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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

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

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3 **Conclusion:** Polypharmacy is common among relatively healthy older adults, with great  
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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.<sup>1</sup>

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).<sup>2-5</sup> For instance, about 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and Portugal.<sup>6-8</sup>

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,<sup>9 10</sup> unplanned hospitalization,<sup>11 12</sup> emergency department and outpatient visits,<sup>10</sup> kidney function decline,<sup>13</sup> and mortality.<sup>4 14-18</sup>

Other studies have evaluated the use of polypharmacy among European older adults.<sup>2 6-8 19</sup> 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).<sup>20 21</sup> 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.<sup>20</sup> 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.<sup>20</sup>

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.<sup>20</sup> Briefly, DO-HEALTH included relatively healthy adults aged 70 years or older, with Mini Mental State Examination Score<sup>22</sup> 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  $\leq$  15 ml/min) or dialysis,

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3 hypercalcemia (> 2.6 mmol/l), history of hypo or primary hyperparathyroidism, severe liver  
4 disease, or living in assisted living situations or a nursing home, were also excluded.  
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7 For the purpose of this cross-sectional analysis we included baseline data from all DO-  
8 HEALTH participants (n=2157).  
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## 10 11 *Data collection*

### 12 13 *Sociodemographic factors and health-related indicators*

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15 Sociodemographic information comprised age, sex, years of education, living situation (alone  
16 vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and  
17 Zurich). Health-related indicators comprised number of comorbidities, cognitive function,  
18 frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking  
19 status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was  
20 designed to recruit 40% of participants with a prior fall in the last 12 months.  
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### 30 31 *Comorbidity*

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33 The number of comorbidities was assessed by the Self-Administered Comorbidity  
34 Questionnaire.<sup>23</sup> This instrument is validated in the older population and evaluates the presence  
35 of 13 common chronic diseases: heart disease, high blood pressure, lung disease, diabetes, ulcer  
36 and stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer,  
37 depression, osteoarthritis or degenerative arthritis, back pain, rheumatoid arthritis.  
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### 44 45 *Cognitive function*

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

Frailty was defined according to Fried et al<sup>26</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup> Each active substance was defined as one medication and received an individual ATC code.

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3 For example, the combination of amlodipine/indapamide/perindopril was counted as 3  
4 medications and received the codes C08CA01, C03BA11, C09AA04, respectively.  
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6 Polypharmacy was defined as the concomitant use of 5 or more drugs (active substances).<sup>4 5</sup>  
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### 9 10 *Polypharmacy index*

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

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30 Descriptive statistics are presented as frequencies and percentages (%) for categorical variables,  
31 and means with standard deviation (SD) for continuous variables (or median and interquartile  
32 range for non-normally distributed variables). Data were checked for normality visually. We  
33 present the prevalence of polypharmacy and median polypharmacy index for the total  
34 population of DO-HEALTH and by city (n=7; Basel, Berlin, Coimbra, Geneva, Innsbruck,  
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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<sup>2</sup> (SD 3.5) and 26.2 kg/m<sup>2</sup> (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

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3 self-rated health scores, and more years of education were associated with a decrease in the  
4 odds of polypharmacy. The associations of living alone and ever smoked with polypharmacy  
5 were non-significant at  $p>0.2$  and, therefore, were not included in the multivariable logistic  
6 regression analysis. In the multivariable logistic regression analysis (including the covariates  
7 age, sex, education, prior fall, BMI, cognitive function, self-rated health, frailty status, number  
8 of comorbidities, and city), age, sex, BMI, number of comorbidities, and city were  
9 independently associated with polypharmacy. For each additional year of age, there was 7%  
10 higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a one unit increase in BMI,  
11 there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-1.12). For one additional  
12 comorbidity, there was a 2-fold increase in the odds of polypharmacy (OR 2.13, 95% CI 1.92-  
13 2.36). Women had 35% lower odds of reporting polypharmacy than men (OR 0.65, 95% CI  
14 0.51-0.84). Participants from Geneva or Toulouse were also less likely to report polypharmacy  
15 than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR 0.64, 95% CI 0.42-0.96,  
16 respectively). Participants from Coimbra had 2 times higher odds of reporting polypharmacy  
17 (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having had a fall in the year prior  
18 to enrollment, education, cognitive function, self-rated health, and frailty status were no longer  
19 significantly associated with polypharmacy in the multivariable analysis.  
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## 45 DISCUSSION

46 In this cross-sectional study of 2157 relatively healthy European older adults, about one quarter  
47 of participants reported polypharmacy. However, despite the same inclusion and exclusion  
48 criteria in this large clinical trial, there was great variability in prevalence of polypharmacy  
49 between the seven cities with the lowest prevalence observed in Geneva and Basel with less  
50 than 20% and the highest prevalence observed in Coimbra with about 60%. Notably, older age,  
51 greater BMI, and number of comorbidities were significantly associated with higher odds of  
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3 polypharmacy after adjusting for education, prior fall, cognitive function, self-rated health, and  
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5 frailty.  
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### 7 8 Comparison with other studies

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10 On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are  
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12 consistent with previous population-based studies. In the population-based CoLaus study, a  
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14 cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-  
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16 aged adults (mean age 58 years) was 16.9%.<sup>19</sup> This is consistent with our results from Geneva  
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18 (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy  
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20 reported in Coimbra (60.8%) is in accordance with a previous population-based study  
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22 conducted in Oporto/Portugal (59%).<sup>7</sup> Yet, a population-based study conducted in Germany  
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24 (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)<sup>29</sup> than we  
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26 observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty  
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28 in the ESTHER cohort in which only 32.8% of participants were robust,<sup>29</sup> while in DO-  
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30 HEALTH about 60% of older adults from Berlin were robust.  
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35 Participants from Coimbra were more likely to report polypharmacy than other centers. This  
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37 increased prevalence could be explained by the fact that Coimbra participants were on average  
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39 older, had higher BMI, and more likely to be prefrail or frail, despite our strict inclusion and  
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41 exclusion criteria and our aim to standardize recruitment strategies. In our analysis, BMI and  
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43 number of comorbidities were strongly associated with polypharmacy even after controlling for  
44  
45 age, city and other covariates. Additionally, participants from Coimbra also reported on  
46  
47 average a higher prevalence of depression and hypertension or heart disease when compared to  
48  
49 other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy,  
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51 since hypertension and depression are associated with increased use of medications, and  
52  
53 initiating or maintaining polypharmacy.<sup>30</sup>  
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58 Other factors, however, may also explain the wide variation in the prevalence of polypharmacy,  
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60 such as: health system organization and coverage, country specific drug policies, medication



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3 costs, prescribing pattern, refund system, clinicians' workload and specialization, and  
4 socioeconomic status.<sup>31-38</sup> A prior study in 57 European nursing homes (SHELTER study) also  
5 found differences in the prevalence of polypharmacy across seven European countries.<sup>34</sup> The  
6 authors suggested that this variation may be caused by the distinct attitudes of physicians when  
7 managing older adults with multimorbidity.<sup>34</sup> Other studies also observed high association  
8 between prescriber characteristics, such as medicine specialization, and polypharmacy.<sup>33 37 38</sup>  
9  
10 For example, a recent national cross-sectional study among Malaysian older adults found that  
11 physicians with family medicine specialization were five times more likely to prescribe more  
12 than five medications at one time.<sup>37</sup> Interestingly, among the five countries included in DO-  
13 HEALTH, Portugal is the only one that does not recognize geriatric medicine as a specialty or  
14 subspecialty.<sup>39</sup>

### 28 Implications for clinical practice

29  
30 The pharmacological treatment of older adults with multimorbidity is complex and poorly  
31 addressed in clinical practice guidelines.<sup>40-42</sup> For instance, the pharmacological  
32 recommendations of the National Institute for Health and Care Excellence (NICE) guidelines  
33 for management of type 2 diabetes, depression, and heart failure rarely account for  
34 multimorbidity.<sup>43</sup> In fact, only a few drug trials include older adults with multimorbidity.<sup>44 45</sup>  
35  
36 Therefore, the cumulative effects of multiple medication use in multimorbid older adults are  
37 unknown, and clinicians are not supported by evidence-based recommendations to manage drug  
38 prescriptions among this population. Furthermore, this lack of evidence may lead to  
39 unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions.  
40  
41 Notably, about 50% of older adults take at least one unnecessary medication<sup>46</sup> and less than  
42 50% have a clear understanding of pharmacotherapy purpose.<sup>47</sup> In this context, the  
43 polypharmacy index could be used to compare the use of medications in the older population,  
44 and to evaluate potential polypharmacy appropriateness, medication burden, and screen for  
45 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.<sup>16</sup> 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.<sup>48</sup> 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<sup>23</sup> and self-reported number of medications, whereas other tools require clinical parameters as drug effectiveness or patients' adherence.<sup>48</sup>

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

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2  
3 the association between polypharmacy and age, BMI, and comorbidities.<sup>7 19 29 30 49</sup> Moreover,  
4 comorbidities were assessed with the validated Self-Administered Comorbidity  
5 Questionnaire.<sup>23</sup> Although this questionnaire is validated in the older population and assesses  
6 the presence of the most common chronic diseases, it does not include some common conditions  
7 in older adults as sleep disorders and obstipation and participants may not be aware of some  
8 conditions.  
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## 19 CONCLUSION

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

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

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

38 CdGRCM and HABF drafted the article.

39 All authors were involved in interpretation and critical review of the results and revising the  
40 manuscript for important intellectual content.  
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49 All authors finally approved the version to be submitted.  
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### 54 b. Competing interests

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

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All other authors declare no competing interests.

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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

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3 In a first step, no data will be made available to researchers external to DO-HEALTH Research  
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5 Group to allow primary researchers to fully exploit the dataset. The data will be shared in a  
6  
7 second step according to a controlled access system.  
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9

10 e. Ethics Statement

11  
12 Patient consent for publication: Not required.

13  
14 Ethics approval: The study protocol was approved by ethical and regulatory agencies of all five  
15  
16 recruitment countries.  
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19 Acknowledgment: We thank all DO-HEALTH participants.

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

## Tables

Table 1. Baseline characteristics by city.

	Total (n=2157) <sup>a</sup>	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)	12.6 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI [Kg/m <sup>2</sup> ], 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)	26.2 (3.6)
	Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.9 (4.4)	25.6 (4.4)
Cognitive function <sup>b</sup> , 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)	26.0 (24.0-28.0)
Self-rated health <sup>c</sup> , 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 (81.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)
Frailty status, N (%) <sup>d</sup>		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	118 (59.6)	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)
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 <sup>e</sup> , 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 (0.0-2.0)	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 <sup>f</sup> , 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.

<sup>a</sup> Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

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

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

<sup>d</sup> 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).<sup>26</sup>

<sup>e</sup> 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.<sup>23</sup>

<sup>f</sup> 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 <sup>a</sup>	Adjusted <sup>b</sup>
		OR (95% CI)	OR (95% CI)
Age		<b>1.07 (1.05, 1.10)</b>	<b>1.07 (1.04, 1.10)</b>
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	<b>0.65 (0.51, 0.84)</b>
Years of education		<b>0.92 (0.90, 0.94)</b>	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	<b>1.35 (1.12, 1.64)</b>	1.08 (0.85, 1.36)
BMI [Kg/m <sup>2</sup> ]		<b>1.15 (1.12, 1.18)</b>	<b>1.09 (1.06, 1.12)</b>
Cognitive function <sup>c</sup>		<b>0.87 (0.85, 0.90)</b>	1.00 (0.96, 1.04)
Self-rated health <sup>d</sup>		<b>0.97 (0.96, 0.97)</b>	0.99 (0.98, 1.00)
Frailty status <sup>e</sup>	Robust	Ref	Ref
	Prefrail	<b>1.63 (1.34, 1.99)</b>	0.92 (0.72, 1.18)
	Frail	<b>10.17 (5.74, 18.03)</b>	1.63 (0.77, 3.45)
Number of comorbidities <sup>f</sup>		<b>2.22 (2.04, 2.42)</b>	<b>2.13 (1.92, 2.36)</b>
City	Zurich	Ref	Ref
	Basel	<b>0.56 (0.40, 0.78)</b>	0.67 (0.44, 1.04)
	Berlin	0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
	Coimbra	<b>5.59 (4.33, 7.23)</b>	<b>2.36 (1.56, 3.55)</b>
	Geneva	<b>0.50 (0.34, 0.73)</b>	<b>0.36 (0.22, 0.59)</b>
	Innsbruck	0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
	Toulouse	0.93 (0.71, 1.23)	<b>0.64 (0.42, 0.96)</b>

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

<sup>a</sup> Values are from bivariate logistic regression analyses.

<sup>b</sup> 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.

<sup>c</sup> Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).<sup>24</sup>

<sup>d</sup> Self-rated health was assessed with a visual analogic scale (0-100 mm).

<sup>e</sup> Frailty was defined according to the Fried definition.<sup>26</sup>

<sup>f</sup> Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.<sup>23</sup>

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3 **Figure**  
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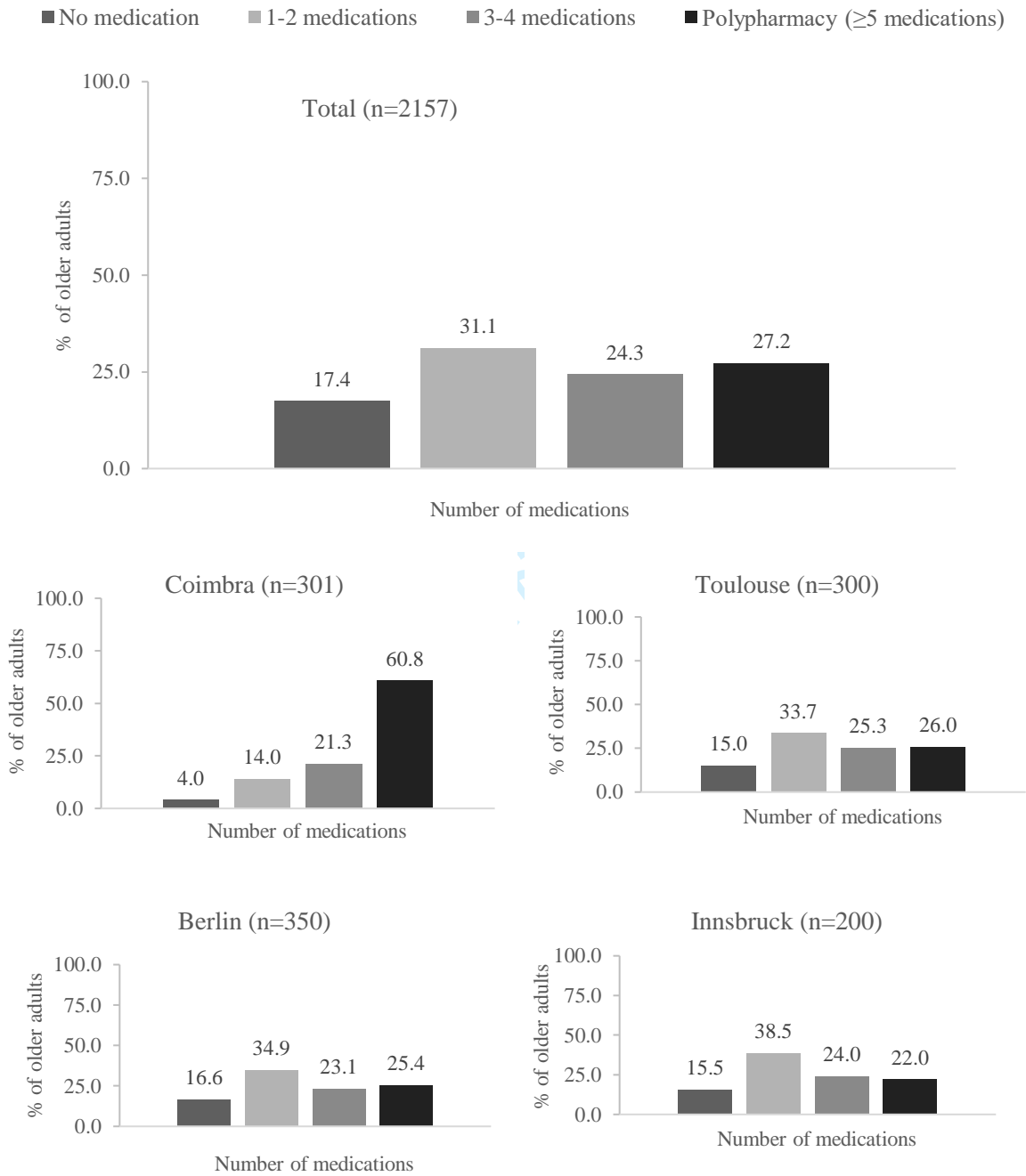
5 **Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by**  
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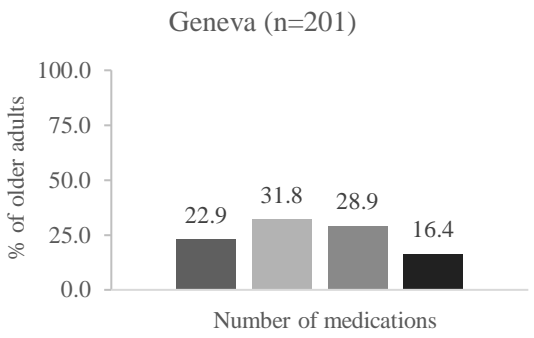
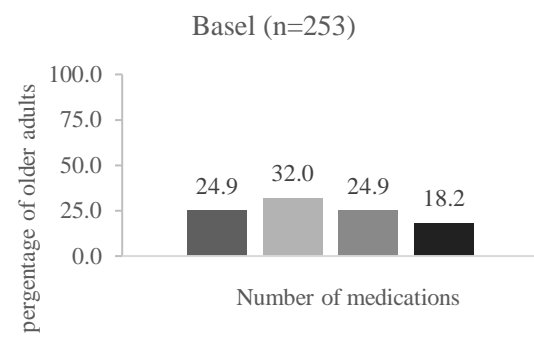
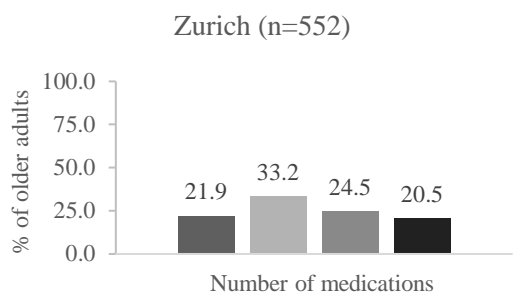
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Figure

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



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

	Item No	Recommendation	Page number
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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

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<b>Primary Subject Heading</b>:	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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3 1 **Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5**  
4 **European countries: a cross-sectional study of DO-HEALTH**

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7 3  
8 4 **Word count:** 3465 (excluding the abstract, references, tables, and figures)  
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12 6 Caroline de Godoi Rezende Costa Molino, PhD <sup>a, b, #</sup>, Patricia O. Chocano-Bedoya, MD, PhD <sup>a,</sup>  
13 <sup>c, d, #</sup>, Angélique Sadlon, MD <sup>a, e</sup>, Robert Theiler, MD, Prof. <sup>a</sup>, E. John Orav, PhD <sup>f</sup>, Bruno Vellas,  
14 7 MD, PhD <sup>g</sup>; René Rizzoli, MD <sup>h</sup>, Reto W. Kressig, MD <sup>i</sup>, John A. Kanis, MD <sup>j</sup>, Sophie  
15 8 Guyonnet, PhD <sup>k</sup>, Wei Lang, PhD <sup>a</sup>, Andreas Egli, MD <sup>a</sup>, Heike A. Bischoff-Ferrari, MD, DrPH,  
16 9 Prof. <sup>a, e, l</sup> for the DO-HEALTH Research Group\*  
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24 12 \* DO-HEALTH Research Group is listed in the Appendix.  
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## 43 ABSTRACT

44 **Word count: 300 (max 300)**

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

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

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

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

58 **Results:** 27.2% of participants reported polypharmacy ranging from 16.4% in Geneva to 60.8%  
59 in Coimbra. In the multivariable logistic regression analyses, older age (OR 1.07; 95% CI 1.04-  
60 1.10), greater BMI (OR 1.09; 95% CI 1.06-1.12), and increased number of comorbidities (OR  
61 2.13; 95% CI 1.92-2.36) were associated with polypharmacy. Women were less likely to report  
62 polypharmacy than men (OR 0.65; 95% CI 0.51-0.84). In comparison to participants from  
63 Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI  
64 1.56-3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy  
65 ((OR 0.36; 95% CI 0.22-0.59 and OR 0.64; 95% CI 0.42-0.96), respectively). Living situation,  
66 smoking status, education, prior fall, cognitive function, self-rated health, and frailty status were  
67 not significantly associated with polypharmacy.

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3 68 **Conclusion:** Polypharmacy is common among relatively healthy older adults, with moderate  
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5 69 variability across seven European cities. Independent of several confounders, being a woman,  
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7 70 older age, greater BMI, and greater number of comorbidities were associated with increased  
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9 71 odds for polypharmacy.

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12 72 **Trial registration:** original RCT DO-HEALTH: NCT01745263  
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## 16 17 74 **Strengths and limitations of this study**

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20 75 • This study takes advantage of the large DO-HEALTH data to estimate the prevalence  
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22 76 of polypharmacy and characteristics associated with polypharmacy among European  
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24 77 community-dwelling older adults.
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27 78 • In this study, the use of medications was extensively assessed and included all regularly  
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29 79 used medications, including both over-the-counter and prescription drugs.
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32 80 • Because DO-HEALTH participants, were comprehensively assessed we were able to  
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34 81 investigate the association of several sociodemographic factors and health-related  
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36 82 indicators with polypharmacy.
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39 83 • Although this was not a population-based study but a selection of relatively healthy  
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41 84 older adults, a comparison between countries is of relevance at the public health level.
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44 85 • This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate  
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46 86 factors associated with polypharmacy.

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## 89 INTRODUCTION

90 By 2050, one in every four people in Europe and Northern America will be aged 65 or over.<sup>1</sup>

91 As population ages, so does the number of chronic conditions and use of polypharmacy  
92 (commonly defined as the concomitant use of 5 or more medications).<sup>2-5</sup> For instance, about  
93 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and  
94 Portugal.<sup>6-8</sup>

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

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

112 DO-HEALTH is a multicenter international trial that recruited relatively healthy seniors  
113 70 years and older from 7 cities in 5 European countries.<sup>25</sup> At baseline, participants did not

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3 114 present major comorbidities,<sup>25 26</sup> however 43% were frail and 26.4% had 3 or more  
4  
5 115 comorbidities.<sup>27</sup> Therefore, to understand the extent of polypharmacy use among European  
6  
7 116 older adults, the goal of the present study was to assess the prevalence of polypharmacy in 7  
8  
9 117 European cities using standardized methods, and its association with socio-demographic factors  
10  
11 118 and health-related indicators among 2157 participants of DO-HEALTH.  
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## 17 120 METHODS

### 20 121 Participants and study design

22 122 This is a cross-sectional study using baseline data from DO-HEALTH, a randomized, double-  
23  
24 123 blind, placebo-controlled, clinical trial designed to assess the effectiveness of the 3  
25  
26 124 interventions (vitamin D, omega-3 fatty acids, and simple home based strength exercise  
27  
28 125 program) in a 2×2×2 factorial design (NCT01745263).<sup>25 26</sup> The six primary endpoints in DO-  
29  
30 126 HEALTH were: change in systolic and diastolic blood pressure, the Short Physical Performance  
31  
32 127 Battery, the Montreal Cognitive Assessment (cognitive function), and incidence of non-  
33  
34 128 vertebral fractures and infections over 3 years.<sup>25 26</sup> From December 2012 to November 2014,  
35  
36 129 DO-HEALTH included a total of 2157 older adults (70 years and older) from seven European  
37  
38 130 cities located in five countries: Basel (n=253), Berlin (n=350), Coimbra (n=301), Geneva  
39  
40 131 (n=201), Innsbruck (n=200), Toulouse (n=300), and Zurich (n=552). DO-HEALTH  
41  
42 132 participants were recruited through mailing lists of retirement authorities, churches, and other  
43  
44 133 community services, public events, flyers, posters, advertisement in newspapers and other  
45  
46 134 media, and educational programs and health care. Additional details about recruitment,  
47  
48 135 randomization and allocation, and blinding details are published elsewhere.<sup>26</sup>  
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54 136 Participants completed detailed questionnaires on demographics, medical events,  
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56 137 lifestyle factors (nutrition, physical activity, living condition), medication intake, and had  
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3 138 extensive clinical examinations of multiple organ and physical functions at baseline and each  
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5 139 year during a three-year follow-up.<sup>26</sup>  
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8 140 DO-HEALTH was approved by each local/national ethics committee and regulatory  
9  
10 141 authorities. The present study was approved by the Ethics Committee Zurich (ID 2018-00684).  
11  
12 142 All participants signed the consent form.  
13

### 14 143 Study population

15  
16  
17 144 Detailed eligibility criteria were published elsewhere.<sup>26</sup> Briefly, DO-HEALTH adults aged 70  
18  
19 145 years or older, with Mini Mental State Examination Score<sup>28</sup> greater or equal to 24, living in the  
20  
21 146 community, and sufficiently mobile to come to the study center. Older adults were excluded if  
22  
23 147 they reported a history of cancer (except non-melanoma skin cancer), myocardial infarction,  
24  
25 148 stroke, or transient ischemic attack in the last 5 years. Older adults with epilepsy and/or use of  
26  
27 149 anti-epileptic drugs, angina pectoris or coronary artery intervention, severe renal impairment  
28  
29 150 (creatinine clearance  $\leq 15$  ml/min) or dialysis, hypercalcemia ( $> 2.6$  mmol/l), history of hypo  
30  
31 151 or primary hyperparathyroidism, severe liver disease, or living in assisted living situations or a  
32  
33 152 nursing home, were also excluded. For the purpose of this cross-sectional analysis we included  
34  
35 153 baseline data from all DO-HEALTH participants (n=2157).  
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### 40 154 Data collection

#### 41 155 Sociodemographic factors and health-related indicators

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44  
45 156 Sociodemographic information comprised age, sex, years of education, living situation (alone  
46  
47 157 vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and  
48  
49 158 Zurich). Health-related indicators comprised number of comorbidities, cognitive function,  
50  
51 159 frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking  
52  
53 160 status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was  
54  
55 161 designed to recruit 40% of participants with a prior fall in the last 12 months.<sup>25</sup>  
56  
57  
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60

### 162 *Comorbidity*

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

### 168 *Cognitive function*

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

### 174 *Frailty*

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

### 184 *Self-rated health*

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

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3 187 you are doing on a scale of 0 to 100”, where 0 represents ‘very poorly’ and 100 represents ‘very  
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5 188 well’. Self-rated health is presented as a continuous variable.

### 189 Medications

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

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

### 205 Statistical analysis

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

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

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3 213 status, BMI, prior fall in the last 12 months, self-rated health, and smoking status) with  
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5 214 polypharmacy (binary outcome), we first performed bivariate logistic regression analyses and  
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7 215 included variables with  $p < 0.2$  in the multivariable logistic regression analyses. The final model  
8  
9 216 presents the adjusted odds ratios and 95% confidence intervals (OR, 95% CI). Analysis were  
10  
11 217 performed with SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary,  
12  
13 218 NC, USA.).

### 17 219 Patient and public involvement

18  
19 220 Patients and the public were not involved in setting up the research question, design, outcome  
20  
21 221 measures, interpretation of the results, or writing the manuscript.  
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24 222

## 26 223 RESULTS

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29 224 Baseline characteristics of the 2157 older adults included in DO-HEALTH are described in  
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31 225 **Table 1**. Median age was 74.0 years (IQR 72.0-77.0) and most participants were women  
32  
33 226 (61.7%). Mean BMI was 26.6 kg/m<sup>2</sup> (SD 3.5) and 26.2 kg/m<sup>2</sup> (SD 4.7) in men and women,  
34  
35 227 respectively. Most participants were classified as robust (53.6%) with only 3.0% of participants  
36  
37 228 classified as frail. The median number of comorbidities was 2.0 (IQR 1.0-3.0), and median  
38  
39 229 number of medications was 3.0 (IQR 1.0-5.0).  
40  
41  
42

43 230 **Table 1** also describes the baseline characteristics by city. Coimbra and Toulouse had  
44  
45 231 the highest median age (median 75 IQR 72.0-79.0 and median 75 IQR 71.0-75.0, respectively).  
46  
47 232 Coimbra had the lowest proportion of participants with no comorbidities, the highest mean  
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49 233 BMI, median number of medications, as well as the highest proportion of prefrail and frail  
50  
51 234 participants. Berlin had, on average, the highest proportion of women, robust participants, and  
52  
53 235 mean years of education.  
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56  
57 236 Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2%  
58  
59 237 and, 17.4% reported no medications at all (**Figure 1**). Regarding the cities, on average Coimbra

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2  
3 238 reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%).  
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5 239 Berlin (25.4%), Innsbruck (22%), Zurich (20.5%), Basel (18.2%), and Geneva (16.4%).  
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8 **Table 2** shows the association of sociodemographic factors and health-related indicators  
9  
10 241 with polypharmacy. In the bivariate analyses (unadjusted models), greater age, BMI, and  
11  
12 242 number of comorbidities, as well as prior fall and frailty were associated with an increase in the  
13  
14 243 odds of polypharmacy. Higher MoCA scores (higher scores mean better cognitive function),  
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16 244 higher self-rated health scores, and more years of education were associated with a decrease in  
17  
18 245 the odds of polypharmacy. The associations of living alone and ever smoked with  
19  
20 246 polypharmacy were non-significant at  $p>0.2$  and, therefore, were not included in the  
21  
22 247 multivariable logistic regression analysis. In the multivariable logistic regression analysis  
23  
24 248 (including the covariates age, sex, education, prior fall, BMI, cognitive function, self-rated  
25  
26 249 health, frailty status, number of comorbidities, and city), age, sex, BMI, number of  
27  
28 250 comorbidities, and city were independently associated with polypharmacy. For each additional  
29  
30 251 year of age, there was 7% higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a  
31  
32 252 one unit increase in BMI, there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-  
33  
34 253 1.12). For one additional comorbidity, there was a 2-fold increase in the odds of polypharmacy  
35  
36 254 (OR 2.13, 95% CI 1.92-2.36). Women had 35% lower odds of reporting polypharmacy than  
37  
38 255 men (OR 0.65, 95% CI 0.51-0.84). Participants from Geneva or Toulouse were also less likely  
39  
40 256 to report polypharmacy than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR  
41  
42 257 0.64, 95% CI 0.42-0.96, respectively). Participants from Coimbra had 2 times higher odds of  
43  
44 258 reporting polypharmacy (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having  
45  
46 259 had a fall in the year prior to enrollment, education, cognitive function, self-rated health, and  
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48 260 frailty status were no longer significantly associated with polypharmacy in the multivariable  
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50 261 analysis.  
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## 263 DISCUSSION

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

### 272 Comparison with other studies

273 On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are  
274 consistent with previous population-based studies. In the population-based CoLaus study, a  
275 cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-  
276 aged adults (mean age 58 years) was 16.9%.<sup>20</sup> This is consistent with our results from Geneva  
277 (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy  
278 reported in Coimbra (60.8%) is in accordance with a previous population-based study  
279 conducted in Oporto/Portugal (59%).<sup>7</sup> Yet, a population-based study conducted in Germany  
280 (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)<sup>38</sup> than we  
281 observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty  
282 in the ESTHER cohort in which only 32.8% of participants were robust,<sup>38</sup> while in DO-  
283 HEALTH about 60% of older adults from Berlin were robust.

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



1  
2  
3 289 controlling for age, city and other covariates. Additionally, participants from Coimbra also  
4  
5 290 reported on average a higher prevalence of depression and hypertension when compared to  
6  
7  
8 291 other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy,  
9  
10 292 since hypertension and depression are associated with increased use of medications, and  
11  
12 293 initiating or maintaining polypharmacy.<sup>39</sup>

14 294 Other factors, however, may also explain the wide variation in the prevalence of  
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16 295 polypharmacy, such as: health system organization and coverage, country specific drug  
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18 296 policies, medication costs, prescribing pattern, refund system, clinicians' workload and  
19  
20 297 specialization, and socioeconomic status.<sup>40-47</sup> A prior study in 57 European nursing homes  
21  
22 298 (SHELTER study) also found differences in the prevalence of polypharmacy across seven  
23  
24 299 European countries.<sup>43</sup> The authors suggested that this variation may be caused by the distinct  
25  
26 300 attitudes of physicians when managing older adults with multimorbidity.<sup>43</sup> Other studies also  
27  
28 301 observed high association between prescriber characteristics, such as medicine specialization,  
29  
30 302 and polypharmacy.<sup>42,46,47</sup> For example, a recent national cross-sectional study among Malaysian  
31  
32 303 older adults found that physicians with family medicine specialization were five times more  
33  
34 304 likely to prescribe more than five medications at one time.<sup>46</sup> Interestingly, among the five  
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36 305 countries included in DO-HEALTH, Portugal is the only one that does not recognize geriatric  
37  
38 306 medicine as a specialty or subspecialty.<sup>48</sup> Moreover, the discrepancy in the prevalence of  
39  
40 307 polypharmacy and health characteristics in Coimbra may be associated to the low expenditure  
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42 308 on prevention activities in Portugal.<sup>49</sup> For example, Portugal spends only half the average  
43  
44 309 expenditure on prevention activities by other Organization for Economic Co-operation and  
45  
46 310 Development (OECD) countries.<sup>49</sup> Health prevention policies are fundamental to improve  
47  
48 311 healthy aging and disease burden.<sup>50</sup> In fact, the life expectancy in Portugal is one of the highest  
49  
50 312 in the world,<sup>51</sup> however less than half of Portuguese reported being in very good or good  
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52 313 health.<sup>49</sup> Future reports, however, may find new insights regarding the health conditions and  
53  
54 314 medication use in Portugal. In 2012 an extended National Health Plan was published in

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3 315 Portugal. This plan aims to guide the public health sector to implement actions to reduce the  
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5 316 risk factors for chronic diseases.<sup>49</sup> Additionally, in 2013, a national list of pharmaceutical  
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7 317 products and prescription guidelines were defined which may also improve the use of  
8  
9 318 medication in this population.<sup>49</sup>  
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12 319

### 13 14 320 [Implications for clinical practice](#)

15  
16 321 The pharmacological treatment of older adults with multimorbidity is complex and poorly  
17  
18 322 addressed in clinical practice guidelines.<sup>52-54</sup> For instance, the pharmacological  
19  
20 323 recommendations of the National Institute for Health and Care Excellence (NICE) guidelines  
21  
22 324 for management of type 2 diabetes, depression, and heart failure rarely account for  
23  
24 325 multimorbidity.<sup>55</sup> In fact, only a few drug trials include older adults with multimorbidity.<sup>56 57</sup>  
25  
26 326 Therefore, the cumulative effects of multiple medication use in multimorbid older adults are  
27  
28 327 unknown, and clinicians are not supported by evidence-based recommendations to manage drug  
29  
30 328 prescriptions among this population. Furthermore, this lack of evidence may lead to  
31  
32 329 unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions.  
33  
34 330 Notably, about 50% of older adults take at least one unnecessary medication<sup>58</sup> and less than  
35  
36 331 50% have a clear understanding of pharmacotherapy purpose.<sup>59</sup> In this context, efforts to  
37  
38 332 minimize polypharmacy and deprescribe unnecessary or inappropriate medications were  
39  
40 333 described around the world.<sup>60-71</sup> Recently, findings from a Swiss cluster-randomized clinical  
41  
42 334 study among 46 primary care physicians suggested that a patient-centered deprescribing  
43  
44 335 intervention may reduce polypharmacy among old multimorbid patients.<sup>69</sup> In Portugal, an  
45  
46 336 ongoing nationwide three-phase study on deprescribing is investigating barriers and facilitators  
47  
48 337 of deprescribing perceived by older adults and their acceptance to have regular medications  
49  
50 338 deprescribed.<sup>67 71</sup> A pilot-study among 16 general practitioners in Germany found that an  
51  
52 339 electronic tool may assist in identifying deprescribing opportunities and promote patient  
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54 340 involvement and shared decision making.<sup>66</sup> Our findings suggest that even among relatively  
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3 341 healthy older adults polypharmacy is common, which makes this population also a target for  
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5 342 deprescribing interventions.

### 6 7 343 [Strengths and limitation of this study](#)

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10 344 In this study, we addressed the literature gap of limited studies including both over-the-counter  
11  
12 345 and prescription medications used regularly. The assessment of both prescription and over-the-  
13  
14 346 counter medications is needed as almost 50% of medication users also use at least one over-  
15  
16 347 the-counter medication, with half of them presenting a potential major drug interaction.<sup>17</sup> The  
17  
18 348 majority of studies investigating medication patterns in Europe use dispensation data from  
19  
20 349 health insurance companies' providers,<sup>72</sup> pharmacy claims,<sup>2,73 74</sup> hospitals<sup>75</sup> or nursing homes,<sup>43</sup>  
21  
22 350 and only few included over-the-counter medications.<sup>21-23</sup> These studies had different  
23  
24 351 methodologies which limits a direct comparison to our results. For example, the study by  
25  
26 352 Mielke et al. in Germany, over-the-counter medications included herbal medicines.<sup>21</sup> In our  
27  
28 353 study, we did not include complementary, homeopathic and herbal medicines as they are not  
29  
30 354 included in the ATC classification system.<sup>34</sup> In the study by Midao et al. based on the SHARE  
31  
32 355 population, participants were simply asked if they took at least five different drugs on a typical  
33  
34 356 day.<sup>22</sup> In our study, a trained medical doctor revised all the medications brought by the  
35  
36 357 participants, as well as medication packages and/or a medication list. Further, because DO-  
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38 358 HEALTH included participants from different European countries and we used the same  
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40 359 definition of polypharmacy, our findings allow cross-country comparisons and provide relevant  
41  
42 360 data for future research and health policy interventions on the pharmacogerontology field.

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44  
45 361 This study has also limitations. This is a cross-sectional study of the DO-HEALTH,  
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47 362 which was not designed to evaluate factors associated with polypharmacy and is not a  
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49 363 population-based study. As there is no consensus on the definition of polypharmacy, we chose  
50  
51 364 the common and arbitrary cut-off of 5 or more medications.<sup>4 5 24 35-37</sup> Due to the scope of this  
52  
53 365 study, the appropriateness of polypharmacy was not investigated. Despite of DO-HEALTH  
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55 366 being the largest European trial on healthy aging, a relatively moderate number of participants

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3 367 were included for each city. Overall, however, our sample size of 2157 older adults is larger  
4  
5 368 than in prior European studies.<sup>7 20 21 23</sup> Because our population consists on volunteers to  
6  
7 369 participate in a trial, they are not representative of the general population of each country,  
8  
9 370 therefore generalizability of our results is limited. Further, the scope of this study is limited in  
10  
11 371 terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered  
12  
13 372 conservative as participants were relatively healthy at baseline (without major chronic diseases  
14  
15 373 such as cancer or major cardiovascular events in the last 5 years), or in use of anti-epileptic  
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17 374 drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence  
18  
19 375 of polypharmacy and longitudinal studies that showed the association between polypharmacy  
20  
21 376 and age, BMI, and comorbidities.<sup>7 20 38 39 76</sup> Moreover, comorbidities were assessed with the  
22  
23 377 validated Self-Administered Comorbidity Questionnaire.<sup>29</sup> Although this questionnaire is  
24  
25 378 validated in the older population and assesses the presence of the most common chronic  
26  
27 379 diseases, it does not include some common conditions in older adults as sleep disorders and  
28  
29 380 obstipation and participants may not be aware of some conditions. Finally, we cannot exclude  
30  
31 381 that we may have missed information on medication use and comorbidities due to poor recall.  
32  
33 382

## 383 CONCLUSION

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

### 389 a. Contributorship statement

390 CdGRCM and PO CB contributed equally as co-first authors, they performed the literature  
391 survey, the drafting of the article, and the statistical analyses. AS, RT, SG, and WL provided  
392

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2  
3 393 critical revision of the manuscript. EJO, BV, RR, RWK, JAK, AE, and HABF designed the  
4  
5 394 study concept, acquired the data and critically revised the manuscript. HABF is the PI of DO-  
6  
7 395 HEALTH.  
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10 396

11  
12 397 b. Competing interests

13  
14 398 As part of the DO-HEALTH independent and investigator initiated clinical trial, HABF reports  
15  
16 399 as the PI of the DO-HEALTH trial, grants from European Commission, from University of  
17  
18 400 Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli Pharma, plus  
19  
20 401 nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche  
21  
22 402 Diagnostics. Further, HABF reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche  
23  
24 403 Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor,  
25  
26 404 outside the submitted work.

27  
28  
29 405 BV reports personal fees from BIOGEN, CERECIN, ROCHE, MSD, outside the submitted  
30  
31 406 work.

32  
33  
34 407 RR reports personal fees from Abiogen, Danone, Echolight, EMF, Mithra, ObsEva, Pfizer  
35  
36 408 Consumer Health, Theramex, outside the submitted work.

37  
38  
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40  
41  
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43  
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14 423 collection, management, analysis, and interpretation of the data; preparation, review, or  
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16 424 approval of the manuscript; or decision to submit the manuscript for publication.

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19 425 d. Data sharing statement

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21 426 In a first step, no data will be made available to researchers external to DO-HEALTH Research  
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23 427 Group to allow primary researchers to fully exploit the dataset. The data will be shared in a  
24  
25 428 second step according to a controlled access system.

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28 429 e. Ethics Statement

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42 435 after scientific publication, be disseminated to the public in general through social media  
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44 436 platforms, and public events organized by our center.  
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## Tables

Table 1. Baseline characteristics by city.

	Total (n=2157) <sup>a</sup>	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)	12.6 (3.7)	13.3 (3.9)	13.1 (3.1)	
BMI [Kg/m <sup>2</sup> ], 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)	25.5 (4.4)	25.1 (4.5)	25.6 (4.4)
Cognitive function <sup>b</sup> , 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)	26.0 (26.0-29.0)	26.0 (24.0-28.0)
Self-rated health <sup>c</sup> , 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 (81.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)	
Frailty status, N (%) <sup>d</sup>		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	118 (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 <sup>e</sup> , 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 (0.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.0)	
Rheumatoid arthritis or osteoarthritis, N (%) <sup>f</sup>	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)	

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3	Depression, N (%)	178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	51 (2.5)	38 (12.7)	15 (2.7)
4	Stomach disease, N (%)	165 (7.7)	6 (2.4)	14 (4.0)	65 (21.7)	17 (8.5)	12 (6.0)	37 (12.3)	14 (2.5)
5	Diabetes, N (%)	150 (7.0)	15 (5.9)	27 (7.7)	44 (14.7)	10 (5.0)	8 (4.0)	23 (7.7)	23 (4.2)
6	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)
7	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)
8	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)
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)
10	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)
11	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.

<sup>a</sup> Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

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

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

<sup>d</sup> 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).<sup>32</sup>

<sup>e</sup> 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.<sup>29</sup>

<sup>f</sup> 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.<sup>29</sup>

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

		Unadjusted <sup>a</sup>	Adjusted <sup>b</sup>
		OR (95% CI)	OR (95% CI)
Age		<b>1.07 (1.05, 1.10)</b>	<b>1.07 (1.04, 1.10)</b>
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	<b>0.65 (0.51, 0.84)</b>
Years of education		<b>0.92 (0.90, 0.94)</b>	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	<b>1.35 (1.12, 1.64)</b>	1.08 (0.85, 1.36)
BMI [Kg/m <sup>2</sup> ]		<b>1.15 (1.12, 1.18)</b>	<b>1.09 (1.06, 1.12)</b>
Cognitive function <sup>c</sup>		<b>0.87 (0.85, 0.90)</b>	1.00 (0.96, 1.04)
Self-rated health <sup>d</sup>		<b>0.97 (0.96, 0.97)</b>	0.99 (0.98, 1.00)
Frailty status <sup>e</sup>	Robust	Ref	Ref
	Prefrail	<b>1.63 (1.34, 1.99)</b>	0.92 (0.72, 1.18)
	Frail	<b>10.17 (5.74, 18.03)</b>	1.63 (0.77, 3.45)
Number of comorbidities <sup>f</sup>		<b>2.22 (2.04, 2.42)</b>	<b>2.13 (1.92, 2.36)</b>
City	Zurich	Ref	Ref
	Basel	<b>0.56 (0.40, 0.78)</b>	0.67 (0.44, 1.04)
	Berlin	0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
	Coimbra	<b>5.59 (4.33, 7.23)</b>	<b>2.36 (1.56, 3.55)</b>
	Geneva	<b>0.50 (0.34, 0.73)</b>	<b>0.36 (0.22, 0.59)</b>
	Innsbruck	0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
	Toulouse	0.93 (0.71, 1.23)	<b>0.64 (0.42, 0.96)</b>

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

<sup>a</sup> Values are from bivariate logistic regression analyses.

<sup>b</sup> 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.

<sup>c</sup> Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).<sup>30</sup>

<sup>d</sup> Self-rated health was assessed with a visual analogic scale (0-100 mm).

<sup>e</sup> Frailty was defined according to the Fried definition.<sup>32</sup>

<sup>f</sup> Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.<sup>29</sup>

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Figure

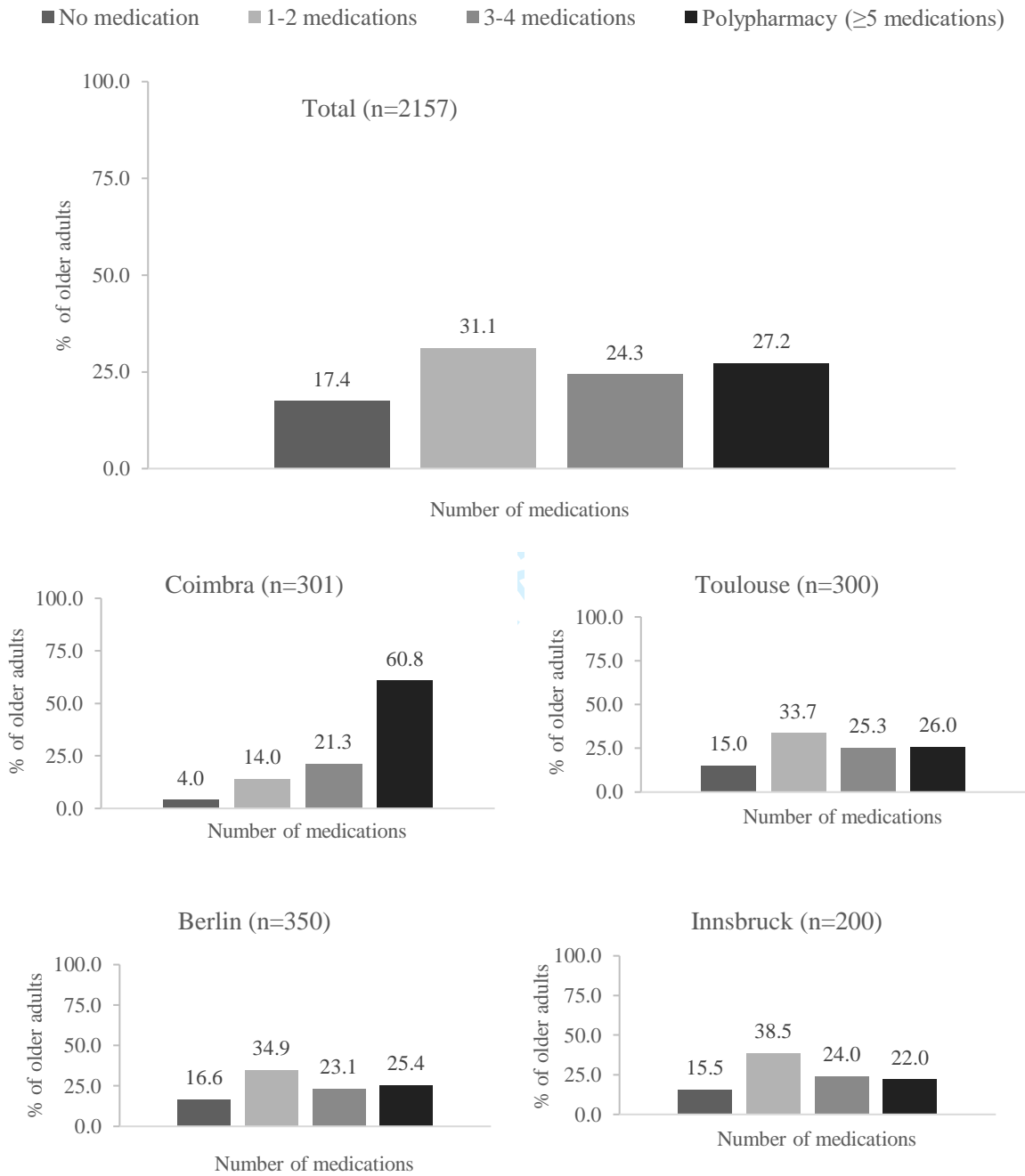
Figure 1. Prevalence of polypharmacy in the total DO-HEALTH participants and by city.

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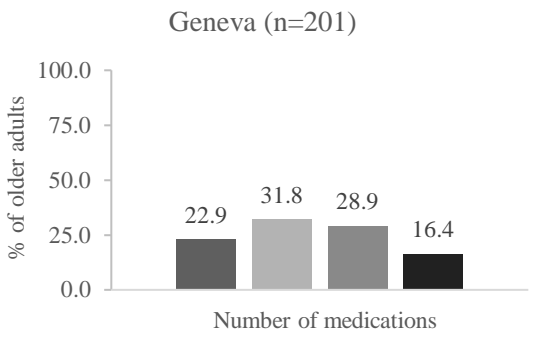
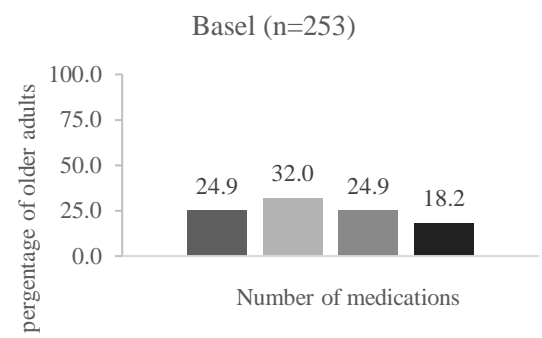
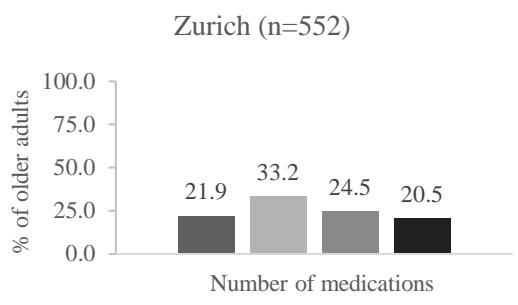
Figure

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





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## 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 Ambrecht 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.

1  
2  
3 **Prof Lorenz Hofbauer MD**, co-leads the study ‘novel biomarkers of muscle and bone  
4 communication’, FOÄ Dr. Elena Tsourdi, and Professor Martina Rauner PhD, Dresden University  
5 Medical Center and Center for Regenerative Therapies Dresden, Dresden, Germany.

6  
7 **Uwe Siebert MD**, co-leads the study ‘DO-HEALTH health economic model’, UMIT - University for  
8 Health Sciences, Medical Informatics and Technology, Hall i.T., Austria and Harvard T.H. Chan School  
9 of Public Health, Boston, MA, USA and Massachusetts General Hospital, Harvard Medical School,  
10 Boston, MA, USA.

11  
12 **Prof John A Kanis MD**, leads DO-HEALTH impact and communication of osteoporosis-related  
13 findings on a broad level, and Philippe Halbout PhD, IOF.

14  
15 **Stephen M Ferrari**, leads DO-HEALTH software development (Electronic Data Capture system and  
16 interactive practical software for seniors and health care professionals that teaches main findings of  
17 DO-HEALTH), Ferrari Data Solutions, Feldmeilen, Switzerland.

18  
19 **Benno Gut**, leads DO-HEALTH visual communication (SHEP avatar) and DO-HEALTH corporate  
20 design structures (logo, website software and communication tools), gut pictures, Horgen, Switzerland.

21  
22 **Marième Ba**, was the DO-HEALTH independent clinical monitoring partner, Pharmalys,  
23 Borehamwood, United Kingdom.

24  
25 **Jonas Wittwer Schegg PhD**, industrial partner representative bringing expertise and facilities in  
26 plasma analytics for 25-Hydroxyvitamin D and Omega-3 Fatty Acids and providing the study  
27 medication (Vitamin D, Omega-3 fatty acids), and Stéphane Etheve, DSM Nutritional Products,  
28 Kaiseraugst, Switzerland, and Manfred Eggersdorfer PhD, University Medical Center Groningen,  
29 Groningen, The Netherlands.

30  
31 **Carla Sofia Delannoy PhD**, industrial partner representative providing financial support to DO-  
32 HEALTH central coordination, Nestlé Health Science, Lausanne, Switzerland.

33  
34 **Monika Reuschling PhD**, industrial partner representative providing assays for the large DO-  
35 HEALTH biomarker study to define reference ranges of common biomarkers in adults age 70+, Roche  
36 diagnostiscs, Rotkreuz, Switzerland.

#### 37 38 39 40 **DO-HEALTH Scientific Advisory Board members and collaborators on specific outcomes**

41  
42 **Prof Endel J Orav PhD** (Head Biostatistician), Harvard T.H. Chan School of Public Health, Boston,  
43 MA, USA.

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45 **Prof Walter C Willett MD** (CVD, Cancer, Omega-3, FFQ), Harvard T H Chan School of Public  
46 Health, Boston, MA, USA.

47  
48 **Prof JoAnn E Manson MD** (PI VITAL, CVD, Diabetes), Brigham and Women's Hospital, Harvard  
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55 **Prof Paul W Walter** (Nutrition – glucose metabolism), University of Basel, Basel, Switzerland.

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

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59 **Prof Michael Fried MD** (Gastro-Intestinal health), University of Zurich, Zurich, Switzerland.

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3 **Prof Arnold von Eckardstein MD** (Biomarkers reference values), University of Zurich, Zurich,  
4 Switzerland.  
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6 **Prof Robert Theiler MD** (Falls, Osteoarthritis, DO-HEALTH Exercise program), University Hospital  
7 Zurich and University of Zurich, Zurich, Switzerland.  
8

9 **Prof Hans-Peter Simmen MD** (Traumatology), University of Zurich, Zurich, Switzerland.

10 **Prof Wolfgang Langhans PhD** (Nutrition – Diabetes), ETH Zurich, Zurich, Switzerland.

11 **Prof Annelies Zinkernagel MD** (Infections – bacterial), University Hospital of Zurich, Zurich,  
12 Switzerland.  
13

14 **Prof Nicolas Mueller MD** (Infections – viral), University Hospital of Zurich, Zurich, Switzerland.  
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16 **Prof Oliver Distler MD** (Inflammatory Arthritis), University Hospital of Zurich, Zurich, Switzerland.  
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18 **Prof Klaus Graetz MD** (Oral/Dental Health), University Hospital of Zurich, Zurich, Switzerland.  
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20 **Prof Ina Nitschke MD** (Dental Health), University Hospital of Zurich, Zurich, Switzerland.  
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22 **Prof. Thomas Dietrich** (Oral Health), University of Birmingham, UK.  
23

24 **Prof Walter Baer MD** (Mortality), University of Zurich, Zurich, Switzerland.  
25

26 **Prof Klara Landau MD** (Visual Acuity), University Hospital of Zurich, Zurich, Switzerland.  
27

28 **Prof Frank Ruschitzka MD** (Cardiology), University Hospital of Zurich, Zurich, Switzerland.  
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30 **Prof Markus Manz MD** (Hematology), University Hospital of Zurich, Zurich, Switzerland.  
31

32 **Prof Peter Burckhardt MD** (Calcium intake, Metabolism), University of Lausanne, Lausanne,  
33 Switzerland.  
34

35  
36 **\* In Memory of Dieter Felsenberg**, a passionate scientist in clinical muscle and bone research  
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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page number
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-051881.R2
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3 1 **Prevalence of polypharmacy in community-dwelling older adults from 7 centers in 5**  
4 **European countries: a cross-sectional study of DO-HEALTH**

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8 4 **Word count:** 3422 (excluding the abstract, references, tables, and figures)  
9 5

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17 13

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## 43 ABSTRACT

44 Word count: 300 (max 300)

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

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

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

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

58 **Results:** 27.2% of participants reported polypharmacy ranging from 16.4% in Geneva to 60.8%  
59 in Coimbra. In the multivariable logistic regression analyses, older age (OR 1.07; 95% CI 1.04-  
60 1.10), greater BMI (OR 1.09; 95% CI 1.06-1.12), and increased number of comorbidities (OR  
61 2.13; 95% CI 1.92-2.36) were associated with polypharmacy. Women were less likely to report  
62 polypharmacy than men (OR 0.65; 95% CI 0.51-0.84). In comparison to participants from  
63 Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI  
64 1.56-3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy  
65 ((OR 0.36; 95% CI 0.22-0.59 and OR 0.64; 95% CI 0.42-0.96), respectively). Living situation,  
66 smoking status, education, prior fall, cognitive function, self-rated health, and frailty status were  
67 not significantly associated with polypharmacy.

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3 68 **Conclusion:** Polypharmacy is common among relatively healthy older adults, with moderate  
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5 69 variability across seven European cities. Independent of several confounders, being a woman,  
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7 70 older age, greater BMI, and greater number of comorbidities were associated with increased  
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9 71 odds for polypharmacy.

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12 72 **Trial registration:** original RCT DO-HEALTH: NCT01745263  
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## 16 17 74 **Strengths and limitations of this study**

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20 75 • This study takes advantage of the large DO-HEALTH data to estimate the prevalence  
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22 76 of polypharmacy and characteristics associated with polypharmacy among European  
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24 77 community-dwelling older adults.
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27 78 • In this study, the use of medications was extensively assessed and included all regularly  
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29 79 used medications, including both over-the-counter and prescription drugs.
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32 80 • Because DO-HEALTH participants, were comprehensively assessed we were able to  
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34 81 investigate the association of several sociodemographic factors and health-related  
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36 82 indicators with polypharmacy.
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39 83 • Although this was not a population-based study but a selection of relatively healthy  
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41 84 older adults, a comparison between countries is of relevance at the public health level.
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44 85 • This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate  
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46 86 factors associated with polypharmacy.

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## 89 INTRODUCTION

90 By 2050, one in every four people in Europe and Northern America will be aged 65 or over.<sup>1</sup>

91 As population ages, so does the number of chronic conditions and use of polypharmacy  
92 (commonly defined as the concomitant use of 5 or more medications).<sup>2-5</sup> For instance, about  
93 60% of individuals aged 65 years or older reported polypharmacy in Ireland, Italy and  
94 Portugal.<sup>6-8</sup>

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

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

112 DO-HEALTH is a multicenter international trial that recruited relatively healthy seniors  
113 70 years and older from 7 cities in 5 European countries.<sup>25</sup> At baseline, participants did not

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3 114 present major comorbidities,<sup>25 26</sup> however 43% were frail and 26.4% had 3 or more  
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5 115 comorbidities.<sup>27</sup> Therefore, to understand the extent of polypharmacy use among European  
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7 116 older adults, the goal of the present study was to assess the prevalence of polypharmacy in 7  
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9 117 European cities using standardized methods, and its association with socio-demographic factors  
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11 118 and health-related indicators among 2157 participants of DO-HEALTH.  
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## 17 120 METHODS

### 18 121 Participants and study design

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20 122 This is a cross-sectional study using baseline data from DO-HEALTH, a randomized, double-  
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22 123 blind, placebo-controlled, clinical trial designed to assess the effectiveness of the 3  
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24 124 interventions (vitamin D, omega-3 fatty acids, and simple home based strength exercise  
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26 125 program) in a 2×2×2 factorial design (NCT01745263).<sup>25 26</sup> The six primary endpoints in DO-  
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28 126 HEALTH were: change in systolic and diastolic blood pressure, the Short Physical Performance  
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30 127 Battery, the Montreal Cognitive Assessment (cognitive function), and incidence of non-  
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32 128 vertebral fractures and infections over 3 years.<sup>25 26</sup> From December 2012 to November 2014,  
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34 129 DO-HEALTH included a total of 2157 community-dwelling older adults (70 years and older)  
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36 130 from seven research centers, located in five European countries: Basel (n=253), Berlin (n=350),  
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38 131 Coimbra (n=301), Geneva (n=201), Innsbruck (n=200), Toulouse (n=300), and Zurich (n=552).  
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40 132 DO-HEALTH participants were recruited through mailing lists of retirement authorities,  
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42 133 churches, and other community services, public events, flyers, posters, advertisement in  
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44 134 newspapers and other media, and educational programs and health care. Additional details  
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46 135 about recruitment, randomization and allocation, and blinding details are published elsewhere.<sup>26</sup>  
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48 136 DO-HEALTH research group is listed in the Appendix.  
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57 137 Participants completed detailed questionnaires on demographics, medical events,  
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59 138 lifestyle factors (nutrition, physical activity, living condition), medication intake, and had  
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3 139 extensive clinical examinations of multiple organ and physical functions at baseline and every  
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5 140 three months by phone calls and yearly clinical visits during a three-year follow-up.<sup>26</sup>  
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8 141 DO-HEALTH was approved by each local/national ethics committee and regulatory  
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10 142 authorities. The present study was approved by the Ethics Committee Zurich (ID 2018-00684).  
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12 143 All participants signed the consent form.  
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## 14 144 Study population

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17 145 Detailed eligibility criteria were published elsewhere.<sup>26</sup> Briefly, DO-HEALTH adults aged 70  
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19 146 years or older, with Mini Mental State Examination Score<sup>28</sup> greater or equal to 24, living in the  
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21 147 community, and sufficiently mobile to come to the study center. Older adults were excluded if  
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23 148 they reported a history of cancer (except non-melanoma skin cancer), myocardial infarction,  
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25 149 stroke, or transient ischemic attack in the last 5 years. Older adults with epilepsy and/or use of  
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27 150 anti-epileptic drugs, angina pectoris or coronary artery intervention, severe renal impairment  
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29 151 (creatinine clearance  $\leq 15$  ml/min) or dialysis, hypercalcemia ( $> 2.6$  mmol/l), history of hypo  
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31 152 or primary hyperparathyroidism, severe liver disease, or living in assisted living situations or a  
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33 153 nursing home, were also excluded. For the purpose of this cross-sectional analysis we included  
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35 154 baseline data from all DO-HEALTH participants (n=2157).  
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## 40 155 Data collection

### 41 156 Sociodemographic factors and health-related indicators

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45 157 Sociodemographic information comprised age, sex, years of education, living situation (alone  
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47 158 vs living with others), and city (Basel, Berlin, Coimbra, Geneva, Innsbruck, Toulouse, and  
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49 159 Zurich). Health-related indicators comprised number of comorbidities, cognitive function,  
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51 160 frailty, body mass index (BMI), prior fall in the last 12 months, self-rated health, and smoking  
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53 161 status (ever smoked vs never smoked). To represent the prefrail population, DO-HEALTH was  
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55 162 designed to recruit 40% of participants with a prior fall in the last 12 months.<sup>25</sup>  
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### 163 *Comorbidity*

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

### 169 *Cognitive function*

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

### 175 *Frailty*

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

### 185 *Self-rated health*

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

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3 188 you are doing on a scale of 0 to 100”, where 0 represents ‘very poorly’ and 100 represents ‘very  
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5 189 well’. Self-rated health is presented as a continuous variable.

## 190 Medications

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

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

## 206 Statistical analysis

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

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

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3 214 status, BMI, prior fall in the last 12 months, self-rated health, and smoking status) with  
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5 215 polypharmacy (binary outcome), we first performed bivariate logistic regression analyses and  
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7 216 included variables with  $p < 0.2$  in the multivariable logistic regression analyses. The final model  
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9 217 presents the adjusted odds ratios and 95% confidence intervals (OR, 95% CI). Analysis were  
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11 218 performed with SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary,  
12  
13 219 NC, USA.).  
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### 16 220 Patient and public involvement

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19 221 Patients and the public were not involved in setting up the research question, design, outcome  
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21 222 measures, interpretation of the results, or writing the manuscript.  
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## 24 223

## 25 224 RESULTS

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29 225 Baseline characteristics of the 2157 older adults included in DO-HEALTH are described in  
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31 226 **Table 1**. Median age was 74.0 years (IQR 72.0-77.0) and most participants were women  
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33 227 (61.7%). Mean BMI was 26.6 kg/m<sup>2</sup> (SD 3.5) and 26.2 kg/m<sup>2</sup> (SD 4.7) in men and women,  
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35 228 respectively. Most participants were classified as robust (53.6%) with only 3.0% of participants  
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37 229 classified as frail. The median number of comorbidities was 2.0 (IQR 1.0-3.0), and median  
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39 230 number of medications was 3.0 (IQR 1.0-5.0).  
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43 231 **Table 1** also describes the baseline characteristics by city. Coimbra and Toulouse had  
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45 232 the highest median age (median 75 IQR 72.0-79.0 and median 75 IQR 71.0-75.0, respectively).  
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47 233 Coimbra had the lowest proportion of participants with no comorbidities, the highest mean  
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49 234 BMI, median number of medications, as well as the highest proportion of prefrail and frail  
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51 235 participants. Berlin had, on average, the highest proportion of women, robust participants, and  
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53 236 mean years of education.  
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57 237 Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2%  
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59 238 and, 17.4% reported no medications at all (**Figure 1**). Regarding the cities, on average Coimbra  
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3 239 reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%).  
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5 240 Berlin (25.4%), Innsbruck (22%), Zurich (20.5%), Basel (18.2%), and Geneva (16.4%).  
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8 **Table 2** shows the association of sociodemographic factors and health-related indicators  
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10 242 with polypharmacy. In the bivariate analyses (unadjusted models), greater age, BMI, and  
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12 243 number of comorbidities, as well as prior fall and frailty were associated with an increase in the  
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14 244 odds of polypharmacy. Higher MoCA scores (higher scores mean better cognitive function),  
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16 245 higher self-rated health scores, and more years of education were associated with a decrease in  
17  
18 246 the odds of polypharmacy. The associations of living alone and ever smoked with  
19  
20 247 polypharmacy were non-significant at  $p>0.2$  and, therefore, were not included in the  
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22 248 multivariable logistic regression analysis. In the multivariable logistic regression analysis  
23  
24 249 (including the covariates age, sex, education, prior fall, BMI, cognitive function, self-rated  
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26 249 health, frailty status, number of comorbidities, and city), age, sex, BMI, number of  
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28 250 comorbidities, and city were independently associated with polypharmacy. For each additional  
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30 251 year of age, there was 7% higher odds for polypharmacy (OR 1.07, 95% CI 1.04-1.10). For a  
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32 252 one unit increase in BMI, there was 9% higher odds for polypharmacy (OR 1.09, 95% 1.06-  
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34 253 1.12). For one additional comorbidity, there was a 2-fold increase in the odds of polypharmacy  
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36 254 (OR 2.13, 95% CI 1.92-2.36). Women had 35% lower odds of reporting polypharmacy than  
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38 255 men (OR 0.65, 95% CI 0.51-0.84). Participants from Geneva or Toulouse were also less likely  
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40 256 to report polypharmacy than participants from Zurich (OR 0.36, 95% CI 0.22-0.59 and OR  
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42 257 0.64, 95% CI 0.42-0.96, respectively). Participants from Coimbra had 2 times higher odds of  
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44 258 reporting polypharmacy (OR 2.36, 95% CI 1.56, 3.55) than participants from Zurich. Having  
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46 259 had a fall in the year prior to enrollment, education, cognitive function, self-rated health, and  
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48 260 frailty status were no longer significantly associated with polypharmacy in the multivariable  
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50 261 analysis.  
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## 264 DISCUSSION

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

### 273 Comparison with other studies

274 On average, the prevalence of polypharmacy was lower in the Swiss cities. Our results are  
275 consistent with previous population-based studies. In the population-based CoLaus study, a  
276 cohort study conducted in Lausanne, Switzerland, the prevalence of polypharmacy among mid-  
277 aged adults (mean age 58 years) was 16.9%.<sup>20</sup> This is consistent with our results from Geneva  
278 (16.4%), nearby Lausanne and also French speaking. The higher prevalence of polypharmacy  
279 reported in Coimbra (60.8%) is in accordance with a previous population-based study  
280 conducted in Oporto/Portugal (59%).<sup>7</sup> Yet, a population-based study conducted in Germany  
281 (ESTHER cohort study) reported higher prevalence of polypharmacy (39.1%)<sup>38</sup> than we  
282 observed in Berlin (25.4%). This difference can be explained by the higher prevalence of frailty  
283 in the ESTHER cohort in which only 32.8% of participants were robust,<sup>38</sup> while in DO-  
284 HEALTH about 60% of older adults from Berlin were robust.

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

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3 290 controlling for age, city and other covariates. Additionally, participants from Coimbra also  
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5 291 reported on average a higher prevalence of depression and hypertension when compared to  
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8 292 other DO-HEALTH centers. This could also explain the highest prevalence of polypharmacy,  
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10 293 since hypertension and depression are associated with increased use of medications, and  
11  
12 294 initiating or maintaining polypharmacy.<sup>39</sup>

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14 295 Other factors, however, may also explain the wide variation in the prevalence of  
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16 296 polypharmacy, such as: health system organization and coverage, country specific drug  
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18 297 policies, medication costs, prescribing pattern, refund system, clinicians' workload and  
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20 298 specialization, and socioeconomic status.<sup>40-47</sup> A prior study in 57 European nursing homes  
21  
22 299 (SHELTER study) also found differences in the prevalence of polypharmacy across seven  
23  
24 300 European countries.<sup>43</sup> The authors suggested that this variation may be caused by the distinct  
25  
26 301 attitudes of physicians when managing older adults with multimorbidity.<sup>43</sup> Other studies also  
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28 302 observed high association between prescriber characteristics, such as medicine specialization,  
29  
30 303 and polypharmacy.<sup>42,46,47</sup> For example, a recent national cross-sectional study among Malaysian  
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32 304 older adults found that physicians with family medicine specialization were five times more  
33  
34 305 likely to prescribe more than five medications at one time.<sup>46</sup> Moreover, the discrepancy in the  
35  
36 306 prevalence of polypharmacy and health characteristics in Coimbra may be associated to the low  
37  
38 307 expenditure on prevention activities in Portugal.<sup>48</sup> For example, Portugal spends only half the  
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40 308 average expenditure on prevention activities by other Organization for Economic Co-operation  
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42 309 and Development (OECD) countries.<sup>48</sup> Health prevention policies are fundamental to improve  
43  
44 310 healthy aging and disease burden.<sup>49</sup> In 2012 an extended National Health Plan was published  
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46 311 in Portugal. This plan aims to guide the public health sector to implement actions to reduce the  
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48 312 risk factors for chronic diseases.<sup>48</sup> Additionally, in 2013, a national list of pharmaceutical  
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50 313 products and prescription guidelines were defined which may also improve the use of  
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52 314 medication in this population.<sup>48</sup>

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### 316 Implications for clinical practice

317 The pharmacological treatment of older adults with multimorbidity is complex and poorly  
318 addressed in clinical practice guidelines.<sup>50-52</sup> For instance, the pharmacological  
319 recommendations of the National Institute for Health and Care Excellence (NICE) guidelines  
320 for management of type 2 diabetes, depression, and heart failure rarely account for  
321 multimorbidity.<sup>53</sup> In fact, only a few drug trials include older adults with multimorbidity.<sup>54 55</sup>  
322 Therefore, the cumulative effects of multiple medication use in multimorbid older adults are  
323 unknown, and clinicians are not supported by evidence-based recommendations to manage drug  
324 prescriptions among this population. Furthermore, this lack of evidence may lead to  
325 unnecessary polypharmacy, adverse drug events, drug-drug and drug-disease interactions.  
326 Notably, about 50% of older adults take at least one unnecessary medication<sup>56</sup> and less than  
327 50% have a clear understanding of pharmacotherapy purpose.<sup>57</sup> In this context, efforts to  
328 minimize polypharmacy and deprescribe unnecessary or inappropriate medications were  
329 described around the world.<sup>58-69</sup> Recently, findings from a Swiss cluster-randomized clinical  
330 study among 46 primary care physicians suggested that a patient-centered deprescribing  
331 intervention may reduce polypharmacy among old multimorbid patients.<sup>67</sup> In Portugal, an  
332 ongoing nationwide three-phase study on deprescribing is investigating barriers and facilitators  
333 of deprescribing perceived by older adults and their acceptance to have regular medications  
334 deprescribed.<sup>65 69</sup> A pilot-study among 16 general practitioners in Germany found that an  
335 electronic tool may assist in identifying deprescribing opportunities and promote patient  
336 involvement and shared decision making.<sup>64</sup> Our findings suggest that even among relatively  
337 healthy older adults polypharmacy is common, which makes this population also a target for  
338 deprescribing interventions.

### 339 Strengths and limitation of this study

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



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3 342 counter medications is needed as almost 50% of medication users also use at least one over-  
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5 343 the-counter medication, with half of them presenting a potential major drug interaction.<sup>17</sup> The  
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7 344 majority of studies investigating medication patterns in Europe use dispensation data from  
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9 345 health insurance companies' providers,<sup>70</sup> pharmacy claims,<sup>2,71 72</sup> hospitals<sup>73</sup> or nursing homes,<sup>43</sup>  
10  
11 346 and only few included over-the-counter medications.<sup>21-23</sup> These studies had different  
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13 347 methodologies which limits a direct comparison to our results. For example, the study by  
14  
15 348 Mielke et al. in Germany, over-the-counter medications included herbal medicines.<sup>21</sup> In our  
16  
17 349 study, we did not include complementary, homeopathic and herbal medicines as they are not  
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19 350 included in the ATC classification system.<sup>34</sup> In the study by Midao et al. based on the SHARE  
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21 351 population, participants were simply asked if they took at least five different drugs on a typical  
22  
23 352 day.<sup>22</sup> In our study, a trained medical doctor revised all the medications brought by the  
24  
25 353 participants, as well as medication packages and/or a medication list. Further, because DO-  
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27 354 HEALTH included participants from different European countries and we used the same  
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29 355 definition of polypharmacy, our findings allow cross-country comparisons and provide relevant  
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31 356 data for future research and health policy interventions on the pharmacogerontology field.

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38 357 This study has also limitations. This is a cross-sectional study of the DO-HEALTH,  
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40 358 which was not designed to evaluate factors associated with polypharmacy and is not a  
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42 359 population-based study. As there is no consensus on the definition of polypharmacy, we chose  
43  
44 360 the common and arbitrary cut-off of 5 or more medications.<sup>4 5 24 35-37</sup> Due to the scope of this  
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46 361 study, the appropriateness of polypharmacy was not investigated. Despite of DO-HEALTH  
47  
48 362 being the largest European trial on healthy aging, a relatively moderate number of participants  
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50 363 were included for each city. Overall, however, our sample size of 2157 older adults is larger  
51  
52 364 than in prior European studies.<sup>7 20 21 23</sup> Because our population consists on volunteers to  
53  
54 365 participate in a trial, they are not representative of the general population of each country,  
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56 366 therefore generalizability of our results is limited. Further, the scope of this study is limited in  
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58 367 terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered

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3 368 conservative as participants were relatively healthy at baseline (without major chronic diseases  
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5 369 such as cancer or major cardiovascular events in the last 5 years), or in use of anti-epileptic  
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7 370 drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence  
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9 371 of polypharmacy and longitudinal studies that showed the association between polypharmacy  
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11 372 and age, BMI, and comorbidities.<sup>7 20 38 39 74</sup> Moreover, comorbidities were assessed with the  
12  
13 373 validated Self-Administered Comorbidity Questionnaire.<sup>29</sup> Although this questionnaire is  
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15 374 validated in the older population and assesses the presence of the most common chronic  
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17 375 diseases, it does not include some common conditions in older adults as sleep disorders and  
18  
19 376 obstipation and participants may not be aware of some conditions. Finally, we cannot exclude  
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21 377 that we may have missed information on medication use and comorbidities due to poor recall.  
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## 27 28 379 CONCLUSION

29  
30 380 About one quarter of European community-dwelling older adults reported polypharmacy. We  
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32 381 found that polypharmacy was associated with being female and increased age, BMI, and  
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34 382 number of comorbidities. Further, variation in the prevalence of polypharmacy between cities  
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36 383 remained even after accounting for demographic and health-related differences between study  
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38 384 participants. These findings highlight the need for targeted interventions to reduce  
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40 385 inappropriate polypharmacy in relatively healthy older adults.  
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### 46 387 a. Contributorship statement

47  
48 388 CdGRCM and POCB contributed equally as co-first authors, they performed the literature  
49  
50 389 survey, the drafting of the article, and the statistical analyses. AS, RT, SG, and WL provided  
51  
52 390 critical revision of the manuscript. EJO, BV, RR, RWK, JAK, AE, and HABF designed the  
53  
54 391 study concept, acquired the data and critically revised the manuscript. HABF is the PI of DO-  
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56 392 HEALTH.  
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3 394 b. Competing interests  
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5 395 As part of the DO-HEALTH independent and investigator initiated clinical trial, HABF reports  
6  
7 396 as the PI of the DO-HEALTH trial, grants from European Commission, from University of  
8  
9  
10 397 Zurich, from NESTEC, from PFIZER Consumer Healthcare, from Streuli Pharma, plus  
11  
12 398 nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche  
13  
14 399 Diagnostics. Further, HABF reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche  
15  
16  
17 400 Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor,  
18  
19 401 outside the submitted work.

20  
21 402 BV reports personal fees from BIOGEN, CERECIN, ROCHE, MSD, outside the submitted  
22  
23 403 work.

24  
25  
26 404 RR reports personal fees from Abiogen, Danone, Echolight, EMF, Mithra, ObsEva, Pfizer  
27  
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42  
43 412 All other authors declare no competing interests.  
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48  
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50

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56  
57  
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2  
3 419 The funding/supporting organizations had no role in the design and conduct of the study;  
4  
5 420 collection, management, analysis, and interpretation of the data; preparation, review, or  
6  
7 421 approval of the manuscript; or decision to submit the manuscript for publication.  
8  
9

10 422 d. Data sharing statement

11  
12 423 In a first step, no data will be made available to researchers external to DO-HEALTH Research  
13  
14 424 Group to allow primary researchers to fully exploit the dataset. The data will be shared in a  
15  
16 425 second step according to a controlled access system.  
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19 426 e. Ethics Statement

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21 427 Patient consent for publication: Not required.  
22  
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24 428 Ethics approval: The study protocol was approved by ethical and regulatory agencies of all five  
25  
26 429 recruitment countries.  
27

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29

30 431 Dissemination to participants and related patient and public communities: Study results will,  
31  
32 432 after scientific publication, be disseminated to the public in general through social media  
33  
34 433 platforms, and public events organized by our center.  
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## Tables

Table 1. Baseline characteristics by city.

	Total (n=2157) <sup>a</sup>	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)	12.6 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI [Kg/m <sup>2</sup> ], 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)	26.2 (3.6)
	Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.5 (4.4)	25.6 (4.4)
Cognitive function <sup>b</sup> , 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)	26.0 (24.0-28.0)
Self-rated health <sup>c</sup> , 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 (81.5-97.0)	80.0 (71.0-88.0)	89.0 (80.0-93.0)
Frailty status, N (%) <sup>d</sup>		1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	118 (59.6)	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)
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 <sup>e</sup> , 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 (0.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.0)
Rheumatoid arthritis or osteoarthritis, N (%) <sup>f</sup>	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 (%) <sup>g</sup>	263 (12.2)	23 (9.1)	31 (8.9)	72 (24.0)	28 (13.9)	18 (9.0)	44 (14.7)	47 (8.5)

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3	Depression, N (%)	178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	51 (2.5)	38 (12.7)	15 (2.7)
4	Stomach disease, N (%)	165 (7.7)	6 (2.4)	14 (4.0)	65 (21.7)	17 (8.5)	12 (6.0)	37 (12.3)	14 (2.5)
5	Diabetes, N (%)	150 (7.0)	15 (5.9)	27 (7.7)	44 (14.7)	10 (5.0)	8 (4.0)	23 (7.7)	23 (4.2)
6	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)
7	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)
8	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)
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)
10	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)
11	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.

<sup>a</sup> Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function, and 33 for frailty status.

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

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

<sup>d</sup> 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).<sup>32</sup>

<sup>e</sup> 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.<sup>29</sup>

<sup>f</sup> 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.<sup>29</sup>

<sup>g</sup> 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 <sup>a</sup>	Adjusted <sup>b</sup>
		OR (95% CI)	OR (95% CI)
Age		<b>1.07 (1.05, 1.10)</b>	<b>1.07 (1.04, 1.10)</b>
Sex	Men	Ref	Ref
	Women	0.94 (0.77, 1.14)	<b>0.65 (0.51, 0.84)</b>
Years of education		<b>0.92 (0.90, 0.94)</b>	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	<b>1.35 (1.12, 1.64)</b>	1.08 (0.85, 1.36)
BMI [Kg/m <sup>2</sup> ]		<b>1.15 (1.12, 1.18)</b>	<b>1.09 (1.06, 1.12)</b>
Cognitive function <sup>c</sup>		<b>0.87 (0.85, 0.90)</b>	1.00 (0.96, 1.04)
Self-rated health <sup>d</sup>		<b>0.97 (0.96, 0.97)</b>	0.99 (0.98, 1.00)
Frailty status <sup>e</sup>	Robust	Ref	Ref
	Prefrail	<b>1.63 (1.34, 1.99)</b>	0.92 (0.72, 1.18)
	Frail	<b>10.17 (5.74, 18.03)</b>	1.63 (0.77, 3.45)
Number of comorbidities <sup>f</sup>		<b>2.22 (2.04, 2.42)</b>	<b>2.13 (1.92, 2.36)</b>
City	Zurich	Ref	Ref
	Basel	<b>0.56 (0.40, 0.78)</b>	0.67 (0.44, 1.04)
	Berlin	0.90 (0.69, 1.17)	0.97 (0.67, 1.42)
	Coimbra	<b>5.59 (4.33, 7.23)</b>	<b>2.36 (1.56, 3.55)</b>
	Geneva	<b>0.50 (0.34, 0.73)</b>	<b>0.36 (0.22, 0.59)</b>
	Innsbruck	0.74 (0.52, 1.04)	0.96 (0.60, 1.51)
	Toulouse	0.93 (0.71, 1.23)	<b>0.64 (0.42, 0.96)</b>

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

<sup>a</sup> Values are from bivariate logistic regression analyses.

<sup>b</sup> 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.

<sup>c</sup> Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA).<sup>30</sup>

<sup>d</sup> Self-rated health was assessed with a visual analogic scale (0-100 mm).

<sup>e</sup> Frailty was defined according to the Fried definition.<sup>32</sup>

<sup>f</sup> Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.<sup>29</sup>

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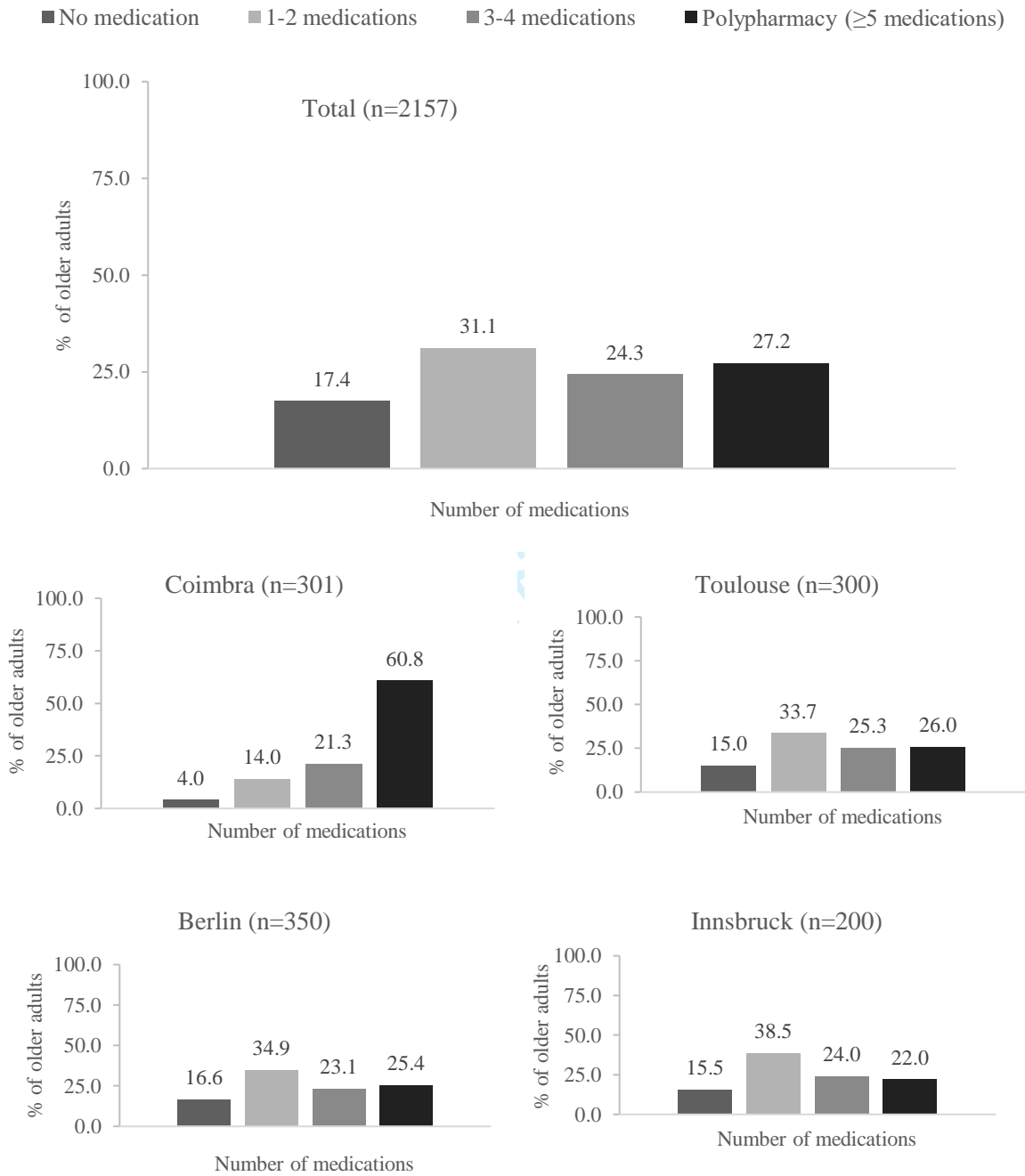
Figure

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

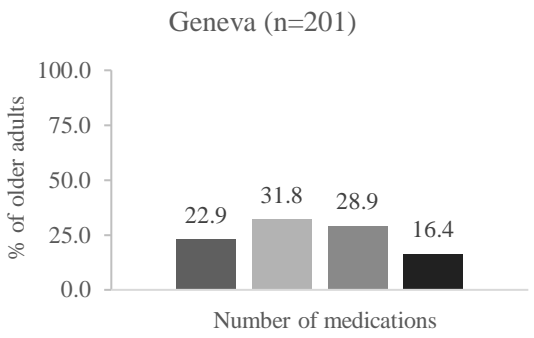
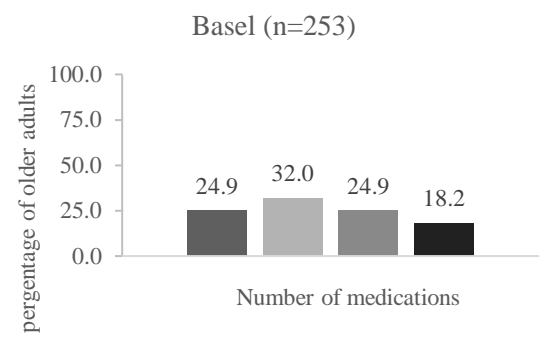
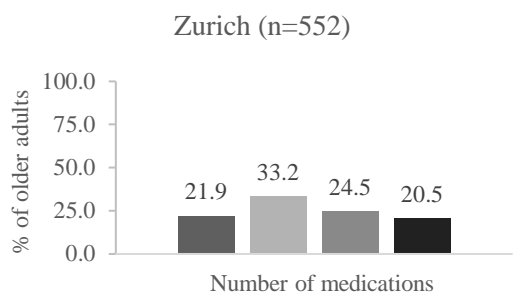
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Figure

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



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3 Appendix. DO-HEALTH Research Group

4 This e-appendix has been provided by the authors to give readers additional information about DO-  
5 HEALTH Research Group.  
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8 **DO-HEALTH Consortium**

9 (in bold: Governing Board members; in bold and underlined: Chair; underlined: Team members).  
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13 **Prof Heike A Bischoff-Ferrari MD**, DO-HEALTH Coordinator, Principal Investigator and Zurich  
14 Site Investigator, leads all endpoints analyses and co-leads the studies ‘DO-HEALTH health economic  
15 model’, ‘novel biomarkers of immunity’, ‘novel biomarkers of muscle and bone communication’,  
16 University Hospital Zurich, University of Zurich and Waid City Hospital, Zurich, Switzerland, Andreas  
17 Egli MD, Sandrine Rival PhD.  
18  
19

20 **Prof Bruno Vellas MD**, Toulouse Site Investigator, contributes to the primary endpoint cognitive  
21 decline, and Sophie Guyonnet PhD, CHU Toulouse and University of Toulouse III, Toulouse, France.  
22

23 **Prof René Rizzoli MD**, Geneva Site Investigator, contributes to all bone and muscle related endpoints  
24 and explores the contribution of protein intake to the benefit of the interventions, Emmanuel Biver MD,  
25 and Fanny Merminod RD, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.  
26

27 **Prof Reto W Kressig MD**, Basel Site Investigator, contributes to gait analyses and dual task  
28 assessments, and Stephanie Bridenbaugh MD, University Department of Geriatric Medicine FELIX  
29 PLATTER and University of Basel, Basel, Switzerland. Prof. Norbert Suhm, Dept. of Traumatology,  
30 University Hospital Basel, contributes to fracture healing study DO-HEALTH.  
31

32 **Prof José A P Da Silva MD**, Coimbra Site Investigator, explores the treatment effects on vertebral  
33 fractures, and musculoskeletal pain and function, Centro Hospitalar e Universitário de Coimbra, and  
34 Faculty of Medicine, University of Coimbra, Coimbra, Portugal, Cátia CM Duarte MD, Centro  
35 Hospitalar e Universitário de Coimbra, Coimbra, Portugal, and Ana Filipa Pinto RN, Faculty of  
36 Medicine, University of Coimbra, Coimbra, Portugal.  
37

38 **Prof Dieter Felsenberg MD**, Berlin Site Investigator, performs the central DO-HEALTH DEXA  
39 quality control and evaluation of DEXA measurements, Hendrikje Börst Dipl.Wiss-org, and Gabriele  
40 Ambrecht MD, Charité Universitätsmedizin Berlin, Berlin, Germany.  
41

42 **Prof Michael Blauth MD**, Innsbruck Site Investigator, explores the functionality after fracture, and  
43 Anna Spicher MD, Medical University of Innsbruck, Innsbruck, Austria.  
44

45 **Prof David T Felson MD**, co-leads ‘DO-HEALTH osteoarthritis study’, Manchester Academic Health  
46 Science Centre, Manchester, United Kingdom and Boston University School of Medicine, Boston, MA,  
47 USA.  
48

49 **Prof John A Kanis MD** leads the study ‘contribution of fall risk to absolute fracture risk within the  
50 FRAX model’, University of Sheffield Medical School, Sheffield, United Kingdom and Australian  
51 Catholic University, Melbourne, Victoria, Australia. Prof Eugene V Mccloskey MD, co-leads the study  
52 ‘contribution of fall risk to absolute fracture risk within the FRAX model’, University of Sheffield,  
53 Sheffield, United Kingdom, and Elena Johansson MD, University of Sheffield Medical School,  
54 Sheffield, United Kingdom and Catholic University of Australia, Melbourne, Victoria, Australia.  
55

56 **Prof Bernhard Watzl PhD**, co-leads the study ‘novel biomarkers of immunity’, Manuel Rodriguez  
57 Gomez PhD, Max Rubner-Institut, Karlsruhe, Germany.  
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3 **Prof Lorenz Hofbauer MD**, co-leads the study ‘novel biomarkers of muscle and bone  
4 communication’, FOÄ Dr. Elena Tsourdi, and Professor Martina Rauner PhD, Dresden University  
5 Medical Center and Center for Regenerative Therapies Dresden, Dresden, Germany.

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

11  
12 **Prof John A Kanis MD**, leads DO-HEALTH impact and communication of osteoporosis-related  
13 findings on a broad level, and Philippe Halbout PhD, IOF.

14  
15 **Stephen M Ferrari**, leads DO-HEALTH software development (Electronic Data Capture system and  
16 interactive practical software for seniors and health care professionals that teaches main findings of  
17 DO-HEALTH), Ferrari Data Solutions, Feldmeilen, Switzerland.

18  
19 **Benno Gut**, leads DO-HEALTH visual communication (SHEP avatar) and DO-HEALTH corporate  
20 design structures (logo, website software and communication tools), gut pictures, Horgen, Switzerland.

21  
22 **Marième Ba**, was the DO-HEALTH independent clinical monitoring partner, Pharmalys,  
23 Borehamwood, United Kingdom.

24  
25 **Jonas Wittwer Schegg PhD**, industrial partner representative bringing expertise and facilities in  
26 plasma analytics for 25-Hydroxyvitamin D and Omega-3 Fatty Acids and providing the study  
27 medication (Vitamin D, Omega-3 fatty acids), and Stéphane Etheve, DSM Nutritional Products,  
28 Kaiseraugst, Switzerland, and Manfred Eggersdorfer PhD, University Medical Center Groningen,  
29 Groningen, The Netherlands.

30  
31 **Carla Sofia Delannoy PhD**, industrial partner representative providing financial support to DO-  
32 HEALTH central coordination, Nestlé Health Science, Lausanne, Switzerland.

33  
34 **Monika Reuschling PhD**, industrial partner representative providing assays for the large DO-  
35 HEALTH biomarker study to define reference ranges of common biomarkers in adults age 70+, Roche  
36 diagnostics, Rotkreuz, Switzerland.

#### 37 38 39 40 **DO-HEALTH Scientific Advisory Board members and collaborators on specific outcomes**

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42 **Prof Endel J Orav PhD** (Head Biostatistician), Harvard T.H. Chan School of Public Health, Boston,  
43 MA, USA.

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45 **Prof Walter C Willett MD** (CVD, Cancer, Omega-3, FFQ), Harvard T H Chan School of Public  
46 Health, Boston, MA, USA.

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48 **Prof JoAnn E Manson MD** (PI VITAL, CVD, Diabetes), Brigham and Women's Hospital, Harvard  
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51 **Prof Bess Dawson-Hughes MD** (Fractures, Falls, Vitamin D), Tufts University, Boston, MA, USA.

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53 **Prof Hannes B Staehelin MD** (Cognition, Function), University of Basel, Basel, Switzerland.

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55 **Prof Paul W Walter** (Nutrition – glucose metabolism), University of Basel, Basel, Switzerland.

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

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59 **Prof Michael Fried MD** (Gastro-Intestinal health), University of Zurich, Zurich, Switzerland.

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

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6 **Prof Robert Theiler MD** (Falls, Osteoarthritis, DO-HEALTH Exercise program), University Hospital  
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9 **Prof Hans-Peter Simmen MD** (Traumatology), University of Zurich, Zurich, Switzerland.

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11 **Prof Wolfgang Langhans PhD** (Nutrition – Diabetes), ETH Zurich, Zurich, Switzerland.

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

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

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

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

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

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34 **Prof Peter Burckhardt MD** (Calcium intake, Metabolism), University of Lausanne, Lausanne,  
35 Switzerland.

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37 **\* In Memory of Dieter Felsenberg**, a passionate scientist in clinical muscle and bone research  
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For peer review only

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

	Item No	Recommendation	Page number
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).