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Measuring Polypharmacy in the Elderly: Impact of the Method on Prevalence and Therapeutic Classes

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Increased life expectancy is accompanied by an increase in years of living with one, or even several, chronic diseases causing an accumulation of drug therapies, thus increasing the iatrogenic risks. In recent years, public policies to reduce polypharmacy in the elderly have been established. Their assessment requires easy-to-produce indicators from large population databases. Two indicators are considered here: the "cumulative" polypharmacy indicator, which takes into account all drugs administered over a given period, and the "continuous" polypharmacy indicator, which focuses on drugs taken regularly over a prolonged period of time. The innovative aspect of this work is the consideration of combination drugs and quarterly packs in the calculations. The polypharmacy prevalence varies from 27% to 40% depending on the indicator, with or without consideration of the combination drugs and large packs.

7n a century, in France, life expectancy at birth has increased from 50 to 80 years. This increase is associated with an increase in the number of people living with several chronic diseases causing an accumulation of drugs, which can lead to polypharmacy. Polypharmacy particularly affects the elderly and exposes to various risks. First is the increase in the iatrogenic risk¹. In France, and at all ages, adverse drug reactions are responsible for 3.6% of hospital admissions and 21% of emergency consultations (Queneau *et al.*, 2003;

Benard-Laribiere *et al.*, 2015). Moreover, when the regimens are complex, taking treatment correctly may become binding and affect quality of life. Finally, the issue of prescribing quality is also economic. With the additional costs generated by the consumption of unnecessary drugs comes the iatrogenic cost in terms of hospitalisations, physician visits and additional medication (Hovstadius, 2013).

Quality and efficiency requirements amongst the elderly have been a concern

in France for a long time: in the plan "Ageing Well 2007-2009" ("*Bien vieillir 2007-2009*") of the French National Authority for Health (*Haute Autorité de santé*), tools were disseminated to improve prescribing practices and better control the iatrogenic risk. Following the publication in 2013 of a report on the drug policy in nursing homes (EHPAD,

¹ Iatrogeny covers adverse consequences on health status of any act performed or prescribed by a professional, which aims to preserve, improve or restore health.

Description of the beneficiary population studied

Demographics characteristics

The general characteristics and coverage of the studied population are detailed in the table below.

T1. General characteristics of the study population (N=43,619)

Variable	Terms	N	%	Average (sd)	Median (Min;Max)
Gender	Male	15,949	36.6		
	Female	27,670	63.4		
Age (years)				82.2 (5.28)	81 (75;112)
Age	[75,85]	32,285	74.02		
	[85,115]	11,334	25.98		
Affiliate regime	RG	34,756	79.68		
	MSA	6,168	14.14		
	RSI	2,695	6.18		
CMU-C ¹ beneficiary		275	0.63		
AME ² beneficiary		2	0		

¹ Complementary universal health coverage (*Couverture maladie universelle complémentaire*).

² State Medical Aid (*Aide médicale d'État*).

Source: IRDES. Data: EGB, CNAMTS 2013.

Long-term illness (LTI)

The status of each LTI depends on a declaration made by the treating physician to the health insurance. The table below presents information on the number of LTI per beneficiary in the study population.

T2. Number of long-term illness (LTI) reported in the study population (N=43,619)

Variable	Terms	N	%	Average (sd)	Median (Min;Max)
Number of LTI				0.79 (0.89)	1 (0;7)
Number of LTI (classes)	0	19,884	45.6		
	1	15,625	35.8		
	2	6,053	13.9		
	3	1,706	3.9		
	More than 3	351	0.8		

Source: IRDES. Data: EGB, CNAMTS 2013.

The five most common LTI in the study population are diabetes, which affects more than 13% of individuals, cancer in 12% of individuals, severe hypertension in over 10% of individuals, heart failure in 10% individuals and coronary diseases in 10% of individuals.

Healthcare pathway factors

Amongst the beneficiaries surveyed, 98.5% had at least one prescription from a general practitioner in 2013, 54.2% at least one prescription by a medical specialist and 32.8% at least one prescription by a doctor of a hospital.

The number of different prescribers per beneficiary in 2013, depending on the type of activity the prescriber (general practitioner, private specialist, hospital doctor) is detailed in the table below.

T3. Number and different types of prescribers per beneficiary (N=43,619)

Variable	Average (sd)	Median (Min;Max)
Number of different general practitioners	1.42 (0.76)	1 (0;15)
Number of different specialists	0.95 (1.19)	1 (0;12)
Number of different hospital doctors	0.44 (0.73)	0 (0;8)
Number of different prescribers	2.81 (1.75)	2 (0;19)

Source: IRDES. Data: EGB, CNAMTS 2013.

DEFINITIONS

Polypharmacy is defined by the World Health Organization (WHO) as "the administration of several drugs simultaneously or administration of an excessive number of drugs" (WHO, 2004).

Polypharmacy is classified into:

- **"Simultaneous" polypharmacy:** drugs taken simultaneously on a given day (a day at random or an average day in the year). This type of polypharmacy is not analysed in the study.
- **"Cumulative" polypharmacy:** all drugs administered over a given period, usually a quarter, or an annual average of quarters. In the study, the cumulative indicator is the average over the year of the number of different ATC5 classes (Anatomical, Therapeutic, Chemical) reimbursed quarterly.
- **"Continuous" polypharmacy:** drugs taken regularly over the long term. Several calculation methods are proposed in the literature, for example the number of drugs present on two periods of time at six months, or drugs taken in a given quarter and that were already taken in the previous quarter. In the study, the continuous indicator is defined as the number of different ATC5 classes issued at least three times a year.

Etablissement d'hébergement pour personnes âgées dépendantes), measures have been proposed to improve its use. Finally, as part of the experimental programme "Seniors' Health Path (Paerpa, *Parcours santé des aînés*)", therapeutic education actions relate to polypharmacy and multiple diseases.

Measuring polypharmacy: a key challenge

Measuring polypharmacy in the elderly is a major challenge for the evaluation of public health policies aimed at reducing polypharmacy. Good knowledge of different calculation methods and their

impact on the extent of polypharmacy is essential to understand the observed phenomena.

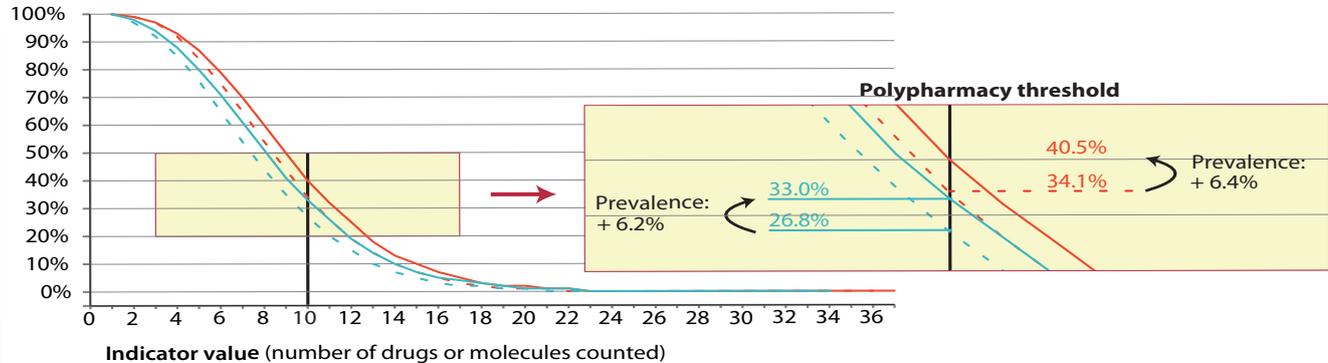
Polypharmacy is classified "simultaneous" if drugs are taken simultaneously on a given day, "cumulative" for drugs administered over a given period of time or "continuous" for drugs taken regularly over an extended period of time. The World Health Organization (WHO) definition does not specify the number of molecules that defines polypharmacy (Definitions insert). In the literature, this number varies depending on the study. The most used thresholds are those of five or more drugs and more recently, due to an increased therapeutic load, a threshold of 10 or more drugs has been proposed.

The objective of our study is to compare the different indicators and methods of calculating polypharmacy in terms of prevalence, targeted therapeutic classes and characteristics of polymedicated patients. Are there differences in the prevalence of polypharmacy according to the indicator or the method of calculation used? Are the therapeutic classes constituting polypharmacy identical? In a second step, some factors associated with polypharmacy are described: patient demographics, health status, geographical factors and healthcare pathways. Finally, details are provided to assist in choosing polypharmacy indicators aimed at population monitoring or the evaluation of health programmes for drugs.

G

Prevalence of polypharmacy depending on the type of indicator and the inclusion of combination drugs and quarterly pack

CONTINUOUS indicator — with — Taking into account combination drugs quarterly packs
 - - without - - without - - Taking into account combination drugs

Prevalence of polypharmacy among patients aged 75 and over


Source: IRDES.

Data: EGB, CNAMTS 2013.

Data available for download

Adopted indicators and calculation methods

In this study, we only retained cumulative polypharmacy and continuous polypharmacy, which are two indicators that can be created from medico-administrative databases, namely the French general sample of beneficiaries of health insurance (*Échantillon généraliste de bénéficiaires*, EGB) (Sources and methods insert). For the calculation of indicators, taking into account combination drugs within a single dosage form, *e.g.* a tablet, provides new insights. Indeed, if the goal is to reduce the risk of adverse events and therefore the number of different molecules, the inclusion of combination drugs is important. However, if the goal is to simplify treatment administration and reduce the number of tablets taken by the patient, incorporation of combination drugs is irrelevant. In general, the goal is twofold.

Considering quarterly packs, which allows derogation in certain chronic diseases² to the rule of the monthly dispensing, also refines the calculation of continuous polypharmacy. A person treated by a drug available in quarterly pack is

supposedly under long-term treatment and receives about 12 monthly or four quarterly issuances per year. Considering quarterly packs does not affect cumulative polypharmacy for which the indicator is incremented from the first issuance and has little impact on the continuous indicator, calculated over a whole year, because whatever the type of packs, the threshold of three deliveries is achieved in the year.

Furthermore, there is no consensus on the threshold to be adopted to define polypharmacy (Monegat and Sermet, 2014), probably in the absence of a medical standard for defining what would be too many drugs. However, in an evaluation perspective, it seems more appropriate to target the individuals most likely to be affected by polypharmacy. The first analyses have helped to highlight that with a threshold of five drugs, about 80% of the outpatient aged 75 and over are targeted as polymedicated. A 10-drug threshold, for which 30% of the same individuals are considered polymedicated, seems more able to detect the impact of actions aiming at reducing polypharmacy. The 10-drug threshold was used for the study analyses.

The prevalence of polypharmacy varies according to the indicator used and the method of calculation

Prevalence of 33% to 40% according to the type of indicator

The prevalence of polypharmacy at the 10-drug threshold in France (excluding territories overseas, Guyana and Mayotte) for the continuous and cumulative polypharmacy indicators (chart) is 33% and 40.5%, respectively, after taking into account the combination drugs and quarterly packs. The prevalence of polypharmacy in individuals age 75 and over increases by 7 points when considering all treatments compared to the consideration of only treatments taken repeatedly over the year. The base of polypharmacy consists of treatment taken over a long period for chronic diseases. Indeed, amongst the 40% of beneficiaries classed as polymedicated with the cumulative indicator, 77.5% are also classed with the continuous indicator. The difference between the two indica-

² Diabetes, high blood pressure, high cholesterol and osteoporosis.

tors is used to quantify the proportion linked to treatment of intercurrent diseases, which occurs when one or more other diseases are present.

Whatever the indicator, the inclusion of combinations and quarterly packs increases prevalence of polypharmacy by six points

Using the cumulative indicator or the continuous indicator, the inclusion of combination drugs (and quarterly packs for the continuous indicator) increases the prevalence of polypharmacy for the 10-drug threshold by 6 points in the population of beneficiaries studied (27% to 33% for the continuous indicator and 34% to 40.5% for the cumulative indicator) [graph]. Moreover, the median number of level 5 ATC (Anatomical, Therapeutic, Chemical) therapeutic classes (chemically identical) to which individuals are exposed increases by 1 with the inclusion of combinations (and quarterly packs for the continuous indicator).

Impact of the type of indicator and the method of calculation on the therapeutic classes

The continuous polypharmacy indicator highlights the therapeutic classes used in the treatment of chronic diseases

Whether using the continuous or cumulative indicators, 11 level 3 ATC therapeutic classes, similar in terms of phar-

macological properties, amongst the 15 most frequent ones are the same (Table 1). For six of these classes, the percentage of beneficiaries concerned increases slightly from the continuous indicator to the cumulative indicator. These therapeutic classes are most often used in the treatment of chronic diseases: drugs acting on the renin-angiotensin system, antithrombotics, lipid modifying agents, diuretics, beta blockers and calcium channel blockers. These drugs are all related to the cardiovascular sphere. For five other classes, the percentage of beneficiaries concerned increases by at least 10 points from the continuous indicator to the cumulative indicator. These drug classes are used not just in the long term, but also in most acute therapies: analgesics (+22 points), medicines for acidity disorder (+17 points), antipsychotics (+10 points), vitamins (+16, 5 points) and ophthalmic drugs (+18 points).

The last four level 3 ATC classes of the 15 concerning the most beneficiaries differ according to the indicator. For the cumulative indicator we observe therapeutic classes commonly used in the treatment of acute conditions: antibacterials for systemic use (amoxicillin with or without clavulanate), anti-inflammatories and antirheumatics (diclofenac, ibuprofen and ketoprofen), topical treatments for joint or muscle pain (diclofenac) and laxatives (macrogol). For the continuous indicator, therapeutic classes less frequently used in the treatment of chronic diseases are found: psychoanaleptics (escitalopram, paroxetine), mineral supplements (calcium car-

bonate), antiarrhythmics (amiodarone), antidiabetic (metformin).

The therapeutic classes involving the largest number of beneficiaries are consistent with the results found in the literature. For those aged 65-90 years in the UK, more frequent use of cardiovascular, central nervous system and gastrointestinal sphere drugs was observed (Kennerfalk *et al.*, 2002). In Sweden, in beneficiaries of 77 years and older who take chronically 5 or more drugs, antithrombotics, beta blockers and diuretics are the most prescribed classes (Haider *et al.*, 2008). In the same context as that of our study (individuals aged 75 and over treated as outpatients, 10-drug threshold), Jyrkkä *et al.* (2009) found cardiovascular drugs in 97% of polymedicated individuals and analgesics in 89%.

Inclusion of combination drugs and quarterly packs increases the estimation of the population exposed to certain therapeutic classes

For therapeutic classes involving the largest number of beneficiaries, the inclusion of combination drugs (and quarterly packs for the continuous indicator) leads to a significant increase in the population estimated as exposed to some level 3 ATC classes, such as diuretics (C03) and vitamins (A11).

For the continuous indicator, this increase is mainly due to the inclusion of combination drugs. Indeed, as mentioned earlier, although the quarterly dispensing of these drugs were counted

SOURCES AND METHOD

General sample of beneficiaries (Échantillon généraliste de bénéficiaires, EGB): The EGB is a permanent representative sample of the population covered by health insurance, whether or not receiving healthcare reimbursements. It results from a survey at 1/97th on the Social Security Number (NIR) of the health insurance beneficiaries with rights or having rights. Since 2010, it covers citizens of the National Health Insurance scheme (excluding the *Sections locales mutualistes* (SLM), *Mutualité sociale agricole* (MSA) and *Régime social des indépendants* (RSI)).

Identifying drugs is made from the ATC (Anatomical Therapeutic Chemical) classification system recommended by the World Health Organization (WHO). Drugs are classified in groups in 5 levels: 14 main groups according to the organ or system on which they act (Level 1), their therapeutic properties (level 2), pharmacological properties (level 3), chemical groups (level 4) and chemical substances (level 5). According to this classification, a drug composed of several molecules in combination will have a different ATC code than the molecules that compose it. For drugs for systemic action

only, issuing an ATC5 code corresponding to a combination of two molecules is converted into two deliveries: one for each molecule composing the combination. Concerning the drug packs, drug delivery in quarterly packs is changed to three monthly deliveries.

The scope of the study is limited to beneficiaries aged 75 and over of the EGB having at least one drug reimbursement for each quarter of 2013 (issued in the town or retrocession). Excluded from our analysis are patients hospitalised in Long-term Care (SLD, *Soins de longue durée*) or Follow-up and Rehabilitation Care (SSR, *Soins de suite et de réadaptation*) (for at least one whole quarter of 2013, and patients in nursing homes with Pharmacy for internal use (PUI) (approximately 1.3% of the elderly), probably the most polymedicated.

Models used. Factors associated with the polymedicated status were examined using logistic regression models adjusted for all the variables studied.

The 15 most relevant therapeutic classes

Cumulative indicator		Continuous indicator	
Raw	With combinations	Raw	With combinations and quarterly packs
Analgesics	Analgesics	Analgesics	Analgesics
RAA system drugs*	RAA system drugs*	RAA system drugs*	RAA system drugs*
Acidity drugs	Acidity drugs	Antithrombotics	Antithrombotics
Antithrombotics	Antithrombotics	Lipid modifying agents	Lipid modifying agents
Antibacterials for systemic use	Antibacterials for systemic use	Acidity drugs	Diuretics
Lipid modifying agents	Diuretics	Beta blockers	Acidity drugs
Psycholeptics	Lipid modifying agents	Psycholeptics	Beta blockers
Ophthalmological drugs	Vitamins	Diuretics	Psycholeptics
Vitamins	Psycholeptics	Calcium channel blockers	Vitamins
Beta blockers	Ophthalmological drugs	Ophthalmological drugs	Calcium channel blockers
Anti-inflammatory/anti-rheumatism drugs	Beta blockers	Vitamins	Ophthalmological drugs
Diuretics	Anti-inflammatory/anti-rheumatism drugs	Psychoanaleptics	Psychoanaleptics

* Renin-angiotensin-aldosterone

Source: IRDES.

Data: EGB, CNAMTS 2013.

as monthly dispensing, the impact on the calculation of the continuous indicator would be relatively limited since there are most often more than two issuances per year.

The inclusion in the calculations of the combination drugs is not found in literature: either the unit used is the molecule and not the level 5 ATC class and the issue of inclusion of combination drugs does not arise, but this is generally found for small-scale studies (Jyrkkä *et al.*, 2009; Herr, Robine *et al.*, 2015), or for large-scale studies using level 5 ATC classes, the question of whether combination drugs are considered is not mentioned (Hovstadius and Petersson, 2013).

Factors associated with polypharmacy do not differ according to the indicators

Major socio-demographic factors associated with polypharmacy: affiliation with the National Health Insurance scheme (NHI) or the Mutual Agricultural fund (MSA) rather than the Social security scheme for self-employed (RSI), being over 85 years old and being female

All things being equal, factors associated with being polymedicated at the 10-drug threshold are the same for both indicators taking into account or not combination

drugs and quarterly packs: affiliation to the National Health Insurance scheme or the agricultural scheme (*Mutualité sociale agricole*, MSA) rather than social security scheme for self-employed (*Régime social des indépendants*, RSI), being over 85 years old and being female.

The finding that women are more polymedicated than men is well known in the literature (Pappa *et al.*, 2011; Venturini *et al.*, 2011) as well as the increase in polypharmacy with age (Jyrkkä *et al.*, 2011; Nobili *et al.*, 2011). However, the issue of the affiliation scheme, specific to France, is difficult to interpret. Are individuals affiliated to the RSI healthier? Is their consumption of care lower because historically the RSI had lower reimbursement rates than the NHI scheme? Few studies have been published on the subject; however, a study on the impact of aligning reimbursement rates of the RSI to those of the NHI scheme in the region Pays de la Loire highlighted an increase in drug consumption for RSI affiliates (*Journal de gestion et d'économie médicale*, 2010). The drug consumption of the RSI beneficiaries has, so far, not necessarily caught up levels of the NHI over the whole of France.

More polymedicated elderly persons in the northern departments and central France

Residing in the north of France (Nord, Pas-de-Calais, Somme, Aisne and

Ardennes) and in some departments of the Centre (Cantal, Corrèze, Creuse, Cher) rather than Paris is also associated with being polymedicated. Conversely, living in Haute-Savoie or Martinique is associated with a lower risk of being polymedicated than living in Paris (Maps 1 and 2).

Some of these results confirm those published in the Atlas Paerpa (Or, 2015) with an increased prevalence of polypharmacy in those aged 75 and older in the Nord-Pas-de-Calais and Limousin in relation to the national average.

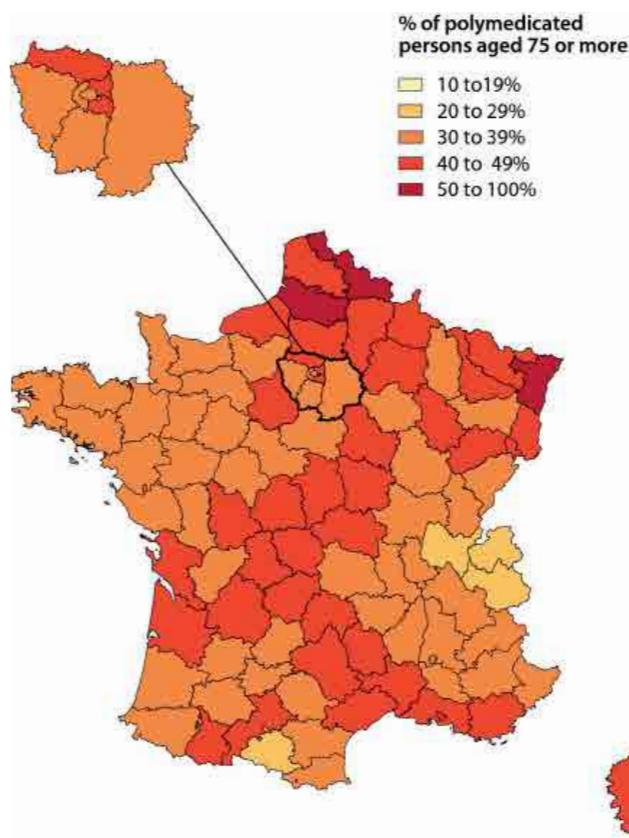
Having a LTI increases the risk of being polymedicated

Having a long-term illness (LTI) increases the risk of being polymedicated, except for LTI 15 (Alzheimer's disease). The LTI most strongly associated with the polymedicated status is LTI 14 (respiratory failure) and then LTI 8 (diabetes), LTI 16 (Parkinson's disease), LTI 13 (coronary disease) and LTI 12 (HTA). For these five LTI, the odds ratios differ little between the cumulative indicator and the continuous indicator, which seems logical as LTIs are pathologies requiring long-term treatment. LTI 15 (Alzheimer's disease) is negatively associated with polypharmacy, especially with the cumulative indicator. LTI for an individual with Alzheimer's disease would be at less risk of polypharmacy,

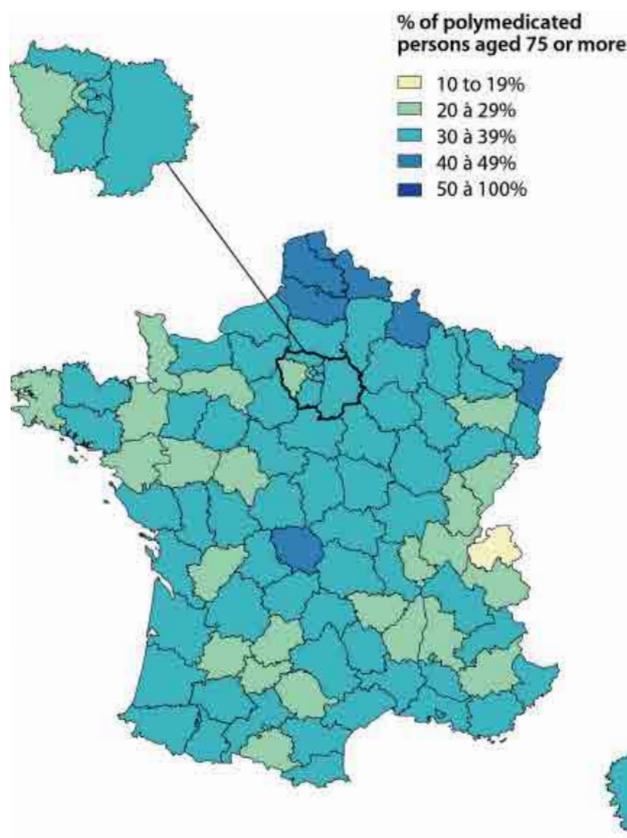
C1

Prevalence of polypharmacy at the 10-drug threshold with cumulative and continuous indicators after taking into account combination drugs (and quarterly packs for the continuous indicator)

a. Cumulative indicator taking into account combination drugs



b. Continuous indicator taking into account quarterly packs and combination drugs



Guadeloupe

Martinique

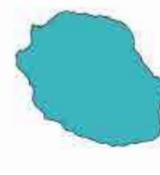
Reunion Island



Guadeloupe

Martinique

Reunion Island



Source: IRDES.

Data: EGB, CNAMTS 2013.

Reading: According to the continuous indicator, the percentage of persons aged 75 and polymedicated over the 10-drug threshold in the Nord department is between 40 and 49%.

and especially less subject to intercurrent acute treatments (Scherder *et al.*, 1999).

Polypharmacy is related to the number of prescribers and the existence of hospital and medical specialists prescriptions

Having at least one hospital or medical specialist prescription in the year is associated with being polymedicated, as well as the number of different prescribers. However, these factors can be both markers of a certain type of health-

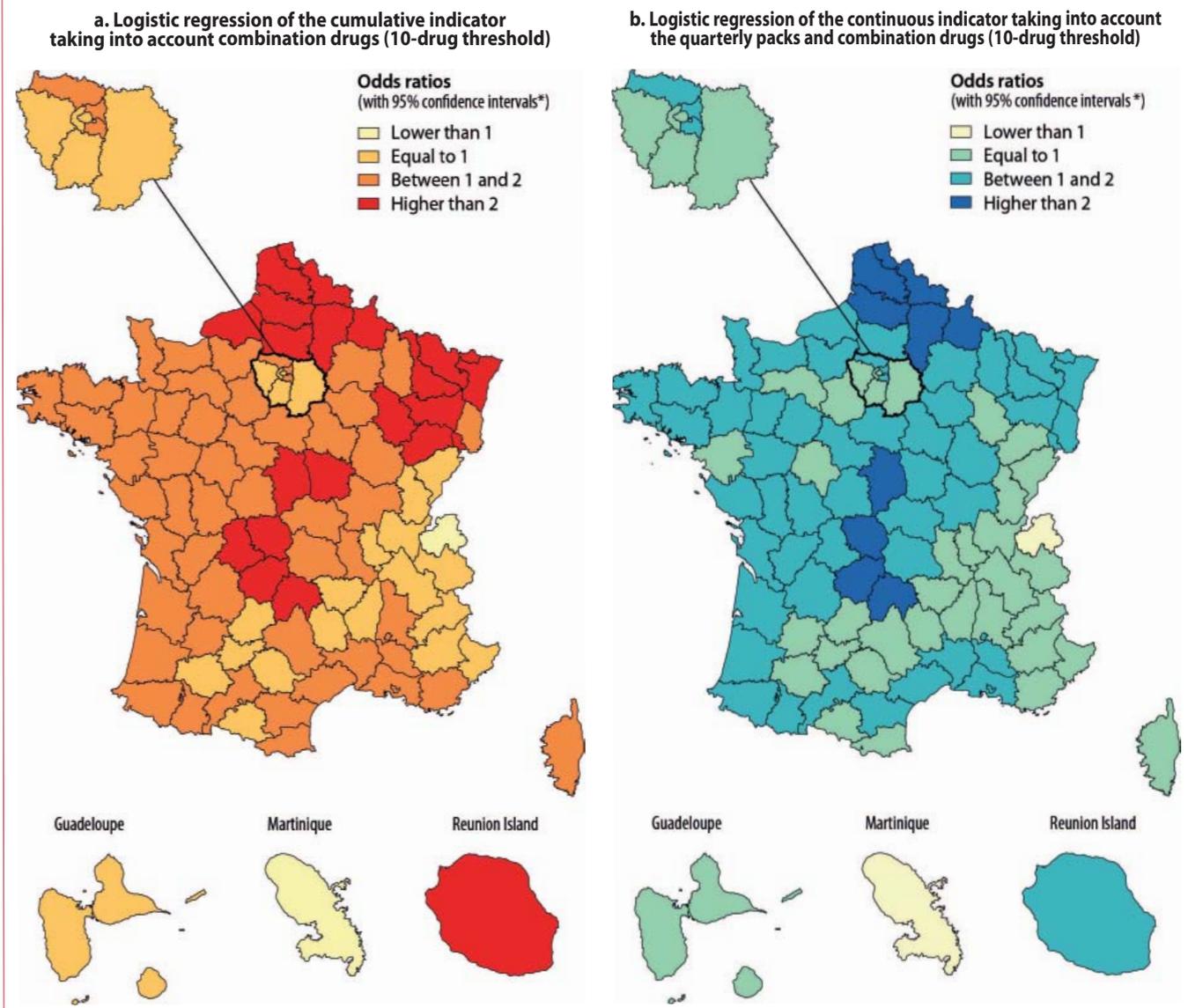
care pathway, but also of the severity of the disease; thus, interpretation of these coefficients is difficult. It should be adjusted on the severity of the health status of individuals whose data are unavailable, in order to assess the impact of healthcare pathways.

This study of the measurement of polypharmacy clarifies the type of indicators and the calculation method to be used in different circumstances. The cumulative

indicator takes into account all drugs, but does not differentiate between long-term treatment and acute treatments. The interest to take into account all administered drugs is mostly related to avoidance of drug interactions or the accumulation of potentially harmful side effects for the patient. This type of indicator, especially if it takes into account combination drugs, is particularly relevant for assessing public policies such as reducing hospitalisations for iatrogenic risks in the elderly. The continuous polypharmacy indicator, however, takes only

C2

Odds ratios (OR) associated with the different departments (ref. Paris) in logistic regressions explaining each of the two indicators



Adjustment for sex, age group (85 and over vs 75-84), the affiliate regime (ref. NHI), the department of residence (ref. Paris), the LTI status (1, 3, 5, 8, 12, 13, 14, 15, 16, 19, 22, 23 and 30), at least one prescription drug in the year by a specialist, at least one prescription in the year by a hospital doctor, the number of different prescribers year.

* Confidence intervals (CI) 95% of OR:

OR < 1: I'IC does not include 1; OR = 1: I'IC include 1; OR > 1 et < 2: I'IC does not include 1; OR > 2: I'IC does not include 1.

Source: IRDES.

Data: EGB, CNAMTS 2013.

Reading: In the logistic regression explaining the continuous indicator, the odds ratio associated with the Nord department is greater than 2.

into account long-term treatment. It is interesting when we question the essential drug therapies given the multiple illnesses of patients or the therapeutic or financial burden posed by chronic diseases on individuals. Finally, actions aimed at reducing polypharmacy target more easily long-term treatments than intercurrent acute conditions.

Monitoring the exposure of the population to certain therapeutic classes or

specific molecules is relevant in addition to a polypharmacy indicator. Tools have been developed to do so for many years, such as the Beers list in 1991, which lists potentially inappropriate drugs for the elderly in institutions (Beers *et al.*, 1991). Many updates have been made to this list and it has been generalised to all individuals aged over 65 years. Versions in countries other than the United States have also been published: the Priscus List in Germany (Holt *et al.*, 2010) and the

Laroche list in France (Laroche *et al.*, 2007).

The use of a polypharmacy indicator for targeting the therapeutic load of chronic diseases quantitatively associated with algorithms identifying drugs with the risk of inappropriate prescription could constitute a comprehensive system of monitoring drug consumption in the elderly. ♦

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www.irdes.fr • Email : publications@irdes.fr

Director of the publication: Denis Raynaud • **Technical senior editor:** Anne Evans • **Associate editor:** Anna Marek • **Translator:** Agence Atenao •
Layout compositor: Damien LeTorrec • **ISSN :** 1283-4769.