Polypharmacy in the general population of a Northern Italian area: analysis of administrative data

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Abstract

Introduction. The aim of this study was to estimate the prevalence and assess patient-related determinants of polypharmacy in the general population of the Italian area around Udine.

Materials and methods. A retrospective cohort study was conducted using administrative databases: drug prescriptions, hospital discharges, ambulatory care prescriptions, exemptions from medical charges. Various definitions of polypharmacy were adopted (coprescription of multiple medications, use of multiple medications for overlapping time periods). The role of patient's characteristics on polypharmacy was assessed through regression analyses.

Results. In 2017, 63.7% of the general population received at least one drug prescription. 25 218 persons were co-prescribed \geq 5 medications at least once. The prevalence of co-prescriptions among persons \geq 65 years was 31.7%. 20 793 persons used \geq 60 DDDs of \geq 5 medications. The prevalence of all these phenomena was much higher in the elderly than in children and adults. The number of comorbidities significantly affected all types of polypharmacy.

Conclusions. In this area, the prevalence of polypharmacy is high, particularly among the elderly. Age and comorbidities significantly affect the risk. Further research will aim at evaluating the health effects and appropriateness of polyphamacy.

INTRODUCTION

As a consequence of multimorbidity, which is common among older persons and whose frequency is expected to rise because of population ageing [1, 2], the use of multiple medicines is widespread. For example, a prevalence survey in 17 European countries reported that from 26.3 to 39.9% of the population \geq 65 years of age responded that they take at least five different drugs on a typical day, including prescribed medication, overthe-counter medications, and dietary supplements [3].

The use of multiple medications by a patient, known as polypharmacy, may be necessary in many cases; nonetheless, it is associated with both adverse outcomes on the patients [4], economic costs for society [5, 6], and, in the primary care setting, increased medication errors [7].

Despite the relevance of this phenomenon for all the above-mentioned issues, a recent systematic review highlighted that there is no uniform definition of polypharmacy [8]: the analysis of more than 100 articles revealed that there were a total of 138 definitions, 80.4% of which were numerical only and an additional 10.7% also specified either a duration of therapy or healthcare setting, the remaining being descriptive definitions. The most common definition, used by almost half of the articles, was numerical (five or more medications daily) [8]. Among descriptive definitions, some addressed coprescribing or simultaneous use [8].

A study conducted in Rome from health administrative databases confirmed that polypharmacy is a relevant issue in Italy, related to age and comorbidities; the study also showed that prevalence estimates changed using different algorithms [9].

The objective of this research was to estimate the prevalence and to assess patient-related determinants of polypharmacy in the Northeastern Italian area served by the Azienda Sanitaria Universitaria Integrata di Udine (ASUIUD), 251 838 inhabitants as of January 1, 2017, using the administrative health databases of ASUIUD.

METHODS

This retrospective cohort study was based on the health administrative data of ASUIUD. In particular,

Key words

- polypharmacy
- drug prescriptions
- administrative databases
- cohort study Italy

the drug prescription database, the hospital discharge database, the ambulatory care prescriptions database, and the database of exemptions from medical charges, which includes patients who receive free medications or outpatient care because of certified chronic conditions defined by the Italian Ministry of Health and which may help identifying patients with a certain disease since each disease or group of diseases is associated with a specific national code [10, 11]. The databases are completely anonymous, nonetheless, they can be linked with each other at the individual patient level through a stochastic key which is univocally attributed to each subject. In-hospital medications were not included in this analysis since medications administered during hospital stay are not recorded electronically at the individual level.

All the analyses were referred to the year 2017. Different definitions of polypharmacy were adopted: 1) prescriptions of ≥ 5 different medications (i.e., different 7-digit Anatomical Therapeutic Chemical (ATC) codes [12]) on exactly the same date (i.e., "co-prescriptions"); 2) use of ≥ 5 different medications for ≥ 60 defined daily doses (DDDs) in the year; and 3) use of ≥ 5 different medications with > 30, >60, and > 90 overlapping days of theoretical medication coverage in the year, where medication coverage was estimated adding the prescribed DDDs to the date of medication retrieval from the pharmacy. The analyses were stratified by sex and age category (0-14 years, pediatric; 15-64, adult; 65-79, younger elderly; ≥ 80 , older elderly).

To assess the influence of comorbidities on polypharmacy, the number of different types of comorbidity per patient was assessed, applying algorithms developed by the Italian Local Health Agency of Brescia [13] to the health administrative data of ASUIUD (hospital discharge records, medication prescriptions, ambulatory care prescriptions, and exemptions from medical charges). Comorbidity types identified by the algorithms include chronic lung diseases, chronic heart failure, other cardiovascular diseases (including hypertension), diabetes mellitus, disorders of lipid metabolism, HIV, chronic kidney disease, rare diseases, cancer, digestive system diseases, autoimmune, endocrine diseases, neurological diseases, transplanted organs. The number of different comorbidities was assessed among patients with medication co-prescriptions. Among all patients with at least one drug prescription in 2017, the association between number of comorbidities and the likelihood of co-prescriptions of ≥ 5 drugs was assessed through multivariate logistic regression adjusting for the potentially confounding effect of patient's sex and age category. The association was assessed trough the odds ratio (OR) with 95% confidence intervals (95% CI).

In addition, the association between the number of comorbidities and both a) the number of different medication used for ≥ 60 DDDs in the year, among subjects using ≥ 60 DDDs of at least one medication, and b) the number of days of overlapping coverage among subjects with ≥ 5 medications with at least one day of overlap, were assessed through two linear regression models, also adjusting for the potentially confounding effect of patient's sex and age category. The associations were expressed by the beta coefficients; results with p-value < 0.05 were considered statistically significant.

Finally, to investigate other characteristics of the population potentially associated with polyphamacy, we assessed the proportion of subjects exempt from medical charges due to low family income (evaluated through an indicator of equivalent economic situation called ISEE) among those fulfilling the 3 above-listed definitions of polypharmacy.

All the analyses of the present study were conducted using SAS v9.4 (SAS Institute Inc. Cary, NC, USA).

Compliance with ethical standards

Since this analysis was based on anonymous administrative data, patient informed consent could not be obtained and Ethical Committee approval was not required in Italy.

RESULTS

In 2017. 3 105 481 prescriptions were retrieved from the prescription database. Of all subjects living in the ASUIUD area, 160 465 (63.7%) received \geq 1 medication prescription in 2017: 55.8% were females; 8.5% were children, 54.5% adults, 25.0% younger elderly, and 10.9% older elderly. In the year of study, 25 218 patients received ≥ 1 co-prescription of ≥ 5 different medications (10.0% of the population), for a total of 82 044 episodes of co-prescription of ≥ 5 medications (polypharmacy *definition 1*). As shown in *Table 1*, the prevalence of coprescriptions is much higher in the elderly than among adults. Overall, the proportion of population ≥ 65 years of age who were co-prescribed ≥ 5 medications at least one in 2017 was 31.7%. The monthly distribution of the number of co-prescriptions of ≥ 5 medications by age category did not show any specific pattern (Figure 1). The 5 most commonly groups of medications found in such co-prescriptions (not necessarily in the same coprescription) by age group are shown in *Table 2*. The observed different co-prescription patterns were 66 206, with frequency ranging from 1 to 119 cases (available as Supplementary materials). Of the 5 most common coprescription patterns, all but one included one drug for peptic ulcer and gastro-esophageal reflux disease, one antithrombotic agent, and three medications acting on the cardiovascular system, as follows:

- A02BC02 + B01AC06 + C07AB07 + C09AA05 + C10AA05 (N=119)

 $\begin{array}{l} - \ A02BC02 \ + \ B01AC06 \ + \ C07AB02 \ + \ C09AA05 \ + \\ C10AA05 \ (N{=}76) \end{array}$

- A02BC02 + B01AC06 + C03CA01 + C07AB07 + C09AA05 (N=30)

- B01AC06 + C07AB07 + C09AA05 + C10AA05 + C10AX09 (N=25)

- A02BC02 + B01AC06 + C08CA01 + C09AA05 + C10AA05 (N=24)

In 2017, 20 793 patients (8.2%) used \geq 60 DDDs of \geq 5 medications (*polypharmacy definition* 2): 1 in the age group 0-14 (0.003%), 3407 in the age group 15-64 (2.2%), 10 752 in the group 65-79 (24.1%), and 6633 in the group \geq 80 (34.3%). The median number of comorbidities for patients with co-prescriptions of \geq 5 medications was 0 among children (interquartile range 0-2)

Та	h	e	1	

Prevalence of co-prescriptions of \geq 5 medications in the population of the Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017

Sex	Age category	N of patients with co-prescriptions	Population	Prevalence (%)	Total N of co-prescriptions
F	0-14	6	15 222	0.04	6
F	15-64	2369	79 510	2.98	5926
F	65-79	6047	24 276	24.91	18 825
F	≥ 80	5080	12 804	39.68	17 097
Μ	0-14	6	15 693	0.04	6
Μ	15-64	2551	77 454	3.29	7891
Μ	65-79	6281	20 334	30.89	22 288
Μ	≥ 80	2878	6538	44.02	10 005
Total		25 218	25 1831	10.01	82 044

and 3 in all other age groups (interquartile range 2-4).

The number of overlapping days covered with ≥ 5 different medications (*polypharmacy definition 3*) is illustrated in *Table 3*. More than 5% of the whole population had ≥ 5 medications overlapping for > 90 days in a year. The prevalence of such an important overlap was much higher in the elderly groups. The prevalence of overlaps of ≥ 5 medications was slightly more frequent among males (*Table 4*).

Of all subjects living in the ASUIUD area, those

with at least one chronic condition were 2.5% in the age group 0-14, 28.3% in the age group 15-64, 80.8% in the age group 65-79, and 99.3% among persons \geq 80 years of age. Among children, there was no one with \geq 5 comorbidities; on the other hand, the coexistence of 5 or more long-term conditions was found in 0.3% of the population 15-64, in 3.7% of those 65-79, and in 5.0% of those \geq 80 years of age. *Table 5* shows the association of the number of comorbidities with the various forms of polytherapy. Among subjects with at



Figure 1

Number of co-prescriptions of \geq 5 medications by month and age category, Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017.

Table 2

The five most common groups of medications found in co-prescriptions of \geq 5 medications by age category, Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017

Age category	4-digit ATC code	Medication group	N of co-prescriptions	% of all co-prescriptions
0-14ª	R03A	adrenergics, inhalants	10	83.3
	H02A	corticosteroids of systemic use	9	75.0
	R03B	drugs for obstructive airway diseases, inhalants, other than adrenergics	9	75.0
	J01C	penicillins	6	50.0
15-64	C10A	lipid modifying agents	8580	62.1
	B01A	antithrombotic agents	8165	59.1
	A02B	drugs for peptic ulcer and gastro- esophageal reflux disease	7919	57.3
	C07A	beta blocking agents	6025	43.6
	A10B	blood glucose lowering drugs, excl. insulins	4264	30.9
65-79	B01A	antithrombotic agents	27 611	67.2%
	C10A	lipid modifying agents	24 550	59.7%
	A02B	drugs for peptic ulcer and gastro- esophageal reflux disease	23 074	56.1%
	C07A	beta blocking agents	18 528	45.1%
	A10B	blood glucose lowering drugs, excl. insulins	12 784	31.1%
≥ 80	B01A	antithrombotic agents	19 106	70.5%
	A02B	drugs for peptic ulcer and gastro- esophageal reflux disease	16 565	61.1%
	C07A	beta blocking agents	11 872	43.8%
	C10A	lipid modifying agents	10 730	39.6%
	C03C	high-ceiling diuretics	8809	32.5%

^aonly the first 4 medication groups are shown since several others were equally frequent

Table 3

Overlapping days covered with \geq 5 different medications in the population of the Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017

Overlap (days)			Ν				Pre	valence (%)	6)	
	00-14	15-64	65-79	≥ 80	Total	00-14	15-64	65-79	≥ 80	Total
≤ 30	91	6444	7320	3680	17535	0.29	4.11	16.41	19.03	6.96
31-60	7	1680	3198	2070	6955	0.02	1.07	7.17	10.70	2.76
61-90	2	955	2291	1504	4752	0.01	0.61	5.14	7.78	1.89
> 90	10	2384	7091	4244	13729	0.03	1.52	15.90	21.94	5.45

least one prescription in 2017, the likelihood of being co-prescribed \geq 5 medications increased by more than 3 times for each additional comorbidity. Among subjects with prescriptions of \geq 60 DDDs of at least one drug in the year, adjusting for the confounding effect of sex and age, a patient is likely to be prescribed \geq 60 DDDs of one additional medication for each additional comorbidity. Also, each additional comorbidity increases the average coverage with \geq 5 medications simultaneously by 27 days. Among all subjects with co-prescriptions of ≥ 5 medications (*polypharmacy definition 1*), no one was exempted from medical charges due to low income in the age group 0-14, 1.6% had such an exemption in the group 15-65, 0.1% in the group 65-79, and < 0.1% in the group ≥ 80 years of age. Among those using ≥ 5 different medications for ≥ 60 DDDs in the year (*polypharmacy definition 2*), no one had exemptions due to low family income in the age group 0-14, 1.2% had such an exemption in the group 15-64, 0.1% in the group

Table 4

Prevalence of overlapping days covered with ≥ 5 different medications in the population of the Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017, by sex

Overlap (days)		Female	s (% of pop	ulation)		Males (% of population)				
	0-14	15-64	65-79	≥ 80	Total	0-14	15-64	65-79	≥ 80	Total
≤ 30	0.18	4.72	17.84	19.80	8.08	0.41	3.48	14.70	17.51	5.74
31-60	0.03	1.06	7.05	10.36	2.95	0.02	1.08	7.31	11.36	2.56
61-90	0.01	0.51	4.65	7.44	1.88	0.01	0.71	5.71	8.44	1.89
> 90	0.03	1.08	12.01	19.32	4.75	0.03	1.97	20.53	27.07	6.23

65-79 and 0.1% in the group \geq 80 years of age. Among patients with an overlap of \geq 5 medications lasting > 30 days (from *polypharmacy definition 3*), the proportion of those with exemption from medical charges due to low family income was 0 among children, 1.4% among subjects 15-64, 0.1% among both subjects 65-79 and subjects \geq 80 years of age.

DISCUSSION

This research illustrated various prescriptive issues related to polypharmacy in the general population of a Northern Italian area using health administrative databases. These results are not affected by sampling error, selection bias, or recall bias. In fact, the data cover the entire population and are collected for administrative purposes in an objective way.

This research showed that polypharmacy is by far more common among the elderly, especially those \geq 80 years of age, than among adults, irrespective of the definition of polypharmacy. Not only are 31.7% of the elderly co-prescribed \geq 5 medications at least one in a year, but more than 15% of younger elderly and more than 20% of older elderly have an overlapping use of \geq 5 medications for more than 90 days in a year.

As expected, the medications that were most frequently involved in polypharmacy differed depending on the age group. Among children, medications were inhalants for obstructive airway disease, antibiotics and systemic corticosteroids; among adults and elderly patients, drugs for peptic ulcer and gastro-esophageal reflux disease, antithrombotic agents, antihypertensive medications, and lipid modifying agents were the most frequently co-prescribed.

In Italy, only few studies had previously been conducted on polypharmacy in the outpatient setting among the general population. One of those studies was conducted in the Italian Region Friuli Venezia Giulia [14], which includes our study area. That study, analvzing polypharmacy in the hospital, general practice, and long term care facility settings, showed a very high prevalence of polypharmacy in the elderly population, as high as 57.7% of patients being co-prescribed 5-9 drugs and 9.7% being prescribed 10 or more. However, such estimates were based on a one-week point-prevalence survey which might have not been representative of the general prescription habits either because of random error or because of systematic error due to the possible existence of seasonal variations, of bias in the selection participating GPs, or of bias in the selection of the surveyed patients.

Another study was conducted [15] in the Emilia-Romagna Region, based on the analysis of outpatient drug prescriptions. The proportion of elderly patients exposed to overlapping treatment with ≥ 5 medications for ≥ 1 day was 39.4%. The most frequent groups of drugs involved in polypharmacy in that study were the same that characterized polypharmacy in the elderly population of the area of Udine.

The European data based on data from the large Survey of Health, Ageing and Retirement in Europe

Table 5

Association between number of comorbidities and likelihood of co-prescription of \geq 5 medications among all subjects with at least one drug prescription, number of different medications with \geq 60 DDDs prescribed in one year among users of \geq 60 DDDs of at least one medication, and number of overlapping days of coverage with \geq 5 medications in one year among users of \geq 5 medications for at least one overlapping day in the Azienda Sanitaria Universitaria Integrata di Udine, Italy, 2017

	Co-prescription of ≥ 5 medications		N of medic with ≥ 60	ations DDDs	N of overlapping days of coverage with ≥ 5 medications		
Variable	OR	95CI	Beta coefficient	p-value	Beta coefficient	p-value	
Sex (F vs M)	0.75	0.73-0.78	-0.4144	< 0.0001	-21.38	< 0.0001	
Age (0-14 <i>vs</i> 15-64)	0.07	0.04-0.13	0.1258	0.0579	16.25	0.0579	
Age (65-79 vs 15-64)	2.70	2.29-2.82	0.6837	< 0.0001	10.71	0.0107	
Age (≥ 80 vs 15-64)	5.44	5.18-5.72	1.1888	< 0.0001	18.35	< 0.0001	
N of comorbidities (continuous)	3.44	3.39-3.50	1.1184	< 0.0001	27.42	< 0.0001	

(SHARE) project, Wave 6, found a prevalence of "use of at least 5 different drugs on a typical day" among participants \geq 65 years ranging from 26.3 to 39.9% [3]. In particular, in Italy the prevalence was 32.9% (95% CI: 32.3-33.5%), increasing with age category from 26.4% in subjects 65-74 to 45.1% in those \geq 85 years, and slightly higher in males (33.2%) than in females (32.5%). Number of chronic diseases was also associated with polypharmacy, as was in the present study.

Due to the absence of social and lifestyle information on the health administrative data of the ASUIUD, the association of those factors on the prevalence of polytherapy could not be assessed, as done in the European survey [3]. Among subjects with polypharmacy in the area of Udine, only a very small proportion had obtained an exemption from medical charges because of low family income: from little more than 1% in the population 15-64 years of age to less than 1% in the other age groups. However, these data should not be interpreted as a lack of association between low income and polypharmacy. In fact, not all economically disadvantaged citizens apply for such an exemption, especially if they are already entitled to exemptions because of chronic conditions or civil invalidity [10, 11]. On the other hand, the present study confirmed that prevalence of polypharmacy increases with increasing age and number of comorbidities, as shown also by Fano et al. [9], exposing patients who are fragile per se to the additional health risks from polypharmacy adverse effects and inappropriate prescribing [14]. These results indicate a situation which deserves interventions to address polypharmacy.

In addition, to better define the impact of polypharmacy on the population health of ASUIUD, a new cohort analysis of administrative data could be conducted to compare health outcomes of patients with and without polypharmacy or with different levels of polypharmacy, taking into account demographic factors and comorbidity level.

This study has some limitations, mainly due to the administrative nature of data. First, in the analyses of the long term use of multiple medications the DDDs were used to estimate duration, however the DDDs may not accurately reflect the actual prescribed doses [16], thus durations might have been misestimated in some cases. Then, as in all studies where the medication is not directly administered by the researcher, there is no guarantee that the drug has been assumed, or assumed as prescribed, by the individual. In addition, intake of overthe-counter medications could not be considered (now including frequently used medications such as treatments for gastroesophageal reflux disease), suggesting

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that the actual prevalence and severity of polypharmacy might be even greater than our estimates. Further, no information was available on socioeconomic characteristics of subjects other than exemptions from medical charges released because of low family income, thus leaving potential associations between social factors and polypharmacy unexplored. Finally, there are cases where co-prescribing multiple medications is appropriate, but this analysis did not assess appropriateness. The information on all the co-prescription patterns was available, but with over 80 000 co-prescription episodes in 2017, the observed different co-prescription patterns were more than 65 000 and an individual evaluation of each one was unfeasible.

Since the vast majority of the elderly population and almost 30% of the adult population in our area is affected by long-term conditions, with 5% of the population ≥ 80 having 5 or more comorbidities, polypharmacy may be the obvious consequence of the justified attempt to control chronic and often multiple diseases. Nonetheless, polypharmacy may be more harmful than beneficial for some patients, due to the possibility of drug-drug interactions [17], that may even result in toxicity or treatment failure [18, 19]. In addition, most clinical trials are conducted and most clinical guidelines are developed as if patients have a single condition; clinical recommendations generally do not consider the possible cumulative impact that multiple guidelines may have on a single patient [20]. Clinical guidelines taking into account multimorbidity and polypharmacy, then, are needed [21].

Despite not being able to assess appropriateness and the potential for drug-drug interactions, this study described the high prevalence of polypharmacy in the general population of ASUIUD, including children, highlighted classes of medications that are more commonly involved in co-prescribing, and identified that the elderly and patients affect by multimorbidity are particularly exposed to this phenomenon and the related health risks. Further research which will help clarify the actual impact of polypharmacy on health outcomes is feasible and will be conducted in this area. Information of GPs on this issue should also be kept as a priority.

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