BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051881
Article Type:	Original research
Date Submitted by the Author:	20-Apr-2021
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Keywords:	GERIATRIC MEDICINE, CLINICAL PHARMACOLOGY, PRIMARY CARE

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Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5 European countries: a cross-sectional study of DO-HEALTH

Word count: 2960 (excluding the abstract, references, tables, and figures)

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ABSTRACT

Word count: 300 (max 300)

Objective: To investigate the prevalence of polypharmacy and characteristics associated with polypharmacy in older adults from seven European cities.

Design: Cross-sectional study of baseline data from DO-HEALTH.

Setting and participants: DO-HEALTH enrolled 2157 community-dwelling adults age 70 and older from seven centers in Europe. Participants were excluded if they had major health problems or Mini Mental State Examination Score <24 at baseline.

Primary outcome measures: Extensive information on prescription and over-the-counter medications were recorded. Polypharmacy was defined as the concomitant use of 5 or more medications, excluding vitamins or dietary supplements. Bivariate and multivariable logistic regression was used to test the association of sociodemographic factors (age, sex, education, living situation, and city) and health-related indicators (number of comorbidities, cognitive function, frailty, body mass index [BMI], prior fall, self-rated health, and smoking status) with polypharmacy.

Results: 27.2% of participants reported polypharmacy ranging from 16.4% in Geneva to 60.8% in Coimbra. In the multivariable logistic regression analyses, older age (OR 1.07; 95% CI 1.04-1.10), greater BMI (OR 1.09; 95% CI 1.06-1.12), and increased number of comorbidities (OR 2.13; 95% CI 1.92-2.36) were associated with polypharmacy. Women were less likely to report polypharmacy than men (OR 0.65; 95% CI 0.51-0.84). In comparison to participants from Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI 1.56-3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy ((OR 0.36; 95% CI 0.22-0.59 and OR 0.64; 95% CI 0.42-0.96), respectively). Living situation, smoking status, education, prior fall, cognitive function, self-rated health, and frailty status were not significantly associated with polypharmacy.

Conclusion: Polypharmacy is common among relatively healthy older adults, with great variability across seven European cities. Independent of several confounders, being a woman, older age, greater BMI, and greater number of comorbidities were associated with increased odds for polypharmacy.

Trial registration: original RCT DO-HEALTH: NCT01745263

Strengths and limitations of this study

- This study takes advantage of the large DO-HEALTH data to estimate the prevalence of polypharmacy and characteristics associated with polypharmacy among European community-dwelling older adults.
- In this study, the use of medications was extensively assessed and included all regularly used medications, including both over-the-counter and prescription drugs.
- Because DO-HEALTH participants, were comprehensively assessed we were able to investigate the association of several sociodemographic factors and health-related indicators with polypharmacy.
- Although this was not a population-based study but a selection of relatively healthy older adults, a comparison between countries is of relevance at the public health level.
- This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy.

INTRODUCTION

By 2050, one in every four people in Europe and Northern America will be aged 65 or over.[1] As population ages, so does the number of chronic conditions and use of polypharmacy (commonly defined as the concomitant use of 5 or more medications).[2-5] For instance, about 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and Portugal.[6-8]

Polypharmacy constitutes a major public health problem because it is associated with increased risk of adverse drug reactions, drug-drug and drug-disease interactions, which can lead to falls, unnecessary or avoidable costs,[9 10] unplanned hospitalization,[11 12] emergency department and outpatient visits,[10] kidney function decline,[13] and mortality.[4 14-18]

Other studies have evaluated the use of polypharmacy among European older adults.[2 6-8 19] However, they considered only prescription medications or pharmacy claims which can either underestimate or overestimate the prevalence of polypharmacy. Further, the definition of polypharmacy, living facilities, and age distribution vary widely, limiting the comparison between regions and the identification of potential health interventions to improve the safe use of medications. Therefore, to understand the extent of polypharmacy use among European older adults, the goal of the present study was to assess the prevalence of polypharmacy in 7 European cities using standardized methods, and its association with socio-demographic factors and health-related indicators among 2157 participants of DO-HEALTH, a multicenter international trial that recruited relatively healthy seniors 70 years and older.

METHODS

Participants and study design

This is a cross-sectional study using baseline data from DO-HEALTH, a randomized, double-blind, placebo-controlled, clinical trial designed to assess the effectiveness of the 3 interventions (vitamin D, omega-3 fatty acids, and simple home based strength exercise program) in a 2×2×2 factorial design (NCT01745263).[20 21] DO-HEALTH included a total of 2157 older adults (70 years and older) from seven European cities located in five countries: Basel (n=253), Berlin (n=350), Coimbra (n=301), Geneva (n=201), Innsbruck (n=200), Toulouse (n=300), and Zurich (n=552). DO-HEALTH recruitment, randomization and allocation, and blinding details are published elsewhere.[20] Participants completed detailed questionnaires on demographics, medical events, lifestyle factors (nutrition, physical activity, living condition), medication intake, and had extensive clinical examinations of multiple organ and physical functions at baseline and each year during a three-year follow-up.[20]

DO-HEALTH was approved by each local/national ethics committee and regulatory authorities. The present study was approved by the Ethics Committee Zurich (ID 2018-00684). All participants signed the consent form.

Eligibility

Detailed eligibility criteria were published elsewhere.[20] Briefly, DO-HEALTH included relatively healthy adults aged 70 years or older, with Mini Mental State Examination Score[22] greater or equal to 24, living in the community, and sufficiently mobile to come to the study center. Older adults were excluded if they reported a history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, or transient ischemic attack in the last 5 years. Older adults with epilepsy and/or use of anti-epileptic drugs, angina pectoris or coronary artery intervention, severe renal impairment (creatinine clearance ≤ 15 ml/min) or dialysis,

hypercalcemia (> 2.6 mmol/l), history of hypo or primary hyperparathyroidism, severe liver disease, or living in assisted living situations or a nursing home, were also excluded.

For the purpose of this cross-sectional analysis we included baseline data from all DO-HEALTH participants (n=2157).

Data collection

Sociodemographic factors and health-related indicators

Sociodemographic information comprised age, sex, years of education, living situation (alone vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich). Health-related indicators comprised number of comorbidities, cognitive function, frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was designed to recruit 40% of participants with a prior fall in the last 12 months.

Comorbidity

The number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[23] This instrument is validated in the older population and evaluates the presence of 13 common chronic diseases: heart disease, high blood pressure, lung disease, diabetes, ulcer and stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, osteoarthritis or degenerative arthritis, back pain, rheumatoid arthritis.

Cognitive function

Cognitive function was assessed by the Montreal Cognitive Assessment questionnaire (MoCA)[24] at baseline and follow-up. MoCA has a maximum score of 30 points, and is presented as a continuous variable. MoCA was chosen because of its higher sensitivity to detect mild cognitive impairment in older adults.[24 25] In a validation study, MoCA had a sensitivity of 90% to detect mild cognitive impairment, while the Mini-Mental State Exam detected only 18%.[24]

Frailty

Frailty was defined according to Fried et al[26] which evaluates five criteria: fatigue (self-reported), unintentional weight loss (self-reported loss more than 5% of total body weight), reduced physical activity (self-reported), slowness (impaired walking speed), and weakness (low grip strength). Slowness was defined as a gait speed below 0.67 m/s and 0.7 m/s respectively, according to gender and height as in the original Fried conceptualization.[26] For weakness, we used grip strength measured by Martin Vigorimeter (KLS Martin Group, Tuttlingen, Germany) with cut-points at the lowest 20% of the cohort based on age, gender and country of origin. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).

Self-rated health

Self-rated health was measured with the EQ5D-3L.[27] Participants were asked to rate their health status on a visual analog scale (0-100 mm) with respect to the question: "Please rate how well you are doing on a scale of 0 to 100", where 0 represents 'very poorly' and 100 represents 'very well'. Self-rated health is presented as a continuous variable.

Medications

Older adults were assessed in detail for the use of medications with standardized questionnaires that addressed the following information for each medication participants reported: brand name, generic name, dose, unit, interval (as needed or regularly), indication, and treatment duration. To minimize recall bias, participants were asked to bring to the baseline visit all medications they had at home.

We included all prescribed and over the counter medications taken regularly, and excluded multivitamins, dietary supplements, herbal, and homeopathic medicines. Regular medication was defined as those drugs taken daily or at regular intervals (e.g. once a week). All medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[28] Each active substance was defined as one medication and received an individual ATC code.

For example, the combination of amlodipine/indapamide/perindopril was counted as 3 medications and received the codes C08CA01, C03BA11, C09AA04, respectively. Polypharmacy was defined as the concomitant use of 5 or more drugs (active substances).[4 5]

Polypharmacy index

To take into account that the number of comorbidities affect the number of drugs taken, we estimated the polypharmacy index as the ratio between the number of medications reported and the number of comorbidities among participants with at least one comorbidity. The polypharmacy index is presented as a continuous variable. We stratified polypharmacy index by cardiovascular conditions (high blood pressure and heart disease), musculoskeletal conditions (back pain and osteoarthritis), and depression to consider that some diseases by default need more medications than others.

Statistical analysis

Descriptive statistics are presented as frequencies and percentages (%) for categorical variables, and means with standard deviation (SD) for continuous variables (or median and interquartile range for non-normally distributed variables). Data were checked for normality visually. We present the prevalence of polypharmacy and median polypharmacy index for the total population of DO-HEALTH and by city (n=7; Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich).

To test the association of sociodemographic factors (age, sex, years of education, and living alone) and health-related indicators (number of comorbidities, cognitive function, frailty status, BMI, prior fall in the last 12 months, self-rated health, and smoking status) with polypharmacy (binary outcome), we first performed bivariate logistic regression analyses and included variables with $p<0.2$ in the multivariable logistic regression analyses. The final model presents the adjusted odds ratios and 95% confidence intervals (OR, 95% CI). Analysis were performed with SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA.).

Patient and public involvement

Patients and the public were not involved in setting up the research question, design, outcome measures, interpretation of the results, or writing the manuscript.

RESULTS

Baseline characteristics of the 2157 older adults included in DO-HEALTH are described in **Table 1**. Median age was 74.0 years (IQR 72.0-77.0) and most participants were women (61.7%). Mean BMI was 26.6 kg/m^2 (SD 3.5) and 26.2 kg/m^2 (SD 4.7) in men and women, respectively. Most participants were classified as robust (53.6%) with only 3.0% of participants classified as frail. The median number of comorbidities was 2.0 (IQR 1.0-3.0), median number of medications was 3.0 (IQR 1.0-5.0), and median polypharmacy index was 1.5 (IQR 1.0-2.5). **Table 1** also describes the baseline characteristics by city. Coimbra and Toulouse had the highest median age (median 75 IQR 72.0-79.0 and median 75 IQR 71.0-75.0, respectively). Coimbra had the lowest proportion of participants with no comorbidities, the highest mean BMI, median number of medications, as well as the highest proportion of prefrail and frail participants. Berlin had, on average, the highest proportion of women, robust participants, and mean years of education. Geneva presented the lowest median polypharmacy index.

Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2% and, 17.4% reported no medications at all (**Figure 1**). Regarding the cities, on average Coimbra reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%). Berlin (25.4%), Innsbruck (22%), Zurich (20.5%), Basel (18.2%), and Geneva (16.4%).

Table 2 shows the association of sociodemographic factors and health-related indicators with polypharmacy. In the bivariate analyses (unadjusted models), greater age, BMI, and number of comorbidities, as well as prior fall and frailty were associated with an increase in the odds of polypharmacy. Higher MoCA scores (higher scores mean better cognitive function), higher

self-rated health scores, and more years of education were associated with a decrease in the odds of polypharmacy. The associations of living alone and ever smoked with polypharmacy were non-significant at p>0.2 and, therefore, were not included in the multivariable logistic regression analysis. In the multivariable logistic regression analysis (including the covariates age, sex, education, prior fall, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city), age, sex, BMI, number of comorbidities, and city were independently associated with polypharmacy. For each additional year of age, there was 7% higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a one unit increase in BMI, there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-1.12). For one additional comorbidity, there was a 2-fold increase in the odds of polypharmacy (OR 2.13, 95% CI 1.92-2.36). Women had 35% lower odds of reporting polypharmacy than men (OR 0.65, 95% CI 0.51-0.84). Participants from Geneva or Toulouse were also less likely to report polypharmacy than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR 0.64, 95% CI 0.42-0.96, respectively). Participants from Coimbra had 2 times higher odds of reporting polypharmacy (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having had a fall in the year prior to enrollment, education, cognitive function, self-rated health, and frailty status were no longer significantly associated with polypharmacy in the multivariable analysis.

DISCUSSION

In this cross-sectional study of 2157 relatively healthy European older adults, about one quarter of participants reported polypharmacy. However, despite the same inclusion and exclusion criteria in this large clinical trial, there was great variability in prevalence of polypharmacy between the seven cities with the lowest prevalence observed in Geneva and Basel with less than 20% and the highest prevalence observed in Coimbra with about 60%. Notably, older age, greater BMI, and number of comorbidities were significantly associated with higher odds of

polypharmacy after adjusting for education, prior fall, cognitive function, self-rated health, and frailty.

Comparison with other studies

On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are consistent with previous population-based studies. In the population-based CoLaus study, a cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-aged adults (mean age 58 years) was 16.9%.[19] This is consistent with our results from Geneva (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy reported in Coimbra (60.8%) is in accordance with a previous population-based study conducted in Oporto/Portugal (59%).[7] Yet, a population-based study conducted in Germany (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)[29] than we observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty in the ESTHER cohort in which only 32.8% of participants were robust,[29] while in DO-HEALTH about 60% of older adults from Berlin were robust.

Participants from Coimbra were more likely to report polypharmacy than other centers. This increased prevalence could be explained by the fact that Coimbra participants were on average older, had higher BMI, and more likely to be prefrail or frail, despite our strict inclusion and exclusion criteria and our aim to standardize recruitment strategies. In our analysis, BMI and number of comorbidities were strongly associated with polypharmacy even after controlling for age, city and other covariates. Additionally, participants from Coimbra also reported on average a higher prevalence of depression and hypertension or heart disease when compared to other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy, since hypertension and depression are associated with increased use of medications, and initiating or maintaining polypharmacy.[30]

Other factors, however, may also explain the wide variation in the prevalence of polypharmacy, such as: health system organization and coverage, country specific drug policies, medication

costs, prescribing pattern, refund system, clinicians' workload and specialization, and socioeconomic status.[31-38] A prior study in 57 European nursing homes (SHELTER study) also found differences in the prevalence of polypharmacy across seven European countries.[34] The authors suggested that this variation may be caused by the distinct attitudes of physicians when managing older adults with multimorbidity.[34] Other studies also observed high association between prescriber characteristics, such as medicine specialization, and polypharmacy.[33 37 38] For example, a recent national cross-sectional study among Malaysian older adults found that physicians with family medicine specialization were five times more likely to prescribe more than five medications at one time.[37] Interestingly, among the five countries included in DO-HEALTH, Portugal is the only one that does not recognize geriatric medicine as a specialty or subspecialty.[39]

Implications for clinical practice

The pharmacological treatment of older adults with multimorbidity is complex and poorly addressed in clinical practice guidelines.[40-42] For instance, the pharmacological recommendations of the National Institute for Health and Care Excellence (NICE) guidelines for management of type 2 diabetes, depression, and heart failure rarely account for multimorbidity.[43] In fact, only a few drug trials include older adults with multimorbidity.[44 45] Therefore, the cumulative effects of multiple medication use in multimorbid older adults are unknown, and clinicians are not supported by evidence-based recommendations to manage drug prescriptions among this population. Furthermore, this lack of evidence may lead to unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions. Notably, about 50% of older adults take at least one unnecessary medication[46] and less than 50% have a clear understanding of pharmacotherapy purpose.[47] In this context, the polypharmacy index could be used to compare the use of medications in the older population, and to evaluate potential polypharmacy appropriateness, medication burden, and screen for undertreat chronic conditions.

Strengths and limitation of this study

In this study, we addressed the literature gap of limited studies including both over-the-counter and prescription medications used regularly. Further, because DO-HEALTH included participants from different European countries and we used the same definition of polypharmacy, our findings allow cross-country comparisons and provide relevant data for future research and health policy interventions on the pharmacogerontology field. To our knowledge, this is the first study to estimate the prevalence of polypharmacy including prescription and over-the-counter medications, among community-dwelling older adults from five European countries. The assessment of both prescription and over-the-counter medications is needed as almost 50% of medication users also use at least one over-the-counter medication, with half of them presenting a potential major drug interaction.[16] Further, this is the first study to report the polypharmacy index. Knowing that older adults with multimorbidity often need to use polypharmacy, a ratio between the number of medications and number of diseases could be used to investigate polypharmacy appropriateness. More complex tools to measure polypharmacy appropriateness have been developed.[48] The polypharmacy index can be easily applied in clinical research and at daily basis since it is simple, fast, and self-administered because it takes advantage of the number of comorbidities assessed by the Self-Administered Comorbidity Questionnaire[23] and self-reported number of medications, whereas other tools require clinical parameters as drug effectiveness or patients' adherence.[48]

This study has also limitations. This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy and is not a population-based study. Further, the scope of this study is limited in terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered conservative as participants were relatively healthy at baseline (without major chronic diseases such as cancer or major cardiovascular events in the last 5 years), or in use of anti-epileptic drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence of polypharmacy and longitudinal studies that showed

the association between polypharmacy and age, BMI, and comorbidities.[7 19 29 30 49] Moreover, comorbidities were assessed with the validated Self-Administered Comorbidity Questionnaire.[23] Although this questionnaire is validated in the older population and assesses the presence of the most common chronic diseases, it does not include some common conditions in older adults as sleep disorders and obstipation and participants may not be aware of some conditions.

CONCLUSION

About one quarter of European community-dwelling older adults reported polypharmacy. We found that polypharmacy was associated with being female and increased age, BMI, and number of comorbidities. Further, substantial variation in the prevalence of polypharmacy between cities remained even after accounting for demographic and health-related differences between study participants.

a. Contributorship statement

HABF, with support of RT, EJO and JAK conceived and designed the study.

CdGRCM, HABF, WL and EJO analysed and interpreted the data.

CdGRCM and HABF drafted the article.

All authors were involved in interpretation and critical review of the results and revising the manuscript for important intellectual content.

All authors finally approved the version to be submitted.

b. Competing interests

As part of the DO-HEALTH independent and investigator initiated clinical trial, HABF reports as the PI of the DO-HEALTH trial, grants from European Commission, from University of Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli

Pharma, plus nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche Diagnostics. Further, HABF reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor, outside the submitted work.

BV reports personal fees from BIOGEN, CERECIN, ROCHE, MSD, outside the submitted work.

RR reports personal fees from Abiogen, Danone, Echolight, EMF, Mithra, ObsEva, Pfizer Consumer Health, Theramex, outside the submitted work.

EJO reports grants from Zurich University, during the conduct of the study.

CdGRCM received funding from the National Council for Scientific and Technological Development (CNPq), with process Nos. 164700/2015-3, from the São Paulo Research Foundation (FAPESP), with process No. 2016/13700-9, and Coordination for the Improvement of Higher Education Personnel/PhD Sandwich Programs Abroad (PDSE), with process No. 88881.132169/2016-01.

All other authors declare no competing interests.

c. Funding

The DO-HEALTH study was funded by the Seventh framework program of the European Commission (Grant Agreement n°278588), the University of Zurich (Chair for Geriatric Medicine and Aging Research), DSM nutritional products, ROCHE Diagnostics (SCHWEIZ), NESTEC, Pfizer Consumer Healthcare and STREULI Pharma.

The funding/supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

d. Data sharing statement

In a first step, no data will be made available to researchers external to DO-HEALTH Research Group to allow primary researchers to fully exploit the dataset. The data will be shared in a second step according to a controlled access system.

e. Ethics Statement

Patient consent for publication: Not required.

Ethics approval: The study protocol was approved by ethical and regulatory agencies of all five recruitment countries.

Acknowledgment: We thank all DO-HEALTH participants.

Dissemination to participants and related patient and public communities: Study results will, after scientific publication, be disseminated to the public in general through social media platforms, and public events organized by our center.

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Tables

Table 1. Baseline characteristics by city.

		Total (n=2157) [a]	Basel (n=253)	Berlin (n=350)	Coimbra (n=301)	Geneva (n=201)	Innsbruck (n=200)	Toulouse (n=300)	Zurich (n=552)
Age, median (IQR)		74.0 (72.0-77.0)	74.0 (72.0-77.0)	73.0 (71.0-74.0)	75.0 (72.0-79.0)	74.0 (72.0-78.0)	73.0 (71.0-75.0)	75.0 (72.0-79.0)	74.0 (71.0-78.0)
Women, N (%)		1331 (61.7)	151 (59.7)	247 (70.6)	192 (63.8)	127 (63.2)	103 (51.5)	181 (60.3)	330 (59.8)
Men, N (%)		826 (38.3)	102 (40.3)	103 (29.4)	109 (36.2)	74 (36.8)	97 (48.5)	119 (39.7)	222 (40.2)
Living alone, N (%)		900 (41.7)	113 (44.7)	134 (38.3)	98 (32.6)	95 (47.3)	73 (36.5)	139 (46.3)	248 (44.9)
Ever smoked, N (%)		797 (37.0)	104 (41.1)	143 (40.9)	65 (21.6)	86 (42.8)	73 (36.5)	135 (45.0)	191 (34.6)
Prior fall in the last 12 months, N (%)		903 (41.9)	109 (43.1)	125 (35.7)	123 (40.9)	88 (43.8)	99 (49.5)	129 (43.0)	230 (41.7)
Years of education, mean (SD)		12.6 (4.3)	13.5 (3.5)	14.5 (3.3)	7.9 (5.3)	13.7 (4.1)	12.4 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI [Kg/m^2], mean (SD)	Men	26.6 (3.5)	27.0 (3.6)	26.7 (3.0)	28.0 (3.5)	26.0 (3.5)	25.9 (3.3)	26.8 (3.3)	26.2 (3.6)
	Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.1 (4.4)	25.1 (4.5)	25.6 (4.4)
Cognitive function [b], median (IQR)		26.0 (24.0-28.0)	28.0 (26.0-30.0)	26.0 (24.0-27.0)	22.0 (19.0-25.0)	27.0 (26.0-29.0)	27.0 (25.0-29.0)	27.0 (26.0-29.0)	26.0 (24.0-28.0)
Self-rated health [c], median (IQR)		82.0 (73.0-91.0)	88.0 (79.0-92.0)	81.0 (71.0-90.0)	78.0 (60.0-90.0)	88.0 (80.0-92.0)	90.0 (80.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)
Frailty status, N (%) [d]		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	119 (59.6)	150 (53.6)	313 (57.3)
Robust									
	Prefrail	922 (43.4)	95 (37.7)	130 (37.4)	172 (57.7)	97 (48.3)	80 (40.4)	122 (43.6)	226 (41.4)
	Frail	64 (3.0)	4 (1.6)	2 (0.6)	41 (13.8)	2 (1.0)	0 (0.0)	8 (2.9)	7 (1.3)
Number of drugs, median (IQR)		3.0 (1.0-5.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	5.0 (3.0-8.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	3.0 (1.0-5.0)	2.0 (1.0-4.0)
Number of comorbidities [e], median (IQR)		2.0 (1.0-3.0)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.0)
Heart disease or high blood pressure, N (%)		967 (44.8)	100 (39.5)	174 (49.9)	208 (69.3)	95 (47.3)	76 (38.0)	134 (44.7)	180 (32.6)
Back pain or osteoarthritis, N (%)		1290 (59.9)	138 (54.6)	207 (59.3)	185 (61.7)	157 (78.1)	119 (59.5)	211 (70.3)	273 (49.5)
Depression, N (%)		178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	5 (2.5)	38 (12.7)	15 (2.7)
Participants with no comorbidities, N (%)		463 (21.5)	67 (26.5)	78 (22.4)	23 (7.7)	19 (9.5)	52 (26.0)	42 (14.0)	182 (33.0)

Polypharmacy index [f], median (IQR)	1.5 (1.0-2.5)	1.5 (0.7-2.5)	1.5 (1.0-2.5)	2.0 (1.3-3.0)	1.0 (0.5-1.8)	1.3 (0.5-2.0)	1.3 (0.7-2.0)	2.0 (1.0-3.0)
Heart disease or high blood pressure (n=967)	1.7 (1.0-2.5)	1.5 (1.0-2.4)	1.7 (1.0-2.5)	2.0 (1.5-3.0)	1.0 (0.8-2.0)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)
Back pain or osteoarthritis (n=1290)	1.3 (0.7-2.0)	1.3 (0.5-2.0)	1.0 (0.7-2.0)	1.8 (1.3-2.5)	1.0 (0.5-1.5)	1.2 (0.5-2.0)	1.0 (0.5-1.8)	1.5 (0.8-2.5)
Depression (n=178)	1.5 (1.0-2.0)	2.0 (1.3-2.3)	1.5 (1.0-2.0)	1.7 (1.3-2.3)	1.0 (0.6-1.3)	1.0 (0.5-2.0)	1.4 (1.0-1.7)	1.5 (1.0-2.3)

Abbreviation: BMI, Body Mass Index. IQR, interquartile range.

[a] Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

[b] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). Scores range from 0 to 30 points, in which higher scores are better.[24]

[c] Self-rated health was assessed with a visual analogic scale (0-100 mm), in which higher scores are better.

[d] Frailty was defined according to the Fried definition which evaluates five criteria: fatigue, unintentional weight loss, reduced physical activity, slowness, and weakness. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).[26]

[e] Number of comorbidities was measured by the Self-Administered Comorbidity Questionnaire, which assesses the presence of current 12 comorbidities. Therefore, the range is from 0 to 12 comorbidities.[23]

[f] Polypharmacy index was estimated by the ratio between number of medications number of comorbidities among participants with at least one comorbidity (n=1692).

Table 2. Sociodemographic factors and health-related indicators associated with polypharmacy among DO-HEALTH participants.

		Unadjusted [a] OR (95% CI)	Adjusted [b] OR (95% CI)
Age		**1.07 (1.05, 1.10)**	**1.07 (1.04, 1.10)**
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	**0.65 (0.51, 0.84)**
Years of education		**0.92 (0.90, 0.94)**	1.01 (0.98, 1.04)
Living alone	No	Ref	-
	Yes	1.01 (0.84, 1.23)	
Ever smoked	No	Ref	-
	Yes	1.10 (0.90, 1.34)	
Prior fall in last 12 months	No	Ref	Ref
	Yes	**1.35 (1.12, 1.64)**	1.08 (0.85, 1.36)
BMI [Kg/m^2]		**1.15 (1.12, 1.18)**	**1.09 (1.06, 1.12)**
Cognitive function [c]		**0.87 (0.85, 0.90)**	1.00 (0.96, 1.04)
Self-rated health [d]		**0.97 (0.96, 0.97)**	0.99 (0.98, 1.00)
Frailty status [e]	Robust	Ref	Ref
	Prefrail	**1.63 (1.34, 1.99)**	0.92 (0.72, 1.18)
	Frail	**10.17 (5.74, 18.03)**	1.63 (0.77, 3.45)
Number of comorbidities [f]		**2.22 (2.04, 2.42)**	**2.13 (1.92, 2.36)**
City			
Zurich		Ref	Ref
Basel		**0.56 (0.40, 0.78)**	0.67 (0.44, 1.04)
Berlin		0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
Coimbra		**5.59 (4.33, 7.23)**	**2.36 (1.56, 3.55)**
Geneva		**0.50 (0.34, 0.73)**	**0.36 (0.22, 0.59)**
Innsbruck		0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
Toulouse		0.93 (0.71, 1.23)	**0.64 (0.42, 0.96)**

Abbreviations: OR, odds ratio; CI confidence interval; BMI, Body Mass Index.

[a] Values are from bivariate logistic regression analyses.

[b] Values are from multivariable logistic regression analyses including as covariates age, sex, prior fall in the last 12 months, years of education, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city.

[c] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).[24]

[d] Self-rated health was assessed with a visual analogic scale (0-100 mm).

[e] Frailty was defined according to the Fried definition.[26]

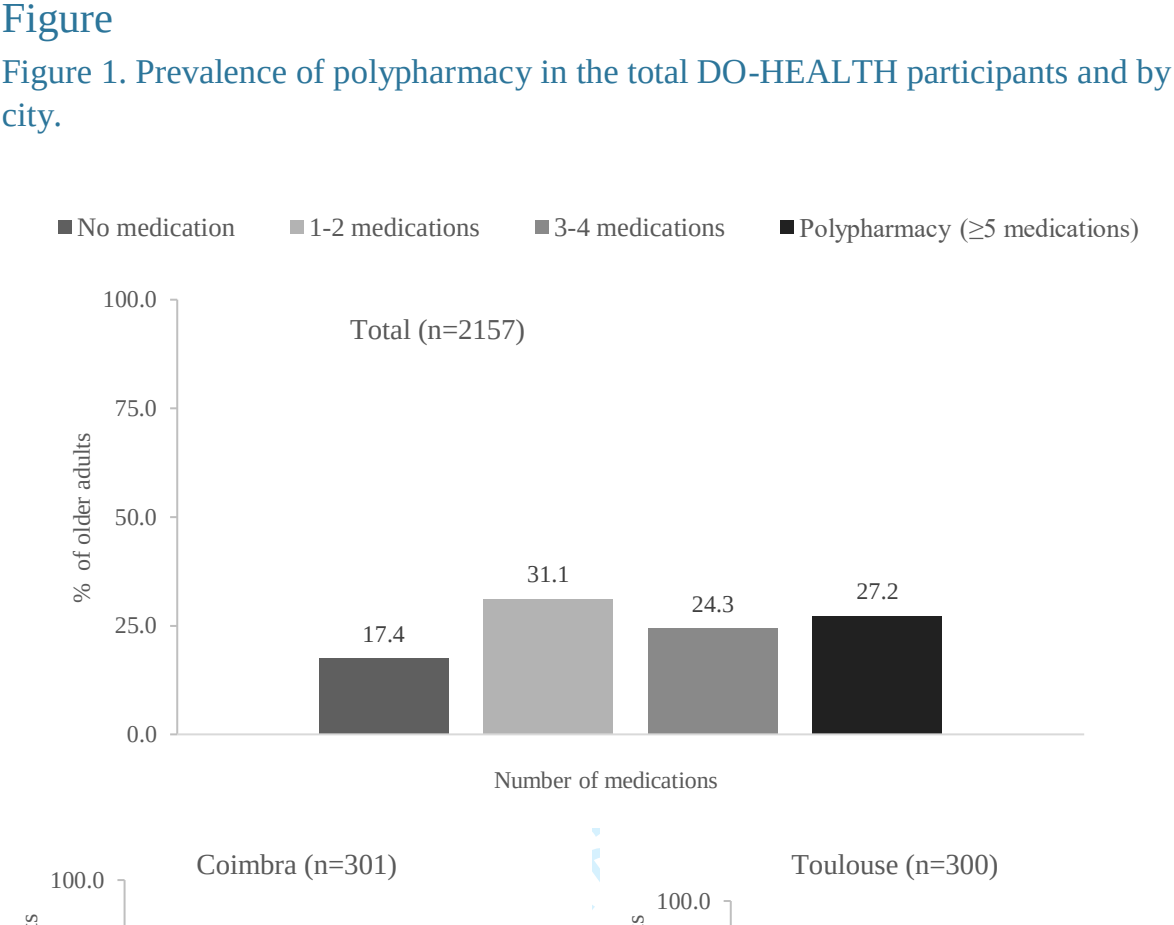
[f] Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[23]

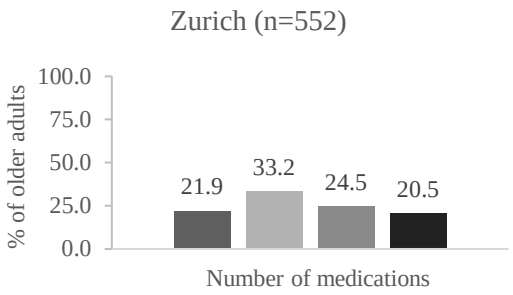
Figure

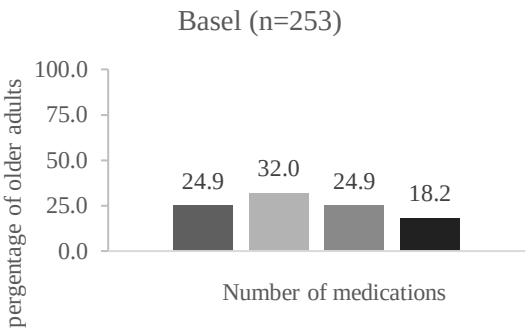
Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.

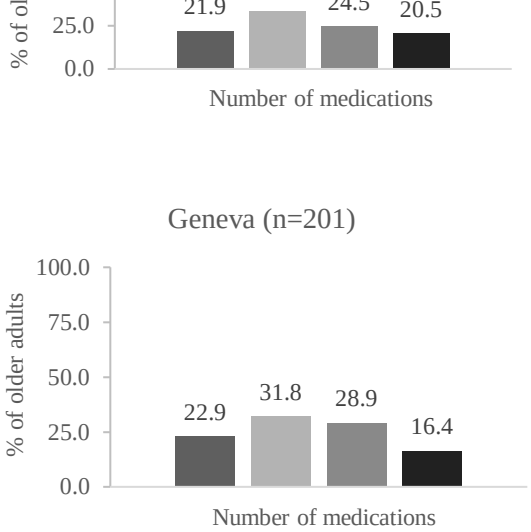
Figure

Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.









STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6 and 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 to 9
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7 to 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 7, and 10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 21, and 22
		(b) Indicate number of participants with missing data for each variable of interest	22
Outcome data	15*	Report numbers of outcome events or summary measures	10 and 24
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11, and 23

		(*b*) Report category boundaries when continuous variables were categorized	21 to 23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11 and 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14 and 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12 and 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15 and 16

*Give information separately for exposed and unexposed groups.

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BMJ Open

Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5 European countries: a cross-sectional study of DO-HEALTH

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051881.R1
Article Type:	Original research
Date Submitted by the Author:	17-Dec-2021
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Public health, General practice / Family practice
Keywords:	GERIATRIC MEDICINE, CLINICAL PHARMACOLOGY, PRIMARY CARE

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Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5 European countries: a cross-sectional study of DO-HEALTH

Word count: 3465 (excluding the abstract, references, tables, and figures)

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ABSTRACT

Word count: 300 (max 300)

Objective: To investigate the prevalence of polypharmacy and characteristics associated with polypharmacy in older adults from seven European cities.

Design: Cross-sectional study of baseline data from DO-HEALTH.

Setting and participants: DO-HEALTH enrolled 2157 community-dwelling adults age 70 and older from seven centers in Europe. Participants were excluded if they had major health problems or Mini Mental State Examination Score <24 at baseline.

Primary outcome measures: Extensive information on prescription and over-the-counter medications were recorded. Polypharmacy was defined as the concomitant use of 5 or more medications, excluding vitamins or dietary supplements. Bivariate and multivariable logistic regression was used to test the association of sociodemographic factors (age, sex, education, living situation, and city) and health-related indicators (number of comorbidities, cognitive function, frailty, body mass index [BMI], prior fall, self-rated health, and smoking status) with polypharmacy.

Results: 27.2% of participants reported polypharmacy ranging from 16.4% in Geneva to 60.8% in Coimbra. In the multivariable logistic regression analyses, older age (OR 1.07; 95% CI 1.04-1.10), greater BMI (OR 1.09; 95% CI 1.06-1.12), and increased number of comorbidities (OR 2.13; 95% CI 1.92-2.36) were associated with polypharmacy. Women were less likely to report polypharmacy than men (OR 0.65; 95% CI 0.51-0.84). In comparison to participants from Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI 1.56-3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy ((OR 0.36; 95% CI 0.22-0.59 and OR 0.64; 95% CI 0.42-0.96), respectively). Living situation, smoking status, education, prior fall, cognitive function, self-rated health, and frailty status were not significantly associated with polypharmacy.

Conclusion: Polypharmacy is common among relatively healthy older adults, with moderate variability across seven European cities. Independent of several confounders, being a woman, older age, greater BMI, and greater number of comorbidities were associated with increased odds for polypharmacy.

Trial registration: original RCT DO-HEALTH: NCT01745263

Strengths and limitations of this study

- This study takes advantage of the large DO-HEALTH data to estimate the prevalence of polypharmacy and characteristics associated with polypharmacy among European community-dwelling older adults.
- In this study, the use of medications was extensively assessed and included all regularly used medications, including both over-the-counter and prescription drugs.
- Because DO-HEALTH participants, were comprehensively assessed we were able to investigate the association of several sociodemographic factors and health-related indicators with polypharmacy.
- Although this was not a population-based study but a selection of relatively healthy older adults, a comparison between countries is of relevance at the public health level.
- This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy.

INTRODUCTION

By 2050, one in every four people in Europe and Northern America will be aged 65 or over.[1] As population ages, so does the number of chronic conditions and use of polypharmacy (commonly defined as the concomitant use of 5 or more medications).[2-5] For instance, about 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and Portugal.[6-8]

Although not all polypharmacy is considered inappropriate,[9] it constitutes a major public health problem because it is associated with increased risk of adverse drug reactions, drug-drug and drug-disease interactions, which can lead to falls, unnecessary or avoidable costs,[10 11] unplanned hospitalization,[12 13] emergency department and outpatient visits,[11] kidney function decline,[14] and mortality.[4 15-19]

Other studies have evaluated the use of polypharmacy among European older adults.[2 6-8 20] However, they considered only prescription medications or pharmacy claims which can either underestimate or overestimate the prevalence of polypharmacy. Only few studies considered all regularly taken medications including over-the-counter medications.[21-23] To the best of our knowledge, except for the Survey of Health Aging and Retirement in Europe (SHARE) wave 6,[22] no multi-center and international study has investigated and compared the prevalence of polypharmacy in European community-dwelling older adults. Moreover, the definition of polypharmacy, living facilities, and age distribution vary widely, limiting the comparison between regions and the identification of potential health interventions to improve the safe use of medications. Country comparison may be relevant for public health in order to detect clustering of high prevalence of polypharmacy,[11] which can inform policy makers and promote the safe use of medications among older adults.[24]

DO-HEALTH is a multicenter international trial that recruited relatively healthy seniors 70 years and older from 7 cities in 5 European countries.[25] At baseline, participants did not

present major comorbidities,[25 26] however 43% were frail and 26.4% had 3 or more comorbidities.[27] Therefore, to understand the extent of polypharmacy use among European older adults, the goal of the present study was to assess the prevalence of polypharmacy in 7 European cities using standardized methods, and its association with socio-demographic factors and health-related indicators among 2157 participants of DO-HEALTH.

METHODS

Participants and study design

This is a cross-sectional study using baseline data from DO-HEALTH, a randomized, double-blind, placebo-controlled, clinical trial designed to assess the effectiveness of the 3 interventions (vitamin D, omega-3 fatty acids, and simple home based strength exercise program) in a 2×2×2 factorial design (NCT01745263).[25 26] The six primary endpoints in DO-HEALTH were: change in systolic and diastolic blood pressure, the Short Physical Performance Battery, the Montreal Cognitive Assessment (cognitive function), and incidence of non-vertebral fractures and infections over 3 years.[25 26] From December 2012 to November 2014, DO-HEALTH included a total of 2157 older adults (70 years and older) from seven European cities located in five countries: Basel (n=253), Berlin (n=350), Coimbra (n=301), Geneva (n=201), Innsbruck (n=200), Toulouse (n=300), and Zurich (n=552). DO-HEALTH participants were recruited through mailing lists of retirement authorities, churches, and other community services, public events, flyers, posters, advertisement in newspapers and other media, and educational programs and health care. Additional details about recruitment, randomization and allocation, and blinding details are published elsewhere.[26]

Participants completed detailed questionnaires on demographics, medical events, lifestyle factors (nutrition, physical activity, living condition), medication intake, and had

extensive clinical examinations of multiple organ and physical functions at baseline and each year during a three-year follow-up.[26]

DO-HEALTH was approved by each local/national ethics committee and regulatory authorities. The present study was approved by the Ethics Committee Zurich (ID 2018-00684). All participants signed the consent form.

Study population

Detailed eligibility criteria were published elsewhere.[26] Briefly, DO-HEALTH adults aged 70 years or older, with Mini Mental State Examination Score[28] greater or equal to 24, living in the community, and sufficiently mobile to come to the study center. Older adults were excluded if they reported a history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, or transient ischemic attack in the last 5 years. Older adults with epilepsy and/or use of anti-epileptic drugs, angina pectoris or coronary artery intervention, severe renal impairment (creatinine clearance ≤ 15 ml/min) or dialysis, hypercalcemia (> 2.6 mmol/l), history of hypo or primary hyperparathyroidism, severe liver disease, or living in assisted living situations or a nursing home, were also excluded. For the purpose of this cross-sectional analysis we included baseline data from all DO-HEALTH participants (n=2157).

Data collection

Sociodemographic factors and health-related indicators

Sociodemographic information comprised age, sex, years of education, living situation (alone vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich). Health-related indicators comprised number of comorbidities, cognitive function, frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was designed to recruit 40% of participants with a prior fall in the last 12 months.[25]

Comorbidity

The number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[29] This instrument is validated in the older population and evaluates the presence of 13 common chronic diseases: heart disease, high blood pressure, lung disease, diabetes, ulcer and stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, osteoarthritis or degenerative arthritis, back pain, rheumatoid arthritis.

Cognitive function

Cognitive function was assessed by the Montreal Cognitive Assessment questionnaire (MoCA)[30] at baseline and follow-up. MoCA has a maximum score of 30 points, and is presented as a continuous variable. MoCA was chosen because of its higher sensitivity to detect mild cognitive impairment in older adults.[30 31] In a validation study, MoCA had a sensitivity of 90% to detect mild cognitive impairment, while the Mini-Mental State Exam detected only 18%.[30]

Frailty

Frailty was defined according to Fried et al[32] which evaluates five criteria: fatigue (self-reported), unintentional weight loss (self-reported loss more than 5% of total body weight), reduced physical activity (self-reported), slowness (impaired walking speed), and weakness (low grip strength). Slowness was defined as a gait speed below 0.67 m/s and 0.7 m/s respectively, according to gender and height as in the original Fried conceptualization.[32] For weakness, we used grip strength measured by Martin Vigorimeter (KLS Martin Group, Tuttlingen, Germany) with cut-points at the lowest 20% of the cohort based on age, gender and country of origin. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).

Self-rated health

Self-rated health was measured with the EQ5D-3L.[33] Participants were asked to rate their health status on a visual analog scale (0-100 mm) with respect to the question: "Please rate how well

you are doing on a scale of 0 to 100", where 0 represents 'very poorly' and 100 represents 'very well'. Self-rated health is presented as a continuous variable.

Medications

Trained study nurses and study medical doctors asked participants in detail for the use of medications with standardized questionnaire. For each medication participants reported: brand name, generic name, dose, unit, interval (as needed or regularly), indication, and treatment duration. To minimize recall bias, participants were asked to bring their medication and/or medication packages and/or a medication-list (from the general practitioner) to the baseline visit. In addition, all participants completed a diary to improve the recall.

We included all prescribed and over the counter medications taken regularly, and excluded multivitamins, dietary supplements, herbal, and homeopathic medicines. Regular medication was defined as those drugs taken daily or at regular intervals (e.g. once a week). All medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[34] Each active substance was defined as one medication and received an individual ATC code. For example, the combination of amlodipine/indapamide/perindopril was counted as 3 medications and received the codes C08CA01, C03BA11, C09AA04, respectively. As no consensus on the definition of polypharmacy exists, we used the most commonly reported threshold of 5 or more drugs (active substances) daily.[4 5 24 35-37]

Statistical analysis

Descriptive statistics are presented as frequencies and percentages (%) for categorical variables, and means with standard deviation (SD) for continuous variables (or median and interquartile range for non-normally distributed variables). Data were checked for normality visually. We present the prevalence of polypharmacy for the total population of DO-HEALTH and by city (n=7; Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich).

To test the association of sociodemographic factors (age, sex, years of education, and living alone) and health-related indicators (number of comorbidities, cognitive function, frailty

status, BMI, prior fall in the last 12 months, self-rated health, and smoking status) with polypharmacy (binary outcome), we first performed bivariate logistic regression analyses and included variables with $p<0.2$ in the multivariable logistic regression analyses. The final model presents the adjusted odds ratios and 95% confidence intervals (OR, 95% CI). Analysis were performed with SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA.).

Patient and public involvement

Patients and the public were not involved in setting up the research question, design, outcome measures, interpretation of the results, or writing the manuscript.

RESULTS

Baseline characteristics of the 2157 older adults included in DO-HEALTH are described in **Table 1**. Median age was 74.0 years (IQR 72.0-77.0) and most participants were women (61.7%). Mean BMI was 26.6 kg/m^2 (SD 3.5) and 26.2 kg/m^2 (SD 4.7) in men and women, respectively. Most participants were classified as robust (53.6%) with only 3.0% of participants classified as frail. The median number of comorbidities was 2.0 (IQR 1.0-3.0), and median number of medications was 3.0 (IQR 1.0-5.0).

Table 1 also describes the baseline characteristics by city. Coimbra and Toulouse had the highest median age (median 75 IQR 72.0-79.0 and median 75 IQR 71.0-75.0, respectively). Coimbra had the lowest proportion of participants with no comorbidities, the highest mean BMI, median number of medications, as well as the highest proportion of prefrail and frail participants. Berlin had, on average, the highest proportion of women, robust participants, and mean years of education.

Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2% and, 17.4% reported no medications at all (**Figure 1**). Regarding the cities, on average Coimbra

reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%). Berlin (25.4%), Innsbruck (22%), Zurich (20.5%), Basel (18.2%), and Geneva (16.4%).

Table 2 shows the association of sociodemographic factors and health-related indicators with polypharmacy. In the bivariate analyses (unadjusted models), greater age, BMI, and number of comorbidities, as well as prior fall and frailty were associated with an increase in the odds of polypharmacy. Higher MoCA scores (higher scores mean better cognitive function), higher self-rated health scores, and more years of education were associated with a decrease in the odds of polypharmacy. The associations of living alone and ever smoked with polypharmacy were non-significant at $p>0.2$ and, therefore, were not included in the multivariable logistic regression analysis. In the multivariable logistic regression analysis (including the covariates age, sex, education, prior fall, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city), age, sex, BMI, number of comorbidities, and city were independently associated with polypharmacy. For each additional year of age, there was 7% higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a one unit increase in BMI, there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-1.12). For one additional comorbidity, there was a 2-fold increase in the odds of polypharmacy (OR 2.13, 95% CI 1.92-2.36). Women had 35% lower odds of reporting polypharmacy than men (OR 0.65, 95% CI 0.51-0.84). Participants from Geneva or Toulouse were also less likely to report polypharmacy than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR 0.64, 95% CI 0.42-0.96, respectively). Participants from Coimbra had 2 times higher odds of reporting polypharmacy (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having had a fall in the year prior to enrollment, education, cognitive function, self-rated health, and frailty status were no longer significantly associated with polypharmacy in the multivariable analysis.

DISCUSSION

In this cross-sectional study of 2157 relatively healthy European older adults, about one quarter of participants reported polypharmacy. However, despite the same inclusion and exclusion criteria in this large clinical trial, there was moderate variability in prevalence of polypharmacy between the seven cities with the lowest prevalence observed in Geneva and Basel with less than 20% and the highest prevalence observed in Coimbra with about 60%. Notably, older age, greater BMI, and number of comorbidities were significantly associated with higher odds of polypharmacy after adjusting for education, prior fall, cognitive function, self-rated health, and frailty.

Comparison with other studies

On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are consistent with previous population-based studies. In the population-based CoLaus study, a cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-aged adults (mean age 58 years) was 16.9%.[20] This is consistent with our results from Geneva (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy reported in Coimbra (60.8%) is in accordance with a previous population-based study conducted in Oporto/Portugal (59%).[7] Yet, a population-based study conducted in Germany (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)[38] than we observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty in the ESTHER cohort in which only 32.8% of participants were robust,[38] while in DO-HEALTH about 60% of older adults from Berlin were robust.

Participants from Coimbra were more likely to report polypharmacy than other centers. This increased prevalence could be explained by the fact that Coimbra participants were on average older, had higher BMI, and more likely to be prefrail or frail, despite our strict inclusion and exclusion criteria and our aim to standardize recruitment strategies. In our analysis, BMI and number of comorbidities were strongly associated with polypharmacy even after

controlling for age, city and other covariates. Additionally, participants from Coimbra also reported on average a higher prevalence of depression and hypertension when compared to other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy, since hypertension and depression are associated with increased use of medications, and initiating or maintaining polypharmacy.[39]

Other factors, however, may also explain the wide variation in the prevalence of polypharmacy, such as: health system organization and coverage, country specific drug policies, medication costs, prescribing pattern, refund system, clinicians' workload and specialization, and socioeconomic status.[40-47] A prior study in 57 European nursing homes (SHELTER study) also found differences in the prevalence of polypharmacy across seven European countries.[43] The authors suggested that this variation may be caused by the distinct attitudes of physicians when managing older adults with multimorbidity.[43] Other studies also observed high association between prescriber characteristics, such as medicine specialization, and polypharmacy.[42 46 47] For example, a recent national cross-sectional study among Malaysian older adults found that physicians with family medicine specialization were five times more likely to prescribe more than five medications at one time.[46] Interestingly, among the five countries included in DO-HEALTH, Portugal is the only one that does not recognize geriatric medicine as a specialty or subspecialty.[48] Moreover, the discrepancy in the prevalence of polypharmacy and health characteristics in Coimbra may be associated to the low expenditure on prevention activities in Portugal.[49] For example, Portugal spends only half the average expenditure on prevention activities by other Organization for Economic Co-operation and Development (OECD) countries.[49] Health prevention policies are fundamental to improve healthy aging and disease burden.[50] In fact, the life expectancy in Portugal is one of the highest in the world,[51] however less than half of Portuguese reported being in very good or good health.[49] Future reports, however, may find new insights regarding the health conditions and medication use in Portugal. In 2012 an extended National Health Plan was published in

Portugal. This plan aims to guide the public health sector to implement actions to reduce the risk factors for chronic diseases.[49] Additionally, in 2013, a national list of pharmaceutical products and prescription guidelines were defined which may also improve the use of medication in this population.[49]

Implications for clinical practice

The pharmacological treatment of older adults with multimorbidity is complex and poorly addressed in clinical practice guidelines.[52-54] For instance, the pharmacological recommendations of the National Institute for Health and Care Excellence (NICE) guidelines for management of type 2 diabetes, depression, and heart failure rarely account for multimorbidity.[55] In fact, only a few drug trials include older adults with multimorbidity.[56 57] Therefore, the cumulative effects of multiple medication use in multimorbid older adults are unknown, and clinicians are not supported by evidence-based recommendations to manage drug prescriptions among this population. Furthermore, this lack of evidence may lead to unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions. Notably, about 50% of older adults take at least one unnecessary medication[58] and less than 50% have a clear understanding of pharmacotherapy purpose.[59] In this context, efforts to minimize polypharmacy and deprescribe unnecessary or inappropriate medications were described around the world.[60-71] Recently, findings from a Swiss cluster-randomized clinical study among 46 primary care physicians suggested that a patient-centered deprescribing intervention may reduce polypharmacy among old multimorbid patients.[69] In Portugal, an ongoing nationwide three-phase study on deprescribing is investigating barriers and facilitators of deprescribing perceived by older adults and their acceptance to have regular medications deprescribed.[67 71] A pilot-study among 16 general practitioners in Germany found that an electronic tool may assist in identifying deprescribing opportunities and promote patient involvement and shared decision making.[66] Our findings suggest that even among relatively

healthy older adults polypharmacy is common, which makes this population also a target for deprescribing interventions.

Strengths and limitation of this study

In this study, we addressed the literature gap of limited studies including both over-the-counter and prescription medications used regularly. The assessment of both prescription and over-the-counter medications is needed as almost 50% of medication users also use at least one over-the-counter medication, with half of them presenting a potential major drug interaction.[17] The majority of studies investigating medication patterns in Europe use dispensation data from health insurance companies' providers,[72] pharmacy claims,[2 73 74] hospitals[75] or nursing homes,[43] and only few included over-the-counter medications.[21-23] These studies had different methodologies which limits a direct comparison to our results. For example, the study by Mielke et al. in Germany, over-the-counter medications included herbal medicines.[21] In our study, we did not include complementary, homeopathic and herbal medicines as they are not included in the ATC classification system.[34] In the study by Midao et al. based on the SHARE population, participants were simply asked if they took at least five different drugs on a typical day.[22] In our study, a trained medical doctor revised all the medications brought by the participants, as well as medication packages and/or a medication list. Further, because DO-HEALTH included participants from different European countries and we used the same definition of polypharmacy, our findings allow cross-country comparisons and provide relevant data for future research and health policy interventions on the pharmacogerontology field.

This study has also limitations. This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy and is not a population-based study. As there is no consensus on the definition of polypharmacy, we chose the common and arbitrary cut-off of 5 or more medications.[4 5 24 35-37] Due to the scope of this study, the appropriateness of polypharmacy was not investigated. Despite of DO-HEALTH being the largest European trial on healthy aging, a relatively moderate number of participants

were included for each city. Overall, however, our sample size of 2157 older adults is larger than in prior European studies.[7 20 21 23] Because our population consists on volunteers to participate in a trial, they are not representative of the general population of each country, therefore generalizability of our results is limited. Further, the scope of this study is limited in terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered conservative as participants were relatively healthy at baseline (without major chronic diseases such as cancer or major cardiovascular events in the last 5 years), or in use of anti-epileptic drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence of polypharmacy and longitudinal studies that showed the association between polypharmacy and age, BMI, and comorbidities.[7 20 38 39 76] Moreover, comorbidities were assessed with the validated Self-Administered Comorbidity Questionnaire.[29] Although this questionnaire is validated in the older population and assesses the presence of the most common chronic diseases, it does not include some common conditions in older adults as sleep disorders and obstipation and participants may not be aware of some conditions. Finally, we cannot exclude that we may have missed information on medication use and comorbidities due to poor recall.

CONCLUSION

About one quarter of European community-dwelling older adults reported polypharmacy. We found that polypharmacy was associated with being female and increased age, BMI, and number of comorbidities. Further, variation in the prevalence of polypharmacy between cities remained even after accounting for demographic and health-related differences between study participants. Deprescribing measures should also target relatively healthy older adults.

a. Contributorship statement

CdGRCM and POCB contributed equally as co-first authors, they performed the literature survey, the drafting of the article, and the statistical analyses. AS, RT, SG, and WL provided

critical revision of the manuscript. EJO, BV, RR, RWK, JAK, AE, and HABF designed the study concept, acquired the data and critically revised the manuscript. HABF is the PI of DO-HEALTH.

b. Competing interests

As part of the DO-HEALTH independent and investigator initiated clinical trial, HABF reports as the PI of the DO-HEALTH trial, grants from European Commission, from University of Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli Pharma, plus nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche Diagnostics. Further, HABF reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor, outside the submitted work.

BV reports personal fees from BIOGEN, CERECIN, ROCHE, MSD, outside the submitted work.

RR reports personal fees from Abiogen, Danone, Echolight, EMF, Mithra, ObsEva, Pfizer Consumer Health, Theramex, outside the submitted work.

EJO reports grants from Zurich University, during the conduct of the study.

CdGRCM received funding from the National Council for Scientific and Technological Development (CNPq), with process Nos. 164700/2015-3, from the São Paulo Research Foundation (FAPESP), with process No. 2016/13700-9, and Coordination for the Improvement of Higher Education Personnel/PhD Sandwich Programs Abroad (PDSE), with process No. 88881.132169/2016-01.

All other authors declare no competing interests.

c. Funding

The DO-HEALTH study was funded by the Seventh framework program of the European Commission (Grant Agreement n°278588), the University of Zurich (Chair for Geriatric Medicine and Aging Research), DSM nutritional products, ROCHE Diagnostics (SCHWEIZ), NESTEC, Pfizer Consumer Healthcare and STREULI Pharma.

The funding/supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

d. Data sharing statement

In a first step, no data will be made available to researchers external to DO-HEALTH Research Group to allow primary researchers to fully exploit the dataset. The data will be shared in a second step according to a controlled access system.

e. Ethics Statement

Patient consent for publication: Not required.

Ethics approval: The study protocol was approved by ethical and regulatory agencies of all five recruitment countries.

Acknowledgment: We thank all DO-HEALTH participants.

Dissemination to participants and related patient and public communities: Study results will, after scientific publication, be disseminated to the public in general through social media platforms, and public events organized by our center.

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Tables

Table 1. Baseline characteristics by city.

		Total (n=2157) [a]	Basel (n=253)	Berlin (n=350)	Coimbra (n=301)	Geneva (n=201)	Innsbruck (n=200)	Toulouse (n=300)	Zurich (n=552)
Age, median (IQR)		74.0 (72.0-77.0)	74.0 (72.0-77.0)	73.0 (71.0-74.0)	75.0 (72.0-79.0)	74.0 (72.0-78.0)	73.0 (71.0-75.0)	75.0 (72.0-79.0)	74.0 (71.0-78.0)
Women, N (%)		1331 (61.7)	151 (59.7)	247 (70.6)	192 (63.8)	127 (63.2)	103 (51.5)	181 (60.3)	330 (59.8)
Men, N (%)		826 (38.3)	102 (40.3)	103 (29.4)	109 (36.2)	74 (36.8)	97 (48.5)	119 (39.7)	222 (40.2)
Living alone, N (%)		900 (41.7)	113 (44.7)	134 (38.3)	98 (32.6)	95 (47.3)	73 (36.5)	139 (46.3)	248 (44.9)
Ever smoked, N (%)		797 (37.0)	104 (41.1)	143 (40.9)	65 (21.6)	86 (42.8)	73 (36.5)	135 (45.0)	191 (34.6)
Prior fall in the last 12 months, N (%)		903 (41.9)	109 (43.1)	125 (35.7)	123 (40.9)	88 (43.8)	99 (49.5)	129 (43.0)	230 (41.7)
Years of education, mean (SD)		12.6 (4.3)	13.5 (3.5)	14.5 (3.3)	7.9 (5.3)	13.7 (4.1)	12.4 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI [Kg/m^2], mean (SD)	Men	26.6 (3.5)	27.0 (3.6)	26.7 (3.0)	28.0 (3.5)	26.0 (3.5)	25.9 (3.3)	26.8 (3.3)	26.2 (3.6)
	Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.1 (4.4)	25.1 (4.5)	25.6 (4.4)
Cognitive function [b], median (IQR)		26.0 (24.0-28.0)	28.0 (26.0-30.0)	26.0 (24.0-27.0)	22.0 (19.0-25.0)	27.0 (26.0-29.0)	27.0 (25.0-29.0)	27.0 (26.0-29.0)	26.0 (24.0-28.0)
Self-rated health [c], median (IQR)		82.0 (73.0-91.0)	88.0 (79.0-92.0)	81.0 (71.0-90.0)	78.0 (60.0-90.0)	88.0 (80.0-92.0)	90.0 (80.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)
Frailty status, N (%) [d]		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	119 (59.6)	150 (53.6)	313 (57.3)
Robust									
	Prefrail	922 (43.4)	95 (37.7)	130 (37.4)	172 (57.7)	97 (48.3)	80 (40.4)	122 (43.6)	226 (41.4)
	Frail	64 (3.0)	4 (1.6)	2 (0.6)	41 (13.8)	2 (1.0)	0 (0.0)	8 (2.9)	7 (1.3)
Number of drugs, median (IQR)		3.0 (1.0-5.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	5.0 (3.0-8.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	3.0 (1.0-5.0)	2.0 (1.0-4.0)
Number of comorbidities [e], median (IQR)		2.0 (1.0-3.0)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.0)
Rheumatoid arthritis or osteoarthritis, N (%) [f]		974 (45.2)	116 (45.9)	168 (48.1)	79 (26.3)	124 (61.7)	98 (49.0)	173 (57.7)	216 (39.1)
High blood pressure, N (%)		844 (39.2)	86 (34.0)	163 (46.7)	186 (62.0)	80 (39.8)	61 (30.5)	112 (37.3)	156 (28.3)
Back pain, N (%)		773 (35.9)	59 (23.3)	104 (29.8)	167 (55.7)	101 (50.3)	72 (36.0)	144 (48.0)	126 (22.8)
Heart disease, N (%)		263 (12.2)	23 (9.1)	31 (8.9)	72 (24.0)	28 (13.9)	18 (9.0)	44 (14.7)	47 (8.5)

Depression, N (%)	178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	52 (12.5)	38 (12.7)	15 (2.7)
Stomach disease, N (%)	165 (7.7)	6 (2.4)	14 (4.0)	65 (21.7)	17 (8.5)	123 (26.0)	37 (12.3)	14 (2.5)
Diabetes, N (%)	150 (7.0)	15 (5.9)	27 (7.7)	44 (14.7)	10 (5.0)	81 (14.0)	23 (7.7)	23 (4.2)
Lung disease, N (%)	109 (5.1)	9 (3.6)	24 (6.7)	17 (5.7)	14 (7.0)	6 (3.0)	21 (7.0)	18 (3.3)
Anemia, N (%)	64 (3.0)	5 (2.0)	4 (1.2)	22 (7.3)	9 (4.5)	4 (2.0)	6 (2.0)	14 (2.5)
Kidney disease, N (%)	54 (2.5)	1 (0.4)	3 (0.9)	35 (11.7)	4 (2.0)	0 (0.0)	6 (2.0)	5 (0.9)
Liver disease, N (%)	37 (1.7)	1 (0.4)	3 (0.9)	23 (7.7)	3 (1.5)	2 (1.0)	4 (1.3)	1 (0.2)
Cancer, N (%)	27 (1.3)	3 (1.2)	2 (0.6)	4 (1.3)	3 (1.5)	2 (1.0)	6 (2.0)	7 (1.3)
Participants with no comorbidities, N (%)	463 (21.5)	67 (26.5)	78 (22.4)	23 (7.7)	19 (9.5)	52 (26.0)	42 (14.0)	182 (33.0)

Abbreviation: BMI, Body Mass Index. IQR, interquartile range.

[a] Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

[b] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). Scores range from 0 to 30 points, in which higher scores are better.[30]

[c] Self-rated health was assessed with a visual analogic scale (0-100 mm), in which higher scores are better.

[d] Frailty was defined according to the Fried definition which evaluates five criteria: fatigue, unintentional weight loss, reduced physical activity, slowness, and weakness. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).[32]

[e] Number of comorbidities was measured by the Self-Administered Comorbidity Questionnaire, which assesses the presence of current 13 comorbidities. Therefore, the range is from 0 to 13 comorbidities.[29]

[f] Following the instructions of the original publication of the Self-Administered Comorbidity Questionnaire, rheumatoid arthritis and osteoarthritis were assessed separately but were combined in the analysis as participants might not distinguish these disorders accurately.[29]

Table 2. Sociodemographic factors and health-related indicators associated with polypharmacy among DO-HEALTH participants.

		Unadjusted [a] OR (95% CI)	Adjusted [b] OR (95% CI)
Age		**1.07 (1.05, 1.10)**	**1.07 (1.04, 1.10)**
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	**0.65 (0.51, 0.84)**
Years of education		**0.92 (0.90, 0.94)**	1.01 (0.98, 1.04)
Living alone	No	Ref	-
	Yes	1.01 (0.84, 1.23)	
Ever smoked	No	Ref	-
	Yes	1.10 (0.90, 1.34)	
Prior fall in last 12 months	No	Ref	Ref
	Yes	**1.35 (1.12, 1.64)**	1.08 (0.85, 1.36)
BMI [Kg/m^2]		**1.15 (1.12, 1.18)**	**1.09 (1.06, 1.12)**
Cognitive function [c]		**0.87 (0.85, 0.90)**	1.00 (0.96, 1.04)
Self-rated health [d]		**0.97 (0.96, 0.97)**	0.99 (0.98, 1.00)
Frailty status [e]	Robust	Ref	Ref
	Prefrail	**1.63 (1.34, 1.99)**	0.92 (0.72, 1.18)
	Frail	**10.17 (5.74, 18.03)**	1.63 (0.77, 3.45)
Number of comorbidities [f]		**2.22 (2.04, 2.42)**	**2.13 (1.92, 2.36)**
City			
Zurich		Ref	Ref
Basel		**0.56 (0.40, 0.78)**	0.67 (0.44, 1.04)
Berlin		0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
Coimbra		**5.59 (4.33, 7.23)**	**2.36 (1.56, 3.55)**
Geneva		**0.50 (0.34, 0.73)**	**0.36 (0.22, 0.59)**
Innsbruck		0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
Toulouse		0.93 (0.71, 1.23)	**0.64 (0.42, 0.96)**

Abbreviations: OR, odds ratio; CI confidence interval; BMI, Body Mass Index.

[a] Values are from bivariate logistic regression analyses.

[b] Values are from multivariable logistic regression analyses including as covariates age, sex, prior fall in the last 12 months, years of education, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city.

[c] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).[30]

[d] Self-rated health was assessed with a visual analogic scale (0-100 mm).

[e] Frailty was defined according to the Fried definition.[32]

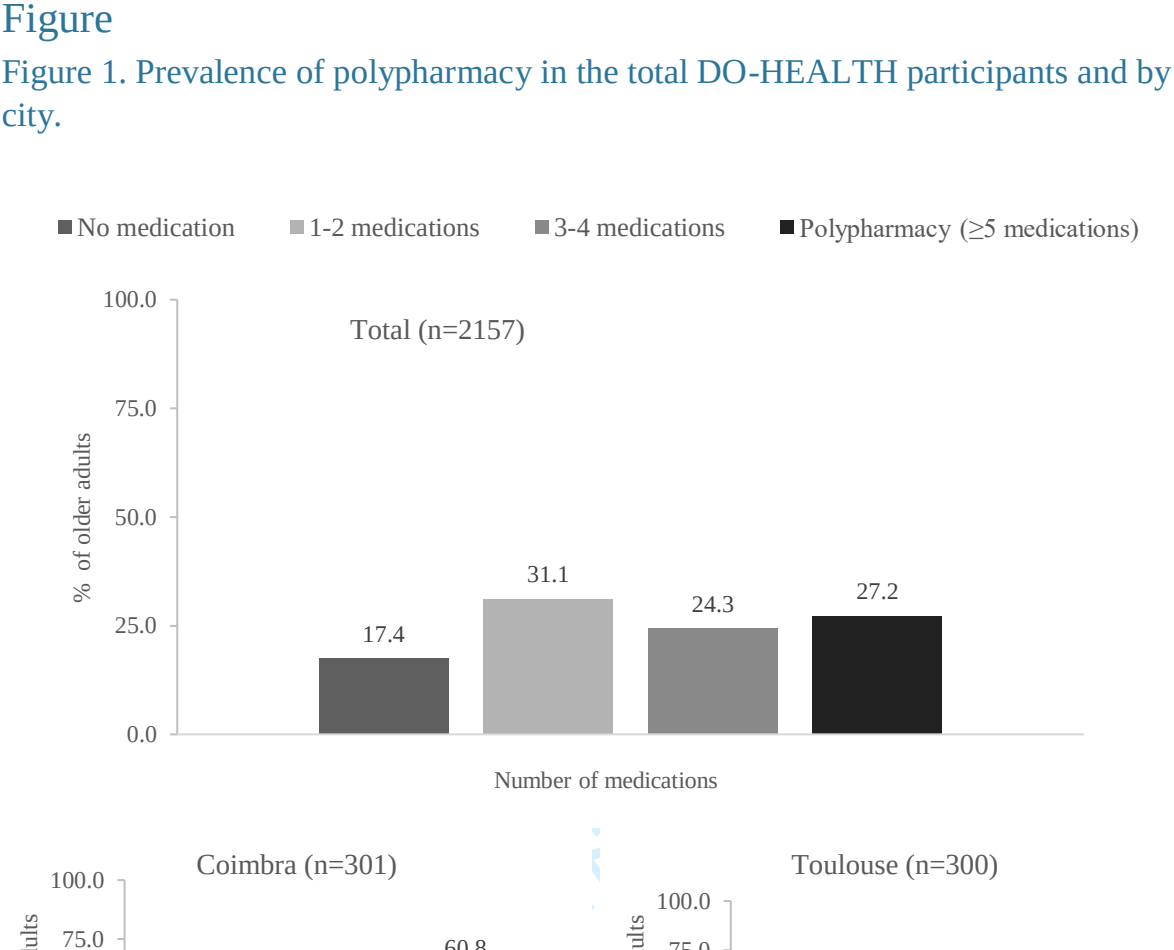
[f] Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[29]

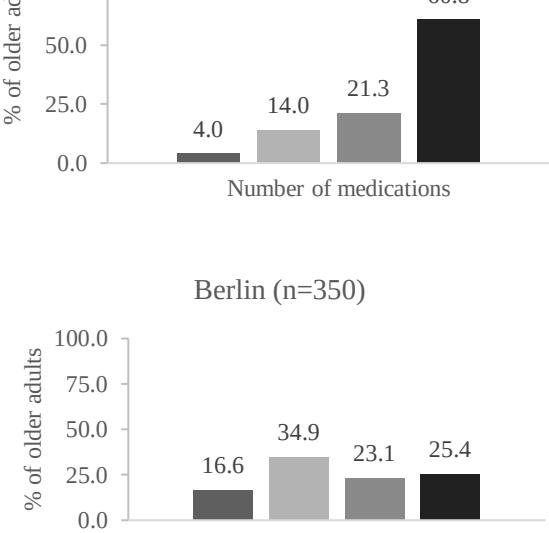
Figure

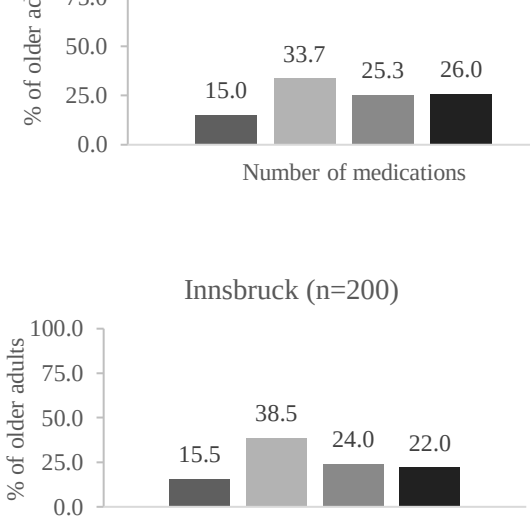
Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.

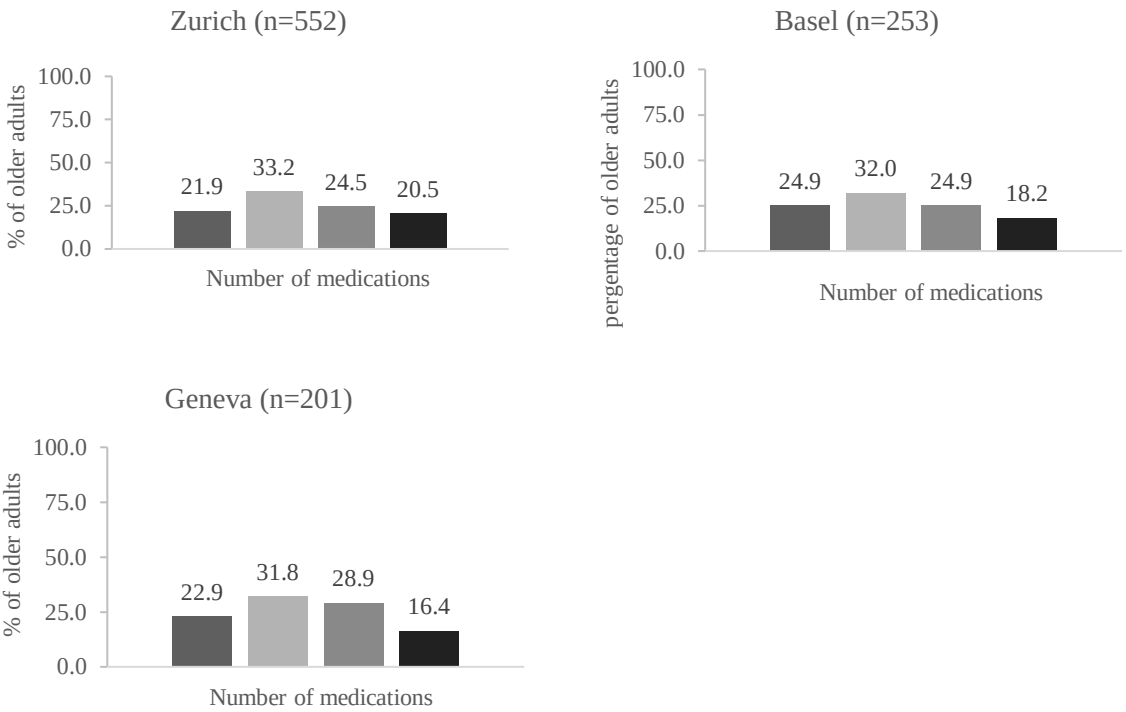
Figure

Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.









Appendix. DO-HEALTH Research Group
This e-appendix has been provided by the authors to give readers additional information about DO-HEALTH Research Group.

DO-HEALTH Consortium

(in bold: Governing Board members; in bold and underlined: Chair; underlined: Team members).

Prof Heike A Bischoff-Ferrari MD, DO-HEALTH Coordinator, Principal Investigator and Zurich Site Investigator, leads all endpoints analyses and co-leads the studies 'DO-HEALTH health economic model', 'novel biomarkers of immunity', 'novel biomarkers of muscle and bone communication', University Hospital Zurich, University of Zurich and Waid City Hospital, Zurich, Switzerland, Andreas Egli MD, Sandrine Rival PhD.

Prof Bruno Vellas MD, Toulouse Site Investigator, contributes to the primary endpoint cognitive decline, and Sophie Guyonnet PhD, CHU Toulouse and University of Toulouse III, Toulouse, France.

Prof René Rizzoli MD, Geneva Site Investigator, contributes to all bone and muscle related endpoints and explores the contribution of protein intake to the benefit of the interventions, Emmanuel Biver MD, and Fanny Merminod RD, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.

Prof Reto W Kressig MD, Basel Site Investigator, contributes to gait analyses and dual task assessments, and Stephanie Bridenbaugh MD, University Department of Geriatric Medicine FELIX PLATTER and University of Basel, Basel, Switzerland. Prof. Norbert Suhm, Dept. of Traumatology, University Hospital Basel, contributes to fracture healing study DO-HEALTH.

Prof José A P Da Silva MD, Coimbra Site Investigator, explores the treatment effects on vertebral fractures, and musculoskeletal pain and function, Centro Hospitalar e Universitário de Coimbra, and Faculty of Medicine, University of Coimbra, Coimbra, Portugal, Cátia CM Duarte MD, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, and Ana Filipa Pinto RN, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

Prof Dieter Felsenberg MD, Berlin Site Investigator, performs the central DO-HEALTH DEXA quality control and evaluation of DEXA measurements, Hendrikje Börst Dipl.Wiss-org, and Gabriele Armbrecht MD, Charité Universitätsmedizin Berlin, Berlin, Germany.

Prof Michael Blauth MD, Innsbruck Site Investigator, explores the functionality after fracture, and Anna Spicher MD, Medical University of Innsbruck, Innsbruck, Austria.

Prof David T Felson MD, co-leads 'DO-HEALTH osteoarthritis study', Manchester Academic Health Science Centre, Manchester, United Kingdom and Boston University School of Medicine, Boston, MA, USA.

Prof John A Kanis MD leads the study 'contribution of fall risk to absolute fracture risk within the FRAX model', University of Sheffield Medical School, Sheffield, United Kingdom and Australian Catholic University, Melbourne, Victoria, Australia. Prof Eugene V Mccloskey MD, co-leads the study 'contribution of fall risk to absolute fracture risk within the FRAX model', University of Sheffield, Sheffield, United Kingdom, and Elena Johansson MD, University of Sheffield Medical School, Sheffield, United Kingdom and Catholic University of Australia, Melbourne, Victoria, Australia.

Prof Bernhard Watzl PhD, co-leads the study 'novel biomarkers of immunity', Manuel Rodriguez Gomez PhD, Max Rubner-Institut, Karlsruhe, Germany.

Prof Lorenz Hofbauer MD, co-leads the study 'novel biomarkers of muscle and bone communication', FOÄ Dr. Elena Tsourdi, and Professor Martina Rauner PhD, Dresden University Medical Center and Center for Regenerative Therapies Dresden, Dresden, Germany.

Uwe Siebert MD, co-leads the study 'DO-HEALTH health economic model', UMIT - University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria and Harvard T.H. Chan School of Public Health, Boston, MA, USA and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Prof John A Kanis MD, leads DO-HEALTH impact and communication of osteoporosis-related findings on a broad level, and Philippe Halbout PhD, IOF.

Stephen M Ferrari, leads DO-HEALTH software development (Electronic Data Capture system and interactive practical software for seniors and health care professionals that teaches main findings of DO-HEALTH), Ferrari Data Solutions, Feldmeilen, Switzerland.

Benno Gut, leads DO-HEALTH visual communication (SHEP avatar) and DO-HEALTH corporate design structures (logo, website software and communication tools), gut pictures, Horgen, Switzerland.

Marième Ba, was the DO-HEALTH independent clinical monitoring partner, Pharmalys, Borehamwood, United Kingdom.

Jonas Wittwer Schegg PhD, industrial partner representative bringing expertise and facilities in plasma analytics for 25-Hydroxyvitamin D and Omega-3 Fatty Acids and providing the study medication (Vitamin D, Omega-3 fatty acids), and Stéphane Etheve, DSM Nutritional Products, Kaiseraugst, Switzerland, and Manfred Eggersdorfer PhD, University Medical Center Groningen, Gronigen, The Netherlands.

Carla Sofia Delannoy PhD, industrial partner representative providing financial support to DO-HEALTH central coordination, Nestlé Health Science, Lausanne, Switzerland.

Monika Reuschling PhD, industrial partner representative providing assays for the large DO-HEALTH biomarker study to define reference ranges of common biomarkers in adults age 70+, Roche diagnostiscs, Rotkreuz, Switzerland.

DO-HEALTH Scientific Advisory Board members and collaborators on specific outcomes

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Prof. Walter Dick (Fractures, Osteoarthritis), University of Basel, Basel, Switzerland.

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Prof Arnold von Eckardstein MD (Biomarkers reference values), University of Zurich, Zurich, Switzerland.

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Prof. Thomas Dietrich (Oral Health), University of Birmingham, UK.

Prof Walter Baer MD (Mortality), University of Zurich, Zurich, Switzerland.

Prof Klara Landau MD (Visual Acuity**)**, University Hospital of Zurich, Zurich, Switzerland.

Prof Frank Ruschitzka MD (Cardiology), University Hospital of Zurich, Zurich, Switzerland.

Prof Markus Manz MD (Hematology), University Hospital of Zurich, Zurich, Switzerland.

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★ In Memory of Dieter Felsenberg, a passionate scientist in clinical muscle and bone research

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6 and 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 to 9
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7 to 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 7, and 10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 21, and 22
		(b) Indicate number of participants with missing data for each variable of interest	22
Outcome data	15*	Report numbers of outcome events or summary measures	10 and 24
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11, and 23

		(*b*) Report category boundaries when continuous variables were categorized	21 to 23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11 and 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14 and 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12 and 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15 and 16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5 European countries: a cross-sectional study of DO-HEALTH

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051881.R2
Article Type:	Original research
Date Submitted by the Author:	25-Mar-2022
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Public health, General practice / Family practice
Keywords:	GERIATRIC MEDICINE, CLINICAL PHARMACOLOGY, PRIMARY CARE

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Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5 European countries: a cross-sectional study of DO-HEALTH

Word count: 3422 (excluding the abstract, references, tables, and figures)

Caroline de Godoi Rezende Costa Molino, PhD [a, b, #], Patricia O. Chocano-Bedoya, MD, PhD [a, c, d, #], Angélique Sadlon, MD [a, e], Robert Theiler, MD, Prof. [a], E. John Orav, PhD [f], Bruno Vellas, MD, PhD [g]; René Rizzoli, MD [h], Reto W. Kressig, MD [i], John A. Kanis, MD [j], Sophie Guyonnet, PhD [k], Wei Lang, PhD [a], Andreas Egli, MD [a], Heike A. Bischoff-Ferrari, MD, DrPH, Prof. [a, e, l] for the DO-HEALTH Research Group*

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ABSTRACT

Word count: 300 (max 300)

Objective: To investigate the prevalence of polypharmacy and characteristics associated with polypharmacy in older adults from seven European cities.

Design: Cross-sectional study of baseline data from DO-HEALTH.

Setting and participants: DO-HEALTH enrolled 2157 community-dwelling adults age 70 and older from seven centers in Europe. Participants were excluded if they had major health problems or Mini Mental State Examination Score <24 at baseline.

Primary outcome measures: Extensive information on prescription and over-the-counter medications were recorded. Polypharmacy was defined as the concomitant use of 5 or more medications, excluding vitamins or dietary supplements. Bivariate and multivariable logistic regression was used to test the association of sociodemographic factors (age, sex, education, living situation, and city) and health-related indicators (number of comorbidities, cognitive function, frailty, body mass index [BMI], prior fall, self-rated health, and smoking status) with polypharmacy.

Results: 27.2% of participants reported polypharmacy ranging from 16.4% in Geneva to 60.8% in Coimbra. In the multivariable logistic regression analyses, older age (OR 1.07; 95% CI 1.04-1.10), greater BMI (OR 1.09; 95% CI 1.06-1.12), and increased number of comorbidities (OR 2.13; 95% CI 1.92-2.36) were associated with polypharmacy. Women were less likely to report polypharmacy than men (OR 0.65; 95% CI 0.51-0.84). In comparison to participants from Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI 1.56-3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy ((OR 0.36; 95% CI 0.22-0.59 and OR 0.64; 95% CI 0.42-0.96), respectively). Living situation, smoking status, education, prior fall, cognitive function, self-rated health, and frailty status were not significantly associated with polypharmacy.

Conclusion: Polypharmacy is common among relatively healthy older adults, with moderate variability across seven European cities. Independent of several confounders, being a woman, older age, greater BMI, and greater number of comorbidities were associated with increased odds for polypharmacy.

Trial registration: original RCT DO-HEALTH: NCT01745263

Strengths and limitations of this study

- This study takes advantage of the large DO-HEALTH data to estimate the prevalence of polypharmacy and characteristics associated with polypharmacy among European community-dwelling older adults.
- In this study, the use of medications was extensively assessed and included all regularly used medications, including both over-the-counter and prescription drugs.
- Because DO-HEALTH participants, were comprehensively assessed we were able to investigate the association of several sociodemographic factors and health-related indicators with polypharmacy.
- Although this was not a population-based study but a selection of relatively healthy older adults, a comparison between countries is of relevance at the public health level.
- This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy.

INTRODUCTION

By 2050, one in every four people in Europe and Northern America will be aged 65 or over.[1] As population ages, so does the number of chronic conditions and use of polypharmacy (commonly defined as the concomitant use of 5 or more medications).[2-5] For instance, about 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and Portugal.[6-8]

Although not all polypharmacy is considered inappropriate,[9] it constitutes a major public health problem because it is associated with increased risk of adverse drug reactions, drug-drug and drug-disease interactions, which can lead to falls, unnecessary or avoidable costs,[10 11] unplanned hospitalization,[12 13] emergency department and outpatient visits,[11] kidney function decline,[14] and mortality.[4 15-19]

Other studies have evaluated the use of polypharmacy among European older adults.[2 6-8 20] However, they considered only prescription medications or pharmacy claims which can either underestimate or overestimate the prevalence of polypharmacy. Only few studies considered all regularly taken medications including over-the-counter medications.[21-23] To the best of our knowledge, except for the Survey of Health Aging and Retirement in Europe (SHARE) wave 6,[22] no multi-center and international study has investigated and compared the prevalence of polypharmacy in European community-dwelling older adults. Moreover, the definition of polypharmacy, living facilities, and age distribution vary widely, limiting the comparison between regions and the identification of potential health interventions to improve the safe use of medications. Country comparison may be relevant for public health in order to detect clustering of high prevalence of polypharmacy,[11] which can inform policy makers and promote the safe use of medications among older adults.[24]

DO-HEALTH is a multicenter international trial that recruited relatively healthy seniors 70 years and older from 7 cities in 5 European countries.[25] At baseline, participants did not

present major comorbidities,[25 26] however 43% were frail and 26.4% had 3 or more comorbidities.[27] Therefore, to understand the extent of polypharmacy use among European older adults, the goal of the present study was to assess the prevalence of polypharmacy in 7 European cities using standardized methods, and its association with socio-demographic factors and health-related indicators among 2157 participants of DO-HEALTH.

METHODS

Participants and study design

This is a cross-sectional study using baseline data from DO-HEALTH, a randomized, double-blind, placebo-controlled, clinical trial designed to assess the effectiveness of the 3 interventions (vitamin D, omega-3 fatty acids, and simple home based strength exercise program) in a 2×2×2 factorial design (NCT01745263).[25 26] The six primary endpoints in DO-HEALTH were: change in systolic and diastolic blood pressure, the Short Physical Performance Battery, the Montreal Cognitive Assessment (cognitive function), and incidence of non-vertebral fractures and infections over 3 years.[25 26] From December 2012 to November 2014, DO-HEALTH included a total of 2157 community-dwelling older adults (70 years and older) from seven research centers, located in five European countries: Basel (n=253), Berlin (n=350), Coimbra (n=301), Geneva (n=201), Innsbruck (n=200), Toulouse (n=300), and Zurich (n=552). DO-HEALTH participants were recruited through mailing lists of retirement authorities, churches, and other community services, public events, flyers, posters, advertisement in newspapers and other media, and educational programs and health care. Additional details about recruitment, randomization and allocation, and blinding details are published elsewhere.[26] DO-HEALTH research group is listed in the Appendix.

Participants completed detailed questionnaires on demographics, medical events, lifestyle factors (nutrition, physical activity, living condition), medication intake, and had

extensive clinical examinations of multiple organ and physical functions at baseline and every three months by phone calls and yearly clinical visits during a three-year follow-up.[26]

DO-HEALTH was approved by each local/national ethics committee and regulatory authorities. The present study was approved by the Ethics Committee Zurich (ID 2018-00684). All participants signed the consent form.

Study population

Detailed eligibility criteria were published elsewhere.[26] Briefly, DO-HEALTH adults aged 70 years or older, with Mini Mental State Examination Score[28] greater or equal to 24, living in the community, and sufficiently mobile to come to the study center. Older adults were excluded if they reported a history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, or transient ischemic attack in the last 5 years. Older adults with epilepsy and/or use of anti-epileptic drugs, angina pectoris or coronary artery intervention, severe renal impairment (creatinine clearance ≤ 15 ml/min) or dialysis, hypercalcemia (> 2.6 mmol/l), history of hypo or primary hyperparathyroidism, severe liver disease, or living in assisted living situations or a nursing home, were also excluded. For the purpose of this cross-sectional analysis we included baseline data from all DO-HEALTH participants (n=2157).

Data collection

Sociodemographic factors and health-related indicators

Sociodemographic information comprised age, sex, years of education, living situation (alone vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich). Health-related indicators comprised number of comorbidities, cognitive function, frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was designed to recruit 40% of participants with a prior fall in the last 12 months.[25]

Comorbidity

The number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[29] This instrument is validated in the older population and evaluates the presence of 13 common chronic diseases: heart disease, high blood pressure, lung disease, diabetes, ulcer and stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, osteoarthritis or degenerative arthritis, back pain, rheumatoid arthritis.

Cognitive function

Cognitive function was assessed by the Montreal Cognitive Assessment questionnaire (MoCA)[30] at baseline and follow-up. MoCA has a maximum score of 30 points, and is presented as a continuous variable. MoCA was chosen because of its higher sensitivity to detect mild cognitive impairment in older adults.[30 31] In a validation study, MoCA had a sensitivity of 90% to detect mild cognitive impairment, while the Mini-Mental State Exam detected only 18%.[30]

Frailty

Frailty was defined according to Fried et al[32] which evaluates five criteria: fatigue (self-reported), unintentional weight loss (self-reported loss more than 5% of total body weight), reduced physical activity (self-reported), slowness (impaired walking speed), and weakness (low grip strength). Slowness was defined as a gait speed below 0.67 m/s and 0.7 m/s respectively, according to gender and height as in the original Fried conceptualization.[32] For weakness, we used grip strength measured by Martin Vigorimeter (KLS Martin Group, Tuttlingen, Germany) with cut-points at the lowest 20% of the cohort based on age, gender and country of origin. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).

Self-rated health

Self-rated health was measured with the EQ5D-3L.[33] Participants were asked to rate their health status on a visual analog scale (0-100 mm) with respect to the question: "Please rate how well

you are doing on a scale of 0 to 100", where 0 represents 'very poorly' and 100 represents 'very well'. Self-rated health is presented as a continuous variable.

Medications

Trained study nurses and study medical doctors asked participants in detail for the use of medications with standardized questionnaire. For each medication participants reported: brand name, generic name, dose, unit, interval (as needed or regularly), indication, and treatment duration. To minimize recall bias, participants were asked to bring their medication and/or medication packages and/or a medication-list (from the general practitioner) to the baseline visit. In addition, all participants completed a diary to improve the recall.

We included all prescribed and over the counter medications taken regularly, and excluded multivitamins, dietary supplements, herbal, and homeopathic medicines. Regular medication was defined as those drugs taken daily or at regular intervals (e.g. once a week). All medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[34] Each active substance was defined as one medication and received an individual ATC code. For example, the combination of amlodipine/indapamide/perindopril was counted as 3 medications and received the codes C08CA01, C03BA11, C09AA04, respectively. As no consensus on the definition of polypharmacy exists, we used the most commonly reported threshold of 5 or more drugs (active substances) daily.[4 5 24 35-37]

Statistical analysis

Descriptive statistics are presented as frequencies and percentages (%) for categorical variables, and means with standard deviation (SD) for continuous variables (or median and interquartile range for non-normally distributed variables). Data were checked for normality visually. We present the prevalence of polypharmacy for the total population of DO-HEALTH and by city (n=7; Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and Zurich).

To test the association of sociodemographic factors (age, sex, years of education, and living alone) and health-related indicators (number of comorbidities, cognitive function, frailty

status, BMI, prior fall in the last 12 months, self-rated health, and smoking status) with polypharmacy (binary outcome), we first performed bivariate logistic regression analyses and included variables with p<0.2 in the multivariable logistic regression analyses. The final model presents the adjusted odds ratios and 95% confidence intervals (OR, 95% CI). Analysis were performed with SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA.).

Patient and public involvement

Patients and the public were not involved in setting up the research question, design, outcome measures, interpretation of the results, or writing the manuscript.

RESULTS

Baseline characteristics of the 2157 older adults included in DO-HEALTH are described in **Table 1**. Median age was 74.0 years (IQR 72.0-77.0) and most participants were women (61.7%). Mean BMI was 26.6 kg/m^2 (SD 3.5) and 26.2 kg/m^2 (SD 4.7) in men and women, respectively. Most participants were classified as robust (53.6%) with only 3.0% of participants classified as frail. The median number of comorbidities was 2.0 (IQR 1.0-3.0), and median number of medications was 3.0 (IQR 1.0-5.0).

Table 1 also describes the baseline characteristics by city. Coimbra and Toulouse had the highest median age (median 75 IQR 72.0-79.0 and median 75 IQR 71.0-75.0, respectively). Coimbra had the lowest proportion of participants with no comorbidities, the highest mean BMI, median number of medications, as well as the highest proportion of prefrail and frail participants. Berlin had, on average, the highest proportion of women, robust participants, and mean years of education.

Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2% and, 17.4% reported no medications at all (**Figure 1**). Regarding the cities, on average Coimbra

reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%). Berlin (25.4%), Innsbruck (22%), Zurich (20.5%), Basel (18.2%), and Geneva (16.4%).

Table 2 shows the association of sociodemographic factors and health-related indicators with polypharmacy. In the bivariate analyses (unadjusted models), greater age, BMI, and number of comorbidities, as well as prior fall and frailty were associated with an increase in the odds of polypharmacy. Higher MoCA scores (higher scores mean better cognitive function), higher self-rated health scores, and more years of education were associated with a decrease in the odds of polypharmacy. The associations of living alone and ever smoked with polypharmacy were non-significant at $p>0.2$ and, therefore, were not included in the multivariable logistic regression analysis. In the multivariable logistic regression analysis (including the covariates age, sex, education, prior fall, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city), age, sex, BMI, number of comorbidities, and city were independently associated with polypharmacy. For each additional year of age, there was 7% higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a one unit increase in BMI, there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-1.12). For one additional comorbidity, there was a 2-fold increase in the odds of polypharmacy (OR 2.13, 95% CI 1.92-2.36). Women had 35% lower odds of reporting polypharmacy than men (OR 0.65, 95% CI 0.51-0.84). Participants from Geneva or Toulouse were also less likely to report polypharmacy than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR 0.64, 95% CI 0.42-0.96, respectively). Participants from Coimbra had 2 times higher odds of reporting polypharmacy (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having had a fall in the year prior to enrollment, education, cognitive function, self-rated health, and frailty status were no longer significantly associated with polypharmacy in the multivariable analysis.

DISCUSSION

In this cross-sectional study of 2157 relatively healthy European older adults, about one quarter of participants reported polypharmacy. However, despite the same inclusion and exclusion criteria in this large clinical trial, there was moderate variability in prevalence of polypharmacy between the seven cities with the lowest prevalence observed in Geneva and Basel with less than 20% and the highest prevalence observed in Coimbra with about 60%. Notably, older age, greater BMI, and number of comorbidities were significantly associated with higher odds of polypharmacy after adjusting for education, prior fall, cognitive function, self-rated health, and frailty.

Comparison with other studies

On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are consistent with previous population-based studies. In the population-based CoLaus study, a cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-aged adults (mean age 58 years) was 16.9%.[20] This is consistent with our results from Geneva (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy reported in Coimbra (60.8%) is in accordance with a previous population-based study conducted in Oporto/Portugal (59%).[7] Yet, a population-based study conducted in Germany (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)[38] than we observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty in the ESTHER cohort in which only 32.8% of participants were robust,[38] while in DO-HEALTH about 60% of older adults from Berlin were robust.

Participants from Coimbra were more likely to report polypharmacy than other centers. This increased prevalence could be explained by the fact that Coimbra participants were on average older, had higher BMI, and more likely to be prefrail or frail, despite our strict inclusion and exclusion criteria and our aim to standardize recruitment strategies. In our analysis, BMI and number of comorbidities were strongly associated with polypharmacy even after

controlling for age, city and other covariates. Additionally, participants from Coimbra also reported on average a higher prevalence of depression and hypertension when compared to other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy, since hypertension and depression are associated with increased use of medications, and initiating or maintaining polypharmacy.[39]

Other factors, however, may also explain the wide variation in the prevalence of polypharmacy, such as: health system organization and coverage, country specific drug policies, medication costs, prescribing pattern, refund system, clinicians' workload and specialization, and socioeconomic status.[40-47] A prior study in 57 European nursing homes (SHELTER study) also found differences in the prevalence of polypharmacy across seven European countries.[43] The authors suggested that this variation may be caused by the distinct attitudes of physicians when managing older adults with multimorbidity.[43] Other studies also observed high association between prescriber characteristics, such as medicine specialization, and polypharmacy.[42 46 47] For example, a recent national cross-sectional study among Malaysian older adults found that physicians with family medicine specialization were five times more likely to prescribe more than five medications at one time.[46] Moreover, the discrepancy in the prevalence of polypharmacy and health characteristics in Coimbra may be associated to the low expenditure on prevention activities in Portugal.[48] For example, Portugal spends only half the average expenditure on prevention activities by other Organization for Economic Co-operation and Development (OECD) countries.[48] Health prevention policies are fundamental to improve healthy aging and disease burden.[49] In 2012 an extended National Health Plan was published in Portugal. This plan aims to guide the public health sector to implement actions to reduce the risk factors for chronic diseases.[48] Additionally, in 2013, a national list of pharmaceutical products and prescription guidelines were defined which may also improve the use of medication in this population.[48]

Implications for clinical practice

The pharmacological treatment of older adults with multimorbidity is complex and poorly addressed in clinical practice guidelines.[50-52] For instance, the pharmacological recommendations of the National Institute for Health and Care Excellence (NICE) guidelines for management of type 2 diabetes, depression, and heart failure rarely account for multimorbidity.[53] In fact, only a few drug trials include older adults with multimorbidity.[54 55] Therefore, the cumulative effects of multiple medication use in multimorbid older adults are unknown, and clinicians are not supported by evidence-based recommendations to manage drug prescriptions among this population. Furthermore, this lack of evidence may lead to unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions. Notably, about 50% of older adults take at least one unnecessary medication[56] and less than 50% have a clear understanding of pharmacotherapy purpose.[57] In this context, efforts to minimize polypharmacy and deprescribe unnecessary or inappropriate medications were described around the world.[58-69] Recently, findings from a Swiss cluster-randomized clinical study among 46 primary care physicians suggested that a patient-centered deprescribing intervention may reduce polypharmacy among old multimorbid patients.[67] In Portugal, an ongoing nationwide three-phase study on deprescribing is investigating barriers and facilitators of deprescribing perceived by older adults and their acceptance to have regular medications deprescribed.[65 69] A pilot-study among 16 general practitioners in Germany found that an electronic tool may assist in identifying deprescribing opportunities and promote patient involvement and shared decision making.[64] Our findings suggest that even among relatively healthy older adults polypharmacy is common, which makes this population also a target for deprescribing interventions.

Strengths and limitation of this study

In this study, we addressed the literature gap of limited studies including both over-the-counter and prescription medications used regularly. The assessment of both prescription and over-the-

counter medications is needed as almost 50% of medication users also use at least one over-the-counter medication, with half of them presenting a potential major drug interaction.[17] The majority of studies investigating medication patterns in Europe use dispensation data from health insurance companies' providers,[70] pharmacy claims,[2 71 72] hospitals[73] or nursing homes,[43] and only few included over-the-counter medications.[21-23] These studies had different methodologies which limits a direct comparison to our results. For example, the study by Mielke et al. in Germany, over-the-counter medications included herbal medicines.[21] In our study, we did not include complementary, homeopathic and herbal medicines as they are not included in the ATC classification system.[34] In the study by Midao et al. based on the SHARE population, participants were simply asked if they took at least five different drugs on a typical day.[22] In our study, a trained medical doctor revised all the medications brought by the participants, as well as medication packages and/or a medication list. Further, because DO-HEALTH included participants from different European countries and we used the same definition of polypharmacy, our findings allow cross-country comparisons and provide relevant data for future research and health policy interventions on the pharmacogerontology field.

This study has also limitations. This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy and is not a population-based study. As there is no consensus on the definition of polypharmacy, we chose the common and arbitrary cut-off of 5 or more medications.[4 5 24 35-37] Due to the scope of this study, the appropriateness of polypharmacy was not investigated. Despite of DO-HEALTH being the largest European trial on healthy aging, a relatively moderate number of participants were included for each city. Overall, however, our sample size of 2157 older adults is larger than in prior European studies.[7 20 21 23] Because our population consists on volunteers to participate in a trial, they are not representative of the general population of each country, therefore generalizability of our results is limited. Further, the scope of this study is limited in terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered

conservative as participants were relatively healthy at baseline (without major chronic diseases such as cancer or major cardiovascular events in the last 5 years), or in use of anti-epileptic drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence of polypharmacy and longitudinal studies that showed the association between polypharmacy and age, BMI, and comorbidities.[7 20 38 39 74] Moreover, comorbidities were assessed with the validated Self-Administered Comorbidity Questionnaire.[29] Although this questionnaire is validated in the older population and assesses the presence of the most common chronic diseases, it does not include some common conditions in older adults as sleep disorders and obstipation and participants may not be aware of some conditions. Finally, we cannot exclude that we may have missed information on medication use and comorbidities due to poor recall.

CONCLUSION

About one quarter of European community-dwelling older adults reported polypharmacy. We found that polypharmacy was associated with being female and increased age, BMI, and number of comorbidities. Further, variation in the prevalence of polypharmacy between cities remained even after accounting for demographic and health-related differences between study participants. These findings highlight the need for targeted interventions to reduce inappropriate polypharmacy in relatively healthy older adults.

a. Contributorship statement

CdGRCM and POCB contributed equally as co-first authors, they performed the literature survey, the drafting of the article, and the statistical analyses. AS, RT, SG, and WL provided critical revision of the manuscript. EJO, BV, RR, RWK, JAK, AE, and HABF designed the study concept, acquired the data and critically revised the manuscript. HABF is the PI of DO-HEALTH.

b. Competing interests

As part of the DO-HEALTH independent and investigator initiated clinical trial, HABF reports as the PI of the DO-HEALTH trial, grants from European Commission, from University of Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli Pharma, plus nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche Diagnostics. Further, HABF reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor, outside the submitted work.

BV reports personal fees from BIOGEN, CERECIN, ROCHE, MSD, outside the submitted work.

RR reports personal fees from Abiogen, Danone, Echolight, EMF, Mithra, ObsEva, Pfizer Consumer Health, Theramex, outside the submitted work.

EJO reports grants from Zurich University, during the conduct of the study.

CdGRCM received funding from the National Council for Scientific and Technological Development (CNPq), with process Nos. 164700/2015-3, from the São Paulo Research Foundation (FAPESP), with process No. 2016/13700-9, and Coordination for the Improvement of Higher Education Personnel/PhD Sandwich Programs Abroad (PDSE), with process No. 88881.132169/2016-01.

All other authors declare no competing interests.

c. Funding

The DO-HEALTH study was funded by the Seventh framework program of the European Commission (Grant Agreement n°278588), the University of Zurich (Chair for Geriatric Medicine and Aging Research), DSM nutritional products, ROCHE Diagnostics (SCHWEIZ), NESTEC, Pfizer Consumer Healthcare and STREULI Pharma.

The funding/supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

d. Data sharing statement

In a first step, no data will be made available to researchers external to DO-HEALTH Research Group to allow primary researchers to fully exploit the dataset. The data will be shared in a second step according to a controlled access system.

e. Ethics Statement

Patient consent for publication: Not required.

Ethics approval: The study protocol was approved by ethical and regulatory agencies of all five recruitment countries.

Acknowledgment: We thank all DO-HEALTH participants.

Dissemination to participants and related patient and public communities: Study results will, after scientific publication, be disseminated to the public in general through social media platforms, and public events organized by our center.

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Tables

Table 1. Baseline characteristics by city.

		Total (n=2157) [a]	Basel (n=253)	Berlin (n=350)	Coimbra (n=301)	Geneva (n=201)	Innsbruck (n=200)	Toulouse (n=300)	Zurich (n=552)
Age, median (IQR)		74.0 (72.0-77.0)	74.0 (72.0-77.0)	73.0 (71.0-74.0)	75.0 (72.0-79.0)	74.0 (72.0-78.0)	73.0 (71.0-75.0)	75.0 (72.0-79.0)	74.0 (71.0-78.0)
Women, N (%)		1331 (61.7)	151 (59.7)	247 (70.6)	192 (63.8)	127 (63.2)	103 (51.5)	181 (60.3)	330 (59.8)
Men, N (%)		826 (38.3)	102 (40.3)	103 (29.4)	109 (36.2)	74 (36.8)	97 (48.5)	119 (39.7)	222 (40.2)
Living alone, N (%)		900 (41.7)	113 (44.7)	134 (38.3)	98 (32.6)	95 (47.3)	73 (36.5)	139 (46.3)	248 (44.9)
Ever smoked, N (%)		797 (37.0)	104 (41.1)	143 (40.9)	65 (21.6)	86 (42.8)	73 (36.5)	135 (45.0)	191 (34.6)
Prior fall in the last 12 months, N (%)		903 (41.9)	109 (43.1)	125 (35.7)	123 (40.9)	88 (43.8)	99 (49.5)	129 (43.0)	230 (41.7)
Years of education, mean (SD)		12.6 (4.3)	13.5 (3.5)	14.5 (3.3)	7.9 (5.3)	13.7 (4.1)	12.4 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI [Kg/m^2], mean (SD)	Men	26.6 (3.5)	27.0 (3.6)	26.7 (3.0)	28.0 (3.5)	26.0 (3.5)	25.9 (3.3)	26.8 (3.3)	26.2 (3.6)
	Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.1 (4.4)	25.1 (4.5)	25.6 (4.4)
Cognitive function [b], median (IQR)		26.0 (24.0-28.0)	28.0 (26.0-30.0)	26.0 (24.0-27.0)	22.0 (19.0-25.0)	27.0 (26.0-29.0)	27.0 (25.0-29.0)	27.0 (26.0-29.0)	26.0 (24.0-28.0)
Self-rated health [c], median (IQR)		82.0 (73.0-91.0)	88.0 (79.0-92.0)	81.0 (71.0-90.0)	78.0 (60.0-90.0)	88.0 (80.0-92.0)	90.0 (80.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)
Frailty status, N (%) [d]		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	119 (59.6)	150 (53.6)	313 (57.3)
Robust									
	Prefrail	922 (43.4)	95 (37.7)	130 (37.4)	172 (57.7)	97 (48.3)	80 (40.4)	122 (43.6)	226 (41.4)
	Frail	64 (3.0)	4 (1.6)	2 (0.6)	41 (13.8)	2 (1.0)	0 (0.0)	8 (2.9)	7 (1.3)
Number of drugs, median (IQR)		3.0 (1.0-5.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	5.0 (3.0-8.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	3.0 (1.0-5.0)	2.0 (1.0-4.0)
Number of comorbidities [e], median (IQR)		2.0 (1.0-3.0)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.0)
Rheumatoid arthritis or osteoarthritis, N (%) [f]		974 (45.2)	116 (45.9)	168 (48.1)	79 (26.3)	124 (61.7)	98 (49.0)	173 (57.7)	216 (39.1)
High blood pressure, N (%)		844 (39.2)	86 (34.0)	163 (46.7)	186 (62.0)	80 (39.8)	61 (30.5)	112 (37.3)	156 (28.3)
Back pain, N (%)		773 (35.9)	59 (23.3)	104 (29.8)	167 (55.7)	101 (50.3)	72 (36.0)	144 (48.0)	126 (22.8)
Heart disease, N (%) [g]		263 (12.2)	23 (9.1)	31 (8.9)	72 (24.0)	28 (13.9)	18 (9.0)	44 (14.7)	47 (8.5)

Depression, N (%)	178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	52 (12.5)	38 (12.7)	15 (2.7)
Stomach disease, N (%)	165 (7.7)	6 (2.4)	14 (4.0)	65 (21.7)	17 (8.5)	123 (26.0)	37 (12.3)	14 (2.5)
Diabetes, N (%)	150 (7.0)	15 (5.9)	27 (7.7)	44 (14.7)	10 (5.0)	81 (4.0)	23 (7.7)	23 (4.2)
Lung disease, N (%)	109 (5.1)	9 (3.6)	24 (6.7)	17 (5.7)	14 (7.0)	6 (3.0)	21 (7.0)	18 (3.3)
Anemia, N (%)	64 (3.0)	5 (2.0)	4 (1.2)	22 (7.3)	9 (4.5)	4 (2.0)	6 (2.0)	14 (2.5)
Kidney disease, N (%)	54 (2.5)	1 (0.4)	3 (0.9)	35 (11.7)	4 (2.0)	0 (0.0)	6 (2.0)	5 (0.9)
Liver disease, N (%)	37 (1.7)	1 (0.4)	3 (0.9)	23 (7.7)	3 (1.5)	2 (1.0)	4 (1.3)	1 (0.2)
Cancer, N (%)	27 (1.3)	3 (1.2)	2 (0.6)	4 (1.3)	3 (1.5)	2 (1.0)	6 (2.0)	7 (1.3)
Participants with no comorbidities, N (%)	463 (21.5)	67 (26.5)	78 (22.4)	23 (7.7)	19 (9.5)	52 (26.0)	42 (14.0)	182 (33.0)

Abbreviation: BMI, Body Mass Index. IQR, interquartile range.

[a] Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

[b] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). Scores range from 0 to 30 points, in which higher scores are better.[30]

[c] Self-rated health was assessed with a visual analogic scale (0-100 mm), in which higher scores are better.

[d] Frailty was defined according to the Fried definition which evaluates five criteria: fatigue, unintentional weight loss, reduced physical activity, slowness, and weakness. Frailty was categorized as robust (none of criteria), pre-frail (1-2 criteria), and frail (3-5 criteria).[32]

[e] Number of comorbidities was measured by the Self-Administered Comorbidity Questionnaire, which assesses the presence of current 13 comorbidities. Therefore, the range is from 0 to 13 comorbidities.[29]

[f] Following the instructions of the original publication of the Self-Administered Comorbidity Questionnaire, rheumatoid arthritis and osteoarthritis were assessed separately but were combined in the analysis as participants might not distinguish these disorders accurately.[29]

[g] In DO-HEALTH, participants with history of myocardial infarction, stroke, or transient ischemic attack in the last 5 years were excluded. Therefore, self-reported heart disease stands for other heart disease than those excluded.

Table 2. Sociodemographic factors and health-related indicators associated with polypharmacy among DO-HEALTH participants.

		Unadjusted [a] OR (95% CI)	Adjusted [b] OR (95% CI)
Age		**1.07 (1.05, 1.10)**	**1.07 (1.04, 1.10)**
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	**0.65 (0.51, 0.84)**
Years of education		**0.92 (0.90, 0.94)**	1.01 (0.98, 1.04)
Living alone	No	Ref	-
	Yes	1.01 (0.84, 1.23)	
Ever smoked	No	Ref	-
	Yes	1.10 (0.90, 1.34)	
Prior fall in last 12 months	No	Ref	Ref
	Yes	**1.35 (1.12, 1.64)**	1.08 (0.85, 1.36)
BMI [Kg/m^2]		**1.15 (1.12, 1.18)**	**1.09 (1.06, 1.12)**
Cognitive function [c]		**0.87 (0.85, 0.90)**	1.00 (0.96, 1.04)
Self-rated health [d]		**0.97 (0.96, 0.97)**	0.99 (0.98, 1.00)
Frailty status [e]	Robust	Ref	Ref
	Prefrail	**1.63 (1.34, 1.99)**	0.92 (0.72, 1.18)
	Frail	**10.17 (5.74, 18.03)**	1.63 (0.77, 3.45)
Number of comorbidities [f]		**2.22 (2.04, 2.42)**	**2.13 (1.92, 2.36)**
City			
Zurich		Ref	Ref
Basel		**0.56 (0.40, 0.78)**	0.67 (0.44, 1.04)
Berlin		0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
Coimbra		**5.59 (4.33, 7.23)**	**2.36 (1.56, 3.55)**
Geneva		**0.50 (0.34, 0.73)**	**0.36 (0.22, 0.59)**
Innsbruck		0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
Toulouse		0.93 (0.71, 1.23)	**0.64 (0.42, 0.96)**

Abbreviations: OR, odds ratio; CI confidence interval; BMI, Body Mass Index.

[a] Values are from bivariate logistic regression analyses.

[b] Values are from multivariable logistic regression analyses including as covariates age, sex, prior fall in the last 12 months, years of education, BMI, cognitive function, self-rated health, frailty status, number of comorbidities, and city.

[c] Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).[30]

[d] Self-rated health was assessed with a visual analogic scale (0-100 mm).

[e] Frailty was defined according to the Fried definition.[32]

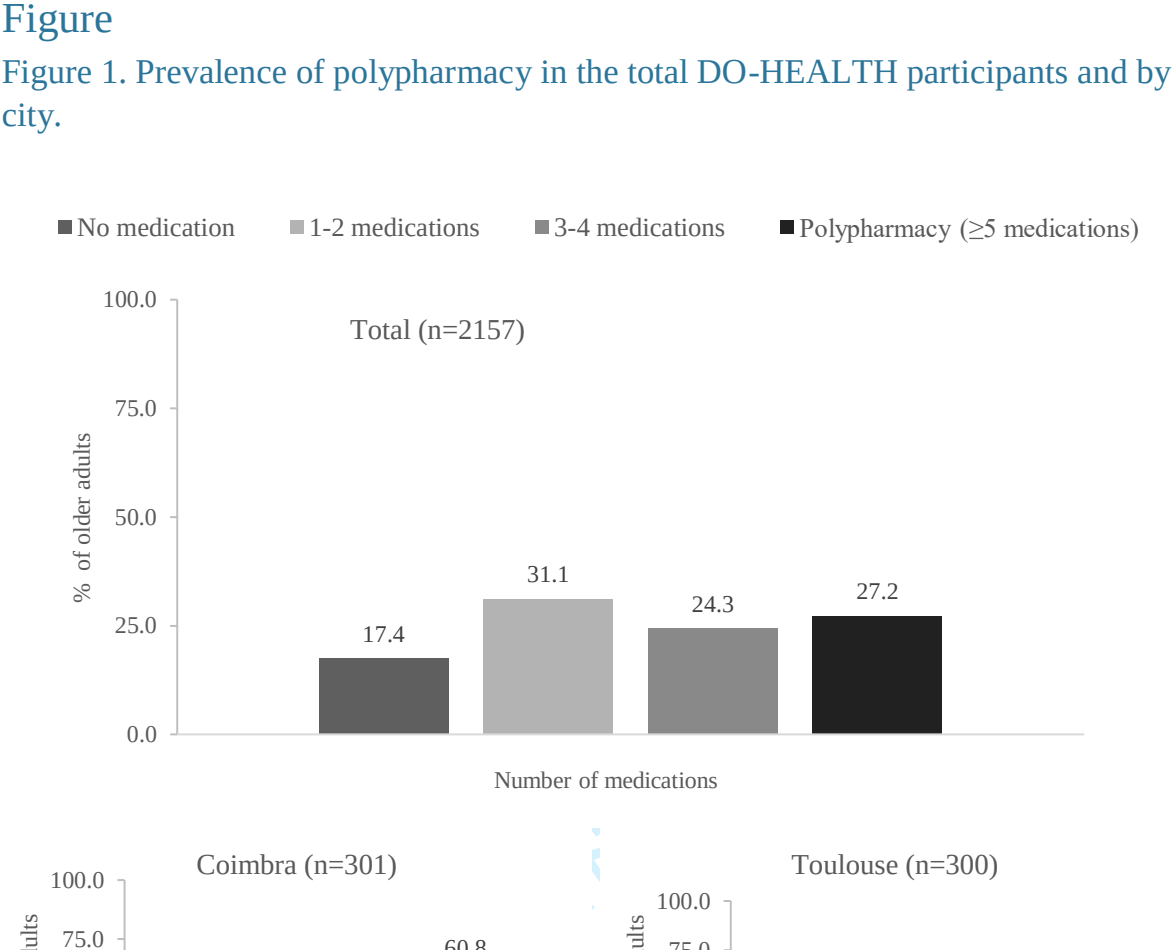
[f] Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[29]

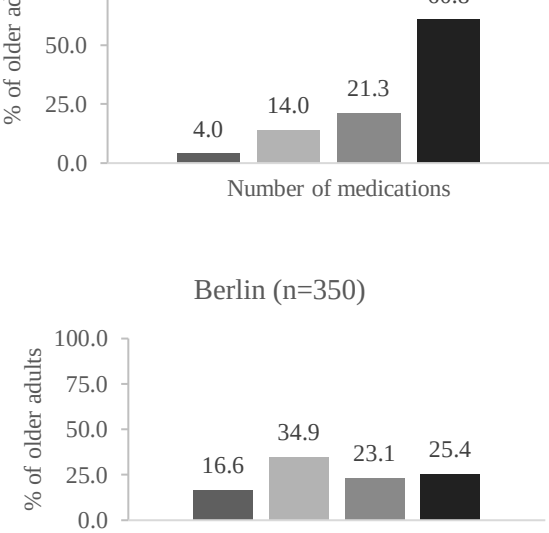
Figure

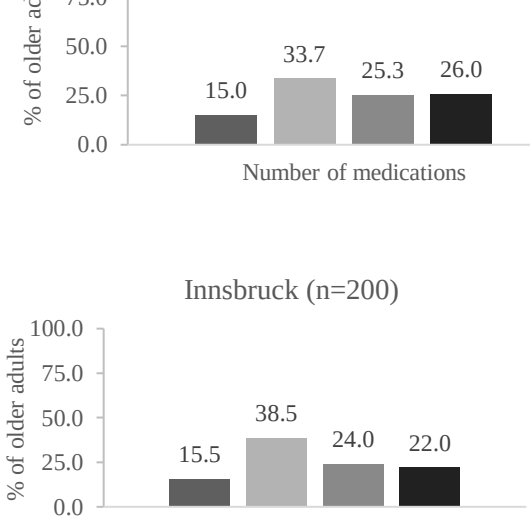
Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.

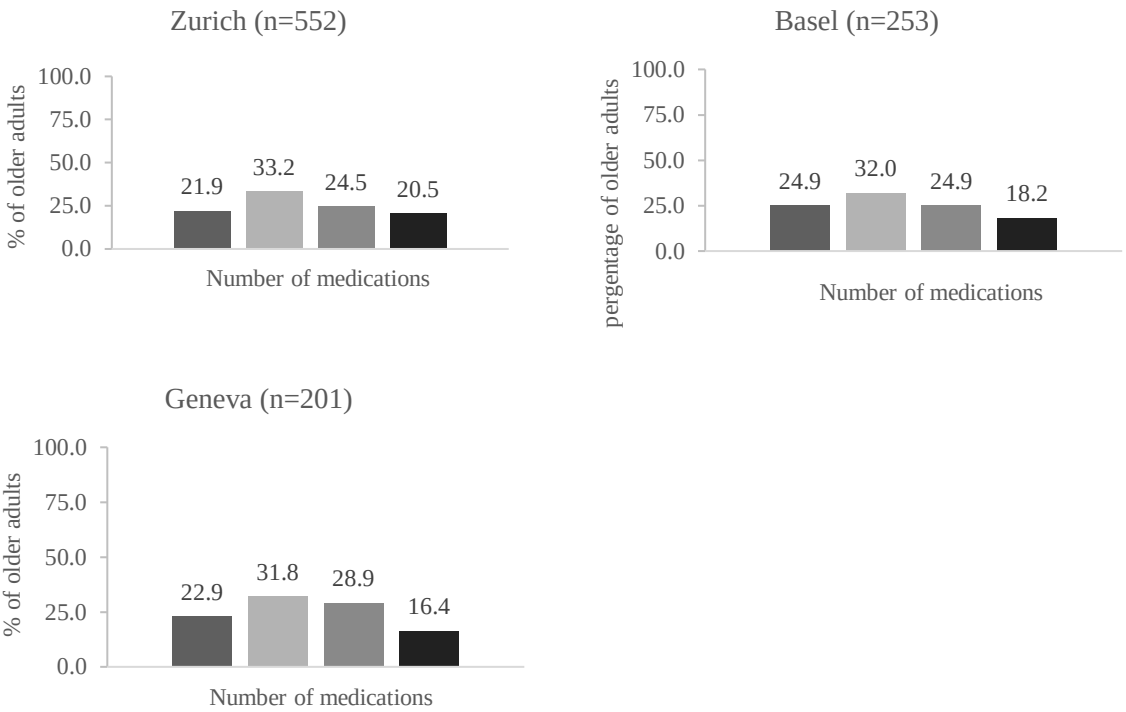
Figure

Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.









Appendix. DO-HEALTH Research Group
This e-appendix has been provided by the authors to give readers additional information about DO-HEALTH Research Group.

DO-HEALTH Consortium

(in bold: Governing Board members; in bold and underlined: Chair; underlined: Team members).

Prof Heike A Bischoff-Ferrari MD, DO-HEALTH Coordinator, Principal Investigator and Zurich Site Investigator, leads all endpoints analyses and co-leads the studies 'DO-HEALTH health economic model', 'novel biomarkers of immunity', 'novel biomarkers of muscle and bone communication', University Hospital Zurich, University of Zurich and Waid City Hospital, Zurich, Switzerland, Andreas Egli MD, Sandrine Rival PhD.

Prof Bruno Vellas MD, Toulouse Site Investigator, contributes to the primary endpoint cognitive decline, and Sophie Guyonnet PhD, CHU Toulouse and University of Toulouse III, Toulouse, France.

Prof René Rizzoli MD, Geneva Site Investigator, contributes to all bone and muscle related endpoints and explores the contribution of protein intake to the benefit of the interventions, Emmanuel Biver MD, and Fanny Merminod RD, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.

Prof Reto W Kressig MD, Basel Site Investigator, contributes to gait analyses and dual task assessments, and Stephanie Bridenbaugh MD, University Department of Geriatric Medicine FELIX PLATTER and University of Basel, Basel, Switzerland. Prof. Norbert Suhm, Dept. of Traumatology, University Hospital Basel, contributes to fracture healing study DO-HEALTH.

Prof José A P Da Silva MD, Coimbra Site Investigator, explores the treatment effects on vertebral fractures, and musculoskeletal pain and function, Centro Hospitalar e Universitário de Coimbra, and Faculty of Medicine, University of Coimbra, Coimbra, Portugal, Cátia CM Duarte MD, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, and Ana Filipa Pinto RN, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

Prof Dieter Felsenberg MD, Berlin Site Investigator, performs the central DO-HEALTH DEXA quality control and evaluation of DEXA measurements, Hendrikje Börst Dipl.Wiss-org, and Gabriele Armbrecht MD, Charité Universitätsmedizin Berlin, Berlin, Germany.

Prof Michael Blauth MD, Innsbruck Site Investigator, explores the functionality after fracture, and Anna Spicher MD, Medical University of Innsbruck, Innsbruck, Austria.

Prof David T Felson MD, co-leads 'DO-HEALTH osteoarthritis study', Manchester Academic Health Science Centre, Manchester, United Kingdom and Boston University School of Medicine, Boston, MA, USA.

Prof John A Kanis MD leads the study 'contribution of fall risk to absolute fracture risk within the FRAX model', University of Sheffield Medical School, Sheffield, United Kingdom and Australian Catholic University, Melbourne, Victoria, Australia. Prof Eugene V Mccloskey MD, co-leads the study 'contribution of fall risk to absolute fracture risk within the FRAX model', University of Sheffield, Sheffield, United Kingdom, and Elena Johansson MD, University of Sheffield Medical School, Sheffield, United Kingdom and Catholic University of Australia, Melbourne, Victoria, Australia.

Prof Bernhard Watzl PhD, co-leads the study 'novel biomarkers of immunity', Manuel Rodriguez Gomez PhD, Max Rubner-Institut, Karlsruhe, Germany.

Prof Lorenz Hofbauer MD, co-leads the study 'novel biomarkers of muscle and bone communication', FOÄ Dr. Elena Tsourdi, and Professor Martina Rauner PhD, Dresden University Medical Center and Center for Regenerative Therapies Dresden, Dresden, Germany.

Uwe Siebert MD, co-leads the study 'DO-HEALTH health economic model', UMIT - University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria and Harvard T.H. Chan School of Public Health, Boston, MA, USA and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Prof John A Kanis MD, leads DO-HEALTH impact and communication of osteoporosis-related findings on a broad level, and Philippe Halbout PhD, IOF.

Stephen M Ferrari, leads DO-HEALTH software development (Electronic Data Capture system and interactive practical software for seniors and health care professionals that teaches main findings of DO-HEALTH), Ferrari Data Solutions, Feldmeilen, Switzerland.

Benno Gut, leads DO-HEALTH visual communication (SHEP avatar) and DO-HEALTH corporate design structures (logo, website software and communication tools), gut pictures, Horgen, Switzerland.

Marième Ba, was the DO-HEALTH independent clinical monitoring partner, Pharmalys, Borehamwood, United Kingdom.

Jonas Wittwer Schegg PhD, industrial partner representative bringing expertise and facilities in plasma analytics for 25-Hydroxyvitamin D and Omega-3 Fatty Acids and providing the study medication (Vitamin D, Omega-3 fatty acids), and Stéphane Etheve, DSM Nutritional Products, Kaiseraugst, Switzerland, and Manfred Eggersdorfer PhD, University Medical Center Groningen, Gronigen, The Netherlands.

Carla Sofia Delannoy PhD, industrial partner representative providing financial support to DO-HEALTH central coordination, Nestlé Health Science, Lausanne, Switzerland.

Monika Reuschling PhD, industrial partner representative providing assays for the large DO-HEALTH biomarker study to define reference ranges of common biomarkers in adults age 70+, Roche diagnostiscs, Rotkreuz, Switzerland.

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★ In Memory of Dieter Felsenberg, a passionate scientist in clinical muscle and bone research

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5 and 6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6 and 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 to 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 to 10
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7 to 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9 and 10
		(*b*) Describe any methods used to examine subgroups and interactions	9 and 10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 7, and 10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 24, and 25
		(b) Indicate number of participants with missing data for each variable of interest	25
Outcome data	15*	Report numbers of outcome events or summary measures	10, 11, 24, and 25
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	11 and 26

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	24 to 26
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14 to 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12 and 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17 and 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.