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Prevalence of polypharmacy in community-dwelling older adults from seven centres in five European countries: a cross-sectional study of DO-HEALTH

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ABSTRACT

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 centres 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 five or more medications, excluding vitamins or dietary supplements. Bivariate and multivariable logistic regression was used to test the association of sociodemographic factors (age, sex, years of education, living situation and city) and health-related indicators (number of comorbidities, cognitive function, frailty status, 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 to 1.10), greater BMI (OR 1.09; 95% CI 1.06 to 1.12) and increased number of comorbidities (OR 2.13; 95% CI 1.92 to 2.36) were associated with polypharmacy. Women were less likely to report polypharmacy than men (OR 0.65; 95% CI 0.51 to 0.84). In comparison to participants from Zurich, participants from Coimbra were more likely to report polypharmacy (OR 2.36; 95% CI 1.56 to 3.55), while participants from Geneva or Toulouse were less likely to report polypharmacy ((OR 0.36; 95% CI 0.22 to 0.59 and OR 0.64; 95% CI 0.42 to 0.96), respectively). Living situation, smoking status, years of education, prior fall, cognitive function, self-rated health and frailty status were not significantly associated with polypharmacy.

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

Trial registration number NCT01745263.

Strengths and limitations of this study

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

INTRODUCTION

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

Although not all polypharmacy is considered inappropriate,[9] it constitutes a major

public health problem because it is associated with increased risk of adverse drug reactions, drug–drug and drug–disease interactions, which can lead to falls, unnecessary or avoidable costs,[10 11] unplanned hospitalisation,[12 13] emergency department and outpatient visits,[11] kidney function decline[14] and mortality.[4 15–19]

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

DO-HEALTH is a multicentre international trial that recruited relatively healthy seniors 70 years and older from seven cities in five European countries.[25] At baseline, participants did not present major comorbidities,[25 26] however, 43% were frail and 26.4% had three or more comorbidities.[27] Therefore, to understand the extent of polypharmacy use among European older adults, the goal of this study was to assess the prevalence of polypharmacy in seven European cities using standardised methods, and its association with sociodemographic factors and health-related indicators among 2157 participants of DO-HEALTH.

METHODS

Participants and study design

This is a cross-sectional study using baseline data from DO-HEALTH, a randomised, double-blind, placebo-controlled, clinical trial designed to assess the effectiveness of the three interventions (vitamin D, omega-3 fatty acids and simple home based strength exercise programme) in a 2×2×2 factorial design.[25 26] The six primary endpoints in DO-HEALTH were: change in systolic and diastolic blood pressure, the Short Physical Performance Battery, the Montreal Cognitive Assessment (MoCA) (cognitive function) and incidence of non-vertebral fractures and infections over 3 years.[25 26] From December 2012 to November 2014, DO-HEALTH included a total of 2157 community-dwelling older adults (70 years and older) from seven research centres, located in five European countries: Basel (n=253), Berlin (n=350), Coimbra (n=301), Geneva (n=201), Innsbruck (n=200), Toulouse (n=300) and Zurich (n=552). DO-HEALTH participants were recruited through mailing lists of retirement authorities, churches and other community services, public events, flyers, posters, advertisement in newspapers and other media, and educational programmes and healthcare. Additional details about recruitment, randomisation and allocation, and blinding details are published elsewhere.[26] DO-HEALTH research group is listed in online supplemental appendix 1.

Participants completed detailed questionnaires on demographics, medical events, lifestyle factors (nutrition, physical activity, living condition), medication intake and had extensive clinical examinations of multiple organ and physical functions at baseline and every 3 months by phone calls and yearly clinical visits during a 3-year follow-up.[26]

Study population

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

Data collection

Sociodemographic factors and health-related indicators

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

Comorbidity

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

Cognitive function

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

Frailty

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

Self-rated health

Self-rated health was measured with the EQ5D-3L.[33] Participants were asked to rate their health status on a Visual Analogue Scale (0–100 mm) with respect to the question: 'Please rate how well you are doing on a scale of 0–100', where 0 represents 'very poorly' and 100 represents 'very well'. Self-rated health is presented as a continuous variable.

Medications

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

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

Statistical analysis

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

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

Patient and public involvement

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

RESULTS

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

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

Overall, the prevalence of polypharmacy among DO-HEALTH participants was 27.2% and, 17.4% reported no medications at all (figure 1). Regarding the cities, on average Coimbra reported the highest prevalence of polypharmacy (60.8%), followed by Toulouse (26.0%). Berlin (25.4%), Innsbruck (22.0%), Zurich (20.5%), Basel (18.2%) and Geneva (16.4%).

Table 1 Baseline characteristics by city

	Total	Basel	Berlin	Coimbra	Geneva	Innsbruck	Toulouse	Zurich
	(n=2157)*	(n=253)	(n=350)	(n=301)	(n=201)	(n=200)	(n=300)	(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)	12.0 (3.7)	13.3 (3.9)	13.1 (3.1)
BMI (Kg/m^2), mean (SD) men	26.6 (3.5)	27.0 (3.6)	26.7 (3.0)	28.0 (3.5)	26.0 (3.5)	25.5 (3.3)	26.8 (3.3)	26.2 (3.6)
Women	26.2 (4.7)	25.6 (4.9)	26.9 (4.7)	29.2 (4.4)	25.1 (4.2)	25.1 (4.4)	25.1 (4.5)	25.6 (4.4)
Cognitive function†, median (IQR)	26.0 (24.0–28.0)	28.0 (26.0–30.0)	26.0 (24.0–27.0)	22.0 (19.0–25.0)	27.0 (26.0–29.0)	27.0 (25.0–29.0)	27.0 (26.0–29.0)	26.0 (24.0–28.0)
Self-rated health‡, median (IQR)	82.0 (73.0–91.0)	88.0 (79.0–92.0)	81.0 (71.0–90.0)	78.0 (60.0–90.0)	88.0 (80.0–92.0)	90.0 (80.5–97.0)	80.0 (71.0–88.0)	89.0 (80.0–93.0)
Frailty status, N (%)§ Robust	1137 (53.6)	153 (60.7)	216 (62.1)	85 (28.5)	102 (50.8)	118 (59.6)	150 (53.6)	313 (57.3)
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 medications, 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¶, 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 (%)**	974 (45.2)	116 (45.9)	168 (48.1)	79 (26.3)	124 (61.7)	98 (49.0)	173 (57.7)	216 (39.1)
High blood pressure, N (%)	844 (39.2)	86 (34.0)	163 (46.7)	186 (62.0)	80 (39.8)	61 (30.5)	112 (37.3)	156 (28.3)
Back pain, N (%)	773 (35.9)	59 (23.3)	104 (29.8)	167 (55.7)	101 (50.3)	72 (36.0)	144 (48.0)	126 (22.8)
Heart disease, N (%)††	263 (12.2)	23 (9.1)	31 (8.9)	72 (24.0)	28 (13.9)	18 (9.0)	44 (14.7)	47 (8.5)
Depression, N (%)	178 (8.3)	11 (4.4)	18 (5.2)	70 (23.3)	21 (10.5)	5 (2.5)	38 (12.7)	15 (2.7)
Stomach disease, N (%)	165 (7.7)	6 (2.4)	14 (4.0)	65 (21.7)	17 (8.5)	12 (6.0)	37 (12.3)	14 (2.5)
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)
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)
Anaemia, N (%)	64 (3.0)	5 (2.0)	4 (1.2)	22 (7.3)	9 (4.5)	4 (2.0)	6 (2.0)	14 (2.5)
Kidney disease, N (%)	54 (2.5)	1 (0.4)	3 (0.9)	35 (11.7)	4 (2.0)	0 (0.0)	6 (2.0)	5 (0.9)
Liver disease, N (%)	37 (1.7)	1 (0.4)	3 (0.9)	23 (7.7)	3 (1.5)	2 (1.0)	4 (1.3)	1 (0.2)
Cancer, N (%)	27 (1.3)	3 (1.2)	2 (0.6)	4 (1.3)	3 (1.5)	2 (1.0)	6 (2.0)	7 (1.3)
Participants with no comorbidities, N (%)	463 (21.5)	67 (26.5)	78 (22.4)	23 (7.7)	19 (9.5)	52 (26.0)	42 (14.0)	182 (33.0)

*Number of missings: 1 for BMI, 2 for years of education and comorbidities, 4 for cognitive function and 33 for frailty status.
†Cognitive function was assessed by the Montreal Cognitive Assessment. Scores range from 0 to 30 points, in which higher scores are better.[30]
‡Self-rated health was assessed with a Visual Analogue Scale (0–100 mm), in which higher scores are better.
§Frailty status was defined according to the Fried definition which evaluates five criteria: fatigue, unintentional weight loss, reduced physical activity, slowness and weakness. Frailty was categorised as robust (none of criteria), prefrail (1–2 criteria) and frail (3–5 criteria).[32]
¶Number of comorbidities was measured by the Self-Administered Comorbidity Questionnaire, which assesses the presence of current 13 comorbidities. Therefore, the range is from 0 to 13 comorbidities.[29]
**Following the instructions of the original publication of the Self-Administered Comorbidity Questionnaire, rheumatoid arthritis and osteoarthritis were assessed separately but were combined in the analysis as participants might not distinguish these disorders accurately.[29]
††In DO-HEALTH, participants with history of myocardial infarction, stroke or transient ischaemic attack in the last 5 years were excluded. Therefore, self-reported heart disease stands for other heart disease than those excluded.
BMI, body mass index.

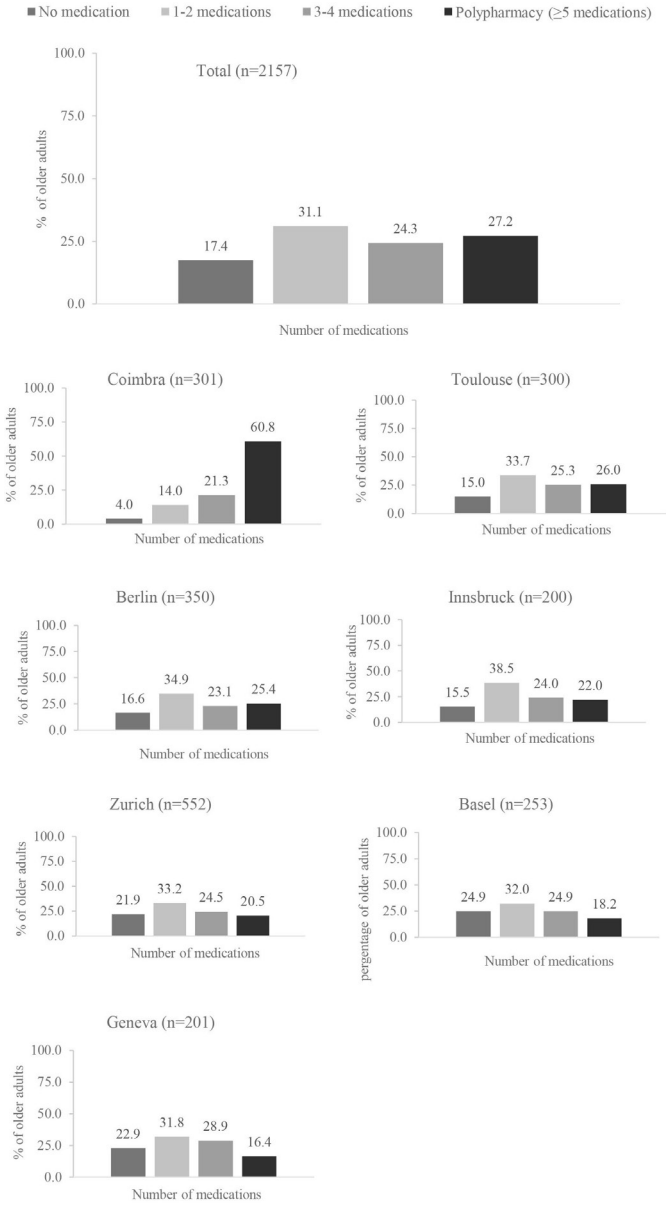

Figure 1 Prevalence of polypharmacy in the total DO-HEALTH participants and by city.

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

DISCUSSION

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

Comparison with other studies

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

Participants from Coimbra were more likely to report polypharmacy than other centres. This increased prevalence could be explained by the fact that Coimbra participants were on average older, had higher BMI and more likely to be prefrail or frail, despite our strict inclusion

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

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

Significant P-values (P < 0.05) are highlighted in bold.

*Values are from bivariate logistic regression analyses.
†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.
‡Cognitive function was assessed by the Montreal Cognitive Assessment.[30]
§Self-rated health was assessed with a Visual Analogue Scale (0–100 mm).
¶Frailty was defined according to the Fried definition.[32]
**Number of comorbidities was assessed by the Self-Administered Comorbidity Questionnaire.[29]
BMI, body mass index; CI, confidence interval; OR, odds ratio.

and exclusion criteria and our aim to standardise recruitment strategies. In our analysis, BMI and number of comorbidities were strongly associated with polypharmacy even after controlling for age, city and other covariates. Additionally, participants from Coimbra also reported on average a higher prevalence of depression and hypertension when compared with other DO-HEALTH centres. This could also explain the highest prevalence of polypharmacy, since hypertension and depression are associated with increased use of medications and initiating or maintaining polypharmacy.[39]

Other factors, however, may also explain the wide variation in the prevalence of polypharmacy, such as: health system organisation and coverage, country specific drug policies, medication costs, prescribing pattern, refund system, clinicians' workload and specialisation, and socioeconomic status.[40–47] A prior study in 57 European nursing homes (SHELTER study) also found differences in the prevalence of polypharmacy across 7 European countries.[43] The authors suggested that this variation may be caused by the distinct attitudes of physicians when managing older adults with multimorbidity.[43] Other studies also observed high association between prescriber characteristics, such as medicine specialisation and polypharmacy.[42 46 47] For example, a recent national cross-sectional study among Malaysian older adults found that

physicians with family medicine specialisation were five times more likely to prescribe more than five medications at one time.[46] Moreover, the discrepancy in the prevalence of polypharmacy and health characteristics in Coimbra may be associated to the low expenditure on prevention activities in Portugal.[48] For example, Portugal spends only half the average expenditure on prevention activities by other Organisation for Economic Co-operation and Development countries.[48] Health prevention policies are fundamental to improve healthy ageing and disease burden.[49] In 2012, an extended National Health Plan was published in Portugal. This plan aims to guide the public health sector to implement actions to reduce the risk factors for chronic diseases.[48] Additionally, in 2013, a national list of pharmaceutical products and prescription guidelines were defined which may also improve the use of medication in this population.[48]

Implications for clinical practice

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

Strengths and limitation of this study

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

This study has also limitations. This is a cross-sectional study of the DO-HEALTH, which was not designed to evaluate factors associated with polypharmacy and is not a population-based study. As there is no consensus on the definition of polypharmacy, we chose the common and arbitrary cut-off of five or more medications.[4 5 24 35–37] Due to the scope of this study, the appropriateness of polypharmacy was not investigated. Despite of DO-HEALTH being the largest European trial on healthy ageing, a relatively moderate number of participants were included for each city. Overall, however, our sample size of 2157 older adults is larger than in prior European studies.[7 20 21 23] Because our population consists on volunteers to participate in a trial, they are not representative of the general population of each country, therefore generalisability of our results is limited. Further, the scope of this study is limited in terms of the DO-HEALTH exclusion criteria. Therefore, our findings may be considered conservative as participants were relatively healthy at baseline (without major chronic diseases such as cancer or major cardiovascular events in the last 5 years), or in use of antiepileptic drugs. However, our findings are consistent with prior cross-sectional studies on the prevalence of polypharmacy and longitudinal studies that showed the association between polypharmacy and age, BMI and comorbidities.[7 20 38 39 74] Moreover, comorbidities were assessed with the validated Self-Administered Comorbidity Questionnaire.[29] Although this questionnaire is validated in the older population and assesses the presence of the most common chronic diseases, it does not include some common conditions in older adults as sleep disorders and obstipation and participants may not be aware of some

conditions. Finally, we cannot exclude that we may have missed information on medication use and comorbidities due to poor recall.

CONCLUSION

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

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REFERENCES

1 United Nations, Department of Economic and Social Affairs, Population Devision. World population prospects 2019. Available: https://population.un.org/wpp/Publications/ [Accessed 10 Feb 2020].
2 Guthrie B, Makubate B, Hernandez-Santiago V, *et al*. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med* 2015;13:74.
3 van den Akker M, Vaes B, Goderis G, *et al*. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. *PLoS One* 2019;14:e0212046.
4 Gnjidic D, Hilmer SN, Blyth FM, *et al*. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012;65:989–95.
5 Masnoon N, Shakib S, Kalisch-Ellett L, *et al*. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017;17:230.
6 Kirchmayer U, Mayer F, Basso M, *et al*. Polypharmacy in the elderly: a population based cross-sectional study in Lazio, Italy. *Eur Geriatr Med* 2016;7:484–7.
7 Eiras A, Teixeira MA, González-Montalvo JI, *et al*. [Consumption of drugs in over 65 in Porto (Portugal) and risk of potentially inappropriate medication prescribing]. *Aten Primaria* 2016;48:110–20.
8 Moriarty F, Hardy C, Bennett K, *et al*. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. *BMJ Open* 2015;5:e008656.
9 Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. *Drug Saf* 2016;39:109–16.
10 Boyd CM, Darer J, Boult C, *et al*. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716–24.
11 Feng X, Tan X, Riley B, *et al*. Prevalence and geographic variations of polypharmacy among West Virginia Medicaid beneficiaries. *Ann Pharmacother* 2017;51:981–9.

12 Leendertse AJ, Egberts ACG, Stoker LJ, *et al*. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008;168:1890–6.
13 Fried TR, O'Leary J, Towle V, *et al*. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261–72.
14 Ernst R, Fischer K, de Godoi Rezende Costa Molino C, *et al*. Polypharmacy and Kidney Function in Community-Dwelling Adults Age 60 Years and Older: A Prospective Observational Study. *J Am Med Dir Assoc* 2020;21:254–9.
15 Bourgeois FT, Shannon MW, Valim C, *et al*. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf* 2010;19:901–10.
16 Gómez C, Vega-Quiroga S, Bermejo-Pareja F, *et al*. Polypharmacy in the elderly: a marker of increased risk of mortality in a population-based prospective study (NEDICES). *Gerontology* 2015;61:301–9.
17 Qato DM, Alexander GC, Conti RM, *et al*. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 2008;300:2867–78.
18 Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults. *Age Ageing* 2015;44:90–6.
19 Dhalwani NN, Fahami R, Sathanapally H, *et al*. Association between polypharmacy and falls in older adults: a longitudinal study from England. *BMJ Open* 2017;7:e016358.
20 Castioni J, Marques-Vidal P, Abolhassani N, *et al*. Prevalence and determinants of polypharmacy in Switzerland: data from the CoLaus study. *BMC Health Serv Res* 2017;17:840.
21 Mielke N, Huscher D, Douros A, *et al*. Self-reported medication in community-dwelling older adults in Germany: results from the Berlin initiative study. *BMC Geriatr* 2020;20:22.
22 Midão L, Giardini A, Menditto E, *et al*. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch Gerontol Geriatr* 2018;78:213–20.
23 Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. *Fam Pract* 2007;24:14–9.
24 WHO. *Medication safety in polypharmacy*. Geneva: World Health Organization, 2019. https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11
25 Bischoff-Ferrari HA, Vellas B, Rizzoli R, *et al*. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA* 2020;324:1855–68.
26 Bischoff-Ferrari HA, CdGRC M, Rival S. DO-HEALTH: Vitamin D3 - Omega3 - Home exercise - Healthy aging and longevity trial - Design of a multinational clinical trial on healthy aging among European seniors. *Contemporary Clin Trial* 2020;106124.
27 Gagesch M, Chocano-Bedoya PO, Abderhalden LA, *et al*. Prevalence of physical frailty: results from the DO-HEALTH study. *J Frailty Aging* 2021:1–8.
28 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
29 Sangha O, Stucki G, Liang MH, *et al*. The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003;49:156–63.
30 Nasreddine ZS, Phillips NA, Bédirian V, *et al*. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
31 Markwick A, Zamboni G, de Jager CA. Profiles of cognitive subtest impairment in the Montreal Cognitive Assessment (MoCA) in a research cohort with normal Mini-Mental state examination (MMSE) scores. *J Clin Exp Neuropsychol* 2012;34:750–7.
32 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
33 EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
34 WHO. Anatomical therapeutic chemical (ATC) classification system Oslo: WHO collaborating centre for drug statistics methodology, 2018. Available: https://www.whocc.no/ [Accessed Feb 2018].
35 Sirois C, Domingues NS, Laroche M-L, *et al*. Polypharmacy definitions for Multimorbid older adults need stronger foundations to guide research, clinical practice and public health. *Pharmacy* 2019;7:7030126 doi:10.3390/pharmacy7030126
36 Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *Eur Geriatr Med* 2021;12:443–52.
37 Molokhia M, Majeed A. Current and future perspectives on the management of polypharmacy. *BMC Fam Pract* 2017;18:70.
38 Saum K-U, Schöttker B, Meid AD, *et al*. Is polypharmacy associated with frailty in older people? results from the ESTHER cohort study. *J Am Geriatr Soc* 2017;65:e27–32.
39 Abolhassani N, Castioni J, Marques-Vidal P, *et al*. Determinants of change in polypharmacy status in Switzerland: the population-based CoLaus study. *Eur J Clin Pharmacol* 2017;73:1187–94.
40 Bjerrum L, Søgaard J, Hallas J, *et al*. Polypharmacy in general practice: differences between practitioners. *Br J Gen Pract* 1999;49:195–8.
41 Franchi C, Cartabia M, Risso P, *et al*. Geographical differences in the prevalence of chronic polypharmacy in older people: eleven years of the EPIFARM-Elderly project. *Eur J Clin Pharmacol* 2013;69:1477–83.
42 Guthrie B, Donnan PT, Murphy DJ, *et al*. Bad apples or spoiled barrels? Multilevel modelling analysis of variation in high-risk prescribing in Scotland between general practitioners and between the practices they work in. *BMJ Open* 2015;5:e008270. doi:10.1136/bmjopen-2015-008270
43 Onder G, Liperoti R, Fialova D, *et al*. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol A Biol Sci Med Sci* 2012;67:698–704.
44 Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med* 2011;171:75–80.
45 Sinnige J, Korevaar JC, van Lieshout J, *et al*. Medication management strategy for older people with polypharmacy in general practice: a qualitative study on prescribing behaviour in primary care. *Br J Gen Pract* 2016;66:e540–51.
46 Ong SM, Lim YMF, Sivasampu S, *et al*. Variation of polypharmacy in older primary care attenders occurs at prescriber level. *BMC Geriatr* 2018;18:59.
47 Cahir C, Fahey T, Teljeur C, *et al*. Prescriber variation in potentially inappropriate prescribing in older populations in Ireland. *BMC Fam Pract* 2014;15:59.
48 OECD. *European Observatory on health systems and policies. Portugal: country health profile 2017, state of health in the EU*. Brussels: OECD Publishing, Paris/European Observatory on Health Systems and Policies, 2017.
49 Sadana R, Blas E, Budhwani S, *et al*. Healthy ageing: raising awareness of inequalities, determinants, and what could be done to improve health equity. *Gerontologist* 2016;56:S178–93.
50 Guthrie B, Payne K, Alderson P, *et al*. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.
51 Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ* 2015;350:h1059.
52 Dumbreck S, Flynn A, Nairn M, *et al*. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ* 2015;350:h949.
53 Guthrie B, Thompson A, Dumbreck S, *et al*. Better guidelines for better care: accounting for multimorbidity in clinical guidelines – structured examination of exemplar guidelines and health economic modelling. *Health Serv Deliv Res* 2017;5:1–150.
54 Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. *BMJ* 2000;321:992–3.
55 Cherubini A, Oristrell J, Pla X, *et al*. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;171:550–6.
56 Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13:57–65.
57 Chan FW-kin, Wong FY-yan, So WY, *et al*. How much do elders with chronic conditions know about their medications? *BMC Geriatr* 2013;13:59.
58 Kaminaga M, Komagamine J, Tatsumi S. The effects of in-hospital deprescribing on potential prescribing omission in hospitalized elderly patients with polypharmacy. *Sci Rep* 2021;11:8898.
59 Motter FR, Cantuaria NM, Lopes LC. Healthcare professionals' knowledge, attitudes and practices toward deprescribing: a protocol of cross-sectional study (Desmedica Study-Brazil). *BMJ Open* 2021;11:e044312.
60 Kua C-H, Reeve E, Tan DSY, *et al*. Patients' and caregivers' attitudes toward deprescribing in Singapore. *J Gerontol A Biol Sci Med Sci* 2021;76:1053–60.
61 Martin P, Tamblyn R, Benedetti A, *et al*. Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: the D-PRESCRIBE randomized clinical trial. *JAMA* 2018;320:1889–98.
62 Tannenbaum C, Martin P, Tamblyn R, *et al*. Reduction of inappropriate benzodiazepine prescriptions among older adults

through direct patient education: the EMPOWER cluster randomized trial. *JAMA Intern Med* 2014;174:890–8.
63 Romano S, Figueira D, Teixeira I, *et al*. Deprescribing for community-dwelling elderly: a systematic review of economic evaluations. *Eur J Public Health* 2021;31.
64 Junius-Walker U, Viniol A, Michiels-Corsten M, *et al*. MediQuit, an electronic deprescribing tool for patients on polypharmacy: results of a feasibility study in German general practice. *Drugs Aging* 2021;38:725–33.
65 Simões PA, Santiago LM, Simões JA. Deprescribing in primary care in Portugal (DePil17-20): a three-phase observational and experimental study protocol. *BMJ Open* 2018;8:e019542.
66 Cateau D, Ballabeni P, Niquille A. Effects of an interprofessional deprescribing intervention in Swiss nursing homes: the individual deprescribing intervention (IDeI) randomised controlled trial. *BMC Geriatr* 2021;21:655.
67 Zechmann S, Senn O, Valeri F, *et al*. Effect of a patient-centred deprescribing procedure in older multimorbid patients in Swiss primary care - A cluster-randomised clinical trial. *BMC Geriatr* 2020;20:471.
68 Tegegn HG, Tefera YG, Erku DA, *et al*. Older patients' perception of deprescribing in resource-limited settings: a cross-sectional study in an Ethiopia university hospital. *BMJ Open* 2018;8:e020590.
69 Jungo KT, Mantelli S, Rozsnyai Z, *et al*. General practitioners' deprescribing decisions in older adults with polypharmacy: a case vignette study in 31 countries. *BMC Geriatr* 2021;21:19.
70 Grimmsmann T, Himmel W. Polypharmacy in primary care practices: an analysis using a large health insurance database. *Pharmacoepidemiol Drug Saf* 2009;18:1206–13.
71 Morin L, Johnell K, Laroche M-L, *et al*. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clin Epidemiol* 2018;10:289–98.
72 Kardas P, Urbański F, Lichwierowicz A, *et al*. Prevalence and Age Structure of Polypharmacy in Poland: Results of the Analysis of the National Real-World Database of 38 Million Citizens. *Front Pharmacol* 2021;12.
73 Al Hamid A, Aslanpour Z, Aljadhey H, *et al*. Hospitalisation resulting from medicine-related problems in adult patients with cardiovascular diseases and diabetes in the United Kingdom and Saudi Arabia. *Int J Environ Res Public Health* 2016;13:479.
74 Veronese N, Stubbs B, Noale M, *et al*. Polypharmacy is associated with higher frailty risk in older people: an 8-year longitudinal cohort study. *J Am Med Dir Assoc* 2017;18:624–8.