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 1.90 (95%CI 1.70-2.20), p&lt;0.01</b>                                                                                                                                                                 |                                                                                                                                                       |
| India                                 |                                           | 5,100; 44,928                                |                                      |       | Questionnaire for allergic rhinitis symptoms (ISAAC)                      | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 1.90 (95%CI 1.70-2.00), p&lt;0.01</b>                                                                                                                                                                 |                                                                                                                                                       |
| 2018                                  |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| Han et al. <sup>59</sup>              | Multicentre cross-sectional study (3b)    | 207; 1,517<br>155; 921<br>52; 596            | < 1 y<br>No<br>Parent questionnaire  | 6-7 y | Questionnaire for allergic rhinoconjunctivitis symptoms (ISAAC)           | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.90 (95%CI 1.30-2.70), p&lt;0.01</b>                                                                                                                                                                | Number of LRTIs, medication use                                                                                                                       |
| Argentina                             |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| 2017                                  |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| Yamamoto-Hanada et al. <sup>157</sup> | Multicentre prospective cohort study (2b) | 96; 902<br>59; 436<br>37; 466                | < 2 y<br>Yes<br>Parent questionnaire | 5 y   | Questionnaire for allergic rhinitis (ISAAC) symptoms plus medical records | Exposure to AB in first 2 y of life associated with increased risk.<br>• <b>aOR 1.65 (95%CI 1.05-2.58), p=0.03</b><br>• penicillins: aOR 0.58 (95%CI 0.22-1.51), p=0.26<br>• cephem: <b>aOR 1.82 (95%CI 1.12-2.93), p=0.02</b><br>• macrolides: aOR 1.50 (95%CI 0.902-4.9), p=0.12 | Sex, maternal age, BMI, education and history of atopy; parity, day care, , smoking during pregnancy, gestational age, delivery mode, number of LRTIs |
| Japan                                 |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| 2017                                  |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| Wang et al. <sup>186</sup>            | Multicentre cross-sectional study (3b)    | 1,624; 13,335<br>nr; nr<br>nr; nr            | < 1 y<br>No<br>Parent questionnaire  | 4-6 y | Questionnaire for allergic rhinitis (ISAAC)                               | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.23 (95%CI 1.09–1.40), p=nr</b>                                                                                                                                                                     | Age, sex, family history of atopy                                                                                                                     |
| China                                 |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| 2016                                  |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| Yang et al. <sup>158</sup>            | Multicentre cross-sectional study (3b)    | 1,768; 6,435<br>1,258; 1,947<br>2,629; 4,488 | < 1 y<br>No<br>Parent questionnaire  | 15 y  | Questionnaire for allergic rhinitis symptoms (ISAAC)                      | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.25 (95%CI 1.04-1.50), p=0.02</b>                                                                                                                                                                   | Age, sex, study centre, family history of atopy, income, BMI                                                                                          |
| Korea                                 |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |
| 2014                                  |                                           |                                              |                                      |       |                                                                           |                                                                                                                                                                                                                                                                                    |                                                                                                                                                       |

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Table 1 (continued)

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|-----------------------------------|---------------------------------------------|-------------|----------------------|--------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alm et al. <sup>16</sup>          | Multicentre prospective cohort study (2b)   | 564; 4,051  | < 1 w                | 8 y          | Questionnaire for allergic rhinitis symptoms (ISAAC and BAMSE) | Exposure to AB in first w of life associated with increased risk.<br><br>• <b>aOR 1.75 (95%CI 1.03-2.97), p=nr</b>                                                                                                                                                                                                                        | Sex, maternal age, family history of atopy, living area, paternal education, maternal medication during pregnancy, weight for gestational age, atopy, diet, pacifier use, time spend outdoors, pet exposure                                                                                                         |
| Sweden                            |                                             | 40*; 187    | No                   |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| 2014                              |                                             | 524*; 3,864 | Parent questionnaire |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| Tamay et al. <sup>187</sup>       | Multicentre prospective cohort study (2b)   | 803; 9,875  | < 1 y                | 6-7 y        | Questionnaire for allergic rhinitis symptoms (ISAAC)           | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.41 (95%CI 1.15-1.73), p&lt;0.05</b>                                                                                                                                                                                                                   | Number of LRTIs, perianal redness, adenotonsillectomy, medication use, pet exposure, environmental factors                                                                                                                                                                                                          |
| Turkey                            |                                             | nr; nr      | No                   |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| 2014                              |                                             | nr; nr      | Parent questionnaire |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| Hoskin-Parr et al. <sup>176</sup> | Single-centre prospective cohort study (2b) | 503; 5,780  | < 2 y                | 7.5 y (mean) | Parents-reported physician's diagnosis                         | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aOR 1.28 (95%CI 1.03-1.60), p=nr</b><br><br>• 1 AB course: aOR 1.17 (95%CI 0.88-1.54), p=nr<br>• 2 AB courses: aOR 1.21 (95%CI 0.90-1.61), p=nr<br>• 3 AB courses: aOR 1.18 (95%CI 0.86-1.61), p=nr<br>• ≥ 4 AB courses: aOR 1.60 (95%CI 1.21-2.10), p=nr | Age, sex, maternal age and education; parental marital status, home ownership status, degree of difficulty in paying for food, smoking during pregnancy, disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure |
| UK                                |                                             | 260*; 2,659 | No                   |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | 243*; 3,121 | Parent questionnaire |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| Muc et al. <sup>97</sup>          | Multicentre cross-sectional study (3b)      | 14; 1,037   | < 1 y                | 6-9 y        | Questionnaire for allergic rhinitis symptoms (ISAAC)           | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.84 (95%CI 1.30-2.59), p&lt;0.01</b>                                                                                                                                                                                                                   | Age, sex, prematurity, atopy                                                                                                                                                                                                                                                                                        |
| Portugal                          |                                             | 5*; 237     | No                   |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | 9*; 800     | Parent questionnaire |              |                                                                |                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                     |

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Table 1 (continued)

|                                 |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
|---------------------------------|---------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|--------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Wang et al. <sup>150</sup>      | Multicentre prospective cohort study (2b)   | 82,292; 263,620<br>nr; 15,663<br>nr; 247,957                                     | < 1 y<br>Yes<br>Medical records     | 2-6 y        | ICD-9-CM codes                                                      | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aHR 1.41 (95%CI 1.35-1.47), p&lt;0.05</b><br><br>Results according to antibiotic class nr                                                                | Sex, living area, socioeconomic status, healthcare use                                     |
| Taiwan                          |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2013                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| Kim et al. <sup>74</sup>        | Multicentre cross-sectional study (3b)      | 1,550; 4,436<br>748*; 1,528<br>802*; 2,908                                       | < 1 y<br>No<br>Parent questionnaire | 9.5 y (mean) | Questionnaire for allergic rhinitis symptoms (ISAAC)                | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.95 (95%CI 1.61-2.36), p&lt;0.01</b><br><br>Strongest risk of children with atopic parents<br>• <b>aOR 6.00 (95%CI 4.63-7.80), p=nr</b>             | Age, sex, study centre, family history of atopy, maternal education, BMI, smoke exposure   |
| Korea                           |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2012                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| Peñaranda et al. <sup>110</sup> | Multicentre cross-sectional study (3b)      | 588; 3,256<br>401; nr<br>163; nr                                                 | < 1 y<br>No<br>Parent questionnaire | 6-7 y        | Questionnaire for allergic rhinitis symptoms (ISAAC)                | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.30 (1.10-1.70), p=0.01</b>                                                                                                                         | Maternal education, delivery mode, atopy, medication use, household smoking                |
| Colombia                        |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2012                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| Sandini et al. <sup>177</sup>   | Single-centre prospective cohort study (2b) | 177; 891<br>nr; nr<br>nr; nr                                                     | < 6 m<br>No<br>Parent questionnaire | 5 y          | Parent-reported allergic rhinitis symptoms                          | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 0.92 (95%CI 0.54-1.56), p=0.75                                                                                                                     |                                                                                            |
| Finland                         |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2011                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| Mai et al. <sup>178</sup>       | Single-centre prospective cohort study (2b) | 369; 3,306<br>176; 1,420<br>193; 1,886<br>447; 3,306<br>202; 1,420<br>245; 1,886 | < 1 y<br>No<br>Parent questionnaire | 4 y<br>8 y   | Questionnaire for allergic rhinitis symptoms (BAMSE based on ISAAC) | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.20 (95%CI 0.90-1.50), p=nr<br><br>Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.10 (95%CI 0.90-1.30), p=nr | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding, |
| Sweden                          |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2010                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| Sultesz et al. <sup>188</sup>   | Single-centre case-control study (3b)       | 883; 3,322<br>473; 1,495<br>410; 1,827                                           | < 1 y<br>No<br>Parent questionnaire | 6-12 y       | Questionnaire for allergic rhinitis symptoms (based on ISAAC)       | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.60 (95%CI 1.37-1.87), p&lt;0.01</b>                                                                                                                 |                                                                                            |
| Hungary                         |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |
| 2010                            |                                             |                                                                                  |                                     |              |                                                                     |                                                                                                                                                                                                                                        |                                                                                            |

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Table 1 (continued)

|                                                                                              |                                                      |                                          |                                     |               |                                                      |                                                                                                                   |                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------|-------------------------------------|---------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Foliaki et al. <sup>50</sup><br>Sweden<br>2009                                               | Multicentre retrospective cross-sectional study (3b) | nr; 193,412<br>nr; 135,775<br>nr; 57,637 | < 1 y<br>No<br>Parent questionnaire | 6–7 y         | Questionnaire for rhinoconjunctivitis (ISAAC)        | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.56 (95%CI 1.46–1.66), p=nr       | Sex, language, living area, income                                                                                                                                                                         |
| Karimi et al. <sup>162</sup><br>Iran<br>2009                                                 | Multicentre cross-sectional study (3b)               | 195; 1,476<br>134; 958*<br>61; 518*      | < 1 y<br>No<br>nr                   | 6–7 y         | Questionnaire for allergic rhinitis symptoms (ISAAC) | Exposure to AB in first y of life not associated with increased risk.<br><br>• OR 1.22 (95%CI 0.87–1.72), p=0.20  |                                                                                                                                                                                                            |
| Harris et al. <sup>90</sup><br>UK<br>2007                                                    | Single-centre prospective cohort study (2b)          | 124; 523<br>43; nr<br>81; nr             | < 5 y<br>No<br>Medical records      | 8 y           | Questionnaire for allergic rhinitis symptoms (ISAAC) | Exposure to AB in first 5 y of life associated with increased risk.<br><br>• aOR 1.06 (95%CI 1.03–1.09), p<0.01   | Family history of atopy, birth order, smoke exposure                                                                                                                                                       |
| Mullooly et al. <sup>98</sup><br>USA<br>2007                                                 | Single-centre case-control study (3b)                | 660; 844<br>nr; nr<br>nr; nr             | < 2 y<br>No<br>Medical records      | 10.3 y (mean) | Parent-reported physician's diagnosis                | Exposure to AB in first 2 y of life not associated with increased risk.<br><br>• aOR 1.03 (95%CI 0.99–1.08), p=nr | Sex, ethnicity, maternal age, birth weight, age of child at time of outcome, breastfeeding, household smoking                                                                                              |
| Tamay et al. <sup>189</sup><br>Turkey<br>2007                                                | Multicentre prospective cohort study (2b)            | 671; 2,500<br>430; nr<br>241; nr         | < 1 y<br>No<br>Parent questionnaire | 6–12 y        | Questionnaire for allergic rhinitis symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.26 (1.01–1.57), p=nr             | Family history of atopy, number of LRTIs and sinusitis, atopy, adenotonsillectomy, perianal redness, medication use, pet, home-dampness and diesel truck exposure                                          |
| Floistrup et al. <sup>49</sup><br>Netherlands, Austria, Germany, Sweden, Switzerland<br>2006 | Multicentre cross-sectional study (3b)               | 216; 4,606<br>67*; 788<br>149*; 3,818    | < 1 y<br>No<br>Parent questionnaire | 7–11 y        | Parent-reported physician's diagnosis                | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.97 (95%CI 1.26–3.08), p=nr       | Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure |

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Table 1 (continued)

|                               |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
|-------------------------------|--------------------------------------------|----------------------------------------|-------------------------------------|--------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Thomsen et al. <sup>190</sup> | Single-centre case-control study (4)       | 44; 470<br>12*; 152<br>32*; 318        | < 2 y<br>No<br>Parent questionnaire | 7–17 y       | Parent-reported physician's diagnosis                   | Exposure to AB in first 2 y of life not associated with increased risk.<br>• OR 0.77 (95%CI 0.38–1.53), p=0.45*                                                                                                                                                                                  |
| Denmark                       |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
| 2006                          |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
| Cohet et al. <sup>37</sup>    | Single-centre case-control study (3b)      | 699; 3,927<br>534; 2,684<br>165; 1,243 | < 1 y<br>No<br>Parent questionnaire | 6–7 y        | Questionnaire for allergic rhinitis symptoms (ISAAC)    | Exposure to AB in first y of life associated with increased risk.<br>• OR 1.52 (95%CI 1.25–1.85), p=nr                                                                                                                                                                                           |
| New Zealand                   |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
| 2004                          |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
| Bremner et al. <sup>29</sup>  | Multicentre nested case-control study (3b) | 2,902; 40,183<br>nr; nr<br>nr; nr      | < 3 y<br>Yes<br>Medical records     | 5.1 y (mean) | Read codes                                              | Exposure to AB in first 3 y of life associated with increased risk.<br>• AB first y: OR 1.15 (95%CI, 1.03–1.29), p=0.02<br>• AB in second y: OR 1.29 (95%CI, 1.15–1.46), p<0.01<br>• AB in third y: OR 1.32 (95%CI, 1.17–1.48), p<0.01<br><br>Results according to antibiotic class nr           |
| UK                            |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
| 2003                          |                                            |                                        |                                     |              |                                                         |                                                                                                                                                                                                                                                                                                  |
|                               |                                            | 4,196; 76,310<br>nr; nr<br>nr; nr      | < 1 y<br>Yes<br>Medical records     | 4.6 y (mean) | Oxford Medical Information System (OXMIS) or Read codes | Exposure to AB in first y of life not associated with increased risk.<br>• AB first y: OR 1.08 (95%CI, 0.98–1.20), p=0.13<br><br>• 1 AB course: aOR 1.11 (95%CI 1.02–1.22), p=0.02<br>• 2 AB courses: aOR 1.26 (95%CI 1.14–1.41), p<0.01<br>• ≥ 3 AB courses: aOR 1.36 (95%CI 1.23–1.50), p<0.01 |

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Table 1 (continued)

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|--------------------------------|---------------------------------------------|------------------------------------------|----------------------|------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
|                                |                                             |                                          |                      |            |                                                                | <ul style="list-style-type: none"> <li>• penicillins: aOR 0.97 (95%CI 0.92–1.03), p=0.35</li> <li>• cephalosporins: aOR 0.95 (95%CI 0.86–1.06), p=0.34</li> <li>• macrolides: aOR 0.97 (95%CI 0.91–1.04), p=0.46</li> <li>• trimethoprim/sulfamethoxazole: aOR 0.92 (95%CI 0.82–1.02), p=0.12</li> </ul>                                              |                                      |
|                                |                                             |                                          | 1–2 y                |            |                                                                | Exposure to AB in second y of life associated with increased risk.                                                                                                                                                                                                                                                                                    |                                      |
|                                |                                             |                                          | Yes                  |            |                                                                | <ul style="list-style-type: none"> <li>• <b>OR 1.40 (95%CI, 1.26–1.56), p&lt;0.01</b></li> </ul>                                                                                                                                                                                                                                                      |                                      |
|                                |                                             |                                          | Medical records      |            |                                                                | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                              |                                      |
|                                |                                             |                                          | 2–3 y                |            |                                                                | Exposure to AB in third y of life associated with increased risk.                                                                                                                                                                                                                                                                                     |                                      |
|                                |                                             |                                          | Yes                  |            |                                                                | <ul style="list-style-type: none"> <li>• <b>OR 1.59 (95%CI, 1.44–1.75), p&lt;0.01</b></li> </ul>                                                                                                                                                                                                                                                      |                                      |
|                                |                                             |                                          | Medical records      |            |                                                                | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                              |                                      |
| Celedon et al. <sup>32</sup>   | Multicentre prospective cohort study (2b)   | 45; 448<br>30; 302<br>15; 146            | < 1 y                | 5 y        | Parent-reported physician's diagnosis                          | Exposure to AB in first y of life not associated with increased risk.                                                                                                                                                                                                                                                                                 | Sex, family history of atopy, income |
| USA                            |                                             |                                          | No                   |            |                                                                | <ul style="list-style-type: none"> <li>• OR 0.96 (95%CI 0.50–1.85), p=0.91*</li> </ul>                                                                                                                                                                                                                                                                |                                      |
| 2002                           |                                             |                                          | Parent questionnaire |            |                                                                | <ul style="list-style-type: none"> <li>• 1 AB course: aOR 0.90 (95%CI 0.40–2.20), p=nr</li> <li>• ≥ 2 AB courses: aOR 0.70 (95%CI 0.30–1.50), p=nr</li> </ul>                                                                                                                                                                                         |                                      |
| McKeever et al. <sup>182</sup> | Single-centre prospective cohort study (2b) | 2,948; 23,604<br>nr; 15,775<br>nr; 7,829 | < 1 y                | < 11 y     | Oxford Medical Information System (OXMIS), ICD-8 or Read codes | Exposure to AB in first y of life not associated with increased risk.                                                                                                                                                                                                                                                                                 | Number of GP visits                  |
| UK                             |                                             |                                          | Yes                  | 3.5 (mean) |                                                                | <ul style="list-style-type: none"> <li>• 1 AB course: aHR 1.14 (95%CI 0.94–1.38), p=nr</li> <li>• 2 AB courses: aHR 1.13 (95%CI 0.92–1.40), p=nr</li> <li>• 3 AB courses: aHR 0.95 (95%CI 0.74–1.22), p=nr</li> <li>• 4 AB courses: aHR 1.29 (95%CI 0.99–1.69), p=nr</li> <li>• &gt; 4 AB courses: aHR 1.14 (95%CI 0.88–1.47), p=nr</li> </ul>        |                                      |
| 2002                           |                                             |                                          | Medical records      |            |                                                                | <ul style="list-style-type: none"> <li>• penicillin: aHR 1.05 (95%CI 0.87–1.26), p=nr</li> <li>• amoxicillin: aHR 1.05 (95%CI 0.91–1.21), p=nr</li> <li>• amoxicillin/clavulanic acid: aHR 0.94 (95%CI 0.67–1.32) p=nr</li> <li>• cephalosporins: aHR 1.01 (95%CI 0.81–1.26), p=nr</li> <li>• macrolides: aHR 1.09 (95%CI 0.94–1.27), p=nr</li> </ul> |                                      |

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Table 1 (continued)

|                                  |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
|----------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------|-----------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Wjst et al. <sup>155</sup>       | Multicentre cross-sectional study (3b)               | 180; 2,512<br>nr; 2,025<br>nr; 487                                             | < 5-14 y<br>No<br>Medical records    | 5-14 y          | Questionnaire for allergic rhinitis symptoms (ISAAC)         | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 2.30 (95%CI 0.80-6.50), p=0.13                                                                                                                  | Age, sex, family history of atopy, season, parental education                                                             |
| Germany<br>2001                  |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
| Droste et al. <sup>43</sup>      | Multicentre cross-sectional study (3b)               | 67; 1,180<br>34; 375<br>33; 805                                                | < 1 y<br>No<br>Parent questionnaire  | 7-8 y           | Questionnaire for allergic rhinitis symptoms (ISAAC)         | Exposure to AB in first y of life associated with increased risk in high-risk children.<br>• aOR 2.30 (95%CI 1.30-3.80) p<0.01                                                                                                 | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure                   |
| Belgium<br>2000                  |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
| Ponsonby et al. <sup>112</sup>   | Multicentre prospective cohort study (2b)            | 162; 864<br>24; 117<br>138; 747                                                | < 1 m<br>No<br>Parent questionnaire  | 2.1 y (mean)    | Questionnaire for allergic rhinitis symptoms (ISAAC)         | Exposure to AB in first m of life not associated with increased risk.<br>• aRR 0.95 (95%CI 0.62-1.44), p=nr                                                                                                                    | Age, prematurity, birth weight, smoking family history of atopy, breastfeeding, household size, gas heater in living room |
| Australia<br>1999                |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
| Von Mutius et al. <sup>181</sup> | Single-centre cross-sectional study (3b)             | 222; 5,006<br>179; 3,904<br>43; 1,102<br>487; 5,267<br>403; 4,006<br>84; 1,261 | < 3 y<br>No<br>Medical records       | 5-7 y<br>9-11 y | Questionnaire for allergic rhinitis symptoms (ISAAC)         | Exposure to AB in first 3 y of life not associated with increased risk.<br>• OR 1.18 (95%CI 0.84-1.66), p=0.33*<br>Exposure to AB in first 3 y of life associated with increased risk.<br>• OR 1.57 (95%CI 1.23-2.00), p<0.01* |                                                                                                                           |
| Germany<br>1999                  |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
| Wickens et al. <sup>154</sup>    | Multicentre retrospective cross-sectional study (3b) | 81; 447<br>70; 334<br>11; 113                                                  | < 10 y<br>No<br>Parent questionnaire | 5-10 y          | Questionnaire for allergic rhinitis symptoms (ISAAC)         | Exposure to AB in first 10 y of life not associated with increased risk.<br>• aOR 1.99 (95%CI 0.93-4.26), p=nr                                                                                                                 | Age, sex, ethnicity, family history of atopy, household size, parental smoking                                            |
| New Zealand<br>1999              |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |
| Farooqi et al. <sup>48</sup>     | Single-centre retrospective cohort study (2b)        | 484; 1,855<br>374*; 1,237<br>110*; 618                                         | < 2 y<br>Yes<br>Medical records      | 6-12 y          | Physician's diagnosis of seasonal nasal or ocular irritation | Exposure to AB in first 2 y of life associated with increased risk.<br>• OR 2.04 (95%CI 1.59-2.62), p<0.01<br>Results according to antibiotic class nr                                                                         |                                                                                                                           |
| UK<br>1998                       |                                                      |                                                                                |                                      |                 |                                                              |                                                                                                                                                                                                                                |                                                                                                                           |

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Table 1 (continued)

| Wheezing                              |                                             |               |                      |       |                                                                  |                                                                                                                                                       |                                                                                                                                                                  |
|---------------------------------------|---------------------------------------------|---------------|----------------------|-------|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zou et al. <sup>161</sup>             | Multicentre cross-sectional study (3b)      | 3,584; 12,667 | < 1 y                | 4–6 y | Questionnaire for wheezing symptoms (ISAAC)                      | Exposure to AB in first y of life associated with increased risk.                                                                                     | Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure                                    |
| China                                 |                                             | 1,082; 3,049  | No                   |       |                                                                  | • aOR 1.44 (95%CI 1.30–1.60), p<0.01                                                                                                                  |                                                                                                                                                                  |
| 2020                                  |                                             | 2,502; 9,618  | Parent questionnaire |       |                                                                  |                                                                                                                                                       |                                                                                                                                                                  |
| Norbäck et al. <sup>103</sup>         | Multicentre retrospective cohort study (2b) | 7,831; 39,782 | < 1 y                | 3–6 y | Parent-reported physician's diagnosis                            | Exposure to AB in first y of life associated with increased risk.                                                                                     | Living city, time spend outdoors, air pollution, temperature in each city                                                                                        |
| China                                 |                                             | 6,442; 29,303 | No                   |       |                                                                  | • aOR 1.66 (95%CI 1.52–1.82), p<0.01                                                                                                                  |                                                                                                                                                                  |
| 2019                                  |                                             | 1,389; 10,479 | Parent questionnaire |       |                                                                  | • 1 AB course: aOR 1.24 (95%CI 1.14–1.34), p<0.01<br>• > 1 AB courses: aOR 1.57 (95%CI 1.46–1.69), p<0.01                                             |                                                                                                                                                                  |
| Oosterloo et al. <sup>105</sup>       | Multicentre prospective cohort study (2b)   | 149; 436      | < 1 w                | 0–1 y | Parent-reported wheezing                                         | Exposure to AB in first w of life not associated with increased risk.                                                                                 | Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking |
| Netherlands                           |                                             | 62; 151       | No                   |       |                                                                  | • aOR 1.56 (95%CI 0.99–2.46), p=0.06                                                                                                                  |                                                                                                                                                                  |
| 2018                                  |                                             | 87; 285       | Parent questionnaire |       |                                                                  |                                                                                                                                                       |                                                                                                                                                                  |
| Yamamoto-Hanada et al. <sup>157</sup> | Multicentre prospective cohort study (2b)   | 148; 902      | < 2 y                | 5 y   | Questionnaire for wheezing symptoms (ISAAC) plus medical records | Exposure to AB in first 2 y of life not associated with increased risk.                                                                               | Sex, maternal age, BMI, education, history of atopy; parity, day care, smoking during pregnancy, gestational age, delivery mode, number of LRTIs                 |
| Japan                                 |                                             | 81; 436       | Yes                  |       |                                                                  | • aOR 1.24 (95%CI 0.86–1.78), p=0.26                                                                                                                  |                                                                                                                                                                  |
| 2017                                  |                                             | 67; 466       | Parent questionnaire |       |                                                                  | • penicillins: aOR 1.16 (95%CI 0.61–2.18), p=0.65<br>• cephem: aOR 1.39 (95%CI 0.92–2.09), p=0.12<br>• macrolides: aOR 1.04 (95%CI 0.66–1.64), p=0.86 |                                                                                                                                                                  |
| Han et al. <sup>59</sup>              | Multicentre cross-sectional study (3b)      | 224; 1,517    | < 1 y                | 6–7 y | Questionnaire for wheezing symptoms (ISAAC)                      | Exposure to AB in first y of life associated with increased risk.                                                                                     | Number of LRTIs, paracetamol use                                                                                                                                 |
| Argentina                             |                                             | 175; 921      | No                   |       |                                                                  | • aOR 1.80 (95%CI 1.30–2.60), p<0.01                                                                                                                  |                                                                                                                                                                  |
| 2017                                  |                                             | 49; 596       | Parent questionnaire |       |                                                                  |                                                                                                                                                       |                                                                                                                                                                  |

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Table 1 (continued)

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|---------------------------------------|---------------------------------------------|--------------------------------------------------|--------------------------------------|---------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eldeirawi et al. <sup>191</sup>       | Multicentre cross-sectional study (3b)      | 107; 1,789<br>63; 803<br>44; 986                 | < 1 y<br>No<br>Parent questionnaire  | 1 y     | Questionnaire for wheezing (ISAAC)          | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.64 (95% CI, 1.53-3.55), p=0.04</b><br><br>• 1-2 AB courses: aOR 1.24 (95%CI 0.73-2.12), p=42<br>• ≥ 3 AB courses: <b>aOR 2.47 (95%CI 1.39-4.38), p&lt;0.01</b>                                                                                                                                                                                                                                                           | Age, sex, country of birth, family history of atopy, having a regular doctor or clinic, number of ear infections                                     |
| USA<br>2015                           |                                             |                                                  |                                      |         |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                      |
| Sun et al. <sup>137</sup>             | Multicentre prospective cohort study (2b)   | 29; 606<br>nr; 142<br>nr; 464                    | < 3 y<br>Yes<br>Parent questionnaire | 6 m-3 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first 3 y of life associated with increased risk in children with high atopic risk factors.<br><br>• <b>aRR 1.09 (95%CI 1.05-1.13), p&lt;0.05</b><br><br>• penicillin: aRR 1.00 (95%CI 0.94-1.05), p=nr<br>• ampicillin: aRR 0.99 (95%CI 0.94-1.03), p=nr<br>• cephalosporins: aRR 1.02 (95%CI 1.00-1.05), p=nr<br>• macrolides: <b>aRR 1.09 (95%CI 1.05-1.13), p&lt;0.05</b><br>• trimethoprim: aRR 0.98 (95%CI 0.88-1.09), p=nr<br>• broad-spectrum AB: aRR 1.02 (95%CI 0.98-1.06), p=nr | Family history of atopy, country, maternal education, birth order                                                                                    |
| China<br>2015                         |                                             |                                                  |                                      |         |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                      |
| Lapin et al. <sup>164</sup>           | Multicentre prospective cohort study (2b)   | 65; 295<br>nr; 162<br>nr; 133                    | < 1 y<br>No<br>nr                    | 2-3 y   | Parent-reported wheezing                    | Exposure to AB in first y of life associated with increased risk in high-risk children.<br><br>• <b>aOR 1.29 (95%CI 1.07-1.55), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                     | Ethnicity, smoking during pregnancy, antibiotic and medication use during pregnancy, maternal asthma, birth weight, breastfeeding, household smoking |
| USA<br>2014                           |                                             |                                                  |                                      |         |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                      |
| Ong et al. <sup>104</sup>             | Multicentre retrospective cohort study (2b) | 5,460; 62,576<br>3,190* 26,693<br>2,270*; 35,883 | < 1 y<br>No<br>Registry              | < 3 y   | ICD-9 codes                                 | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 2.00 (95%CI 1.90-2.20), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                      |
| Australia<br>2014                     |                                             |                                                  |                                      |         |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                      |
| Semic-Jusufagic et al. <sup>126</sup> | Multicentre prospective cohort study (2b)   | 199; 684<br>nr; nr<br>nr; nr                     | < 1 y<br>No<br>Parent questionnaire  | 1-11 y  | Parent-reported plus medical records        | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.91 (95%CI, 1.29-2.83), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                      |
| UK<br>2014                            |                                             |                                                  |                                      |         |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                      |

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Table 1 (continued)

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|----------------------------------|---------------------------------------------|---------------|----------------------|--------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Muc et al. <sup>97</sup>         | Multicentre cross-sectional study (3b)      | 357; 1,037    | < 1 y                | 6–9 y        | Questionnaire for wheezing symptoms (ISAAC)                 | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 2.33 (95%CI 1.70–3.18), p&lt;0.01</b>                                                   | Age, sex, prematurity, atopy                                                                                                         |
| Portugal                         |                                             | 117*; 237     | No                   |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
| 2013                             |                                             | 240*; 800     | Parent questionnaire |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
| Raciborski et al. <sup>115</sup> | Multicentre retrospective cohort study (2b) | 197; 1,330    | < 1 y                | 6–8 y        | Questionnaire for wheezing symptoms (ISAAC and ECRHS II)    | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 2.21 (95%CI 1.56–3.12), p&lt;0.01*</b>                                                   |                                                                                                                                      |
| Poland                           |                                             | 150; 820      | No                   |              |                                                             | • 1 AB course: OR 1.12 (95%CI nr), p=0.61<br>• 2–3 AB courses: <b>OR 1.93 (95%CI nr), p&lt;0.01</b><br>• > 3 AB courses: <b>OR 4.68 (95%CI 2.60–12.01), p&lt;0.01</b> |                                                                                                                                      |
| 2012                             |                                             | 47; 510       | Parent questionnaire |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
|                                  |                                             | 197; 1,321    | 1–3 y                |              |                                                             | Exposure to AB in first to third y of life associated with increased risk.                                                                                            |                                                                                                                                      |
|                                  |                                             | 185; 1,145    | No                   |              |                                                             | • <b>OR 2.63 (95%CI 1.44–4.83), p&lt;0.01*</b>                                                                                                                        |                                                                                                                                      |
|                                  |                                             | 12; 176       | Parent questionnaire |              |                                                             | • 1–2 AB courses: OR 1.41 (95%CI nr), p=0.31<br>• 3–4 AB courses: <b>OR 1.89 (95%CI nr), p=0.06</b><br>• > 4 AB courses: <b>OR 4.73 (95%CI 1.41–15.90), p&lt;0.01</b> |                                                                                                                                      |
| Kwon et al. <sup>165</sup>       | Multicentre cross-sectional study (3b)      | 442; 3,765    | < 1 y                | 9.5 y (mean) | Questionnaire for wheezing (ISAAC)                          | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.88 (95%CI 1.35–2.62), p&lt;0.01</b>                                                   | Age, sex, parental asthma, maternal education and BMI; smoke exposure                                                                |
| Korea                            |                                             | nr; nr        | No                   |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
| 2011                             |                                             | nr; nr        | Parent questionnaire |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
| Rusconi et al. <sup>119</sup>    | Multicentre cross-sectional study (3b)      | 1,598; 16,933 | < 1 y                | < 2 y        | Early transient wheezing Questionnaire for wheezing (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 3.76 (95%CI 3.31–4.27), p=nr</b>                                                        | Age, sex, study centre, person who completed the questionnaire, maternal age, family history of atopy, day care, number of siblings, |
| Italy                            |                                             | 1,114; 5,863  | No                   |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |
|                                  |                                             | 484; 11,070   |                      |              |                                                             |                                                                                                                                                                       |                                                                                                                                      |

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Table 1 (continued)

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|-----------------------------|---------------------------------------------|--------------------------------------------|----------------------|---------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2011                        |                                             | 910; 16,933                                | Parent questionnaire | < 4-5 y | Persistent wheezing Questionnaire for wheezing (ISAAC)     | Exposure to AB in first y of life associated with increased risk.                                              | sharing a bedroom, parental education, smoking during pregnancy, prematurity, season, breastfeeding, dampness-related exposure                                                                                                       |
|                             |                                             | 596; 5,345<br>314; 11,588                  |                      |         |                                                            | • <b>aOR 3.06 (95%CI 2.60-3.60), p=nr</b>                                                                      |                                                                                                                                                                                                                                      |
|                             |                                             | 1,011; 16,933<br>412; 5,161<br>599; 11,772 |                      |         |                                                            | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.18 (95%CI 1.02-1.38), p=nr</b> |                                                                                                                                                                                                                                      |
| Goksor et al. <sup>56</sup> | Multicentre prospective cohort study (2b)   | 245; 4,495                                 | < 1 w                | 4.5 y   | Questionnaire for wheezing symptoms (ISAAC and BAMSE)      | Exposure to AB in first w of life associated with increased risk.                                              | Prematurity, delivery mode                                                                                                                                                                                                           |
| Sweden                      |                                             | 26; 203<br>219; 4,292                      | No                   |         |                                                            | • <b>aOR 2.20 (95%CI 1.30-3.80), p&lt;0.05</b>                                                                 |                                                                                                                                                                                                                                      |
| 2011                        |                                             |                                            | Parent questionnaire |         |                                                            |                                                                                                                |                                                                                                                                                                                                                                      |
| Dom et al. <sup>40</sup>    | Multicentre prospective cohort study (2b)   | 235; 667                                   | < 4 y                | 6 m-4 y | Questionnaire for wheezing symptoms (ISAAC)                | Exposure to AB before first y of life not associated with increased risk.                                      | Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking during pregnancy, pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure |
| Belgium                     |                                             | 210; 586                                   | No                   |         |                                                            | • OR 1.25 (95%CI 0.76-2.06), p=0.38*                                                                           |                                                                                                                                                                                                                                      |
| 2010                        |                                             | 25; 81                                     | Parent questionnaire |         |                                                            |                                                                                                                |                                                                                                                                                                                                                                      |
| Mai et al. <sup>178</sup>   | Single-centre prospective cohort study (2b) | 482; 3,306                                 | < 1 y                | 4 y     | Questionnaire for wheezing symptoms (BAMSE based on ISAAC) | Exposure to AB in first y of life associated with increased risk.                                              | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding                                                                                                                                            |
| Sweden                      |                                             | 254; 1,420<br>228; 1,886                   | No                   |         |                                                            | • <b>aOR 1.40 (95%CI 1.20-1.80), p=nr</b><br>• <b>≥ 2 AB courses: aOR 1.60 (95%CI 1.10-2.20), p&lt;0.01</b>    |                                                                                                                                                                                                                                      |
| 2010                        |                                             | 330; 3,306                                 | Parent questionnaire |         |                                                            | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.40 (95%CI 1.10-1.70), p=nr</b> |                                                                                                                                                                                                                                      |
|                             |                                             | 170; 1,420<br>160; 1,886                   |                      | 8 y     |                                                            |                                                                                                                |                                                                                                                                                                                                                                      |

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Table 1 (continued)

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|------------------------------------------------------|-------------------------------------------|---------------------------------------------|--------------------------------------|-------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Karimi et al. <sup>162</sup><br>Iran<br>2009         | Multicentre cross-sectional study (3b)    | 141; 1,476<br>95; 953*<br>46; 523*          | < 1 y<br>No<br>nr                    | 6–7 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life not associated with increased risk.<br><br>• OR 1.13 (95%CI 0.77–1.67), p=0.50                                                |                                                                                                                                                                    |
| Mitchell et al. <sup>95</sup><br>New Zealand<br>2009 | Multicentre cross-sectional study (3b)    | 2,315; 10,423<br>1,764; 6,476<br>551; 3,947 | < 1 y<br>No<br>Parent questionnaire  | 6–7 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.78 (95%CI 1.56–2.04), p<0.01                                                   | Sex, ethnicity, country of birth, number of siblings, socioeconomic status, medication use, maternal smoking                                                       |
| Alm et al. <sup>15</sup><br>Sweden<br>2008           | Multicentre prospective cohort study (2b) | 994, 4,921<br>67; 219<br>927; 4,702         | < 1 m<br>No<br>Parent questionnaire  | 1 y   | Questionnaire for wheezing (BAMSE study)    | Exposure to AB in first m of life associated with increased risk.<br><br>• aOR 1.60 (95%CI 1.00–2.50), p=0.04                                                   | Sex, prematurity, neonatal intensive-care unit admission, smoking during pregnancy, family history of atopy, light sleep at 12 months, breastfeeding, pacifier use |
| Kusel et al. <sup>80</sup><br>Australia<br>2008      | Multicentre prospective cohort study (2b) | 56; 198<br>34*; 107<br>22*; 91              | < 1 y<br>Yes<br>Parent questionnaire | 0–5 y | Parent-reported current wheeze              | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.00 (95%CI 0.50–2.20), p=nr<br><br>Results according to antibiotic class nr | Sex, day care, number of GP visits, pet exposure                                                                                                                   |
| Simon et al. <sup>192</sup><br>USA<br>2008           | Multicentre prospective cohort study (2b) | 117; 239<br>67; 142<br>50; 97               | < 6 m<br>No<br>Medical records       | 1–4 y | Parent-reported                             | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• aRR 1.60 (95%CI 1.00–2.60), p=0.05                                                 | Sex, family history of atopy, day care, birth order, fever, breastfeeding, pet exposure                                                                            |
| Verhulst et al. <sup>193</sup><br>Belgium<br>2008    | Multicentre prospective cohort study (2b) | 36; 154<br>25*; 76<br>11*; 78               | < 1 y<br>No<br>Parent questionnaire  | 1 y   | Questionnaire for wheezing (ISAAC)          | Exposure to AB in first y of life associated with increased risk.<br><br>• OR 2.94 (95%CI 1.59–5.43), p<0.01                                                    |                                                                                                                                                                    |

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Table 1 (continued)

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|----------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------------|--------------------------------------|--------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Harris et al. <sup>bu</sup><br>UK<br>2007                                                    | Single-centre prospective cohort study (2b) | 79; 523<br>30; nr<br>49; nr                  | < 5 y<br>No<br>Medical records       | 8 y    | Questionnaire for wheezing (ISAAC)          | Exposure to AB in first 5 y of life associated with increased risk.<br><br>• <b>aOR 1.07 (95%CI 1.03-1.10), p&lt;0.01</b>                                                                                                                                  | Family history of atopy, birth order, smoke exposure                                                                                                                                                       |
| Sharma et al. <sup>166</sup><br>India<br>2007                                                | Multicentre prospective cohort study (2b)   | 300; 8,470<br>147*; 3,260<br>153*; 5,210     | 5-13 y<br>No<br>Parent questionnaire | 6-14 y | Questionnaire for wheezing (ISAAC)          | Exposure to AB in infancy associated with increased risk.<br><br>• <b>OR 1.60 (95%CI 1.10-2.10), p&lt;0.01</b>                                                                                                                                             |                                                                                                                                                                                                            |
| Kummeling et al. <sup>79</sup><br>Netherlands<br>2007                                        | Multicentre prospective cohort study (2b)   | 265; 2,462<br>93; 489<br>172; 1,973          | < 6 m<br>No<br>Parent questionnaire  | 2 y    | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• <b>aOR 2.65 (95%CI, 1.95-3.60), p=nr</b>                                                                                                                                      | Sex, family history of atopy, day care, number of siblings, delivery mode, vaccination status, fever, breastfeeding, pet and smoke exposure                                                                |
| Floistrup et al. <sup>49</sup><br>Netherlands, Austria, Germany, Sweden, Switzerland<br>2006 | Multicentre cross-sectional study (3b)      | 396; 4,606<br>113*; 788<br>283*; 3,818       | < 1 y<br>No<br>Parent questionnaire  | 7-11 y | Parent-reported physician's diagnosis       | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 2.05 (95%CI 1.48-2.85), p=nr</b>                                                                                                                                         | Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure |
| Ahn et al. <sup>13</sup><br>Korea<br>2005                                                    | Multicentre cross-sectional study (3b)      | 1,352; 25,787<br>480*; 6,273<br>872*; 19,514 | < 1 y<br>No<br>Parent questionnaire  | 7-12 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.52 (95%CI 1.32-1.75), p&lt;0.01</b><br><br>• 1-2 AB courses: <b>aOR 1.31 (95%CI 1.11-1.56), p&lt;0.01</b><br>• 3-4 AB courses: <b>aOR 1.23 (95%CI 0.94-1.61), p=nr</b> | Episodes of fever or acute gastroenteritis                                                                                                                                                                 |

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Table 1 (continued)

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|-------------------------------|------------------------------------------------------|--------------------------------------------|----------------------------------------|--------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Awasthi et al. <sup>194</sup> | Multicentre cross-sectional study (3b)               | 188; 1,492<br>46; 142<br>142; 1,350        | < 1 y<br>No<br>Parent questionnaire    | 6–7 y  | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 3.06 (95%CI 1.92–4.88), p=nr     | Maternal education, diet, exercise                                                                                         |
| India                         |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| 2004                          |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| Cohet et al. <sup>37</sup>    | Single-centre case-control study (3b)                | 938; 3,927<br>738; 2,684<br>200; 1,243     | < 1 y<br>No<br>Parent questionnaire    | 6–7 y  | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• OR 1.78 (95%CI 1.49–2.14), p=nr      |                                                                                                                            |
| New Zealand                   |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| 2004                          |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| Wjst et al. <sup>155</sup>    | Multicentre cross-sectional study (3b)               | 562; 2,512<br>171; 2,025<br>391; 487       | < 5–14 y<br>No<br>Parent questionnaire | 5–14 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.90 (95%CI 1.20–3.30), p=0.01   | Age, sex, family history of atopy, season, parental education                                                              |
| Germany                       |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| 2001                          |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| Wickens et al. <sup>154</sup> | Multicentre retrospective cross-sectional study (3b) | 138; 447<br>117; 334<br>21; 113            | < 10 y<br>No<br>Parent questionnaire   | 5–10 y | Questionnaire for wheezing symptoms (ISAAC) | Exposure to AB in first 10 y of life associated with increased risk.<br><br>• aOR 1.86 (95%CI 1.06–3.26), p=nr  | Age, sex, ethnicity, family history of atopy, household size, parental smoking                                             |
| New Zealand                   |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| 1999                          |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| <b>Asthma</b>                 |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| Aversa et al. <sup>172</sup>  | Multicentre prospective cohort study (2b)            | 1,176; 14,572<br>964; 10,220<br>212; 4,352 | < 2 y<br>Yes<br>Medical records        | 6–11 y | ICD-9 and ICD-10 codes                      | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• aHR 1.90 (95%CI 1.63–2.20), p<0.01 | Sex, ethnicity, maternal age and education, antibiotic use during pregnancy, birth weight, delivery mode, maternal smoking |
| USA                           |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |
| 2021                          |                                                      |                                            |                                        |        |                                             |                                                                                                                 |                                                                                                                            |

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Table 1 (continued)

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|------------------------------|----------------------------------------------|-----------------|----------------------|---------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                                              |                 |                      |         |                                                    | <p>Girls</p> <ul style="list-style-type: none"> <li>• penicillins: <b>HR 1.50 (95%CI 1.21-1.87), p&lt;0.01</b></li> <li>• cephalosporins: <b>HR 1.39 (95%CI 1.13-1.71), p&lt;0.01</b></li> <li>• macrolides: <b>HR 1.33 (95%CI 1.08-1.62), p&lt;0.01</b></li> <li>• sulfonamides: HR 1.27 (95%CI 0.93-1.74), p=0.13</li> </ul> <p>Boys</p> <ul style="list-style-type: none"> <li>• penicillins: <b>HR 1.35 (95%CI 1.12-1.62), p&lt;0.01</b></li> <li>• cephalosporins: <b>HR 1.29 (95%CI 1.09-1.53), p&lt;0.01</b></li> <li>• macrolides: <b>HR 1.34 (95%CI 1.14-1.58), p&lt;0.01</b></li> <li>• sulfonamides: HR 0.92 (95%CI 0.66-1.27), p=0.60</li> </ul> |                                                                                                                                                                                                                     |
| Neto et al. <sup>101</sup>   | Multicentre cross-sectional study (3b)       | 339; 850        | < 6 m                | 9-12 y  | Questionnaire for asthma symptoms (ISAAC)          | Exposure to AB in first 6 m of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Maternal asthma, shared bedroom, number of LRTIs, atopy, medication use, pet exposure                                                                                                                               |
| Brazil                       |                                              | 180*; 368       | No                   |         |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                     |
| 2020                         |                                              | 159*; 482       | Parent questionnaire |         |                                                    | • <b>aOR 1.57 (95%CI 1.13-2.17), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                     |
| Donovan et al. <sup>41</sup> | Single-centre retrospective cohort study (4) | 20,984; 152,622 | < 1 y                | 4.5-6 y | ICD-9-CM codes plus prescription records           | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Age, sex, ethnicity, maternal age and education; household size, living area, marital status, smoking during pregnancy, gestational age, birth weight, season of birth, delivery mode, medication use, pet exposure |
| USA                          |                                              | 18,233; 120,973 | Yes                  |         |                                                    | • <b>aOR 1.88 (95%CI 1.80-1.96), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                     |
| 2020                         |                                              | 2,751; 31,649   | Medical records      |         |                                                    | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                     |
| Levin et al. <sup>82</sup>   | Multicentre prospective cohort study (2b)    | 106; 1,185      | < 1 y                | 12-36 m | Questionnaire for asthma symptoms (based on ISAAC) | Exposure to AB in first y of life associated with increased risk in urban cohort.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                     |
| South Africa                 |                                              | 83; 654         | No                   |         |                                                    | • <b>OR 3.21 (95%CI 1.99-5.17), p&lt;0.01*</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                     |
| 2020                         |                                              | 23; 531         | Parent questionnaire |         |                                                    | Exposure to AB in first y of life not associated with increased risk in rural cohort.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                     |
|                              |                                              | 4; 398          |                      |         |                                                    | • <b>OR 1.35 (95%CI 0.07-25.43), p=0.84*</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                     |
|                              |                                              | 4; 347          |                      |         |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                     |
|                              |                                              | 0; 51           |                      |         |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                     |

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Table 1 (continued)

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|-------------------------------|----------------------------------------------|-------------------------------------------|-------------------------------------|--------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patrick et al. <sup>109</sup> | Multicentre prospective cohort study         | 118; 1,947<br>29; 289                     | < 1 y<br>Yes                        | 5 y    | Questionnaire for asthma symptoms (ISAAC)                                                     | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 2.15 (95%CI 1.37-3.39), p&lt;0.01</b><br><br>• 1 AB course: <b>aOR 1.93 (95%CI 1.15-3.26), p=0.01</b><br>• 2 AB courses: aOR 2.66 (95%CI 0.99-7.18), p=0.05<br>• ≥ 3 AB courses: <b>aOR 3.25 (95%CI 1.05-10.08), p=0.04</b><br><br>Results according to antibiotic class nr | Sex, ethnicity, study centre, family history of atopy, number of siblings, birth weight, season of birth, delivery mode, breastfeeding, smoke and environmental nitrogen dioxide exposure |
| Canada<br>2020                | (2b)                                         | 89; 1,658                                 | Registry                            |        |                                                                                               |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                           |
| Zou et al. <sup>161</sup>     | Multicentre cross-sectional study (3b)       | 1,285; 12,667<br>412; 3,049<br>873; 9,618 | < 1 y<br>No<br>Parent questionnaire | 4-6 y  | Questionnaire for asthma symptoms (ISAAC)                                                     | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.38 (95%CI 1.19-1.61), p&lt;0.01</b>                                                                                                                                                                                                                                       | Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure                                                             |
| Ni et al. <sup>102</sup>      | Single-centre retrospective cohort study (4) | 177; 2,398<br>128*; 1,060<br>49*; 1,338   | < 1 y<br>Yes<br>Medical records     | 1-10 y | ICD-9 and ICD-10 codes                                                                        | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 2.66 (95%CI 1.11-6.40), p=0.03</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                          | Age, sex, ethnicity, socioeconomic status, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission                                                               |
| USA<br>2019                   |                                              | 253; 2,398<br>211*; 1,755<br>42*; 643     | < 10 y<br>Yes<br>Medical records    |        |                                                                                               | Exposure to AB in first 10 y of life associated with increased risk.<br><br>• <b>aOR 3.54 (95%CI 1.99-6.30), p&lt;0.01</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                    |                                                                                                                                                                                           |
| Metzler et al. <sup>93</sup>  | Multicentre prospective cohort study (2b)    | 73; 1,019<br>35; 419<br>38; 600           | < 1 y<br>No<br>Parent questionnaire | < 6 y  | Questionnaire for asthma symptoms (based on ISAAC) plus parent-reported physician's diagnosis | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.65 (95%CI 0.95-2.86), p&lt;0.05</b>                                                                                                                                                                                                                                       | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, pet exposure during pregnancy, delivery mode, duration of breastfeeding, pet exposure            |
| Switzerland<br>2019           |                                              |                                           |                                     |        |                                                                                               |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                           |

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Table 1 (continued)

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|-------------------------------------|---------------------------------------------|------------------|------------------------|--------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Norbäck et al. <sup>103</sup>       | Multicentre retrospective cohort study      | 2,936; 39,782    | < 1 y                  | 3–6 y  | Parent-reported physician's diagnosis                                 | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                         | Living area, time spend outdoors, air pollution, temperature in each city       |
| China                               | (2b)                                        | 2,586; 29,303    | No                     |        |                                                                       | • <b>aOR 2.03 (95%CI 1.72–2.40), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                            |                                                                                 |
| 2019                                |                                             | 250; 10,479      | Parent questionnaire   |        |                                                                       | • 1 AB course: <b>aOR 1.26 (95%CI 1.11–1.44), p&lt;0.01</b><br>• > 1 AB courses: <b>aOR 2.08 (95%CI 1.87–2.33), p&lt;0.01</b>                                                                                                                                                                                                                                                             |                                                                                 |
| Soto-Martinez et al. <sup>132</sup> | Multicentre cross-sectional study (3b)      | 595; 2,689       | < 1 y                  | 6–13 y | Questionnaire for asthma symptoms (ISAAC)                             | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                         | Atopy, dry cough, medication use, traffic exposure                              |
| Costa Rica                          |                                             | 380; 1,290       | No                     |        |                                                                       | • <b>aOR 1.20 (95%CI 1.01–1.43), p=0.04</b>                                                                                                                                                                                                                                                                                                                                               |                                                                                 |
| 2019                                |                                             | 215; 1,399       | Parent questionnaire   |        |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                 |
| Chen et al. <sup>34</sup>           | Multicentre case-control study (3b)         | 2,082; 4,164     | < 5 y before diagnosis | 2–18 y | ICD-9-CM codes plus prescription records (ATC codes)                  | Exposure to AB in 5 y before diagnosis associated with increased risk.                                                                                                                                                                                                                                                                                                                    | Age, sex, living area, comorbidities, medication use                            |
| Taiwan                              |                                             | 1,849; 3,512     | Yes                    |        |                                                                       | • <b>aOR 2.10 (95%CI 1.75–2.52), p&lt;0.01</b>                                                                                                                                                                                                                                                                                                                                            |                                                                                 |
| 2018                                |                                             | 233; 652         | Registry               |        |                                                                       | • low-dose: <b>aOR 1.64 (95%CI 1.35–2.01), p&lt;0.01</b><br>• moderate-dose: <b>aOR 2.23 (95%CI 1.81–2.74), p&lt;0.01</b><br>• high-dose: <b>aOR 3.33 (95%CI 2.67–4.15), p&lt;0.01</b><br><br>• penicillins: <b>aOR 1.77 (95%CI 1.43–2.20), p&lt;0.01</b><br>• cephalosporins: <b>aOR 1.67 (95%CI 1.32–2.11), p&lt;0.01</b><br>• macrolides: <b>aOR 2.02 (95%CI 1.48–2.76), p&lt;0.01</b> |                                                                                 |
| Mitre et al. <sup>96</sup>          | Multicentre retrospective cohort study (2b) | 111,792; 792,130 | < 6 m                  | 1–6 y  | ICD-9-CM codes                                                        | Exposure to AB in first 6 m of life associated with increased risk.                                                                                                                                                                                                                                                                                                                       | Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use  |
| USA                                 |                                             | 27,488; 131,708  | No                     |        |                                                                       | • <b>aHR 2.09 (95%CI 2.05–2.13), p=nr</b>                                                                                                                                                                                                                                                                                                                                                 |                                                                                 |
| 2018                                |                                             | 84,304; 660,422  | Registry               |        |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                 |
| Strömberg et al. <sup>134</sup>     | Multicentre prospective cohort study (2b)   | 233; 3,637       | < 1 w                  | 12 y   | Atopic asthma Questionnaire for asthma symptoms (ISAAC and BAMSE)     | Exposure to AB in first w of life associated with increased risk.                                                                                                                                                                                                                                                                                                                         | Family history of atopy, prematurity, weight for gestational age, delivery mode |
| Sweden                              |                                             | 19; 152          | No                     |        |                                                                       | • <b>aOR 2.20 (95%CI 1.20–4.20), p&lt;0.05</b>                                                                                                                                                                                                                                                                                                                                            |                                                                                 |
| 2018                                |                                             | 214; 3,485       | Parent questionnaire   |        | Non-atopic asthma Questionnaire for asthma symptoms (ISAAC and BAMSE) | Exposure to AB in first w of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                     |                                                                                 |
|                                     |                                             |                  |                        |        |                                                                       | • <b>aOR 1.40 (95%CI 0.50–3.40), p=nr</b>                                                                                                                                                                                                                                                                                                                                                 |                                                                                 |

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Table 1 (continued)

|                                |                                             |                                                 |                                     |        |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                               |
|--------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------|--------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Yoshida et al. <sup>195</sup>  | Multicentre retrospective cohort study (2b) | 3,633; 83,470<br>2,517; 46,562<br>1,116; 36,908 | < 1 y<br>Yes<br>Registry            | 1-3 y  | ICD-10 codes plus prescription records | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aHR 2.43 (95%CI 2.20-2.69), p=nr</b><br><br>• 1-2 AB courses: <b>aHR 1.89 (95%CI 1.69-2.11), p=nr</b><br>• 3-4 AB courses: <b>aHR 2.93 (95%CI 2.58-3.33), p=nr</b><br>• > 5 AB courses: <b>aHR 4.66 (95%CI 4.04-5.36), p=nr</b><br><br>• penicillins: <b>aHR 1.39 (95%CI 1.26-1.53), p=nr</b><br>• cephalosporins: <b>aHR 1.55 (95%CI 1.41-1.70), p=nr</b><br>• macrolides: <b>aHR 2.00 (95%CI 1.83-2.20), p=nr</b> | Sex                           |
| Japan                          |                                             |                                                 |                                     | 3-6 y  |                                        | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aHR 1.23 (95%CI 1.11-1.36), p=nr</b><br><br>• 1-2 AB courses: <b>aHR 1.15 (95%CI 1.03-1.29), p=nr</b><br>• 3-4 AB courses: <b>aHR 1.28 (95%CI 1.11-1.48), p=nr</b><br>• > 5 AB courses: <b>aHR 1.53 (95%CI 1.28-1.83), p=nr</b><br><br>• penicillins: <b>aHR 0.87 (95%CI 0.76-0.98), p=nr</b><br>• cephalosporins: <b>aHR 1.20 (95%CI 1.08-1.33), p=nr</b><br>• macrolides: <b>aHR 1.17 (95%CI 1.05-1.31), p=nr</b> |                               |
| Ahmadizar et al. <sup>12</sup> | Multicentre prospective cohort study (2b)   | 74; 891<br>28*; 260<br>46*; 631                 | < 6 m<br>No<br>Parent questionnaire | 9-10 y | Parent-reported physician's diagnosis  | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• <b>aOR 1.50 (95%CI 0.91-2.46), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                          | Sex, family history of asthma |
| Netherlands Scotland           |                                             |                                                 |                                     | 10 y   |                                        | Exposure to AB in first 3 y of life associated with increased risk.<br><br>• <b>aOR 2.84 (95%CI 1.70-4.75), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                              | Sex, family history of atopy  |
| 2017                           |                                             | 448, 3,960<br>414*; 3,178<br>34*; 782           | < 3 y<br>No<br>Parent questionnaire |        |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                               |

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Table 1 (continued)

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|---------------------------------------|---------------------------------------------|-----------------|----------------------|-----------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Han et al. <sup>59</sup>              | Multicentre cross-sectional study (3b)      | 58; 1,517       | < 1 y                | 6–7 y     | Questionnaire for asthma symptoms (ISAAC)                      | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 1.30 (95%CI 0.60–2.60), p=nr             | Number of LRTIs, medication use                                                                                                                                                                                                         |
| Argentina                             |                                             | 44; 921         | No                   |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| 2017                                  |                                             | 14; 596         | Parent questionnaire |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| Yamamoto-Hanada et al. <sup>157</sup> | Multicentre prospective cohort study (2b)   | 95; 902         | < 2 y                | 5 y       | Questionnaire for asthma symptoms (ISAAC) plus medical records | Exposure to AB in first 2 y of life associated with increased risk.<br>• aOR 1.72 (95%CI 1.10–2.70), p=0.02             | Sex, maternal age, BMI, education, maternal and history of atopy, parity, day care, smoking during pregnancy, gestational age, delivery mode, number of LRTIs,                                                                          |
| Japan                                 |                                             | 58; 436         | Yes                  |           |                                                                | • penicillins: aOR 1.21 (95%CI 0.58–2.56), p=0.61                                                                       |                                                                                                                                                                                                                                         |
| 2017                                  |                                             | 37; 466         | Parent questionnaire |           |                                                                | • cephem: aOR 1.97 (95%CI 1.23–3.16), p<0.01                                                                            |                                                                                                                                                                                                                                         |
|                                       |                                             |                 |                      |           |                                                                | • macrolides: aOR 1.46 (95%CI 0.88–2.44), p=0.15                                                                        |                                                                                                                                                                                                                                         |
| Wu et al. <sup>156</sup>              | Multicentric prospective cohort study (2b)  | 18,087; 136,098 | < 1 y                | 4.5–6 y   | ICD-9-CM codes                                                 | Exposure to AB in first y of life associated with increased risk.<br>• aOR 1.16 (95% CI, 1.15–1.18), p=nr               | Sex, ethnicity, maternal age, education, and asthma; number of siblings, smoking during pregnancy, gestational age, neonatal intensive-care unit admission, birth weight, delivery mode, number of LRTIs, comorbidities, healthcare use |
| USA                                   |                                             | 13,740*; 99,054 | No                   |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| 2016                                  |                                             | 4,347*; 37,044  | Medical records      |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| Korpela et al. <sup>75</sup>          | Multicentre case-control study (3b)         | 16*; 148        | < 2 y                | 2–7 y     | Parent-reported physician's diagnosis                          | Exposure to AB in first 2 y of life associated with increased risk.<br>• macrolides: OR 6.11 (95%CI 1.53–26.58), p<0.01 |                                                                                                                                                                                                                                         |
| Finland                               |                                             | 9*; 32          | Yes                  |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| 2016                                  |                                             | 7*; 116         | Registry             |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| Pitter et al. <sup>111</sup>          | Multicentre retrospective cohort study (2b) | 34,957; 143,163 | < 1 y                | 13 m–18 y | ICD-9 codes plus prescription records (ATC codes)              | Exposure to AB in first y associated with increased risk.<br>• aIRR 1.50 (95%CI 1.46–1.53), p<0.05                      | Age, sex, maternal age, and education; gestational age, birth weight, hospital admissions for infections                                                                                                                                |
| Italy                                 |                                             | 16,406; 54,685  | Yes                  |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |
| 2016                                  |                                             | 18,551; 88,478  | Registry             |           |                                                                |                                                                                                                         |                                                                                                                                                                                                                                         |

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Table 1 (continued)

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|-------------------------------------|----------------------------------------|--------------------------------------------|-------------------------------|---------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                     |                                        |                                            |                               |               |                                                    | <ul style="list-style-type: none"> <li>• penicillins: <b>aIRR 1.43 (95%CI 1.40-1.46), p&lt;0.05</b></li> <li>• cephalosporins: <b>aIRR 1.36 (95%CI 1.32-1.40), p&lt;0.05</b></li> <li>• macrolides: <b>aIRR 1.57 (95%CI 1.52-1.63), p&lt;0.05</b></li> </ul>                                                                                                                                                                                        |
|                                     |                                        |                                            |                               |               |                                                    | <ul style="list-style-type: none"> <li>• 1-2 AB courses: <b>aIRR 1.41 (95%CI 1.38-1.44), p&lt;0.01</b></li> <li>• 3-4 AB courses: <b>aIRR 1.84 (95%CI 1.77-1.92), p&lt;0.01</b></li> <li>• ≥ 5 AB courses: <b>aIRR 2.13 (95%CI 2.00-2.28), p&lt;0.01</b></li> </ul>                                                                                                                                                                                 |
| Krenz-Niedbala et al. <sup>77</sup> | Multicentre cross-sectional study (3b) | 130; 1,277<br>59*; 433<br>71*; 844         | < 1 y<br>No                   | 8 y           | Questionnaire for asthma symptoms (ISAAC)          | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                   |
| Poland                              |                                        |                                            | Parent questionnaire          |               |                                                    | • <b>OR 1.71 (95%CI 1.29-2.26) p=nr</b>                                                                                                                                                                                                                                                                                                                                                                                                             |
| 2015                                |                                        |                                            |                               |               |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Metsälä et al. <sup>92</sup>        | Multicentre case-control study (3b)    | 1,419; 6,690<br>1,212; 5,352<br>207; 1,338 | < 6 m before diagnosis<br>Yes | 3-10 y        | ICD-10 codes plus prescription records (ATC codes) | Exposure to AB 6 m before diagnosis associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                 |
| Finland                             |                                        |                                            | Registry                      |               |                                                    | Parity, maternal asthma, gestational age                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2015                                |                                        |                                            |                               |               |                                                    | <ul style="list-style-type: none"> <li>• <b>aOR 1.60 (95%CI 1.48-1.73), p&lt;0.05</b></li> <li>• penicillin: <b>aOR 1.33 (95%CI 1.21-1.47), p=nr</b></li> <li>• amoxicillin: <b>aOR 2.35 (95%CI 2.10-2.63), p=nr</b></li> <li>• cephalosporins: <b>aOR 1.91 (95%CI 1.76-2.07), p=nr</b></li> <li>• macrolides: <b>aOR 2.74 (95%CI 2.50-2.99), p=nr</b></li> <li>• trimethoprim/sulfamethoxazole: <b>aOR 1.98 (95%CI 1.80-2.18), p=nr</b></li> </ul> |
| Lee et al. <sup>169</sup>           | Multicentre cross-sectional study (3b) | 459; 6,161<br>189; 1,865<br>270; 4,296     | < 1 y<br>No                   | 13.9 y (mean) | Questionnaire for asthma symptoms (based on ISAAC) | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                   |
| Korea                               |                                        |                                            | Parent questionnaire          |               |                                                    | Age, sex, family history of atopy, income, BMI, smoke exposure                                                                                                                                                                                                                                                                                                                                                                                      |
| 2015                                |                                        |                                            |                               |               |                                                    | • <b>aOR 1.94 (95%CI 1.49-2.53) p=nr</b>                                                                                                                                                                                                                                                                                                                                                                                                            |
| Eldeirawi et al. <sup>191</sup>     | Multicentre cross-sectional study (3b) | 133; 1,786<br>92; 799<br>41; 987           | < 1 y<br>No                   | 1 y           | Parent-reported physician's diagnosis              | Exposure to AB in first y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                   |
| USA                                 |                                        |                                            | Parent questionnaire          |               |                                                    | Age, sex, country of birth, family history of atopy, having a regular doctor or clinic, number of ear infections                                                                                                                                                                                                                                                                                                                                    |
| 2015                                |                                        |                                            |                               |               |                                                    | <ul style="list-style-type: none"> <li>• <b>aOR 2.33 (95% CI, 1.53-3.55), p&lt;0.01</b></li> <li>• 1-2 AB courses: <b>aOR 1.81 (95%CI 1.13-2.88), p=0.01</b></li> <li>• ≥ 3 AB courses: <b>aOR 3.43 (95%CI 2.06-5.73), p&lt;0.01</b></li> </ul>                                                                                                                                                                                                     |

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Table 1 (continued)

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| Khalkhali et al. <sup>168</sup>       | Single-centre prospective case-control study (3b) | 157; 361<br>120; 230<br>47; 131                                                                        | < 1 y<br>No<br>Parent questionnaire | 2-8 y                        | Global Initiative for Asthma (GINA) criteria     | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.91 (95%CI 1.27-2.88), p=0.03</b>                                                                                                                                  | Family history of atopy, prematurity, delivery mode, birth order                                                                                             |
| Iran                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| 2014                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| Lapin et al. <sup>164</sup>           | Multicentre prospective cohort study (2b)         | 44; 295<br>nr; 162<br>nr; 133                                                                          | < 1 y<br>No<br>nr                   | 3 y                          | Parent-reported physician's diagnosis            | Exposure to AB in first y of life associated with increased risk in high-risk children.<br><br>• <b>aOR 1.58 (95%CI 1.27-1.96), p=nr</b>                                                                                                              | Ethnicity, smoking during pregnancy, antibiotic and medication use during pregnancy, maternal asthma, birth weight, breastfeeding, household smoking         |
| USA                                   |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| 2014                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| Ong et al. <sup>104</sup>             | Multicentre retrospective cohort study (2b)       | 5,946; 62,576<br>3,162*; 26,693<br>2,784*; 35,883<br>6,418; 62,576<br>2,875*; 26,693<br>3,543*; 35,883 | < 1 y<br>No<br>Registry             | < 3 y<br><br>Registry<br>3 y | ICD-9 codes                                      | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.60 (95%CI 1.50-1.70), p&lt;0.01</b><br><br>Exposure to AB in first y of life not associated with increased risk.<br><br>• <b>OR 1.10 (95%CI 1.00-1.10), p=0.10</b> |                                                                                                                                                              |
| Australia                             |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| 2014                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| Semic-Jusufagic et al. <sup>126</sup> | Multicentre prospective cohort study (2b)         | 529; 800<br>nr; 564<br>nr; 236                                                                         | < 1 y<br>No<br>Parent questionnaire | 1-11 y                       | Parent-reported plus medical records             | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>HR 2.26 (95%CI 1.03-4.94), p=0.04</b>                                                                                                                                   |                                                                                                                                                              |
| UK                                    |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| 2014                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| Örtqvist et al. <sup>198</sup>        | Multicentre prospective cohort study (2b)         | 29,753; 493,785<br>25,306; 305,938<br>4,447; 187,847                                                   | < 2 y<br>Yes<br>Registry            | < 5 y<br>3 y                 | ICD-10 codes or prescription records (ATC codes) | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aHR 2.03 (95%CI 1.93-2.12), p=nr</b><br><br>Results according to antibiotic class nr                                                                                  | Sex, maternal country of birth and age; parity, parental marital status, parental education, antibiotic use during pregnancy, gestational age, birth weight, |
| Sweden                                |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |
| 2014                                  |                                                   |                                                                                                        |                                     |                              |                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                              |

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Table 1 (continued)

|                                   |                                             |                 |                      |              |                                                     |                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|---------------------------------------------|-----------------|----------------------|--------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |                                             |                 |                      |              |                                                     |                                                                                                                                                                                                               | delivery mode, respiratory diagnosis (respiratory distress, congenital pneumonia, neonatal aspiration syndromes, interstitial emphysema, pulmonary haemorrhage, chronic respiratory disease)                                                                                                                        |
| Goksor et al. <sup>55</sup>       | Multicentre prospective cohort study (2b)   | 231; 4,051      | < 1 w                | 8 y          | Questionnaire for asthma symptoms (ISAAC and BAMSE) | Exposure to AB in first w of life associated with increased risk.                                                                                                                                             | Family history of atopy, prematurity, weight for gestational age, delivery mode                                                                                                                                                                                                                                     |
| Sweden                            |                                             | 19; 187         | No                   |              |                                                     | • aOR 2.30 (95%CI 1.20-4.20), p<0.05                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | 212; 3,864      | Parent questionnaire |              |                                                     |                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                     |
| Hoskin-Parr et al. <sup>176</sup> | Single-centre prospective cohort study (2b) | 630; 5,780      | < 2 y                | 7.5 y (mean) | Parents-reported physician's diagnosis              | Exposure to AB in first 2 y of life associated with increased risk.                                                                                                                                           | Age, sex, maternal age and education; parental marital status, home ownership status, degree of difficulty in paying for food, smoking during pregnancy, disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure |
| UK                                |                                             | 367*; 2,659     | No                   |              |                                                     | • aOR 1.75 (95%CI 1.40-2.17), p=nr                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | 263*; 3,121     | Parent questionnaire |              |                                                     | • 1 AB course: aOR 1.11 (95%CI 0.84-1.48), p=nr<br>• 2 AB courses: aOR 1.50 (95%CI 1.14-1.98), p=nr<br>• 3 AB courses: aOR 1.79 (95%CI 1.34-2.40), p=nr<br>• ≥ 4 AB courses: aOR 2.82 (95%CI 2.19-3.63), p=nr |                                                                                                                                                                                                                                                                                                                     |
| Muc et al. <sup>97</sup>          | Multicentre cross-sectional study (3b)      | 106; 1,037      | < 1 y                | 6-9 y        | Questionnaire for asthma symptoms (ISAAC)           | Exposure to AB in first y of life associated with increased risk.                                                                                                                                             | Age, sex, prematurity, atopy                                                                                                                                                                                                                                                                                        |
| Portugal                          |                                             | 38*; 237        | No                   |              |                                                     | • aOR 1.96 (95%CI 1.25-3.08), p<0.01                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | 68*; 800        | Parent questionnaire |              |                                                     |                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                     |
| Wang et al. <sup>150</sup>        | Multicentre prospective cohort study (2b)   | 57,328; 263,620 | < 1 y                | 2-6 y        | ICD-9-CM codes                                      | Exposure to AB in first y of life associated with increased risk.                                                                                                                                             | Sex, living area, socioeconomic status, healthcare use                                                                                                                                                                                                                                                              |
| Taiwan                            |                                             | nr; 15,663      | Yes                  |              |                                                     | • aHR 1.38 (95%CI 1.32-1.46), p<0.05                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                     |
| 2013                              |                                             | nr; 247,957     | Medical records      |              |                                                     | Results according to antibiotic class nr                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                     |

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Table 1 (continued)

|                                |                                           |                                                   |                          |       |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------|-------------------------------------------|---------------------------------------------------|--------------------------|-------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Almqvist et al. <sup>197</sup> | Multicentre prospective cohort study (2b) | nr; 9,400,000<br>95,628; 211,192<br>nr; 9,188,808 | < 3 y<br>Yes<br>Registry | <1 y  | Prescription records (ATC codes) | Exposure to AB in first 3 y of life associated with increased risk.<br><br>• <b>HR 2.20 (95%CI 2.12-2.28), p=nr</b><br><br>• 1-2 AB courses: <b>HR 1.72 (95%CI 1.45-2.05), p=nr</b><br>• 3-5 AB courses: <b>HR 1.25 (95%CI 1.86-2.72), p=nr</b><br>• ≥ 6 AB courses: <b>HR 2.36 (95%CI 1.76-3.16), p=nr</b><br><br>• narrow-spectrum: <b>HR 1.60 (95%CI 1.35-1.91), p=nr</b><br>• broad-spectrum: <b>HR 2.04 (95%CI 1.71-2.42), p=nr</b><br><br>Results according to antibiotic class nr |
| Sweden                         |                                           |                                                   |                          | 1 y   |                                  | • <b>HR 1.73 (95%CI 1.66-1.82), p=nr</b><br><br>• 1-2 AB courses: <b>HR 1.37 (95%CI 1.16-1.61), p=nr</b><br>• 3-5 AB courses: <b>HR 2.03 (95%CI 1.72-2.40), p=nr</b><br>• ≥ 6 AB courses: <b>HR 2.50 (95%CI 2.09-3.01), p=nr</b><br><br>• narrow-spectrum: <b>HR 1.28 (95%CI 1.09-1.50), p=nr</b><br>• broad-spectrum: <b>HR 1.83 (95%CI 1.56-2.15), p=nr</b><br><br>Results according to antibiotic class nr                                                                            |
| 2012                           |                                           |                                                   |                          | 2 y   |                                  | • <b>HR 1.29 (95%CI 1.15-1.45), p=nr</b><br><br>• 1-2 AB courses: HR 0.85 (95%CI 0.53-1.36), p=nr<br>• 3-5 AB courses: HR 1.26 (95%CI 0.78-2.02), p=nr<br>• ≥ 6 AB courses: <b>HR 1.77 (95%CI 1.10-2.86), p=nr</b><br><br>• narrow-spectrum: HR 0.96 (95%CI 0.65-1.41), p=nr<br>• broad-spectrum: HR 1.38 (95%CI 0.94-2.04), p=nr<br><br>Results according to antibiotic class nr                                                                                                        |
|                                |                                           |                                                   |                          | ≥ 3 y |                                  | • <b>HR 1.15 (95%CI 0.73-1.83), p=nr</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                 |

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Table 1 (continued)

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|-----------------------------------|---------------------------------------------|----------------------------------|--------------------------------------|-------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Raciborski et al. <sup>115</sup>  | Multicentre retrospective cohort study (2b) | 63; 1,330<br>52; 820<br>11; 510  | < 1 y<br>No<br>Parent questionnaire  | 6–8 y | Questionnaire for asthma symptoms (ISAAC and ECRHS II) | Exposure in first y of life associated with increased risk when $\geq 2$ AB courses.<br><br>• 1 AB course: OR 1.54 (95%CI nr), p=0.30<br>• 2 AB courses: <b>OR 2.55 (95%CI nr), p=0.02</b><br>• > 3 AB courses: <b>OR 5.59 (95%CI 2.6–12.01), p&lt;0.01</b>                                       |                                                                 |
| Poland                            |                                             | 63; 1,321<br>60; 1,145<br>3; 176 | 1–3 y<br>No<br>Parent questionnaire  |       |                                                        | Exposure in second and third y of life associated with increased risk when > 4 AB courses.<br><br>• 1–2 AB courses: OR 1.42 (95%CI nr), p=0.59<br>• 3–4 AB courses: OR 2.87 (95%CI nr), p=0.09<br>• > 4 AB courses: <b>OR 4.73 (95%CI 1.41–15.90), p&lt;0.01</b>                                  |                                                                 |
| Jedrychowski et al. <sup>69</sup> | Multicentre prospective cohort study (2b)   | 29; 310<br>26*; 244<br>3*; 66    | < 2 y<br>Yes<br>Parent questionnaire | 5 y   | Parent-reported physician's diagnosis                  | Exposure to AB in first 5 y of life associated with increased risk.<br><br>• <b>aOR 2.08 (95%CI 1.32–3.28), p=nr</b><br><br>• penicillins: aOR 1.49 (95%CI 0.89–2.49), p=nr<br>• cephalosporins: <b>aOR 2.45 (95%CI 1.49–4.02), p=nr</b><br>• macrolides: <b>aOR 2.14 (95%CI 1.16–3.95), p=nr</b> | Age, maternal atopy and education, parity, smoke exposure       |
| Risnes et al. <sup>116</sup>      | Multicentric prospective cohort study (2b)  | 164; 1,401<br>65; 464<br>99; 937 | < 6 m<br>No<br>Parent questionnaire  | 6 y   | ICD-9 codes                                            | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• <b>aOR 1.52 (95% CI, 1.07–2.16), p=nr</b><br><br>• 1 AB course: aOR 1.40 (95%CI 0.90–2.15), p=nr<br>• $\geq 2$ AB courses: aOR 1.72 (95%CI 1.11–2.65), p=0.01                                                        | Maternal age, family history of asthma, income, number of LRTIs |
| Sandini et al. <sup>177</sup>     | Single-centre prospective cohort study (2b) | 121; 891<br>nr; nr<br>nr; nr     | < 6 m<br>No<br>Parent questionnaire  | 5 y   | Parent-reported physician's diagnosis                  | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• OR 0.90 (95%CI 0.41–1.98), p=0.79                                                                                                                                                                                |                                                                 |

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Table 1 (continued)

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|------------------------------|------------------------------------------------------|-------------|----------------------|-------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Yeh et al. <sup>159</sup>    | Multicentre cross-sectional study (3b)               | 566; 2,037  | < 1 y                | 3–6 y | Questionnaire for asthma symptoms (ISAAC) plus parent-reported physician's diagnosis | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 2.35 (95%CI 1.52–3.66), p&lt;0.01</b>                                                               |                                                                                           |
| Taiwan                       |                                                      | nr; nr      | No                   |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| 2011                         |                                                      | nr; nr      | Parent questionnaire |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| Su et al. <sup>135</sup>     | Multicentre prospective cohort study (2b)            | 50; 424     | < 9 m                | 1–5 y | Parent-reported physician's diagnosis (questionnaire for respiratory symptoms)       | Exposure to AB in first 9 m of life associated with increased risk.<br>• <b>aOR 1.50 (95%CI 1.10–2.10), p=0.02</b>                                                               | Number of illness visits                                                                  |
| USA                          |                                                      | 22; 136     | No                   |       |                                                                                      | Exposure to AB in first 9 m of life not associated with increased risk after adjustment for number of illness visits.<br>• aOR 1.20 (95%CI 0.60–2.30), p=0.70                    |                                                                                           |
| 2010                         |                                                      | 28; 288     | Parent questionnaire |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| Mai et al. <sup>178</sup>    | Single-centre prospective cohort study (2b)          | 228; 3,306  | < 1 y                | 4 y   | Questionnaire for asthma symptoms (BAMSE based on ISAAC)                             | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.50 (95%CI 1.10–2.00), p=nr</b><br>• <b>≥ 2 AB courses: aOR 1.90 (95%CI 1.20–3.00), p&lt;0.01</b> | Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding |
| Sweden                       |                                                      | 125; 1,420  | No                   |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| 2010                         |                                                      | 103; 1,886  | Parent questionnaire |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
|                              |                                                      | 210; 3,306  |                      | 8 y   |                                                                                      | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 1.20 (95%CI 0.90–1.60), p=nr                                                                      |                                                                                           |
|                              |                                                      | 104; 1,420  |                      |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
|                              |                                                      | 106; 1,886  |                      |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| Foljaki et al. <sup>50</sup> | Multicentre retrospective cross-sectional study (3b) | nr; 193,412 | < 1 y                | 6–7 y | Questionnaire for asthma symptoms (ISAAC)                                            | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.94 (95%CI 1.83–2.06), p=nr</b>                                                                   | Sex, language, living area, income                                                        |
| Sweden                       |                                                      | nr; 135,775 | No                   |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| 2009                         |                                                      | nr; 57,637  | Parent questionnaire |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| Karimi et al. <sup>162</sup> | Multicentre cross-sectional study (3b)               | 49; 1,476   | < 1 y                | 6–7 y | Questionnaire for asthma symptoms (ISAAC)                                            | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 2.21 (95%CI 1.05–4.80), p=0.02</b>                                                                  |                                                                                           |
| Iran                         |                                                      | 39; 950*    | No                   |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |
| 2009                         |                                                      | 10; 526*    | nr                   |       |                                                                                      |                                                                                                                                                                                  |                                                                                           |

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Table 1 (continued)

|                               |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
|-------------------------------|-------------------------------------------------|--------------------------------------------------|--------------------------------------|--------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Martel et al. <sup>88</sup>   | Multicentre prospective case-control study (3b) | 5,226; 109,746<br>2,057; 29,509<br>3,169; 80,237 | < 6 m<br>No<br>Registry              | < 10 y | ICD-9 codes                               | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• aOR 1.70 (95%CI 1.34-2.15), p=nr                                                   | Maternal asthma                                                                   |
| Canada                        |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| 2009                          |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| Garcia et al. <sup>52</sup>   | Multicentre cross-sectional study (3b)          | 175; 641<br>nr; 420<br>nr; 221                   | < 1 y<br>No<br>Parent questionnaire  | 6-7 y  | Questionnaire for asthma symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• aOR 1.90 (95%CI 1.40-2.50), p<0.01                                                   | Maternal and medication use; time spent watching television per day, pet exposure |
| Colombia                      |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| 2008                          |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| Wickens et al. <sup>153</sup> | Multicentre prospective cohort study (2b)       | 119; 1,064<br>29*; 148<br>90*; 916               | < 3 m<br>No<br>Parent questionnaire  | 15 m   | Questionnaire for asthma symptoms (ISAAC) | Exposure to AB in first 3 m of life not associated with increased risk after adjustment for chest infections.<br><br>• aOR 1.58 (95% CI, 0.96-2.60), p=0.07     | Number of LRTIs                                                                   |
| New Zealand                   |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| 2008                          |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
|                               |                                                 | 168; 1,011                                       | < 15 m                               | 4 y    |                                           | Exposure to AB in first 15 m of life not associated with increased risk.<br><br>• aOR 0.98 (95%CI 0.60-1.59), p=0.92                                            |                                                                                   |
|                               |                                                 | 128*; 722<br>40*; 289                            | No<br>Parent questionnaire           |        |                                           |                                                                                                                                                                 |                                                                                   |
| Kusel et al. <sup>80</sup>    | Multicentre prospective cohort study (2b)       | 37; 198<br>24*; 107<br>13*; 91                   | < 1 y<br>Yes<br>Parent questionnaire | 0-5 y  | Parent-reported current asthma            | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 0.90 (95%CI 0.40-2.30), p=nr<br><br>Results according to antibiotic class nr | Sex, day care, number of GP visits, pet exposure                                  |
| Australia                     |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
| 2008                          |                                                 |                                                  |                                      |        |                                           |                                                                                                                                                                 |                                                                                   |
|                               |                                                 | 57; 198<br>39*; 107<br>18*; 91                   |                                      |        | Parent-reported physician's diagnosis     | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.50 (95%CI 0.70-3.20), p=nr<br><br>Results according to antibiotic class nr |                                                                                   |

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Table 1 (continued)

|                                                        |                                           |                                                                                                                                                          |                                     |               |                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                       |
|--------------------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|---------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Kozyrskyj et al. <sup>76</sup><br>Canada<br>2007       | Multicentre prospective cohort study (2b) | 787; 13,116<br>nr; 8,525<br>nr; 4,591                                                                                                                    | < 1 y<br>Yes<br>Registry            | 7 y           | ≥ 1 physician visits or hospitalizations for asthma or 2 prescriptions for asthma | Exposure to AB in first y of life associated with increased risk.<br>• <b>aOR 1.86 (95%CI 1.02-3.37), p=nr</b><br>• 1-2 AB courses: <b>aOR 1.21 (95%CI 1.011-1.46), p=nr</b><br>• 3-4 AB courses: <b>aOR 1.30 (95%CI 1.04-1.63), p=nr</b><br>• > 4 AB courses: <b>aOR 1.46 (95%CI 1.14-1.88), p=nr</b><br><br>Results according to antibiotic class nr                                       | Sex, maternal history of asthma, living area, number of siblings, number of LRTIs, healthcare use     |
| Mullooly et al. <sup>98</sup><br>USA<br>2007           | Single-centre case-control study (3b)     | 383; 844<br>nr; nr<br>nr; nr                                                                                                                             | < 2 y<br>No<br>Medical records      | 10.3 y (mean) | Parent-reported physician's diagnosis                                             | Exposure to AB in first 2 y of life not associated with increased risk.<br>• <b>aOR 1.02 (95%CI 0.98-1.06), p=nr</b>                                                                                                                                                                                                                                                                         | Sex, ethnicity, maternal age, birth weight, age of child at outcome, breastfeeding, household smoking |
| Del-Rio-Navarro et al. <sup>39</sup><br>Mexico<br>2006 | Multicentre cross-sectional study (3b)    | 794; 4,106<br>601*; 2,583<br>193*; 1,523<br><br>Boys: 451; 2,098<br><br>342*; 1,364<br>109*; 734<br><br>Girls: 343; 2,008<br><br>259*; 1,219<br>84*; 789 | < 1 y<br>No<br>Parent questionnaire | 6-7 y         | Questionnaire for asthma symptoms (ISAAC)                                         | Exposure to AB in first y of life associated with increased risk.<br>• <b>OR 2.09 (95%CI 1.75-2.49), p&lt;0.01</b><br><br>Exposure to AB in first y of life associated with increased risk boys.<br><br>• <b>OR 1.92 (95%CI 1.41-2.62), p&lt;0.01</b><br><br>Exposure to AB in first y of life associated with increased risk in girls.<br><br>• <b>OR 2.27 (95%CI 1.49-3.44), p&lt;0.01</b> |                                                                                                       |

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Table 1 (continued)

|                                                    |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
|----------------------------------------------------|-------------------------------------------|------------------------------------------------|--------------------------------------|--------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Flostrup et al. <sup>49</sup>                      | Multicentre cross-sectional study (3b)    | 419; 4,606<br>161*; 788<br>258*; 3,818         | < 1 y<br>No<br>Parent questionnaire  | 7-11 y | Parent-reported physician's diagnosis     | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 2.79 (95%CI 2.03-3.83), p=nr</b>                                                                                                                                                                                                                                                   | Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure |
| Netherlands, Austria, Germany, Sweden, Switzerland |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| 2006                                               |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| Ahn et al. <sup>13</sup>                           | Multicentre cross-sectional study (3b)    | 2,354; 25,787<br>976*; 6,273<br>1,378*; 19,514 | < 1 y<br>No<br>Parent questionnaire  | 7-12 y | Questionnaire for asthma symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.86 (95%CI 1.67-2.08), p&lt;0.01</b><br><br>• 1-2 AB courses: <b>aOR 1.54 (95%CI 1.35-1.76), p&lt;0.01</b><br>• 3-4 AB courses: <b>aOR 1.79 (95%CI 1.47-2.18), p&lt;0.01</b><br>• ≥ 5 AB courses: <b>aOR 2.53 (95%CI 2.10-3.06), p&lt;0.01</b>                                    | Episodes of fever or acute gastroenteritis                                                                                                                                                                 |
| Korea                                              |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| 2005                                               |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| Celedon et al. <sup>198</sup>                      | Multicentre prospective cohort study (2b) | 323; 4,408<br>280; 3,292<br>43; 1,116          | < 1 y<br>Yes<br>Prescription records | 1-2 y  | ICD-9 codes                               | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 2.32 (95%CI 1.67-3.22), p&lt;0.01*</b><br><br>• 1-2 AB courses: <b>aOR 1.90 (95%CI 1.30-2.70), p&lt;0.01</b><br>• 3-4 AB courses: <b>aOR 1.60 (95%CI 1.10-2.40), p=0.03</b><br>• > 4 AB courses: <b>aOR 2.10 (95%CI 1.50-3.20), p&lt;0.01</b>                                       | Number of respiratory tract infections                                                                                                                                                                     |
| USA                                                |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| 2004                                               |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
|                                                    |                                           | 314; 4,178                                     |                                      | 2-5 y  |                                           | Results according to antibiotic class nr<br>Exposure to AB in first y of life not associated with increased risk.<br><br>• <b>OR 1.17 (95%CI 0.89-1.54), p=0.25</b><br><br>• 1-2 AB courses: <b>aOR 1.10 (95%CI 0.80-1.40), p=0.72</b><br>• 3-4 AB courses: <b>aOR 1.30 (95%CI 0.90-1.80), p=0.14</b><br>• > 4 AB courses: <b>aOR 1.00 (95%CI 0.70-1.40), p=0.87</b> |                                                                                                                                                                                                            |
|                                                    |                                           | 241; 3,092<br>73; 1,086                        |                                      |        |                                           | Results according to antibiotic class nr<br>Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 2.10 (95%CI 1.79-2.48), p=nr</b>                                                                                                                                                                                                        |                                                                                                                                                                                                            |
| Cohet et al. <sup>37</sup>                         | Single-centre case-control study (3b)     | 1,277; 3,927<br>1,020; 2,684<br>257; 1,243     | < 1 y<br>No<br>Parent questionnaire  | 6-7 y  | Questionnaire for asthma symptoms (ISAAC) | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 2.10 (95%CI 1.79-2.48), p=nr</b>                                                                                                                                                                                                                                                    |                                                                                                                                                                                                            |
| New Zealand                                        |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |
| 2004                                               |                                           |                                                |                                      |        |                                           |                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                            |

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Table 1 (continued)

|                                |                                             |                                        |                                     |              |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                  |
|--------------------------------|---------------------------------------------|----------------------------------------|-------------------------------------|--------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Celedon et al. <sup>32</sup>   | Multicentre prospective cohort study (2b)   | 38; 448<br>24; 314<br>14; 134          | < 1 y<br>No<br>Parent questionnaire | 5 y          | Parent-reported physician's diagnosis (telephone questionnaire) | Exposure to AB in first y of life not associated with increased risk.<br>• OR 0.71 (95%CI 0.35-1.42), p=0.33<br>• 1 AB course: aOR 0.50 (95%CI 0.20-1.40), p=nr<br>• ≥ 2 AB courses: aOR 0.90 (0.40-1.80), p=nr                                                                                                                                                                                                                                                                                                                                                                                                            | Sex, family history of atopy, income                                                                             |
| McKeever et al. <sup>182</sup> | Single-centre prospective cohort study (2b) | 915; 21,129<br>nr; 13,497<br>nr; 7,632 | < 1 y<br>Yes<br>Medical records     | 2.2 y (mean) | Oxford Medical Information System (OXMIS), ICD-8 or Read codes  | Exposure to AB in first y of life associated with increased risk.<br>• 1 AB course: aHR 1.26 (95%CI 1.13-1.40), p=nr<br>• 2 AB courses: aHR 1.46 (95%CI 1.30-1.65), p=nr<br>• 3 AB courses: aHR 1.76 (95%CI 1.56-2.13), p=nr<br>• 4 AB courses: aHR 1.82 (95%CI 1.56-2.13), p=nr<br>• > 4 AB courses: aHR 1.99 (95%CI 1.72-2.31), p=nr<br><br>• penicillin: aHR 0.99 (95%CI 0.89-1.10), p=nr<br>• amoxicillin: aHR 1.25 (95%CI 1.16-1.36), p=nr<br>• amoxicillin/clavulanic acid: aHR 1.43 (95%CI 1.19-1.72), p=nr<br>• cephalosporins: aHR 1.44 (95%CI 1.28-1.63), p=nr<br>• macrolides: aHR 1.41 (95%CI 1.30-1.53), p=nr | Number of GP visits                                                                                              |
| Illii et al. <sup>167</sup>    | Multicentre prospective cohort study (2b)   | 57; 937<br>22; 338<br>35; 599          | < 3 y<br>No<br>Parent questionnaire | 0-7 y        | Parent-reported physician's diagnosis                           | Exposure to AB in first 3 y of life not associated with increased risk.<br>• aOR 1.08 (95%CI 0.59-1.99), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | High risk of atopy at birth (elevated cord blood IgE or family history of atopy), parental education and smoking |
| Wjst et al. <sup>155</sup>     | Multicentre cross-sectional study (3b)      | 37; 2,512<br>nr; 2,025<br>nr; 487      | < 5-14 y<br>No<br>Medical records   | 5-14 y       | Questionnaire for asthma symptoms (ISAAC)                       | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 0.90 (95%CI 0.60-1.40), p=0.71                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Age, sex, family history of atopy, season, parental education                                                    |

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Table 1 (continued)

|                                  |                                                      |                                                                                |                                      |                     |                                            |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                          |
|----------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------|---------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Droste et al. <sup>43</sup>      | Multicentre cross-sectional study (3b)               | 55; 1,206<br>27; 384<br>28; 822                                                | < 1 y<br>No<br>Parent questionnaire  | 7-8 y               | Questionnaire for asthma symptoms (ISAAC)  | Exposure to AB in first y of life associated with increased risk in high-risk children.<br><br>• <b>aOR 1.70 (95%CI 1.00-3.10), p&lt;0.01</b>                                                                                                                                                                         | Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure                                                                                  |
| Ponsonby et al. <sup>112</sup>   | Multicentre prospective cohort study (2b)            | 276; 856<br>40; 114<br>236; 742                                                | < 1 m<br>No<br>Parent questionnaire  | 2.1 y (mean)        | Questionnaire for asthma symptoms (ISAAC)  | Exposure to AB in first m of life not associated with increased risk.<br><br>• <b>aRR 1.04 (95%CI 0.78-1.37), p=nr</b>                                                                                                                                                                                                | Age, family history of asthma, household size, prematurity, birth weight, age of child at time of outcome, breastfeeding, maternal smoking, household smoking, gas heater in living room |
| Von Mutius et al. <sup>181</sup> | Single-centre cross-sectional study (3b)             | 374; 5,006<br>340; 3,904<br>34; 1,102<br>461; 5,267<br>397; 4,006<br>64; 1,261 | < 3 y<br>No<br>Medical records       | 5-7 y<br><br>9-11 y | Questionnaire for asthma symptoms (ISAAC)  | Exposure to AB in first 3 y of life associated with increased risk.<br><br>• <b>aOR 1.64 (95%CI 1.26-2.13), p=nr</b><br><br>• $\geq 6$ AB courses: aOR 7.95 (95%CI 6.02-10.50), p=nr<br><br>Exposure to AB in first 3 y of life associated with increased risk.<br><br>• <b>OR 2.06 (95%CI 1.57-2.70), p&lt;0.01*</b> | Family history of atopy, number of siblings, parental education, study area, school grade                                                                                                |
| Wickens et al. <sup>154</sup>    | Multicentre retrospective cross-sectional study (3b) | 71; 447<br>65; 334<br>6; 113                                                   | < 10 y<br>No<br>Parent questionnaire | 5-10 y              | Questionnaire for asthma symptoms (ISAAC)  | Exposure to AB in first 10 y of life associated with increased risk.<br><br>• <b>aOR 2.74 (95%CI 1.10-6.85), p=nr</b><br><br>• 1-2 AB courses: aOR 2.27 (95%CI 1.14-4.51), p=nr<br>• $\geq 3$ AB courses: aOR 4.02 (95%CI 1.57-10.31), p=nr                                                                           | Age, sex, ethnicity, family history of atopy, household size, parental smoking                                                                                                           |
| Farooqi et al. <sup>48</sup>     | Single-centre retrospective cohort study (2b)        | 484; 1,855<br>402*; 1,237<br>82*; 618                                          | < 2 y<br>Yes<br>Medical records      | 6-12 y              | Recurrent episodes of wheeze > 2 y of life | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>OR 3.19 (95%CI 2.43-4.18), p&lt;0.01</b><br><br>Results according to antibiotic class nr                                                                                                                                              |                                                                                                                                                                                          |

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Table 1 (continued)

| Allergic symptoms             |                                             |               |                        |         |                                                                                                                                                    |                                                                                       |
|-------------------------------|---------------------------------------------|---------------|------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Levin et al. <sup>82</sup>    | Multicentre prospective cohort study (2b)   | 528; 1,185    | < 1 y                  | 12–36 m | Questionnaire for allergic symptoms (based on ISAAC)                                                                                               | Exposure to AB in first y of life associated with increased risk in urban cohort.     |
| South-Africa                  |                                             | 326; 654      | No                     |         |                                                                                                                                                    | • OR 1.62 (95%CI 1.28–2.04), p<0.01*                                                  |
| 2020                          |                                             | 202; 531      | Parent questionnaire   |         |                                                                                                                                                    | Exposure to AB in first y of life not associated with increased risk in rural cohort. |
|                               |                                             | 23; 398       |                        |         |                                                                                                                                                    | • OR 1.58 (95%CI 0.36–6.94), p=0.55*                                                  |
|                               |                                             | 21; 347       |                        |         |                                                                                                                                                    |                                                                                       |
|                               |                                             | 2; 51         |                        |         |                                                                                                                                                    |                                                                                       |
| Hirsch et al. <sup>61</sup>   | Multicentre case-control study (3b)         | 3,652; 21,912 | 1–2 m before diagnosis | < 7 y   | ICD-9 codes plus medical or prescription records for milk allergy, non-milk food allergies and other unspecified allergies incl. allergic rhinitis | Exposure to AB in 2 m before diagnosis associated with increased risk.                |
| USA                           |                                             | 3,145; 16,967 | Yes                    |         |                                                                                                                                                    | • aOR 2.32 (95%CI 2.07–2.59), p=nr                                                    |
| 2017                          |                                             | 507; 4,945    | Medical records        |         |                                                                                                                                                    | • 1–2 AB courses: aOR 1.69 (95%CI 1.50–1.92), p=nr                                    |
|                               |                                             |               |                        |         |                                                                                                                                                    | • ≥ 3 AB courses: aOR 3.07 (95%CI 2.72–3.46), p=nr                                    |
|                               |                                             |               |                        |         |                                                                                                                                                    | • penicillins: aOR 2.28 (95%CI 2.06–2.53), p=nr                                       |
|                               |                                             |               |                        |         |                                                                                                                                                    | • cephalosporins: aOR 1.70 (95%CI 1.57–1.83), p=nr                                    |
|                               |                                             |               |                        |         |                                                                                                                                                    | • macrolides: aOR 1.98 (95%CI 1.83–2.15), p=nr                                        |
| Batool et al. <sup>183</sup>  | Multicentre prospective cohort study (2b)   | 360; 818      | < 1 y                  | 1 y     | Parent-reported allergic symptoms (atopic dermatitis, allergic rhinitis, wheezing or asthma)                                                       | Exposure to AB in first y of life associated with increased risk.                     |
| Canada                        |                                             | 163; 285      | No                     |         |                                                                                                                                                    | • OR 2.28 (95%CI 1.70–3.6), p<0.01*                                                   |
| 2016                          |                                             | 197; 533      | Parent questionnaire   |         |                                                                                                                                                    |                                                                                       |
| Sandini et al. <sup>177</sup> | Single-centre prospective cohort study (2b) | 308; 925      | < 6 m                  | 2 y     | Parent-reported allergic symptoms (atopic dermatitis, food allergy, allergic rhinitis, asthma)                                                     | Exposure to AB in first 6 m of life not associated with increased risk.               |
| Finland                       |                                             | nr; nr        | No                     |         |                                                                                                                                                    | • OR 1.25 (95%CI 0.82–1.90), p=0.30                                                   |
| 2011                          |                                             | nr; nr        | Parent questionnaire   | 5 y     |                                                                                                                                                    | Exposure to AB in first 6 m of life not associated with increased risk.               |
|                               |                                             | 479; 891      |                        |         |                                                                                                                                                    | • OR 1.26 (95%CI 0.83–1.92), p=0.27                                                   |
|                               |                                             | nr; nr        |                        |         |                                                                                                                                                    |                                                                                       |
|                               |                                             | nr; nr        |                        |         |                                                                                                                                                    |                                                                                       |

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Table 1 (continued)

| Infantile colic                 |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
|---------------------------------|---------------------------------------------------|-------------------------------------|--------------------------------------|---------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oosterloo et al. <sup>105</sup> | Multicentre prospective cohort study (2b)         | 74; 436<br>33; 151<br>41; 285       | < 1 w<br>No<br>Parent questionnaire  | 0-1 y   | Parent-reported                                               | Exposure to AB in first w of life not associated with increased risk.<br><br>• aOR 1.66 (95%CI 1.00-2.77), p=0.05                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking |
| Netherlands                     |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
| 2018                            |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
| Abdominal pain                  |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
| Uusijarvi et al. <sup>144</sup> | Multicentre prospective cohort study (2b)         | 231; 2,654<br>87; 861<br>144; 1,793 | < 2 y<br>Yes<br>Parent questionnaire | 11-14 y | Questionnaire for abdominal pain and GI disorders (QPGS-RIII) | Exposure to AB in first 2 y of life not associated with increased risk abdominal pain.<br><br>• aOR 1.37 (95%CI 0.94-1.99), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                                        | Sex, asthma at 12 years of age                                                                                                                                   |
| Sweden                          |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
| 2014                            |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
|                                 |                                                   | 245; 2,732                          | 9-12 y                               |         |                                                               | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                  |
|                                 |                                                   | 94; 1,045<br>151; 1,687             | Yes<br>Parent questionnaire          |         |                                                               | Exposure to AB between 9 and 12 y of life not associated with increased risk.<br><br>• 1 AB course: aOR 0.88 (95%CI 0.61-1.25), p=nr<br>• 2 AB courses: aOR 0.76 (95%CI 0.44-1.31), p=nr<br>• ≥ 3 AB courses: aOR 1.18 (95%CI 0.71-1.98), p=nr<br><br>• penicillin: aOR 1.04 (95%CI 0.76-1.43), p=nr<br>• amoxicillin: aOR 1.27 (95%CI 0.76-2.11), p=nr<br>• flucloxacillin: aOR 0.80 (95%CI 0.46-1.41), p=nr<br>• erythromycin: aOR 1.01 (95%CI 0.53-1.94), p=nr<br>• cefadroxil: aOR 0.65 (95%CI 0.28-1.53), p=nr<br>• tetracycline: aOR 1.75 (95%CI 0.71-4.31), p=nr |                                                                                                                                                                  |
| Inflammatory bowel disease      |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |
| Canova et al. <sup>30</sup>     | Multicentre retrospective case-control study (3b) | 70; 770<br>33; 353<br>37; 417       | < 1 y<br>No<br>Registry              | < 18 y  | ICD-9-CM codes                                                | Exposure to AB in first 12 m of life not associated with increased risk.<br><br>• aOR 1.07 (95%CI 0.64-1.80), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Age, sex, maternal age and education; parity, number of siblings, gestational age, birth weight, Apgar scores, season of birth, gastrointestinal infections      |
| Italy                           |                                                   |                                     |                                      |         |                                                               | Exposure to AB for ≥ 4 AB courses associated with increased risk.<br><br>• first 6 m: aOR 6.34 (95%CI 1.68-24.02), p=0.01<br>• first 12 m: aOR 2.91 (95%CI 1.31-6.45), p=0.01                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                  |
| 2020                            |                                                   |                                     |                                      |         |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                  |

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Table 1 (continued)

|                                |                                             |                                                |                                           |        |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                      |
|--------------------------------|---------------------------------------------|------------------------------------------------|-------------------------------------------|--------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Örtqvist et al. <sup>106</sup> | Multicentre prospective cohort study (2b)   | 51; 827,239<br>43; 539,809<br>8; 287,430       | < 1 y before diagnosis<br>Yes<br>Registry | < 6 y  | ICD-10 codes                                      | Exposure to AB in 12 m before diagnosis associated with increased risk.<br><br>• <b>OR 2.86 (95%CI 1.35-6.09), p&lt;0.01*</b><br>• aHR 1.11 (95%CI 0.57-2.15), p=nr<br><br>• 1 AB course: aHR 0.73 (95%CI 0.28-1.89), p=nr<br>• 2 AB courses: aHR 1.85 (95%CI 0.80-4.30), p=nr<br>• ≥ 3 AB courses: aHR 1.12 (95%CI 0.47-2.65), p=nr<br><br>• penicillin: aHR 1.25 (95%CI 0.70-2.26), p=nr                                                                                                                                                                                                                                                                                                                           | Parental country of birth, education and history of IBD; mode of delivery, gastroenteritis                           |
| Kronman et al. <sup>78</sup>   | Multicentre retrospective cohort study (2b) | 748; 1,072,426<br>436; 618,663<br>312; 453,763 | < 1 y<br>Yes<br>Registry                  | < 17 y | Read codes                                        | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aHR 5.51 (95%CI 1.66-18.28), p&lt;0.01</b><br><br>• 1-2 AB courses: <b>aHR 3.13 (95%CI 1.54-6.36), p&lt;0.01</b><br>• > 2 AB courses: <b>aHR 5.15 (95%CI 2.36-11.25), p&lt;0.01</b><br><br>• penicillins: <b>aHR 5.26 (95%CI 1.60-17.25), p&lt;0.01</b><br>• cephalosporins: <b>aHR 1.58 (95%CI 1.21-2.05), p&lt;0.01</b><br>• macrolides: aHR 1.21 (95%CI 0.96-1.51), p=0.10<br>• sulfonamides: aHR 1.31 (95%CI 0.98-1.74), p=0.07<br>• metronidazole: <b>aHR 337.78 (95%CI 37.42-3,048.96), p&lt;0.01</b><br>• fluoroquinolones: <b>aHR 3.70 (95%CI 2.25-6.08), p&lt;0.01</b><br>• tetracyclines: aHR 1.05 (95%CI 0.65-1.69), p=0.85 | Sex, chronic granulomatous disease, primary sclerosing cholangitis, socioeconomic deprivation, family history of IBD |
| Virta et al. <sup>148</sup>    | Multicentric case-control study (3b)        | 595; 2,975<br>359; 1,576<br>236; 1,399         | < 1 y<br>Yes<br>Registry                  | 1-16 y | ICD-10 plus endoscopy and histologic verification | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.45 (95%CI, 1.21-1.75), p&lt;0.01</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Additional chronic diseases                                                                                          |

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Table 1 (continued)

|                            |                                           |              |          |        |              |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------|-------------------------------------------|--------------|----------|--------|--------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |                                           |              |          |        |              | <p>Crohn's disease: 233; 1,165</p> <p>152; 613<br/>81; 552</p>     | <p>Exposure to AB in first y of life associated with increased risk of Crohn's disease.</p> <ul style="list-style-type: none"> <li>• <b>aOR 1.87 (95%CI 1.37-2.56), p=nr</b></li> <li>• 1 AB course: aOR 1.32 (95%CI 0.92-1.88), p=nr</li> <li>• 2 AB courses: <b>aOR 1.98 (95%CI 1.22-3.20), p=nr</b></li> <li>• ≥ 3 AB courses: aOR 1.42 (95%CI 0.87-2.33), p=nr</li> <li>• 3 cephalosporin courses: <b>aOR 2.82 (95%CI 1.65-4.81), p=nr</b></li> </ul> <p>Results according to antibiotic class nr</p> <p>Exposure to AB in first y of life not associated with increased risk of ulcerative colitis.</p> <ul style="list-style-type: none"> <li>• aOR 1.18 (95%CI, 0.92-1.52), p=nr</li> <li>• 1 AB course: aOR 0.98 (95%CI 0.72-1.34), p=nr</li> <li>• 2 AB courses: aOR 1.45 (95%CI 0.98-2.16), p=nr</li> <li>• ≥ 3 AB courses: aOR 1.26 (95%CI 0.87-1.82), p=nr</li> </ul> <p>Results according to antibiotic class nr</p> |
| Hviid et al. <sup>68</sup> | Multicentre prospective cohort study (2b) | 117; 577,627 | < 10 y   | < 10 y | ICD-10 codes | <p>Ulcerative colitis: 362; 1,810</p> <p>207; 963<br/>155; 847</p> | <p>Exposure to AB in first y of life associated with increased risk.</p> <ul style="list-style-type: none"> <li>• <b>aRR 1.84 (95% CI 1.08-3.15), p=nr</b></li> </ul> <p>Results according to antibiotic class nr</p> <p>Strongest association for AB &lt; 3 m before diagnosis and risk of Crohn's disease.</p> <ul style="list-style-type: none"> <li>• <b>aRR 4.43 (95% CI 1.88-10.44), p=nr</b></li> <li>• narrow-spectrum penicillins: <b>aRR 2.92 (95%CI 1.22-6.97), p=nr</b></li> <li>• broad-spectrum penicillins: <b>aRR 3.13 (95%CI 1.33-7.40), p=nr</b></li> <li>• macrolides: aRR 0.97 (95%CI 0.13-7.14), p=nr</li> </ul>                                                                                                                                                                                                                                                                                             |
| Denmark                    |                                           | 84; 489,946  | Yes      |        |              |                                                                    | Age, season                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2011                       |                                           | 33; 87,681   | Registry |        |              |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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Table 1 (continued)

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|--------------------------------|-------------------------------------------|--------------------------------------------------------|---------------------------------|----------------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Shaw et al. <sup>127</sup>     | Multicentre case-control study (3b)       | 36; 396<br>21; 160<br>15; 236                          | < 1 y<br>No<br>Registry         | < 12 y                                       | ICD-9-CM and ICD-10-CA codes | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 2.91 (95%CI 1.21-6.97), p=0.02</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Age, sex, living area                                                                                                                                                                |
| Canada                         |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| 2010                           |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| <b>Celiac disease</b>          |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| Aversa et al. <sup>172</sup>   | Multicentre prospective cohort study (2b) | 45; 14,572<br>40; 10,220<br>5; 4,352                   | < 2 y<br>Yes<br>Medical records | 6-11 y                                       | ICD-9 and ICD-10 codes       | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aHR 2.89 (95%CI 1.14-7.35), p=0.03</b><br><br>Girls<br>• penicillins: <b>HR 6.74 (95%CI 1.56-29.23), p=0.01</b><br>• cephalosporins: HR 0.49 (95%CI 0.16-1.50), p=0.21<br>• macrolides: HR 1.26 (95%CI 0.53-3.03), p=0.60<br>• sulfonamides: HR 0.57 (95%CI 0.07-4.28), p=0.58<br><br>Boys<br>• penicillins: HR 1.61 (95%CI 0.51-5.12), p=0.42<br>• cephalosporins: HR 1.53 (95%CI 0.59-3.95), p=0.38<br>• macrolides: HR 1.08 (95%CI 0.42-2.79), p=0.87<br>• sulfonamides: HR 1.42 (95%CI 0.32-6.34), p=0.65 | Sex, ethnicity, maternal age and education; antibiotic use during pregnancy, birth weight, delivery mode, maternal smoking                                                           |
| USA                            |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| 2021                           |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| Dydenborg et al. <sup>44</sup> | Multicentre prospective cohort study (2b) | 3,346; 1,706,113<br>1,012; 550,746<br>2,334; 1,155,367 | < 1 y<br>No<br>Registry         | 11.6 y (mean Denmark)<br>5.4 y (mean Norway) | ICD-10 codes                 | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>aOR 1.26 (95%CI 1.16-1.36), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Maternal age, BMI, country of birth, autoimmune diseases and education; parity, smoking during pregnancy, gestational age, weight for gestational age, birth weight, season of birth |
| Denmark                        |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| Norway                         |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |
| 2019                           |                                           |                                                        |                                 |                                              |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                      |

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Table 1 (continued)

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|---------------------------------------------|-------------------------------------------|------------------------------------------------|-------------------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kemppainen et al. <sup>73</sup>             | Multicentre prospective cohort study (2b) | 783; 6,558<br>nr; nr<br>nr; nr                 | 3 m–4 y<br>Yes<br>Medical records   | 2–4 y  | Islet or tissue transglutaminase autoantibodies                                                                                 | Exposure to AB in first 4 y of life not associated with increased risk.<br>• aHR 1.00 (95%CI 0.98–1.02), p=nr<br>• penicillin: aHR 1.03 (95%CI 0.92–1.09), p=nr<br>• amoxicillin: aHR 0.99 (95%CI 0.96–1.02), p=nr<br>• cephalosporins: aHR 1.01 (95%CI 0.94–1.09), p=nr<br>• macrolides: aHR 0.99 (95%CI 0.91–1.08), p=nr                                                                                                                                                                                                                                                               | Sex, HLA genotype, family history of type 1 diabetes or celiac disease, country, antibiotic use during pregnancy, season of birth, delivery mode, probiotic use, breastfeeding |
| USA                                         |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| 2017                                        |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| Myleus et al. <sup>199</sup>                | Multicentric case-control study (3b)      | 373; 954<br>97; 231<br>276; 723                | < 6 m<br>No<br>Parent questionnaire | < 2 y  | Small intestinal biopsy or diagnostic criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition | Exposure to AB in first 6 m of life not associated with increased risk.<br>• OR 1.20 (95%CI 0.87–1.60), p=0.27                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                |
| Sweden                                      |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| 2012                                        |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| <b>Increased weight gain and overweight</b> |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| Aversa et al. <sup>172</sup>                | Multicentre prospective cohort study (2b) | 4,856; 14,572<br>3,637; 10,220<br>1,219; 4,352 | < 2 y<br>Yes<br>Medical records     | 6–11 y | BMI ≥ 85 <sup>th</sup> percentile                                                                                               | Exposure to AB in first 2 y of life associated with increased risk of overweight.<br>• aHR 1.22 (95%CI 1.14–1.30), p<0.01<br><br>Girls<br>• penicillins: HR 1.11 (95%CI 1.02–1.22), p=0.02<br>• cephalosporins: HR 1.10 (95%CI 1.00–1.22), p=0.06<br>• macrolides: HR 1.16 (95%CI 1.05–1.28), p<0.01<br>• sulfonamides: HR 1.11 (95%CI 0.94–1.31), p=0.23<br><br>Boys<br>• penicillins: HR 1.13 (95%CI 1.03–1.24), p<0.01<br>• cephalosporins: HR 1.11 (95%CI 1.01–1.22), p=0.03<br>• macrolides: HR 1.11 (95%CI 1.01–1.21), p=0.03<br>• sulfonamides: HR 1.20 (95%CI 1.01–1.41), p=0.03 | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode                                                              |
| USA                                         |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| 2021                                        |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| Chelimo et al. <sup>33</sup>                | Multicentre prospective cohort study (2b) | 1,051; 5,128<br>1,010; 4,886<br>41; 242        | < 2 y<br>Yes<br>Registry            | 4.5 y  | BMI                                                                                                                             | Exposure to AB in first 2 y of life not associated with increased risk of d overweight.<br>• OR 1.22 (95%CI 0.87–1.71), p=0.25*<br>• < 1 y of age: aOR: 1.21 (95%CI 0.81–1.81), p=0.36<br>• > 1 y of age: aOR: 1.18 (95%CI 0.79–1.78), p=0.42                                                                                                                                                                                                                                                                                                                                            | Sex, ethnicity, maternal age, parity, pre-pregnancy weight, socioeconomic status, school grade, alcohol and antibiotic use during pregnancy, birth weight,                     |
| New Zealand                                 |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |
| 2020                                        |                                           |                                                |                                     |        |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                |

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Table 1 (continued)

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|-----------------------------------|---------------------------------------------|---------------------------------|----------------------|-------|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |                                             |                                 |                      |       |                                                      | <ul style="list-style-type: none"> <li>• 1-3 AB courses: aOR 0.95 (95%CI 0.63-1.46), p=0.83</li> <li>• 4-6 AB courses: aOR 1.36 (95%CI 0.90-2.07), p=0.15</li> <li>• 7-9 AB courses: aOR 1.38 (95%CI 0.90-2.13), p=0.14</li> <li>• &gt; 9 AB courses: aOR 1.23 (95%CI 0.81-1.86), p=0.34</li> <li>• penicillins: aOR 0.95 (95%CI 0.67-1.34), p=0.77</li> <li>• macrolides: aOR 1.16 (95%CI 0.94-1.43), p=0.17</li> <li>• cephalosporins: aOR 1.19 (95%CI 0.97-1.47), p=0.10</li> <li>• trimethoprim/sulfamethoxazole: aOR 1.05 (95%CI 0.85-1.30), p=0.64</li> </ul> | season of birth, delivery mode, birth order, anti-reflux medication use, breastfeeding, diet, sleep duration, time spent watching television, DVDs, or videos |
| Dawson-Hahn et al. <sup>200</sup> | Multicentre retrospective cohort study (2b) | 65; 586<br>39*; 355<br>25*; 231 | < 1 y<br>No          | 6 y   | BMI z-score                                          | Exposure to AB in first y of life associated with increased risk of overweight.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                               |
| USA                               |                                             |                                 | Parent questionnaire |       |                                                      | <ul style="list-style-type: none"> <li>• <b>OR 1.03 (95%CI 1.01-1.05), p=nr</b> (from<sup>240</sup>)</li> <li>• BMI z-score: +0.17 (95%CI 0.09-0.25), p=nr</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                               |
| 2019                              |                                             |                                 |                      |       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                               |
| Kamphorst et al. <sup>71</sup>    | Multicentre prospective cohort study (2b)   | nr, 436<br>nr; 151<br>nr 285    | < 1 y<br>Yes         | 1 y   | Weight                                               | Exposure to AB in first y of life associated with increased risk of increased weight gain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                               |
| Netherlands                       |                                             |                                 | Parent questionnaire |       |                                                      | <ul style="list-style-type: none"> <li>• <b>weight gain of 76 g after every AB course, p=0.03</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                               |
| 2019                              |                                             |                                 |                      |       |                                                      | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                               |
| Sejerssen et al. <sup>170</sup>   | Multicentre prospective cohort study (2b)   | nr; 661<br>nr; 306<br>nr; 355   | < 1 y<br>Yes         | 6 y   | BMI z-score                                          | Exposure to AB in first y of life not associated with increased risk of overweight.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |
| Denmark                           |                                             |                                 | Parent questionnaire |       |                                                      | <ul style="list-style-type: none"> <li>• BMI z-score: -0.06 (95%CI -0.17-0.06), p=0.33</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                               |
| 2019                              |                                             | nr; 467<br>nr; 216<br>nr; 251   |                      | 3.5 y | Fat percentage with dual-energy X-ray absorptiometry | Exposure to AB in first y of life not associated with increased risk of increased fat percentage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                               |
|                                   |                                             |                                 |                      |       |                                                      | <ul style="list-style-type: none"> <li>• difference in fat percentage: 0.85% (95%CI -1.84-3.55), p=0.53</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                               |
|                                   |                                             |                                 |                      |       |                                                      | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                               |

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Table 1 (continued)

|                                   |                                             |                                                       |                                     |        |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                    |
|-----------------------------------|---------------------------------------------|-------------------------------------------------------|-------------------------------------|--------|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
|                                   |                                             | nr; 500                                               |                                     | 6 y    |                                                   | Exposure to AB in first y of life not associated with increased risk of increased fat percentage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                    |
|                                   |                                             | nr; 221<br>nr; 279                                    |                                     |        |                                                   | • difference in fat percentage: 0.60% (95%CI -0.21-1.41), p=0.15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                    |
|                                   |                                             |                                                       |                                     |        |                                                   | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                    |
| Smith-Brown et al. <sup>131</sup> | Single-centre cross-sectional study (3b)    | 11; 50<br>nr, 11<br>nr; 39                            | < 1 m<br>No<br>Parent questionnaire | 6-24 m | BMI z-score plus bioelectrical impedance analysis | Exposure to AB in first m of life associated with increased risk of increased BMI z-score and body fat.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                    |
| Australia                         |                                             |                                                       |                                     |        |                                                   | • BMI z-score: <b>+1.17 (p&lt;0.01) (mean increase 1.1 vs mean of 0.025)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                    |
| 2019                              |                                             |                                                       |                                     |        |                                                   | • bioelectrical impedance analysis: <b>+3.5% (p&lt;0.01)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                    |
| Block et al. <sup>27</sup>        | Multicentre retrospective cohort study (2b) | 45,295; 310,947<br>27,225; 180,739<br>18,070; 130,208 | < 2 y<br>Yes<br>Registry            | 5 y    | BMI z-score (≥ 85 <sup>th</sup> percentile)       | Exposure to AB in first 2 y of life associated with increased risk of overweight.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Age, sex, prematurity, ethnicity, asthma, corticosteroid use, number of infections |
| USA                               |                                             |                                                       |                                     |        |                                                   | • <b>aOR 1.05 (95%CI 1.03-1.07), p=nr</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                    |
| 2018                              |                                             |                                                       |                                     |        |                                                   | Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                    |
| Poulsen et al. <sup>201</sup>     | Multicentre retrospective cohort study (2b) | nr; 8,793<br>nr; 7,224<br>nr; 1,569                   | < 3 y<br>Yes<br>Medical records     | 3 y    | BMI z-score                                       | Exposure to AB in first 3 y of life associated with increased risk of increased BMI.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                    |
| USA                               |                                             |                                                       |                                     |        |                                                   | • <b>OR 1.17 (95%CI 1.06-1.29), p=nr</b> (from <sup>240</sup> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                    |
| 2017                              |                                             |                                                       |                                     |        |                                                   | • 1 AB course: BMI z-score + 0.04 (95%CI -0.04-0.11), p=0.39<br>• 2-3 AB courses: BMI z-score +0.02 (95%CI -0.05-0.09), p=0.58<br>• 4-5 AB courses: BMI z-score +0.09 (95%CI 0.01-0.17), p=0.03<br>• 6-8 AB courses: BMI z-score +0.11 (95%CI 0.03-0.20), p<0.01<br>• ≥ 9 AB courses: BMI z-score +0.175 (95%CI 0.09-0.26), p<0.01<br><br>• ≥ 4 courses of penicillins: BMI z-score +0.08 (95%CI 0.01-0.15), p=0.08<br>• ≥ 3 courses of cephalosporins: BMI z-score +0.11 (95%CI 0.03-0.29), p=0.02<br>• ≥ 2 courses of macrolides: BMI z-score +0.10 (95%CI 0.01-0.19), p=0.04 |                                                                                    |

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Table 1 (continued)

|                                |                                                 |                                   |                                      |       |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                 |
|--------------------------------|-------------------------------------------------|-----------------------------------|--------------------------------------|-------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rogawski et al. <sup>202</sup> | Multicentre prospective cohort study (2b)       | nr; 1,954<br>nr; 1,284<br>nr; 670 | < 6 m<br>Yes<br>Parent questionnaire | 2 y   | Weight-for-age (WAZ) z-score | Exposure to AB in first 6 m of life associated with increased risk of increased weight gain.<br><br>• <b>OR 1.23 (95%CI 1.04-1.45), p=nr</b> (from <sup>240</sup> )<br>• WAZ difference: +0.03 (95%CI 0.00-0.05), p=ns<br><br>• penicillins, WAZ difference: +0.09 (95%CI -0.02-0.19), p=ns<br>• cephalosporins, WAZ difference: +0.03 (95%CI -0.09-0.16), p=ns<br>• metronidazole, WAZ difference: +0.14 (95%CI -0.01-0.29), p=ns<br>• macrolides, WAZ difference: +0.09 (95%CI -0.03-0.21), p=ns<br>• sulfonamides, WAZ difference: +0.03 (95%CI -0.09-0.15), p=ns<br>• fluoroquinolones, WAZ difference: +0.08 (95%CI -0.14-0.30), p=ns |                                                                                                                                                                                                                                                                 |
| 8 countries<br>2017            |                                                 |                                   |                                      |       |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                 |
| Korpela et al. <sup>75</sup>   | Multicentre prospective case-control study (3b) | 28; 148<br>nr; 32<br>nr; 116      | < 2 y<br>Yes<br>Registry             | 2-7 y | BMI z-score                  | Exposure to AB in first 2 y of life not associated with increased risk of overweight.<br><br>Results according to antibiotic class nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                 |
| Finland<br>2016                |                                                 |                                   |                                      |       |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                 |
| Mbakwa et al. <sup>69</sup>    | Multicentre prospective cohort study (2b)       | 135; 979<br>90*; 613<br>45*; 366  | < 1 y<br>Yes<br>Parent questionnaire | 1 y   | BMI z-score                  | Exposure to AB in first y of life not associated with increased risk of overweight.<br><br>• OR 1.23 (95%CI 0.84-1.80), p=0.30*<br><br>• 1 AB course: aOR 1.09 (95%CI 0.76-1.57), p=0.64<br>• 2-3 AB courses: aOR 1.13 (95%CI 0.79-1.63), p=0.51<br>• ≥ 4 AB courses: aOR 1.03 (95%CI 0.66-1.60), p=0.89<br><br>• narrow-spectrum penicillins: aOR 0.95 (95%CI 0.68-1.34), p=0.79<br>• broad-spectrum penicillins: aOR 1.00 (95%CI 0.57-1.76), p=0.99<br>• macrolides: aOR 1.29 (95%CI 0.89-1.86), p=0.18                                                                                                                                  | Age, sex, maternal education, weight and pregnancy weight gain, household size, gestational diabetes, gestational hypertension, smoking during pregnancy, gestational age, birth weight, delivery mode, breastfeeding duration, diet, child's physical activity |
| Netherlands<br>2016            |                                                 |                                   |                                      |       |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                 |

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Table 1 (continued)

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|--------------------------------|---------------------------------------------|-------------------------------------------------------|------------------------------------------|--------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Schwartz et al. <sup>124</sup> | Multicentre prospective cohort study (2b)   | 79,752; 142,824<br>54,802*; 97,120<br>24,950*; 45,704 | < 1 y before each BMI<br>Yes<br>Registry | 3–18 y | BMI         | Exposure to AB 1 y before BMI measure associated with increased risk of weight gain.<br><br>• <b>OR 1.08 (95%CI 1.06–1.10), p=nr</b> (from <sup>240</sup> )<br><br>Strongest association with macrolides: BMI +0.43<br><br>Results according to antibiotic class nr                                                                                                                         |
| Gerber et al. <sup>54</sup>    | Multicentre retrospective cohort study (2b) | nr; 38,522<br>nr; 5,287<br>nr; 33,235                 | < 6 m<br>Yes<br>Registry                 | < 8 y  | Weight      | Exposure to AB in first 6 m of life not associated with increased weight gain.<br><br>• <b>OR* 1.02 (95%CI 0.86–1.20), p=nr</b> (from <sup>240</sup> )<br>• weight gain difference: +0.07% (95%CI -0.10–1.50), p=0.07<br><br>• narrow-spectrum: +0.40% (95%CI -0.60–1.30), p=0.45<br>• broad-spectrum: -0.30% (95%CI -2.10–1.50), p=0.72<br>• macrolides: +2.20% (95%CI -1.20–5.70), p=0.20 |
|                                |                                             |                                                       | < 2 y<br>Yes<br>Registry                 |        |             | Exposure to AB in first 2 y of life associated with increased risk of weight gain.<br><br>• <b>weight gain difference: +2.10% (95%CI 0.80–3.30), p&lt;0.01</b><br><br>• narrow-spectrum: +1.90% (95%CI 0.50–3.20), p<0.01<br>• broad-spectrum: +2.20% (95%CI 0.70–3.80), p<0.01<br>• macrolides: +2.40% (95%CI 0.60–4.20), p<0.01                                                           |
| Saari et al. <sup>121</sup>    | Multicentre prospective cohort study (2b)   | 2,094; 12,062<br>1,673; 9,236<br>421; 2826            | < 2 y<br>Yes<br>Registry                 | 2–3 y  | BMI z-score | Exposure to AB in first 2 y of life associated with increased risk of overweight.<br><br>• <b>OR 1.26 (95%CI 1.12–1.42), p&lt;0.01*</b>                                                                                                                                                                                                                                                     |
| Finland                        |                                             | Boys: 1,376;<br>6,114                                 |                                          |        |             | Exposure to AB in first 2 y of life associated with increased risk of overweight.<br><br>Birth weight, birth length, delivery mode,                                                                                                                                                                                                                                                         |

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Table 1 (continued)

|                           |                                                             |                                                   |                 |      |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                  |
|---------------------------|-------------------------------------------------------------|---------------------------------------------------|-----------------|------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                             | 1,121; 4,828<br>255; 1,286                        |                 |      |                                     | <ul style="list-style-type: none"> <li>• <b>OR 1.26 (95%CI 1.04-1.49), p&lt;0.01</b></li> <li>• 1 AB course: aOR 1.16 (95% CI, 0.92-1.48), p=nr</li> <li>• 2-3 AB courses: <b>aOR 1.28 (95%CI 1.04-1.59), p&lt;0.05</b></li> <li>• ≥ 4 AB courses: <b>aOR 1.27 (95%CI 1.04-1.55), p&lt;0.05</b></li> <li>Strongest effects in boys, exposures before &lt; 6 m of life</li> <li>• &lt; 6 m: <b>aOR 1.34 (95%CI 1.06-1.66), p&lt;0.05</b></li> <li>• 1 penicillin course: aOR 1.13 (95%CI 0.90-1.41), p=ns</li> <li>• 1 cephalosporin course: <b>aOR 1.39 (95%CI 1.10-1.76), p&lt;0.05</b></li> <li>• 1 macrolide course: aOR 1.20 (95%CI 0.96-1.49), p=ns</li> <li>• ≥ 2 macrolide courses: <b>aOR 1.47 (95%CI 1.16-1.86), p&lt;0.05</b></li> </ul> | smoking during pregnancy, parental relationship                                                                                                  |
|                           |                                                             | Girls: 718; 5,948<br><br>552; 4,408<br>166; 1,540 |                 |      |                                     | <p>Exposure to AB in first 2 y of life not associated with increased risk of overweight.</p> <ul style="list-style-type: none"> <li>• 1 AB course: aOR 1.03 (95% CI, 0.81-1.32), p=nr</li> <li>• 2-3 AB courses: aOR 1.14 (95%CI 0.91-1.42), p=nr</li> <li>• ≥ 4 AB courses: aOR 1.19 (95%CI 0.96-1.48), p=nr</li> <li>• 1 penicillin course: aOR 1.11 (95%CI 0.89-1.40), p=ns</li> <li>• 1 cephalosporin course: aOR 1.05 (95%CI 0.80-1.38), p=ns</li> <li>• 1 macrolide course: aOR 0.94 (95%CI 0.94-1.50), p=ns</li> </ul>                                                                                                                                                                                                                      | Birth weight, delivery mode, smoking during pregnancy                                                                                            |
| Azad et al. <sup>23</sup> | Single-centre, retrospective nested case-control study (3b) | 181; 616                                          | < 1 y           | 9 y  | BMI (> 85 <sup>th</sup> percentile) | <p>Exposure to AB in first y of life associated with increased risk of overweight.</p> <ul style="list-style-type: none"> <li>• <b>aOR 1.74 (95%CI 1.04-2.94), p=nr</b></li> <li>• girls: aOR 1.20 (95%CI 0.53-2.70), p=nr</li> <li>• <b>boys: aOR 2.19 (95%CI 1.06-4.54), p=nr</b></li> </ul> <p>Results according to antibiotic class nr</p>                                                                                                                                                                                                                                                                                                                                                                                                     | Maternal asthma and overweight; number of siblings, income, birth weight, asthma, breastfeeding, diet, child's physical activity, smoke exposure |
| Canada                    |                                                             | 144; 438<br>37; 178                               | Yes             |      |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                  |
| 2014                      |                                                             |                                                   | Medical records |      |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                  |
|                           |                                                             | 121; 431                                          |                 | 12 y |                                     | <p>Exposure to AB in first y of life associated with increased risk of overweight.</p> <ul style="list-style-type: none"> <li>• <b>aOR 2.56 (95%CI 1.36-4.79), p=nr</b></li> <li>• girls: aOR 1.13 (95%CI 0.46-2.81), p=nr</li> <li>• <b>boys: aOR 5.35 (95%CI 1.94-14.72), p=nr</b></li> </ul> <p>Results according to antibiotic class nr</p>                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                  |
|                           |                                                             | 97; 299<br>24; 132                                |                 |      |                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                  |

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Table 1 (continued)

|                                               |                                             |                              |                      |      |             |                                                                                          |                                                                                                                                                                                                                          |
|-----------------------------------------------|---------------------------------------------|------------------------------|----------------------|------|-------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Trasande et al. <sup>143</sup><br>USA<br>2013 | Single-centre prospective cohort study (2b) | 1,700; 8,881                 | < 6 m                | 38 m | BMI z-score | Exposure to AB in first 6 m of life associated with increased risk of overweight.        | Ethnicity, parity, parental education, BMI and socioeconomic status; smoking during pregnancy, birth weight, breastfeeding, diet, timing of solid food introduction, sleep duration, time watching television and in car |
|                                               |                                             | 1,322*; 6,598<br>378*; 2,283 | No                   |      |             | • aOR 1.22 (95%CI nr), p<0.05                                                            |                                                                                                                                                                                                                          |
|                                               |                                             | 1,700; 8,881                 | < 6-14 m             |      |             | Exposure to AB in at 6 to 14 m of life not associated with increased risk of overweight. |                                                                                                                                                                                                                          |
|                                               |                                             | 1,274*; 6,598<br>426*; 2,283 | No                   |      |             | • aOR 1.04 (95%CI nr), p=0.63                                                            |                                                                                                                                                                                                                          |
|                                               |                                             | 1,700; 8,881                 | < 15-23 m            |      |             | Exposure to AB at 15 to 23 m of life not associated with increased risk of overweight.   |                                                                                                                                                                                                                          |
|                                               |                                             | 1,317*; 6,598<br>383*; 2,283 | No                   |      |             | • aOR 1.24 (95%CI nr), p=0.09                                                            |                                                                                                                                                                                                                          |
|                                               |                                             | 1,962; 8,881                 | < 6 m                | 7 y  |             | Exposure to AB in first 6 m of life not associated with increased risk of overweight.    |                                                                                                                                                                                                                          |
|                                               |                                             | 1,467*; 6,598<br>495*; 2,283 | No                   |      |             | • aOR 1.03 (95%CI nr), p=0.78                                                            |                                                                                                                                                                                                                          |
|                                               |                                             | 1,962; 8,881                 | < 6-14 m             |      |             | Exposure to AB in at 6 to 14 m of life not associated with increased risk of overweight. |                                                                                                                                                                                                                          |
|                                               |                                             | 1,442*; 6,598<br>520*; 2,283 | No                   |      |             | • aOR 0.95 (95%CI nr), p=0.58                                                            |                                                                                                                                                                                                                          |
|                                               |                                             | 1,962; 8,881                 | < 15-23 m            |      |             | Exposure to AB at 15 to 23 m of life not associated with increased risk of overweight.   |                                                                                                                                                                                                                          |
|                                               |                                             | 1,464*; 6,598<br>498*; 2,283 | No                   |      |             | • aOR 1.02 (95%CI nr), p=0.87                                                            |                                                                                                                                                                                                                          |
|                                               |                                             |                              | Parent questionnaire |      |             |                                                                                          |                                                                                                                                                                                                                          |

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Table 1 (continued)

|                              |                                           |                |                      |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
|------------------------------|-------------------------------------------|----------------|----------------------|--------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ajslev et al. <sup>14</sup>  | Multicentre prospective cohort study (2b) | 2,333; 22,368  | < 6 m                | 7 y    | BMI                               | Exposure to AB in first 6 m of life not associated with increased risk of overweight.<br>• aOR 1.04 (95%CI 0.79-1.37), p<0.78                                                                                                                                                                                                                                                                                                                                                | Sex, maternal age, BMI, and smoking; weight gain during pregnancy, parity, paternal BMI, socioeconomic status, birth weight, delivery mode, breastfeeding,                                                                                                                                                               |
| Denmark                      |                                           | 197*; 1,628    | No                   |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
| 2011                         |                                           | 2,136*; 20,740 | Parent questionnaire |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
| <b>Obesity</b>               |                                           |                |                      |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
| Aversa et al. <sup>172</sup> | Multicentre prospective cohort study (2b) | 2,567; 14,572  | < 2 y                | 6–11 y | BMI ≥ 95 <sup>th</sup> percentile | Exposure to AB in first 2 y of life associated with increased risk.<br>• aHR 1.20 (95%CI 1.10-1.32), p<0.01                                                                                                                                                                                                                                                                                                                                                                  | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode                                                                                                                                                                                                        |
| USA                          |                                           | 1,932; 10,220  | Yes                  |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
| 2021                         |                                           | 635; 4,352     | Medical records      |        |                                   | Girls<br>• penicillins: HR 1.05 (95%CI 0.92-1.19), p=0.50<br>• cephalosporins: <b>HR 1.17 (95%CI 1.02-1.35), p=0.03</b><br>• macrolides: HR 1.08 (95%CI 0.94-1.24), p=0.26<br>• sulfonamides: HR 1.15 (95%CI 0.92-1.45), p=0.22<br><br>Boys<br>• penicillins: <b>HR 1.15 (95%CI 1.02-1.31), p=0.02</b><br>• cephalosporins: HR 1.08 (95%CI 0.96-1.22), p=0.22<br>• macrolides: <b>HR 1.15 (95%CI 1.02-1.29), p=0.02</b><br>• sulfonamides: HR 1.11 (95%CI 0.89-1.39), p=0.34 |                                                                                                                                                                                                                                                                                                                          |
| Chelimo et al. <sup>33</sup> | Multicentre prospective cohort study (2b) | 437; 5,128     | < 2 y                | 4.5 y  | BMI                               | Exposure to AB in first 2 y of life not associated with increased risk, except trimethoprim/sulfamethoxazole<br>• penicillins: aOR 0.95 (95%CI 0.51-1.78), p=0.87<br>• cephalosporins: aOR 1.11 (95%CI 0.97-1.47), p=0.52<br>• macrolides: aOR 1.24 (95%CI 0.94-1.43), p=0.19<br>• trimethoprim/sulfamethoxazole: <b>aOR 1.60 (95%CI 1.18-2.17), p&lt;0.01</b>                                                                                                               | Sex, ethnicity, maternal age, parity, pre-pregnancy weight, socioeconomic status, school grade, alcohol and antibiotic use during pregnancy, birth weight, season of birth, delivery mode, birth order, anti-reflux medication use, breastfeeding, diet, sleep duration, time spent watching television, DVDs, or videos |
| New Zealand                  |                                           | 428; 4,886     | Yes                  |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
| 2020                         |                                           | 9; 242         | Registry             |        |                                   | Exposure to AB in first y of life not associated with increased risk.<br>• aOR 1.90 (95%CI 0.86-4.23), p=0.11                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                          |
|                              |                                           |                | < 1 y                |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
|                              |                                           |                | Yes                  |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |
|                              |                                           |                | Registry             |        |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                          |

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Table 1 (continued)

|                             |                                                       |                                                      |                        |     |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------|-------------------------------------------------------|------------------------------------------------------|------------------------|-----|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |                                                       |                                                      | 1-2 y                  |     |                                   | Exposure to AB in second y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                   |
|                             |                                                       |                                                      | Yes                    |     |                                   | • aOR 1.69 (95%CI 0.75-3.82), p=0.20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                   |
|                             |                                                       |                                                      | Registry               |     |                                   | More than 9 AB courses in first 2 y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                   |
|                             |                                                       |                                                      |                        |     |                                   | • aOR 2.41 (95%CI 1.07-5.41), p=0.03                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                   |
| Leong et al. <sup>81</sup>  | Single-centre retrospective cross-sectional study (4) | 23,921; 151,359<br>nr; 124,506<br>nr; 26,853         | < 2 y                  | 4 y | BMI                               | Exposure to AB in first 2 y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Sex, ethnicity, maternal age, parity and diabetes, living area, socioeconomic status, hyperemesis gravidarum, prolonged hospitalisation during pregnancy, gestational age, birth weight, season of birth, delivery mode, prolonged hospitalisation during the first 2 y of life, number of days overseas during first 2 y of life |
| New Zealand 2020            |                                                       |                                                      | No<br>Medical records  |     |                                   | • aOR 1.04 (95%CI 1.04-1.05), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                   |
| Stark et al. <sup>133</sup> | Multicentre retrospective cohort study (2b)           | 46,993; 333,353<br>36,899; 241,502<br>10,094; 91,851 | < 2 y                  | 3 y | BMI ≥ 95 <sup>th</sup> percentile | Exposure to AB in first 2 y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Sex, delivery mode, medication use                                                                                                                                                                                                                                                                                                |
| USA 2019                    |                                                       |                                                      | Yes<br>Medical records |     |                                   | • HR 1.26 (95%CI 1.23-1.28), p=nr<br><br>• 1 AB course: aHR 1.12 (95%CI 1.09-1.15), p=nr<br>• 2 AB courses: aHR 1.23 (95%CI 1.20-1.26), p=nr<br>• 3 AB courses: aHR 1.33 (95%CI 1.29-1.37), p=nr<br>• ≥ 4 AB courses: aHR 1.42 (95%CI 1.37-1.46), p=nr<br><br>• penicillins: aHR 1.11 (95%CI 1.09-1.13), p=nr<br>• cephalosporins: aHR 1.03 (95%CI 1.01-1.06), p=nr<br>• macrolides: aHR 1.12 (95%CI 1.10-1.15), p=nr<br>• sulfonamides boys: aHR 1.05 (95%CI 1.01-1.10), p=nr<br>• sulfonamides girls: aHR 1.19 (95%CI 1.14-1.15), p=nr |                                                                                                                                                                                                                                                                                                                                   |

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Table 1 (continued)

|                                               |                                              |                                                           |                                             |         |             |                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                              |
|-----------------------------------------------|----------------------------------------------|-----------------------------------------------------------|---------------------------------------------|---------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kelly et al. <sup>72</sup><br>Ireland<br>2019 | Multicentre cross-sectional study (3b)       | 1,034; 8,186                                              | 2-3 y                                       | 3 y     | BMI         | Exposure to AB between second and third y of life not associated with increased risk.<br><br>• OR 1.07 (95%CI 0.75-1.52), p=0.26<br><br>• 1 AB course: OR 0.88 (95%CI 0.61-.127), p=nr<br>• 2 AB courses: OR 0.95 (95%CI 0.66-1.38), p=nr<br>• 3 AB courses: OR 1.16 (95%CI 0.80-1.69), p=nr<br>• ≥ 4 AB courses: <b>OR 1.60 (95%CI 1.11-2.31), p=0.04</b> |                                                                                                                                                              |
|                                               |                                              | 470; 8,186<br><br>279*; 4,594<br>191*; 3,592              | 4-5 y<br><br>No<br><br>Parent questionnaire | 5 y     |             | Exposure to AB between fourth and fifth y of life not associated with increased risk.<br><br>• 1 AB course: OR 1.15 (95%CI 0.80-1.64), p=0.09<br>• 2 AB courses: OR 1.04 (95%CI 0.65-1.67), p=0.20<br>• 3 AB courses: OR 1.16 (95%CI 0.63-2.16), p=0.59<br>• ≥ 4 AB courses: OR 1.37 (95%CI 0.74-2.53), p=0.37                                             |                                                                                                                                                              |
| Block et al. <sup>27</sup><br>USA<br>2018     | Multicentre retrospective cohort study (2b)  | 40,797; 310,947<br><br>24,162; 180,739<br>16,635; 130,208 | < 2 y<br><br>Yes<br><br>Registry            | 5 y     | BMI z-score | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aOR 1.05 (95%CI 1.03-1.07), p=nr</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                       | Age, sex, prematurity, ethnicity, asthma, corticosteroid use, number of infections                                                                           |
| Edmonson et al. <sup>45</sup><br>USA<br>2017  | Multicentre randomised controlled trial (1b) | 74; 607<br><br>29; 302<br>45; 305                         | 2 m-6 y<br><br>Yes<br><br>Randomly assigned | 2 m-6 y | BMI z-score | Exposure to AB in first 6 y of life not associated with increased risk.<br><br>• aOR 0.65 (95%CI 0.33-1.28), p=0.22<br><br>Results according to antibiotic class nr                                                                                                                                                                                        | Age, sex, ethnicity, parental education, health insurance, vesicoureteral reflux, hydronephrosis, scarring or pyelonephritis on baseline scan, breastfeeding |
| Li et al. <sup>83</sup><br>USA<br>2017        | Multicentre prospective cohort study (2b)    | nr; 216,306<br><br>nr; 138,417<br>nr; 77,889              | < 1 y<br><br>No<br><br>Registry             | 1-18 y  | BMI z-score | Exposure to AB in first y of life not associated with increased risk.<br><br>• aOR 1.01 (95% CI, 0.98-1.04), p=nr                                                                                                                                                                                                                                          | Ethnicity, maternal age, pre-pregnancy BMI, antibiotic use and infection during pregnancy, prematurity, birth weight, infection type and severity            |

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Table 1 (continued)

|                                |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |
|--------------------------------|---------------------------------------------|---------------------------------------------------|-------------------------------------|-------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Ville et al. <sup>147</sup>    | Single-centre prospective cohort study (2b) | 10; 97<br>5; 16<br>5; 81                          | < 6 m<br>No<br>Parent questionnaire | 2 y   | BMI         | Exposure to AB in first 6 m of life associated with increased risk.<br><br>• <b>aOR 6.15 (95%CI 1.03-36.70), p&lt;0.05</b>                                                                                                                                                                                                                                                                                                            | Sex, maternal BMI, weight for length z-score at birth, breastfeeding                                            |
| USA<br>2017                    |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |
| Scott et al. <sup>125</sup>    | Multicentre retrospective cohort study (2b) | 1,306; 21,714<br>951; 14,870<br>355; 6,844        | < 2 y<br>Yes<br>Medical records     | 4 y   | BMI z-score | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aOR 1.24 (95%CI 1.09-1.41), p=nr</b><br><br>Results according to antibiotic class nr                                                                                                                                                                                                                                                                  | Age, country, maternal and sibling obesity, maternal diabetes, urban environment, Townsend score, delivery mode |
| USA<br>2016                    |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |
| Bailey et al. <sup>25</sup>    | Single-centre prospective cohort study (2b) | 9,822; 65,480<br>6,967*; 45,181<br>2,855*; 20,299 | < 2 y<br>No<br>Medical records      | 2-5 y | BMI         | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>OR 1.11 (95%CI 1.03-1.19), p=nr (from<sup>240</sup>)</b><br>• 1 AB course: RR 1.03 (95% CI, 0.97-1.09), p=0.31<br>• 2 AB courses: RR 1.04 (95%CI 0.96-1.13), p=0.36<br>• 3 AB courses: RR 1.04 (95%CI 0.95-1.14), p=0.37<br>• ≥ 4 AB courses: <b>RR 1.11 (95%CI 1.02-1.21), p=0.02</b><br><br>• < 6 m of life: <b>RR 1.11 (95%CI 1.03-1.19), p=nr</b> |                                                                                                                 |
| USA<br>2014                    |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |
| Murphy et al. <sup>99</sup>    | Multicentre cross-sectional study (3b)      | nr; 74,946<br>nr; nr<br>nr; nr                    | < 1 y<br>No<br>Parent questionnaire | 5-8 y | BMI z-score | Exposure to AB in first y of life associated with increased risk.<br><br>• <b>OR 1.02 (95%CI 1.00-1.04), p=nr (from<sup>240</sup>)</b><br><br>• boys: +0.107 SD units, p<0.01<br>• girls: +0.008 SD units, p=0.75                                                                                                                                                                                                                     |                                                                                                                 |
| 18 countries<br>2014           |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |
| Trasande et al. <sup>143</sup> | Single-centre prospective cohort study (2b) | 793; 8,881<br>622*; 6,598<br>171*; 2,283          | < 6 m<br>No<br>Parent questionnaire | 38 m  | BMI z-score | Exposure to AB in first 6 m of life not associated with increased risk.<br><br>• aOR 1.23 (95%CI nr), p=0.10                                                                                                                                                                                                                                                                                                                          | Ethnicity, parity, parental education, BMI, and socioeconomic status; smoking during pregnancy, birth weight,   |
| USA                            |                                             |                                                   |                                     |       |             |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                 |

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Table 1 (continued)

|                             |                                           |                            |                                |     |                                     |                                                                                                                                               |                                                                                                                                                                   |
|-----------------------------|-------------------------------------------|----------------------------|--------------------------------|-----|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2013                        |                                           | 793; 8,881                 | 6-14 m                         |     |                                     | Exposure to AB in first 6 to 14 m of life not associated with increased risk.                                                                 | breastfeeding, diet, timing of solid food introduction, sleep duration, time spent watching television and in car                                                 |
|                             |                                           | 603*; 6,598<br>190*; 2,283 | No<br><br>Parent questionnaire |     |                                     | • aOR 1.11 (95%CI nr), p=0.37                                                                                                                 |                                                                                                                                                                   |
|                             |                                           | 793; 8,881                 | 15-23 m                        |     |                                     | Exposure to AB in first 15 to 23 m of life not associated with increased risk.                                                                |                                                                                                                                                                   |
|                             |                                           | 613*; 6,598<br>180*; 2,283 | No<br><br>Parent questionnaire |     |                                     | • aOR 1.20 (95%CI nr), p=0.14                                                                                                                 |                                                                                                                                                                   |
|                             |                                           | 706; 8,881                 | < 6 m                          | 7 y |                                     | Exposure to AB in first 6 m of life not associated with increased risk.                                                                       |                                                                                                                                                                   |
|                             |                                           | 537*; 6,598<br>169*; 2,283 | No<br><br>Parent questionnaire |     |                                     | • aOR 1.06 (95%CI nr), p=0.66                                                                                                                 |                                                                                                                                                                   |
|                             |                                           | 706; 8,881                 | 6-14 m                         |     |                                     | Exposure to AB in first 6 to 14 m of life not associated with increased risk.                                                                 |                                                                                                                                                                   |
|                             |                                           | 531*; 6,598<br>175*; 2,283 | No<br><br>Parent questionnaire |     |                                     | • aOR 1.05 (95%CI nr), p=0.70                                                                                                                 |                                                                                                                                                                   |
|                             |                                           | 706; 8,881                 | 15-23 m                        |     |                                     | Exposure to AB in first 15 to 23 m of life not associated with increased risk.                                                                |                                                                                                                                                                   |
|                             |                                           | 534*; 6,598<br>172*; 2,283 | No<br><br>Parent questionnaire |     |                                     | • aOR 0.99 (95%CI nr), p=0.93                                                                                                                 |                                                                                                                                                                   |
| Ajslev et al. <sup>14</sup> | Multicentre prospective cohort study (2b) | 378; 22,368                | < 6 m                          | 7 y | BMI (> 85 <sup>th</sup> percentile) | Exposure to AB in first 6 m of life associated with increased risk among children of normal-weight mothers.                                   | Sex, maternal age and smoking; parity, pre-pregnancy BMI, gestational weight gain, paternal BMI, socioeconomic status, birth weight, delivery mode, breastfeeding |
| Denmark                     |                                           | nr; 1,628<br>nr; 20,740    | No<br><br>Parent questionnaire |     |                                     | • aOR 1.54 (95%CI 1.09-2.17), p=nr                                                                                                            |                                                                                                                                                                   |
| 2011                        |                                           |                            |                                |     |                                     | Exposure to AB in first 6 m of life associated with decreased risk among children of obese mothers.<br><br>• aOR 0.54 (95%CI 0.30-0.98), p=nr |                                                                                                                                                                   |

(continued on next page)

Table 1 (continued)

| Growth failure                     |                                             |                       |                      |         |                                  |                                                                                                                                                                                                                                      |  |
|------------------------------------|---------------------------------------------|-----------------------|----------------------|---------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Uzan-Yulzari et al. <sup>145</sup> | Multicentre prospective cohort study (2b)   | Boys: nr; 6,316       | < 2 w                | 6 y     | Weight z-score<br>BMI z-score    | Exposure to AB in first w of life not associated with decreased weight gain in boys.                                                                                                                                                 |  |
| Israel                             |                                             | nr; 673<br>nr; 5,643  | No                   |         |                                  | • weight z-score: -0.43 (95%CI -0.96- -0.00), p=0.05<br>• BMI z-score: -0.11 (95%CI -0.68-0.47), p=0.71                                                                                                                              |  |
| 2021                               |                                             | Girls: nr; 6,115      | Medical records      |         |                                  | Exposure to AB in first w of life not associated with decreased weight gain in girls.                                                                                                                                                |  |
|                                    |                                             | nr; 478<br>nr; 5,637  |                      |         |                                  | • weight z-score: 0.28 (95%CI -0.21-0.77), p=0.26<br>• BMI z-score: 0.62 (95%CI -0.19-1.44), p=0.13                                                                                                                                  |  |
| Kamphorst et al. <sup>71</sup>     | Multicentre prospective cohort study (2b)   | nr, 436               | < 1 w                | 1 y     | Weight                           | Exposure to AB in first w of life associated with decreased weight gain.                                                                                                                                                             |  |
| Netherlands                        |                                             | nr; 151<br>nr 285     | Yes                  |         |                                  | • weight gain: <b>6.26 kg (SE 0.07 kg) vs 6.47 (SE 0.06 kg), p&lt;0.05</b>                                                                                                                                                           |  |
| 2019                               |                                             |                       | Parent questionnaire |         |                                  | Results according to antibiotic class nr                                                                                                                                                                                             |  |
| Rogawski et al. <sup>203</sup>     | Single-centre prospective cohort study (2b) | 140; 497              | < 6 m                | 6 m-3 y | Weight-for-age (WAZ)             | Exposure to AB in first 6 m of life not associated with decreased weight gain.                                                                                                                                                       |  |
| India                              |                                             | nr; 276<br>nr; 221    | No                   |         |                                  | • RR 0.98 (95%CI 0.86-1.13), p=nr                                                                                                                                                                                                    |  |
| 2015                               |                                             | 68; 497               | Parent questionnaire |         | Weight-for-height (WHZ) z-scores | Exposure to AB in first 6 m of life not associated with decreased weight gain.                                                                                                                                                       |  |
|                                    |                                             | nr; 276<br>nr; 221    |                      |         |                                  | • RR 0.96 (95%CI 0.78-1.18), p=nr                                                                                                                                                                                                    |  |
| Juvenile idiopathic arthritis      |                                             |                       |                      |         |                                  |                                                                                                                                                                                                                                      |  |
| Horton et al. <sup>64</sup>        | Multicentre nested case-control study (3b)  | 152; 1,672            | Before diagnosis     | 1-15 y  | ICD-9 and ICD-10 codes           | Exposure to AB associated with increased risk.                                                                                                                                                                                       |  |
| USA                                |                                             | 133; 1,280<br>19; 392 | Yes                  |         |                                  | • <b>aOR 2.10 (95%CI 1.20-3.50), p&lt;0.01</b>                                                                                                                                                                                       |  |
| 2015                               |                                             |                       | Medical records      |         |                                  | • AB within 1 y before diagnosis: <b>aOR 2.90 (95% 1.60-5.30), p&lt;0.01</b>                                                                                                                                                         |  |
|                                    |                                             |                       |                      |         |                                  | • 1-2 AB courses: aOR 1.50 (95%CI 0.80-2.70), p=0.16<br>• 3-5 AB courses: <b>aOR 2.50 (95%CI 1.40-4.40), p&lt;0.01</b><br>• > 5 AB courses: <b>aOR 3.00 (95%CI 1.60-5.60), p&lt;0.01</b><br>Results according to antibiotic class nr |  |

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Table 1 (continued)

|                                                         |                                            |              |                        |        |              |                                                                                                                                                                                                                                                                           |                                                                          |
|---------------------------------------------------------|--------------------------------------------|--------------|------------------------|--------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Arvonen et al. <sup>18</sup><br><br>Finland<br><br>2015 | Multicentre case-control study (3b)        | 1,298; 6,477 | < 1 y                  | < 13 y | ICD 10 codes | Exposure to AB in first y associated with increased risk.                                                                                                                                                                                                                 |                                                                          |
|                                                         |                                            | 644; 2,986   | Yes                    |        |              | • <b>OR 1.20 (95%CI 1.10-1.40), p=nr</b>                                                                                                                                                                                                                                  |                                                                          |
|                                                         |                                            | 654; 3,491   | Registry               |        |              | • penicillins: <b>OR 1.20 (95%CI 1.10-1.40), p=nr</b><br>• cephalosporins: <b>OR 1.30 (95%CI 1.10-1.70), p=nr</b><br>• macrolides: OR 1.20 (95%CI 1.02-1.40), p=nr<br>• sulfonamides: OR 1.20 (95%CI 0.90-1.50), p=nr<br>• lincosamides: OR 1.00 (95%CI 0.10-8.90), p=nr  |                                                                          |
|                                                         |                                            | 1,298; 6,477 | < 2 y                  |        |              | Exposure to AB in first 2 y associated with increased risk.                                                                                                                                                                                                               |                                                                          |
|                                                         |                                            | 1,015; 4,737 | Yes                    |        |              | • <b>OR 1.40 (95%CI 1.20-1.60), p&lt;0.01</b>                                                                                                                                                                                                                             |                                                                          |
|                                                         |                                            | 283; 1,740   | Registry               |        |              | • penicillins: OR 1.50 (95%CI 1.30-1.70), p=nr<br>• cephalosporins: OR 1.30 (95%CI 0.99-1.60), p=nr<br>• macrolides: OR 1.30 (95%CI 1.10-1.50), p=nr<br>• sulfonamides: OR 1.30 (95%CI 0.90-1.70), p=nr<br>• lincosamides: <b>OR 3.50 (95%CI 1.30-9.70), p=0.01</b>       |                                                                          |
|                                                         |                                            | 1,298; 6,477 | Before diagnosis       |        |              | Exposure to AB from birth to diagnosis associated with increased risk.                                                                                                                                                                                                    |                                                                          |
|                                                         |                                            | 1,158; 5,529 | Yes                    |        |              | • <b>OR 1.60 (95%CI 1.30-1.90), p&lt;0.01</b>                                                                                                                                                                                                                             |                                                                          |
|                                                         |                                            | 140; 948     | Registry               |        |              | • penicillins: OR 1.80 (95%CI 1.50-2.20), p=nr<br>• cephalosporins: <b>OR 1.60 (95%CI 1.40-1.80), p=nr</b><br>• macrolides: OR 1.50 (95%CI 1.20-1.90), p=nr<br>• sulfonamides: OR 1.60 (95%CI 1.20-2.20), p=nr<br>• lincosamides: <b>OR 6.60 (95%CI 3.70-11.70), p=nr</b> |                                                                          |
| <b>Psoriasis</b>                                        |                                            |              |                        |        |              |                                                                                                                                                                                                                                                                           |                                                                          |
| Horton et al. <sup>65</sup>                             | Multicentre nested case-control study (3b) | 845; 9,295   | < 2 y before diagnosis | 1-15 y | ICD-9 codes  | Exposure to AB within 2 y before diagnosis associated with increased risk.                                                                                                                                                                                                | Age, sex, country, socioeconomic status, infections, number of GP visits |
| USA                                                     |                                            | 710; 7,053   | Yes                    |        |              | • <b>aOR 1.20 (95%CI 1.00-1.50), p=0.05</b>                                                                                                                                                                                                                               |                                                                          |
| 2016                                                    |                                            | 135; 2,242   | Medical records        |        |              | Results according to antibiotic class nr                                                                                                                                                                                                                                  |                                                                          |

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Table 1 (continued)

| Type 1 diabetes                  |                                            |                |                      |               |              |                                                                                                                                |                                                                                                                                                                                                      |
|----------------------------------|--------------------------------------------|----------------|----------------------|---------------|--------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antvorskov et al. <sup>171</sup> | Multicentre prospective cohort study       | 322; 91,998    | < 2 y                | 14.3 y (mean) | ICD-10 codes | Exposure to AB in first 2 y of life not associated with increased risk.                                                        | Breastfeeding                                                                                                                                                                                        |
| Denmark                          | (2b)                                       | 235; 64,793    | Yes                  |               |              | • aHR 1.26 (95%CI 0.89-1.79), p=nr                                                                                             |                                                                                                                                                                                                      |
| 2020                             |                                            | 87; 27,205     | Registry             |               |              | • penicillins: aHR 1.30 (95%CI 0.92-1.85), p=nr<br>• macrolides/lincosamides/ streptogramins: aHR 1.29 (95%CI 0.75-2.22), p=nr |                                                                                                                                                                                                      |
| Wernroth et al. <sup>152</sup>   | Multicentre prospective cohort study       | 1,297; 797,318 | < 1 y                | < 10 y        | ICD-10 codes | Exposure to AB in first y of life associated with increased risk.                                                              | Age, sex, maternal age, parental country of birth, education, income and type 1 diabetes; living area, population density, smoking during pregnancy, gestational age, season of birth, delivery mode |
| Sweden                           | (2b)                                       | 347; 189,682   | Yes                  |               |              | • aHR 1.19 (95%CI 1.05-1.36), p=nr                                                                                             |                                                                                                                                                                                                      |
| 2020                             |                                            | 950; 607,636   | Registry             |               |              | • narrow-spectrum: HR 1.26 (95%CI 1.09-1.47), p=nr<br>• broad-spectrum: 1.06 (95%CI 0.80-1.40), p=nr                           |                                                                                                                                                                                                      |
|                                  |                                            |                |                      |               |              | Results according to antibiotic class nr                                                                                       |                                                                                                                                                                                                      |
| Tapia et al. <sup>140</sup>      | Multicentre prospective cohort study       | 403, 101,842   | < 18 m               | 7.4 y (mean)  | ICD-10 codes | Exposure to AB in first 6 m of life not associated with increased risk.                                                        | Sex, maternal age, education and type 1 diabetes; parity, pre-pregnancy BMI, smoking during pregnancy, birth weight, number of infections, medication use                                            |
| Norway                           | (2b)                                       | nr; 32,386     | Yes                  |               |              | • aHR 1.05 (95%CI 0.68-1.63), p=0.82                                                                                           |                                                                                                                                                                                                      |
| 2018                             |                                            | nr; 69,456     | Parent questionnaire |               |              | • 1 AB course: aHR 1.10 (95%CI 0.83-1.41), p=0.51<br>• ≥ 2 AB courses: aHR 1.03 (95%CI 0.65-1.65), p=0.88                      |                                                                                                                                                                                                      |
|                                  |                                            |                |                      |               |              | Results according to antibiotic class nr                                                                                       |                                                                                                                                                                                                      |
| Mikkelsen et al. <sup>94</sup>   | Multicentre prospective case-control study | 1,578; 14,188  | < 2 y                | < 16 y        | ICD-10 codes | Exposure to AB in first 2 y of life not associated with increased risk.                                                        |                                                                                                                                                                                                      |
| Denmark                          | (3b)                                       | 1,366; 12,239  | No                   |               |              | • 1-4 AB courses: OR 1.02 (95%CI 0.85-1.22), p=nr                                                                              |                                                                                                                                                                                                      |
| 2016                             |                                            | 212; 1,949     | Registry             |               |              | • > 5 AB courses: OR 1.01 (95%CI 0.85-1.22), p=nr                                                                              |                                                                                                                                                                                                      |

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Table 1 (continued)

|                              |                                           |                |          |        |                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                              |
|------------------------------|-------------------------------------------|----------------|----------|--------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                              |                                           |                |          |        |                                            | <ul style="list-style-type: none"> <li>• narrow-spectrum 1-4 AB courses: OR 0.90 (95%CI 0.78-1.03), p=nr</li> <li>• narrow-spectrum ≥ 5 AB courses: OR 0.98 (95%CI 0.80-1.21), p=nr</li> <li>• broad-spectrum 1-4 AB courses: OR 1.11 (95%CI 0.98-1.24), p=nr</li> <li>• broad-spectrum ≥ 5 AB courses: OR 1.15 (95%CI 0.95-1.39), p=nr</li> </ul>                                                                                                    |                                                                              |
| Clausen et al. <sup>36</sup> | Multicentre prospective cohort study (2b) | 1,503; 858,201 | < 2 y    | 2-14 y | Hospital discharge or prescription records | Overall exposure to AB in first 2 y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                       | Age, sex, parental education, age and type 1 diabetes, parity, delivery mode |
| Denmark                      |                                           | 1,107; 615,782 | Yes      |        |                                            | • aHR 1.06 (95%CI 0.94-1.19), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                              |
| 2016                         |                                           | 396; 242,419   | Registry |        |                                            | <ul style="list-style-type: none"> <li>• narrow-spectrum: aHR 1.02 (95%CI 0.92-1.13), p=nr</li> <li>• broad-spectrum: <b>aHR 1.13 (95%CI 1.02-1.25), p=nr</b></li> </ul> <p>Exposure to broad-spectrum AB in first 2 y of life associated with increased risk in children delivered by delivery mode.</p> <ul style="list-style-type: none"> <li>• <b>aHR 1.70 (95%CI 1.15-2.51), p=nr</b></li> </ul> <p>Results according to antibiotic class nr</p> |                                                                              |
| Hviid et al. <sup>204</sup>  | Multicentre prospective cohort study (2b) | 454; 606,420   | < 9 y    | < 9 y  | ICD-10 codes                               | Exposure to AB in first w of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                 | Age, ethnicity, season                                                       |
| Denmark                      |                                           | 373; 538,298   | Yes      |        |                                            | • aRR 1.16 (95%CI 0.91-1.50), p=nr                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                              |
| 2009                         |                                           | 81; 68,122     | Registry |        |                                            | <ul style="list-style-type: none"> <li>• penicillins: aRR 1.10 (95%CI 0.90-1.34), p=nr</li> <li>• macrolides: aRR 1.15 (95%CI 0.92-1.43), p=nr</li> </ul>                                                                                                                                                                                                                                                                                             |                                                                              |

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Table 1 (continued)

| Fluorosis                        |                                      |                                |                      |        |                        |                                                                                  |                                                                                                                                                                                                                                                                                                 |
|----------------------------------|--------------------------------------|--------------------------------|----------------------|--------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hong <i>et al.</i> <sup>63</sup> | Single-centre prospective            | 68; 192                        | < 32 m               | 13 y   | Fluorosis risk index   | Overall exposure to AB in first 32 m of life not associated with increased risk. |                                                                                                                                                                                                                                                                                                 |
| USA                              | case-control study (3b)              | 62; 174                        | Yes                  |        |                        | • amoxicillin: RR 1.07 (95%CI 0.54-2.12), p=0.85                                 |                                                                                                                                                                                                                                                                                                 |
| 2011                             |                                      | 6; 18                          | Parent questionnaire |        |                        |                                                                                  |                                                                                                                                                                                                                                                                                                 |
| Autism spectrum disorders        |                                      |                                |                      |        |                        |                                                                                  |                                                                                                                                                                                                                                                                                                 |
| Aversa et al. <sup>172</sup>     | Multicentre prospective cohort study | 142; 14,572                    | < 2 y                | 6-11 y | ICD-9 and ICD-10 codes | Exposure to AB in first 2 y of life not associated with increased risk.          | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode                                                                                                                                                                               |
| USA                              | (2b)                                 | 108; 10,220                    | Yes                  |        |                        | • aHR 1.19 (95%CI 0.81-1.75), p=0.39                                             |                                                                                                                                                                                                                                                                                                 |
| 2021                             |                                      | 34; 4,352                      | Medical records      |        |                        | Girls                                                                            |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • penicillins: <b>HR 0.39 (95%CI 0.16-0.95), p=0.04</b>                          |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • cephalosporins: <b>HR 2.77 (95%CI 1.09-7.02), p=0.03</b>                       |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • macrolides: HR 1.21 (95%CI 0.47-3.14), p=0.70                                  |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • sulfonamides: HR 1.08 (95%CI 0.24-4.81), p=0.92                                |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | Boys                                                                             |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • penicillins: HR 0.96 (95%CI 0.62-1.47), p=0.84                                 |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • cephalosporins: <b>HR 1.89 (95%CI 1.25-2.84), p&lt;0.01</b>                    |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • macrolides: HR 0.83 (95%CI 0.55-1.28), p=0.41                                  |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      |                                |                      |        |                        | • sulfonamides: HR 1.13 (95%CI 0.54-2.35), p=0.75                                |                                                                                                                                                                                                                                                                                                 |
| Axelsson et al. <sup>21</sup>    | Multicentre prospective cohort study | 8,267; 671,606                 | < 2 y                | < 15 y | ICD-10 codes           | Exposure to AB in first y of life associated with increased risk.                | Sex, maternal age and smoking; parental education, age difference, marital status epilepsy and psychiatric history; parity, preeclampsia or hypertension, gestational diabetes, antibiotic use and infections during pregnancy, Apgar score, delivery mode, use of CPAP or ventilator, asphyxia |
| Denmark                          | (2b)                                 | Penicillins: 6,316; 483,423    | Yes                  |        |                        | • <b>OR 1.26 (95%CI 1.20-1.33), p&lt;0.01*</b>                                   |                                                                                                                                                                                                                                                                                                 |
| 2019                             |                                      | 1,951; 188,183                 | Registry             |        |                        | • penicillins: aHR 1.09 (95%CI 0.91-1.29), p=nr                                  |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      | Broad-spectrum: 4,943; 377,254 |                      |        |                        | • <b>OR 1.16 (95%CI 1.11-1.21), p&lt;0.01*</b>                                   |                                                                                                                                                                                                                                                                                                 |
|                                  |                                      | 3,324; 294,352                 |                      |        |                        | • broad-spectrum AB: <b>aHR 1.16 (95%CI 1.01-1.36), p=nr</b>                     |                                                                                                                                                                                                                                                                                                 |

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Table 1 (continued)

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|-------------------------------------------------|-------------------------------------------|---------------------------------------------------|---------------------------------|-----------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hamad et al. <sup>57</sup>                      | Multicentre prospective cohort study (2b) | 2,965; 214,834<br>1,355; 94,024<br>1,610; 120,810 | < 1 y<br>Yes<br>Registry        | 18 m-18 y | ICD-9 and ICD-10 codes | Exposure to AB in first y of life not associated with increased risk.<br><br>• aHR 0.91 (95%CI 0.84-0.99), p=0.05<br><br>• 1 AB course: aHR 0.92 (95%CI 0.83-1.01), p=nr<br>• 2 AB courses: aHR 0.89 (95%CI 0.78-1.01), p=nr<br>• 3 AB courses: aHR 0.93 (95%CI 0.79-1.09), p=nr<br>• ≥ 4 AB courses: aHR 0.90 (95%CI 0.76-1.06), p=nr<br><br>• penicillins: <b>aHR 0.92 (95%CI 0.84-1.00), p&lt;0.05</b><br>• macrolides: <b>aHR 0.87 (95%CI 0.77-0.99), p&lt;0.05</b>                                                                                                                            | Age, sex, maternal age, and mental disorders (mood and anxiety disorders, schizophrenia, diabetes, prenatal infections), parity, living area, socioeconomic status, healthcare access, antidepressants use during pregnancy, size for gestational age, season of birth, delivery mode, birth complications, multiple birth, childhood medical disorders (epilepsy, infections, neonatal jaundice, asthma and diagnosis with other developmental disability disorder), breastfeeding |
| Canada                                          |                                           |                                                   |                                 |           |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 2018                                            |                                           |                                                   |                                 |           |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Attention deficit hyperactivity disorder</b> |                                           |                                                   |                                 |           |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Aversa et al. <sup>172</sup>                    | Multicentre prospective cohort study (2b) | 1,085; 14,572<br>841; 10,220<br>244; 4,352        | < 2 y<br>Yes<br>Medical records | 6-11 y    | ICD-9 and ICD-10 codes | Exposure to AB in first 2 y of life associated with increased risk.<br><br>• <b>aHR 1.32 (95%CI 1.15-1.53), p&lt;0.01</b><br><br>Girls<br>• penicillins: <b>HR 1.50 (95%CI 1.14-1.96), p&lt;0.01</b><br>• cephalosporins: HR 1.21 (95%CI 0.92-1.59), p=0.18<br>• macrolides: HR 1.03 (95%CI 0.79-1.34), p=0.85<br>• sulfonamides: HR 0.65 (95%CI 0.38-1.10), p=0.11<br><br>Boys<br>• penicillins: HR 1.08 (95%CI 0.91-1.27), p=0.38<br>• cephalosporins: HR 1.18 (95%CI 1.00-1.39), p=0.05<br>• macrolides: HR 1.09 (95%CI 0.93-1.28), p=0.28<br>• sulfonamides: HR 1.19 (95%CI 0.89-1.58), p=0.23 | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode                                                                                                                                                                                                                                                                                                                                                                   |
| USA                                             |                                           |                                                   |                                 |           |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 2021                                            |                                           |                                                   |                                 |           |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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Table 1 (continued)

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|---------------------------------|-------------------------------------------|---------------------------------------------------|----------------------|--------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Axelsson et al. <sup>22</sup>   | Multicentre prospective cohort study (2b) | 17,971; 671,592                                   | < 2 y                | 2–17 y | ICD-10 codes                                                                       | Exposure to AB in first 2 y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                             | Sex, maternal age, parental education, age difference, marital status, epilepsy, and ADHD history, parity, preeclampsia or hypertension, gestational diabetes, antibiotic use and infections during pregnancy, Apgar score, delivery mode, instrument use at delivery, induction of labour or contraction, use of CPAP or ventilator, asphyxia, maternal smoking |
| Denmark                         |                                           | Penicillins: 2,822; 106,170<br>15;149; 565,422    | Yes                  |        |                                                                                    | <ul style="list-style-type: none"> <li>• <b>OR 1.47 (95%CI 1.42–1.53), p&lt;0.01*</b></li> <li>• penicillins: aHR 0.98 (95%CI 0.90–1.07), p=nr</li> </ul>                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                  |
| 2019                            |                                           | Broad-spectrum: 11,365; 377,238<br>6,606; 294,354 | Registry             |        |                                                                                    | <ul style="list-style-type: none"> <li>• <b>OR 1.35 (95%CI 1.31–1.40), p&lt;0.01*</b></li> <li>• broad-spectrum AB: aHR 0.99 (95%CI 0.92–1.06), p=nr</li> </ul>                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                  |
| Hamad et al. <sup>58</sup>      | Multicentre prospective cohort study (2b) | 6,087; 69,738                                     | < 1 y                | > 4 y  | ICD-9 and ICD-10 codes                                                             | Exposure to AB in first y of life not associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                               | Age, sex, maternal age, antidepressants use and infections during pregnancy, size for gestational age, season of birth, delivery mode, birth order, birth complications, childhood medical disorders (asthma, epilepsy, infections, neonatal jaundice, diagnosis with other developmental disorder), breastfeeding                                               |
| Canada                          |                                           | 3,045; 34,869<br>3,042; 34,869                    | Yes                  |        |                                                                                    | <ul style="list-style-type: none"> <li>• aHR 1.02 (95%CI 0.97–1.08), p=nr</li> <li>• 1 AB course: aHR 0.94 (95%CI 0.87–1.02), p=nr</li> <li>• 2 AB courses: aHR 1.09 (95%CI 0.94–1.27), p=nr</li> <li>• 3 AB courses: aHR 1.09 (95%CI 0.83–1.43), p=nr</li> <li>• ≥ 4 AB courses: <b>aHR 1.57 (95%CI 1.23–2.00), p=nr</b></li> <li>• penicillins: <b>aHR 1.11 (95%CI 1.03–1.19), p=nr</b></li> <li>• macrolides: <b>aHR 1.11 (95%CI 1.04–1.34), p=nr</b></li> </ul> |                                                                                                                                                                                                                                                                                                                                                                  |
| 2019                            |                                           |                                                   | Registry             |        |                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                  |
| Slykerman et al. <sup>130</sup> | Multicentre prospective cohort study (2b) | nr; 446                                           | < 2 y                | 11 y   | Psychologist-administered, parent-reported and self-reported measures <sup>1</sup> | Exposure to AB in first 2 y of life associated with increased risk.                                                                                                                                                                                                                                                                                                                                                                                                 | Income, delivery mode, probiotic use, breastfeeding                                                                                                                                                                                                                                                                                                              |
| New Zealand                     |                                           | nr; 376<br>nr; 70                                 | No                   |        |                                                                                    | <ul style="list-style-type: none"> <li>• <b>aOR 2.40 (95%CI 1.00–5.90), p=0.02</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                  |
| 2019                            |                                           |                                                   | Parent questionnaire |        |                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                  |

(continued on next page)

Table 1 (continued)

| Neurodevelopmental disorders    |                                           |                                          |                                     |        |                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                   |
|---------------------------------|-------------------------------------------|------------------------------------------|-------------------------------------|--------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Aversa et al. <sup>172</sup>    | Multicentre prospective cohort study (2b) | 751; 14,572<br>563; 10,220<br>188; 4,352 | < 2 y<br>Yes<br>Medical records     | 6–11 y | ICD-9 and ICD-10 codes                                                             | Exposure to AB in first 2 y of life associated with increased risk of learning disorders.<br><br>• <b>aHR 1.21 (95%CI 1.03–1.43), p=0.02</b><br><br>Girls<br>• penicillins: HR 1.18 (95%CI 0.88–1.58), p=0.28<br>• cephalosporins: HR 1.36 (95%CI 0.99–1.85), p=0.06<br>• macrolides: HR 0.93 (95%CI 0.68–1.28), p=0.67<br>• sulfonamides: HR 0.96 (95%CI 0.56–1.64), p=0.87<br><br>Boys<br>• penicillins: HR 1.06 (95%CI 0.87–1.29), p=0.56<br>• cephalosporins: <b>HR 1.48 (95%CI 1.21–1.80), p&lt;0.01</b><br>• macrolides: <b>HR 0.79 (95%CI 0.65–0.98), p=0.03</b><br>• sulfonamides: HR 1.03 (95%CI 0.71–1.51), p=0.87                                                                                                                                                                                                                                     | Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode |
| Slykerman et al. <sup>130</sup> | Multicentre prospective cohort study (2b) | nr; 446<br>nr; 376<br>nr; 70             | < 2 y<br>No<br>Parent questionnaire | 11 y   | Psychologist-administered, parent-reported and self-reported measures <sup>1</sup> | Exposure to AB in first 6 m of life associated with lower overall cognitive and verbal comprehension abilities, increased risk of problems with metacognition, executive function, impulsivity, hyperactivity, ADHD, anxiety and emotional problems.<br><br>• <b>full scale IQ: mean difference -5.70 (95%CI -10.30, -1.20), p=0.04</b><br>• <b>verbal comprehension index: mean difference -8.40 (95%CI -14.00, -2.80), p=0.02</b><br>• metacognition index: aOR 2.20 (95%CI 0.90, 5.50), p=0.05<br>• <b>impulsivity/hyperactivity: aOR 2.10 (95%CI 0.90–5.00), p=0.02</b><br>• <b>executive function: aOR 3.80 (95%CI 1.20–11.70), p=0.04</b><br>• <b>emotional problems: aOR 9.20 (95%CI 2.00–43.00), p&lt;0.01</b><br>• <b>hyperactivity: aOR 8.20 (95%CI 0.90–73.10), p&lt;0.01</b><br>• <b>total anxiety score: aOR 5.40 (95%CI 1.40–20.70), p&lt;0.01</b> | Income, delivery mode, probiotic use, breastfeeding                                                               |

(continued on next page)

**Table 1** (continued)

\* calculated from reported data

<sup>1</sup>WISC-IV (Wechsler Intelligence Scale for Children-fourth edition), CPT 3 (Conners Continuous Performance Test-third edition), CANTAB (Cambridge Automated Neuropsychological Test Battery), BRIEF (Behavior Rating Inventory of Executive Function), Conners 3, SDQ (Strengths and Difficulties Questionnaire), MASC 2 (Multidimensional Anxiety Scale for Children), CES-DC (Center for Epidemiological Studies for Children)

AB – antibiotic

ADHD – attention deficit hyperactivity disorder

a – adjusted

ASD – autism spectrum disorders

ATC – anatomical-therapeutic-chemical

BASME – Barn, Allergi, Miljö, Stockhol, Epidemiologi

BMI – body mass index

CI – confidence interval

ECRHS II – European Community Respiratory Health Survey second version

GP – general practitioner

HLA – human leucocyte antigen

HR – hazard ratio

IBD – inflammatory bowel disease

ICD-10-CA – international classification of disease, tenth revision, Canadian Edition

ICD-9-CM – international classification of disease, ninth revision, clinical modification

ICD-9/10 – international classification of disease, ninth/tenth revision

IgE – immunoglobulin E

IRR – incidence rate ratio

ISAAC – International Study of Allergy and Asthma in Childhood

JIA – juvenile idiopathic arthritis

LRTI – lower respiratory tract infections

m – month

nr – not reported

OR – odds ratio

RP – ratio of proportion

RR – risk ratio

RRR – prevalence ratio

SPT – skin prick test

w – week

y – year

diagnosed by ISAAC questionnaire, ICD codes, skin prick test or serum IgE levels in 1,859,024 children (45,479 cases) (Table 1).<sup>42,46,51,61,82,91,93,96,115,161,163,172,178,183,185</sup> Of the 15 studies, 13 (87%) investigated the effect of antibiotic exposure in the first two years of life.<sup>42,46,51,82,93,96,115,161,163,172,178,183,185</sup> Nine (60%) reported a significantly increased incidence of food allergies in children who were exposed to antibiotics.<sup>61,91,96,115,161,163,172,178,183,185</sup> Two studies reported a positive correlation between the risk of developing food allergies and the number of antibiotic courses.<sup>61,115</sup> One study reported that the risk of developing food allergies was higher when children were exposed in the first year of life compared to the second or third year of life.<sup>115</sup> Four studies investigated the effect of different antibiotic classes.<sup>61,91,163,172</sup> One reported an increased risk of food allergies only after the exposure to cephalosporins, but not penicillins, macrolides and sulfonamides.<sup>172</sup> Three studies reported an increased risk of all investigated antibiotic classes: penicillins, cephalosporins and macrolides<sup>61</sup>; penicillins, cephalosporins, macrolides and sulfonamides<sup>163</sup>; and penicillin, amoxicillin, cephalosporins, macrolides and trimethoprim/sulfamethoxazole,<sup>91</sup> respectively.

All studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 3).<sup>42,46,51,61,82,91,93,96,115,161,163,172,178,183,185</sup> Of the 659,863 children exposed to antibiotics 16,703 (2.5%) developed food allergies compared to 28,776 (2.4%) of the 1,199,161 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing food allergies (OR 1.35, 95%CI 1.20–1.52,  $p < 0.01$ ) (Fig. 2).

### Allergic rhinoconjunctivitis

Forty studies investigated the association between antibiotic exposure and the risk of developing allergic rhinoconjunctivitis diagnosed by ISAAC questionnaire, ICD codes or parent's-reported diagnosis in 1,554,337 children (359,568 cases with one study not reporting number of cases) (Table 1).<sup>16,29,32,35,37,43,48–50,59,60,74,82,93,96–98,102,103,110,112,129,150,154,155,157,158,161,162,172,176–178,181,182,186–190</sup> Of the 40 studies, 38 (95%) investigated the effect of antibiotic exposure in the first five years of life (35 (88%) in the first two years of life).<sup>16,29,32,35,37,43,48–50,59,60,74,82,93,96–98,102,103,110,112,129,150,157,158,161,162,172,176–178,172,181,186–190</sup> Twenty-nine (73%) reported a significantly increased incidence of allergic rhinoconjunctivitis in children who were exposed to antibiotics.<sup>16,29,35,37,43,48–50,59,60,74,82,96,97,102,103,110,129,150,157,158,161,172,176,181,186–189</sup> One study reported that the risk of developing allergic rhinitis was higher when children were exposed to antibiotics in the third year of life compared to the second or first year of life.<sup>29</sup> Three studies reported that the risk increased after more than one antibiotic course,<sup>29,103,176</sup> while another could not confirm this finding.<sup>182</sup> Four studies investigated the effect of antibiotic class.<sup>29,157,172,182</sup> One study reported that the risk of developing allergic rhinoconjunctivitis was higher after exposure to cephalosporins and macrolides compared to penicillins and sulfonamides,<sup>172</sup> and one study after exposure to cephem compared to penicillins or macrolides.<sup>157</sup> Two studies did not find a difference between antibiotic classes and the risk of allergic rhinoconjunctivitis.<sup>29,182</sup>

Twenty-seven (68%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 4).<sup>16,32,35,37,43,48,49,59,74,82,93,96,97,102,103,112,154,157,158,161,162,172,176,178,181,188,190</sup> Of the 200,029 children exposed to antibiotics 61,899 (30%) developed allergic rhinoconjunctivitis compared to 204,006 (28%) of the 718,124 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of

allergic rhinoconjunctivitis (OR 1.66, 95%CI 1.51–1.83,  $p < 0.01$ ) (Fig. 2).

### Wheezing

Thirty-two studies investigated the association between antibiotic exposure and the risk of developing wheezing in 220,415 children (29,229 cases) diagnosed by ISAAC questionnaire, ICD codes or parent-reported diagnosis (Table 1).<sup>13,15,37,40,49,56,59,60,79,80,95,97,103–105,115,119,126,137,154,155,157,161,162,164–166,178,191–194</sup> Of the 32 studies, 29 (91%) investigated the effect of antibiotic exposure in the first five years of life (26 (81%) in the first two years of life).<sup>13,15,37,40,49,56,59,60,69,79,80,95,97,103–105,115,119,126,137,157,161,162,164,165,178,191–194</sup>

Twenty-seven (84%) reported a significantly increased incidence of wheezing in children who were exposed to antibiotics.<sup>13,15,37,49,56,59,60,79,95,97,103,104,115,119,126,137,154,155,161,164–166,178,191–194</sup> Five studies reported that the risk of developing wheezing increased with the number of antibiotics courses.<sup>13,103,115,178,191</sup> One study reported that the risk of wheezing was higher after exposure to cephem compared to penicillins or macrolides<sup>157</sup> and one study after exposure to macrolides compared to other antibiotic classes.<sup>137</sup>

Twenty-seven (84%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 5).<sup>13,15,37,40,49,56,59,79,80,95,97,103–105,115,119,154,155,157,161,162,166,178,191–194</sup> Of the 94,076 children exposed to antibiotics 16,172 (17%) developed wheezing compared to 11,169 (9%) of the 120,466 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing wheezing (OR 1.81, 95%CI 1.65–1.97,  $p < 0.01$ ) (Fig. 2).

### Asthma

Sixty-three studies investigated the association between antibiotic exposure and the risk of developing asthma mainly diagnosed by ISAAC questionnaire, ICD codes or parent-reported diagnosis in 12,366,759 children (312,230 cases with two studies not reporting number of cases) (Table 1).<sup>12,13,32,34,37,39,41,43,48–50,52,55,59,69,75–77,80,82,88,92,93,96–98,101–104,109,111,112,115,116,126,132,134,135,150,153–157,159,161,162,164,167–169,172,176–178,181,182,191,195–197,175</sup> Of the 63 studies, 59 (94%) investigated the effect of antibiotic exposure in the first five years of life (56 (89%) in the first two years of life).<sup>12,13,31,32,37,39,41,43,48–50,52,55,59,69,75–77,80,82,88,93,96–98,101–104,109,111,112,115,116,126,132,134,135,150,154,156,157,159,161,162,164,167–169,172,176–178,172,181,191,195–197</sup>

Fifty-four (86%) reported a significantly increased incidence of asthma in children who were exposed to antibiotics.<sup>12,13,31,34,37,39,41,43,48–50,52,55,69,75–77,82,88,92,93,96,97,101–104,109,111,115,116,126,132,134,135,150,154,156,157,159,161,162,164,168,169,172,176,178,172,181,191,195–197</sup> However, one study only after two courses of antibiotics.<sup>115</sup> One study reported that the risk of developing asthma was higher when higher doses of antibiotics were used.<sup>34</sup> Another study reported that the risk of asthma was not increased after antibiotic exposure in the first six months of life, but it was increased when exposed during the first three years of life<sup>12</sup>; and one study that the effect of antibiotics on the incidence of asthma was stronger in children with younger age at onset.<sup>197</sup> Six studies reported that the risk of asthma was highest after exposure to macrolides,<sup>34,69,92,111,195</sup> three studies that it was higher after exposure to cephalosporins compared to penicillins and macrolides,<sup>69,157,182</sup> and one study after exposure to penicillins, cephalosporins and macrolides compared to sulfonamides.<sup>172</sup> One study reported that the risk of asthma was higher after exposure to broad-spectrum compared to narrow-spectrum antibiotics.<sup>197</sup> Many studies reported that the risk of



developing asthma increased with the number of antibiotics courses<sup>13,32,48,76,103,109,111,115,116,154,176,178,181,182,191,195,197,175</sup> and one study that the risk was higher after higher doses of antibiotics.<sup>34</sup> Two studies did not find an association between antibiotic exposure and the development of asthma after adjusting for number of illnesses or chest infections.<sup>135,153</sup> One study found a higher risk in girls to develop asthma after exposure to antibiotics.<sup>39</sup>

Fifty-one (81%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 6).<sup>12,13,31,32,34,37,39,41,43,48,49,55,59,69,75,77,80,82,88,92,93,96,97,101–104,109,111,115,116,132,134,135,153,154,156,157,161,162,167–169,172,176,178,181,191,195,196</sup> Of the 909,797 children exposed to antibiotics 122,450 (13%) developed asthma compared to 128,778 (10%) of the 1,245,440 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing asthma (OR 1.96, 95%CI 1.76–2.17,  $p < 0.01$ ) (Fig. 2).

### Allergic symptoms

Four studies including 24,840 children (5019 cases) investigated the association between antibiotic exposure and the development of allergic symptoms without specifying the symptoms or reporting results separately for atopic dermatitis, allergic rhinitis, food allergies, wheezing or asthma (Table 1).<sup>61,82,177,183</sup> All four studies investigated the effect of antibiotic exposure in the first year of life.<sup>61,82,177,183</sup> Three (75%) of the studies reported a significantly increased risk of developing allergic symptoms in children who were exposed to antibiotics.<sup>61,82,183</sup> One study reported that the risk of allergic sensitisation increased with the number of antibiotic courses and that it was higher after exposure to penicillin compared to cephalosporins and macrolides.<sup>61</sup>

Three (75%) studies could be included in the meta-analysis (supplementary Fig. 7).<sup>61,82,183</sup> Of the 17,906 children exposed to antibiotics 3634 (20%) developed allergic symptoms compared to 906 (15%) of 6009 children not exposed to antibiotics. The overall OR for developing allergic symptoms after antibiotic exposure was 1.93, 95%CI 1.66–2.26,  $p < 0.01$  (Fig. 2).

### Infantile colic

One study investigated the association between antibiotic exposure and the development of infantile colic in 436 neonates (74 cases) (Table 1 and supplementary Fig. 8).<sup>105</sup> Of the 151 neonates exposed to antibiotics in the first week of life, 33 (22%) developed infantile colic compared to 41 (14%) of the 285 neonates not exposed. The OR was 1.66 (95%CI 1.00–2.77,  $p = 0.05$ ) (Fig. 2 and supplementary Fig. 8).

### Abdominal pain

One study investigated the association between antibiotic exposure and the development of abdominal pain in 2732 children (245 cases) diagnosed by a validated questionnaire (Table 1 and supplementary Fig. 9).<sup>144</sup> Of the 861 children exposed to antibiotics in the first two years of life, 87 (10%) developed abdominal pain compared to 144 (8%) of the 1793 children not exposed to antibiotics. Of the children exposed to antibiotics between the age of nine to twelve years these numbers were 94 (9%) of 1045 and 151 (9%) of 1687, respectively. The risk of abdominal pain increased with the number of antibiotic courses and was highest after exposure to tetracycline compared to other antibiotics. Overall, the evidence did not support an association between exposure to antibiotics and the incidence of abdominal pain later in life (Fig. 2 and supplementary Fig. 9). OR 1.01 (95%CI 0.77–1.32,  $p = 0.37$ ).

## Inflammatory bowel disease

Six studies investigated the association between exposure to antibiotics and the development of inflammatory bowel disease (IBD) in 2481,433 children (1617 cases) (Table 1).<sup>30,68,78,106,127,148</sup> Four (67%) studies investigated the effect of antibiotic exposure in the first year of life.<sup>30,78,127,148</sup> Five (83%) of the studies reported a significant association between antibiotic exposure and developing IBD.<sup>68,78,106,127,148</sup> One study reported a higher association between Crohn's disease than ulcerative colitis<sup>68</sup> and another study an association between antibiotic exposure and developing Crohn's disease but not ulcerative colitis.<sup>148</sup> Two studies found an association between the number of antibiotic courses and the risk of IBD.<sup>30,78</sup> However two other studies could not confirm this association.<sup>106,148</sup> One study reported that the risk was highest after exposure to metronidazole, penicillins, cephalosporins and fluoroquinolones compared to other antibiotic classes,<sup>78</sup> one after cephalosporins,<sup>148</sup> and one that it was after exposure to penicillins compared to macrolides.<sup>68</sup>

All six studies were included in the meta-analysis (supplementary Fig. 10).<sup>30,68,78,106,127,148</sup> Of the 1,650,507 children exposed to antibiotics 976 (0.06%) developed IBD compared to 641 (0.08%) of the 830,926 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing IBD (OR 1.19, 95%CI 0.83–1.71,  $p = 0.35$ ) (Fig. 2).

### Celiac disease

Four studies investigated the association between antibiotic exposure and developing celiac disease by ICD codes, antibody measurement or the criteria by the European Society for pediatric Gastroenterology, Hepatology and Nutrition in 1728,197 children (4,547 cases) (Table 1).<sup>44,73,172,199</sup> All of the studies were done in children less than 4 years of age (three (75%) in children less than 2 years of age).<sup>44,73,172,199</sup> Two (50%) of the studies found a positive association between antibiotic exposure and developing celiac disease.<sup>44,172</sup> One study reported that the risk was highest in girls after exposure to penicillins<sup>172</sup> and one study did not find a difference in the risk of celiac disease after exposure to different antibiotic classes.<sup>73</sup>

Three (75%) studies were included in the meta-analysis (supplementary Fig. 11).<sup>44,172,199</sup> Of the 531,197 children exposed to antibiotics 1149 (0.22%) developed celiac disease compared to 2615 (0.23%) of the 1160,442 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing celiac disease (OR 1.21, 95%CI 0.80–1.83,  $p = 0.37$ ) (Fig. 2).

## Increased weight gain or overweight

Seventeen studies investigated the association between antibiotic exposure and the risk of developing increased weight gain or overweight evaluated by weight, weight-for-age z-scores, body mass index (BMI), BMI z-scores, or fat percentage in 569,527 children (137,744 cases with five studies not reporting number of cases) (Table 1).<sup>14,23,27,33,54,71,75,89,121,124,131,143,170,172,176,200–202</sup> Of the 17 studies, 16 (94%) investigated the effect of antibiotic exposure in the first five years of life (15 (88%) in the first two years of life).<sup>162–171</sup> Overall, 12 (71%) studies reported a significant increased weight gain in children who were exposed to antibiotics.<sup>23,27,38,54,71,121,124,131,143,172,201,202</sup> Three studies reported that the strongest association with antibiotic exposure and developing increased weight gain was observed after exposure to macrolides.<sup>121,124,201</sup> Two studies reported that the association between antibiotic exposure and increased weight gain was stronger in boys.<sup>23,121</sup> In two studies the risk of increased weight gain

increased the number of antibiotic courses given<sup>33,121</sup> and in one study an association could only be found when antibiotics were given in the first six months of life.<sup>143</sup> In contrast, another study did not find increased weight gain after antibiotic exposure in the first six months of life but in first two years of life.<sup>54</sup> Four studies found a higher risk of overweight after exposure to macrolides,<sup>54,89,121,124</sup> while no clear influence of different antibiotic classes and the risk of increased weight gain could be found in other studies.<sup>33,172,201,202</sup>

Of the 17 studies, 10 (59%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 12).<sup>14,23,27,33,38,89,121,124,143,172</sup> Of the 311,694 children exposed to antibiotics 90,234 (29%) developed increased weight gain or overweight compared to 47,429 (23%) of the 207,084 children not exposed to antibiotics. Overall, the OR for developing increased weight gain or overweight after antibiotic exposure was 1.18, 95% CI 1.11 to 1.26,  $p < 0.01$  (Fig. 2).

## Obesity

Fourteen studies investigated the association between antibiotic exposure and the risk of developing obesity evaluated by BMI or BMI z-scores in 1,233,944 children (128,132 cases with two studies not reporting number of cases) (Table 1).<sup>14,25,27,33,45,72,81,83,99,125,133,143,147,172</sup> Of the 14 studies, 13 (93%) investigated the effect of antibiotic exposure in the first five years of life (12 (86%) in the first two years of life).<sup>14,25,27,33,72,81,83,99,125,133,143,147,172</sup> Overall, nine (64%) studies reported a significant increased incidence of obesity in children who were exposed to antibiotics.<sup>14,25,27,81,99,125,133,147,172</sup> Three studies reported that the risk of obesity increased with the number of antibiotic courses.<sup>33,72,133</sup> One study reported that the risk of developing obesity was highest with antibiotic exposure in the first six months of life.<sup>25</sup> One study found an increased risk of obesity only after exposure to trimethoprim/sulfamethoxazole but not penicillins, cephalosporins and macrolides.<sup>33</sup> No influence of different antibiotic classes and the risk of increased weight gain was found in two other studies.<sup>133,172</sup>

Of the 14 studies, 10 (71%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 13).<sup>25,27,33,45,72,125,133,143,147,172</sup> Of the 508,908 children exposed to antibiotics 72,186 (14%) developed obesity compared to 30,996 (12%) of the 260,057 children not exposed to antibiotics 47,429 (23%). The overall OR for developing obesity after antibiotic exposure was 1.21, 95% CI 1.05 to 1.40,  $p < 0.01$  (Fig. 2).

## Growth failure

Three studies investigated the association between antibiotic exposure and growth failure evaluated by weight, weight z-scores or weight-for-height z-scores in 13,364 children.<sup>71,145,203</sup> Only one study found that antibiotics were associated with decreased weight gain, this was a small study investigating antibiotic exposure in the first week of life and weight at one year of age.<sup>71</sup>

## Juvenile idiopathic arthritis

Two studies investigated the association between antibiotic exposure and the risk of developing juvenile idiopathic arthritis (JIA) by evaluating ICD codes in 8149 children (1450 cases).<sup>18,64</sup> One study investigated antibiotic exposure in the first and second year of life and any antibiotic exposure before diagnosis<sup>18</sup> and the other study any antibiotic exposure before diagnosis.<sup>64</sup> The risk of developing JIA was increased after antibiotic exposure at all these time points. In the first year of life the strongest association was found after exposure to penicillins and cephalosporins and at the later

time points after exposure to lincosamides and cephalosporins.<sup>18</sup> One study reported that the risk of JIA increased with the number of antibiotic courses.<sup>64</sup>

Both studies were included in the meta-analysis the OR was 1.74 (95%CI 1.21–2.52),  $p < 0.01$  (Fig. 2 and supplementary data Fig. 14).<sup>18,64</sup> Of the 6809 children exposed to antibiotics 1291 (19%) developed JIA compared to 159 (12%) of the 1340 children not exposed to antibiotics.

## Psoriasis

One study investigated the association between antibiotic exposure and the risk of developing psoriasis by evaluating ICD codes in 9295 children (845 cases).<sup>65</sup> They investigated antibiotic exposure in the two years before diagnosis. The OR was 1.75 (95%CI 1.44–2.11),  $p < 0.01$  (adjusted OR 1.20 ((95%CI 1.00–1.50),  $p = 0.05$ )) (Fig. 2 and supplementary data Fig. 15). Of the 7053 children exposed to antibiotics 710 (10%) developed psoriasis compared to 135 (6%) of the 2242 children not exposed to antibiotics.

## Type 1 diabetes

Six studies investigated the association between antibiotic exposure and the risk of developing type 1 diabetes in 2,469,967 children (5557 cases).<sup>36,94,140,152,171,204</sup> The diagnosis was mainly made by ICD codes; in one study by hospital discharge or prescription records. Of the six studies, five (83%) evaluated antibiotic exposure before the age of two years.<sup>36,94,140,152,171</sup> Only one of the studies reported an increased risk of developing type 1 diabetes in children who were exposed to antibiotics, this was in children who had an exposure in the first year of life.<sup>152</sup> No association between the number of antibiotic courses and the risk of type 1 diabetes could be found.<sup>94,140</sup> Two studies found a slightly higher risk of type 1 diabetes after exposure to broad-spectrum antibiotics<sup>36,94</sup> and one after exposure to macrolides compared to penicillins.<sup>204</sup>

Five (83%) studies were included in the meta-analysis the overall OR was 0.99 (95%CI 0.82–1.19),  $p = 0.93$  (Fig. 2 and supplementary data Fig. 16).<sup>36,67,94,152,171</sup> Of the 1,420,794 children exposed to antibiotics 3428 (0.24%) developed type 1 diabetes compared to 1726 (0.18%) of the 947,331 children not exposed to antibiotics.

## Fluorosis

One study investigated the association between antibiotic exposure and the development of fluorosis.<sup>63</sup> The study did not find an increased risk of developing fluorosis in children who were exposed to antibiotics. The OR was 1.11 (95%CI 0.40–3.09),  $p = 0.85$  (Fig. 2 and supplementary data Fig. 17). Of the 174 children exposed to antibiotics 62 (36%) developed fluorosis compared to 6 (33%) of the 18 children not exposed to antibiotics.

## Autism spectrum disorders

Three studies investigated the association between antibiotic exposure and the risk of developing autism spectrum disorders evaluated by ICD codes in 901,012 children (11,374 cases).<sup>21,57,172</sup> All three studies investigated antibiotic exposure in the first two years of life.<sup>21,57,172</sup> Two studies found an association between antibiotic exposure and the development of autism spectrum disorders.<sup>21,172</sup> However, one study only after exposure to cephalosporins and not penicillins, macrolides or sulfonamides.<sup>172</sup> The other study reported that the risk of autism was higher for broad-spectrum antibiotics compared to penicillins.<sup>21</sup> Two studies reported a decreased risk of autism spectrum disorders after exposure to penicillins and one after exposure to macrolides.<sup>57,172</sup> The one study which investigated the effect of the number of antibiotic

courses on the risk of autism spectrum disorders could not find an association.<sup>57</sup>

All three studies were included in the meta-analysis the overall OR was 1.19 (95%CI 1.04–1.36),  $p=0.01$ ) (Fig. 2 and supplementary data Fig. 18).<sup>21,57,172</sup> Of the 587,667 children exposed to antibiotics 7779 (1.3%) developed autism spectrum disorders compared to 3595 (1.1%) of the 313,345 children not exposed to antibiotics.

### Attention deficit hyperactivity disorder

Four studies investigated the association between antibiotic exposure and the development of attention deficit hyperactivity disorders (ADHD) in 756,348 children (25,143 cases with one study not reporting number of cases).<sup>22,58,130,172</sup> They evaluated children by ICD codes. All four studies evaluated antibiotic exposure before two years of age.<sup>22,58,130,172</sup> Two studies reported a significant increased risk of developing ADHD in children who were exposed to antibiotics.<sup>130,172</sup> One study could not find a difference in the risk of developing ADHD after exposure to penicillins or broad-spectrum antibiotics,<sup>22</sup> while another study found an increased risk after exposure to penicillin in girls compared to other antibiotic classes.<sup>172</sup>

Three (75%) studies were included in the meta-analysis and the overall OR was 1.30 (95%CI 0.97–1.75),  $p=0.08$ ) (Fig. 2 and supplementary data Fig. 19).<sup>22,58,172</sup> Of the 528,497 children exposed to antibiotics 18,073 (3%) developed ADHD compared to 7070 (3%) of the 227,405 children not exposed to antibiotics.

### Neurodevelopmental disorders

Two studies investigated the association between antibiotic exposure and the development of neurodevelopmental disorders.<sup>130,172</sup> Both studies evaluated antibiotic exposure before two years of age. The first study found an increased risk of developing learning disorders in children who were exposed to antibiotics in the first two years of life (Fig. 2 and supplementary data Fig. 20).<sup>172</sup> The second study found that exposure to antibiotics in first 6 months of life was associated with lower overall cognitive and verbal comprehension abilities, an increased risk of developing problems with metacognition, executive function, impulsivity, hyperactivity, ADHD, anxiety and emotional problems.<sup>130</sup>

### Discussion

Our rigorous systematic review and meta-analysis suggest an association between antibiotic exposure and the development of several immunological, metabolic, and neurobehavioural adverse long-term health outcomes in children. For developing wheezing and asthma the risk is nearly double in children who are exposed to antibiotics, for JIA and allergic rhinoconjunctivitis up to 75% higher, for food allergies and atopic dermatitis up to 38% higher and for increased weight gain, overweight and obesity 20% higher. No association was found between antibiotic exposure and the risk of developing allergic sensitisation, abdominal pain, inflammatory bowel diseases, celiac disease, type 1 diabetes, psoriasis, fluorosis. There is limited data in relation to the association between antibiotic exposure and developing neuropsychological diseases, however three studies suggest an association between antibiotic exposure and the development of ADHD or learning disorders.<sup>22,130,172</sup>

Our findings are in line with these from smaller systematic reviews which indicated that antibiotic exposure is associated with the development of allergic symptoms such as allergic rhinoconjunctivitis, atopic dermatitis, food allergies, as well as asthma and obesity, but not celiac disease or autism spectrum disorder.<sup>205–218</sup> In contrast, previous reviews have reported an association between antibiotic exposure and the development of inflammatory bowel

diseases, especially Crohn's disease.<sup>219–222</sup> However, these reviews either included less studies, did not pool the results from different studies or included children who were born preterm.

There is an association between the timing, number and type of antibiotic exposure and the risk of adverse health outcomes. Most of the studies included in this review investigated early-life exposure to antibiotics (in the first two years of age). This coincides with the time when antibiotic consumption is at its highest.<sup>4,5</sup> Up to 70% of children receive antibiotics during the second year of life.<sup>4,5</sup> One of the main reasons for antibiotic exposure in this age group are respiratory tract infections, including otitis media, for which antibiotics could be deferred or even avoided.<sup>223–225</sup> Additionally, many studies show that the risk of adverse long-term health outcomes increases with the number of antibiotic courses, particularly for asthma.<sup>13,25,29,32,61,64,76,78,93,103,109,111,115,116,121,123,148,154,176,181,182,191,195,197,198,201</sup> Moreover, the risk of adverse long-term health outcomes is often higher for antibiotics with a broad-spectrum including cephalosporins and macrolides.<sup>18,21,34,36,57,58,61,69,78,91,92,111,121,123,137,157,163,172,182,195,197</sup> These findings underline the importance of antibiotic stewardship, specifically to avoid antibiotics for infections that are likely viral and to use the most narrow-spectrum antibiotic possible.<sup>226</sup> A recent large population-based prospective study showed that a reduction in the incidence of asthma in children correlated with the decrease in antibiotic exposure during infancy.<sup>227</sup>

One of the most probable mechanism underlying the association between antibiotic exposure and adverse long-term health outcomes is changes in the microbiota. It is well known that antibiotics cause profound changes in the microbiota.<sup>228,229</sup> The disruption of intestinal microbiota in the early-life period, during which the microbiota and the immune response develop concurrently, is likely associated with the development of immune- and non-immune-mediated diseases.<sup>230,231</sup> Even transient perturbations of the microbiota during this 'critical window' may compromise immune tolerance and inflammatory responses.<sup>232</sup>

The disruption of intestinal microbiota in the early-life period has been associated with an increased risk of development of the same diseases as antibiotic exposure, including allergies, eczema, asthma, chronic inflammatory bowel disease, obesity and type 1 diabetes.<sup>125,230,233,234</sup> In adolescents with ADHD, perturbations of the intestinal microbiota has also been described.<sup>235</sup>

The strengths of this review are the comprehensive literature search and depth of the review. Most of the included studies defined outcomes using validated tools, adjusted their estimates appropriately, and investigated antibiotic exposure in the first two years of life, which decreases heterogeneity. However, any antibiotic exposure beyond this period could impact the outcome and ignoring them could dilute the effect observed. The same is true for any antibiotic exposure not measured due to the multiple potential sources (e.g. emergency department, general practice, hospital, relative, other country, self-administration), and the availability of antibiotics over the counter in some settings.

The studies included are also limited by their observational nature and potential bias, mainly recall. There are also other potential confounding factors, for example the possibility that early or frequent respiratory infections for which antibiotics are prescribed increase the risk of subsequent asthma. In addition, it can be difficult to differentiate the effect of antibiotic exposure from that of the infection being treated.

Protopathic bias, a false conclusion on a causal relationship between exposure and outcome, is also important to consider. For example, it is possible that children who are predisposed to immune-mediated diseases are more likely to have infections that need antibiotics or seek antibiotics. For example, early symptoms of undiagnosed asthma could be mis-



taken for a respiratory tract infection and be treated with antibiotics. Furthermore, the risk of infection in children with a predisposition to immune-mediated diseases is increased in the years preceding the diagnosis,<sup>236</sup> and therefore causation could be in the opposite direction. Likewise for autism spectrum disorders, in which symptoms can be present from birth but is rarely diagnosed before three years of age, difference in antibiotic exposure could reflect difference in practice. Finally, many unmeasured socio-economics factors could also influence both the exposure to antibiotics and the outcomes.

However, the fact that, in many studies, an association between antibiotic exposure and adverse health-outcomes was only found after broad-spectrum antibiotics and the influence of number of doses of antibiotics supports the notion that antibiotics are the cause.

In summary, the studies in our review suggest that antibiotic exposure plays an important role in the development of childhood immune disorders, likely through disruption of the microbiota during early-life.<sup>227</sup> Although a definite causal association cannot be determined from these studies, the results support the meticulous application of sound antibiotic stewardship to avoid potential adverse long-term health outcomes. It also questions the use of antibiotic prophylaxis outside well-recognised indications. Further assessment of long-term outcomes should be included within RCTs comparing antibiotic treatment or prophylaxis to placebo. Future studies are needed to provide evidence-based interventions to prevent adverse long-term outcomes when antibiotics cannot be avoided, such as modifying the intestinal microbiota with directed pre- and probiotics, bacteriophages, or microbial DNA.<sup>237–239</sup>

## Declaration of Competing Interest

The authors declare no conflict of interest.

## CRediT authorship contribution statement

**Quynh A Duong:** Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Laure F Pittet:** Writing – review & editing. **Nigel Curtis:** Writing – review & editing. **Petra Zimmermann:** Investigation, Formal analysis, Writing – review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jinf.2022.01.005](https://doi.org/10.1016/j.jinf.2022.01.005).

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