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Potentially inappropriate medications and polypharmacy in the older population: A nationwide cross-sectional study in France in 2019

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Summary

Aim of the study. – To assess the prevalence of potentially inappropriate medications (PIMs) and polypharmacy in adults aged 75 years and over in France in 2019 based on data from the French health insurance claims database, at the national level and by region.

Methods. – We conducted a cross-sectional study in French adults aged 75 years or over in 2019. We assessed the prevalence of seventeen PIM criteria adapted from the 2015 Beers and STOPP lists, as well as cumulative polypharmacy. Polypharmacy (5 to 9 drugs) and hyper-polypharmacy (≥ 10 drugs) were defined as the average number of drugs dispensed per quarter. The regional analysis used the age- and sex-standardized prevalence.

Abbreviations: ADR, adverse drug reaction ; ATC, anatomical therapeutic chemical ; BZD, benzodiazepine ; CNS, central nervous system ; DCIR, French health insurance claims database ; EGB, Subsample of the French Health National Data System ; EHIS, European Health Interview Survey ; INSEE, French National Institute of Statistics and Economic Studies ; NSAID, non-steroidal anti-inflammatory drug ; PIM, potentially inappropriate medication ; SNDS, French Health National Data System ; STOPP, Screening Tool of Older People's Prescriptions.

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Results. — Of 6,707,897 older adults, 39.6% were exposed to at least one PIM in 2019, 46.7% were exposed to polypharmacy (5 to 9 drugs), and 25.2% to hyper-polypharmacy (≥ 10 drugs). Benzodiazepine PIMs were the most frequent (26.9%), followed by atropinic PIMs (8.3%), non-steroidal anti-inflammatory PIMs (7.8%), concomitant use of three or more central nervous system-active drugs (7.3%), and antihypertensive PIMs (6.0%). There was a gradient in the level of exposure to PIMs according to the level of polypharmacy for every PIM category. We observed regional variations in PIM prevalence, from 36.5% in Pays-de-la-Loire to 44.8% in Hauts-de-France in mainland France.

Conclusion. — These results show that PIMs concerned more than one in three older adults after age 75 years in France in 2019 and support the need to secure medication use in this population. The reasons for geographic variations in PIM prevalence should be investigated in further studies.

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Background

As multimorbidity increases with age, medication use is frequent in the older population [1–3]. The 2019 European Health Interview Survey (EHIS) has shown that 86% of Europeans aged 75 years or older had used prescription drugs in the prior two weeks [4,5]. This wide use of medications is accompanied by an increased risk of adverse drug reactions (ADRs), partly due to polypharmacy (concomitant use of multiple medications) and age-related changes in the pharmacokinetic and pharmacodynamic properties of drugs. A literature review estimated that ADRs are involved in 9% of hospitalizations in older adults [6]. In this context, specific attention must be paid to the appropriateness of medications in the older population, to reduce the overuse and misuse of medications, and in turn, the burden of ADRs.

Potentially inappropriate medications (PIMs) are drugs that should be avoided whenever possible in older adults because of their potentially poor benefit-risk ratio in old age [7,8]. Polypharmacy and PIMs have been associated with an increased risk of ADRs, hospitalization and higher health-care costs [9–11]. Expert consensus groups in pharmacology, medicine, and geriatrics have developed multiple tools to assess PIMs in older adults [12]. PIM lists gather explicit criteria corresponding to drugs, drug-drug interactions, and drug-disease interactions to be avoided in older adults or patients with particular chronic diseases such as dementia. It is essential to specify that these lists are recommendations and not contra-indications, as the evaluation of the benefit-risk ratio could be modulated by individual factors.

Epidemiology provides insight into the frequency, type, and distribution of PIMs in the older population, thereby contributing to ADR prevention. Studies reporting PIM prevalence have been conducted worldwide, and a recent meta-analysis of published studies estimated that 33% of older adults were exposed to PIMs [10]. Few studies reported PIM prevalence in France, especially in recent years, and their results vary significantly according to study population, study period, and selected PIM criteria [13–18]. Healthcare

claims databases are valuable sources for evaluating PIMs, although the available information does not always allow for the study of PIM criteria requiring clinical data or information about the indication [19]. In France, the Health National Data System (*système national des données de santé* [SNDS]) has become a major data source for pharmacoepidemiology studies. A study based on the 1/97th subsample of the SNDS (*échantillon généraliste des bénéficiaires* [EGB]) estimated that 34% of older adults aged 75 years or over were exposed to hyper-polypharmacy in 2013 [20]. This study also reported geographical variations in polypharmacy prevalence, with figures comprised between approximately 20% and 50% depending on the French department [20]. PIM frequency measured from the SNDS or EGB was 53% in 2007 [14] and 57% in 2017 [16]. A regional study in the North of France also assessed the prevalence of PIMs over three months in 2012, with a result of 32% [18].

In this context, we aimed to assess the prevalence of PIMs and polypharmacy in older adults aged 75 years and over in France in 2019 based on data from the SNDS. Secondly, we aimed to describe the prevalence of PIMs by French region.

Methods

Study design and data source

We conducted a cross-sectional study in older adults aged 75 years and over in France between January 1st and December 31st, 2019. This study is part of a larger study on the evolution of PIMs and polypharmacy in France between 2011 and 2019 [21].

This study is based on the French health insurance claims database (*données de consommation inter-régime* [DCIR]), which has been widely used for epidemiological studies [22–24]. A description of the DCIR and the French Health insurance system is available in previous publications [25,26]. Briefly, the DCIR covers about 99% of the French population (approximately 67 million people in 2019) from

birth (or immigration) to death (or emigration). A unique anonymous number identifies beneficiaries. DCIR includes information on demographic characteristics (age, gender, place of residence, date of death), reimbursed outpatient medical care, and reimbursed drugs dispensed in pharmacies. The drugs are coded according to the anatomical therapeutic chemical (ATC) classification.

Study population

The study population included people aged 75 years and over, who had received at least one reimbursement for outpatient care in 2019. The study population included all individuals who met the inclusion criteria regardless of their living place (community or nursing home), as this information was not available in the DCIR at the time of the study. Individuals who died during the study period were excluded as end-of-life management may modify drug use and in order to have a comparable duration of observation for all individuals. Individuals with an abnormal date of birth (prior to 1900), unknown gender, and temporary identifier (e.g., related to recent immigration) were also excluded.

PIM and polypharmacy measurement

PIM criteria involving drugs marketed and reimbursed in France were adapted from the 2015 updates of the Beers' and STOPP (Screening Tool of Older People's Prescriptions) criteria [8,27]. Indeed, the Beers list is internationally recognized and has been frequently updated. The STOPP list is also internationally recognized and has the benefit of having been drawn up by a consensus of European experts, thus justifying its applicability in France. We studied seventeen PIM criteria that could be fully assessed in the DCIR. Criteria requiring information about drug dosage or indication (e.g., proton-pump inhibitors beyond eight weeks without justification) were not studied. The detail of the studied criteria is available elsewhere [21] and in the [Supplementary Table 1](#).

The final set of criteria included criteria in four drug categories: benzodiazepines (BZDs), oral non-steroidal anti-inflammatory drugs (NSAIDs), atropinic drugs, and anti-hypertensive drugs, as well as an indicator of concomitant use of any combination of three or more central nervous system (CNS)-active drugs (antipsychotics, BZDs, hypnotic Z-drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, and antiepileptic drugs). PIMs were defined by at least one occurrence of the corresponding ATC code in the database, except for NSAIDs and short- and intermediate-acting BZDs for which potentially inappropriate use was defined from three dispensations during the year (not necessarily consecutive). Criteria related to drug-drug interactions were assessed by considering that drugs delivered on the same day were used concomitantly.

Three main approaches for measuring polypharmacy have been reported: simultaneous, continuous, and cumulative polypharmacy [20,28,29]. We have chosen to measure cumulative polypharmacy, defined as the annual average of the number of drugs with different ATC codes dispensed in a quarter [20,29]. Vaccines, homeopathy, diagnostics agents, antiseptics and disinfectants, medical gases, medicated and surgical dressings, blood substitutes and perfusion solutions,

immune sera and immunoglobulins were excluded from the count of drugs. This approach has the advantage of considering all drugs dispensed, i.e., those used regularly and on a one-time basis, yet giving them the same weight. Polypharmacy was categorized into three classes: no polypharmacy (0 to 4 drugs), polypharmacy (5 to 9 drugs), and hyperpolypharmacy (≥ 10 drugs).

Other variables

Other variables considered in this study were sex, age, and region of residence. Age was considered a binary variable, with a threshold of 85 years to distinguish the oldest old. The region of residence was determined from information about the department and municipality of residence. If the department and municipality of residence were missing, the department of the health insurance fund to which the person was affiliated was considered as a surrogate for the department of residence.

Analyses

Prevalence of PIM criteria and polypharmacy were described for the study population and by age and sex category in number and percentage. A composite indicator was also created to assess the overall exposure to PIMs, encompassing the 17 individual PIM criteria. Prevalence of PIMs according to the level of polypharmacy was also described. The prevalence of exposure to at least one PIM in 2019 was described by region of residence. In order to account for demographic differences between regions, the prevalence of at least one PIM in 2019 was standardized based on the structure of the French population in 2019, as reported by the French National Institute of Statistics and Economic Studies (INSEE). Regional prevalence was mapped by quartiles of the distribution of the prevalence of exposure to at least one PIM in 2019.

Analyses were performed using SAS, version 9.4 software (SAS Institute, Cary, North Carolina, USA).

Results

In 2019, 6,707,897 persons aged 75 years and over received at least one reimbursement for outpatient care. After the exclusion of persons with unknown gender ($n=484$), abnormal date of birth ($n=3$), and temporary identifier ($n=29,943$), and those who died during the year ($n=349,312$), the study population included 6,328,155 older adults. As reported in [Table 1](#), 59.9% were women, and 35.9% were aged over 85 years.

The prevalence of PIMs in 2019 is presented in [Table 2](#). In France, 39.6% of older adults aged 75 years and over had been exposed to at least one PIM in 2019. Among them, 21.0%, 10.3%, and 10.9% had received two, three, and four or more different PIMs, respectively. BZD PIMs were the most frequent (26.9%), followed by atropinic PIMs (8.3%), non-steroidal anti-inflammatory PIMs (7.8%), concomitant use of three or more CNS-active drugs (7.3%), and anti-hypertensive PIMs (6.0%). The most common PIM criteria were those involving BZDs, namely repeated dispensation (≥ 3 during the year) of short- or intermediate-acting BZDs

Table 1 Characteristics of people aged 75 years or over with a health care reimbursement in 2019, France, French Health National Data System (SNDS).

	n or mean (n = 6,328,155)	% or S.D.
Sex		
Men	2,535,597	40.1
Women	3,792,558	59.9
Age (years)	82.8	5.8
75 to 79	2,194,379	34.7
80–84	1,861,395	29.4
85–89	1,368,345	21.6
Over 90	904,036	14.3
At least one drug dispensation in 2019	6,106,212	96.5

(12.4%), hypnotics Z-drugs (10.3%) and long-acting BZDs (9.2%). First-generation antihistamine H1 drugs accounted for about three-quarters of atropinic PIMs. Repeated use of NSAIDs was the main non-steroidal anti-inflammatory PIMs (6.0%). Women and the oldest old group (≥ 85 years) were more frequently exposed to at least one PIM during the year (44.6% and 42.1%, respectively), although the prevalence remained high in people aged 75 to 84 years (38.2%) and in men (32.2%). Of note, concomitant use of three or more CNS-active drugs was almost twice as high in older women as in older men (9.2% versus 4.4%).

During the study period, 46.7% of older adults were exposed to polypharmacy (5 to 9 drugs) and 25.2% to hyper-polypharmacy (≥ 10 drugs) (Table 2). Fig. 1 presents PIM frequency according to polypharmacy. Older adults exposed to hyper-polypharmacy received at least one PIM during the year (64.2%) more frequently than those exposed to polypharmacy (40.4%) and not exposed to polypharmacy (13.9%). There was a gradient in the level of exposure to PIMs according to polypharmacy for each class of PIM.

Fig. 2 reports the age and sex-standardized prevalence of exposure to at least one PIM during 2019 by French regions. In mainland France, PIM prevalence ranged from 36.5% in Pays-de-la-Loire to 44.8% in Hauts-de-France. PIMs were less frequent in the French overseas departments, with a prevalence ranging from 26.3% in Mayotte and 37.3% in French Guiana.

Discussion

This cross-sectional study based on nationwide data from the French health insurance database shows that 39.6% of older adults aged 75 years and over were exposed to at least one PIM in 2019 in France. Psychotropic PIMs were the most frequent. Older women and older adults with hyper-polypharmacy were the most exposed to PIMs. Moreover, our results show that PIM prevalence may vary according to the region, from 26% to 44%. In addition, almost three-quarters of older adults were exposed to polypharmacy (≥ 5 drugs).

The prevalence of PIMs observed in our study is higher than the pooled prevalence reported in a recent

meta-analysis (39% versus 33%), reflecting a high exposure to PIMs in older French adults. However, the fact that we considered medications dispensed over an entire year likely increased the likelihood of observing PIMs compared to studies assessing PIM exposure over shorter periods. In addition, the use of claims data prevents drug-underreporting issues. These results are part of a repeated cross-sectional study, which assessed the trends in the prevalence of PIMs and polypharmacy between 2011 and 2019 [21]. Although PIM prevalence was high in French older adults in 2019, this study reported that PIM prevalence has decreased by an average of 1.19% per year (from 49% in 2011 to 39% in 2019) [21]. A decreasing trend in the prevalence of all PIM categories was observed, but with differences in magnitude [21].

Geographical variations in drug use and PIMs in particular have rarely been studied [30]. However, consistent with our result, some studies have reported geographical variations for specific drug classes [31,32]. For example, the use of antidiabetic drug dipeptidyl peptidase-4 ranged from 11.3% to 16% across England in 2017 [32]. In Italy, the prevalence of the use of proton-pump inhibitors was higher in Lombardy than in Campania region (21.9% versus 41.3%) [31]. These results raise questions about the factors explaining these regional variations. A study conducted in the North of France during the first quarter of 2012 found that PIM use was associated with socioeconomic factors; specifically, PIMs were more frequent in municipalities with lower population density and income [18]. Other factors related to the availability of health services, such as low medical density, should also be considered [33].

The prevalence of polypharmacy was higher in our study compared to the pooled prevalence of polypharmacy assessed in a recent meta-analysis of 54 studies published between 1997 and 2019 (72% versus 45%) [34]. However, the polypharmacy measure is sensitive to how it is measured (definition, threshold, setting). Indeed, a literature review reported a prevalence of polypharmacy ranging from 4% to 57% in older adults [35]. Moreover, cumulative polypharmacy, as the most inclusive approach, may have led to overestimating the prevalence. For example, in Australia, the frequency of continuous polypharmacy was 36.2% and increased to 52.7% for cumulative polypharmacy over three months in 2017 [36]. However, the level of polypharmacy we observed was consistent with results of the French SIPAF study (*système d'information sur la perte d'autonomie fonctionnelle de la personne âgée*), which estimated the frequency of polypharmacy (5 to 9 drugs) at 53.6% and that of hyper-polypharmacy (≥ 10 drugs) at 13.8% in a sample of people aged 70 years and over interviewed between 2008 and 2010 [37]. We observed an increase in the frequency of PIMs according to the level of polypharmacy, which is consistent with results from previous studies [19,38,39]. PIMs and polypharmacy are strongly linked and should be addressed conjointly in the older population; in this respect the concept of "inappropriate polypharmacy", which designates avoidable polypharmacy, may be particularly useful [28].

The wide use of psychotropic drugs remains a critical concern among French older adults, especially among older women and the oldest old group. France was the second largest consumer of BZDs out of eight European countries in 2015 (Denmark, France, Germany, Italy, Norway, Spain,

Table 2 Age and sex frequency of potentially inappropriate medication (PIM) dispensations in people aged 75 years or over in France in 2019, French Health National Data System (SNDS).

	75 to 84 years (n = 4,055,774) n (%)	≥85 years (n = 2,272,381) n (%)	Women (n = 3,792,558) n (%)	Men (n = 2,535,597) n (%)	Overall (n = 6,328,155) n (%)
<i>At least one PIM</i>	1,548,856 (38.2)	957,410 (42.1)	1,689,605 (44.6)	816,661 (32.2)	2,506,266 (39.6)
<i>Benzodiazepine(BZD)PIMs</i>	997,878 (24.6)	702,896 (30.9)	1,205,028 (31.8)	495,746 (19.6)	1,700,774 (26.9)
Three or more dispensations of short- or intermediate-acting BZDs	407,717 (10.1)	375,478 (16.5)	576,092 (15.2)	207,103 (8.2)	783,195 (12.4)
Long-acting BZDs	372,742 (9.2)	179,041 (7.9)	397,885 (10.5)	153,898 (6.1)	551,783 (8.7)
Hypnotic Z-drugs	385,960 (9.5)	263,544 (11.6)	440,012 (11.6)	209,492 (8.3)	649,504 (10.3)
Concurrent use of 2 or more BZDs	58,643 (1.4)	34,928 (1.5)	71,140 (1.9)	22,431 (0.9)	93,571 (1.5)
Concurrent use of BZDs and hypnotic Z-drugs	110,020 (2.7)	78,409 (3.5)	139,162 (3.7)	49,267 (1.9)	188,429 (3.0)
Concurrent use of opioid receptor agonists and BZDs	186,810 (4.6)	124,692 (5.5)	237,956 (6.3)	73,546 (2.9)	311,502 (4.9)
<i>AtropinicPIMs</i>	349,344 (8.6)	173,374 (7.6)	354,392 (9.3)	168,326 (6.6)	522,718 (8.3)
First-generation antihistamine H1 drugs	238,670 (5.9)	113,044 (5.0)	229,489 (6.1)	122,225 (4.8)	351,714 (5.6)
Tricyclic antidepressants	100,782 (2.5)	49,911 (2.2)	112,856 (3.0)	37,837 (1.5)	150,693 (2.4)
Phenothiazines	26,494 (0.7)	17,521 (0.8)	29,556 (0.8)	14,459 (0.6)	44,015 (0.7)
<i>Non-steroidal anti-inflammatoryPIMs</i>	369,103 (9.1)	126,617 (5.6)	314,041 (8.3)	181,679 (7.2)	495,720 (7.8)
Three or more dispensations of oral non-steroidal anti-inflammatory drugs (NSAIDs)	285,013 (7.0)	92,557 (4.1)	248,699 (6.6)	128,871 (5.1)	377,570 (6.0)
Concurrent use of two NSAIDs or more NSAIDs in combination with antiplatelet agents	18,734 (0.5)	4890 (0.2)	15,643 (0.4)	7981 (0.3)	23,624 (0.4)
NSAIDs in combination with antiplatelet agents	115,728 (2.9)	44,994 (2.0)	90,818 (2.4)	69,904 (2.8)	160,722 (2.5)
NSAIDs in combination with vitamin K antagonist or non-vitamin K antagonist oral anti-coagulant	25,774 (0.6)	11,948 (0.5)	20,132 (0.5)	17,590 (0.7)	37,722 (0.6)
<i>AntihypertensivePIMs</i>	220,602 (5.4)	156,675 (6.9)	244,282 (6.4)	132,995 (5.2)	377,277 (6.0)
Central alpha-blockers	98,873 (2.4)	62,377 (2.7)	103,140 (2.7)	58,110 (2.3)	161,250 (2.6)

Table 2 (Continued)

	75 to 84 years (n = 4,055,774) n (%)	≥85 years (n = 2,272,381) n (%)	Women (n = 3,792,558) n (%)	Men (n = 2,535,597) n (%)	Overall (n = 6,328,155) n (%)
Selective calcium channel blockers with immediate release	124,866 (3.1)	97,592 (4.3)	145,884 (3.8)	76,574 (3.0)	222,458 (3.5)
Concurrent use of β -blockers and verapamil or diltiazem	8305 (0.2)	4935 (0.2)	8154 (0.2)	5086 (0.2)	13,240 (0.2)
Concomitant use of three or more central nervous system-active drugs	268,465 (6.6)	192,348 (8.5)	34,867 (9.2)	112,143 (4.4)	460,813 (7.3)
Polypharmacy (5 to 9 drugs)	3,022,030 (47.8)	1,918,708 (47.0)	1,103,322 (48.6)	1,838,757 (48.5)	1,183,273 (46.7)
Hyper-polypharmacy (≥ 10 drugs)	1,640,911 (25.9)	969,317 (24.0)	671,594 (29.6)	1,001,171 (26.4)	639,740 (25.2)

BZD: benzodiazepine; PIM: potentially inappropriate medication; NSAIDs: non-steroidal anti-inflammatory drugs

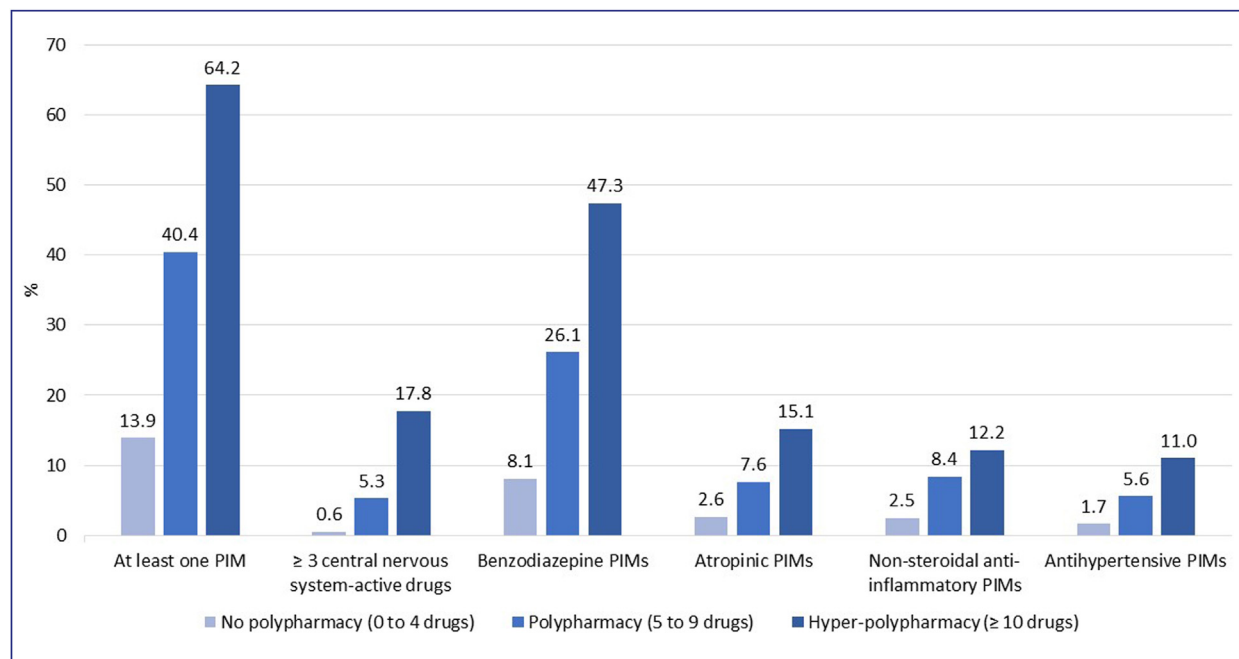


Figure 1. Frequency of potentially inappropriate medications (PIMs) according to the level of polypharmacy in adults aged 75 years or over in France in 2019, French Health National Data System (SNDS). PIMs: potentially inappropriate medications.

Sweden, and United Kingdom) [40]. At the same time, a previous study based on data from the SNDS found that 30% of hypnotic and 20% anxiolytic new dispensations between 2007 and 2012 did not comply with French guidelines [41]. The trend analysis of PIM criteria and polypharmacy from which this analysis is drawn reported a significant decrease in the use of BZDs and in the concomitant use of three or more CNS-active drugs prevalence (of 1.34% and 1.07% per year respectively), although it was less pronounced in

women and the oldest old group [21]. While encouraging, these reductions are not sufficient.

Several measures have been implemented in France to reduce PIMs and polypharmacy in the older population. Actions directed to the prescribers can be cited, including initial and ongoing training for physicians on appropriate use of drugs in older adults, development of electronic clinical decision support system, financial incentives from the French health insurance to rationalize the use of drugs, and

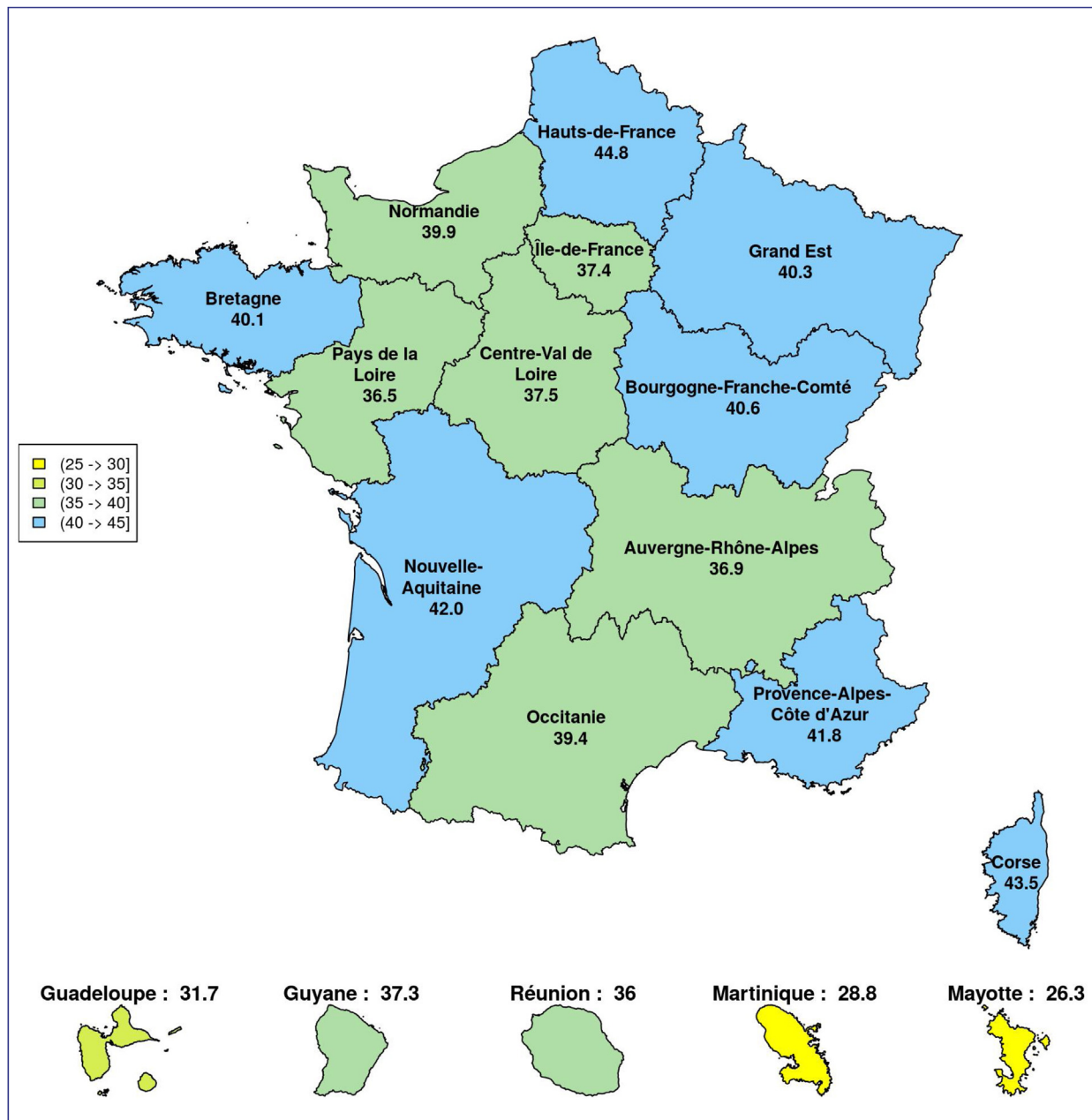


Figure 2. Age and sex-standardized prevalence (%) of potentially inappropriate medication (PIM) dispensations in adults aged 75 years or over by French region in 2019, French Health National Data System (SNDS).

medication reviews in the hospital setting. However, barriers exist, both at the patient and at the prescriber level, when it comes to deprescribing or modifying therapeutic regimens [42]. Multifaceted interventions (e.g., pharmacist intervention, electronic clinical decision support system, and medication reviews), which have been shown to be useful tools to reduce the level of exposure to PIMs [43], may help to overcome these barriers. At the national level, restrictions regarding drug delivery (e.g., for hypnotic Z-drugs since 2017) and the withdrawal of drugs judged to be ineffective by the French National Health Authority are also levers to reduce the use of PIMs.

The SNDS is one of the largest health data sources in the world since it covers the entire French population. This resource allowed us to provide results stratified by age and sex, as well as representative results by regions. However, the use of claims data presents some limitations. Firstly, SNDS includes only data on reimbursement of drugs dispensed. Therefore, over-the-counter drugs could not be taken into account in PIM and polypharmacy measurement, such as NSAIDs and some atropinic drugs. However, the impact of self-medication on our results may be limited as it concerns a restricted number of PIMs. Secondly, we restricted the assessment of PIMs to the criteria that could be assessed

with as little uncertainty as possible in the SNDS. Therefore, PIM criteria requiring information on dosage or indication were not assessed in this study. Furthermore, once a drug has been dispensed, there is no guarantee it has been used and how.

Conclusion

This study contributes to the update of knowledge on exposure to PIMs in almost the entire population aged 75 years or more in France. The results confirm that French older adults are particularly exposed to PIMs and polypharmacy, and support the need to secure medication use in this population. Our results also showed regional variations in PIM prevalence, which should be further investigated.

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Sponsor's role

The French National Agency for Medicines and Health Products Safety had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Ethics approval and consent to participate

This study has been authorized and conducted according to decree 2016-1871 of December 26, 2016 relating to personal data processing under the French National Health Data System (SNDS), and French law articles Art. R. 1461-1323 and 1424(5). As permanent user of SNDS, the author's team is exempted from Institutional Review Board approval. Given that data are anonymous, informed consent to participate is not required.

Availability of data and materials

In accordance with data protection legislation and French regulations, the authors cannot publicly release data from the French National Health Data System (SNDS). However, any person or structure, public or private, for-profit or non-profit, is entitled to access SNDS data upon authorization from the French Data Protection Office (CNIL), for the purposes of carrying out a study, research or an evaluation in the public interest (<https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees> and <https://www.indsante.fr/>). EPI-PHARE has permanent regulatory access to data from the French National Health Data System (SNDS) via its constitutive bodies ANSM and CNAM. This permanent access is given in accordance with French Decree No. 2016-1871 of

December 26, 2016 relating to personal data processing under the French National Health Data System (SNDS), and French law articles Art. R. 1461-13 and 14. All requests in the database were made by duly authorized people. In accordance with the permanent regulatory access granted to EPI-PHARE via ANSM and CNAM, this work did not require the approval of the French Data Protection Authority (CNIL). The study was registered on the study register of EPI-PHARE for studies based on SNDS data.

Authors' contributions

This study is a part of S.D.'s PhD thesis supervised by M.H. and M.Z. M.H. and M.Z. conceptualized the study. M.H., M.Z. and S.D. designed the methodology, S.D. extracted and managed the data, S.D. performed the analyses under the supervision of M.H.; S.D. wrote the manuscript; M.H. and M.Z. reviewed and edited the manuscript. M.Z. and S.D. have full access to the data.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.therap.2023.02.001](https://doi.org/10.1016/j.therap.2023.02.001).

Disclosure of interests

The authors declare that they have no competing interest.

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