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## Abstract

Purpose: This study analyses the relationship between medication use and frailty by considering the quantity of medications prescribed (polypharmacy) and the quality of medication prescribing (according to French criteria for Potentially Inappropriate Medications - PIMs) in people aged 65 and over.

Methods: This is a cross-sectional study based on the data from a nationally representative study about health and use of healthcare resources in France (ESPS 2012). The number of frailty criteria was assessed among exhaustion, unintentional weight loss, muscle weakness, impaired mobility, and low level of physical activity. Polypharmacy and PIMs were assessed from the data of reimbursement by the National Health Insurance over the whole year 2012. PIMs were defined according to the Laroche list plus additional criteria dealing with inappropriate prolonged use of medications. The analyses used Poisson regression models, with the number of frailty criteria as dependent variable.

Results: The study population was composed of 1003 women and 887 men, of mean age 74.7 +/- 7.4 years. Polypharmacy (5 to 9 drugs) and excessive polypharmacy (≥10 drugs) were reported in 42.9% and 27.4% of the study population respectively, while 46.7% of the study population received at least one PIM during the year 2012. Polypharmacy and PIMs were both associated with the number of frailty criteria in models adjusted for socio-demographic and health characteristics of the participants. The prescription of anticholinergic medications was the only PIM that remained significantly associated with the number of frailty criteria after adjustment for polypharmacy.

Conclusions: Polypharmacy and use of anticholinergic medications are independently associated with frailty in old people.

Key words: aged; anticholinergic medications; frailty; inappropriate prescribing; polypharmacy

## Introduction

Frailty is defined as an increased vulnerability to stressors, resulting from a decrease in physiological reserves of multiple systems. It has been operationalized as a phenotype, determined by the presence of a critical number of impairments in physical strength, physical activity, nutrition, mobility and energy [1]. Epidemiological studies have shown that frailty is associated with a higher use of healthcare resources [2, 3] and predicts health outcomes such as occurrence or aggravation of functional limitations, falls, hospitalisations, and mortality [4, 5].

The concept of frailty is now well recognized by geriatricians and prevention stakeholders. Primary care physicians are encouraged to screen their patients for frailty and to address them when necessary to day hospitals where an evaluation of the causes of frailty will lead to a personalized care plan [6]. The reduction of polypharmacy is part of the intervention to manage frailty.

Epidemiological studies have shown that frail people are more likely to receive polypharmacy compared to non-frail individuals [7-11]. Polypharmacy exposes old people to various risks [12], notably adverse drugs events [13], falls [14], increased use of healthcare services, and mortality [15, 16]. Polypharmacy also increases the risk of receiving "potentially inappropriate medications" (PIMs), i.e. medications with a well-established risk of adverse effect in old people or medications with questionable efficacy. The first set of explicit criteria for PIMs was developed in 1991 by Beers et al to be used in nursing homes [17] and has since been updated several times and adapted in different countries.

In this context, this study aimed to analyse the relationship between medication use and frailty by considering the quantity of medications prescribed (polypharmacy) and the quality of medication prescribing (according to French criteria for PIMs) in people aged 65 and over participating in a

nationally representative study about health and use of healthcare resources in France where data about frailty and medications were thoroughly assessed.

## Methods

*Study design and population*

We used cross-sectional data from the 2012 French health, health care, and insurance survey (Enquête sur la santé et la protection sociale, ESPS) matched with National Health Insurance data. The survey, coordinated by the Institute for Research and Information in Health Economics (IRDES, Paris), was designed to be representative of the French population (1 individual included in ESPS being representative of 2231 individuals on average in general population). The source population consisted of the 599,544 individuals included in the EGB (Echantillon Généraliste des Bénéficiaires) in 2012, a permanent representative sample of the population covered by the French public health insurance. A random subsample of community-dwellers was drawn from the EGB; these reference individuals together with members of their household were eligible for the survey. A total of 8413 households representing 23,047 French residents took part in the 2012 survey. Among them, 14.2 % were 65 years old or more (3271 observations remaining). Survey respondents were then matched with National Health Insurance data (in the EGB) for 1955 observations. Unmatched individuals were those household members whose public health insurance was independent from the reference individual's health insurance known in the EGB. An additional 65 observations were discarded because we did not have information about medications for these individuals. Our analysis sample eventually consisted in 1890 community-dwellers aged 65 and over.

*Data collection*

Participants were first interviewed by telephone (or directly at home for people who did not have the telephone or for whom the telephone number was wrong) about the socio-demographic characteristics of their household. Information about their health status, access to health care services, health insurance, and the economic and social status of individuals were then collected by using self-administered questionnaires. Participants gave their informed consent and ESPS received the approval of the National Commission for Data Protection and Liberties (CNIL).

*Frailty definition*

Frailty was defined according to the construct derived from the Cardiovascular Health Study [1] adapted to declarative data. The five frailty dimensions were defined as follows:

- Exhaustion: self-reported physical fatigue or weakness or lack of energy;
- Unintentional weight loss of 5% of body weight during the past 12 months;
- Muscle weakness: difficulty carrying a bag weighting 5 kg (in the absence of difficulty using hands or fingers) or difficulty bending of kneeling down without help;
- Impaired mobility: difficulty walking 500 meters without help or difficulty going up or down a dozen or more steps without help;
- Low level of physical activity: no practice of walk, bicycle or sport (jogging, fitness, swimming, biking, etc.).

Further details about the assessment of frailty (exact formulation of the question and coding) are given in Appendix 1. Frail individuals were those reporting three criteria or more. Previous work

in ESPS 2012 showed consistency with other measures of the frailty phenotype in the general population [2], as in SHARE (the Survey of Health Ageing and Retirement in Europe) where objective measurements of gait speed and grip strength are available [18].

*Polypharmacy and potentially inappropriate medications*

The EGB contains exhaustive information on all the medications that were reimbursed to people during the year 2012. Medications are coded using the Anatomical Therapeutic Chemical (ATC) system. We estimated the number of medications used during the year 2012 by calculating the mean of the total number of medications used per 3-month periods. Polypharmacy was defined as five or more and excessive polypharmacy as 10 medications or more [7]. It included both regular and as required medications. PIMs were assessed over the whole year 2012 according to the Laroche list [19], which results from an expert consensus and takes into account drugs marketed in France. We excluded 5 criteria that required information about underlying conditions that could not be assessed here. Concomitant use of drugs corresponded to cases where two drugs were delivered on the same day. Based on current literature and national recommendations, we also considered inappropriate duration of treatment (3 reimbursements over a 4-month period) for some a priori selected drug classes, which were non-steroidal anti-inflammatory drugs [20] and benzodiazepines [20, 21], especially hypnotics [22].

*Other variables*

In addition to sociodemographic characteristics (age, gender, marital status, and education), information was collected about difficulties in doing alone 5 activities of daily living (ADL:

eating, dressing and undressing, getting in and out of bed, using the toilets, bathing or showering) and 7 instrumental activities of daily living (IADL: food preparation, using the telephone, shopping, managing medications, light housekeeping, heavy housekeeping, managing finances and administrative tasks). Participants were asked about their body mass index, self-perceived health on a 5-point scale, social isolation, and tobacco smoking. Chronic diseases (over the last 12 months) were assessed among a standard list of 13 diseases including asthma, chronic bronchitis/emphysema, heart attack, stroke/cerebral haemorrhage, coronary disease/angina, high blood pressure, osteoarthritis, back pain, neck pain, diabetes, allergy, liver cirrhosis, and depression. Some diseases were grouped as follows:

- Respiratory diseases: asthma, chronic bronchitis/emphysema;
- Cardiovascular diseases: heart attack, stroke/cerebral haemorrhage, coronary disease/angina, high blood pressure;
- Musculoskeletal diseases: osteoarthritis, back pain, neck pain.

*Statistical analyses*

The statistical analysis describes sociodemographic and health variables, including frailty and medication use. We used individual sampling weights (the inverse of the probability that the observation is included considering sampling design, age, gender, household size, and social security scheme) to provide representative estimates.

Complete information about the five frailty criteria was available in 70.7% of the study population. In the remaining 29.3% cases, we imputed missing data regarding frailty criteria according to age and gender (logit modelling and imputation of the variable as 1 when the

probability was more than 0.5, 0 otherwise). The proportion of frail individuals did not differ between the original and the imputed dataset (p=0.11). The prevalence of the original and imputed variables is given in the descriptive statistics.

The independent and combined effects of polypharmacy and PIMs on the progression of the frailty score from 0 to 5 were assessed by using Poisson regression models with the number of frailty criteria as the dependent variable. As first step of a multi-stage approach, we modelled the effect of polypharmacy and PIMs separately. Second, we adjusted the models for confounders, corresponding to the variables associated with the number of frailty criteria with a $p<0.20$. The final adjustment was obtained by progressively removing variables associated with frailty with a $p>0.10$. Third, we entered simultaneously polypharmacy and PIMs, as well as confounders, in the model. Eventually, we added an interaction term between polypharmacy and PIMs. Results are presented in terms of Incidence Rate Ratios (IRR, i.e. exponentiated coefficients) with 95% Confidence Interval (95%CI).

Note that the analytical choices (imputation, use of sampling weights, Poisson modelling, and robust standard errors) aimed to maximise the statistical power of the analysis, which is of particular importance when introducing interaction terms in the models. Sensitivity analyses were conducted to test the influence of imputation on the frailty variables by repeating the analysis with the original variables. Analyses were performed by using Stata® version 14.

## Results

*Population*

The study population was composed of 1003 women and 887 men, of mean age 74.7 +/- 7.4 years. They estimated their health good or very good in 39.7% of the cases. Musculoskeletal disorders were reported in more than half of the participants, followed by cardiovascular diseases, diabetes, and respiratory diseases. Frail people accounted for 16.4% of the study population, 14.8% when using the imputed variables. The characteristics of the study population are further described in table 1.

*Medication use*

Polypharmacy concerned 42.9% of the study population (n=799), and excessive polypharmacy 27.4% (n=474). Potentially inappropriate prescribing according to the Laroche list concerned 36.8% of the study population (n=664). When criteria assessing prolonged use of NSAIDs, benzodiazepines, and hypnotics were added, the prevalence of PIMs reached 46.7% (n=841). The most frequent PIMs involved benzodiazepines, anticholinergic drugs, NSAIDs, and cerebral vasodilators. Table 2 displays the frequency of the PIMs that concerned at least 1% of the study population. A complete description of the prevalence of PIMs is given in Appendix 2.

*Relationship between frailty, polypharmacy, and PIMs*

Models 1 and 2 of Table 3 show that both polypharmacy and inappropriateness of medications are associated with the number of frailty criteria in bivariate analysis. The Figure 1 illustrates the gradual increase in the prevalence of polypharmacy and PIMs with the number of frailty criteria. These associations remained significant after adjustment for confounders, including comorbidities in models 3 and 4 ($IRR_{5 \text{ to } 9 \text{ drugs}}$ =1.16, 95%CI [1.01-1.34]; $IRR_{10 \text{ drugs or more}}$ =1.45,

95%CI [1.25-1.69]; and $IRR_{PIM}$=1.18, 95%CI [1.07-1.30]). When polypharmacy and PIMs were both introduced in the model (model 5), excessive polypharmacy only remained significantly associated with the number of frailty criteria. Several PIMs were specifically associated with the number of frailty criteria in bivariate analysis but the only one that remained significantly associated with the number of frailty criteria after the introduction of confounders and polypharmacy in the model was the prescription of anticholinergic drugs as defined in the Laroche list. There was no significant interaction between polypharmacy and PIMs, meaning that there was no indication to stratify the analyses on the level of polypharmacy.

*Sensitivity analyses*

We obtained similar results concerning the association of the number of frailty criteria with polypharmacy and PIMs when analyses were replicated using the non-imputed variables for frailty (see table in Appendix 3), though the association with the prescription of anticholinergic drugs hardly remained significant.

## Discussion

*Main findings*

By analysing the data from a nationally representative study matched with National Health Insurance data, this study provides insights about the prevalence of polypharmacy and PIMs and about their relationships with frailty in community-dwelling people aged 65 years and over. Polypharmacy and excessive polypharmacy were reported in 42.9% and 27.4% of the study population respectively, while 46.7% of the study population received at least one PIM,

especially benzodiazepines, anticholinergic drugs, NSAIDs, and cerebral vasodilators. Polypharmacy and PIMs were both associated with the number of frailty criteria in models adjusted for socio-demographic and health characteristics of the individuals. The prescription of anticholinergic medications was the only PIM that remained significantly associated with the number of frailty criteria after adjustment for polypharmacy.

*Prevalence of polypharmacy and PIMs*

Our estimates of the prevalence of polypharmacy and PIMs are relatively high compared to previous estimates [7, 9, 11, 23], which was expected considering our methodology. Indeed, the prevalence of polypharmacy should be considered with regard to our definition that encompasses all the medications prescribed over 3-month periods. Considering PIMs, their prevalence was assessed over an entire year and not at a given time point, which obviously increased the chance of having one PIM for a given subject compared to a punctual assessment. Moreover, we added 3 criteria (assessing potentially inappropriate prolonged use of medications) to those of the Laroche list, which happened to increase by nearly 10% the prevalence of PIMs. Consistently with the review by Tommelein et al [23], we found benzodiazepines and NSAIDs among the most reported PIMs. Conversely, inappropriate use of antidepressants was limited in our study.

*PIMs and frailty*

The relationship between PIMs and frailty initially observed in unadjusted and partially adjusted models became non-significant when polypharmacy was introduced in the multivariate models. This result suggests that the association between PIMs and frailty reflects the association between

PIMs and polypharmacy in the one hand and between polypharmacy and frailty in the other hand. Nevertheless, this result should be considered with caution because PIMs still tended to be associated with frailty in the model adjusted for polypharmacy and we cannot exclude a lack of power to detect a significant association. Collinearity between polypharmacy and PIMs may have increased estimates of parameter variance, hence reducing the likelihood of showing a significant association between PIMs and frailty. Nevertheless, this hypothesis is unlikely regarding the results of diagnostic tests for colinearity between polypharmacy and PIMs; both the Variance Inflation Factor (VIF) and the condition number were inferior to admitted thresholds (VIF=1.21 <10 and condition number < 15) [24]. Besides, PIMs include heterogeneous situations in terms of risk. Some medications are said inappropriate because of their safety profile, whereas others are said inappropriate because of uncertainty about their efficacy. That is why we considered PIMs altogether and by criteria. Doing this, we actually showed a significant association between frailty and anticholinergic medications that persisted after adjustment for polypharmacy.

*Polypharmacy, anticholinergic medications, and frailty*

Our results confirm the previously reported association between excessive polypharmacy and frailty [7], and extend to the general population the results of Moulis et al [25] who showed that medications with anticholinergic properties were associated with frailty in people attending a frailty clinic in France, after adjustment for polypharmacy. Anticholinergic medications can cause peripheral (dry mouth and constipation) and central (falls, dizziness, delirium, and cognitive decline) adverse effects [26] that could participate in the development of frailty through altered nutritional intake, limitation of mobility or cognitive impairment. Gnjidic et al [27] suggested the potential contribution of medicines to the development of frailty, consistently with

the results of previous studies showing an increased risk of incident frailty in people with polypharmacy [9, 28].

*Strength and limitations*

The strength of this study is that we used a unique dataset combining a nationally representative health survey with respondents' National Health Insurance data on medication reimbursements. Nevertheless, this study has limitations. Though nationally representative, we had a limited sample of people aged 65 years and over. Concerning the assessment of frailty, we used self-reported variables in the absence of objective measures of grip strength and walking speed. Another limitation is that 29.7% had missing data regarding one or more frailty variable. Considering only people with complete information would have led to a selection bias and a loss of power, which is why we imputed missing data based on available information. Results were similar with regard to the estimated coefficients but differed somehow with regard to the standard error of the estimates. The lack of statistical power was substantial in the case of the sample with non-missing observation. However, imputation of frailty criteria conditional on age and sex helped improve the statistical power without introducing bias in the estimates because (i) age and sex are exogenous covariates (not determined by frailty or its determinants) and (ii) these two variables are included as covariates in the model, thus assigning the observations to the average individual. Though highly reliable, data about medication use only reflect medication bought by people and not those actually taken. In the case of concomitant use, defined as situations where two drugs of the same class were delivered on the same day, we miss cases where people buy their medications on different days and use medications they have left at home. Furthermore, we did not have information about the use of over-the-counter products and medications received during hospitalisation. Eventually, the

cross-sectional design of this study did not enable to conclude on the causality of the relationships between frailty, polypharmacy and PIMs.

## Conclusion

This study shows that polypharmacy and use of anticholinergic medications are independently associated with frailty in old people. This should increase awareness towards the overuse of medications in old people and should encourage physicians to supress the prescriptions that are known to have a poor benefit-risk ratio in their patients, especially anticholinergic medications. Longitudinal studies are required to establish the respective role of polypharmacy and PIMs on the development of frailty.

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**Table 1. Characteristics of the people aged 65+ included in ESPS 2012 (N=1890)**

| Variable | N | Prevalence (%) |
|---|---|---|
| Age (years) | | |
| 65-69 | 616 | 26.1 |
| 70-74 | 386 | 17.2 |
| 75-79 | 389 | 18.2 |
| 80-84 | 273 | 20.5 |
| 85+ | 226 | 17.9 |
| Gender | | |
| Male | 887 | 39.5 |
| Female | 1003 | 60.5 |
| Married / living as a couple | 1253 | 94.9 |
| Education | | |
| No diploma | 443 | 23.9 |
| < A-level | 1057 | 56.8 |
| A-level | 158 | 8.4 |
| > A-level | 209 | 9.5 |
| Other | 23 | 1.3 |
| Difficulty in activities of daily living | | |
| No | 812 | 44.7 |
| In ≥1 IADL, but not in ADL | 541 | 34.3 |
| In ≥1 ADL | 311 | 21.1 |
| BMI | | |
| <18.5 kg / m² | 36 | 2.5 |
| ≥18.5 et <25 kg / m² | 643 | 41.9 |
| ≥25 et <30 kg / m² | 630 | 36.6 |
| ≥30 kg / m² | 316 | 19.1 |
| Tobacco smoking | | |
| Never | 1066 | 67.6 |

| | | |
|---|---|---|
| Yes, in the past | 428 | 24.3 |
| Yes, currently | 140 | 8.1 |
| Social isolation during at least one period of life | 233 | 15.7 |
| Self-perceived health | | |
| Good or very good | 681 | 39.7 |
| Fair | 676 | 40.9 |
| Poor or very poor | 291 | 19.4 |
| Chronic diseases | | |
| Musculoskeletal | 849 | 54.6 |
| Cardiovascular | 575 | 36.8 |
| Diabetes | 278 | 17.2 |
| Respiratory | 259 | 16.6 |
| Allergy | 209 | 13.0 |
| Depression | 110 | 7.4 |
| Liver | 6 | 0.0 |
| Frailty criteria (original / imputed) | | |
| Exhaustion | 561 / 563 | 35.1 / 30.3 |
| Unintentional weight loss | 175 / 175 | 11.2 / 9.8 |
| Muscle weakness | 443 / 471 | 32.7 / 31.0 |
| Impaired mobility | 258 / 261 | 19.5 / 17.3 |
| Low level of physical activity | 312 / 316 | 23.5 / 18.5 |
| Number of frailty criteria (original / imputed) | | |
| 0 | 544 / 873 | 37.1 / 42.1 |
| 1 | 417 / 561 | 30.4 / 29.2 |
| 2 | 191 / 229 | 16.1 / 13.9 |
| 3 | 118 / 148 | 10.3 / 9.7 |
| 4 | 60 / 71 | 5.6 / 4.8 |
| 5 | 8 / 8 | 0.5 / 0.4 |

*Note: prevalence takes into account sampling weights.*

**Table 2. Potentially inappropriate medications received by 1% or more of the participants aged 65+ in ESPS 2012 (N=1890)**

| Potentially inappropriate medications | ATC | N | Prevalence (%) |
|---|---|---|---|
| **Laroche list criteria**[a] | | | |
| Non-steroidal anti-inflammatory drugs (NSAIDs) | | 74 | 3.9 |
| ≥ 2 NSAIDs | M01A | 72 | 3.8 |
| Anticholinergic drugs | | 161 | 9.2 |
| Tricyclic antidepressant | | 47 | 2.4 |
| Amitriptyline | N06AA09 | 31 | 1.8 |
| Antihistamins H1 | | 79 | 4.7 |
| Hydroxyzine | N05BB01 | 69 | 4.0 |
| Anticholinergic urinary antispasmodics | | 28 | 1.7 |
| Solifenacine | G04BD08 | 28 | 1.5 |
| Long-acting benzodiazepines | | 232 | 12.6 |
| Bromazepam | N05BA08 | 138 | 7.7 |
| Prazepam | N05BA11 | 45 | 2.5 |
| Clonazepam | N03AE01 | 25 | 1.2 |
| Antihyperthensives | | 98 | 6.2 |
| Centrally acting | | 60 | 4.0 |
| Rilmenidine | C02AC06 | 51 | 3.4 |
| Short-acting calcium-channel blockers | | 42 | 2.4 |
| Nicardipine | C08CA04 | 35 | 1.9 |

| Potentially inappropriate medications | ATC | N | Prevalence (%) |
|---|---|---|---|
| Cerebral vasodilators | | 144 | 8.5 |
| Ginkgo | N06DX02 | 71 | 4.5 |
| Naftidrofuryl | C04AX21 | 35 | 1.7 |
| Piribedil | N04BC08 | 23 | 1.3 |
| Other drugs with anticholinergic properties and questionable efficacy | | 139 | 7.2 |
| Oxomemazine | R06AD08 | 77 | 3.6 |
| Metopimazine | A04AD05 | 54 | 3.4 |
| Antimicrobial | | 17 | 1.0 |
| Nitrofurantoïne | J01XE01 | 17 | 1.0 |
| Concomitant dispensation of psychotropic drugs of the same the same class | | 34 | 2.0 |
| Concomitant dispensation of 2 benzodiazepines | N05BA<br>N05CD<br>N05CF<br>N03AE01<br>M03BX07 | 28 | 1.7 |
| **Additional criteria** | | | |
| Prolonged use of hypnotics (≥ 3 reimbursements over a 4-month period)[b] | N05CF01<br>N05CF02 | 123 | 7.4 |
| Prolonged use of benzodiazepines (≥ 3 reimbursements over a 4-month period)[c] | N05BA<br>N05CD<br>N05CF<br>N03AE01<br>M03BX07 | 338 | 19.9 |

| Potentially inappropriate medications | ATC | N | Prevalence (%) |
|---|---|---|---|
| Prolonged use of NSAIDs (≥ 3 reimbursements over a 4-month period)[c] | M01A | 211 | 11.3 |
| **At least one PIM of the Laroche list** | | 664 | 36.8 |
| **At least one PIM of the Laroche list + other criteria** | | 841 | 46.7 |

*Note: Prevalence takes into account sample weights.*

**Table 3. Poisson regression models of the number of frailty criteria according to medications among participants aged 65+ in ESPS 2012 (N=1542)**

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| **Polypharmacy** | | | | | | |
| 5-9 versus 0-4 drugs | 1.587*** | | 1.163** | | 1.139* | 1.171* |
| 10+ versus 0-4 drugs | 2.710*** | | 1.451*** | | 1.392*** | 1.501*** |
| **PIMs** | | | | | | |
| At least one PIM of the Laroche list + other criteria | | 1.578*** | | 1.180*** | 1.102* | 1.221* |
| Anticholinergic drugs | | 1.521*** | | 1.192** | 1.169** | 1.337** |
| Long-acting benzodiazepines | | 1.266** | | 1.072 | 1.012 | 1.062 |
| Antihyperthensives | | 1.384** | | 0.967 | 0.958 | 1.018 |
| Cerebral vasodilators | | 1.211** | | 1.085 | 1.015 | 1.201 |
| Concomitant dispensation of psychotropic drugs of the same class | | 1.454** | | 1.110 | 1.093 | 1.093 |
| Prolonged use of hypnotics (≥ 3 reimbursements over a 4-month period)[b] | | 1.454*** | | 1.095 | 1.007 | 1.190 |
| Prolonged use of benzodiazepines (≥ 3 reimbursements over a 4-month period)[c] | | 1.556*** | | 1.112** | 1.034 | 1.201 |
| Prolonged use of NSAIDs (≥ 3 reimbursements over a 4-month period)[c] | | 1.165* | | 1.166** | 1.106 | 0.807 |

*Note:*

*Values are Incidence Rate Ratio (IRR)*

** p<.1; ** p<.05; *** p<.001*

*Model 1: number of frailty criteria ~ polypharmacy*

*Model 2: number of frailty criteria ~ PIMs*

*Model 3: number of frailty criteria ~ polypharmacy + confounders*

*Model 4: number of frailty criteria ~ PIMs + confounders*

*Model 5: number of frailty criteria ~ polypharmacy + PIMs + confounders*

*Model 6: number of frailty criteria ~ polypharmacy + PIMs + interaction term + confounders*

*Confounders: age, gender, difficulties in activities of daily living, self-perceived heath, cardiovascular diseases, musculoskeletal diseases, diabetes, depression, and BMI*

**Figure 1. Prevalence of polypharmacy and PIMs according to the number of frailty criteria (N=1890)**