WHICH INTERACTIONS BETWEEN HEALTHCARE EVENTS AND POLYPHARMACY? AN ANALYSIS FROM FRENCH DATA

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INTRODUCTION

Ageing of the population is associated with an increase in the number of people living with several chronic diseases leading to the administration of many drugs, also called polypharmacy. Polypharmacy particularly affects the elderly and exposes to various risks such as adverse drug events, falls or related conditions, increased use of healthcare services including hospital mortality and others health conditions. Furthermore, polypharmacy significantly increases the risk of potentially inappropriate prescribing of patient-related administration errors and of adherence issues. From an economic perspective, unjustified polypharmacy can be associated with an inefficient use of resources since it generates additional expenses linked to the consumption of unnecessary drugs as well as extra expenses related to the treatment of adverse effects of polypharmacy. Polypharmacy can be regarded as a negative externality because it induces an overconsumption of medications from the individual point of view and an overuse of financial resources from a collective point of view which are not internalized by the various care providers that prescribe excessively. Whether these extra expenses are supported by National Public Health Insurance, private insurances or patients, a reduction of unjustified polypharmacy would increase both individual and social welfare.

Polypharmacy does not suddenly occur, but the number of medications more or less regularly increases over the lifecycle depending on healthcare events staking the life of individuals. Multimorbidity is the first cause of polypharmacy. As a matter of fact, the number of medicines used increases with the occurrence of chronic diseases, such as cardiovascular diseases and among them hypertension, heart failure, coronary heart disease, osteoporosis, neurological diseases, endocrine diseases or diabetes, chronic obstructive pulmonary diseases, but also mental health...
conditions, depression or cognitive impairments including delirium or dementia (an exception has to be made concerning cognitive impairments for which some studies found a negative impact on drugs consumption). More generally, poor self-assessed health, suffering from a longstanding illness, chronic condition or disability, activities of daily living limitations or frailty are as well associated with polypharmacy.

Some demographic and socio-economic features are also associated with polypharmacy. Most of studies using multivariate logistic regression model highlight the positive impact of high age, female gender, low-level of education and deprived socioeconomic status on polypharmacy (between 5 and 10 drugs) and/or excessive polypharmacy (more than 9 or 10 drugs). Moreover, patients with private insurance or covered by insurance plans dedicated to the badly-offs (such as Medicare/Medicaid plans) seem to have more office-based visits resulting in polypharmacy than other patients.

Although number of studies have proposed interventions to reduce polypharmacy once installed, very little is known about the channels through which polypharmacy builds up over life and how each interaction with the healthcare system changes the number of the already prescribed medicines possibly leading to polypharmacy. Most of studies focus on hospitalization and their findings are contrasted. Some studies compare the number of drugs at admission and at discharge and most of them describe an increase in the number of prescribed drugs in the elderly (increase which could only be transitory but studies do not allow to answer this question). This increase may be related to the prescription of drugs for a brief period to complete a short course (as antibiotics for instance) or to treat an acute condition or exacerbation of a chronic condition. Otherwise, Hubbard and colleagues found, for people aged 70 and over, that hospitalization led to a statistically significant change in the level of polypharmacy between admission and discharge, either upward (some patients move from polypharmacy, i.e. from 5 to 9 drugs, to hyperpolypharmacy, i.e. more than 9 drugs) or downward (from hyperpolypharmacy to polypharmacy). Other studies consider lagged hospitalization (the past year) as a driver of polypharmacy. Using the European Health Interview Survey for Belgium, Walckiers found that having one inpatient hospitalization in the past 12 months was associated with polypharmacy whereas one day patient hospitalization had no impact. The comparison of two groups of patients, one with polypharmacy and the other without,
showed that 30% of the excessive polypharmacy group spent one or more nights in hospital compared with less than 8% of those with no polypharmacy\textsuperscript{23}. By contrast, a few studies found no association between polypharmacy at a given time and hospitalization or emergency room visits the previous year\textsuperscript{43, 44}, but one of these evidenced a change in the type of prescribed medications which drove costs upward\textsuperscript{45} whereas others did not notice any change in the clinical use of drugs or in the prevalence of specific drug classes.

Studying one year of healthcare claims data in Switzerland, six months before and six months after hospitalization, Blozik described an increase in the number of medications in the two quarters prior to hospitalization and a decrease in the two quarters after with the mean number of medications returning to its initial value in the last quarter\textsuperscript{46}. Interestingly, in this study, the mean number of additional drugs between the prehospitalization quarter and the post hospitalization quarter was higher for former users of medicines than for non-users.

We found a smaller number of studies about the impact of other types of healthcare on polypharmacy and no consensus seems to arise from this literature. For instance, Rohrer and colleagues found that polypharmacy is independent from the use of medical services in the previous year and that no seasonal pattern drives polypharmacy\textsuperscript{43}. Fano and colleagues’ study failed to emphasize an impact of GP’s characteristics on polypharmacy\textsuperscript{37}. In the primary care sector, results strongly depend on the definition of polypharmacy both concerning the elected threshold in terms of number of drugs and the simultaneity/continuity of drug prescriptions\textsuperscript{45}. Among studies evidencing the influence of healthcare providers on polypharmacy, one showed, all things else being equal, that having at least one contact with a GP or a specialist in the last two months was associated with polypharmacy\textsuperscript{34}. Another found a bivariate association between the number of GPs consultations and outpatient visits in the previous year and polypharmacy status\textsuperscript{23}. This was confirmed by Jörgensen who showed a relationship between the number of physician visits and multiple drug use\textsuperscript{47}. The number of different prescribers was also highlighted by some authors\textsuperscript{25, 48, 49} as a factor encouraging polypharmacy. One study highlighted that primary care providers’ visits were much more associated with polypharmacy compared to other care providers visits\textsuperscript{39}. Some studies dealt with the role played by care providers’ characteristics and found that heavy workload (high rate of surgery consultations and
telephone consultations), low number of listed patients and GP’s intrinsically high prescribing pattern were positively associated with polypharmacy whereas GP’s age or experience were not statistically significant. Finally, a study of Kim and colleagues pointed out that polypharmacy increased with the number of visits to different healthcare facilities.

Improving quality and efficiency of drug prescriptions among elderly patients has been an ongoing concern in France as well as in other countries in the recent years and numerous policies for monitoring and limiting polypharmacy have been regularly put forward. To target those policies, it is important to understand how polypharmacy builds up. The aim of this article is to identify which event(s) in the healthcare pathway can explain, all things else being equal, the (downward or upward) evolution of the number of drugs paying particular attention on people with polypharmacy. Based on the follow-up period from 2011 to 2014 of a panel representative of the French population covered by the public health insurance system, we were able to follow the changes in the number of reimbursed medicines for each quarter over four years. The novelty of our approach consists in the possibility of exploiting objective health insurance claims data in France over a long period (longitudinal data).

1 METHODOLOGY

1.1 DATABASE

Data used in this study have been extracted from the Permanent Sample of Health Insurance Beneficiaries “Echantillon généraliste de bénéficiaires” (EGB) which includes data from National Public Health Insurance comprising the three main schemes of the Statutory National Health Insurance which represent around 85% of National Health Insurance beneficiaries: the National Health Insurance Fund for Salaried Workers (CNAMTS, Caisse nationale d’assurance maladie des travailleurs salariés), the Mutual Fund for Agriculturals and Farmers (MSA, Mutualité Sociale Agricole) and the National Health Insurance Fund for Self-employed workers (RSI, Régime Social des Indépendants). EGB is a permanent representative sample of the French 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. This database contains anonymous
information on healthcare consumptions as well as on socio-demographic characteristics (age, sex, geographical information ...).

The specific database considered in this study, which is extracted from EGB, includes all persons who were aged 50 or over in 2011 and who received at least one reimbursement from National Public Health Insurance in 2011. Sample size is composed by 187,743 persons at the beginning of year 2011. For each person in the sample, information on their reimbursed drug consumption is collected over a four year period (from 2011 to 2014 or over a shorter period if the person dies before). From this information on drug reimbursement, a monthly indicator is created for each person in order to count the distinct level 5 Anatomical Therapeutic Chemical (ATC) classes (molecular level) reimbursed in the past three months. This period of three months is a common standard in drug studies because it corresponds to the maximum period for which the pharmacist is authorized to deliver drugs. Studying drug use through a three-month period enables to detect regularities. Hence, indicator for March 2011 is calculated by considering all distinct level 5 ATC classes that were reimbursed in January, February and March 2011. This indicator enables to follow changes in number of drugs reimbursed to each patient over time.

Moreover, various events of the care pathway of each person are collected as well over the same four year period (from 2011 to 2014 or a shorter period if the individual dies before) every time they occur and with the precise date of the events: hospital care, emergency admissions, outpatient consultations, GPs or specialists’ consultations and admission into the Long Term Disease scheme (LTD), the so-called ALD scheme in France which aims at reducing the financial burden of medical care for national insurance beneficiaries suffering from a long-term and costly illness and which also provides a protocol of care based on good practice recommendations to its beneficiaries. For each type of event and for each person in the sample, a monthly dummy variable takes the value 1 when the event occurred at least once during one month, 0 otherwise. Consequently, it is possible to reconstruct the entire care pathway of each person in the sample, with 48 dummies for each event corresponding to a 48-months observation period. The completed database enables to link for each person changes in number of drugs with specific events of care pathways.

However, for some individuals, it is possible to observe variations in the number of prescribed drugs while these persons do not have any identified healthcare event during one
semester or more. This surprising result may be explained by the fact that some specialist’s consultations were not included in our database, such as technical procedures or psychiatric hospitalisations, because the extraction of data on consultations was solely based on GPs consultations (identified as C consultations in the database) or on specialists consultations (identified as CS consultations in the database). Consequently, a consultation related to, for instance, a technical procedure, will not appear as a consultation in the database (the code CS does not apply), thus potentially suggesting that the patient did not experience any healthcare event while he has been prescribed numerous drugs during this “invisible” consultation.

1.2 STATISTICAL ANALYSIS

A double classification has been considered in this paper, integrating two different dimensions: the number of reimbursed drugs at baseline and the evolution of this number over time (2011-2014). In order to work on a homogenous sample, we only select a balanced panel allowing to follow people during the entire period.

This approach allows analysing people’s drug consumption profiles considering both the initial drug consumption in 2011, and its evolution during the next three years. Consequently, we should be able to explain whether a single healthcare event can increase or decrease people’s number of drugs reimbursed.

We proceeded in three steps:

1) In the first step, individuals are classified according to the number of drugs they were reimbursed during the first year of observation i.e. the year 2011. We obtain a classification noted $C_b$.

2) In a second step, people are classified according to the evolution of their consumption between 2011 and 2014. We obtain a second classification noted $C_e$.

3) In a third step, we cross the variables of classes obtained through $C_b$ and $C_e$ and we thus split our population sample depending on each combination of classes people belong to.

In the first step (classification regarding the baseline), proximity between people reflects close level of drugs consumption in 2011, and in the second step, it reflects positive
correlation between month-to-month variations of the indicator of drug consumption over the 4 years of observation.

For the first and the second step, we implement an ascending hierarchical classification followed by a K-mean clustering. Ascending hierarchical classifications enable to determine how many clusters should be retained with regard to intra-cluster inertia. It also produces a first approximation of the k clusters “centroids”. On the basis of these initial centroids, K-mean clustering determine by a stepwise procedure the best classification (i.e. the one with the lowest intra-cluster inertia) among the k-groups partitions.

The classification regarding the baseline levels of the number of prescribed drugs (step 1) provides 4 groups (See Table 1: Distribution of population according to baseline level and drug profile evolution).

- The group 1 (4.5% of individuals) which is composed of persons who are reimbursed for a very high number of drugs per month (average above 15 drugs);
- The group 2 (20.2% of individual) which aggregates people who are reimbursed a high number of drugs per month (average around 13 drugs);
- The group 3 (26.8% of individuals) which is defined by people who are reimbursed a medium number of drugs per month (average around 8 drugs);
- The group 4 (48.6% of the individuals) which corresponds to people who are reimbursed a low number of drugs per month (average below 5 drugs).

Then, the classification regarding the evolution of drug consumption (step 2) has been set up from 2011 to 2014, independently of the first classification. This second approach also provided 4 classes:

- The group 1 (23.5% of the sample; see Table ) which corresponds to a decrease in the number of drugs;
- The group 2 (33% of the sample) which corresponds to a cyclic evolution of the number of drugs (a transitory increase during winter times). It is the biggest cluster;
- The group 3 (23.85% of the sample) which gathers people whose number of drugs progressively increased from 2011 to 2012 and decreased until 2014;
- The group 4 (19.65% of the sample) which corresponds to an increase of drugs consumed over the whole period. We decided to split this group into three sub-
groups depending on the scope of the increase. The group 4-1 (3.7% of the sample) consists of people with a weak progressive increase of drug use, group 4-2 (5.9% of the sample) includes people with a medium or a strong progressive increase of drug use and group 4-3 (10% of the sample) gathers other profiles.

Finally, due to the subclustering of the group 4, we obtain six groups concerning the profile of the evolution of drug consumption.

Combining both classifications, our analysis was conducted for all 24 possible configurations, 4 times 6 classes (see table 1). In the following part, each case is identified by \( I – j \) where \( I \) is the index of the group from classification \( C_p \), and \( j \) the index of the group from classification \( C_e \). For instance, the class noted “1-4-2” consists of people with a very high level of drug consumption at baseline which progressively increases over time in a medium/strong way (see table 2). Graph 1 displays the 24 different drug consumption profiles.

<table>
<thead>
<tr>
<th>Baseline consumption</th>
<th>1 (very high)</th>
<th>2 (high)</th>
<th>3 (medium)</th>
<th>4 (low)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Decrease</td>
<td>1828 (2.12%)</td>
<td>6369 (7.38%)</td>
<td>5481 (6.35%)</td>
<td>6628 (7.68%)</td>
<td>20306 (23.53%)</td>
</tr>
<tr>
<td>2 Increase in winter</td>
<td>1086 (1.26%)</td>
<td>5687 (6.59%)</td>
<td>8393 (9.72%)</td>
<td>13314 (15.43%)</td>
<td>28480 (33.00%)</td>
</tr>
<tr>
<td>3 Increase until 2012 and then decrease until 2014</td>
<td>505 (0.59%)</td>
<td>3116 (3.61%)</td>
<td>4944 (5.73%)</td>
<td>12022 (13.93%)</td>
<td>20587 (23.85%)</td>
</tr>
<tr>
<td>4 – 1 Weak progressive increase</td>
<td>112 (0.13%)</td>
<td>363 (0.42%)</td>
<td>744 (0.86%)</td>
<td>2004 (2.32%)</td>
<td>3223 (3.73%)</td>
</tr>
<tr>
<td>4 – 2 Medium and strong progressive increase</td>
<td>137 (0.16%)</td>
<td>757 (0.88%)</td>
<td>1384 (1.60%)</td>
<td>2823 (3.27%)</td>
<td>5101 (5.91%)</td>
</tr>
<tr>
<td>4 – 3 Other increase profiles</td>
<td>170 (0.20%)</td>
<td>1136 (1.32%)</td>
<td>2147 (2.49%)</td>
<td>5162 (5.98%)</td>
<td>8615 (10.00%)</td>
</tr>
<tr>
<td>All</td>
<td>3838 (4.45%)</td>
<td>17428 (20.19%)</td>
<td>23093 (26.76%)</td>
<td>41953 (48.61%)</td>
<td>86312 (100%)</td>
</tr>
</tbody>
</table>

Note for the reader: the columns display the number of drugs reimbursed at baseline and the lines display the different evolution profiles of the drug consumption. Persons with a very high base line consumption (column 1) and with a decreasing trend of drug consumption (line 1) are 1828 and represent 2.12% of the sample.

Source: Permanent Sample of Health Insurance Beneficiaries (Échantillon Généraliste de Bénéficiaires, EGB), Cnamts
Table 2: Two steps typology

<table>
<thead>
<tr>
<th>1\textsuperscript{st} number</th>
<th>2\textsuperscript{nd} number</th>
</tr>
</thead>
<tbody>
<tr>
<td>corresponds to the baseline number of drugs</td>
<td>corresponds to the evolution of drug use</td>
</tr>
<tr>
<td>1: very high</td>
<td>1: decrease</td>
</tr>
<tr>
<td>2: high</td>
<td>2: cyclic consumption (standard)</td>
</tr>
<tr>
<td>3: medium</td>
<td>3: increase from 2011 to 2012 followed by a decrease from 2013 to 2014</td>
</tr>
<tr>
<td>4: low</td>
<td>4-1: weak progressive increase</td>
</tr>
<tr>
<td></td>
<td>4-2: medium and strong progressive increase</td>
</tr>
<tr>
<td></td>
<td>4-3: profiles with a consumption peak</td>
</tr>
</tbody>
</table>

Graph 1: double classification including the baseline level and the evolution over time
1.3 **ECONOMETRIC STRATEGY**

Multinomial (unordered) logistic regression models have been used on persons who had at least one healthcare event (hospitalisation, consultation...) over the 2011-2014 period and who were still alive in 2014. We model the probability to be in a specific drug consumption profile in function of the number of month spent with a specific event. The general equation of the multinomial logistic regression is as follows:

$$\ln \left( \frac{P(Y_i = S_j | X_i)}{P(Y_i = S_{0,j} | X_i)} \right) = b_0 + b \cdot X_i + u_i$$

With:

- The outcome variable \(Y_i\) is a categorical (polytomous) response variable corresponding to 6 drug consumption profiles (see table 2).
- \(P(Y_i = S_j | X_i)\) corresponds to the probability to be in the considered drug consumption profile
- \(P(Y_i = S_{0,j} | X_i)\) corresponds to the probability to be in the reference group
  - The ratio \(\frac{P(Y_i = S_j | X_i)}{P(Y_i = S_{0,j} | X_i)}\) corresponds to the probability to be in the considered group relatively to the probability to be in the reference group.
- \(X_i\) corresponds to the vector of explanatory variable ‘number of month’ with hospitalization, specialist care and generalist care and admission in the LTD scheme. For admission in the LTD scheme, we have separated the variable in ten categories, using six months intervals. Thus, categories are the following: people who never benefit from the scheme during the observation period, people who benefit from the scheme for 1 to 6 months, those who benefit for 7 to 12 months, etc...and finally people who benefit from the scheme for 43 to 48 months. Those who benefited from the LTD scheme before January 2011 represent the tenth category. \(b\) corresponds to the vector of the coefficient associated with regressors and control variables (results are controlled for gender and age).
- \(b_0\) corresponds to the intercept
We performed multinomial logistic regression by the baseline drug consumption level and, in fine, we have set up 4 regressions on our sample. We used for each baseline level the group who had a cyclic increase during winter times as reference. Modalities of reference are the groups $X - 2$ with X being the baseline drug consumption level. This point matches with the standard consumption of each baseline drug consumption level. This approach allows us to identify, for a specific baseline drug consumption level, which of the events most contribute to the increase in drug consumption, and whether there is some behaviour differences between the 4 baseline groups.

2 DESCRIPTIVE STATISTICS

Our results show that the most frequent healthcare events are GPs’ consultations (G), since individuals in our database consult their GPs for at least 20 months over the 2011-2014 period (table 3). GPs consultations are even more frequent with increasing age (20 months spent in GPs consultations for people aged 50-59 and nearly 28 months for people aged 80-89). Women consult their GPs for a significantly higher number of months (24 months versus 22 months for men). On the contrary, specialist’s visits (S) are notably less common with only 7 months for people aged 50-59. Increasing age before 80 is associated with a higher number of months spent in consulting specialists (7.9 at the age of 80) before a decrease beyond the age of 80. Women consult their specialists for a higher number of months comparatively to men (7.4 versus 6.6). Not surprisingly, hospitalization (H) is a very rare healthcare event, with no more than 2 months spent in hospital on average. The number of months spent in hospitalization seems to increase with age but does not vary according to gender.

Being admitted in the LTD scheme can be considered as a specific event, even if it simultaneously occurs with other events (hospitalisation, consultation...) because admission forms to the LTD scheme are generally filled in during a healthcare event.

The absence of healthcare event ("No event", table 3) is very frequent: on average, people aged 50-59 years spend 24 months with no healthcare event over the period 2011-2014.
This number of months significantly decreases with age (only 17 months for people aged 80-89).

Table 3: Average number of months spent in each healthcare event over the four year period (2011-2014)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalisation</th>
<th>GP</th>
<th>Specialist</th>
<th>&quot;No event&quot;</th>
<th>LTD scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 years</td>
<td>0.71</td>
<td>20.31</td>
<td>6.76</td>
<td>24.08</td>
<td>3.23</td>
</tr>
<tr>
<td>60-69 years</td>
<td>0.93</td>
<td>21.96</td>
<td>7.42</td>
<td>22.15</td>
<td>4.41</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.34</td>
<td>25.17</td>
<td>7.90</td>
<td>19.01</td>
<td>5.45</td>
</tr>
<tr>
<td>80-89 years</td>
<td>1.81</td>
<td>27.81</td>
<td>6.21</td>
<td>17.25</td>
<td>6.11</td>
</tr>
<tr>
<td>90 and over</td>
<td>2.02</td>
<td>27.36</td>
<td>3.58</td>
<td>18.79</td>
<td>6.80</td>
</tr>
<tr>
<td>Men</td>
<td>1.15</td>
<td>21.73</td>
<td>6.56</td>
<td>22.80</td>
<td>5.13</td>
</tr>
<tr>
<td>Women</td>
<td>1.06</td>
<td>23.98</td>
<td>7.41</td>
<td>20.31</td>
<td>4.15</td>
</tr>
</tbody>
</table>

Note for the reader: over the period 2011-2014, individuals aged 50-59 consult their GPs for a period of 20 months on average.

Source: Permanent Sample of Health Insurance Beneficiaries (Échantillon Généraliste de Bénéficiaires, EGB), Cnamts

The proportion of people admitted in the LTD scheme from 2011 to 2014 (table 4) who consult their GPs (94.6%) is not statistically different from the proportion of other persons who consult their GPs (95.5%). On the contrary, people admitted in the LTD scheme more frequently consult a specialist than other insured people (70% versus 61%). Similarly, people in the LTD scheme are more frequently hospitalized (24% versus 10%).

Table 4: Healthcare event frequency according to the LTD scheme status

<table>
<thead>
<tr>
<th>LTD Modalities/ At least one healthcare event</th>
<th>Hospitalisation</th>
<th>GPs</th>
<th>Specialists</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTD: admission</td>
<td>45.5%</td>
<td>92.5%</td>
<td>79.9</td>
<td>100</td>
</tr>
<tr>
<td>LTD: No</td>
<td>10.4%</td>
<td>95.5%</td>
<td>60.7</td>
<td>100</td>
</tr>
<tr>
<td>LTD: Yes</td>
<td>24.5%</td>
<td>94.6%</td>
<td>70.1</td>
<td>100</td>
</tr>
<tr>
<td>LTD: before 2011</td>
<td>22.3%</td>
<td>94.8%</td>
<td>69.1</td>
<td>100</td>
</tr>
</tbody>
</table>

Number of persons (%)  
LTD: admission  
LTD: No  
LTD: Yes  
LTD: before 2011  

Source: Permanent Sample of Health Insurance Beneficiaries (Échantillon Généraliste de Bénéficiaires, EGB), Cnamts

Note for the reader: over the period 2011-2014, 94.8% of people who were admitted in the LTD scheme before 2011 consulted a GP at least once.
On average, French people aged 50 or more have been reimbursed seven different drugs every month in 2011. This figure remains constant during the follow-up period. The number of drugs being reimbursed also varies with patient age (Graph 2). Before the age of 80, getting older is associated with a higher number of drugs (less than 4 on average for people aged 50-59 years old and more than 8 drugs on average for people aged 80-89 years old), which may be explained by a deterioration in health. From 80 to 90 years old, the number of drugs reaches a steady level before decreasing after 90 years old (a selection effect due to the fact that people still alive at this age are in better health may explain the decrease in the number of drugs).

Furthermore, the prescription of drugs in the female population is significantly higher than men. However, the gap was larger in 2011 (1.1 drug) than in 2014 (0.7 drug).

In our database, the number of reimbursed drugs mainly varies over time as a result of healthcare events.

However, 26% of the people with no interaction with the healthcare system experienced an increase in the number of reimbursed drugs in 2011 (results not shown, EGB, CNAMTs). In this population “without interaction with the healthcare system”, one part does not really have any healthcare event during a period of time, which is not surprising if we consider that
people were selected from the age of 50 and over and that some of them must be healthy. At the same time, another part of this population of people “without interaction” may be composed of people who consult physicians for specific consultations such as technical procedures, nursery care or psychiatric hospitalisations. In the French database, those specific consultations are differently coded comparatively to usual consultations and were not considered in our analysis.

Mean values of month-to-month variations of reimbursed drugs were computed for the 3 months before and 3 months after each event considered: generalist visit, specialist visit, hospitalization and admission in the long term disease scheme (see graph 3). For all events, except for admission in the LTD scheme, the number of reimbursed drugs progressively increases in the three months before the event (+0.3 drug, whatever the type of event). At the time of the event, the increase in the number of reimbursed drugs reaches a peak (+1 drug). Then, the number of reimbursed drugs decreases 3 months after the event (-1.3 drugs). These results tend to suggest that none of these events, taken alone, can be responsible for an increase in the number of reimbursed drugs.

Regarding admission in the LTD scheme (3), the number of reimbursed drugs differs at three various stages. Firstly, we note a progressive increase in the number of drugs during the 3 months before admission (+0.4 drug in average), then follows a peak at the moment of admission and one month after (+1.4 drugs in average). Finally, three months after, the number of reimbursed drugs decreases (-0.7 drug in average), but not in a proportion sufficient to compensate for the initial increase. Consequently, our results might suggest that admission in the LTD scheme could potentially be associated with an increase in the number of reimbursed drugs.
3 Results

Due to the multiplicity of cases described by the outcome variable, we focus only on people with increasing or decreasing trend of drugs consumption. Results were produced for each baseline group using a reference specific to the baseline group (see tables 4A and 4B). These results enable to evaluate the probability that a given healthcare event is associated with the drug consumption profile considered, for a given baseline group.

For the groups with very high drug consumption at baseline (indexed as “1-X”), our results show that health events are not associated with a significantly greater or lower probability to pertain to the group with an increase of the drug consumption (group 1-4) and the reference group 1 – 2. None of the health events analysed is significantly associated with the group 1-4 compared to the group 1-2. On the contrary, hospitalisation and “no-event” are associated with the group with a decreasing drug consumption (group 1 – 1).
Except for the lowest baseline level of drug consumption (4-1), we find that hospitalisation is positively associated with all decreasing profiles (1-1; 2-1 and 3-1). This point suggests that hospitalisation could be associated with a rationalisation of drug consumption. However, we also found an opposed effect of hospitalisation with a positive association with groups with an increase in drug consumption (2-4; 3-4 and 4-4) with the exception of the group with the highest baseline level (1-4) in reference to group 1-2.

We also note that there is no difference in terms of GP visits between groups with increasing drug consumption. For the two lowest baseline groups with decreasing trends in drug consumption, we find a negative association of GP visits: the higher the number of GPs visits the lower the probability to belong to a decreasing profile group.

Visits to a medical specialist are most of the time negatively associated with drug consumption profiles. These results may highlight a potential substitution effect between drug and specialist care resulting from a GP strategy. The negative impact of medical specialists on profiles with decreasing trends suggests that people with decreasing drug consumption profiles do not often see a specialist. For profiles with increasing trends, people with low levels of baseline consumption have lower probability to visit medical specialists whereas people with high consumption at baseline have higher probabilities.

**Association of LTD enrolment with increasing trends**

For groups with an increase in drug consumption and low, moderate and high baseline levels (1-1, 1-2, 1-3), we note a positive association with spells of enrolment in the LTD scheme, with comparable patterns (table 4B). In particular, effects are slightly lower for individual who were enrolled in the two first semesters of the observation period than for people who were enrolled later (people who benefited from the scheme for 1 to 6 months or for 7 to 12 months). For the very high baseline level (group 1-4) switching to the LTD scheme is not associated with a higher probability to have an increasing trend, except for individuals who were admitted during the first semester of 2013.

**Association of LTD enrolment with decreasing trends**

For people with a very high baseline level and a trend of decrease (group 1 – 1), we observe no significant association of the spell of enrolment into LTD while there is a significantly negative association between the spells of enrolment and the decreasing trend level for
groups with high and medium baseline levels (3-1 and 2-1). Finally, for the lowest baseline level with decreasing drug consumption profile (group 4-1), effect of spells of enrollment are contrasted: the latest spells are negatively associated with this profile whereas the earliest spells of enrollment and being enrolled before 2011 are positively associated.

Table 4A: results on the global effect of the considered events

<table>
<thead>
<tr>
<th>Baseline number of drugs (2011)</th>
<th>Trend (2011-2014)</th>
<th>Hospitalisation effect</th>
<th>GP’s visits effect</th>
<th>Specialist visits effect</th>
<th>No events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : very high</td>
<td>1 : decrease</td>
<td>Positive</td>
<td>NS</td>
<td>NS</td>
<td>Positive +</td>
</tr>
<tr>
<td>2 : high</td>
<td>1 : decrease</td>
<td>Positive +</td>
<td>NS</td>
<td>Negative -</td>
<td>Positive +</td>
</tr>
<tr>
<td>3 : medium</td>
<td>1 : decrease</td>
<td>Positive +</td>
<td>Negative -</td>
<td>Negative -</td>
<td>Positive +</td>
</tr>
<tr>
<td>4 : low</td>
<td>1 : decrease</td>
<td></td>
<td>Negative -</td>
<td></td>
<td>Negative -</td>
</tr>
<tr>
<td>1 : very high</td>
<td>4 : increase</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2 : high</td>
<td>4 : increase</td>
<td>Positive +</td>
<td>NS</td>
<td>Positive +</td>
<td>Negative -</td>
</tr>
<tr>
<td>3 : medium</td>
<td>4 : increase</td>
<td>Positive +</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>4 : low</td>
<td>4 : increase</td>
<td>Positive +</td>
<td>NS</td>
<td>Negative -</td>
<td>Negative -</td>
</tr>
</tbody>
</table>

Source: Permanent Sample of Health Insurance Beneficiaries (Échantillon Généraliste de Bénéficiaires, EGB), Cnamts

Note for the reader: the reference group is 1 – 2 (very high level of drugs at baseline and cyclic consumption during the follow-up)

Table 4B: Effect of spells of enrolment into LTD on the probability to have decreasing or increasing trends

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Trend</th>
<th>Length of enrolment in LTD during the observation period (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1-6 1.08 1.08 1.25 1.06 0.69 0.93 0.75 1.10 (NS) (NS) (NS) (NS) (NS) (NS) (NS) (NS)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.65 0.58 1.01 0.64 0.93 0.69 0.82 0.88 0.86 (-) (-) (-) (-) (-) (-) (-) (-)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.82 0.76 0.57 0.93 0.83 0.90 0.67 1.20 0.91 (NS) (NS) (NS) (NS) (NS) (NS) (NS) (NS)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.67 0.71 0.81 0.94 1.02 1.73 0.98 1.63 1.30 (-) (-) (NS) (NS) (NS) (NS) (NS) (NS)</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>1.03 0.38 1.45 4.65 0.51 1.64 1.02 1.05 1.47 (NS) (NS) (NS) (NS) (NS) (NS) (NS) (NS)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1.44 1.69 1.38 2.08 1.77 0.87 1.34 1.67 1.46 (+) (+) (+) (+) (+) (+) (+) (+)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1.37 2.22 1.15 1.82 1.96 1.68 1.09 1.46 1.39 (NS) (NS) (NS) (NS) (NS) (NS) (NS) (NS)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1.29 2.82 1.64 2.26 1.95 1.76 0.80 1.18 1.35 (+) (+) (+) (+) (+) (+) (NS) (NS)</td>
</tr>
</tbody>
</table>

Note for the reader: effects are displayed as odds-ratio. They are positive when the value is above 1 and negative when the value is below 1.

Source: Permanent Sample of Health Insurance Beneficiaries (Échantillon Généraliste de Bénéficiaires, EGB), Cnamts

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4 DISCUSSION

Among the four healthcare events whose impact on drug consumption is analysed, admission to the LTD scheme favours the increase in the number of medicines in almost all situations. Indeed, admission to the LTD scheme is positively associated with the probability of belonging to profiles with an increasing trend of drug consumption and negatively associated with profiles with decreasing trends. On the contrary, hospitalization has a contrasted effect: it is positively associated with both increasing and decreasing profiles. Visits to medical specialists are in almost all situations negatively associated with drug consumption profiles, whereas visits to GPs are also negatively associated with drug consumption profiles but only with the two decreasing profiles with low or medium baseline levels.

Admission to the LTD scheme has a strong association with all profiles except for the profiles with the highest level of drug consumption at baseline. Although our methodology does not allow detecting a causal relation between admission to the LTD scheme and increase in the number of medications, it is very likely that this causal relation is real. Actually, LTD scheme was designed by National Public Health Insurance in 1945 in order to reduce out of pocket payments of certain groups of chronic diseases (four groups of diseases in 1945 and 32 at this time). Cardiovascular diseases, malignant tumors, diabetes and psychiatric disorders are currently the most frequent diseases concerned by the LTD scheme\textsuperscript{51}. In 2016, individuals covered by the LTD scheme represent 16% of National Health Insurance Beneficiaries\textsuperscript{52}. For each disease in the scheme, National Public Health Insurance covers health expenditure that is linked to the disease whatever the patient’s level income and leaves the patient a co-payment for other healthcare expense not related to the disease. At the same time, each patient admitted in the LTD scheme is theoretically being delivered healthcare that is in line with good practice guidance, also in terms of drug prescription, in the framework of a treatment protocol. Thus, admission to the LTD scheme is possibly linked to an intensification of the treatment of certain diseases which can take the form of an addition of one or more medications. The link between polypharmacy (or the increase in the number of medications taken by individuals) and the occurrence of chronic diseases has been well established in the literature for chronic diseases like heart failure\textsuperscript{30-32}, coronary heart
disease\textsuperscript{30-33}, diabetes\textsuperscript{23, 25, 30, 32, 33}, chronic obstructive pulmonary diseases\textsuperscript{30-33}, all diseases that are amongst the most frequent diseases included in the LTD scheme. The negative association of admission to the LTD scheme with profiles with a decreasing trend of drug consumption can also be interpreted in the same way. Given the fact that having a chronic disease increases the number of medications, it is expected that people who have been admitted to the LTD scheme have a lower probability to belong to profiles with a decreasing trend of drug consumption.

When initial level of consumption of drug is low, being enrolled into LTD scheme as early as 2011 increases the probability to belong to decreasing profiles compared to profiles with stable drug consumption, suggesting that suffering from LTD can be associated in the long run with decreasing drug consumption. This could be explained by the fact that we did not take into account some temporary LTD schemes (myocardial infarction, cancer...) which we kept as permanent for the length of the study. For people enrolled in temporary LTD schemes before 2011, it is possible that they had exited the scheme at the time of the study, and because they don’t need any treatment for the LTD anymore, have a higher probability to belong to decreasing profiles.

Although significant, the association between hospitalisation and profiles of drug consumption is weaker with ORs not exceeding 1.06. The fact that the associations are positive in both increasing and decreasing profiles leads to opposite interpretations. As before, our methodology does not permit to establish the sequence of events and therefore we don’t know whether hospitalisations precede the change in the number of medicines or occur as a consequence of the increase in the number of drugs.

A positive association with profiles with increasing trends of drug consumption can be interpreted twofold, depending on the timing of hospitalisation. If hospitalisation occurs before the increase in the number of drugs, we can assume that the reason for hospitalization was the onset or the exacerbation of a condition requiring the addition of a new treatment for a shorter or longer period. This can result in polypharmacy as it was shown in several studies\textsuperscript{25, 30-32, 34, 36, 53}. If hospitalization occurs after the increase in the number of drugs, this could indicate that the reason for hospitalisation was linked to the change in the number of drugs. This has been largely described in previous studies which
showed that polypharmacy increased the use of several healthcare services, including hospitalisation. Both interpretations are consistent with our results.

Positive associations with profiles with decreasing trends of drug consumption suggest that hospitalisation could also be associated with a rationalisation of drug consumption. As more and more attention is paid to the need to reduce polypharmacy, the fact that we observe a higher probability of being hospitalized for the three highest baseline level of drug consumption (respectively an average number of drugs of 8, 13 and superior to 15) and not for the lowest (average inferior to 5) supports this assumption.

For the two other events that we analysed, GP visits and medical specialist visits, results are mixed and more uncertain.

Concerning visits of GPs, we observe only two significant associations and both are negative with profiles with decreasing trends and the lowest consumption at baseline. This means that the probability for consulting a GP was lower for people who experienced a decrease in the number of drugs they were reimbursed for, which is quite consistent as only prescribed drug can be reimbursed by National Public Health Insurance in France. Our results also show that GPs consultations never play a role in explaining increasing profiles, which is quite consistent with Rohrer et al., 2013, who shows that polypharmacy is independent to the use of medical services in the previous year. By contrast other studies support the hypothesis of polypharmacy as a consequence of recent contact with GPs.

Profiles with decreasing trends of drug consumption are negatively associated with medical specialists’ visits, meaning that the probability for consulting a medical specialist is lower in case of decreasing trends than for stable trends of drug consumption. Another way to interpret this result is that the decrease in drug consumption is lower when people mostly consult specialists. As for GPs this result was expected because only prescribed drugs can be reimbursed by National Public Health Insurance. It also confirms our inverse hypothesis that consulting a medical specialist can lead to an increase in the number of prescribed drugs. The literature is not unanimous about the impact of specialist’s visits on polypharmacy. Some works found no effect whereas other highlighted a positive influence.

Finally, we find contrasted results for profiles with increasing trends of drug consumption. For already high baseline levels of consumption, the probability of consulting a MS was
higher which means that for those profiles, consulting a specialist may increase drug prescription. On the contrary, for low baseline levels of prescription but associated with an increasing trend, the probability of consulting a specialist was lower. For this latter profile, the increase in the number of drugs prescribed is mainly associated with more exceptional events such as admission to the LTD scheme or hospitalization.

Our results concerning the “no healthcare event” are quite consistent with what was expected: “no healthcare events” are most of the time positively associated with decreasing trends and on the contrary negatively associated with increasing trends, which shows that our population that experiences this type of event is mostly composed of persons who really are non-consulting patients: they do not have any contact with physicians or the health system for a long period of time. On the contrary, the part of the population concerned by specific consultations such as technical procedures, nursery care or psychiatric hospitalizations, i.e. false non-consulting patients must represent a very small proportion because they do not seem to have any impact on the results of the whole “no healthcare event” category.

Our study has some limitations.

Our measure of polypharmacy is limited to drugs reimbursed by National Public Health Insurance. Consequently, OTC drugs are not recorded in the total number of drugs being prescribed to individuals. However, this limit is not specific to our study.

Individuals in long term care institutions are excluded from our sample which could lead either to an underestimation of polypharmacy, if we consider that people not living in institutions are in better health, or to an overestimation if we think that care and non-care providers in these institutions contribute to improve the rationalization of medication use.

LTD schemes are all considered to be permanent whereas we know that some can be temporary and stop when treatment is completed, as for example in cancer or myocardial infarction. However, following an analysis from the French Court of Auditors¹ in 2016 we believe that the number of individuals who exit the LTD scheme is small and unlikely to change the results except for the case of low baseline level with decreasing consumption which we mentioned before.

¹ http://www.ccomptes.fr/Accueil/Publications/Publications/La-securite-sociale4
Some specialist’s consultations were not included in our database since extraction was solely based on GPs consultations, identified as “C” consultations, and specialists consultations, identified as CS consultations in the database. Consequently, a consultation related to a technical procedure, for instance, not identified as a CS consultation in the EGB database, will not appear in our database. However, our results tend to show that the magnitude of this bias is probably low, because the “no event” category mainly reflects what is expected from real non-consulting patients.

Our results do not allow understanding which events explain the increase in the number of drugs being prescribed to patients with a very high level of drugs at baseline, while it would be of a great policy interest.

Furthermore, the impact of healthcare events on polypharmacy must hide some confounding factors because we do not control for health state and/or the nature of health events leading to encounter the healthcare system (casemix effect). Unfortunately, database does not provide this information. In a second step, we could perform a panel analysis based on difference-in-differences (before/after the healthcare event) allowing to evaluate the evolution of number of reimbursed drugs. This methodology could take into account reverse causality and unobserved heterogeneity.

Finally, this work analyzes the impact of healthcare events on the evolution of drug consumption during four years by controlling for the level of drugs consumed at baseline. It could be of interest to study the impact of healthcare events on drug consumption at baseline. The sum of both effects could explain the whole impact of different healthcare events on the gap in terms of drug consumption between two dates of a given period.

5 Conclusion

This study provides new insights on the healthcare events linked to the onset and/or increase of polypharmacy. The major role played by the LTD scheme in explaining the increase in the number of drugs delivered to patients suggest that chronic diseases are the first reason for polypharmacy which is often legitimate in cases of concomitant pathologies.
or in complex medical situations. Inversely, it becomes problematic when one or more medications are inappropriately prescribed or when the anticipated benefit for the patient is not obtained. Hospitalization has a contrasted effect. Associated with increasing profiles it suggest that it contributes to polypharmacy when needed by the treatment protocol. When associated with decreasing profiles it suggests that deprescribing processes are already underway in some patients. GPs and medical specialists role seems to be of minor importance in building polypharmacy.

Consequently, from a public policy perspective, fighting polypharmacy includes upstream interventions in order to prevent the increase of the number of prescribed drug. This can be achieved by providing prescription guidance for elderly people and for people with multiple chronic diseases. It seems also important to regularly check that all LTD protocols follow very closely recommendations issued by health authorities —as soon as they are updated—, in order to ensure that no unnecessary drugs appear in those protocols. Finally, once polypharmacy is established, downstream interventions include extensive promotion of medication reviews and diffusion of deprescribing guidelines.