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How to cite

STREIT, Sven, GUSSEKLOO, Jacobijn. Burden of cardiovascular disease across 29 countries and GPs" decision to treat hypertension in oldest-old. In: Scandinavian Journal of Primary Health Care, 2018, vol. 36, n° 1, p. 89–98. doi: 10.1080/02813432.2018.1426142

This publication URL: https://archive-ouverte.unige.ch/unige:102585

Publication DOI: 10.1080/02813432.2018.1426142

SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE, 2018
https://doi.org/10.1080/02813432.2018.1426142

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RESEARCH ARTICLE

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Burden of cardiovascular disease across 29 countries and GPs' decision to treat hypertension in oldest-old

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ABSTRACT

Objectives: We previously found large variations in general practitioner (GP) hypertension treatment probability in oldest-old (>80 years) between countries. We wanted to explore whether differences in country-specific cardiovascular disease (CVD) burden and life expectancy could explain the differences.

Design: This is a survey study using case-vignettes of oldest-old patients with different comorbidities and blood pressure levels. An ecological multilevel model analysis was performed.

Setting: GP respondents from European General Practice Research Network (EGPRN) countries, Brazil and New Zeeland.

Subjects: This study included 2543 GPs from 29 countries.

Main outcome measures: GP treatment probability to start or not start antihypertensive treatment based on responses to case-vignettes; either low (<50% started treatment) or high (≥50% started treatment). CVD burden is defined as ratio of disability-adjusted life years (DALYs) lost

ARTICLE HISTORY
Received 7 November 2017
Accepted 3 January 2018

KEYWORDS
Oldest-old; hypertension; clinical decision-making; cardiovascular disease burden; life expectancy

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due to ischemic heart disease and/or stroke and total DALYs lost per country; life expectancy at age 60 and prevalence of oldest-old per country.
Results: Of 1947 GPs (76%) responding to all vignettes, 787 (40%) scored high treatment probability and 1160 (60%) scored low. GPs in high CVD burden countries had higher odds of treatment probability (OR 3.70; 95% confidence interval (CI) 3.00–4.57); in countries with low life expectancy at 60, CVD was associated with high treatment probability (OR 2.18, 95% CI 1.12–4.25); but not in countries with high life expectancy (OR 1.06, 95% CI 0.56–1.98).
Conclusions: GPs' choice to treat/not treat hypertension in oldest-old was explained by differences in country-specific health characteristics. GPs in countries with high CVD burden and low life expectancy at age 60 were most likely to treat hypertension in oldest-old.

KEY POINTS

- General practitioners (GPs) are in a clinical dilemma when deciding whether (or not) to treat hypertension in the oldest-old (>80 years of age).
- In this study including 1947 GPs from 29 countries, we found that a high country-specific cardiovascular disease (CVD) burden (i.e. myocardial infarction and/or stroke) was associated with a higher GP treatment probability in patients aged >80 years.
- However, the association was modified by country-specific life expectancy at age 60. While there was a positive association for GPs in countries with a low life expectancy at age 60, there was no association in countries with a high life expectancy at age 60.
- These findings help explaining some of the large variation seen in the decision as to whether or not to treat hypertension in the oldest-old.

Introduction

In the Global Burden of Disease (GBD) study (2015), elevated blood pressure was among the leading risk factors for disability-adjusted life years (DALYs) [1]. Globally, about 10% of all DALYs are lost due to hypertension. To improve management of hypertension, the Lancet Commission issued a 10-point action plan in which one of these points was to individualize antihypertensive treatment according to cardiovascular risk, cultural differences, age, etc. [2].

The group of the oldest-old (patients aged >80 years) is both the fastest growing and also the most heterogeneous age group [3]. Some are healthy with very few chronic conditions, whereas others are frail, have multimorbidity (≥2 chronic conditions), or other complex problems [4]. This heterogeneity makes it particularly challenging for general practitioners (GPs) to find the best strategy (with optimal benefit to risk ratio) when deciding whether or not elevated blood pressure should be treated in this group [5]. This clinical dilemma can lead to variation in treating hypertension in oldest-old [6–9].

In the ATTENTIVE study [10], a large variation was found in GPs' decision to start antihypertensive treatment in oldest-old. In that study, eight case vignettes of oldest-old were presented to >2500 GPs from 29 (mainly) European countries and, for each case, they were asked whether or not they would start treatment. In the Netherlands, 34% of all cases would have been treated compared with 88% in Ukraine. Part of this variation was explained by the differences in patient characteristics, i.e. level of blood pressure, cardiovascular disease (CVD) and frailty. However, given the variation across countries, it seems feasible that country-specific health characteristics could explain part of the variation.

Therefore, the present study investigates whether country-specific health differences in CVD burden in older patients, and life expectancy at age 60 years, are related to GP treatment probability to start antihypertensive treatment. We hypothesized that there would be a positive association between CVD burden and GP treatment probability, but that life expectancy at age 60 years would modify that association.

Materials and methods

Design and setting

This was an ecological study using a multilevel model. Aggregated country-specific data were used from publicly available sources (see section 'Variables') and individual-level data (level of GPs) were used from the *A*ntihypertensive *T*rea*T*m*ENT* *I*n *V*ery *E*lderly (ATTENTIVE) study. In the ATTENTIVE study, GPs from 29 countries (including Brazil, Israel and New Zealand) were enrolled (March–July 2016) [10].

Ethical considerations

The ATTENTIVE study was conducted in compliance with the Declaration of Helsinki [11]. GPs provided informed consent by responding to the questionnaire. Since the participating GPs responded anonymously, no formal medical ethics approval was required from

most of the countries. However, in Brazil and Switzerland, the research ethics committees issued a waiver, and in New Zealand the research ethics committee of the University of Auckland approved this study.

Participants

The only inclusion criterion for ATTENTIVE was that each participant had to be a practicing GP; this was established from the first question in the survey. Non-practicing GPs were excluded. GPs were invited by email without offering an incentive. For this study, only GPs that provided an answer for all eight case vignettes were included; this stipulation enabled us to calculate GP treatment probability over all the cases.

Survey

In short, the survey contained eight case vignettes of oldest-old patients (aged >80 years; males and females) that consulted their GPs for a routine visit without showing blood pressure-related symptoms or receiving antihypertensive treatment. All case vignettes differed in three primary characteristics: systolic blood pressure (SBP) of 140 or 160 mm Hg, CVD present or absent, and frailty (yes or no). For each case vignette, GPs were asked to decide if they would start antihypertensive treatment. We piloted and then translated the questionnaire into 21 languages (Additional file 1 in [10]). SurveyMonkey (www.surveymonkey.com, Palo Alto, CA) was used to build the online questionnaire. As an exception, in Ukraine (where web access was limited) a paper questionnaire was used.

Variables

The outcome of this study was the proportion of case vignettes for which GPs decided to start antihypertensive treatment, i.e. GP treatment probability. GPs were dichotomised into two groups according to the median of GP treatment probability, i.e. ≤50% 'low', >50% 'high'.

The exposure was CVD burden per country. CVD burden per country was defined as: the ratio of DALYs in persons aged >70 years lost due to ischemic heart disease and/or stroke and the total DALYs lost in persons aged >70 years. These data were retrieved from the GBD database (hosted by the Institute for Health Metrics and Evaluation). Data specific for individuals >80 years were not available why we chose the next best estimate (>70). The GBD is a public database capturing national estimates on total and disease-specific DALYs [12]. The country-specific CVD burden ranged from 16% in France to 59% in Ukraine (Appendix 1). The countries were divided into two groups according to the median of CVD burden, i.e. <22.5% ('low') and ≥22.5% ('high').

Country-specific life expectancy at age 60 years was considered a possible effect modifier, and the prevalence of persons aged ≥80 years per country was considered a possible confounder for the association between CVD burden and GP treatment probability. Life expectancy at age 60 years was obtained from the 2015 Global Health Observatory data repository of the World Health Organisation [13]. Prevalence of oldest-old was available from the 2015 report of the United Nations [14]. Data specific for individuals >80 years were not available why we chose the next best estimate (>60). Both covariates were dichotomized in two quantiles according to their medians: life expectancy at age 60 years, low (<24 years) and high (≥24 years) and prevalence of oldest-old, low (<4.6%) and high (≥4.6%).

Per GP, we included gender and years of experience on an individual level from the ATTENTIVE data. Years of experience was categorized into two groups of about equal sizes: <15 years ('low') and ≥15 years ('high').

The previous ATTENTIVE study [10] showed that patient characteristics (SBP, CVD and frailty) were independently associated with the GPs' decisions to start antihypertensive treatment. However, for the present study, we were only interested in the overall effect of CVD burden on GP treatment probability; therefore, as an outcome, we chose the proportion of all case vignettes for which GPs decided to start treatment, and neglected the case characteristics (SBP, CVD and frailty).

Statistical analysis

The ATTENTIVE dataset was visually explored and checked for missing data, outliers and inconsistencies. New dichotomized variables were generated (after visual checks) by grouping of the distributions using histograms. The exposure and all covariates were checked for multicollinearity by calculating pairwise correlation coefficients.

Chi-squared tests and unadjusted odds ratios (OR), as well as 95% confidence intervals (CI), were used to investigate whether the exposure (CVD burden) and the other independent variables (GP gender/years of experience, life expectancy at age 60, and prevalence of oldest-old) were associated with the outcome (GP treatment probability).

Table 1. Baseline characteristics of general practitioners (GPs) and countries, and their association with high GP treatment probability to start antihypertensive treatment in oldest-old ($n = 1947$).

Characteristics	GP treatment probability: Low (≤50%) ($n = 1160$)	GP treatment probability: High (>50%) ($n = 787$)	Crude odds ratio of high GP treatment probability (95% CI)	*p* Value
GP gender				
Female	535 (54.6)	445 (45.4)	1.00 (reference)	
Male	625 (64.6)	342 (35.4)	0.66 (0.55, 0.79)	<.001
Experience as GP				
<15 years	558 (56.7)	427 (43.4)	1.00 (reference)	
>15 years	602 (62.7)	358 (37.3)	0.78 (0.65, 0.93)	.007
Prevalence of oldest-old				
Low	404 (45.0)	493 (55.0)	1.00 (reference)	
High	756 (72.0)	294 (28.0)	0.32 (0.26, 0.38)	<.001
Life expectancy at age 60 years				
Low	216 (36.4)	378 (63.6)	1.00 (reference)	
High	944 (69.8)	409 (30.2)	0.25 (0.20, 0.30)	<.001
Cardiovascular disease burden				
Low	930 (69.4)	411 (30.7)	1.00 (reference)	
High	230 (38.0)	376 (62.1)	3.70 (3.03, 4.52)	<.001

p Values are from univariate logistic regression.

On a country level, continuous data of CVD burden and averaged GP treatment probability per country were visualized using scatter plots. A linear regression line with 95% CI was derived using a univariate linear regression model. In a sensitivity analysis, this analysis was restricted to those countries where >60% of the GPs responded to the survey.

Chi-squared tests were then used to investigate whether CVD burden was associated with any of the independent variables and, if not on a causal pathway, these were considered to be potential confounders.

All potential confounders were tested for the degree of confounding and/or effect modification using the Mantel–Haenszel test of homogeneity of ORs (detailed in Appendix 3). As pre-specified, the causal model presented stratum-specific ORs and 95% CI for low and high life expectancy at age 60 years. Variables that confounded the association between the exposure and the outcome were included in the final model.

A two-sided *p* value of .05 was considered statistically significant. All analyses were performed in STATA release 14.2 (Stata Corp, College Station, TX).

Results

In the ATTENTIVE study, 2543 GPs from 29 countries participated. The median response rate for all countries was 26% (21 countries with <60%, eight countries with ≥60%). Of those participating, 1947 GPs (76.6%), provided an answer for all eight case vignettes.

Table 1 presents the baseline characteristics of the participating GPs and the countries, stratified by GP treatment probability. There were 1160 (59.6%) GPs with a low and 787 (40.4%) GPs with a high GP treatment probability. Countries with a high CVD burden showed a positive association with GP treatment probability (OR 3.70, 95% CI 3.03, 4.52; $p < .001$).

Figure 1 shows the association between CVD burden and GP treatment probability on a country level using continuous data. Strong evidence was found for an association between CVD burden and GP treatment probability ($p < .001$). Of all countries, the Netherlands had the lowest GP treatment probability (34%) and one of the lowest CVD burdens (16%), whereas Ukraine was among the countries with both the highest GP treatment probability (88%) and CVD burden (59%). When restricting the analysis to countries with a response rate of >60%, the sensitivity analysis confirmed this association ($p = .001$) (Appendix 2).

In countries with a high CVD burden, the ORs for treatment were higher compared to countries with a low CVD burden (3.70, 95% CI 3.00, 4.57). Country-specific prevalence of oldest-old was a significant confounder (adjusted OR 2.71, 95% CI 2.17, 3.38) while GP gender and GP years of experience were not confounders. Life-expectancy at age 60 years was an effect modifier (the Mantel–Haenszel test of homogeneity $p = .005$) of the association between CVD burden and GP treatment probability. Therefore, we included country-specific prevalence of oldest-old in the multivariate model and present stratum specific estimates for low and high life expectancy at age 60 years.

In the final model (Table 2), GPs working in countries with a high CVD burden and a low life expectancy at age 60 years were more likely to start antihypertensive treatment in the oldest-old (adjusted OR 2.18, 95% CI 1.12, 4.25) compared to their counterparts in countries with a low CVD burden. In countries

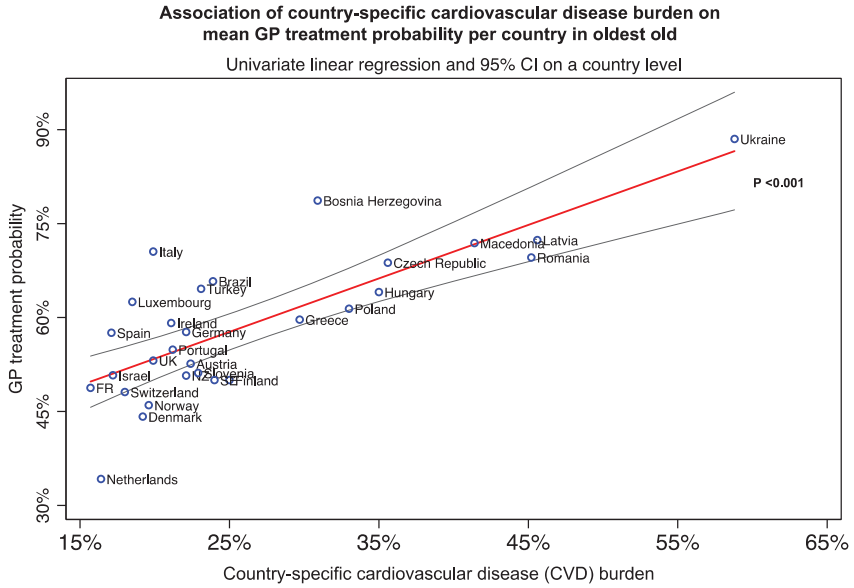

Figure 1. Association between country-specific cardiovascular disease burden and mean general practitioner (GP) treatment probability per country in oldest-old. Univariate linear regression was used (straight line), 95% confidence intervals (outer lines) and *p* value. FR: France; NZ: New Zealand; SE: Sweden; UK: United Kingdom.

Table 2. Final model including 1947 GPs for the association of cardiovascular disease (CVD) burden on GP treatment probability in oldest-old.

	Fully-adjusted odds ratio of GP treatment probability (95% CI)
CVD burden (stratum-specific)	
Low life expectancy at age 60	2.18 (1.12, 4.25)
High life expectancy at age 60	1.06 (0.56, 1.98)
Prevalence of oldest-old	0.48 (0.39, 0.59)

with a high life expectancy at age 60 years, there was no evidence for such an association (adjusted OR 1.06, 95% CI 0.56, 1.98).

Discussion

Statement of principle findings

The clinical dilemma when deciding whether (or not) to start antihypertensive treatment in the oldest-old may not only be explained by differences in patient characteristics but also in country-specific characteristics. In the present study including 1947 GPs from 29 countries, a high country-specific CVD burden was associated with a higher probability of GPs deciding to start antihypertensive treatment in patients aged >80 years. However, the association was modified by country-specific life expectancy at age 60 years. While there was a positive association for GPs in countries with a low life expectancy at age 60 years, there was no association for GPs in countries with a high life expectancy at age 60 years. These findings (partly) explain some of the large variation seen in the decision as to whether or not to treat hypertension in the oldest-old [10].

Strengths and limitations

The inclusion of a large number of GPs from a large number of countries (in Europe and beyond) is a strength of this study; this allowed us to study the relation between country-specific health characteristics and GP decisions in an ecological analysis. Also, we could describe GP treatment probabilities in countries that are not usually included in international studies.

This study also has limitations. First, GP treatment probability was self-reported and based on fictive cases stories and not on, for example, chart reviews. Second, the overall response rate was only 26% across all countries, which is not uncommon in surveys involving GPs [15]. However, our response rate was not lower than in other GP survey studies [16,17] and low response rates of GPs do not necessarily result in selection bias [18,19]. In addition, when restricting our analysis to countries where the GPs responded for ≥60%, the results remained unchanged. Third, we can only report associations and not causation as this was an observational study with limitations such as residual confounding. However, we explored and reported patient-related factors associated with GP treatment probability in an earlier study [10].

Findings in relation to other studies

The results from this study suggest that GPs in countries where their 60-year-old patients will die (on average) before the age of 84 years, base their decision to start antihypertensive treatment in the oldest-old not only on the individual risk or prevalence of oldest-old, but also on the CVD burden of their country. In our opinion, the daily experience and case load provide GPs with sufficient knowledge to assess CVD burden and country-specific DALY of the patients that they see and treat, even without knowing the exact burden. DALYs due to CVD burden are not only a problem in high-income countries but mostly in low- and middle-income countries (LMIC) [20]. The inequity in cardiovascular health in LMIC compared to high-income countries, calls for empowering GPs with the knowledge/skills to meet the requirements in these countries [21]. While our study shows that, in countries with a lower life-expectancy, GPs are more inclined to treat hypertension when CVD burden is high, the effects of such treatment on e.g. mortality or patient-relevant outcomes such as quality of life, remain unclear. Treatment goals for hypertension (especially in older patients) are constantly changing [22]. Although trials including oldest-old show a clear benefit of lowering blood pressure [23,24], the generalizability of these studies is still debated [22,25–27]. In this clinical dilemma, prognosis and life expectancy are issues that GPs relate to in the decision-making process in older patients [6].

Meaning of the study

Future high-quality observational studies, or new trials including the otherwise excluded frail patients with multimorbidity, should be conducted to provide more evidence for decision-making with respect to hypertension treatment in the oldest-old. With evidence that can be generalized for GP patients that are frail and multimorbid, the implementation into daily practice should be thoughtfully planned. Our study found also a crude association of female GPs and GPs with a shorter than 15-year experience to treat more often hypertension in oldest-old. Future studies could further investigate if this association is real. These steps are needed to overcome inequities in treatment decisions across countries with different CVD burdens and life expectancies.

Conclusions

The clinical dilemma when deciding whether (or not) to start antihypertensive treatment in the oldest-old appears not only to be explained by differences in patient characteristics but also in country-specific health characteristics. In this ecological comparative study, GPs living in countries with a high CVD burden and low life expectancy at age 60 years were more likely to start antihypertensive treatment in the oldest-old than GPs in countries with a low CVD burden and a high life expectancy at age 60 years.

Acknowledgements

The authors thank all the general practitioners who participated in this study.

Ethical approval

This study was conducted in compliance with the Declaration of Helsinki [11]. Since the participating GPs responded anonymously, no formal medical ethics approval was required from most of the countries. However, in Brazil and Switzerland, the research ethics committees issued a waiver, and in New Zealand the research ethics committee of the University of Auckland approved this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

Dr. Streit's research is supported by grants (P2BEP3_165353) from the Swiss National Science Foundation (SNF) and the Gottfried and Julia Bangerter-Rhyner Foundation, Switzerland. This study was supported by the Swiss University Conference and the State Secretariat for Education, Research and Innovation (SUC project P-10).

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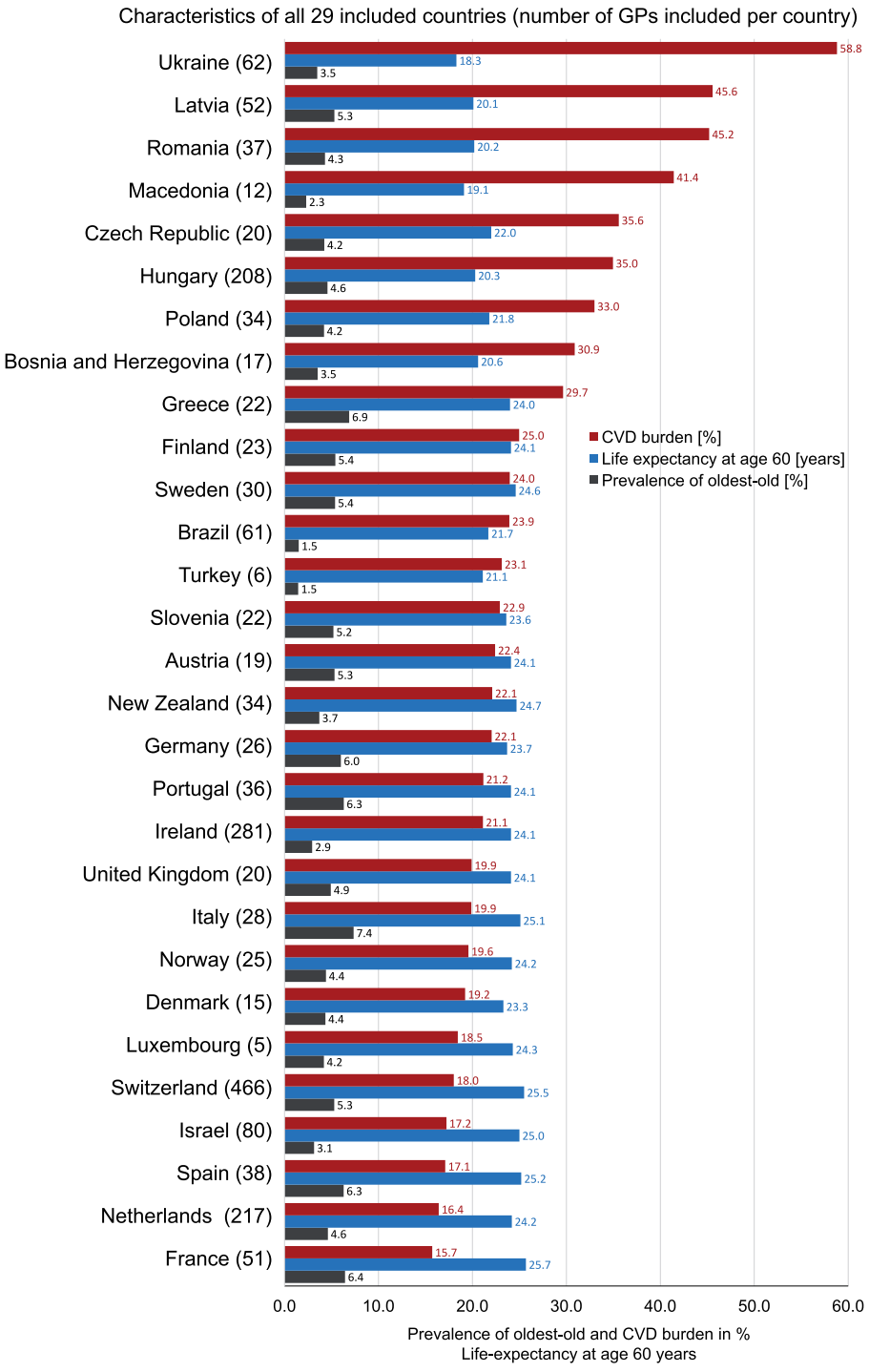
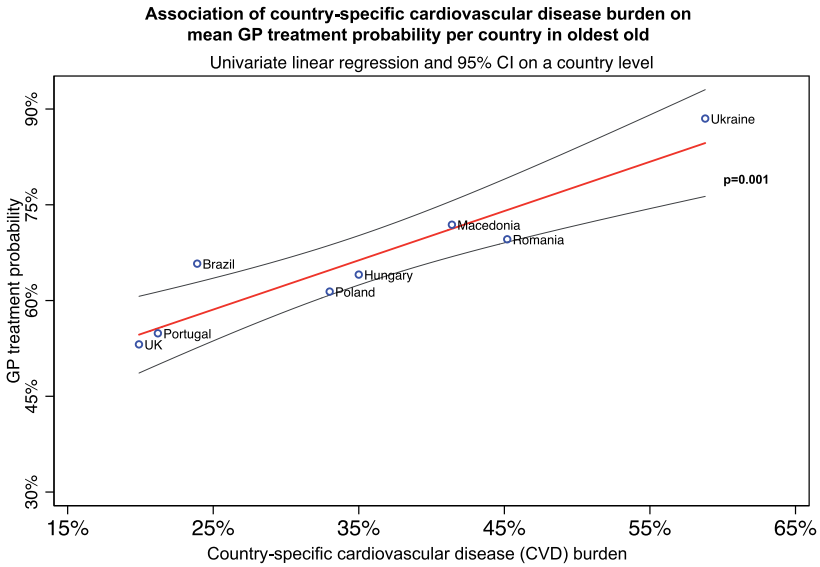
Appendix 1

Characteristics of all 29 included countries (number of GPs included per country)



Appendix 2

Sensitivity analysis including only countries with a response rate of >60% (n = 8). Association between countryspecific cardiovascular disease (CVD) burden on mean general practitioner (GP) treatment probability per country in oldestold. Univariate linear regression was used (red line), 95% confidence intervals (grey lines) and p-value. UK = United Kingdom



Appendix 3

Assessing confounding and testing for effect modification on the association of cardiovascular disease (CVD) burden on GP treatment probability in oldest-old.

	Odds ratio of GP treatment probability (95% CI)	P-value
Unadjusted effect of CVD burden	3.70 (3.00, 4.57)	
Effect of CVD burden adjusted for …		
Gender	3.55 (2.87, 4.41)	0.19
Female	4.01 (3.01, 5.34)	
Male	3.01 (2.18, 4.16)	
High experience (15 years)	3.73 (3.02, 4.60)	0.87
Low	3.79 (2.81, 5.12)	
High	3.66 (2.71, 4.93)	
Life expectancy at age 60	1.48 (0.97, 2.29)	0.005
Low	2.96 (1.53, 5.72)	
High	0.82 (0.44, 1.53)	
Prevalence of oldest old	2.71 (2.17, 3.38)	0.57
Low	2.59 (1.96, 3.41)	
High	2.96 (2.06, 4.24)	

P-values are from Mantel-Haenszel test of homogeneity of odds ratios. Variables in grey were chosen for the final model.