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RESEARCH PAPER

Investigation of a possible association of potentially inappropriate medication for older adults and frailty in a prospective cohort study from Germany

Dana Clarissa Muhlack[1,2], Liesa Katharina Hoppe[1,2], Kai-Uwe Saum[1], Walter E. Haefeli[3], Hermann Brenner[1,2], Ben Schöttker[1,2]

[1]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany
[2]Network Aging Research, University of Heidelberg, Bergheimer Straße 20, 69115 Heidelberg, Germany
[3]Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg University Hospital, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

Address correspondence to: Ben Schöttker. Tel: +(0049) 6221-421355; Fax: +(0049) 6221-421302.
Email: b.schoettker@dkfz-heidelberg.de

Abstract

Objective: potentially inappropriate medications (PIMs) are commonly defined as drugs that should be avoided in older adults because they are considered to have a negative risk-benefit ratio. PIMs are suspected to increase the risk for frailty, but this has yet to be examined.
Design: prospective population-based cohort study.
Setting and participants: a German cohort of community-dwelling older adults (≥60 years) was followed from October 2008 to September 2016.
Methods: in propensity score-adjusted logistic and Cox regression models, associations between baseline PIM use and prevalent/incident frailty were investigated. Frailty was assessed using the definition by Fried and co-workers, PIM were defined with the *2015 BEERS criteria*, the BEERS criteria to avoid in cognitively impaired patients (*BEERS dementia PIM*), the *EU(7)-PIM* and the *PRISCUS list*.
Results: of 2,865 participants, 261 were frail at baseline and 423 became frail during follow-up. Only *BEERS dementia PIM* use was statistically significantly associated with prevalent frailty (odds ratio (95% confidence interval), 1.51 (1.04–2.17)). The strength of the association was comparable for all frailty components. Similarly, in longitudinal analyses, only *BEERS dementia PIM* use was associated with incident frailty albeit not statistically significant (hazard ratio, 1.19 (0.84–1.68)).
Conclusions: the association of PIM use and frailty seems to be restricted to drug classes, which can induce frailty symptoms (anticholinergics, benzodiazepines, z-substances and antipsychotics). Physicians are advised to perform frailty assessments before and after prescribing these drug classes to older patients and to reconsider treatment decisions in case of negative performance changes.

Keywords: *drugs to avoid in cognitively impaired patients, fried frailty phenotype, PRISCUS list, EU(7)-PIM list, 2015 BEERS criteria, older people*

Key Points

- In propensity score-adjusted analyses, we found an association for intake of PIMs and frailty.
- The association was restricted to drug classes, which can induce frailty symptoms.

- The research supports physicians in deciding, which drug classes they should try to avoid in (vulnerable) geriatric patients.

Introduction

Frailty is commonly known as a state of high vulnerability for adverse health outcomes such as hospitalisations or premature death [1, 2]. Evidence is growing that age, low physical activity, sub-clinical inflammation and polypharmacy are associated with frailty [2–4]. Previous research not only indicates that robust older adults tolerate polypharmacy better than their frail peers [5], but also that polypharmacy contributes to the development of frailty [6–9]. Nevertheless, the relationship between medication quality and frailty is still poorly examined. Possibly, the underlying reason for an association of polypharmacy and frailty is the intake of certain drugs that are inappropriate for older adults. For instance, some sedating and/or muscle relaxing medications are suspected to increase the risk of falling. Although falls are discussed as an outcome of frailty [10], they also likely cause the condition [11]. Drugs that may increase the risk of falling are often included in lists of potentially inappropriate medications (PIMs).

Despite the possible correlation between PIMs and frailty, their longitudinal association has been investigated only by one study so far [12]. This study, however, has some methodological limitations as discussed in this article. We considered these methodological issues in our study and aimed to examine whether the use of PIM, defined with the *2015 BEERS criteria* [13], the BEERS "to avoid in patients with dementia or cognitive impairment" sub-list, from here on entitled as *2015 BEERS dementia sub-list* [13], the *PRISCUS list* [14] and the *EU(7)-PIM list* [15], is associated with higher frailty prevalence and incidence in a cohort of community-dwelling older German adults.

Methods

Study design

The analyses were carried out using data from the ESTHER study [16]. For this on-going population-based cohort study, 9,940 participants were recruited as part of a routine health check in Saarland, Germany between 2000 and 2002. Inclusion criteria were age between 50 and 75 years and an adequate knowledge of the German language. Every 2–3 years, participants and their general practitioners were asked to complete questionnaires on the health of the participants. During the follow-ups (FUPs) after 8, 11 and 14 years, participants could additionally agree to be visited at home by a study physician for a detailed health examination.

For this project, data from the 8-year-FUP home-visit (October 2008–February 2011, $N = 3{,}124$) were used as a baseline. The 11-year-FUP (September 2011–January 2014, $N = 2{,}761$) and 14-year-FUP home-visits (October 2014–September 2016, $N = 2{,}217$) served as FUP1 and FUP2. We excluded participants younger than 60 and individuals whose frailty status was not assessed or whose medications could not be fully recorded during the 8-year-FUP (Supplementary Appendix 1). The resulting baseline sample size was $N = 2{,}865$. For longitudinal analyses, we further excluded study participants with prevalent frailty ($N = 261$) or missing frailty assessments in both FUP home visits ($N = 593$), leaving $N = 2{,}011$ participants (Supplementary Appendix 1). The ESTHER study has been approved by the responsible ethics committees of the Medical Faculty of the University of Heidelberg and of the Medical Association of Saarland. It is conducted in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Data collection and variable definitions

The data collection and the assessments of frailty and PIMs are described in Supplementary Appendix 2.

Statistical methods

PIM use and frailty were operationalised as dichotomous variables (0 or ≥ 1 PIM, robust/pre-frail or frail). Separate analyses were conducted for each of the four PIM lists and the drug classes of the *BEERS dementia sub-list* (anticholinergics, benzodiazepines, H_2-receptor antagonists, z-substances and antipsychotics). To assess the cross-sectional association of PIM use and prevalent frailty, logistic regression models were used. Cox proportional hazard regression models considering mortality as a competing risk were applied to ascertain the longitudinal association with incident frailty. FUP time was the time until outcome of interest (home visit where frailty was first detected), death, dropout or end of the study (whichever occurred first).

In addition to an unadjusted/crude model, three multivariable-adjusted models were carried out. The first model adjusted for sex and age, the second additionally for number of medicines and the third further for school education, net household income, smoking status, body mass index (BMI), pre-frailty (longitudinal analysis only) and total comorbidity score (TCS) (modelled as shown in Table 1).

In order to further decrease the potential bias through residual confounding by indication, we additionally conducted a model with adjustment for propensity score (PS) deciles. PSs were developed separately for the different PIM criteria as dependent variables. Overall, 53 health status-related variables were used as independent parameters. The results of the logistic regression models are reported in Supplementary Appendix 3. Supplementary Appendix 4

Table 1. Characteristics of the 2,865 ESTHER 8-year-FUP home-visit participants

Characteristics	*N* =	*(%)*	Mean	*(SD)*
Sex (female)	1,480	*(51.7)*		
Age [years]			70.2	*(5.9)*
School education [years]				
≤9	1,901	*(66.4)*		
10–11	513	*(18.9)*		
≥12	451	*(15.7)*		
Monthly net household income [€]				
<1,000	410	*(14.3)*		
≥1,000 to <3,000	2,122	*(74.1)*		
≥3,000	333	*(11.6)*		
BMI [kg/m^2]			28.7	(4.8)
Smoking				
Never	1,545	*(53.9)*		
Former	1,105	*(38.6)*		
Current	215	*(7.5)*		
Frailty[a]				
Robust	919	*(32.1)*		
Pre-frail	1,685	*(58.8)*		
Frail	261	*(9.1)*		
Frailty criterion "low gait speed"	1,079	*(37.7)*		
Frailty criterion "weakness"	930	*(32.5)*		
Frailty criterion "low physical activity"	599	*(20.9)*		
Frailty criterion "exhaustion"	358	*(12.5)*		
Frailty criterion "weight loss"	130	*(4.5)*		
Total comorbidity score[b]			6.9	*(5.3)*
Number of medicines			4.7	*(3.4)*
PRISCUS PIM users	392	*(13.7)*		
EU(7) PIM users	1,074	*(37.5)*		
BEERS PIM users	757	*(26.4)*		
BEERS dementia PIM users	263	*(9.2)*		

Note. Exemplarily, data of imputed dataset 1 are shown. BMI, body mass index; FUP, follow-up; HbA_{1c}, glycosylated haemoglobin [a]Measured with the Fried criteria. Robust: fried index = 0, pre-frail: fried index = 1–2. [b]Measured with the Cumulative Illness Rating Scale for geriatrics (0–56 possible points).

provides additional information on statistical methods as well as conducted sensitivity analyses.

Results

Participant characteristics

Participant characteristics are depicted in Table 1. Roughly half of the baseline population was female (51.7%) and never smoked (53.9%). The mean age was 70.2 years. The majority went to school for 9 years or less (66.4%) and had a monthly net household income of 1,000–3,000 euros (74.1%). The mean BMI (28.7 kg/m^2) was far above normal weight according to WHO standards [17]. The prevalence of pre-frailty (58.8%) and frailty (9.1%) was quite high. The most frequently fulfilled frailty criteria were low gait speed (37.7%), weakness (32.5%) and low physical activity (20.9%). Exhaustion (12.5%) and involuntary weight loss (4.5%) were observed less frequently. The mean TCS was 7 out of 56 points. On average, participants used five different drugs simultaneously. The baseline PIM prevalence varied between 9.2% (*BEERS dementia PIM*) and 37.5% (*EU(7) PIM*). Further participant characteristics used to calculate the PSs are shown in Supplementary Appendix 5.

Association with prevalent frailty

A total of 261 (9.1%) participants were frail at baseline. Use of PIM was strongly and significantly associated with prevalent frailty in the unadjusted models and in those adjusted for age and sex, independent of the criteria applied (Table 2). However, additional adjustment for number of medicines strongly attenuated all odds ratios (ORs), while further adjustment resulted in almost identical point estimates. Only the association with *BEERS dementia PIM* remained statistically significant. Users of these PIMs were roughly 50% more likely to be frail compared to their peers in the PS-adjusted model (OR (95%CI), 1.51 (1.04–2.17)). The pattern also remained in sensitivity analyses with frailty as an ordinal variable: Only the association with *BEERS dementia PIM* was statistically significant in the PS-adjusted model (Supplementary Appendix 6). To elucidate this further, we examined the drug classes of the *BEERS dementia sub-list* individually (Supplementary Appendix 7). Except for the H_2-receptor antagonists, all effect estimates were increased in all models. Due to the small number of users of these drug classes in our dataset (between $N = 20$ and $N = 92$), PS-adjusted analyses could not be performed and only the association with antipsychotics was statistically significant in the fully adjusted model 3 (OR (95%CI) and 3.94 (1.39–11.13)).

In order to investigate, which frailty criteria are associated with *BEERS dementia PIM* use, we repeated the logistic regression analyses and used the single components of the frailty phenotype as dichotomous outcomes (Supplementary Appendix 8). To make results comparable, the same robust study participants were used as reference group in all analyses. The OR point estimates obtained by the PS-adjusted analyses revealed that the association was comparably strong for all frailty criteria: Increases in odds ranged from 32% (slow gait speed) to 43% (exhaustion). However, none of the estimates was statistically significant.

Association with incident frailty

The average FUP time was 4.8 years. During FUP, 423 (21.0%) of 2,011 participants became frail. In agreement with the cross-sectional analyses, all PIM criteria were statistically significantly associated with incident frailty in the unadjusted and in the age and sex-adjusted analyses. The associations were also considerably attenuated by further adjustments for the number of medicines or adjustment for the PS (Table 3).

Again, *BEERS dementia PIM* showed the strongest association in the PS-adjusted model, but this time, it was not statistically significant (hazards ratio (HR) (95%CI), 1.19 (0.84–1.68)). The weaker association may be partly explained by the fact that 24% of the *BEERS dementia PIM* users included in the longitudinal analysis discontinued

Table 2. Cross-sectional association of PIM use, defined by four different criteria, and prevalent frailty (N = 2,865 community-dwelling older adults; N = 261 frail at baseline)

Model	PRISCUS PIM users (N = 392)	EU(7) PIM users (N = 1,074)	BEERS PIM users (N = 757)	BEERS dementia PIM users (N = 263)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Crude model	*2.54 (1.88, 3.42)*	*2.46 (1.90, 3.18)*	*2.49 (1.92, 3.23)*	*3.16 (2.28, 4.39)*
Multivariable model 1[a]	*2.16 (1.58, 2.95)*	*1.95 (1.49, 2.55)*	*2.03 (1.55, 2.66)*	*2.49 (1.77, 3.51)*
Multivariable model 2[b]	1.31 (0.94, 1.83)	1.07 (0.80, 1.45)	1.23 (0.92, 1.64)	*1.58 (1.10, 2.27)*
Multivariable model 3[c]	1.32 (0.94, 1.85)	1.09 (0.81, 1.48)	1.17 (0.87, 1.58)	*1.59 (1.10, 2.30)*
Propensity score model[d]	1.20 (0.86, 1.68)	1.13 (0.84, 1.53)	1.00 (0.73, 1.37)	*1.51 (1.04, 2.17)*

Note. Statistically significant results are in italics. CI, confidence interval; OR, odds ratio; PIM, potentially inappropriate medication [a]Adjusted for age and sex. [b]Adjusted for age, sex and the number of medicines. [c]Adjusted for age, sex, the number of medicines, school education, net household income, smoking status, body mass index and total comorbidity score. [d]Adjusted for propensity score deciles.

Table 3. Longitudinal association of PIM use, defined by four different criteria, and incident frailty (N = 2,011 community-dwelling older adults, N = 423 incident frailty cases during 6 years for FUP)

Model	PRISCUS PIM users (N = 250)	EU(7) PIM users (N = 689)	BEERS PIM users (N = 498)	BEERS dementia PIM users (N = 161)
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Crude model	*1.50 (1.16, 1.93)*	*1.63 (1.35, 1.97)*	*1.89 (1.55, 2.31)*	*1.80 (1.32, 2.46)*
Multivariable model 1[a]	*1.43 (1.11, 1.84)*	*1.42 (1.17, 1.73)*	*1.65 (1.35, 2.02)*	*1.58 (1.15, 2.19)*
Multivariable model 2[b]	1.09 (0.84, 1.41)	1.07 (0.86, 1.32)	*1.31 (1.06, 1.63)*	1.22 (0.88, 1.70)
Multivariable model 3[c]	0.99 (0.75, 1.30)	1.00 (0.81, 1.23)	*1.34 (1.08, 1.66)*	1.17 (0.83, 1.65)
Propensity score model[d]	0.92 (0.69, 1.23)	0.97 (0.78, 1.21)	1.17 (0.92, 1.48)	1.19 (0.84, 1.68)

Note. Statistically significant results are in italics. CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication [a]Adjusted for age and sex. [b]Adjusted for age, sex and the number of medicines. [c]Adjusted for age, sex, the number of medicines, school education, net household income, smoking status, body mass index, total comorbidity score and baseline pre-frailty. [d]Adjusted for propensity score deciles.

treatment and did not have any of these PIM at home in both FUP contacts. The associations of *PRISCUS* and *EU(7) PIM* were close to the null effect value of HR = 1. To elucidate whether the non-significantly increased HR for *BEERS PIM* (1.17 (0.92–1.48)) was caused by *BEERS dementia PIM*, users of drugs listed in the *BEERS dementia sub-list* were excluded. The resulting longitudinal association of *BEERS PIM* and frailty was a null result (1.00 (0.78–1.29)).

Discussion

Overall, 9.1% of the participants were frail at the beginning of this study and 21.0% became frail during FUP. Only use of *BEERS dementia PIM* was strongly and statistically significantly associated with prevalent frailty in fully adjusted models. In the longitudinal analyses, none of the associations were statistically significant in PS-adjusted models. However, the point estimate for *BEERS dementia PIM* use was increased.

Of all drug classes included in the various PIM criteria, those of the *BEERS dementia sub-list* have the highest biological plausibility for causing frailty symptoms (see Supplementary Appendix 9 for a more detailed discussion), and indeed all except H_2-receptor antagonists showed increased odds for frailty in our analyses. However, except for antipsychotics, associations were not statistically significant due to the low numbers of *BEERS dementia PIM* users in our dataset. Larger studies are required to corroborate our findings.

Our results are in line with a previous cross-sectional study. Herr and co-workers [18] examined the association of *Laroche list* PIMs [19] with the number of frailty criteria (0–5) in 1,890 community-dwelling adults aged ≥65 years. Only use of anticholinergic PIMs remained statistically significantly associated with the number of frailty criteria after adjusting for polypharmacy (intake of ≥5 drugs) and other variables (rate ratio 1.17, P-value <0.05). Similarly, our results show a notable attenuation of point estimates after adjusting for number of medicines. In fact, the variable was one of the major risk factors for the transition from a robust/pre-frail to a frail stage in older adults. These results are in line with previous analyses, which found a statistically significant association between polypharmacy and frailty that persisted after adjusting for co-morbidities [6–9]. Part of this association is likely explained by the use of PIMs, whose prevalence increases with the number of drugs taken [20, 21]. Interestingly, in both the study of Herr and co-workers [18] and our study, polypharmacy remained a strong risk factor for frailty after adjusting for PIM, indicating an independent association with frailty.

The use of *BEERS dementia PIM* was similarly strongly associated with all frailty phenotype components. This is not surprising for exhaustion, gait speed, muscle strength and physical activity. As described above, the four frailty components are possibly directly influenced by some of the *BEERS dementia PIM*. Furthermore, they interact: reduced muscle strength leads to exhaustion, which in turn decreases the walking speed and physical activity, which may further

diminish muscle strength [1]. The association with weight loss, on the other hand, does not seem as obvious since especially anticholinergic and antipsychotic drug effects are more commonly associated with weight gain. However, it is possible that reduced physical activity may lead to loss of muscle mass (sarcopenia), resulting in lower weight. Evidence for the association between cognitive impairment and malnutrition in older adults supports this hypothesis [22], since malnutrition is a well-known cause of sarcopenia [23]. Findings from the literature are in line with our results. Three smaller studies reported no statistically significant associations for the full *BEERS criteria* with gait speed or grip strength [24–26]. In contrary, exposure to anticholinergic/sedative or psychotropic drugs was statistically significantly associated with these frailty criteria [25, 26]. This leads to the interesting question whether the corresponding PIMs rather cause symptoms of the frailty phenotype or frailty itself, which is defined as high vulnerability to stressors. Further studies are needed to answer this issue.

The lack of an association between *BEERS dementia PIM* and frailty in fully adjusted models of our longitudinal study indicates that the effect may be rather immediate. Two previous population-based cohort studies, investigating the longitudinal association of the anticholinergic drug burden index (DBI) and frailty, reported statistically significant findings [8, 27]. However, neither study adjusted for polypharmacy, which proved to be important in our study since statistical significance got lost after accounting for polypharmacy by adjusting for number of medicines. A recently published longitudinal study investigating the association between use of *Laroche list* PIMs [19] and incident frailty also found a statistically significant association, even after adjustment for polypharmacy (HR (95%CI), 1.15 (1.01–1.32)) [12]. However, frailty was assessed using a rarely applied questionnaire tool [28] with limited power to predict health outcomes [12], and residual confounding by indication may be present since the authors only adjusted for number of chronic diseases and not for PS. Nevertheless, in our study, the HR point estimates for *BEERS PIM* (1.17 (0.92–1.48)) and *BEERS dementia PIM* use (1.19 (0.84–1.68)) were similar to the findings of this study and it is possible that only statistical power was missing to reach statistical significance. Moreover, our study, as well as the two studies using the DBI and the study investigating *Laroche list* PIMs [19] examined prevalent drug users, which introduced a risk for the sick-stopper/healthy-user bias [29]. Prevalent drug users have usually been taking their medication (including PIM) for a long time and mostly tolerate it well. Those who took a PIM in the past but discontinued it because of side effects are not caught in the dataset. Therefore, it is possible that the association of PIM/anticholinergic drug use and incident frailty is underestimated. In addition, about every fourth (24%) baseline user discontinued *BEERS dementia PIM* early during FUP, which may also explain why the longitudinal association of *BEERS dementia PIM* and frailty was weaker than the cross-sectional association and not statistically significant. New-user-design studies, using data that allow longitudinal analyses with shorter FUP-times, are needed. However, it is unlikely that such studies will become available, as this would require regular frailty assessments over several years and additional links to health claims data.

Our analyses were conducted with German adults aged 60–84 who agreed to participate in home visits with extensive health assessments. These volunteers were generally healthier than those who did not participate in the home visit [6]. Therefore, the present results should only be generalised to rather robust older Caucasian adults. A limitation of the study is that a small portion of the *BEERS* and the *EU(7)-PIM criteria* could not be coded because necessary information was not available (Supplementary Appendix 10). Strengths of the study are the large sample size, the comprehensive recording of all prescription and non-prescription drugs and the long-term FUP with repeated frailty assessments. Furthermore, analyses were adjusted for PSs, allowing adjusting for numerous exposure-related variables without losing degrees of freedom and thereby reducing residual confounding as much as possible.

Conclusion

We found an association between PIM use and the frailty phenotype, which was restricted to drug classes summed up in the *BEERS dementia sub-list* (especially antipsychotics, anticholinergics, benzodiazepines and z-substances). Physicians are advised to perform frailty assessments before and after prescribing these drugs to older adults and to reconsider treatment decisions in case of deteriorations.

Supplementary data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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