



Article scientifique

Article

2017

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies

Albanese, Emiliano; Launer, Lenore J; Egger, Matthias; Prince, Martin J; Giannakopoulos, Panteleimon; Wolters, Frank J; Egan, Kieren

How to cite

ALBANESE, Emiliano et al. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. In: Alzheimer's & Dementia, 2017, vol. 8, p. 165–178. doi: 10.1016/j.dadm.2017.05.007

This publication URL: <https://archive-ouverte.unige.ch/unige:100222>

Publication DOI: [10.1016/j.dadm.2017.05.007](https://doi.org/10.1016/j.dadm.2017.05.007)

Diagnostic Assessment & Prognosis

Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies

Emiliano Albanese^{a,*}, Lenore J. Launer^b, Matthias Egger^c, Martin J. Prince^d,
Panteleimon Giannakopoulos^a, Frank J. Wolters^e, Kieren Egan^f

^aDepartment of Psychiatry, University of Geneva, Switzerland

^bNational Institute on Aging, National Institutes of Health, Bethesda, MD, USA

^cInstitute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

^dInstitute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^eDepartment of Epidemiology, Erasmus MC, Rotterdam, The Netherlands

^fFaculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Abstract

Introduction: We conducted a meta-analysis of the conflicting epidemiologic evidence on the association between midlife body mass index (BMI) and dementia.

Methods: We searched standard databases to identify prospective, population-based studies of dementia risk by midlife underweight, overweight, and obesity. We performed random-effects meta-analyses and meta-regressions of adjusted relative risk (RR) estimates and formally explored between-study heterogeneity.

Results: We included 19 studies on 589,649 participants (2040 incident dementia cases) followed up for up to 42 years. Midlife (age 35 to 65 years) obesity (BMI ≥ 30) (RR, 1.33; 95% confidence interval [CI], 1.08–1.63), but not overweight (25 < BMI < 30) (RR, 1.07; 95% CI, 0.96–1.20), was associated with dementia in late life. The association with midlife underweight (RR, 1.39; 95% CI, 1.13–1.70) was potentially driven by residual confounding (P from meta-regression = .004), selection ($P = .046$), and information bias ($P = .007$).

Discussion: Obesity in midlife increases the risk of dementia. The association between underweight and dementia remains controversial.

© 2017 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords:

Dementia; Body mass index; BMI; Obesity; Meta-analysis

1. Introduction

Underweight, overweight, and obesity have been related to all-cause mortality risk [1] and to various poorer health outcomes [2], but their impact on the risk of dementia

remains debated [3]. Although global epidemic of overweight and obesity accrues, underweight endures in poorer countries [4]. Therefore, the association of both obesity and underweight with dementia has enormous public health implications [5,6].

Excess body weight may increase dementia risk in late life by contributing to the accumulation of brain lesions, through vascular and dysmetabolic pathways [7,8]. However, because body weight tends to decline after midlife, and neuropathology subtly progresses during the long preclinical phase of dementia [9], issues of directionality may arise with age and high body mass index (BMI)

Conflicts of interests: All authors declare no conflicts of interests.

Role of funding source: The funding source had no role in the conduction of this review.

Ethical committee approval: N/A.

*Corresponding author. Tel.: +41-0-793750629; Fax: +41-0-22 372 5754.

E-mail address: Emiliano.albanese@gmail.com

<http://dx.doi.org/10.1016/j.dadm.2017.05.007>

2352-8729/© 2017 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

in late life may appear to be protective [10,11]. Any excess risk is plausibly related to adiposity in midlife, when weight gain is more pronounced [12], and associations with dementia are least likely disease- and age-confounded. However, whether midlife underweight relates to dementia risk remains to be established.

Several systematic reviews and meta-analyses have been published of epidemiologic studies that explored the relationship of standard BMI (body weight in kilograms divided by height in meter square) definitions of underweight ($\text{BMI} < 18.5$), overweight ($25 < \text{BMI} < 30$), and obesity ($\text{BMI} \geq 30$) in midlife with risk of dementia at old age [13–17]. However, the evidence is rapidly expanding and has become highly conflicting. Positive [18,19], null [10,20,21], and inverse [22], associations between midlife BMI and dementia risk have been reported, but whether the study design and methods of primary studies introduced bias and errors, which may explain the marked heterogeneity of results across studies, is not known. A comprehensive and updated systematic review and meta-analysis, coupled with a formal exploration of sources of biases, is warranted. We undertook a systematic review of epidemiologic studies assessing the association of late-life dementia risk to midlife underweight, overweight, and obesity, and we quantified and formally explored the anticipated heterogeneity of results across studies.

2. Materials and methods

2.1. Search strategy and selection criteria

We used the Population, Intervention, Comparison, and Outcome (PICO) framework [23] to search PubMed, Embase, Google Scholar, and the Cochrane library. We searched for prospective, population-based studies published in English between January 1966 and October 2016 reporting risk of dementia in old age (65 years or more) as a function of exposure to underweight, overweight, or obesity in midlife, defined as the period between early adulthood and old age (35–65 years). To complement the electronic searches, we hand-searched the bibliographies of relevant publications and contacted experts in the field. Two independent reviewers (E.A. and K.E.) examined titles and abstracts using the following inclusion criteria: (1) cohort studies or studies conducted using observational routinely collected health data [24], with a 10 years or longer midlife to late-life follow-ups; (2) measures of midlife underweight, overweight, and obesity modeled as independent variables in the analysis, and (3) dementia diagnosis in late life (i.e., 65 years or more). We excluded clinical, cross-sectional and experimental studies, studies on trajectories of body weight by dementia status [25], and duplicated publications. Final decisions on inclusion were made by consensus. In the meta-analysis, we included studies that reported risk estimates for the association of midlife underweight, overweight, and obesity with a dementia diagnosis in late life.

2.2. Definitions

All included studies used BMI as a measure of total adiposity, with the standard World Health Organization BMI groups for underweight ($\text{BMI} \leq 18.5$), normal weight ($18.5 < \text{BMI} < 25$), overweight ($25 \leq \text{BMI} < 30$), and obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$); slightly different BMI cutoffs of underweight (i.e., $\text{BMI} < 20 \text{ kg/m}^2$) were deemed appropriate for our analysis (Launer LJ, personal communication, 2015) [22]. We considered dementia diagnosis according to standard diagnostic criteria, established using validated multiphase diagnostic procedures, or based on death certificates, medical records, and hospital records. We contacted the authors of primary studies to obtain further data and information when needed.

2.3. Data extraction

Two reviewers (E.A. and K.E.) used purposely designed forms to independently abstract the following information: study design, place, participants, outcome (e.g., dementia diagnosis), and exposure's ascertainment methods; covariates and confounders (including lifestyle, sociodemographic, health characteristics, and *APOE* polymorphisms); and the statistical methods used. The main results of the most adjusted models were abstracted and retained for the meta-analysis.

2.4. Assessment of risk of bias

We assessed the susceptibility to bias of the included studies combining the approaches recommended by the Methods in Longitudinal Research on Dementia (MELODEM) Initiative for dementia research [26] and by Sanderson et al. for cohort studies [27]. Two independent researchers (E.A. and K.E.) appraised the methodological quality (0 = low, 1 = adequate, and 2 = optimal) across seven criteria: (1) study design; (2) participants' mean (or median) age when body mass was measured; (3) underweight, overweight, and obesity ascertainment methods; (4) dementia diagnostic criteria and ascertainment procedures; (5) adjustment for potential confounders and relevant covariates [28]; (6) follow-up length between exposure assessment in midlife and dementia diagnosis at older ages; and (7) study sample attrition and proportion of participants at follow-up.

2.5. Statistical analysis

We combined the dementia risk estimates separately by midlife underweight, overweight, and obesity compared with normal BMI in random-effects models, pooling the log-transformed relative risks (RRs), hazard ratios, and odds ratios under the equivalence assumption for noncommon events. If multiple results were reported for the same cohort we used the later (i.e., with more years of follow-up) [29,30] or the most comprehensive findings [31], we combined risk estimates of men and women (except when

the sex \times BMI interaction terms in the primary study were statistically significant [19]), and we conducted sensitivity analyses stratified by sex. Because proneness to errors and bias in population-based cohort studies and in studies conducted using routinely collected health data differ substantially [24], we stratified the main meta-analyses by study design and compared the pooled dementia risk estimates and heterogeneities accordingly.

We quantified heterogeneity using the standard low (25%), moderate (50%), and high (75%) Higgins I^2 values cutoffs [32], and we investigated whether, and the extent to which, any difference between studies in dementia risk estimates could be explained by their study design characteristics in a set of meta-regression analyses.

In sensitivity analyses, we reran the meta-analyses for underweight, overweight, and obesity by length of follow-up time (the interval between ascertainment of midlife BMI and dementia diagnosis at old age, equal, or more than vs. less than 20 years), sex (studies conducted in men or women only, or both), method of dementia diagnosis, and statistical adjustment, and we formally explored the variation in between-study variance (tau squared) across models [33].

Finally we investigated any suggestion of publication bias and small-study effects by visual inspection of Funnel plots, and we calculated asymmetry with modified Egger regression using the Stata metabias routine [34,35]. For illustrative purposes, we presented graphically a meta-regression “bubble plot” by proneness to bias in the primary studies. Further details about our methods are reported in Appendix A. We used Stata 14 for all analyses (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Included and excluded studies

Of the 512 records identified 426 were excluded after title and abstract review. We examined the 86 potentially eligible publications and two more retrieved from other sources as full texts, 30 reports met the inclusion criteria. Of these, 11 were excluded because midlife BMI was predicted rather than measured in midlife [14], was modeled as a continuous variable [36], as a covariate in multivariate models [37,38], or data were previously published [21,39–43]. We retained

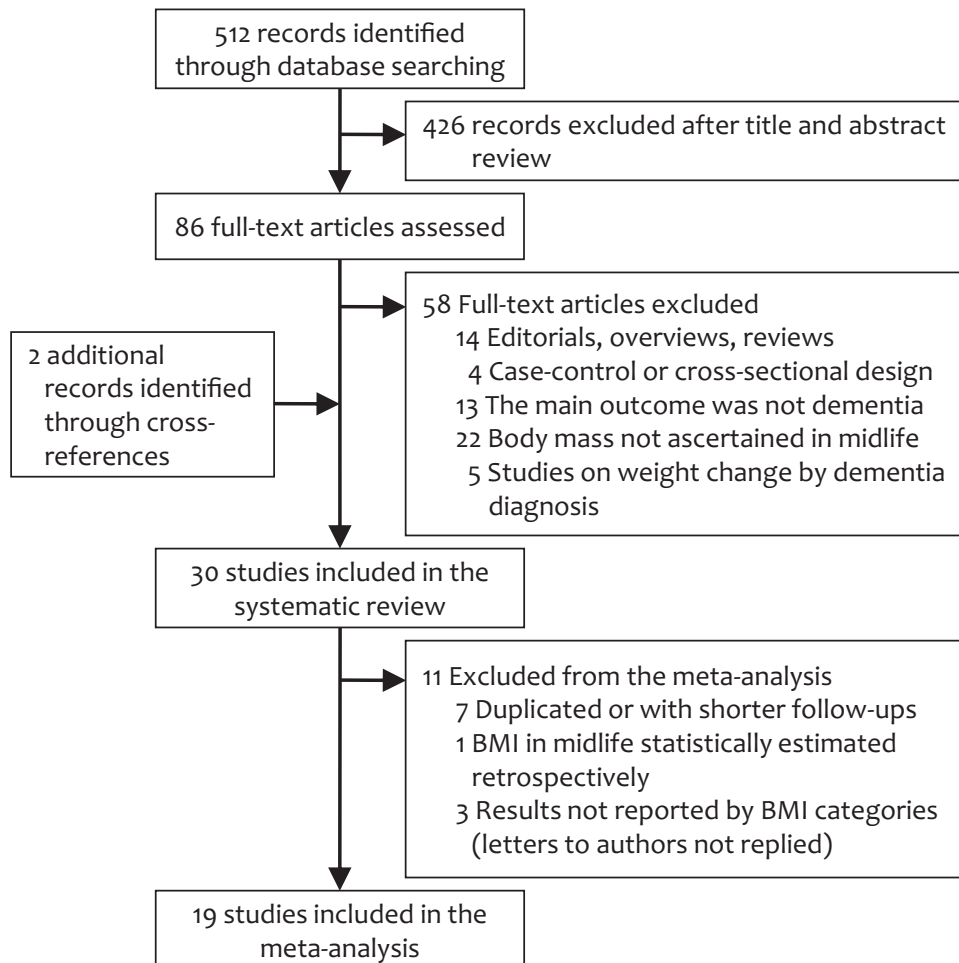


Fig. 1. Identification and selection of eligible studies.

Table 1
Characteristics of included studies

| Study acronym or name (location) | Analytic sample (% of female) | Mean follow-up, years (SD) | Body mass ascertainment procedures | Mean age, y (SD or range) when BMI was ascertained | Dementia ascertainment (diagnostic criteria), number of cases | Confounders included in the adjusted model |
|--|-------------------------------|----------------------------|--|--|---|--|
| Cohort studies | | | | | | |
| CHS (USA) [48] | 2616 (59) | 20.0 (N/A) | Retrospectively self-reported estimates, obtained in late life | 50 (N/A) | Multiphase consensus diagnosis (clinical consensus), 461 | Age, race, sex, education, <i>APOE</i> ϵ 4 allele, late life: CRP, IL-6, hypertension, cholesterol, diabetes, CHD, ankle-arm index, smoking, total kilocalories intake |
| PPSW (Sweden) [10] | 651 (100) | 32.0 (4.0) | Standard, direct measures of body height and weight (results on overweight only) | 47 (N/A) | Clinical consensus (DSM-III-R), 161 | Age, triglycerides, cholesterol, SBP, age at menopause, education, diabetes |
| Twin Registry (Sweden) [30] | 8534 (60) | 30.0 (N/A) | Self-reported estimates, obtained in midlife | 43 (15) | Multiphase consensus diagnosis (DSM-IV), 464 | Age, sex, education, diabetes, hypertension, stroke, and heart disease |
| IIHD (Israel) [51] | 1620 (0) | 37.0 (6.0) | Standardized direct measure of weight and self-reported height | 44 (N/A) | Multiphase consensus diagnosis (DSM-IV), 307 | Age, diabetes, body height, SES |
| Twin Registry (Finland) [52] | 1601 (49) | 22.6 (2.3) | Self-reported estimates, obtained in midlife (no results on underweight) | 51 (6.1) | Automated algorithm (TELE; 16 cutoff), 650 | Age, sex, education, <i>APOE</i> ϵ 4 allele, follow-up years |
| CAIDE (Finland) [29] | 1304 (61) | 26.0 (5.1) | Standardized direct measures | 50 (N/A) | Multiphase consensus diagnosis (DSM-IV), 169 | Age, sex, <i>APOE</i> , residence, smoking, education, income, diabetes, CVD, cerebrovascular diseases, SBP, cholesterol |
| AGES (Island) [20] | 3864 (57) | 26.2 (4.9) | Standard, direct measures of body height and weight | 50 (4.7) | Multiphase consensus diagnosis (DSM-IV), 190 | Age, sex, follow-up years, <i>APOE</i> ϵ 4 allele; midlife: education, exercise, SBP, DBP, cholesterol; late life: coronary artery calcium, coronary artery disease, hypertension, diabetes, depression, alcohol and smoking habits, and MRI brain measures (white matter lesions and intracranial volumes) |
| HAAS (USA) (Launer LJ, personal communication, 2015) | 3733 (0) | 23.0 (4.0) | Standard, direct measures of body height and weight | 59 (51–74) | Multiphase consensus diagnosis (DSM-III-R) 112 | Age, education, stroke, hypertension, diabetes, smoking, <i>APOE</i> ϵ 4, impaired physical function, CES-D |

| | | | | | | |
|---|--------------|------------|--|-------------|--|--|
| Rotterdam study (the Netherlands) [47] | 2085 (58) | 15.0 (5.7) | Standard, direct measures of body height and weight | 58 (1.4) | Multiphase consensus diagnosis, integrated with medical records (DSM-III-R) 81 | Age, sex, study cohort, systolic and diastolic blood pressure, serum cholesterol and HDL, use of antihypertensive medication, use of lipid-lowering medication, diabetes mellitus, smoking (never, former, current), level of education, <i>APOE</i> genotype, history of stroke |
| Studies that used, in part or entirely, observational routinely collected health data | | | | | | |
| MPPS (Sweden) [18] | 7402 (0) | 25.0 (7.0) | Standard, direct measures of body height and weight | 52 (2) | Hospital discharge or death certificates (ICD-9; ICD-10) 254 | Age, smoke, exercise, occupation; midlife: diabetes, SBP, cholesterol |
| Kaiser Permanent (USA) [19] | 10,276 (55) | 26.0 (9.0) | Standard, direct measures of body height and weight | 43 (N/A) | Outpatient medical records (ICD-9; ICD-10) 713 | Age, sex; midlife: education, race, marital status, hypertension, diabetes, cholesterol; and late-life hypertension, stroke, diabetes, IHD, cholesterol |
| MRMD and CSP (Taiwan) [46] | 785 (45) | 15.0 (4.0) | Standard, direct measures of body height and weight | 58 (N/A) | Hospital records (DSM-IV, Chinese version) 157 | Self-reported cardiovascular diseases and hypertension |
| ARIC (USA) [45] | 11,151 (57) | 12.8 (N/A) | Standard, direct measures of body height and weight | 55 (N/A) | Medical records (ICD-9) 203 | Age, sex, race, study site, education, occupational level, cognitive tests at baseline, CVRFs, <i>APOE</i> ϵ 4 allele |
| 7 Countries (Finland, Greece, Italy, the Netherlands, ex-Yugoslavia; Japan, USA) [44] | 10,211 (0) | 25.3 (6.0) | Standard, direct measures of body height and weight | 49 (40–59) | Death certificates (ICD-8, code 290) 160 | Age, study cohort, occupation, body height, smoking; midlife cholesterol, hypertension, FVC, CVD |
| LSUHCS (USA) [49] | 44,660 (N/A) | 12.9 (N/A) | Midlife body height and weight direct measures (no results on underweight) | N/A (30–96) | Revised medical records (DSM-IV or ICD-9) 388 | Age, sex, smoking, BP, cholesterol, triglycerides; diabetes, medications |
| HES (UK) [53] | 241,146 (57) | 15.0 (N/A) | Admission for clinically diagnosed obesity | 50 (N/A) | Hospital records or death certificates (ICD-10) 321 | Sex, place of residence |
| CPRD (UK) [22] | 172,313 (55) | 18.3 (2.2) | Standard, direct measures of body height and weight | 55 (N/A) | Clinical records or death certificates (dementia subtypes diagnoses) 620 | Age, sex, smoking, alcohol, statins, antihypertensive use, diabetes, myocardial infarction |
| Whitehall (UK) [50] | 18,823 (0) | 42.0 (N/A) | Standard, direct measures of body height and weight | 55 (40–69) | Death certificates (not specified) 283 | Smoking habit and birth cohort |
| NCS and CONOR (Norway) [31] | 46,874 (51) | 33.0 (N/A) | Standard, direct measures of body height and weight | 43 (N/A) | Death certificates (ICD-9; ICD-10) 711 | Age, sex, study site (county); midlife diabetes, physical inactivity, smoking, SBP, DBP, cholesterol, and education |

Abbreviations: AGES, Age, Gene/Environment Susceptibility—Reykjavik Study (Reykjavik, Iceland); ARIC, atherosclerosis risk in communities; BMI, body mass index; CAIDE, cardiovascular risk factors aging and dementia; CES-D, centers for epidemiologic studies depression scale; CHD, coronary heart disease; CHS, Cardiovascular Health Study (four US centers in MD, CA, PA, NC); CONOR, the cohort of Norway; CPRD, Clinical Practice Research Datalink; CRP, C-reactive protein; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DBP, diastolic blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; FVC, forced vital capacity; HAAS, Honolulu-Asia Aging Study; HDL, high-density lipoproteins; HES, English National Hospital Episodes Statistics; ICD, International Statistical Classification of Diseases and Related Health Problems; IHD, ischemic heart disease; IIHD, Israel Ischemic Heart Disease Project; IL-6, interleukin 6; LSUHCS, Louisiana State University Hospital-Based Longitudinal Study; MPPS, Multifactor Primary Prevention Study (Goteborg, Sweden); MRI, magnetic resonance imaging scan; MRMD and CSP, Multiple Risk Factors for Major Diseases and Cancer Screening Program; NCS, The Norwegian Counties Study; PPSW, Prospective Population Study of Women in Sweden; SD, standard deviation; SBP, systolic blood pressure; SES, socioeconomic status; TELE, validated telephone interview to detect cognitive impairment.

19 studies for further analysis (Launer LJ, personal communication, 2015) [10,18–20,22,29–31,44–53]. The selection process is shown in Fig. 1 and reported in detail in Appendix B and C.

Except for one multicenter study [44], one in Israel [51], and one in Taiwan [46], studies were conducted in Northern European countries including the UK [10,18,20,22,29–31,49,50,52,53], or the USA (Launer LJ, personal communication, 2015) [19,45,48,49]. Nine were purposely designed population-based prospective cohort studies (Launer LJ, personal communication, 2015) [10,20,29,30,47,48,51,52], the other 10 were cohort studies that used, to different extents, routinely collected health data of exposure status (i.e., height and weight measured during routine health checks or visits in midlife) or outcome (i.e., dementia diagnosis from hospital records or death certificates). The sample sizes ranged from 651 [10] to 241,146 [53] for a total of 589,649 participants who were followed up for up to 42 years from midlife to late life [50]. There were 2040 incident dementia cases. Most studies included men and women, one study included only women [10], and five studies included only men (Launer LJ, personal communication, 2015) [18,44,50,51]. In one study, the first recorded clinical diagnosis of obesity was extracted from hospital admission records [53], in three studies body height and weight were self-reported in midlife [30,52], or retrospectively in late life by dementia-free participants [48]. Standard, direct measures of height and weight were collected at baseline and used to calculate BMI in the remaining studies. The participants' ages at baseline did not substantially differ, but the exact age ranges could be determined only for six studies [18,20,30,44,47,52]. All purposely designed cohort studies adjudicated dementia diagnosis through clinical consensus using validated, multiphase diagnostic procedures based on various screening instruments followed by in-depth clinical evaluation of screen positives. Dementia was ascertained from death certificates in three cohort studies [31,44,50], a combination of data extracted from medical and hospital records [18,19,22,45,46,49,53], or a validated algorithm of a telephone interview [52]. Dementia diagnostic criteria included the International Classification of Diseases [54], the Diagnostic and Statistical Manual of Mental Disorders (DSM, III-R and IV Edition) for all dementias and dementia subtypes including Alzheimer's disease (AD) and Vascular dementia (VaD) according to standard criteria (Table 1) [55–57].

3.2. Risk of bias assessment

In four studies, age ranges of participants were wide and a small proportion were likely older than 65 years at baseline when midlife exposure status was assessed (Launer LJ, personal communication, 2015) [49–51]. With two exceptions, recall bias [48] and measurement errors or inconsistencies [53] in exposure ascertainment were

unlikely. Outcome ascertainment was considered unbiased in the eight studies that did not rely on death certificates or hospital records (Launer LJ, personal communication, 2015) [10,20,29,30,47,51]. Adjustment for confounders attenuated associations [29,48,52] and residual confounding was probable in the five studies that did not adjust for education [22,46,49,50,53]. The potential confounding effect of stroke or cerebrovascular damage was adjusted for in four studies only. Only few studies had relatively short midlife to late life follow-up periods (i.e., less than 20 years) [22,45–47,49,53]. Finally, relevant proportions of participants were lost at the follow-ups (i.e., up to 50%) in several studies, and potential bias because of attrition was addressed in only three studies (Table 2) [10,20,22].

3.3. Meta-analyses and meta-regressions

There were 12 studies contributing data on midlife underweight (with the Kaiser Permanente study contributing two data points, one for men and one for women). Compared with healthy weight being underweight in midlife was associated with 39% higher risk of dementia (RR, 1.39; 95% confidence interval [CI], 1.13–1.70). Results were heterogeneous across studies (Higgins' $I^2 = 42.1\%$; Cochrane $Q P = .055$) and the increased risk for dementia was evident in studies that relied on routinely collected health data (RR, 1.73; 95% CI, 1.43–2.09), but not in the purposely designed cohort studies (RR, 1.03; 95% CI, 0.85–1.25; Fig. 2); P value for the interaction by study design in dementia risk from meta-regression = .007. The meta-regression results are presented in Appendix D.

Our random-effects meta-analysis indicated that being overweight in midlife does not increase dementia risk (RR, 1.07; 95% CI, 0.96–1.20) (Fig. 3). Results were heterogeneous across cohort studies ($I^2 = 59.3\%$; $P = .002$), and the effect modification by study design in dementia risk was not significant ($P = .434$) (Appendix D).

The risk of dementia in those who were obese in midlife was 33% higher (RR, 1.33; 95% CI, 1.08–1.634), and the heterogeneity among studies was high ($I^2 = 77.1\%$; $P < .001$). Among purposely designed cohort studies the combined RR indicated a significant 47% higher risk of dementia (RR, 1.47; 95% CI, 1.06–2.03). Results were markedly heterogeneous between studies that made use of routinely collected health data, including hospital records and death certificates ($I^2 = 83.4\%$; $P < .001$), and the CIs for the meta-analyzed dementia risk of midlife obesity were wide and included one (RR, 1.23; 95% CI, 0.93–1.64) (Fig. 4). There was no interaction by study design in the association between midlife obesity and dementia ($P = .826$) (Appendix D). Fig. 5 displays the pooled adjusted RRs of dementia (with 95% CI) by midlife underweight, overweight, and obesity in all studies and by study design.

In the meta-regression, the association between midlife underweight and dementia was significantly more likely

Table 2
Critical appraisal of included studies

| Study name or acronym (location) | Sampling procedure | Age at baseline | Exposure | Outcome | Adjustment | Follow-up length | Losses at follow-up |
|---|--------------------|-----------------|----------|---------|------------|------------------|---------------------|
| Cohort studies | | | | | | | |
| CHS (USA) [48] | 1 | 2 | 0 | 1 | 2 | 2 | 0 |
| PPSW (Sweden) [10] | 2 | 2 | 2 | 2 | 1 | 2 | 0 |
| Twin Registry (Sweden) [30] | 1 | 2 | 1 | 1 | 1 | 2 | 0 |
| IHD (Israel) [51] | 2 | 1 | 2 | 1 | 1 | 2 | 0 |
| Twin Registry (Finland) [52] | 1 | 2 | 1 | 0 | 2 | 2 | 1 |
| CAIDE (Finland) [29] | 2 | 2 | 2 | 1 | 2 | 2 | 0 |
| AGES (Iceland) [20] | 2 | 2 | 2 | 1 | 2 | 2 | 2 |
| HAAS (USA) (Launer LJ, personal communication, 2015) | 2 | 0 | 2 | 1 | 2 | 2 | 2 |
| Rotterdam study (the Netherlands) [47] | 2 | 2 | 2 | 1 | 2 | 1 | 2 |
| Studies that used, in part or entirely, observational routinely collected health data | | | | | | | |
| MPPS (Sweden) [18] | 1 | 2 | 2 | 0 | 1 | 2 | 2 |
| Kaiser Permanente (USA) [19] | 0 | 2 | 2 | 0 | 1 | 2 | 0 |
| MRMD and CSP (Taiwan) [46] | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| ARIC (USA) [45] | 0 | 2 | 2 | 0 | 2 | 0 | 2 |
| 7 Countries (Finland, Greece, Italy, the Netherlands, ex-Yugoslavia; Japan, USA) [44] | 1 | 2 | 2 | 0 | 1 | 2 | 2 |
| LSUHCS (USA) [49] | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| HES (UK) [53] | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| CPRD (UK) [22] | 0 | 2 | 2 | 0 | 0 | 1 | 0 |
| Whitehall (UK) [50] | 2 | 0 | 2 | 0 | 0 | 2 | 0 |
| NCS and CONOR (Norway) [31] | 1 | 2 | 2 | 0 | 1 | 2 | 2 |

Abbreviations: AGES, Age, Gene/Environment Susceptibility—Reykjavik Study (Reykjavik, Iceland); ARIC, atherosclerosis risk in communities; CAIDE, cardiovascular risk factors aging and dementia; CHS, Cardiovascular Health Study (four US centers in MD, CA, PA, NC); CONOR, The Cohort of Norway; CPRD, Clinical Practice Research Datalink; HAAS, Honolulu-Asia Aging Study; HES, English National Hospital Episodes Statistics; IHD, Israel Ischemic Heart Disease Project; MPPS, Multifactor Primary Prevention Study (Goteborg, Sweden); MRMD and CSP, Multiple Risk Factors for Major Diseases and Cancer Screening Program; NCS, The Norwegian Counties Study; PPSW, Prospective Population Study of Women in Sweden.

NOTE. The critical appraisal criteria were defined as follows: *Sampling*: 0 = inadequate (sampling is neither random nor systematic or does not guarantee the representativeness of the target or frame population; twin studies are not considered representative of the general population); 1 = adequate (systematic samples drawn from community dwelling people); 2 = optimal (random, representative samples of the target population based on electoral or other registries). *Age at baseline* when BMI was measured: 0 = inadequate (wide age ranges that may exceed 60 years); 1 = adequate mean age for “midlife” (i.e., younger than 65 years) with wide ranges; 2 = optimal: mean age limited to midlife and narrow age ranges. *Exposure* ascertainment: 0 = inadequate (self-reported in late life; nonstandard measures); 1 = adequate (self-reported in midlife with validation of the procedure); 2 = optimal (direct, standard measures in midlife). *Outcome* ascertainment: 0 = record-linkage (based on hospital records and death certificates); 1 = clinical consensus diagnosis based on one or multiphase design with screening; 2 = one-phase designs or correctly applied multiphase designs (i.e., correct weighing back of those who screened negative in phase 1). *Adjustment*: 0 = inadequate (established potential confounders are missing, ex. education, sex, or age); 1 = adequate (includes sociodemographic and health characteristics); 2 = complete (includes established potential confounders spanning sociodemographic, health characteristics, and APOE e4 polymorphism). *Follow-up length* (from midlife to late life): 0 = less than 15 years; 1 = more than 15 years for the all sample; 2 = 20 years or more than for the all sample. *Proportion of participants at follow-up*: 0 = less than 50%; 1 = 50.1% to 75%; 2 = 75.1% or more (for registry-based study we considered the size of the study sample relative to the database population). *Overall quality score*: this is obtained by summing up the scores of the eight quality criteria (range 0–14).

found in studies more prone to selection bias ($P = .046$) and outcome ascertainment bias ($P = .007$), with shorter follow-up periods ($P = .024$) and greater participants' attrition ($P = .007$), and in which potential confounders were less adequately controlled for ($P = .004$) (Appendix D). Overall, the RR of dementia by midlife underweight decreased by 9% (95% CI, 0.15–0.03; $P = .009$) per unit increase in the overall score obtained combining the individual elements of our critical appraisal tool. No such differences were found for the associations of dementia with midlife overweight and obesity when we accounted for the study design features of the included studies (Appendix D and e-Fig. 2).

In the sensitivity analysis, there was no association between obesity and dementia in the six studies with shorter follow-ups (i.e., less than 20 years) (RR, 1.18; 95% CI, 0.75–1.85), with less adequate adjustment (RR, 1.23; 95%

CI, 0.78–1.95), or those conducted in men only (RR, 1.28; 95% CI, 0.92–1.78) (Appendix E). Finally, on inspection of the underweight funnel plot there was some suggestion of asymmetry owing to missing positive studies for underweight and dementia based on small registry-derived data. However, the formal asymmetry tests were not significant for cohort (Egger's test P value = .158) and in studies that (also) used routinely collected health data ($P = .266$). We noticed no asymmetry inspecting funnel plots, nor were the formal asymmetry tests significant for overweight ($P > .208$) and obesity ($P > .482$) (e-Fig. 2).

4. Discussion

We have conducted the most comprehensive systematic review to date of longitudinal studies that have investigated

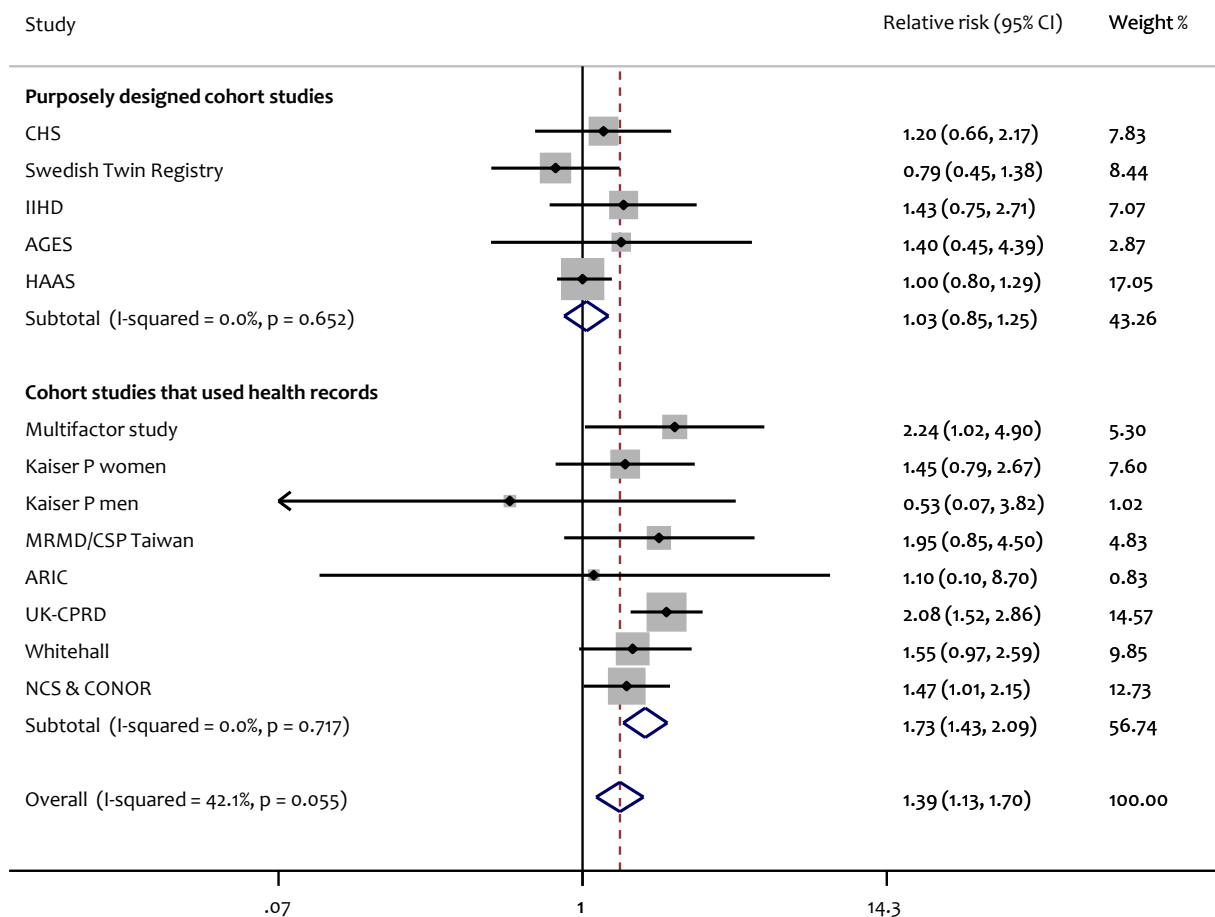


Fig. 2. Adjusted dementia relative risk by midlife underweight compared with normal body mass index.

the association between BMI in midlife and dementia risk. Our results are based on 589,649 participants from up to 19 cohort studies and indicate that while being overweight does not and being obese in midlife does confer a significant increased risk of developing dementia at older ages. The results on the positive association between midlife underweight and dementia were inconsistent across studies.

Excess body weight in midlife may contribute to vascular and neurodegenerative damage that underpins dementia through vascular and dysmetabolic pathways [7], and directly through cell-signaling proteins secreted by the adipose tissue (e.g., leptin and adiponectin) [58]. Yet, mechanistic [59] and epidemiologic evidence [60] suggests that dementia may cause involuntary weight loss well before its clinical onset [25,61], and low BMI may spuriously appear to be detrimental for dementia (and high BMI protective) [62]. Therefore, focusing on midlife exposure was important to assessing any differences in dementia risk, and our meta-regressions suggest that the positive associations between midlife underweight and dementia, which were reported only in studies with follow-up periods less than 20 years [22,45–47,49,53], may be disease-confounded and be explained, at least in part, by reverse causality.

Numerous factors, including depression, diabetes, hypertension, and stroke may confound or mediate the association between BMI and dementia [63], and the covariates in the statistical models varied significantly between the included studies. Although some factors may lay on the causal pathway between obesity and dementia, residual confounding may not be excluded and the lack of adjustment for educational level [22,49,50,53], or type 2 diabetes [44–46,50,52], which are strongly associated with both BMI [64,65], and dementia [66,67], may have contributed to the heterogeneity of findings.

Ascertainment procedures for dementia varied significantly across studies from multiphase clinical consensus approaches (Launer LJ, personal communication, 2015) [10,20,29,30,47,48,51] to routinely recorded health data and death certificates [31,44,50]. The use of medical records and administrative data presents both great opportunities and challenges for dementia research [24,26], because the use of these records as proxies for dementia is hampered by underreporting and measurement variability that may move the risk estimates toward the null effect [68,69], and the diagnosis may be more likely in obese subjects who tend to be sicker and make more

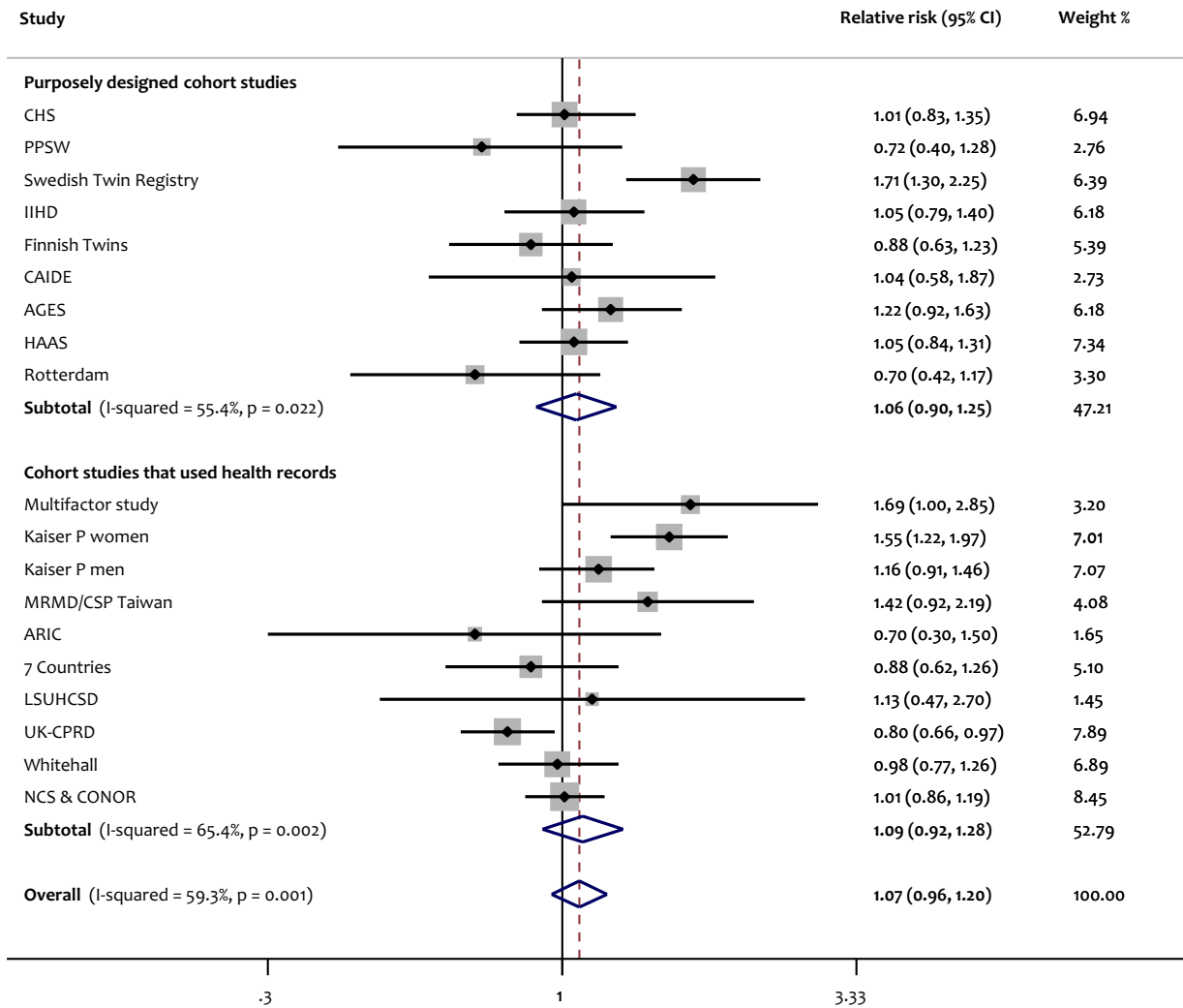


Fig. 3. Adjusted dementia relative risk by midlife overweight compared with normal body mass index.

use of health services. This potential surveillance bias may explain some of the most extreme positive results among some of the studies included in our review [18,19,46,53]. A subtle length/survival bias may not be excluded either [70]. Obesity increases mortality risk and may significantly reduce survival in those with dementia because of poorer health [1]. The use of routine data for dementia diagnosis is biased by the severity of the disease [71]; therefore, the shorter survival in those with dementia and obesity-related comorbidities make them less likely to receive a diagnosis before they die. Participants may be systematically misclassified as disease-free, and competing risks model may not counteract this misclassification error because the assumption of nondifferential effects of exposure status on the analytic sample derivation may not hold [72].

Other sources of bias may exist. Underweight and obesity are plausibly related to access and use of primary care services, and they may influence data collection [24]. Lack of clinical measures and missing values were more likely in

those with worse cardiovascular risk profiles who were thus excluded from the analytic samples [20,30], and an unknown number of people who were obese or underweight in midlife and at higher risk of dementia could have been systematically excluded because of differential study enrollment, and differential attrition and survival after enrollment. Both length and selection biases could explain some recent findings on a seeming protective effect of excess body weight in midlife for dementia risk [22]. Nevertheless, across cohort studies there was a significant and consistent 47% higher dementia risk associated with obesity in midlife compared with normal BMI, and the magnitude of the overall effect in the main analysis (i.e., 33%) may be only a slight underestimate.

Some limitations are worth noting. We focused on “all dementia” diagnosis as a proxy of the prevalence of the dementia syndrome in general populations and did not explore separately AD, VaD, and other dementia subtypes. However, clear distinctions and differential diagnoses require a more

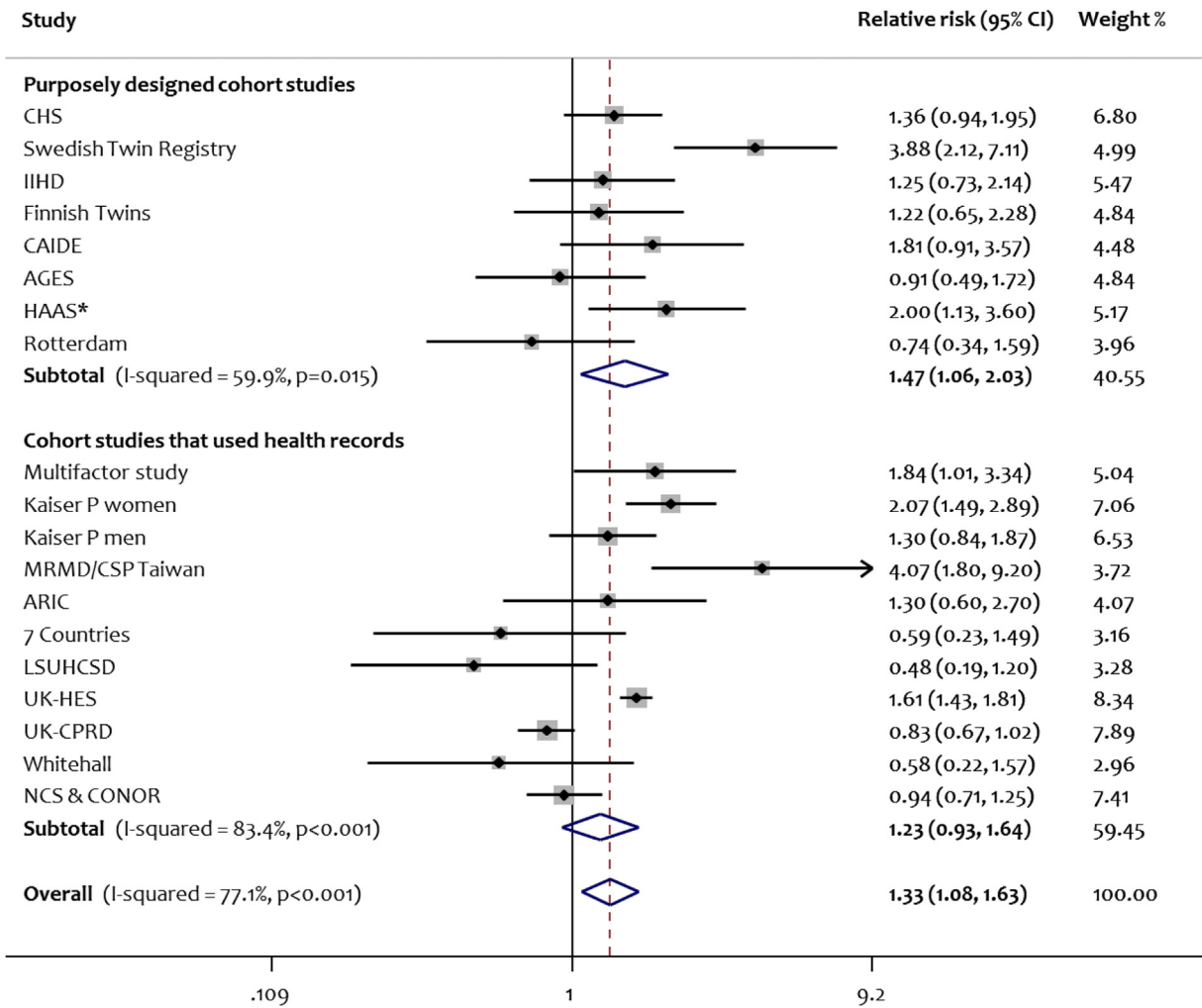


Fig. 4. Adjusted dementia relative risk by midlife obesity compared with normal body mass index.

detailed clinical evaluation over time, which is not usually possible in epidemiologic studies. We used standard World Health Organization categories of midlife BMI in our analysis. BMI is a surrogate measure of global adiposity and has

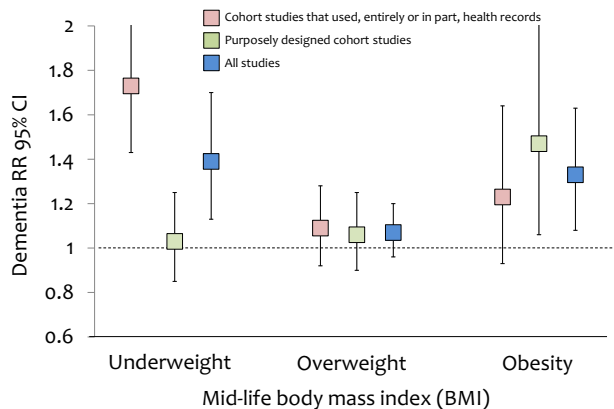


Fig. 5. Pooled dementia risks by midlife underweight, overweight, and obesity.

limitations, although particularly in older adults [73]. However, BMI can accurately distinguish between categories of percentage of body fat, it performs similar to other anthropometric measures in the population (including waist circumference) [74], and is associated with mortality greater than and less than the conventional normal range of 22.5 to 25 kg/m² [1]. Thus, we integrated our searches contacting several authors, retrieved, and included twice the number of reports compared with previous reviews [13,15], and gathered missing information to harmonize results of primary studies on dementia risk by midlife BMI categories are all major strengths of our review along with the formal exploration of the sources of heterogeneity of results.

Although comparisons are not straightforward, because among the 19 studies that met our inclusion criteria 12 were published only recently (Launer LJ, personal communication, 2015) [20,22,29–31,47,49–53], our findings on midlife obesity are in line with those of previous reviews [13,14]. Namely, a meta-analysis of three studies found a 64% significantly higher all-dementia risk associated with

Box 1**Future directions, a roadmap to further explore the link of adiposity and dementia**

1. *Life course observational epidemiologic research* aimed at providing clues to the etiology of dementia, building and testing theoretical models of causal pathways to dementia in late life that account for the timing and duration of exposure to high and low adiposity throughout the life course, and for the concomitant potential modifying or mediating effect of other exposures.
2. *Basic science research* to explore biologically plausible mechanisms and pathways through which high (and low) adiposity may modulate the risk of dementia, its biological underpinnings and its clinical expression, at both the induction and latency phase of the disease.
3. *Clinical-translational and implementation research* aimed at designing complex interventions for brain and cognitive health promotion, and prevention and treatment of impairment, in patients and target populations, testing their efficacy and effectiveness, and the scalability of their provision through health and social care services.

midlife obesity compared with healthy body weight [13], and a similar magnitude (i.e., 60%) was found combining the results of five cohort studies for Alzheimer's disease risk by others [75]. An increased risk of dementia by midlife overweight was found in a previous meta-analysis [13] of three cohort studies [18,19,48]. Our results are based on 14 additional data points, which became available only in recent years, and indicate that there is no association between midlife overweight and any dementia, which is consistent with the findings of other systematic reviews [15–17]. As outlined earlier, weight loss in people with dementia begins decades before clinical onset and accrues gradually through stages of dementia [59,76,77], such that midlife to late-life trajectories of body weight have been found to vary by dementia status at older ages [25,61,78,79]. However, the biological plausibility of the link between underweight in midlife and risk of dementia in late life remains a matter of debate, and the scanty epidemiologic evidence limits comparisons with our results. Evidence is urgently needed particularly from low and middle income countries, where prevalence of underweight is highest.

Our main findings are consistent with the hypothesis of a causal link between obesity and dementia [8]. Because the prevalence of obesity exceeded 10% in most countries in 2014 [4], and the steepest increases in obesity prevalences are occurring in those regions where populations are also more rapidly aging [80], the detrimental contribution of obesity to the catastrophic projections of dementia prevalence in the coming years [81] seems destined to accrue heftily, particularly in low and middle income countries [6]. In addition, because dementia risk may further increase with longer duration and accumulation of exposure to high adiposity throughout the life course [7], there is an urgent need to investigate the association of obesity in childhood and throughout adulthood with dementia in late life. Future directions in research could also include the use of individual-participant data meta-analysis [1] and Mendelian randomization designs (that exploit gene polymorphisms of known function to examine the causal effect of

a modifiable exposure on disease in nonexperimental studies) [82], which may have the potential to advance significantly our knowledge on modifiable risk and protective factors of dementia. Mechanistic studies are also warranted to identify the pathways through which obesity (and underweight) may increase dementia risk, and translational research should investigate whether weight loss in midlife can influence metabolic flexibility and vascular reactivity through long-term positive effects on intermediate metabolism, endothelial function, inflammation, and oxidative stress (Box 1). Nonetheless, we maintain that the lack of any such evidence should not delay public health actions on a global scale aimed at reducing the population exposure to interrelated vascular risk factors (including obesity, diabetes, high blood pressure, and physical inactivity), and that these actions should target young, middle aged, and older people alike to reduce dementia risk and to attain better and longer lasting health results for individuals, and greater benefits to societies at large.

Acknowledgments

E.A. is supported by a Swiss School of Public Health (SSPH+) professorship grant. We thank all authors of primary studies who kindly responded to our requests to provide unpublished data and results used in this analysis.

Authors' contributions: E.A. conceived the study and drafted the manuscript. E.A. and K.I. designed the systematic review and meta-analysis methods with M.E. E.A. and K.I. conducted the systematic review, extracted data, and performed the statistical analyses with assistance from M.E. and P.G. L.J.L. and F.J.W. extensively revised the manuscript and provided relevant inputs at all stages, including the interpretation of the results. M.J.P., M.E., and P.G. revised the manuscript. All authors approved the final version of the manuscript.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.dadm.2017.05.007>.

RESEARCH IN CONTEXT

1. Systematic review: We retrieved prospective, population-based studies of midlife body mass index and dementia risk using PubMed and contacted authors to maximize the comprehensiveness of the analysis. The evidence is highly conflicting and has rapidly expanded in recent years.
2. Interpretation: Our findings resolve the current uncertainty about the detrimental role of obesity in midlife for dementia risk at old ages and question the potential harm of low body mass index, thus suggesting that the obesity paradox does not extend to dementia.
3. Future directions: Future studies should focus on whether sensitive periods and/or cumulative effects of exposure to obesity throughout the life course exist; mechanistic and observational studies are needed to explore the potential role of underweight in midlife in dementia risk modulation. Finally, the effectiveness of public health actions aimed at tackling the global obesity epidemic in lessening the global burden of dementia should be formally investigated.

References

- [1] Danesh J, The Global, BMI, Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016; 388:776–86.
- [2] Huxley R. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;383:970–83.
- [3] Gustafson D. BMI and dementia: feast or famine for the brain? *Lancet Diabetes Endocrinol* 2015;3:397–8.
- [4] NCD-RisC. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 2016; 387:1377–96.
- [5] Anand SS, Yusuf S. Stemming the global tsunami of cardiovascular disease. *Lancet* 2011;377:529–32.
- [6] Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring)* 2013;21:E51–5.
- [7] Gustafson D. Adiposity indices and dementia. *Lancet Neurol* 2006; 5:713–20.
- [8] Luchsinger JA, Gustafson DR. Adiposity and Alzheimer's disease. *Curr Opin Clin Nutr Metab Care* 2009;12:15–21.
- [9] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9:119–28.
- [10] Gustafson DR, Backman K, Waern M, Ostling S, Guo X, Zandi P, et al. Adiposity indicators and dementia over 32 years in Sweden. *Neurology* 2009;73:1559–66.
- [11] Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. *Arch Neurol* 2007; 64:392–8.
- [12] Wills AK, Hardy RJ, Black S, Kuh DJ. Trajectories of overweight and body mass index in adulthood and blood pressure at age 53: the 1946 British birth cohort study. *J Hypertens* 2010;28:679–86.
- [13] Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev* 2011;12:e426–37.
- [14] Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev* 2008;9:204–18.
- [15] Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003-2013: A decade of body mass index, Alzheimer's disease, and dementia. *J Alzheimers Dis* 2015;43:739–55.
- [16] Gorospe EC, Dave JK. The risk of dementia with increased body mass index. *Age Ageing* 2007;36:23–9.
- [17] Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing* 2016;45:14–21.
- [18] Rosengren A, Skoog I, Gustafson D, Wilhelmsen L. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. *Arch Intern Med* 2005;165:321–6.
- [19] Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005;330:1360.
- [20] Albanese E, Davis B, Jonsson PV, Chang M, Aspelund T, Garcia M, et al. Overweight and obesity in midlife and brain structure and dementia 26 years later the AGES-Reykjavik Study. *Am J Epidemiol* 2015;18:672–9.
- [21] Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005; 62:1556–60.
- [22] Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2015;3:431–6.
- [23] Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:1.
- [24] Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al. The reporting of studies conducted using observational routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; 12:e1001885.
- [25] Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol* 2005;62:55–60.
- [26] Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaud R, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement* 2015;11:1098–109.
- [27] Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007; 36:666–76.
- [28] Prince M, Albanese E, Guerchet M, Prina M. *World Alzheimer's Report 2014. Dementia and Risk Reduction—An Analysis of Protective and Modifiable Factors*. London, England: Alzheimer's Disease International; 2014.
- [29] Tolppanen AM, Ngandu T, Kareholt I, Laatikainen T, Rusanen M, Soiminen H, et al. Midlife and late-life body mass index and late-life dementia: results from a prospective population-based cohort. *J Alzheimers Dis* 2014;38:201–9.
- [30] Xu W, Atti A, Gatz M, Pedersen N, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk. A population-based twin study. *Neurology* 2011;76:1568–74.

- [31] Strand BH, Langballe EM, Rosness TA, Engedal K, Bjertness E. Does midlife obesity really lower dementia risk? *Lancet Diabetes Endocrinol* 2015;3:498–9.
- [32] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557.
- [33] Sidik K, Jonkman JN. A comparison of heterogeneity variance estimators in combining results of studies. *Stat Med* 2007;26:1964–81.
- [34] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [35] Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–57.
- [36] Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. *Dement Geriatr Cogn Disord* 2011;31:460–6.
- [37] Kimm H, Lee PH, Shin YJ, Park KS, Jo J, Lee Y, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. *Arch Gerontol Geriatr* 2011;52:e117–22.
- [38] Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc* 2003; 51:410–4.
- [39] Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. *Int J Obes* 2005;2009:893–8.
- [40] Kalmijn S, Foley D, White L, Burchfiel CM, Curb JD, Petrovitch H, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia Aging study. *Arterioscler Thromb Vasc Biol* 2000;20:2255–60.
- [41] Mehlig K, Skoog I, Waern M, Miao JJ, Lapidus L, Björkelund C, et al. Physical activity, weight status, diabetes and dementia: a 34-year follow-up of the population study of women in Gothenburg. *Neuroepidemiology* 2014;42:252–9.
- [42] Strand BH, Langballe EM, Hjellvik V, Handal M, Næss Ø, Knudsen GP, et al. Midlife vascular risk factors and their association with dementia deaths: results from a Norwegian prospective study followed up for 35 years. *J Neurol Sci* 2013;324:124–30.
- [43] Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res* 2007;4:103–9.
- [44] Alonso A, Jacobs DR Jr, Menotti A, Nissinen A, Dontas A, Kafatos A, et al. Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the Seven Countries Study. *J Neurol Sci* 2009;280:79–83.
- [45] Alonso A, Mosley T, Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry* 2009; 80:1194–201.
- [46] Chiang CJ, Yip PK, Wu SC, Lu CS, Liou CW, Liu HC, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. *Am J Geriatr Psychiatry* 2007;15:762–71.
- [47] de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med* 2015;13:1.
- [48] Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009;66:336–42.
- [49] Hu G, Horswell R, Wang Y, Li W, Besse J, Xiao K, et al. Body mass index and the risk of dementia among Louisiana low income diabetic patients. *PLoS One* 2012;7:e44537.
- [50] Kivimäki M, Singh-Manoux A, Shipley MJ, Elbaz A. Does midlife obesity really lower dementia risk? *Lancet Diabetes Endocrinol* 2015;3:498.
- [51] Ravona-Springer R, Schnaider-Beeri M, Goldbourt U. Body weight variability in midlife and risk for dementia in old age. *Neurology* 2013;80:1677–83.
- [52] Virta JJ, Heikkilä K, Perola M, Koskenvuo M, Raiha I, Rinne JO, et al. Midlife cardiovascular risk factors and late cognitive impairment. *Eur J Epidemiol* 2013;28:405–16.
- [53] Wotton CJ, Goldacre MJ. Age at obesity and association with subsequent dementia: record linkage study. *Postgrad Med J* 2014; 90:547–51.
- [54] WHO. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
- [55] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Arlington, VA: American Psychiatric Association; 1994.
- [56] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [57] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250–60.
- [58] Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia? *Lancet Neurol* 2014;13:913–23.
- [59] Aziz NA, van der Marck MA, Pijl H, Olde Rikkert MG, Bloem BR, Roos RA. Weight loss in neurodegenerative disorders. *J Neurol* 2008;255:1872–80.
- [60] Buchman AS, Schneider JA, Wilson RS, Bienias JL, Bennett DA. Body mass index in older persons is associated with Alzheimer disease pathology. *Neurology* 2006;67:1949–54.
- [61] Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. *Arch Neurol* 2006; 63:1312–7.
- [62] van der Burg JM, Pijl H, Campman YJ, Roos RA, Aziz NA. Does midlife obesity really lower dementia risk? *Lancet Diabetes Endocrinol* 2015;3:499–500.
- [63] Corley J, Gow AJ, Starr JM, Deary IJ. Is body mass index in old age related to cognitive abilities? The Lothian Birth Cohort 1936 Study. *Psychol Aging* 2010;25:867–75.
- [64] McLaren L. Socioeconomic status and obesity. *Epidemiol Rev* 2007; 29:29–48.
- [65] Narayan KV, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the US. *Diabetes Care* 2007; 30:1562–6.
- [66] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64–74.
- [67] Sharp ES, Gatz M. The relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord* 2011; 25:289.
- [68] Ives DG, Samuel P, Psaty BM, Kuller LH. Agreement between nosologist and cardiovascular health study review of deaths: implications of coding differences. *J Am Geriatr Soc* 2009;57:133–9.
- [69] Storandt M, Morris JC. Ascertainment bias in the clinical diagnosis of Alzheimer disease. *Arch Neurol* 2010;67:1364–9.
- [70] Kukull WA, Ganguli M. Generalizability: the trees, the forest, and the low-hanging fruit. *Neurology* 2012;78:1886–91.
- [71] Kokmen E, Beard CM, Offord KP, Kurland L. Prevalence of medically diagnosed dementia in a defined United States population Rochester, Minnesota, January 1, 1975. *Neurology* 1989;39:773–6.
- [72] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- [73] Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996;143:228–39.
- [74] Flegal KM, Shepherd JA, Looker AC, Graubard BI, Borrud LG, Ogden CL, et al. Comparisons of percentage body fat, body mass

- index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr* 2009;89:500–8.
- [75] Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: the late-life dementia risk index. *Neurology* 2009;73:173–9.
- [76] Albanese E, Taylor C, Siervo M, Stewart R, Prince MJ, Acosta D. Dementia severity and weight loss: a comparison across eight cohorts. The 10/66 study. *Alzheimers Dement* 2013;9:649–56.
- [77] Gillette Guyonnet S, Abellan Van Kan G, Alix E, Andrieu S, Belmin J, Berrut G, et al. IANA (International Academy on Nutrition and Aging) Expert Group: weight loss and Alzheimer's disease. *J Nutr Health Aging* 2007;11:38–48.
- [78] Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. *Neurology* 2005;65:892–7.
- [79] Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 2007;69:739–46.
- [80] Howse K. Review of longevity trends to 2025 and beyond. Review for the Beyond Current Horizons Programme Bristol: Futurelab; 2009. Available at: www.beyondcurrenthorizons.org.uk/evidence/generations-and-life-course. Accessed November 21, 2016.
- [81] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9:63–75.e2.
- [82] Mukherjee S, Walter S, Kauwe JSK, Saykin AJ, Bennett DA, Larson EB, et al. Genetically predicted body mass index and Alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses. *Alzheimers Dement* 2015; 11:1439–51.