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Association Between Potentially Inappropriate Medications and Frailty in the Early Old Age: A Longitudinal Study in the GAZEL Cohort

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A B S T R A C T

Objectives: High-risk prescribing can have deleterious effects on the health of older people. This study aimed to assess the role of inappropriate prescribing on changes in frailty status over 3 years of follow-up.
Design, setting: This is a prospective observational study nested in the GAZEL cohort.
Participants: The study sample included 12,405 community-dwelling people aged 58 to 73 in 2012, and followed for 3 years.
Measurement: Polypharmacy and potentially inappropriate medications (PIMs) were assessed from reimbursement data by the French National Health Insurance. Frailty was evaluated each year with the Strawbridge questionnaire. PIMs were defined according to the Laroche list plus additional criteria dealing with inappropriate prolonged use of medications. The relationship between PIMs and changes in frailty status (incident frailty and recovery) was analyzed with Markov multistate modeling.
Results: The prevalence of frailty increased from 14% in 2012 to 17% in 2014, whereas the frequency of PIMs was 29% in 2012 and 23% in 2014. Polypharmacy (5-9 drugs: aHR 1.31, 95% CI 1.14-1.50; and 10 drugs or more: aHR 1.57, 95% CI 1.28-1.92) and potentially inappropriate use of nonsteroidal anti-inflammatory drugs (aHR 1.33, 95% CI 1.04-1.71) were significantly associated with incident frailty, when the presence of at least 1 PIM presented a small association with the risk of becoming frail (aHR 1.15, 95% CI 1.01-1.32).
Conclusions/Implications: This study brings new elements to our knowledge regarding the association between inappropriate prescribing and frailty in older adults, which support research development to alert on inappropriate prescribing and to improve drug prescribing among old people, especially with polypharmacy.

Frailty corresponds to a decrease of physiologic reserves, which enhances the vulnerability to stressors among older adults.[1] Frailty has been associated with an increased risk of falls, functional limitations, hospitalizations and death[2,3], as well as an increased use of health care resources.[4] In research and clinical settings, multiple definitions are used to identify frailty among older people, generally grounded on a critical number of deficits in multiple domains (physical, nutritional, cognitive, psychosocial, sensory).[5] The average prevalence of frailty among community-dwelling people older than 65 years is estimated between 11% and 17%.[6,7] Screening for frailty is the first step of a preventive approach aiming to preserve better health for older adults and to delay dependence.[8,9]

Prevention of frailty itself should be considered in the early old age, long before the occurrence of functional limitations. Numerous factors were associated with the onset of frailty in longitudinal settings: sociodemographic (eg, age, gender, socioeconomic position), physical

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(eg, obesity, functional limitations), lifestyle (eg, diet, tobacco), psychological (eg, depression, cognition), and biologic (eg, inflammation).[10] In addition to these determinants, cross-sectional and longitudinal studies associated polypharmacy and frailty,[11–16] suggesting its role as a predictor of frailty. Polypharmacy, defined as the concomitant use of many medications simultaneously, is common in older adults with chronic diseases, with a prevalence between 40% and 70% depending on the study.[11,16,17] Multiple prescriptions increase the risk of adverse drugs events, falls, hospital admissions, and death among the elderly.[18] Older adults are more likely to experience adverse drugs events compared to their younger counterparts, notably because of age-associated organ changes, modifying pharmacokinetic and pharmacodynamic drug properties.[19] Besides, polypharmacy increases the risk of receiving potentially inappropriate medications (PIMs)—defined as medications with unfavorable benefit-risk ratio and/or questionable efficacy in older adults.[20] PIMs received a sustained attention from the scientific and medical community as they represent a main target in the reduction of polypharmacy. Lists of PIMs have been published to help adapting older people's drug regimen, notably the Beers criteria[21] and, in France, the Laroche list.[20]

Epidemiologic studies highlighted the greater exposure of frail people to medications, with on average 2 to 3 medications more prescribed to frail people compared to nonfrail people,[11,22] when frail people may be more vulnerable to drug-related problems. Frail people also significantly receive more of certain types of drugs: analgesic, anticholinergic, sedative, and fall risk–increasing drugs, most of them carrying a significant risk of adverse events.[6,22–24] In addition, cross-sectional associations do not allow the conclusion of a causal relationship between high-risk prescribing and frailty. Although longitudinal studies incriminated the use of polypharmacy in the onset of frailty,[12–14] the role of PIMs remains poorly explored.

This study aimed to evaluate the relationship between exposure to PIMs, defined with explicit criteria, and changes in frailty status among older people aged 58-73, included in a prospective cohort in France. We hypothesized that PIMs, as well as polypharmacy, were risk factors for frailty.

Material and Methods

Study Design and Population

This study is part of the GAZEL cohort, a prospective cohort study in France that began in 1989 and is still ongoing with a total of 20,625 participants aged 35-50 years at baseline who were recruited among employees of the French national electricity and gas utility (EDF-GDF).[25] Participants have been followed by yearly postal auto-questionnaires including a diversity of items regarding health status, lifestyle, and socioeconomic factors. The participation rate approached 70% every year. Since 2008, additional information has been collected about the use of health care resources of the participants from the French National Health Insurance, including reimbursements of medications and hospitalizations. In 2012, the Strawbridge questionnaire[26] was included in the yearly auto-questionnaire to assess frailty in the ageing cohort. The study population consisted of the 12,405 individuals for whom frailty status could be assessed in at least 2 consecutive questionnaires between 2012 and 2014.

Ethical Approval

The GAZEL Cohort study was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL) and by the Ethics Evaluation Committee of INSERM. Participants provided written informed consent.

Frailty Assessment

There is no consensual tool to assess frailty.[27] In this study, the Strawbridge questionnaire[26] was selected for its multidimensional and declarative assessment of frailty. Its limited but efficient power for predicting poor health outcomes (disability and hospitalization) in the GAZEL cohort was demonstrated by Linard et al.[28] Furthermore, this tool is currently used in ongoing clinical investigations such as the PreFIT trial.[29] The Strawbridge frailty assessment includes 16 items that evaluate 4 domains: physical, nutritional, cognitive, and sensory. Four items assess physical health (sudden loss of balance, weakness in the arms, weakness in the legs, feeling dizzy when standing up quickly), 2 items assess nutrition (unexplained weight loss, loss of appetite), 4 items assess cognition (difficulty paying attention, finding the appropriate word, remembering things, forgetting where one put something), and 6 items assess the sensory domain (difficulty reading newspapers, recognizing a friend across the street, reading signs at night, hearing over the phone, hearing a normal conversation, hearing a conversation in a noisy room). Scores for the first 10 items were rated as follows: 1 = rarely or never had the problem in the last 12 months, 2 = sometimes had the problem, 3 = often had the problem, or 4 = very often had the problem. For the last 6 items regarding the sensory domain, scores ranged from 1 to 4 with 1 = no difficulty, 2 = little difficulty, 3 = some difficulty, and 4 = major difficulty. One domain was considered as loss-making if a participant rated as 3 or 4 to at least 1 item of the dimension. Subjects were considered as frail if they reported difficulties in 2 or more domains.

Polypharmacy and PIMs

Data of the French National Health Insurance contain exhaustive information on all the medications that were reimbursed to people during the years 2012, 2013, and 2014. Medications were coded using the Anatomical Therapeutic Chemical (ATC) system. For each participant, we estimated the average number of medications used by calculating the mean of the total number of medications reimbursed over 3-month periods, including both regular and as-required medications.[3,30] Three categories were created: no polypharmacy (0-4 drugs), moderate polypharmacy (5-9 drugs), and excessive polypharmacy (10 or more drugs). The assessment of PIMs in the GAZEL cohort used an adapted Laroche list.[20] This list was published in 2007 by a panel of French experts. It is similar to the 2003 Beers list, although it includes only drugs marketed in France and PIMs related to inappropriate drug-drug associations. We modified this list by deleting drugs withdrawn from the market since 2007 and by adding PIMs related to inappropriate duration of treatment ($\geq$3 reimbursements over a 4-month period) of benzodiazepines or related drugs and nonsteroidal anti-inflammatory drugs (NSAIDs),[31] as well as drugs considered as potentially inappropriate in the last update of the Beers criteria (metoclopramide and desmopressin).[32]

Concomitant use of drugs corresponded to cases where 2 drugs were delivered on the same day. We excluded the 5 criteria that required information about underlying conditions (eg, chronic constipation) that could not be completely assessed here.

Other Variables

Other variables dealt with sociodemographic characteristics (age, gender, and socioeconomic position), health information (anthropometric parameters, self-reported depression and chronic diseases, and hospitalizations), and lifestyle factors (marital status and tobacco smoking). Socioeconomic position was assessed by using a Likert-type scale, with 10 levels representing the social scale. Body mass index (BMI) was considered low if $\leq$21 for women and $\leq$23 for men and high if $>$27 for both women and men. A comorbidity score was created

using 7 self-reported diseases (high blood pressure, cancer, diabetes, respiratory disease, cardiac disease, stroke, and joint pain). We defined 3 different levels of comorbidity: 0, 1, and ≥2 self-reported diseases. Tobacco consumption was categorized as follows: nonsmoker (0 cigarette), light smoker (1-10 cigarettes), median smoker (11-20 cigarettes), and heavy smoker (≥21 cigarettes per day). Except for socioeconomic position that was reported only once in 2013, other variables were updated each year.

Statistical Analysis

The characteristics of the study sample were described using categorical variables in terms of numbers and proportions. As recommended for panel data where individuals are observed at arbitrary continuous times (here through yearly questionnaires), we used multistate Markov modeling to describe changes in frailty status during the follow-up. Intensity of transition (ie, instantaneous risk of becoming frail or recovering from frailty) depended on time *t* and also on a set of individual-level and time-dependent explanatory variables.[33] The model was specified with a set of covariates selected a priori, which applied to both transitions. Exposure to PIMs was defined over the period between 2 consecutive frailty assessments, so that exposure preceded the frailty assessment. To describe the frequency of PIMs over the same period of time for all participants, we used the frequency of PIMs per calendar year in the descriptive analysis (ie, from January 1 to December 31 of each year) (Figure 1). Exposure to PIMs was considered as a binary variable in the main analysis (≥1 PIM) and additional models were carried out to consider the exposure to specific groups of PIMs (for instance long-acting benzodiazepines). Furthermore, we assessed the relationship between PIMs and changes in each one of the 4 frailty dimensions. Adjustments were made on the following variables: age, gender, marital status, self-perceived social position, BMI, tobacco consumption, number of chronic diseases, self-reported depression, and polypharmacy. Results were given in terms of hazard ratios (HRs) and 95% confidence intervals (CIs) for each covariate. All the analyses were performed using R software ("msm" package).

Results

Characteristics of the Study Sample

The study sample included a majority of men (74%), mainly aged between 65 and 70 years (Table 1). The most frequent health problems were joint pain and high blood pressure. Polypharmacy (on average 5-9 drugs per 3-month periods) concerned 32.8% to 34.3% of the participants depending on the year considered, and excessive polypharmacy (10 drugs or more) concerned 8.2% to 8.7%. The prevalence of frailty was estimated at 14% in 2012 and 2013 and 17% in 2014. Among the 4 frailty dimensions, the sensory dimension was the most frequently impaired (41% of the participants in 2012). A total of 23,623 pairs of consecutive measures of frailty were analyzed over the 3 years of follow-up. In most cases, the frailty status remained unchanged (N = 20,908; 88.5%). However, we recorded 1519 transitions toward frailty and 1196 transitions toward recovery.

Exposure to PIMs

Frequencies of PIMs were 28.9% in 2012, 26.1% in 2013, and 23.3% in 2014 (Table 2). NSAIDs, benzodiazepines, anticholinergic drugs, and cerebral vasodilator drugs were the most involved drugs in PIMs (see full list of PIMs in Appendix 1). The decreasing trend observed in the frequency of PIMs over time was largely explained by the decreasing use of tetrazepam and cerebral vasodilator drugs.

Association of PIMs on Changes in Frailty Status

Having at least 1 PIM was associated with incident frailty with an HR 1.57 (95% CI 1.40-1.75) and with recovery from frailty with an HR 0.76 (95% CI 0.67-0.86) in unadjusted analysis, suggesting that PIMs acted as a risk factor for frailty and as an obstacle to recovery. The multivariate multistate model confirmed the association between presence of PIMs and the transition toward frailty, with an adjusted HR (aHR) of 1.15 (95% CI 1.01-1.32) (Table 3). Complementary analysis using the Laroche list without additional criteria did not show an increased risk of frailty but indicated difficulty to recover from the frailty status when treated with PIMs (aHR1.07, 95% CI 0.93-1.23, and 0.84, 95% CI 0.72-0.98, respectively). Other factors associated with incident frailty were polypharmacy, number of chronic diseases, self-reported depression, and socioeconomic position. Four factors were associated with lower likelihood of recovery from frailty: older age, excessive polypharmacy, self-reported depression, and low BMI. When the different types of PIMs were considered in the analysis (1 model for each PIM), the only PIM that was significantly associated with incident frailty was the potentially inappropriate use of NSAIDs as defined in the Laroche list (indomethacin or concomitant use of ≥2 NSAIDs) (Table 4). Of note, this association persisted in complementary analysis where joint pain was introduced as a covariate in the model (see full model in Appendix 2). The association with anticholinergic medications was close to being statistically significant. Complementary analyses regarding each one of

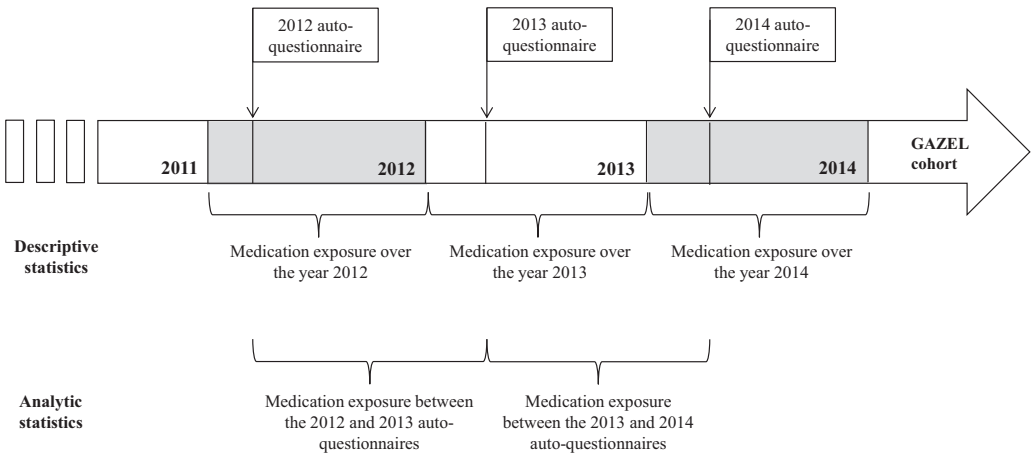

Fig. 1. Definition of the periods of exposure to medications in the different analyses.

Table 1
Characteristics of the Study Sample, by Year

Variables	2012 N = 11,891		2013 N = 12,405		2014 N = 11,732	
Gender						
Women	3089	26.0%	3233	26.1%	3051	26.0%
Men	8802	74.0%	9172	73.9%	8681	74.0%
Age						
< 65	3847	32.4%	2488	20.1%	1165	9.9%
65 to 70	5492	46.2%	6259	50.5%	6125	52.2%
≥ 70	2552	21.5%	3658	29.5%	4442	37.9%
Marital status						
In couple	9787	82.3%	10113	81.5%	9541	81.3%
Single	1964	16.5%	2116	17.1%	2000	17.0%
Self-perceived social position*						
Underprivileged	1214	10.2%	715	5.8%	645	5.5%
Intermediate	9094	76.5%	9648	77.8%	9132	77.8%
Privileged	1582	13.3%	2042	16.5%	1955	16.7%
BMI (kg/m^2) †						
Low	1614	13.6%	1638	13.2%	1564	13.3%
Intermediate	5908	49.7%	6010	48.4%	5645	48.1%
High	4219	35.5%	4344	35.0%	4128	35.2%
Tobacco consumption‡						
No	10476	88.1%	10709	86.3%	9356	79.7%
Light	537	4.5%	546	4.4%	485	4.1%
Medium or heavy	359	3.0%	333	2.7%	290	2.5%
Self-reported chronic diseases						
High blood pressure	3603	30.3%	3829	30.9%	3652	31.1%
Respiratory disease	2074	17.4%	2296	18.5%	2072	17.7%
Cancer	638	5.4%	695	5.6%	773	6.6%
Joint pain	7906	66.5%	8123	65.5%	8039	68.5%
Diabetes	962	8%	1106	9%	1059	9%
Stroke	125	1.1%	156	1.3%	128	1.1%
Cardiac disease	1480	12.4%	1537	12.4%	1618	13.8%
Number of self-reported chronic diseases						
0	1973	16.6%	2119	17.1%	1827	15.6%
1	4941	41.6%	4996	40.3%	4672	39.8%
≥ 2	4977	41.9%	5290	42.6%	5233	44.6%
Self-reported depression	2943	25%	3096	25%	3247	28%
Polypharmacy						
No (0 to 4 drugs)	6958	58.5%	7193	58.0%	6750	57.5%
Moderate (5 to 9 drugs)	3904	32.8%	4153	33.5%	4019	34.3%
Excessive (10 drugs or more)	1029	8.7%	1059	8.5%	963	8.2%
Frailty	1664	14.0%	1766	14.2%	1945	16.6%
Physical	1176	9.9%	1177	9.4%	1264	10.8%
Nutritional	160	1.2%	148	1.2%	240	2.0%
Cognitive	1472	13.0%	1611	13.0%	1686	14.4%
Sensory	4927	41.3%	5128	41.3%	5357	45.7%
Hospitalizations	1569	13.2%	1598	12.9%	1545	13.2%

BMI, Body Mass Index.

*Self-perceived social position on a 10-level Likert scale in 2013.

†low BMI if ≤21kg/m^2 for women and ≤23kg/m^2 for men; High BMI if > 27kg/m^2 for both women and men: criteria of the cohort GAZEL, not following the national standardization of BMI.

‡Tobacco: Non-smoker: 0 cigarette, light smoker 1 to 10 cigarettes, medium smoker 11 to 20 cigarettes, Heavy smoker ≥ 21 cigarettes.

Table 2
Frequency of PIMs, by Year

Variables	2012 N = 11,891		2013 n = 12,405		2014 n = 11,732	
At least 1 PIM						
According to the Laroche list	3277	27.6%	3108	25.1%	2588	22.1%
According to the Laroche list + additional criteria	3438	28.9%	3242	26.1%	2735	23.3%
PIMs of the Laroche list*						
NSAIDs	607	5.1%	555	4.5%	448	3.8%
Anticholinergic drugs						
Tricyclic antidepressants	145	1.2%	184	1.5%	154	1.3%
Antipsychotic drugs	42	0.4%	44	0.4%	40	0.3%
Hypnotic drugs	26	0.2%	39	0.3%	30	0.3%
Antihistaminic drugs	363	3.1%	323	2.6%	307	2.6%
Urinary antispasmodic drugs	108	0.9%	146	1.2%	153	1.3%
Long-acting benzodiazepine	826	6.9%	835	6.7%	746	6.4%
Centrally acting antihypertensive drugs	127	1.1%	134	1.1%	119	1.0%
Short-acting calcium channel blockers	111	0.9%	128	1.0%	130	1.1%
Muscle relaxants	981	8.3%	19	0.2%	19	0.2%
Cerebral vasodilators	454	3.8%	255	2.1%	92	0.8%
Other drugs with anticholinergic properties and questionable efficacy	923	7.8%	940	7.6%	713	6.1%
Concomitant use of ≥2 benzodiazepines	283	2.4%	233	1.9%	210	1.8%
Concomitant use of ≥2 antidepressants	48	0.4%	49	0.4%	39	0.3%
Additional PIMs						
Prolonged use of benzodiazepine (or related)	388	3.3%	380	3.1%	336	2.9%
Prolonged use of NSAIDs	1103	9.3%	1057	8.5%	898	7.7%
Medications of the 2015 Beers list (metoclopramide and desmopressine)	134	1.1%	94	0.8%	101	0.9%

PIM, Potentially Inappropriate Medication; NSAID, Non-Steroidal Anti-Inflammatory Drug

*Most frequent PIMs, see complete list in Appendix 1.

the 4 frailty dimensions showed that the presence of PIMs was positively associated with decline in the physical and nutritional dimensions and negatively associated with improvement of the sensory dimension (see Appendix 3).

Discussion

In a cohort of 12,405 people aged 58-73 years in 2012 and followed for 3 years, we showed that the presence of PIMs was associated with an increased risk of becoming frail during the follow-up, as well as polypharmacy. These results add a new dimension to our knowledge, as the association between frailty and polypharmacy was already described, but rare studies demonstrated an association between inappropriate prescribing and frailty.

We estimated the frequency of PIMs to be 28.9% in 2012 and 23.3% in 2014. This frequency is in line with the pooled prevalence estimated by Tommelein et al based on 82 studies among community-dwelling older people in Europe, which amounted to 22.6%.[34] However, it is lower than previous estimates in French samples, for instance 48.4% in a sample of people aged 70 years and older in the South of France[31] and 46.7% in a representative sample of French people aged 65 years and older.[23] This difference was expected with the younger age of our study sample and its high proportion of men, 2 factors often negatively associated with PIMs in the literature.[34] Also, in our study sample, the frequency of PIMs decreased with time, as previously described in other settings.[35,36] This result suggests the increase in adherence to guidelines of good practice of drug prescriptions in older adults. Moreover, the market withdrawal of a frequent PIM, tetrazepam, and the decision of the French Health Insurance to stop reimbursing cerebral vasodilators containing ginkgo between 2012 and 2013, significantly reduced the frequency of these PIMs. Consistently with previous studies,[23,34] our results show benzodiazepines, anticholinergic drugs, and NSAIDs to be the most reported PIMs.

This study confirms that polypharmacy (moderate and excessive) is common in the early old age (about 40%) and increases the risk of incident frailty, as previously described in Australian,[16] Chinese,[12] and German cohorts.[13] Potential mechanisms of this association involve the accumulation of risks of adverse events of medications, reduced mobility (because of dizziness and fear of falling), and deleterious effects of medications on the nutritional state of older adults (anorexia, changes in taste, mouth dryness, nausea, etc).[37] However, polypharmacy is necessary in certain circumstances, notably among people with multiple chronic diseases with age.[38]

Another way to assess drug exposure in this study was to consider the appropriateness of each drug prescribed. Previous studies did not

Table 3
Model Assessing the Influence of ≥1 PIM on Changes in Frailty Status

Variables	From non-frailty to frailty (N = 1519)	From frailty to non-frailty (N = 1196)
	aHR (95% CI)	aHR (95% CI)
Age		
58-64	1	1
65-70	1.03 (0.85-1.26)	**0.74 (0.60-0.90)**
≥ 70	**1.30 (1.06-1.60)**	**0.60 (0.48-0.74)**
Gender		
Male	1	1
Female	1.09 (0.93-1.27)	0.89 (0.75-1.06)
Marital status		
In couple	1	1
Single	0.90 (0.77-1.06)	0.93 (0.78-1.11)
Self-perceived social position		
Underpriviledged	1.03 (0.78-1.30)	0.81 (0.62-1.07)
Intermediate	1	1
Priviledged	**0.83 (0.70-0.99)**	1.08 (0.89-1.32)
BMI		
Low	1.14 (0.96-1.35)	**0.67 (0.54-0.82)**
Intermediate	1	1
High	0.93 (0.81-1.06)	0.86 (0.74-1.00)
Tobacco consumption		
No	1	1
Light	1.02 (0.77-1.36)	1.20 (0.87-1.66)
Medium or high	1.06 (0.76-1.48)	0.78 (0.52-1.16)
Number of chronic diseases		
0	1	1
1	**1.54 (1.23-1.92)**	1.03 (0.80-1.33)
≥2	**2.11 (1.69-2.63)**	0.89 (0.69-1.14)
Self-reported depression	**2.00 (1.77-2.27)**	**0.75 (0.65-0.86)**
Polypharmacy		
No (0 to 4 drugs)	1	1
Moderate (5 to 9 drugs)	**1.31 (1.14-1.50)**	0.90 (0.77-1.05)
Excessive (10 drugs or more)	**1.57 (1.28-1.92)**	**0.77 (0.62-0.97)**
≥1 PIM according to the Laroche list + additional criteria	**1.15 (1.01-1.32)**	0.88 (0.75-1.03)

PIM, Potentially Inappropriate Medication; BMI, Body Mass Index
Boldface indicates significance, ie HR with 95% CI excluding 1.

use lists of explicit criteria to assess inappropriate use of drugs in relation to frailty, but tools to measure the anticholinergic burden of drug regimen[16] or lists of medications increasing the risk of falls.[22] By using a modified version of the French Laroche list of PIMs, we found an increased risk of incident frailty in cases of exposure to at least 1 PIM. However, this result should be considered with caution because the effect size is modest (aHR 1.15, 95% CI 1.01-1.32) and likely to vary with the definition of PIMs. Indeed, when only the original Laroche criteria were considered (without the additional criteria related to prolonged use of benzodiazepines or NSAIDs and to drugs recently added to the Beers criteria), the presence of PIMs acted as an obstacle to recovery from frailty. Additional criteria did not explain this difference as they were not independently associated with frailty transitions (Table 4). Focusing on other categories of PIMs, we found that inappropriate use of NSAIDs (indomethacin or concomitant use of ≥2 NSAIDs) was specifically associated with incident frailty. The persistence of the association between NSAIDs and frailty when the model was adjusted for joint pain suggested the possible implication of adverse drug effects of NSAIDs—acute renal deficiency, digestive hemorrhages, and ulcers—in the elevated incidence of frailty among people inappropriately using NSAIDs. However, this result should be considered with caution as our assessment of joint pain was mostly centered on back pain, and thus confounding by indication is still possible. Although previous studies reported an association between the use of anticholinergic drugs and frailty,[6,23,39] we could not confirm this association in a longitudinal setting, even though we noticed a trend.

Table 4
Multistate Model Assessing the Influence of the Different PIMs on Changes in Frailty Status

PIMs	From non-frailty to frailty (N = 1519)	From frailty to non-frailty (N = 1196)
	aHR (95% CI)	aHR (95% CI)
NSAIDs	**1.33 (1.04-1.71)**	1.10 (0.80-1.50)
Anticholinergic drugs	1.20 (0.96-1.49)	0.84 (0.64-1.09)
Long-acting benzodiazepines	0.80 (0.64-1.00)	0.89 (0.70-1.14)
Antihypertensives	0.96 (0.65-1.41)	1.11 (0.72-1.70)
Muscle relaxants	0.98 (0.54-3.99)	0.76 (0.19-3.19)
Cerebral vasodilators	1.12 (0.75-1.68)	0.64 (0.39-1.03)
Other anticholinergic drugs with questionable efficacy	0.99 (0.80-1.22)	0.86 (0.67-1.11)
Concomitant use of 2 benzodiazepines	0.90 (0.61-1.33)	0.93 (0.61-1.41)
Concomitant use of 2 antidepressant drugs	0.96 (0.39-2.38)	0.57 (0.25-1.32)
Prolonged use of benzodiazepine (or related)	1.00 (0.76-1.32)	1.01 (0.74-1.37)
Prolonged use of NSAIDs	0.94 (0.77-1.15)	0.84 (0.66-1.06)

PIM, Potentially Inappropriate Medication; NSAID, Non-Steroidal Anti-Inflammatory Drug.
Model adjusted for age, gender, self-perceived social position, marital status, BMI, tobacco consumption, number of chronic diseases, and polypharmacy.
Boldface indicates significance, ie HR with 95% CI excluding 1.

Opening the way to interventions that reduce inappropriate prescribing, the term *deprescribing* was introduced in the scientific literature to describe a process of discontinuing or reducing the dose of drugs that may be causing harm, may no longer be providing benefit, or may be considered inappropriate for other reasons, meanwhile maintaining or improving quality of life.[40,41] Our results indicate a relationship between polypharmacy, PIMs, and frailty, and suggest positive benefits from deprescribing in older people. However, there is limited evidence to guide deprescribing for older people with multimorbidity or frailty.[42] In addition to the aforementioned lists, existing tools to guide deprescribing include the STOPP and START criteria (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment)[43] and the Medication Appropriateness Index.[44] A Cochrane review article by Cooper et al showed that interventions to improve appropriate use of polypharmacy can actually reduce inappropriate prescribing, but that benefits on health outcomes remain debated.[45] The possibility of confounding by indication, where it is the disease that is responsible for the health outcomes and not the drugs prescribed, could explain the absence of effect on health outcomes in some studies and should be considered in the interpretation of our own results.

The strong methodologic aspects of this study includes the use of data coming from the French National Health Insurance, where all the medications reimbursed over the study period of time are registered. The reunion of data of quality regarding both the drug consumption and the health of the participants in the GAZEL cohort enabled the evaluation of the drug consumption in the study sample and also the evaluation of its impact on health. We previously ensured that the definition of frailty we used was predictive of poor health outcomes (hospitalization and difficulty performing every day movements) in our study sample.[28] Although causality cannot be claimed from cross-sectional studies, the measurement of medication exposure—prior to the assessment of frailty in this longitudinal study—allowed us to indicate the direction of the relationship. On the other hand, we cannot ascertain the temporality of this association, as we do not know when the change in the frailty status occurred during the interval of time between the 2 questionnaires.

The representativeness of our study sample compared to the general population can be discussed, notably with the imbalance of the sex ratio with a majority of men (74%). Also, even if mostly retired, participants were initially recruited at their workplace in one French

company, Clarify this sentence, perhaps: “thus it is possible that the employees of EDF GDF are not representative of the entire population.” Our assessment of frailty used self-reported information that allowed assessing frailty in a large population, but it introduced some subjectivity in the measurement, unlike objective measurements of grip strength or walking speed.[2] In addition, high levels of frailty could have impaired its own measure, thus possibly generating a bias by exclusion of patients presenting a high level of frailty. We actually observed that respondents whose frailty status could not be determined because of missing data were more likely to be women and were older than respondents with information on frailty status (data not shown), 2 factors associated with higher levels of frailty in the literature.[6] Last, the use of Strawbridge’s definition of frailty limits the comparison with other studies, mostly using the physical frailty phenotype or the accumulation of deficits index.[46] Another limit regards the medication exposure that did not include the non-reimbursed drugs (which may also cause side effects among the older population, especially anticholinergic drugs used for colds). Also, we did not have information about medications delivered while at the hospital, and 13% of the study participants were hospitalized at least once during the follow-up. Lastly, we were not aware if the bought medications were actually taken by the participants or not.

Conclusions/Relevance

This study brings new elements to our knowledge regarding the association between inappropriate prescribing and frailty in older adults. These results should reinforce the awareness of healthcare providers about both potentially inappropriate prescribing and frailty. Further pharmacoepidemiologic research is needed to describe adverse health outcomes of PIMs and to understand the mechanisms of their relation to frailty. While enriching the knowledge about the consequences of PIMs among older adults, we need to evaluate the effectiveness of rising interventions of deprescribing inappropriate medications.

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Appendix 1
Frequency of PIMs, Complete List, by Year

PIMS	ATC CODE	2012		2013		2014	
		N = 11,891		N = 12,405		N = 11,732	
PIMS OF THE LAROCHE LIST							
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)							
INDOMETACINE	M01AB01	17	0.1%	14	0.1%	12	0.1%
COMBINATION OF 2 NSAIDs	M01A	591	5.0%	543	4.4%	438	3.7%
ANTICHOLINERGIC DRUGS							
TRICYCLIC ANTIDEPRESSANTS							
AMITRIPTYLINE	N06AA09	88	0.7%	122	1.0%	109	0.9%
CLOMIPRAMINE	N06AA04	43	0.4%	46	0.4%	37	0.3%
DOSUELPINE	N06AA16	5	0.0%	7	0.1%	3	0.0%
TRIMIPRAMINE	N06AA06	9	0.1%	6	0.0%	6	0.1%
AMOXAPINE	N06AA14	0	0.0%	0	0.0%	0	0.0%
MAPROPTILINE	N06AA21	3	0.0%	6	0.0%	5	0.0%
DOXEPINE	N06AA12	0	0.0%	0	0.0%	0	0.0%
IMIPRAMINE	N06AA02	1	0.0%	1	0.0%	0	0.0%
ANTIPSYCHOTIC DRUGS							
CYAMEMAZINE	N05AA06	36	0.3%	38	0.3%	35	0.3%
LEVOMEPROMAZINE	N05AA02	4	0.0%	3	0.0%	3	0.0%
CHLORPROMAZINE	N05AA01	1	0.0%	3	0.0%	2	0.0%
FLUPHENAZINE	N05AB02	0	0.0%	0	0.0%	0	0.0%
PIMSOTIAZINE	N05AC04	0	0.0%	1	0.0%	1	0.0%
PERPHENAZINE	N05AB03	0	0.0%	0	0.0%	0	0.0%
PERICIAZINE	N05AC01	1	0.0%	1	0.0%	0	0.0%
HYPNOTIC DRUGS							
ALIMEMAZINE	R06AD01	26	0.2%	39	0.3%	30	0.3%
DOXYLAMINE	R06AA09	0	0.0%	0	0.0%	0	0.0%
ANTIHISTAMINIC DRUGS							
HYDROXYZINE	N05BB01	310	2.6%	274	2.2%	279	2.4%
MEQUITAZINE	R06AD07	52	0.4%	51	0.4%	30	0.3%
CYPROHEPTADINE	R06AX02	0	0.0%	0	0.0%	0	0.0%
DEXCHLORPHENIRAMINE	R06AB02	0	0.0%	0	0.0%	0	0.0%
BROMPHENIRAMINE	R06AB01	2	0.0%	1	0.0%	0	0.0%
PROMETHAZINE	R06AD02	2	0.0%	0	0.0%	0	0.0%
URINARY ANTISPASMODIC DRUGS							
SOLIFENACINE	G04BD08	63	0.5%	112	0.9%	114	1.0%
OXYBUTYNINE	G04BD04	55	0.5%	48	0.4%	44	0.4%
TOLTERODINE	G04BD07	0	0.0%	0	0.0%	0	0.0%
LONG-ACTING BENZODIAZEPINES							
BROMAZEPAM	N05BA08	576	4.8%	585	4.7%	500	4.3%
PRAZEPAM	N05BA11	166	1.4%	150	1.2%	140	1.2%
CLONAZEPAM	N03AE01	0	0.0%	0	0.0%	0	0.0%
LOFLAZEPATE	N05BA18	18	0.2%	18	0.1%	16	0.1%
CLORAZEPATE DIPOTASSIQUE	N05BA05	31	0.3%	27	0.2%	26	0.2%
DIAZEPAM	N05BA01	24	0.2%	26	0.2%	55	0.5%
CLOBAZAM	N05BA09	20	0.2%	24	0.2%	24	0.2%
NORDAZEPAM	N05BA16	18	0.2%	22	0.2%	11	0.1%
NITRAZEPAM	N05CD02	7	0.1%	7	0.1%	3	0.0%
FLUNITRAZEPAM	N05CD03	3	0.0%	2	0.0%	2	0.0%
ANTIHYPERTENSIVE DRUGS							
CENTRALLY ACTING ANTIHYPERTENSIVES							
RILMENIDINE	C02AC06	103	0.9%	111	0.9%	102	0.9%
MOXONIDINE	C02AC05	22	0.2%	23	0.2%	17	0.1%
CLONIDINE	C02AC01	2	0.0%	0	0.0%	1	0.0%
METHYLDOPA	C02AB02	1	0.0%	0	0.0%	1	0.0%
SHORT-ACTING CALCIUM-CHANNEL BLOCKERS							
NICARDIPINE	C08CA04	82	0.7%	96	0.8%	98	0.8%
NIFEDIPINE	C08CA05	30	0.3%	32	0.3%	33	0.3%
RESERPINE	C02AA02	0	0.0%	0	0.0%	0	0.0%
ANTIARYTHMICS							
DISOPYRAMIDE	C01BA03	6	0.1%	6	0.0%	2	0.0%
GASTROINTESTINAL DRUGS							
STIMULANT LAXATIVES							
DOCUSATE	A06AA02	0	0.0%	0	0.0%	0	0.0%
BISACODYL	A06AB02	0	0.0%	0	0.0%	0	0.0%
RICIN OIL	A06AB05	0	0.0%	0	0.0%	0	0.0%
SENNOSIDES	A06AB06	0	0.0%	0	0.0%	0	0.0%
CASCARA	A06AB07	0	0.0%	0	0.0%	0	0.0%
SODIUM PICOSULFATE	A06AB08	0	0.0%	0	0.0%	0	0.0%

(*continued on next page*)

Appendix 1 (*continued*)

PIMS	ATC CODE	2012		2013		2014	
		N = 11,891		N = 12,405		N = 11,732	
CIMETIDINE	A02BA01	0	0.0%	0	0.0%	0	0.0%
MEPROBAMATE	N05BC01	16	0.1%	0	0.0%	0	0.0%
GASTROINTESTINAL ANTISPASMODIC DRUGS							
CHLORDIAZEPOXIDE-CLINIDIUM	A03CA02	0	0.0%	0	0.0%	0	0.0%
TIEMONIUM	A03AB17	0	0.0%	0	0.0%	0	0.0%
DIHEXYVERINE	A03AA08	0	0.0%	0	0.0%	0	0.0%
SCOPOLAMINE	A04AD01	0	0.0%	0	0.0%	0	0.0%
LONG-ACTING SULFONYUREAS							
GLIPIZIDE	A10BB07	3	0.0%	2	0.0%	3	0.0%
CARBUTAMIDE	A10BB06	0	0.0%	0	0.0%	0	0.0%
MUSCLE RELAXANTS							
TETRAZEPAM	M03BX07	828	7.0%	0	0.0%	0	0.0%
BACLOFENE	M03BX01	19	0.2%	19	0.2%	19	0.2%
METHOCARBAMOL	M03BA03	175	1.5%	0	0.0%	0	0.0%
CEREBRAL VASODILATORS							
GINKGO	N06DX02	235	2.0%	92	0.7%	0	0.0%
NAFTIDROFURYL	C04AX21	65	0.5%	76	0.6%	55	0.5%
PIRIBEDIL	N04BC08	32	0.3%	42	0.3%	35	0.3%
NICERGOLINE	C04AZ02	0	0.0%	0	0.0%	0	0.0%
PIRACETAM	N06BX03	65	0.5%	27	0.2%	2	0.0%
DIHYDROERGOCRISTINE	C04AE54	36	0.3%	10	0.1%	0	0.0%
PENTOXIFYLLINE	C04AD03	23	0.2%	8	0.1%	0	0.0%
MOXISYLYTE	C04AX10	6	0.1%	3	0.0%	0	0.0%
VINBURNINE	C04AX17	14	0.1%	6	0.0%	0	0.0%
VINCAMINE	C04AX07	0	0.0%	0	0.0%	0	0.0%
RUTOSIDE	C05CA01	0	0.0%	0	0.0%	0	0.0%
TROXERUTINE	C05CA04	0	0.0%	0	0.0%	0	0.0%
DIHYDROERGOCRYPTINE	N04BC03	0	0.0%	0	0.0%	0	0.0%
DIHYDROERGOTOXINE	C04AE01	1	0.0%	0	0.0%	0	0.0%
OTHER ANTICHOLINERGIC DRUGS WITH QUESTIONNABLE EFFICACY							
DIPHENHYDRAMINE	R06AA02	0	0.0%	0	0.0%	0	0.0%
OXOMEMAZINE	R06AD08	492	4.1%	575	4.6%	463	3.9%
METOPIMSAZINE	A04AD05	209	1.8%	291	2.3%	250	2.1%
DIPHENHYDRAMINE IN COMBINATION	R01BA52	263	2.2%	97	0.8%	0	0.0%
TRIPROLIDINE IN COMBINATION	R01BA52	263	2.2%	97	0.8%	0	0.0%
MECLOZINE	R06AE05	7	0.1%	11	0.1%	10	0.1%
ALIZAPRIDE	A03FA05	0	0.0%	0	0.0%	1	0.0%
PIMETIXENE	R06AX23	0	0.0%	0	0.0%	0	0.0%
PROMETHAZINE	R06AD02	2	0.0%	0	0.0%	0	0.0%
PHENIRAMINE	R06AB05	0	0.0%	0	0.0%	0	0.0%
ANTPLATELET DRUGS							
TICLOPIDINE	B01AC05	5	0.0%	4	0.0%	3	0.0%
DIPYRIDAMOLE	B01AC07	0	0.0%	0	0.0%	0	0.0%
ANTIMICROBIAL							
NITROFURANTOINE	J01XE01	94	0.8%	84	0.7%	79	0.7%
DRUG-DRUG ASSOCIATIONS							
CONCOMITANT USE OF 2 BENZODIAZEPINES	N05BA N05CD N05CF N03AE01 M03BX07	283	2.4%	233	1.9%	210	1.8%
CONCOMITANT USE OF 2 ANTIDEPRESSANTS	N06A	48	0.4%	49	0.4%	39	0.3%
CONCOMITANT USE OF 2 ANTIPSYCHOTIC DRUGS	N05A	8	0.1%	11	0.1%	9	0.1%
CONCOMITANT USE OF ANTICHOLINESTERASE DRUGS WITH ANTICHOLINERGIC DRUGS	N06DA	3	0.0%	5	0.0%	2	0.0%
ADDITIONAL CRITERIA							
PROLONGED USE OF BENZODIAZEPINES	N05BA N05CD N05CF N03AE01 M03BX07	388	3.3%	380	3.1%	336	2.9%
PROLONGED USE OF NSAIDS	M01A	1103	9.3%	1057	8.5%	898	7.7%
MEDICATIONS OF THE 2015 BEERS LIST		134	1.1%	94	0.8%	101	0.9%
METOCLOPRAMIDE	A03FA01	131	1.1%	91	0.7%	98	0.8%
DESMOPRESSINE	H01BA02	3	0.0%	3	0.0%	3	0.0%

Appendix 2

Multistate Model Assessing the Influence of ≥1 PIM on Changes in Frailty Status, Where Multiple Pathologies-Including Joint Pain-Are Introduced as Covariates in the Model

Variables	From non-frailty to frailty (N = 1519)	From frailty to non-frailty (N = 1196)
	aHR (95% CI)	aHR (95% CI)
Age		
<65	1	1
65-69	1.04 (0.85-1.27)	0.74 (0.60-0.91)
≥70	1.30 (1.06-1.60)	0.60 (0.48-0.74)
Gender		
Male	1	1
Female	1.07 (0.91-1.24)	0.90 (0.48-1.06)
Self-perceived social situation		
Underpriviledged	0.99 (0.77-1.28)	0.80 (0.60-1.05)
Intermediate	1	1
Priviledged	0.84 (0.71-1.00)	1.07 (0.87-1.30)
Marital status		
In couple	1	1
Single	0.90 (0.76-1.05)	0.93 (0.78-1.11)
BMI		
Low	1.12 (0.94-1.33)	0,67 (0.55-0.83)
Intermediate	1	1
High	0.94 (0.82-1.07)	0,85 (0.73-0.98)
Tobacco consumption		
No	1	1
Light	1.02 (0.77-1.36)	1.20 (0.87-1.66)
Medium or heavy	1.07 (0.76-1.48)	0.78 (0.52-1.16)
Polypharmacy		
No (0 to 4 drugs)	1	1
Moderate (5 to 9 drugs)	1.34 (1.17-1.53)	0.85 (0.73-0.98)
Excessive (≥ 10 drugs)	1.58 (1.29-1.94)	0.71 (0.56-0.88)
Self-reported depression		
No	1	1
Yes	1.96 (1.73-2.22)	0.76 (0.67-0.87)
High blood pressure		
No	1	1
Yes	1.05 (0.93-1.20)	1.08 (0.93-1.25)
Respiratory disease		
No	1	1
Yes	1.31 (1.14-1.51)	0.92 (0.79-1.08)
Cancer		
No	1	1
Yes	1.46 (1.18-1.82)	1.20 (0.94-1.53)
Diabetes		
No	1	1
Yes	1.07 (0.88-1.31)	1.04 (0.83-1.29)
Stroke		
No	1	1
Yes	1.32 (0.82-2.14)	1.16 (0.70-1.93)
Cardiac disease		
No	1	1
Yes	1.35 (1.16-1.57)	0.78 (0.65-0.94)
Joint pain		
No	1	1
Yes	1.35 (1.16-1.57)	0.86 (0.72-1.01)
≥ 1 PIM according to Laroche list + additional criteria		
Non Prescribed	1	1
Prescribed	1.29 (1.00-1.66)	1.08 (0.79-1.48)

PIM, Potentially Inappropriate Medication; BMI, Body Mass Index

Appendix 3

Multistate Model Assessing the Influence of ≥1 PIM on Changes in the 4 Frailty Dimensions

Frailty dimension	From absence to presence of the frailty dimension		From presence to absence of the frailty dimension	
	Number of transitions	aHR (95% CI)*	Number of transitions	aHR (95% CI)*
Physical	1141	1.20 (1.03-1.40)	1017	0.87 (0.74-1.03)
Nutritional	317	1.65 (1.21-2.25)	252	1.05 (0.75-1.47)
Cognitive	1328	1.09 (0.94-1.26)	1088	0.87 (0.73-1.03)
Sensory	2347	0.92 (0.83-1.04)	1864	0.85 (0.75 -0.97)

*Adjusted Hazard Ratio with 95% Confidence Interval corresponding to 1 PIM according to the Laroche list + additional criteria.