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ORIGINAL ARTICLE

The prevalence of polypharmacy in older Europeans: A multi-national database study of general practitioner prescribing

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Aims: The aims of this study were to measure the prevalence of polypharmacy and describe the prescribing of selected medications known for overuse in older people with polypharmacy in primary care.

Methods: This was a multinational retrospective cohort study across six countries: Belgium, France, Germany, Italy, Spain and the UK. We used anonymized longitudinal patient-level information from general practice databases hosted by IQVIA. Patients ≥65 years were included. Polypharmacy was defined as having 5–9 and ≥10 distinct drug classes (ATC Level 3) prescribed during a 6-month period. Selected medications were: opioids, antipsychotics, proton pump inhibitors (PPI), benzodiazepines (ATC Level 5). We included country experts on the healthcare context to interpret findings.

Results: Age and gender distribution was similar across the six countries (mean age 75–76 years; 54–56% female). The prevalence of polypharmacy of 5–9 drugs was 22.8% (UK) to 58.3% (Germany); ≥10 drugs from 11.3% (UK) to 28.5% (Germany). In the polypharmacy population prescribed ≥5 drugs, opioid prescribing ranged from 11.5% (France) to 27.5% (Spain). Prescribing of PPI was highest with almost half of patients receiving a PPI, 42.3% (Germany) to 65.5% (Spain). Benzodiazepine prescribing showed a marked variation between countries, 2.7% (UK) to 34.9% (Spain). The healthcare context information explained possible underreporting for selected medications.

Conclusions: We have found a high prevalence of polypharmacy with more than half of the older population being prescribed ≥5 drugs in four of the six countries. Whilst polypharmacy may be appropriate in many patients, worryingly high usage of PPIs and benzodiazepines supports current efforts to improve polypharmacy management across Europe.

KEYWORDS
crossnational comparison, elderly, polypharmacy, potentially inappropriate medication, primary care

1 | INTRODUCTION

The European population is ageing.[1] Multimorbidity, the coexistence of two or more chronic health conditions in the same individual is common in older people and associated with polypharmacy—the concurrent use of multiple medications by the same individual.[2,3] The prevalence of polypharmacy, defined as taking ≥5 medications, ranged between 26% and 40% in older adults ≥65 years in a study in 17 European countries and Israel,[4] but higher and lower rates have also been reported across the world based on recent systematic reviews.[5–7] Variation in the prevalence of polypharmacy relates to differences in the populations studied (e.g. age range, comorbidities, frailty and socioeconomic characteristics). For example, higher rates of polypharmacy have been found in deprived areas[3] and in frail individuals.[8] Also, differences exist between countries in management strategies to handle polypharmacy, guidelines and prescribing preferences.[9] Finally, differences in methodology may also explain some of the variations. There is no consensus on the definition of polypharmacy.[5,10] Although all of the cited studies used a cut-off value of ≥5 medications to define polypharmacy, operationalization of this definition remains highly heterogeneous, limiting the possibilities to compare the prevalence of polypharmacy across countries. For example, studies vary as to whether or not short-term medication use, topical preparations and over-the-counter medication use are included in the count of medications.[11] Other differences between studies include the length of time of observing medication use and the data sources (e.g. dispensing data *vs.* prescribing data *vs.* patient self-report).[12]

Polypharmacy is often beneficial and appropriate as many chronic conditions, such as cardiovascular diseases or diabetes mellitus, require the use of multiple medicines for better management. But, especially in older people, polypharmacy has been associated with negative effects including adverse drug events, morbidities and mortality.[13] Polypharmacy increases the likelihood of potentially inappropriate medication (PIM) use as well as underuse of medications.[14,15] In general, PIMs are seen as medications that have an unfavourable risk/benefit balance in many older adults. Harmful clinical consequences of PIM use are decline in physical and cognitive function, falls, frailty, hospitalizations and mortality.[2,16,17]

Determining PIM use is a challenge.[18] Recently, a European repository of explicit criteria of PIMs in old age has been created based on three widely recognized lists, i.e., European Union 7-PIM, STOPP/START and Beers criteria).[19] A subset of criteria has been applied in an administrative database showing that this approach is feasible and provides clinically valuable data.[12,20,21] Two groups of medicines—antipsychotics and benzodiazepines—are among the most frequently used PIMs,[22,23] and are therefore of central interest for PIM prevalence estimates. In addition, much concern has been raised about the prolonged and inappropriate use of proton pump inhibitors (PPIs) and opioids.[24–26]

Crossnational studies stimulate discussions to explain observed differences and find areas for improvement of medication use.[27] Recently, a Europe-wide survey has identified strategies of polypharmacy management.[9] This survey needs to be validated with a crossnational study, measuring trends in the prevalence of polypharmacy across Europe. Thus far, few studies have been conducted across multiple European countries[4] and most studies have focused on nursing home residents only.[28–31]

Therefore, this study aims firstly, to measure the prevalence of polypharmacy by describing the use of drugs (at ATC3 level) in older people (≥65 years) in primary care; secondly to describe in older people with polypharmacy (≥65 years) a limited number of patient characteristics; and thirdly to describe the use of opioids, antipsychotics, benzodiazepines, PPIs in older people (≥65 years) with polypharmacy in primary care in six European countries.

What is already known about this subject

- In an ageing European population, multimorbidity and associated polypharmacy, including potentially inappropriate medication (PIM), are an increasing challenge for health systems.
- There is a lack of crossnational studies, using standardized methodology and comparable study populations, to determine the prevalence of polypharmacy and PIM use in primary care across Europe.

What this study adds

- More than half of older people were prescribied ≥5 drugs in four of the six countries.
- High usage of PPIs and benzodiazepines is concerning given the known adverse effects and should be a focus for polypharmacy management.
- Crossnational studies using routine data is an efficient tool for surveillance and evaluation.

2 | METHODS

2.1 | Study design and data sources

A multinational retrospective cohort study was conducted on data obtained from IQVIA electronic medical record (EMR) databases across six European countries. The databases included: IQVIA Medical Research Data (IMRD) in the UK; Disease Analyser (DA) in Germany; and Longitudinal Patient Data (LPD) in France, Italy, Belgium and Spain. Table S1 presents the main characteristics of these databases using the Cross National Comparison (population coverage) template produced by the European Drug Utilization Research Group (EuroDURG).[32] These databases comprise anonymized longitudinal patient-level information collected in each country by a panel of

volunteering general practitioners (GPs). In France, Germany, Italy, Belgium and the UK, GP panels are representative of primary care physicians according to three criteria known to influence prescribing: age, sex and geographical distribution (see Table S4). In Spain the database comprises all GPs in one of the 17 regions of Spain. In all countries, the patient populations are representative of the country population according to age and gender distribution, as provided by national statistics authorities (see Table S4). Data are collected from practice management software used by the GPs to record patients' information in their EMR; prescribing provided by specialists may be variably recorded (see Table S2). Data are entered during usual patient care and submitted regularly to the IQVIA coordinating centre, cleaned and de-identified. Databases contain patients' demographic details that are linked by an encrypted code with clinical records (diagnoses, referrals, test prescriptions and test results) and GP drug prescriptions (name of drug, date of prescription and number of days' supply). Medical diagnoses and comorbidities are coded either directly or mapped to 9th (Italy and Spain) and 10th (France, Germany and Belgium) versions of the International Classification of Disease (ICD-9 and ICD-10) or Read codes in UK.[33] Drugs are coded either directly or mapped to the WHO Anatomical Therapeutic Chemical (ATC) classification system.[34] Both DA in Germany and IMRD in UK were assessed through the E360 Real World Data Platform (IQVIA).

2.2 | Study population

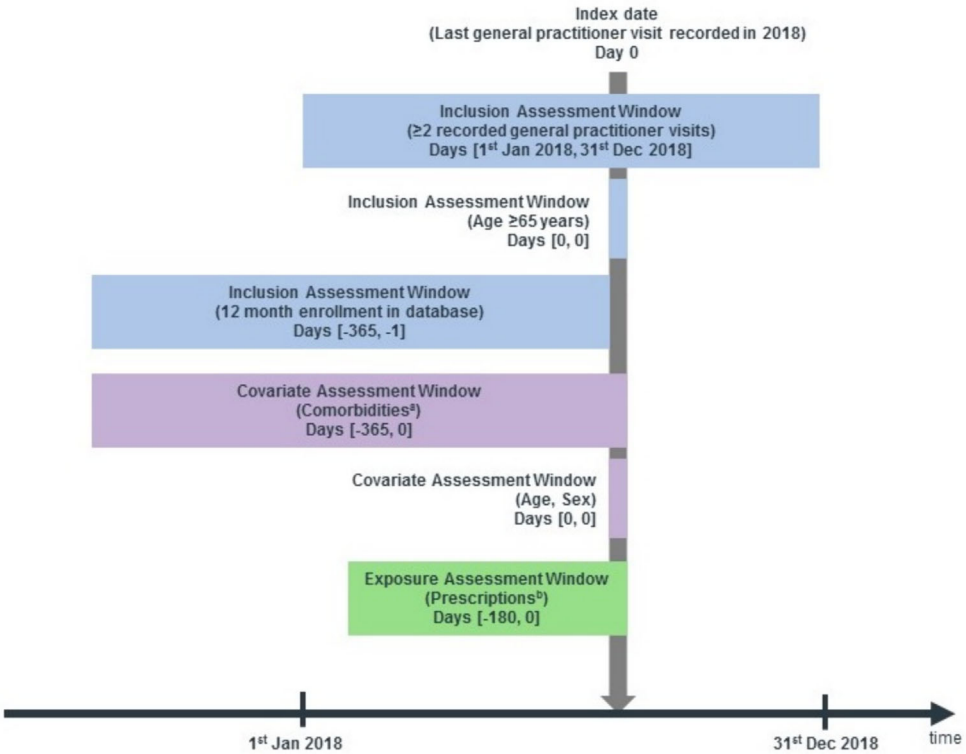
Patients included in the study were aged at least 65 years, at index date, and had to have been registered at their practice 12 months prior to the index date with a minimum of two recorded general practitioner visits in 2018. The study time period was from 1 January 2018 to 31 December 2018, and the index date was defined as the day of the last physician visit recorded in the practice EMR during 2018.

All drugs prescribed to these patients by the GPs were recorded based on the prescriptions issued at and during a 6-month period before the index date, whereas their comorbidities were captured at and during 12 months prior to the index date applying the Charlson Comorbidity Index (CCI). Patients' age and gender were collected at index date. Figure 1 illustrates the cohort identification and overall study design.

2.3 | Outcome measures

2.3.1 | Primary outcome

The prevalence of polypharmacy was determined by estimating the presence of distinct drug classes ATC Level 3. Patients were considered as exposed if they received at least one prescription of a drug



(A) Comorbidities for the Charlson Comorbidity index including myocardia infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia or paraplegia, renal disease, any malignancy including leukaemia and lymphoma, AIDS/HIV
(B) All drugs except those that are known to be used short-term (e.g., antibiotics), used irregularly (e.g., dermatologicals) and mainly prescribed by specialists (e.g., oncological medication). Medical devices, dressings, stoma are also excluded.

FIGURE 1 Summary of study design.

during the 6 months prior to the index date. We excluded drugs that are usually prescribed for short-term ailments (e.g. anti-infective agents); topical medicines (e.g. dermatological drugs); medical devices; and those that are primarily prescribed by specialists (e.g. chemotherapeutic agents) (Table S5). Polypharmacy was defined using two levels: 5–9 and ≥10 drugs prescribed.[10]

2.3.2 | Secondary outcome

A limited number of demographic characteristics (age, gender) and selected comorbidities at index date for patients with polypharmacy was examined. Comorbidities were reported as a composite endpoint displayed as the Charlson Comorbidity Index (CCI), as well as the number and proportion of each comorbidity of which the CCI is composed.[35]

2.3.3 | Exploratory outcome

The number and proportion of patients with polypharmacy prescribed selected potentially inappropriate medicines (ATC Level 5) from the following drug groups were identified and analysed: opioids, antipsychotics, benzodiazepines and PPIs. The full list evaluated in this study is outlined in Table S3.

2.4 | Analysis

2.4.1 | Country validation process

To support contextualization of the data for each country, we identified an individual from EuroDURG, a Europe-wide network of researchers/policy makers/clinicians established in 1994 and associated with the International Society of Pharmacoepidemiology,[36] with experience of working with healthcare data from that country. For each country we organized a meeting to provide: face validity of the IQVIA-generated data in the context of wider studies/databases available for the designated country; intelligence on the health system, in particular on healthcare delivery which may have impacted the IQVIA data collection[32]; and support with interpretation of the results.

2.4.2 | Statistical analyses

Polypharmacy was described as a continuous variable as well as categorically as: 5–9 and ≥10 number of distinct drug classes prescribed. The CCI was described categorically as: 0, 1–3, ≥4. Furthermore, the number and proportion of patients for each comorbidity were also analysed. Analyses for Belgium, France, Italy and Spain were performed using SAS software (version 9.3; SAS Institute, Cary, NC); analyses for Germany and the UK were performed using Stata Statistical Software (Release 14; College Station, TX: StataCorp LP). Values ≤ 10 were masked to maintain confidentiality and comply with data protection criteria.

3 | RESULTS

Table S2 presents some broad contextual information, captured as part of the country validation process, to aid in the interpretation of our findings. These data show differences in: the extent of public/private healthcare provision and consequent reimbursement; how prescribing by physicians, other than GPs, may be captured, often dependent on the disease area as illustrated for the selected medications that were investigated; and a recognition that residents of nursing homes, although managed through GPs may have variable levels of recording within GP systems, as in some case this is only undertaken within the nursing home healthcare record.

3.1 | Primary outcome

The study population for each of the six European countries is presented in Table 1. Age and gender distribution were similar across the six countries with a mean age of between 75 and 76 years (with minimal differences across age groups) and approximately 54–56% female. The prevalence of polypharmacy for those aged 65 and older, >5 drugs prescribed (ATC level 3) during 6 months, ranged from 22.8% in the UK to 58.3% in Germany. Patients with polypharmacy exposed to ≥10 drugs was lowest in the UK (11.3%) and highest in Germany (28.5%). The frequency of the selected medications across the six countries was highest for PPIs (range 19.2%, UK to 44.4%, Spain) and lowest for antipsychotics (range 1.4%, France to 6.3%, Spain). Benzodiazepine prescribing had the largest variation between countries with only 1.3% in the UK and 25.0% in Spain. Opioid prescribing, of increasing concern globally, ranged from 7.7% to 17.1% in our study population.

3.2 | Secondary outcome

Table 2 presents the polypharmacy population, overall and by polypharmacy category (5–9 drugs and ≥10 drugs) described using key patient characteristics and selected comorbidities used in the generation of the CCI. There was minimal difference observed in mean (SD) age overall and by category of polypharmacy with approximately 80% of patients aged between 65 and 84 years overall across all six countries and ≥ 90 years accounting for between 3.4% (Belgium) to 7.6% (Spain) overall. The CCI was zero in a large proportion of patients, ranging from 33.7% in Germany to 68.7% in the UK. Our data indicated that *diabetes without complications* and *chronic pulmonary disease* were among the most frequently recorded comorbidities across the six countries in the GP systems, with over 25% of patients on ≥10 drugs having a recorded diagnosis of *diabetes without complications* and *chronic pulmonary disease*.

TABLE 1 Study population: demographics and overview of medicines.

		Belgium ($n = 72\,140$)	France ($n = 257\,020$)	Germany ($n = 376\,641$)	Italy ($n = 315\,453$)	Spain ($n = 156\,144$)	UK ($n = 590\,310$)
Age at index date (years)	Mean (SD)	75.8 (7.83)	75.4 (7.65)	76 (7.4)	76.3 (7.82)	75.8 (7.83)	75.5 (7.66)
Age at index (years) – group	[65;74]	36 338 (50.4)	135 872 (52.9)	166 236 (44.1)	147 165 (46.8)	79 204 (50.8)	310 397 (52.6)
	[75;84]	23 879 (33.1)	83 146 (32.4)	163 021 (43.3)	113 672 (36.1)	51 260 (32.9)	194 528 (32.9)
	[85;89]	7736 (10.7)	25 148 (9.8)	32 321 (8.6)	33 564 (10.7)	16 267 (10.4)	53 024 (9.0)
	≥90 years	4101 (5.7)	12 673 (4.9)	15 063 (4.0)	20 245 (6.4)	9257 (5.9)	32 361 (5.5)
	Missing (*n*)	86	181	-	807	156	-
Gender	Male	31 686 (43.9)	114 272 (44.5)	188 429 (43.7)	137 724 (43.7)	68 224 (43.7)	267 751 (45.4)
	Female	40 454 (56.1)	142 748 (55.5)	242 910 (56.3)	177 713 (56.3)	87 920 (56.3)	322 559 (54.6)
	Missing (*n*)	–	–	–	16	–	–
Exposed to drug	No	14 730 (20.4)	21 466 (8.4)	2463 (6.5)	14 999 (4.8)	6732 (4.3)	59 933 (10.2)
	Yes	57 410 (79.6)	235 554 (91.6)	374 178 (93.5)	300 454 (95.2)	149 412 (95.7)	530 377 (89.8)
Patients with polypharmacy **(>5 ATC 3rd level classes)**	No	44 590 (61.8)	107 931 (42.0)	155 020 (41.7)	146 726 (46.5)	68 715 (44.0)	456 009 (77.2)
	Yes	27 550 (38.2)	149 089 (58.0)	217 095 (58.3)	168 727 (53.5)	87 429 (56.0)	134 301 (22.8)
Polypharmacy by category	5–9	23 239 (84.4)	114 976 (77.1)	159 628 (71.5)	135 998 (80.6)	68 792 (78.7)	119 123 (88.7)
	> = 10	4311 (15.6)	34 113 (22.9)	57 467 (28.5)	32 729 (19.4)	18 637 (21.3)	15 178 (11.3)
Potentially inappropriate medicines	*n*	72 054	256 839	376 641	314 646	155 988	590 310
	Opioids	7512 (10.4)	19 852 (7.7)	41 977 (11.1)	34 079 (10.8)	26 666 (17.1)	59 177 (10.0)
	Antipsychotics	2019 (2.8)	3712 (1.4)	13 253 (3.5)	16 747 (5.3)	9868 (6.3)	11 270 (1.9)
	Benzodiazepines	9269 (12.9)	36 338 (14.1)	16 219 (4.3)	30 231 (9.6)	38 989 (25.0)	7614 (1.3)
	Proton pump inhibitors	16 484 (22.9)	84 579 (32.9)	127 006 (33.7)	125 989 (40.0)	69 253 (44.4)	113 551 (19.2)

TABLE 2 Polypharmacy population: demographics and selected comorbidities stratified by category of polypharmacy.

	Polypharmacy patients (>5 ATC 3rd level classes)									
	Overall						5–9 drugs			
	Belgium (*n* = 27 550)	France (*n* = 149 089)	Germany (*n* = 217 095)	Italy (*n* = 168 727)	Spain (*n* = 87 429)	UK (*n* = 134 301)	Belgium (*n* = 23 239)	France (*n* = 114 976)	Germany (*n* = 159 628)	Italy (*n* = 135 998)
Age at index date (years)										
Mean (SD)	75.6 (7.17)	75.9 (7.5)	77.3 (7.5)	77.8 (7.67)	77.2 (7.8)	77.2 (7.8)	75.5 (7.17)	75.6 (7.48)	76.7 (7.4)	77.4 (7.71)
Median [Q1 – Q3]	75 [70–81]	75 [70–82]	77 [71–82]	77 [71–83]	76 [65–100]	76 [71–83]	74 [70–81]	74 [69–81]	77 [70–82]	77 [71–83]
Missing (n)	<10 (0.0)	48 (0.0)	–	241 (0.1)	79 (0.1)	–	<10 (0.0)	39 (0.0)	–	205 (0.2)
Age at index (years) – group										
n	27 544	149 041	217 095	168 486	91 948	134 301	23 236	114 937	159 628	135 793
[65;74]	13 718 (49.8)	72 920 (48.9)	80 153 (36.9)	63 522 (37.7)	39 219 (42.7)	56 318 (41.9)	11 744 (50.5)	58 309 (50.7)	63 772 (40.0)	53 976 (39.7)
[75;84]	10 210 (37.1)	53 222 (35.7)	101 272 (46.7)	69 732 (41.4)	34 326 (37.3)	51 476 (38.3)	8490 (36.5)	39 819 (34.6)	73 290 (45.9)	54 738 (40.3)
[85;89]	2679 (9.7)	16 147 (10.8)	23 993 (11.0)	22 470 (13.3)	12 027 (13.1)	16 459 (12.3)	2216 (9.5)	11 768 (10.2)	15 441 (9.7)	17 049 (12.6)
≥90 years	937 (3.4)	6752 (4.5)	11 677 (5.4)	12 762 (7.6)	6376 (6.9)	10 048 (7.5)	786 (3.4)	5041 (4.4)	7125 (4.5)	10 030 (7.4)
Missing (*n*)	<10	48	–	241	80	–	<10	39	–	205
Gender										
n	27 550	149 089	217 095	168 716	92 028	134 301	23 239	114 976	159 628	135 990
Male	12 361 (44.9)	65 674 (44.1)	93 662 (43.1)	70 585 (41.8)	39 032 (42.4)	64 193 (47.8)	10 601 (45.6)	51 018 (44.4)	70 587 (44.2)	57 483 (42.3)
Female	15 189 (55.1)	83 415 (55.9)	123 433 (56.9)	98 131 (58.2)	52 996 (57.6)	70 108 (52.2)	12 638 (54.4)	63 958 (55.6)	89 041 (55.8)	78 507 (57.7)
Missing (*n*)	–	–	–	11	–	–	–	–	–	<10
Charlson Comorbidity Index										
Median [Q1 – Q3]	0 [0–1]	0 [0–1]	1 [0–3]	0 [0–2]	0 [0–1]	0 [0–1]	0 [0–1]	0 [0–1]	1 [0–2]	0 [0–2]
Charlson Comorbidity Index – group										
0	17 149 (62.2)	87 720 (58.8)	73 114 (33.7)	95 773 (56.8)	59 802 (68.4)	92 272 (68.7)	15 347 (66.0)	71 923 (62.6)	60 252 (37.7)	82 884 (60.9)
1–3	9858 (35.8)	56 458 (37.9)	110 315 (50.8)	66 416 (39.4)	26 596 (30.4)	40 918 (30.5)	7537 (32.4)	39 985 (34.8)	80 639 (50.5)	49 171 (36.2)
≥ 4	543 (2.0)	4911 (3.3)	33 666 (15.5)	6538 (3.9)	1031 (1.2)	1111 (0.8)	355 (1.5)	3068 (2.7)	18 737 (11.7)	3943 (2.9)
Charlson comorbidity category										
Myocardial infarction	929 (3.4)	6459 (4.3)	9960 (4.6)	3554 (2.1)	2140 (2.4)	1263 (0.9)	725 (3.1)	4232 (3.7)	6285 (3.9)	2455 (1.8)
Congestive heart failure	2218 (8.1)	7185 (4.8)	30 661 (14.1)	14 565 (8.6)	2212 (2.5)	2268 (1.7)	1494 (6.4)	4137 (3.6)	17 519 (11.0)	9009 (6.6)
Peripheral vascular disease	330 (1.2)	11 635 (7.8)	24 155 (11.1)	12 273 (7.3)	2949 (3.4)	942 (0.7)	249 (1.1)	7973 (6.9)	15 982 (10.0)	8922 (6.6)
Cerebrovascular disease	1964 (7.1)	18 048 (12.1)	25 541 (11.8)	21 685 (12.9)	7248 (8.3)	2145 (1.6)	1534 (6.6)	12 981 (11.3)	16 664 (10.4)	16 128 (11.9)
Dementia	708 (2.6)	2232 (1.5)	12 663 (5.8)	5351 (3.2)	4552 (5.2)	6702 (5.0)	564 (2.4)	1652 (1.4)	7649 (4.8)	3950 (2.9)
Chronic pulmonary disease	6519 (23.7)	31 426 (21.1)	40 934 (18.9)	28 800 (17.1)	14 634 (16.7)	20 814 (15.5)	4831 (20.8)	20 873 (18.2)	26 059 (16.3)	19 933 (14.7)
Rheumatologic disease	573 (2.1)	3634 (2.4)	7685 (3.5)	6625 (3.9)	2013 (2.3)	2804 (2.1)	431 (1.9)	2493 (2.2)	4882 (3.1)	4556 (3.4)

TABLE 2 (Continued)

	Polypharmacy patients (>5 ATC 3rd level classes)									
	Overall						5–9 drugs			
	Belgium (*n* = 27 550)	France (*n* = 149 089)	Germany (*n* = 217 095)	Italy (*n* = 168 727)	Spain (*n* = 87 429)	UK (*n* = 134 301)	Belgium (*n* = 23 239)	France (*n* = 114 976)	Germany (*n* = 159 628)	Italy (*n* = 135 998)
Peptic ulcer disease	632 (2.3)	4211 (2.8)	3181 (1.5)	267 (0.2)	69 (0.1)	232 (0.2)	489 (2.1)	2900 (2.5)	1999 (1.3)	208 (0.2)
Mild liver disease	279 (1.0)	3322 (2.2)	13 857 (6.4)	6933 (4.1)	794 (0.9)	177 (0.1)	206 (0.9)	2346 (2.0)	9682 (6.1)	5239 (3.9)
Diabetes without chronic complications	7117 (25.8)	36 916 (24.8)	51 821 (23.9)	31 467 (18.6)	21 800 (24.9)	24 848 (18.50)	5468 (23.5)	24 579 (21.4)	34 023 (21.3)	22 728 (16.7)
Diabetes with chronic complications	356 (1.3)	2007 (1.3)	23 267 (10.7)	2481 (1.5)	455 (0.5)	8011 (6.0)	222 (1.0)	1060 (0.9)	13 608 (8.5)	1429 (1.1)
Hemiplegia or paraplegia	61 (0.2)	742 (0.5)	3734 (1.7)	177 (0.1)	83 (0.1)	13 (0.0)	51 (0.2)	496 (0.4)	2013 (1.3)	131 (0.1)
Renal disease	593 (2.2)	5718 (3.8)	24 746 (11.4)	4094 (2.4)	3307 (3.8)	2675 (2.0)	431 (1.9)	3568 (3.1)	14 841 (9.3)	2538 (1.9)
Any malignancy, including leukaemia and lymphoma	1271 (4.6)	20 057 (13.5)	12 783 (5.9)	23 786 (14.1)	3563 (4.1)	4576 (3.4)	1002 (4.3)	14 997 (13.0)	8724 (5.5)	17 910 (13.2)
Moderate or severe liver disease	20 (0.1)	525 (0.4)	617 (0.3)	234 (0.1)	86 (0.1)	74 (0.1)	15 (0.1)	373 (0.3)	357 (0.2)	159 (0.1)
Metastatic solid tumour	133 (0.5)	1214 (0.8)	3840 (1.8)	955 (0.6)	334 (0.4)	314 (0.2)	95 (0.4)	879 (0.8)	2450 (1.5)	596 (0.4)
AIDS/HIV	<10 (0.0)	33 (0.0)	22 (0.0)	20 (0.0)	<10 (0.0)	<10 (0.0)	<10 (0.0)	20 (0.0)	18 (0.0)	17 (0.0)

TABLE 2 (Continued)

	Polypharmacy patients (>5 ATC 3rd level classes)							
	5–9 drugs		≥10 drugs					
	Spain (*n* = 68 792)	UK (*n* = 119 123)	Belgium (*n* = 4311)	France (*n* = 34 113)	Germany (*n* = 57 467)	Italy (*n* = 32 729)	Spain (*n* = 18 737)	UK (*n* = 15 178)
Age at index date (years)								
Mean (SD)	76.8 (7.85)	77.2 (7.8)	76.2 (7.14)	76.8 (7.48)	79.0 (7.6)	79.1 (7.36)	78.6 (7.45)	77.2 (7.8)
Median [Q1 – Q3]	76 [70–83]	76 [71–83]	75 [70–81]	76 [71–83]	79 [74–84]	79 [73–84]	78 [73–84]	77 [71–83]
Missing (n)	69 (0.1)	–	<10 (0.1)	<10 (0.0)	–	36 (0.1)	10 (0.1)	–
Age at index (years) – group								
n	68 723	119 123	4308	34 104	57 467	32 693	18 672	15 178
[65;74]	30 715 (44.7)	50 096 (42.1)	1974 (45.8)	14 611 (42.8)	16 381 (28.5)	9546 (29.2)	6121 (32.9)	6222 (41.0)
[75;84]	24 783 (36.1)	45 485 (38.2)	1720 (39.9)	13 403 (39.3)	27 982 (48.7)	14 994 (45.9)	8054 (43.2)	5991 (39.5)
[85;89]	8466 (12.3)	14 554 (12.2)	463 (10.7)	4379 (12.8)	8552 (14.9)	5421 (16.6)	3081 (16.5)	1905 (12.6)
≥90 years	4756 (6.9)	8988 (7.6)	151 (3.5)	1711 (5.0)	4552 (7.9)	2732 (8.4)	1371 (7.4)	1060 (7.0)
Missing (*n*)	69	–	<10	<10	–	36	10	–

TABLE 2 (Continued)

	Polypharmacy patients (>5 ATC 3rd level classes)							
	5–9 drugs		≥10 drugs					
	Spain (n = 68 792)	UK (n = 119 123)	Belgium (n = 4311)	France (n = 34 113)	Germany (n = 57 467)	Italy (n = 32 729)	Spain (n = 18 737)	UK (n = 15 178)
Gender								
n	68 792	119 123	4311	34 113	57 467	32 726	18 637	15 178
Male	29 200 (42.4)	57 111 (47.9)	1760 (40.8)	14 656 (43.0)	23 075 (40.2)	13 102 (40.0)	7689 (41.3)	7082 (46.7)
Female	39 592 (57.6)	62 012 (52.1)	2551 (59.2)	19 457 (57.0)	34 392 (59.8)	19 624 (60.0)	10 948 (58.7)	8096 (53.3)
Missing (*n*)	–	–	–	–	–	<10	–	–
Charlson Comorbidity Index								
Median [Q1 – Q3]	0 [0–1]	0 [0–1]	1 [0–2]	1 [0–2]	2 [1–4]	1 [0–2]	1 [0–1]	0 [0–1]
Charlson Comorbidity Index – group								
0	50 111 (72.8)	84 055 (70.6)	1802 (41.8)	15 797 (46.3)	12 862 (22.4)	12 889 (39.4)	9691 (52.0)	8217 54.1)
1–3	18 125 (26.4)	34 182 28.7)	2321 (53.8)	16 473 (48.3)	29 676 (51.6)	17 245 (52.7)	8471 (45.5)	6736 (44.4)
≥ 4	556 (0.8)	886 (0.8)	188 (4.4)	1843 (5.4)	14 929 (26.0)	2595 (7.9)	475 (2.5)	225 (1.5)
Charlson comorbidity category								
Myocardial infarction	1490 (2.2)	1041 (0.9)	204 (4.7)	2227 (6.5)	3675 (6.4)	1099 (3.4)	650 (3.5)	222 (1.5)
Congestive heart failure	1154 (1.7)	1733 (1.5)	724 (16.8)	3048 (8.9)	13 142 (22.9)	5556 (17.0)	1058 (5.7)	535 (3.5)
Peripheral vascular disease	1942 (2.8)	785 (0.7)	81 (1.9)	3662 (10.7)	8173 (14.2)	3351 (10.2)	1007 (5.4)	157 (1.0)
Cerebrovascular disease	5148 (7.5)	1817 (1.5)	430 (10.0)	5067 (14.9)	8877 (15.4)	5557 (17.0)	2100 (11.3)	328 (2.2)
Dementia	3254 (4.7)	5748 (4.8)	144 (3.3)	580 (1.7)	5014 (8.7)	1401 (4.3)	1298 (7.0)	954 (6.3)
Chronic pulmonary disease	9585 (13.9)	17 060 (14.3)	1688 (39.2)	10 553 (30.9)	14 875 (25.9)	8867 (27.1)	5049 (27.1)	3754 (24.7)
Rheumatologic disease	1320 (1.9)	2292 (1.9)	142 (3.3)	1141 (3.3)	2803 (4.9)	2069 (6.3)	693 (3.7)	512 (3.4)
Peptic ulcer disease	59 (0.1)	198 (0.2)	143 (3.3)	1311 (3.8)	1182 (2.1)	59 (0.2)	10 (0.1)	34 (0.2)
Mild liver disease	588 (0.9)	143 (0.1)	73 (1.7)	976 (2.9)	4175 (7.3)	1694 (5.2)	206 (1.1)	34 (0.2)
Diabetes without chronic complications	14 991 (21.8)	21 032 (17.6)	1649 (38.3)	12 337 (36.2)	17 798 (31.0)	8739 (26.7)	6809 (36.5)	3816 (25.1)
Diabetes with chronic complications	218 (0.3)	6252 (5.3)	134 (3.1)	947 (2.8)	9659 (16.8)	1052 (3.2)	273 (1.3)	1759 (11.6)
Hemiplegia or paraplegia	62 (0.1)	11 (0.0)	10 (0.2)	246 (0.7)	1721 (3.0)	46 (0.1)	21 (0.1)	<10 (0.0)
Renal disease	1910 (2.8)	2255 (1.9)	162 (3.8)	2150 (6.3)	9905 (17.2)	1556 (4.8)	1397 (7.5)	420 (2.8)
Any malignancy, including leukaemia and lymphoma	2502 (3.6)	4038 (3.4)	269 (6.2)	5060 (14.8)	4059 (7.1)	5876 (18.0)	1061 (5.7)	538 (3.5)
Moderate or severe liver disease	62 (0.1)	56 (0.1)	<10 (0.1)	152 (0.4)	260 (0.5)	75 (0.2)	24 (0.1)	18 (0.1)
Metastatic solid tumour	211 (0.3)	278 (0.2)	38 (0.9)	335 (1.0)	1390 (2.4)	359 (1.1)	123 (0.7)	36 (0.2)
AIDS/HIV	<10 (0.0)	<10 (0.0)	–	13 (0.0)	<10 (0.0)	<10 (0.0)	–	–

Figure 2 illustrates the most common medicines (described at ATC level 5) prescribed in our polypharmacy population across the six countries. The most common groupings, prescribed to approximately a third to a half of patients, comprised gastrointestinal and cardiovascular medicines, i.e *peptic ulcer treatment* (A02B); *antithrombotic agents* (B01A); *beta blocking agents* (C07A); and *lipid lowering agents* (C10A). Variation across the six countries was most notable for *other analgesics and antipyretics* (N02B) and *anxiolytics* (N05B). Notably three of the four medications that were examined—*opioids* (N02A), *proton pump inhibitors* (A02BC) and *benzodiazepine derivatives* (N05BA)—are captured within these most common medicine groupings.

3.3 | Exploratory outcome

Figure 3 illustrates the number and proportion of patients prescribed with selected medications (ATC Level 5) in the polypharmacy population. Opioid prescribing ranged from 11.5% (France) to 27.5% (Spain) with prescribing in Germany, Italy, Belgium and the UK approximately 15–20%. Prescribing of PPIs was highest across all six countries with almost half of all patients receiving a PPI, ranging from 42.3% (Germany) to 65.5% (Spain). Benzodiazepine prescribing showed a marked variation between countries, from 2.7% (UK) to 34.9% (Spain). Within each country antipsychotics were the lowest of the four selected medication classes recorded (with the exception of the UK where benzodiazepine prescribing was lower) ranging from 2.1% (France) to 10.8% (Spain).

4 | DISCUSSION

4.1 | Summary of main findings

In four of the six countries studied, more than half of older people were prescribed five or more medications within 6 months by their general practitioner. The most common comorbidities—assessed with the CCI—in the patients on polypharmacy were chronic pulmonary disease and diabetes. PPIs were among the most frequently used medications in the polypharmacy patients in all countries. We found remarkable differences in prescribing of the four selected medications like benzodiazepines between the countries. Most likely those differences are due to country-specific healthcare delivery pathways, reimbursement status of medicines and differences in documentation practice of prescriptions (Table S2).

4.2 | Comparison with existing literature

The high prevalence of polypharmacy in older people that we found in four of the six countries is in line with the prevalence reported in recent systematic reviews.[5,6,37] Slightly lower prevalences have been reported in a number of studies using databases similar to this study, in individual European countries, including France[38] and Germany.[39] Some of the observed differences may be due to the fact that we counted the presence of distinct drug classes at the level 3 of the ATC system over 6 months. To prevent overestimating polypharmacy, we took two measures. First, we excluded drug classes

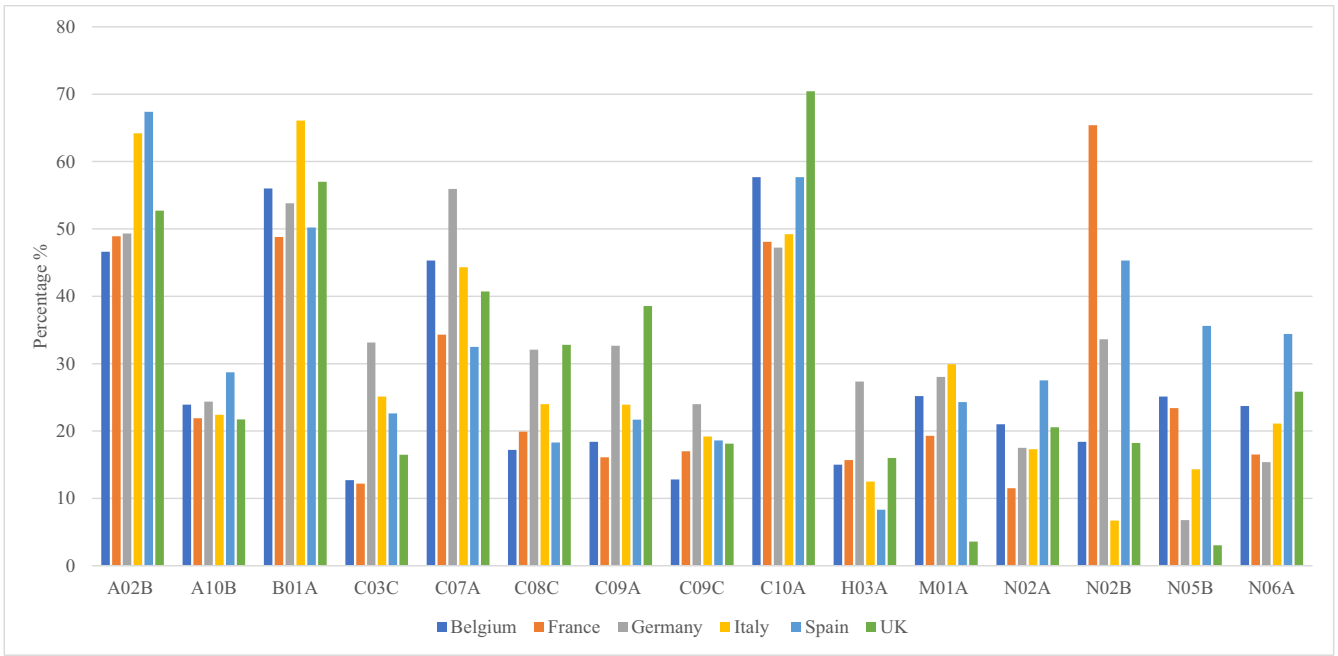


FIGURE 2 Polypharmacy population: percentage of the population for the 15 most prescribed drug classes in each country (ATC level 5).

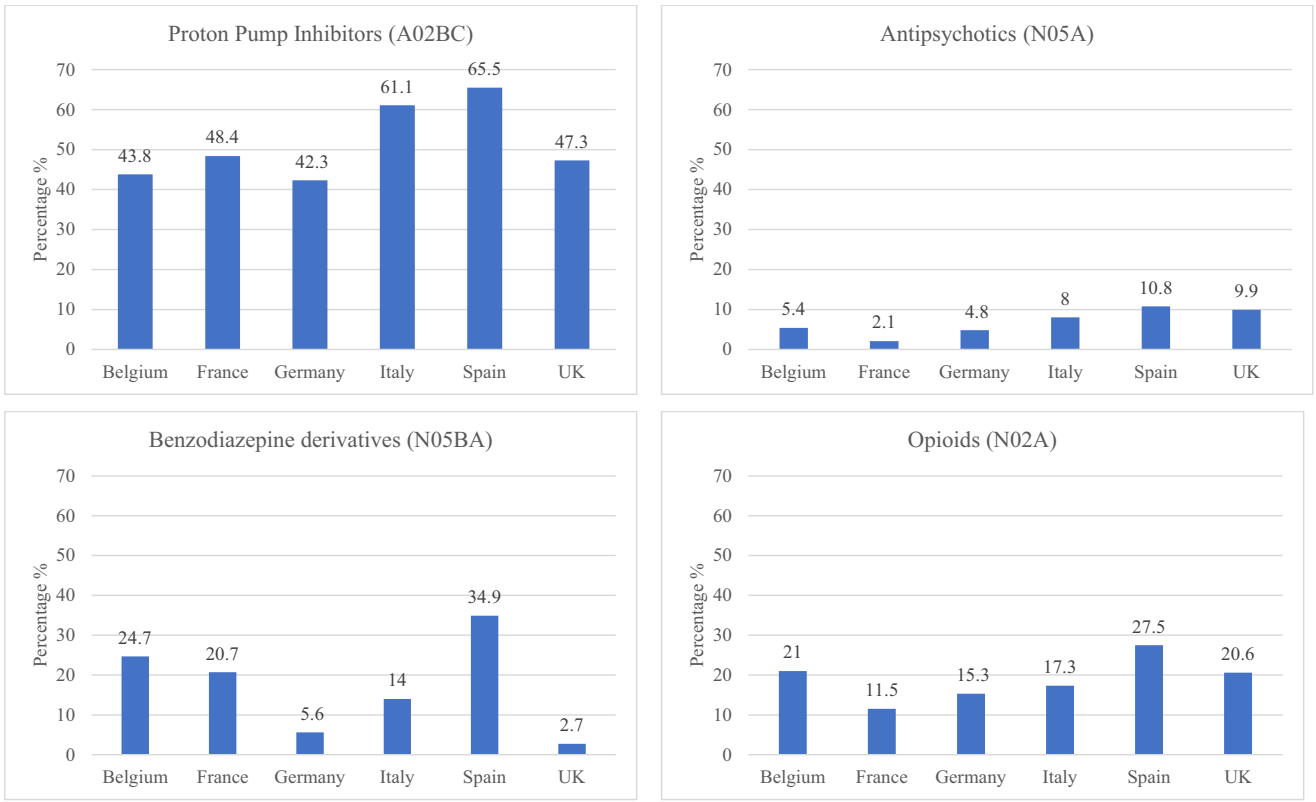


FIGURE 3 Polypharmacy population: percentage of use of the four selected medication classes.

intended for short-term use such as anti-infectives, in line with the notion of polypharmacy refering to long-term use of medication.[10] Second, our method ensured that taking two different antihypertensives from the same pharmacological class consecutively was not counted as two different drugs. Nevertheless, we may have overestimated the prevalences of polypharmacy if medications of different classes were used consecutively rather than concurrently. Furthermore, we did not assess the chronicity of the medication use. There are also studies reporting considerably lower rates of prevalence of polypharmacy. Midão et al.[4] observed polypharmacy in only about 30% of older individuals across 17 European countries. Their data were based on self-reporting of the number of medications taken on a particular day, i.e. they determined a point prevalence estimate in contrast to our approach using a period prevalence. Besides the expected difference between the point and period prevalence approach, a lower prevalence in medication use may be due to individuals only reporting medication actually taken, recall bias and study population selection criteria.[27] In addition, older adults with a large number of comorbidities may have been excluded from this study. As we have already highlighted, comparisons with other studies are hampered by the methodology such as the definition of polypharmacy and the database used. The study methods to assess polypharmacy impact on the results and therefore have to be carefully considered when comparing different studies.

In two countries, Belgium and the UK, we found a strikingly low prevalence of polypharmacy, 38.2% and 22.8%, respectively, compared to the other countries. In both countries, initiatives have been reported to manage medication use in older adults,[9,40] but those are also known for the other countries like Germany[41] and Italy.[42] We have already discussed a number of methodological factors which have an impact on the prevalence of polypharmacy. Since we used the same methods across all the countries, those should be less relevant to explain the relatively low prevalence in Belgium and the UK. The differences and similarities in country health systems and GP documentation practices as presented in Table S2 also do not provide an obvious explanation for our findings. This unexpected finding of our study needs to be further investigated by performing more cross-national studies comparing the prevalence of polypharmacy across European countries before being able to draw definite conclusions.

Proton pump inhibitors were among the most frequently used medications of the polypharmacy patients across all countries. Use may be even higher because of the availability of PPIs without prescription in all countries (Table S2). There is increasing concern about widespread use, in particular in the absence of a clear indication, because of adverse drug reactions with long-term use.[24,25] Drug use of antipsychotics was found to be relatively low in all six countries, but one has to bear in mind that these drugs are often prescribed by other specialists which we did not include in this study. The high proportion of polypharmacy patients being prescribed benzodiazepines in Spain, Belgium, France and Italy is worrying because of the many known negative effects, especially in older people.[22] We observed relatively low use in Germany and the UK. Given the possible

underrecording by GPs of benzodiazepines in Germany, this finding should be interpreted with caution (Table S2). Finally, between a fifth and a quarter of patients on polypharmacy were prescribed opioids. Undertreatment of pain as well as inappropriate use of opioids have been reported in older people.[26,43]

4.3 | Strengths

We performed a study across six European countries contributing to the large body of literature on polypharmacy in a unique way, as we used the same methods and definitions, applying a systematic approach outlined in a newly developed guideline to assess crossnational drug utilization.[32] We were able to include databases which are representative for primary care and reflect routine clinical practice in the participating countries. We included country-specific knowledge of the healthcare system, prescribing practices and policies to complement our prescribing data and systematically documented and reported these country health system characteristics with potential to influence determination of polypharmacy.[32] This approach gave valuable insight when interpreting the results. For example, the national prescribing practices of specialists to recognize possible underestimation of use for some drug classes like benzodiazepines. These findings highlight the importance of the good practice to systematically include national experts in crossnational studies and illustrates how this intelligence can be robustly collated and reported to support contextualization of the findings.

4.4 | Limitations

Firstly, we assessed polypharmacy on the basis of GPs' prescribing, thus underestimating for all countries the polypharmacy prevalence as prescriptions from other medical disciplines were not included and therefore not taken into account. As already highlighted within the scope of our study, because of the high volume of data due to the large number of patients and medication included, it was not possible to assess concurrent medication use sensu stricto and chronicity of medication use. This may have overestimated the prevalence of polypharmacy. Additionally, like all database-driven drug utilization studies, we were not able to ascertain medication consumption by patients. Furthermore, there were country-specific documentation practices which meant that probably some prescribing for nursing home patients, and for patients during home visits, may not have been recorded.

4.5 | Implications for practice and research

The high prevalence of polypharmacy, although already reported in other studies, again emphasizes the urgent need to develop, evaluate and implement strategies to manage polypharmacy to reduce medication-related harm. A central prerequisite for drug therapy safety is the availability of an up-to-date medication plan in the patient's own hands. Routine data, e.g. from sickness funds, which are made available to physicians, could reduce the information deficit regarding prescriptions from other physicians. Many different successful interventions for how to deal with inappropriate medication use in practice have been developed, for example how to deprescribe PPIs or benzodiazepines.[44,45] National guidelines present tools for better management of polypharmacy, for example in Germany.[41] National PIM lists also address the problem and raise awareness of the issue of unintended and uncontrolled polypharmacy.[21] In practice, regular medication reviews by multidisciplinary teams of health professionals using a patient-centred care approach seem to be useful for polypharmacy optimization, but most studies did not show effects on improved clinical and patient-reported outcomes.[46] Changes in practice should be complemented by using routine data as an efficient tool for surveillance and to monitor improvement strategies.[47,48] Finally, our study provides a good basis and a blueprint for more crossnational studies. We wish to stimulate performing more detailed drug utilization studies, comparing the quality of prescribing for polypharmacy and selected medications known for overuse among different countries (as well as among different geographical areas of the same country).

We have found a high prevalence of polypharmacy with more than half of the older population being prescribed ≥5 medications in 6 months by their GP in four of the six European countries. Whilst polypharmacy may be appropriate in many of the patients, worryingly high usage of potentially inappropriate medications such as PPIs and benzodiazepines supports all current efforts to improve polypharmacy management across Europe. We strongly recommend that when conducting crossnational drug utilization studies using databases that researchers systematically collate and document the health system practices and policies with the potential to impact the interpretation of findings.

AUTHOR CONTRIBUTIONS

MB, KT and PN conceptualized the study design. PN and LSJ supported data acquisition and data interpretation. YSAT, GFG, JT and JD contributed to data analysis. MB and KT drafted and revised the manuscript. EP, LC, IS, SMS and MS contributed to data interpretation and reviewed the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from IQVIA but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly

available. Data are, however, available from the authors upon reasonable request and with permission of IQVIA.

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REFERENCES

1. Eurostat. *Population structure and ageing—statistics explained*. Accessed November 23, 2021. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing#The_share_of_elderly_people_continues_to_increase
2. Leelakanok N, Holcombe AL, Lund BC, Gu X, Schweizer ML. Association between polypharmacy and death: a systematic review and meta-analysis. *J Am Pharm Assoc*. 2003;2017(57):729-738.e10.
3. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2
4. Midão L, Giardini A, Menditto E, Kardas P, Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch Gerontol Geriatr*. 2018;78:213-220. doi:10.1016/j.archger.2018.06.018
5. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *Eur Geriatr Med*. 2021;12(3):443-452. doi:10.1007/s41999-021-00479-3
6. Elmståhl S, Linder H, Linder E. Polypharmacy and inappropriate drug use among older people—a systematic review. *Healthy Aging Clin Care Elder*. 2013;5-6.
7. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. *Ther AdvDrug Saf*. 2020;11:11. doi:10.1177/2042098620933741
8. Midão L, Brochado P, Almada M, Duarte M, Paúl C, Costa E. Frailty status and polypharmacy predict all-cause mortality in community dwelling older adults in Europe. *Int J Environ Res Public Health*. 2021;18(7):3580. doi:10.3390/ijerph18073580
9. Mair A, Fernandez-Llimos F, Alonso A, et al. *Polypharmacy management by 2030: a patient safety challenge*. SIMPATHY Consortium; 2017.
10. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230. doi:10.1186/s12877-017-0621-2
11. Sirois C, Tannenbaum C, Gagnon M-E, Milhomme D, Émond V. Monitoring polypharmacy at the population level entails complex decisions: results of a survey of experts in geriatrics and pharmacotherapy. *Drugs Therapy Perspectives*. 2016;32(6):257-264. doi:10.1007/s40267-016-0299-0
12. Ivanova I, Elseviers M, Wettermark B, Schmidt Mende K, Vander Stichele R, Christiaens T. Electronic assessment of cardiovascular potentially inappropriate medications in an administrative population database. *Basic Clin Pharmacol Toxicol*. 2019;124(1):62-73. doi:10.1111/bcpt.13095
13. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse outcomes of polypharmacy in older people: systematic review of reviews. *J Am Med Dir Assoc*. 2020;21(2):181-187. doi:10.1016/j.jamda.2019.10.022
14. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol*. 71(12):1415-1427. doi:10.1007/s00228-015-1954-4
15. Meid AD, Quinzler R, Groll A, et al. Longitudinal evaluation of medication underuse in older outpatients and its association with quality of life. *Eur J Clin Pharmacol*. 2016;72(7):877-885. doi:10.1007/s00228-016-2047-8
16. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opin Drug Saf*. 2018;17(12):1185-1196. doi:10.1080/14740338.2018.1546841
17. Swart F, Bianchi G, Lenzi J, et al. Risk of hospitalization from drug-drug interactions in the elderly: real-world evidence in a large administrative database. *Aging*. 2020;12(19):19711-19739. doi:10.18632/aging.104018
18. Burt J, Elmore N, Campbell SM, Rodgers S, Avery AJ, Payne RA. Developing a measure of polypharmacy appropriateness in primary care: systematic review and expert consensus study. *BMC Med*. 2018;16(1):91. doi:10.1186/s12916-018-1078-7
19. Ivanova I, Elseviers M, Wauters M, Christiaens T, Vander SR. European repository of explicit criteria of potentially inappropriate medications in old age. *Geriatr Gerontol Int*. 2018;18(8):1293-1297. doi:10.1111/ggi.13331
20. Renom-Guiteras A, Thürmann PA, Miralles R, et al. Potentially inappropriate medication among people with dementia in eight European countries. *Age Ageing*. 2018;47(1):68-74. doi:10.1093/ageing/afx147
21. Schubert I, Küpper-Nybelen J, Ihle P, Thürmann P. Prescribing potentially inappropriate medication (PIM) in Germany's elderly as indicated by the PRISCUS list. An analysis based on regional claims data. *Pharmacoepidemiol Drug Saf*. 2013;22(7):719-727. doi:10.1002/pds.3429
22. Manias E, Kabir MZ, Maier AB. Inappropriate medications and physical function: a systematic review. *Ther Adv Drug Saf*. 2021;12:1-24.
23. Malakouti SK, Javan-Noughabi J, Yousefzadeh N, et al. A systematic review of potentially inappropriate medications use and related costs among the elderly. *Value Health Reg Issues*. 2021;25:172-179. doi:10.1016/j.vhri.2021.05.003
24. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Ther Adv Drug Saf*. 2017;8(9):273-297. doi:10.1177/2042098617715381
25. Ben-Eltriki M, Green CJ, Maclure M, Musini V, Bassett KL, Wright JM. Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. *Pharmacol Res Perspect*. 2020;8.
26. Dufort A, Samaan Z. Problematic opioid use among older adults: epidemiology, adverse outcomes and treatment considerations. *Drugs Aging*. 2021;38(12):1043-1053. doi:10.1007/s40266-021-00893-z
27. Elseviers M, Wettermark B, Almarsdóttir AB, et al. (Eds). *Drug utilization research: methods and applications*. 1st ed; 2016. doi:10.1002/9781118949740
28. Giovannini S, van der Roest HG, Carfi A, et al. Polypharmacy in home care in Europe: cross-sectional data from the IBenC study. *Drugs Aging*. 2018;35(2):145-152. doi:10.1007/s40266-018-0521-y
29. 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(6):698-704. doi:10.1093/gerona/glr233
30. Burato S, Leonardi L, Antonazzo IC, et al. Comparing the prevalence of polypharmacy and potential drug-drug interactions in nursing homes and in the community dwelling elderly of Emilia Romagna region. *Front Pharmacol*. 2021;11:11. doi:10.3389/fphar.2020.624888
31. Taxis K, Kochen S, Wouters H, et al. Cross-national comparison of medication use in Australian and Dutch nursing homes. *Age Ageing*. 2017;46(2):320-323. doi:10.1093/ageing/afw218
32. Santa-Ana-Tellez Y, Ibanez L, Duran C, et al. Good practice guidelines for designing, conducting, analyzing and reporting cross-national comparison drug utilization studies. *Pharmacoepidemiol Drug Saf*. 2016;25(suppl 3:630.
33. READ. *Coded clinical terms*. Accessed March 2, 2022. https://www.datadictionary.nhs.uk/supporting_information/read_coded_clinical_terms.html
34. WHOCC. - *ATC/DDD index*. Accessed March 2, 2022. https://www.whocc.no/atc_ddd_index/

35. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433
36. *European Drug Utilization Research Network (EuroDURG)*. https://www.pharmacoepi.org/eurodurg/
37. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. *Ther Adv Drug Saf*. 2020;11:1-10. doi:10.1177/2042098620933741
38. Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population. *Eur J Clin Pharmacol*. 2017;73(9):1165-1172. doi:10.1007/s00228-017-2276-5
39. Moßhammer D, Haumann H, Mörike K, Joos S. Polypharmacy—an upward trend with unpredictable effects. *Dtsch Arztebl Int*. 2016;113(38):627-633. doi:10.3238/arztebl.2016.0627
40. Blum MR, Sallevelt BTGM, Spinewine A, et al. Optimizing therapy to prevent avoidable hospital admissions in multimorbid older adults (OPERAM): cluster randomised controlled trial. *BMJ*. 2021;374:n1585.
41. AWMF. *Detail*. Accessed March 4, 2022. https://www.awmf.org/leitlinien/detail/ll/053-043.html
42. Onder G, Liborio Vetrano D, Palmer K, et al. Italian guidelines on management of persons with multimorbidity and polypharmacy. *Aging Clin Exp Res*. 2022;34(5):989-996. doi:10.1007/s40520-022-02094-z
43. Mikelyte R, Abrahamson V, Hill E, Wilson PM. Factors influencing trends in opioid prescribing for older people: a scoping review. *Prim Health Care Res Dev*. 2020;21.
44. Wilsdon TD, Hendrix I, Thynne TRJ, Mangoni AA. Effectiveness of interventions to deprescribe inappropriate proton pump inhibitors in older adults. *Drugs Aging*. 2017;34(4):265-287. doi:10.1007/s40266-017-0442-1
45. Airagnes G, Pelissolo A, Lavallée M, Flament M, Limosin F. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. *Curr Psychiatry Rep*. 2016;18(10):89. doi:10.1007/s11920-016-0727-9
46. Anderson LJ, Schnipper JL, Nuckols TK, et al. A systematic overview of systematic reviews evaluating interventions addressing polypharmacy. *Am J Health-Syst Pharm*. 2019;76(21):1777-1787. doi:10.1093/ajhp/zxz196
47. Bennie M, Malcolm W, McTaggart S, Mueller T. Improving prescribing through big data approaches—ten years of the Scottish prescribing information system. *Br J Clin Pharmacol*. 2020;86(2):250-257. doi:10.1111/bcp.14184
48. Guthrie B, Kavanagh K, Robertson C, et al. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. *BMJ*. 2016;354:i4079. doi:10.1136/bmj.i4079

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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