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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study

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Abstract

Purpose To assess the changes in use of potentially inappropriate medication (PIM) as defined by the 2015 Beers criteria, the EU(7)-PIM, and the PRISCUS list over a 6-year period and to identify determinants for current and future PIM use with a particular focus on geriatric syndromes.

Methods In a German cohort of 2878 community-dwelling adults aged ≥ 60 years, determinants of the use of ≥ 1 PIM were identified in multivariable logistic regression (cross-sectional analysis) and weighted generalized estimating equation models (longitudinal analysis).

Results Prevalences for Beers, EU(7), and PRISCUS PIM were 26.4, 37.4, and 13.7% at baseline and decreased to 23.1, 36.5, and 12.3%, respectively, 6 years later. Unadjusted prevalences in participants with any geriatric syndrome (frailty, co-morbidity, functional, or cognitive impairment) were approximately twice as high as in robust older adults. In multivariable analyses, cognitive impairment was statistically significantly associated with the use of PIM of all three criteria in the cross-sectional (odds ratio (OR) point estimates 1.90–2.21) but not in the longitudinal models. In contrast, frailty, co-morbidity, and functional impairment were statistically significantly associated with the use of PIM of at least one of the three criteria in both models. However, the associations varied for the PIM criteria, and in the longitudinal analysis, associations were only statistically significant for Beers PIM (ORs [95% confidence intervals]: frailty (2.23 [1.15, 4.31]), co-morbidity by five total co-morbidity score points (1.21 [1.05, 1.38]), and functional impairment (1.51 [1.00, 2.27]). Other statistically significant determinants of the incidence of PIM (any definition) were female sex, age, coronary heart disease, heart failure, biomarkers of the metabolic syndrome, and history of ulcer, depressive episodes, hip fracture, or any cancer.

Conclusions Older adults with frailty, co-morbidity, cognitive, and functional impairment had higher odds of taking PIM or getting a PIM prescription in the future (exception: cognitive impairment). Physicians should be especially cautious when prescribing drugs for these patients who are particularly susceptible to adverse reactions.

Keywords Potentially inappropriate medication · Determinants · Prevalence · Longitudinal analysis · Frailty · Cognitive impairment

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Introduction

Potentially inappropriate medications (PIMs) are commonly described as drugs and drug classes that should be avoided in older adults whenever possible because they are likely to bring more harm than benefit to the user and safer alternatives are available [1]. There are two approaches to define PIM, namely implicit and explicit measurements [2]. Implicit methods are based on the judgment of a single practitioner or expert and are specifically indicated for one individual person. Therefore, applying them can be time-consuming, costly, and not completely reproducible [2]. In contrast, explicit measurements are criteria-based, meaning that particular drugs have been defined as being potentially inappropriate. The application of explicit PIM criteria requires relatively little effort from the physician and is reproducible. According to a systematic overview, there were 28 explicit assessment tools for PIM published in 2013 [3], and various systematic reviews showed that PIM lists are rather different [3–6]. This raises the question which PIM list physicians should apply and how their consideration relates to beneficial and adverse drug effects.

The Beers criteria were developed for the US-American pharmaceutical market and are the most widely used explicit assessment tool [3, 7]. Because national therapeutic guidelines and pharmaceutical markets vary, many countries have developed their own PIM lists. Germany, for example, designed the PRISCUS list [8], and in 2015, the EU(7)-PIM list was developed for use across European countries [9].

We aim to compare the prevalences of PIM, determined by the aforementioned three explicit criteria, and their change over time in the general older German population. Moreover, we want to identify risk factors for the use of PIM. Although many studies have already assessed both aspects in a community-dwelling population, only a few examined large cohorts and compared different PIM criteria [10]. In addition, only a few studies have investigated risk factors for PIM use in a longitudinal manner [11–14]. Most studies used a cross-sectional design and therefore only show associations between a risk factor and PIM use, but do not allow any causal inferences. A further limitation of previous studies is the use of health insurance claims data. Since these databases lack clinical information, PIM that depend on kidney function or particular doses usually had to be excluded [10]. In addition, claims data and data of questionnaire-based observational studies lack robust assessments of geriatric syndromes, such as frailty, multimorbidity, functional, and cognitive impairment. To the best of our knowledge, no previous study jointly addressed the potential associations of all four geriatric syndromes with PIM use.

The objectives of this study are (i) to compare the prevalence of PIM use according to three different PIM lists in a cohort of the general older German population at three different time points between 2008 and 2016 and (ii) to identify risk factors and protective parameters for the use of PIM in a cross-sectional and longitudinal study design with a special focus on geriatric syndromes.

Methods

Study design

The analyses were conducted using the data of the ESTHER study (German name: „**E**pidemiologische **S**tudie zu Chancen der Verhütung, Früherkennung und optimierten **TH**erapie chronischer **ER**krankungen in der älteren Bevölkerung“), an ongoing, population-based cohort study from Germany [15]. In the years 2000 to 2002, 9940 participants were recruited via their general practitioner (GP) during a routine health check-up in the German federal state of Saarland. Inclusion criteria were an age between 50 and 75 years and sufficient knowledge of the German language. Every 2 to 3 years, participants and their GPs were asked to complete questionnaires to provide current information on the participant's health.

During the 8-, 11-, and 14-year follow-up (FUP) of the ESTHER cohort, participants could additionally consent to be visited at home by a study physician for an extensive health examination including detailed geriatric and pharmacologic assessments. Data of the 8-year-FUP home visit (10/2008–02/2011, $n = 3124$) were used as the baseline for this project, while the 11-year-FUP (09/2011–01/2014, $n = 2761$) and the 14-year-FUP home visit (10/2014–09/2016, $n = 2217$) served as FUP 1 and FUP 2 for this analysis (Fig. 1, Appendix). Of 3124 8-year-FUP home visit participants, we excluded those for whom the study physician documented that medications were not completely recorded (because of refusal of the study participant to show medications or technical problems) and we excluded study participants who were younger than 60 years of age, resulting in a sample size of $n = 2878$ for the cross-sectional analysis. For the assessment of changes in PIM prevalence over time, individuals had to participate in the baseline examination and at least one of the FUP home visits. A total of 2046 participants of FUP 1 and 1544 participants of FUP 2 fulfilled this inclusion criterion. For the longitudinal analysis of the determinants of PIM, participants who already used one or more PIM at baseline were additionally excluded (Fig. 1, Appendix).

Data collection and variable definitions

Demographic information, namely sex, age, school education, monthly net household income, marital status (living with a partner: yes or no), and smoking status were gathered with the participant questionnaires. Information regarding chronic diseases and past disease events were collected by asking the participants as well as their GPs in the questionnaires about

specific diagnoses. To identify patients with hypertension, the use of antihypertensive medication was additionally considered. The questionnaire for the GP also contained the cumulative illness rating scale for geriatrics (CIRS-G) [16]. The instrument assesses the total co-morbidity score (TCS) as the sum of all points of the CIRS-G (0 to 56) and the clinically relevant co-morbidity score as the number of organ classes with severe or very severe impairments (0 to 14). We defined multimorbidity as having serious impairments in at least two organ categories. Moreover, the GPs took blood samples from the participants. Various disease biomarkers, including HbA_{1c}, total cholesterol, high-density lipoprotein (HDL) cholesterol, non-fasting triglycerides, serum creatinine, and C-reactive protein (CRP), were measured with routine methods in a central laboratory (Synlab, Heidelberg, Germany). We estimated the creatinine clearance using the Cockcroft-Gault formula.

The home visit assessments included the measurement of blood pressure, waist circumference, weight, and height. Furthermore, physical activity, frailty, and cognitive function were examined. Physical activity was assessed with the validated questionnaire instrument developed by Voorrips et al. for older adults [17]. For grading cognitive performance, the mini-mental state examination (MMSE) was applied [18]. The participant can score a maximum of 30 points [18]. We ascertained cognitive impairment at MMSE < 24. To assess frailty, we used the classification of Fried et al. [19] who define persons meeting one or two of overall five criteria (unintended weight loss, weakness, exhaustion, slow gait, and low physical activity) as pre-frail and patients who fulfill at least three criteria as frail. Moreover, the Barthel index [20] was used for a self-evaluation of performing activities of daily living (ADL). Patients can reach a maximum of 100 points indicating complete independence. As adopted in most studies [21], we used ≤ 95 points as a cut-off to define functional impairment.

Finally, according to the "brown bag method," the study physicians asked the participants to show them all medicinal products they had at home (including prescription and non-prescription drugs, nutritional supplements, and medical devices). All medications taken regularly or occasionally were recorded, and participants provided information regarding the dosage.

Assessment of PIMs

To detect PIMs, the 2015 Beers criteria, the EU(7)-PIM list, and the PRISCUS list were used [7–9]. The PRISCUS list contains 83 drugs to be avoided in older adults [8] and the EU(7)-PIM list defines 282 drugs and drug classes as PIM [9]. The 2015 Beers criteria consist of overall six tables listing drugs and drug interactions that should generally be avoided in older adults or that should be avoided in the presence of specific diseases, as well as drugs that should be used with caution [7]. We excluded the latter from the PIM definition because "use with caution" does not imply an explicit avoidance. A few other PIM criteria could not be applied due to lack of information in the ESTHER study (e.g., duration of drug use) and were excluded or modified. Table A1 (Appendix) lists the criteria affected. Finally, all PIMs were divided into pharmaceutical classes.

Statistical methods

Prevalences of PIM use (current use of at least one PIM) were calculated, applying the Beers, the EU(7), and the PRISCUS criteria at baseline, FUP 1, and FUP 2, and stratified by age, sex, frailty, multimorbidity, functional disability, and cognitive impairment. The level of consistency of the lists in identifying PIM users was determined with Cohen's Kappa. In addition, the relative frequencies of the pharmacological drug classes were calculated for each PIM list.

To identify risk factors and protective parameters for the use of PIMs, a cross-sectional and a longitudinal analysis were conducted using multivariable logistic regression analyses. The longitudinal models were fitted using subject-specific weighted generalized estimation equations (GEE). This approach assigns each participant a weight for his/her probability to drop out of the study during the FUP time [22]. The weighted GEEs thus consider the dropouts of study participants that do not happen completely at random, for example, due to death, age, or frailty. The dependent variable in both analyses was "use of one or more PIM," and therefore, the logit function for a binary endpoint was applied in the GEE model which derives odds ratios (ORs) with 95% confidence intervals (95%CI). The independent variables were selected in a stepwise approach using a p value < 0.05 for both the entry and stay criterion. All variables shown in Table A2 were considered in the variable selection process, except physical activity and number of medications to avoid collinearity with geriatric syndromes: Both variables had a Spearman correlation coefficient > 0.30 with one of the geriatric syndromes. Continuous variables were tested continuously and categorically with the categories shown in Table A2. Initially, the selection process of the variables was carried out for each of the three PIM lists individually. The final model then contained all variables that were selected for any of the three PIM lists.

Missing values were imputed using the Markov Chain Monte Carlo technique [23]. Table A3 shows all variables with missing values. The imputation model included all variables listed in Table A2. Five imputed data sets were created with 200 iterations before the first and 100 iterations between imputations. For all analyses, SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), was used. Statistical tests were two-sided, using an alpha level of 0.05.

Results

Description of the study population

At baseline (ESTHER 8-year-FUP home visit), the average age of the study population was 70.2 ± 5.9 years, which increased to 72.3 ± 5.8 years in the 11-year-FUP home visit and to 74.9 ± 5.8 years in the 14-year-FUP home visit. Approximately half of the participants were female at each of the FUP home visits (51.7% in the 8-year-FUP, 51.0% in the 11-year-FUP, and 51.5% in the 14-year-FUP home visit). Table A2 shows further characteristics of the study sample at baseline (8-year-FUP home visit). The vast majority attended school for 9 years or less, had a monthly net household income of 1000 to 3000 euros, and were living with a partner. About half of the participants reported being highly physically active. However, the waist circumference of more than 70% of the study sample indicated a level of internal fat deposits that increases the risk of metabolic complications according to the WHO [24]. In addition, almost 80% had a body mass index (BMI) over 25 kg/m^2. Cardiometabolic diseases such as diabetes, dyslipidemia, hypertension, coronary heart disease (CHD), and heart failure were widespread. In accordance, the proportions of participants with related disease biomarker values above clinical cut-offs were rather high. The prevalences of past disease events lay between 1.6% (hip fracture) and 22.4% (depressive episode). Regarding geriatric syndromes, the prevalences were as follows: 9.2% frailty, 9.6% multimorbidity, 2.2% cognitive impairment, and 13.9% functional impairment. On average, the participants took 4.7 ± 3.4 drugs.

Prevalence of PIM

The prevalences of receiving at least one PIM varied among the three PIM criteria. For example, baseline prevalence was 37.4% for the EU(7)-PIM list, 26.4% for the Beers criteria, and 13.7% for the PRISCUS list. The Cohen's Kappa coefficients were between 0.34 and 0.40 for pairwise comparisons of the three PIM lists, which indicates moderate inter-rater agreement (Tables A4 to A6).

Table 1 shows the prevalences of PIMs at baseline, FUP 1, and FUP 2 in the total cohort and stratified by age and sex. Independent of the assessment tool, prevalence for PIM use increased with the age of the participants (with few exceptions for the oldest age group) and was higher in women. Regarding the development over time, the prevalence of all three PIM criteria slightly decreased throughout the study with one exception (minor increase for EU(7) PIM between FUP 1 and FUP 2).

The prevalence of PIM use was also higher in participants with geriatric syndromes, irrespective of the PIM list applied. Table A7 lists the corresponding baseline prevalences of PIM users who were frail, cognitively or functionally impaired, or had co-morbidity. The prevalence of Beers PIM ranged from 36.8 to 50.0% in patients with geriatric syndromes compared to 22.0% in participants free of any of the four geriatric syndromes. For EU(7) PIM, the prevalence varied between 51.4 and 64.5% compared to 32.3% in healthy participants. Finally, for PRISCUS PIM, the prevalence ranged from 20.1 to 33.9% in patients with geriatric syndromes compared to 10.8% in participants free of geriatric impairments. Consistently for all PIM criteria, participants with cognitive impairments showed the highest PIM prevalence. Prevalences were again higher in women than in men. The stratification according to age groups showed no obvious trends.

Relative frequency of use of the pharmacological drug classes appearing in the PIM lists

The prevalences of the three PIM lists varied because the criteria contain different drug classes and/or specify different conditions under which drugs are considered a PIM (e.g., renal impairment, dosage or interaction with other drug classes). The relative frequency of use of the pharmacological drug classes named in the 2015 Beers criteria, the EU(7)-PIM list, and the PRISCUS list is shown in Figs. 2 to 4 (Appendix). Changes from baseline to FUP 1 and FUP 2 are discussed in the supplementary text A1. Non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, antihypertensives, and benzodiazepines are among the most frequent drug classes for all three PIM lists. However, the ranking differed. For example, although NSAIDs had by far the highest relative frequencies among the drug classes of the Beers criteria, they ranked only fifth in the PRISCUS list. In addition, some of the top drug classes of the Beers and the EU(7)-PIM lists do not appear at all in the PRISCUS list, namely sex hormones and blood glucose-lowering drugs (only sulfonylureas).

Risk factors and protective parameters for PIM use

Table 2 contains the ORs of the cross-sectional, and Table 3 the ORs of the longitudinal analysis. In the cross-sectional analysis, 759, 1076, and 393 participants had ≥ 1 PIM according to the 2015 Beers criteria, the EU(7)-PIM list, and the PRISCUS list, respectively. These persons were excluded from the longitudinal analysis. In the FUP, 229, 338, and 156 participants newly received ≥ 1 PIM (Beers, EU(7), and PRISCUS, respectively). The potential determinants of PIM use were divided into four content-related groups: (1) sociodemographic characteristics, (2) diseases and biomarkers of the metabolic syndrome, (3) other diseases and disease events, and (4) geriatric syndromes. The results of the analyses are described below.

Table 1 Changes of PIM prevalences over time (in %) in the sample study participants

	Beers Criteria			EU(7)-PIM List			PRISCUS List		
	Baseline (2008-2010) *N* = 2878	FUP 1 (2010-2013) *N* = 2046	FUP 2 (2014-2016) *N* = 1544	Baseline (2008-2010) *N* = 2878	FUP 1 (2010-2013) *N* = 2046	FUP 2 (2014-2016) *N* = 1544	Baseline (2008-2010) *N* = 2878	FUP 1 (2010-2013) *N* = 2046	FUP 2 (2014-2016) *N* = 1544
Total cohort	26.4	25.3	23.1	37.4	36.4	36.5	13.7	13.2	12.3
Age groups									
60-64	20.3	20.8	n.a.[a]	27.0	29.0	n.a.[a]	10.4	7.3	n.a.[a]
65-69	22.0	20.9	15.1	34.0	32.2	27.9	11.1	12.2	9.0
70-74	28.4	24.5	21.4	37.3	35.2	34.7	14.1	13.2	12.2
75-79	31.7	31.2	25.7	49.7	41.0	37.8	18.4	13.8	12.5
≥ 80	37.4	28.0	29.3	49.2	44.9	45.1	17.6	20.2	15.5
Sex									
Female	30.2	29.3	24.5	39.7	38.7	38.7	15.5	14.3	14.0
Male	22.3	21.2	21.6	34.9	33.9	34.0	11.7	12.2	10.5

FUP follow-up, *n.a.* not applicable

[a] No participant was younger than 65 years in FUP 2

Sociodemographic characteristics

Female sex was a strong risk factor for all three PIM criteria in the cross-sectional and the longitudinal analysis, albeit not statistically significant for the Beers and the PRISCUS PIM in the longitudinal model. Higher age was associated with the current use of all criteria. The variable also increased the odds of taking a PRISCUS PIM in the future but was not a significant predictive factor for Beers or EU(7) PIM.

Diseases and biomarkers of the metabolic syndrome

The metabolic syndrome consists of the four conditions: central obesity, hypertension, diabetes mellitus, and dyslipidemia, which are often jointly present in older adults [25]. Biomarkers that play a role in the assessment of the metabolic syndrome include BMI/waist circumference, systolic blood pressure, HbA_{1c}, the lipoproteins, and triglycerides. Furthermore, it was suggested to include CRP as a risk factor in the definition of the metabolic syndrome [26].

As a proxy for obesity, increasing BMI was a statistically significant risk factor for all PIM criteria in the cross-sectional analysis, but not in the longitudinal analysis. Hypertension was significantly associated with the current use of all PIM criteria. While the variable hypertension did not enter the longitudinal model, systolic blood pressure (as a substitute for hypertension) was significantly associated with future use of Beers PIM. The lipid biomarkers total cholesterol and triglycerides also stayed in the longitudinal model as statistically significant determinants of future use of PIM defined by the EU(7) and the PRISCUS list. Diabetes was strongly associated with the usage of EU(7) PIM in the cross-sectional model. In addition, in the longitudinal analysis, the odds for the future use of EU(7) PIM were elevated with increasing values of the diabetes biomarker HbA_{1c}. Finally, the inflammatory marker CRP was only associated with the use of PRISCUS PIM in the longitudinal model.

Other diseases and disease events

CHD was not associated with PIM in the cross-sectional analysis. However, the variable increased the odds of future use of PIM according to all three criteria. Nevertheless, only the association with PRISCUS PIM reached statistical significance. Ulcer, depressive episodes, and heart failure were strongly associated with the current and future use of PIM, but only depressive episodes were consistently significantly associated with all PIM definitions. History of hip fracture showed a protective direction in the longitudinal analysis, which was statistically significant for EU(7) PIM. Likewise, a history of any cancer was significantly associated with lower odds of future use of Beers PIM.

Geriatric syndromes

Cognitive impairment was strongly associated with the use of PIM of all three criteria in the cross-sectional analysis. However, the variable was not a predictor of future PIM use. In contrast, frailty, co-morbidity (measured by the TCS), and functional impairment appeared in both the cross-sectional and longitudinal models. However, their association with

Table 2. Odds ratios of determinants of PIM use – Results of the stepwise logistic regression model (cross-sectional analysis)

	Independent variables	Beers Criteria OR (95%CI)	EU(7)-PIM List OR (95%CI)	PRISCUS List OR (95%CI)
Sociodemographic variables	Sex (female)	*1.71 (1.41, 2.09)*	*1.26 (1.07, 1.49)*	*1.27 (1.00, 1.60)*
	Age (per 5 years)	*1.10 (1.01, 1.20)*	*1.22 (1.13, 1.31)*	*1.11 (1.00, 1.23)*
Biomarkers and diseases of the metabolic syndrome	BMI (per 5 units)	*1.13 (1.02, 1.25)*	*1.17 (1.07, 1.28)*	*1.14 (1.02, 1.28)*
	Hypertension	*1.29 (1.01, 1.63)*	*1.62 (1.32, 1.99)*	*1.66 (1.22, 2.27)*
	Diabetes	*1.00 (0.79, 1.27)*	*1.75 (1.43, 2.14)*	1.12 (0.86, 1.47)
Other diseases and disease events	History of ulcer	*1.31 (1.03, 1.68)*	1.23 (0.99, 1.53)	*1.38 (1.05, 1.82)*
	History of depressive episodes	*2.22 (1.79, 2.75)*	*1.72 (1.41, 2.09)*	*2.46 (1.93, 3.14)*
	Heart failure	*7.73 (6.08, 9.83)*	*1.35 (1.08, 1.68)*	*1.52 (1.15, 2.01)*
Geriatric syndromes	Mild cognitive impairment	*1.90 (1.07, 3.39)*	*1.97 (1.11, 3.49)*	*2.21 (1.23, 3.97)*
	Pre-Frailty	1.16 (0.93, 1.45)	*1.39 (1.15, 1.68)*	*1.52 (1.14, 2.02)*
	Frailty	1.18 (0.82, 1.72)	*1.40 (1.01, 1.94)*	*1.74 (1.14, 2.64)*
	Co-morbidity (per 5 TCS points)	*1.11 (1.01, 1.22)*	*1.16 (1.06, 1.26)*	*1.12 (1.00, 1.25)*
	Functional impairment	1.18 (0.90, 1.54)	*1.33 (1.05, 1.68)*	1.12 (0.82, 1.53)

Statistically significant results are printed in Italics

BMI body mass index, *CI* confidence interval, *OR* odds ratio, *TCS* total co-morbidity score

PIM use varied according to the criterion. The following pattern emerged: The association was statistically significant either in the cross-sectional or in the longitudinal analysis. For example, frailty was statistically significantly associated with PRISCUS PIM (OR [95%CI] 1.74 [1.14; 2.64]) and borderline statistically significant for EU(7) PIM (OR [95%CI] 1.40 [1.01; 1.94], $p = 0.046$) in the cross-sectional analysis, as well as statistically significantly associated with Beers PIM in the longitudinal analysis (OR [95%CI] 2.23 [1.15; 4.31]). A similar pattern was observed for functional impairment with a cross-sectional association with EU(7)-PIM and longitudinal associations with Beers and PRISCUS PIM, though the latter was not statistically significant. Only co-morbidity was an exception: The variable was statistically significantly associated with both the current use of all PIM criteria and the future use of Beers PIM.

Data availability The datasets generated and/or analyzed during the current study are not publicly available due to data protection regulations but are available from the corresponding author on reasonable request.

Discussion

Summary of key results

PIM prevalences differed when applying the three mentioned PIM criteria, ranging from 13.7 to 37.4% at baseline. Nevertheless, there was an overall decline of PIM prevalence over time, independent of the criteria. PIM use was more common in people with geriatric syndromes, especially those with cognitive impairments or frailty. In multivariable analyses, cognitive impairment was strongly associated with the use of PIM of all three criteria in cross-sectional but not in longitudinal analyses. In contrast, frailty, co-morbidity, and functional impairment were associated with use of PIM according to at least one of the three PIM criteria in both the cross-sectional and longitudinal models.

Prevalence of PIM use

The prevalence of PRISCUS PIM use in the present study (13.7%) is nearly identical with the findings of a recently published study in a representative sample of the German population aged 65–79 years (13.0%) [27]. The prevalence of Beers PIM use was higher in our study (26.4%) compared to other studies conducted in Germany, which reported prevalences between 17 and 22% [11, 28, 29]. However, these studies used older versions of the Beers criteria, and at least one of the studies excluded criteria depending on underlying medical conditions or dosage [28]. A study using the complete 2015 Beers criteria to detect PIM in non-institutionalized Medicare beneficiaries in the USA reported a prevalence of 29% [30], which matched the prevalence in our study better. To the best of our knowledge, no previous study examined the prevalence of PIM use defined by the EU(7)-PIM list in Germany so far. Until now, two studies from Brazil [31] and Lithuania [32] applied the EU(7)-PIM list in community-dwelling older adults and reported a higher PIM prevalence (59.5 and 57.2%, respectively) than we obtained in our German cohort (37.4%).

The prevalences of PIM use determined with the 2015 Beers criteria, the EU(7)-PIM list and the PRISCUS list,

Table 3. Odds ratios of determinants of PIM use – Results of the longitudinal analysis

	Independent variables	Beers Criteria OR (95%CI)	EU(7)-PIM List OR (95%CI)	PRISCUS List OR (95%CI)
Sociodemographic variables	Sex (female)	1.08 (0.78, 1.49)	*1.68 (1.26, 2.25)*	1.39 (0.94, 2.07)
	Age (per 5 years)	1.06 (0.92, 1.23)	1.11 (0.99, 1.25)	*1.24 (1.06, 1.46)*
Biomarkers and diseases of the metabolic syndrome	Systolic BP (per 10 mmHg)	*1.07 (1.00, 1.15)*	0.99 (0.93, 1.06)	1.02 (0.92, 1.12)
	Total cholesterol (per 10 mg/dL)	1.01 (0.97, 1.05)	*0.96 (0.93, 0.99)*	1.00 (0.97, 1.04)
	Triglycerides (per 10 mg/dl)	1.01 (0.99, 1.02)	*1.01 (1.00, 1.03)*	*1.02 (1.00, 1.03)*
	C-reactive protein (per mg/L)	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)	*1.01 (1.00, 1.03)*
	HbA_{1c} (per 0.5 %)	1.10 (0.99, 1.21)	*1.11 (1.01, 1.22)*	1.01 (0.88, 1.16)
Other diseases and disease events	Coronary heart disease	1.36 (0.90, 2.05)	1.26 (0.90, 1.77)	*1.83 (1.20, 2.78)*
	History of ulcer	*1.72 (1.17, 2.51)*	1.12 (0.78, 1.61)	1.41 (0.90, 2.18)
	History of depressive episodes	*1.96 (1.37, 2.82)*	*1.37 (1.00, 1.89)*	*2.12 (1.43, 3.16)*
	Heart failure	*2.40 (1.52, 3.80)*	1.31 (0.93, 1.85)	*1.62 (1.03, 2.56)*
	History of hip fracture	1.19 (0.50, 2.81)	*0.17 (0.03, 0.87)*	0.55 (0.12, 2.49)
	History of cancer	*0.60 (0.39, 0.94)*	1.16 (0.81, 1.64)	0.96 (0.59, 1.54)
Geriatric syndromes	Pre-Frailty	*1.81 (1.25, 2.63)*	1.18 (0.88, 1.58)	1.36 (0.89, 2.06)
	Frailty	*2.23 (1.15, 4.31)*	1.22 (0.70, 2.13)	1.00 (0.53, 1.89)
	Co-morbidity (per 5 TCS points)	*1.21 (1.05, 1.38)*	1.12 (0.99, 1.27)	1.06 (0.90, 1.24)
	Functional impairment	*1.51 (1.00, 2.27)*	1.18 (0.80, 1.74)	1.45 (0.91, 2.32)

Note: Individuals who did not participate at FUP 1, but FUP 2 were only included with their baseline information. Statistically significant results are printed in Italics

BP blood pressure, *CI* confidence interval, *FUP* follow-up, *HbA_{1c}* glycosylated hemoglobin, *OR* odds ratio, *TCS* total co-morbidity score

differed largely in our study. This is due to the fact that the lists include varying drugs and drug classes and cover different conditions under which drugs are considered potentially inappropriate. For example, while the EU(7)-PIM list comprises a total of 282 drugs, the PRISCUS list contains only 83 drugs. The 2015 Beers criteria also specify a large number of PIMs, but the assessment tool often defines conditions (e.g., renal impairment) that have to be met. Not surprisingly, the EU(7)-PIM list detected the most PIMs, the PRISCUS list the least. However, tools that detect a large number of PIM among a patient's medication are not desired, since every change of medication requires efforts from physicians and can cause withdrawal effects in the patients. In the optimal case, PIM criteria define as few drugs as possible as PIM without losing predictive value for adverse drug events. Novaes et al. recently compared four explicit PIM assessment tools, including the 2015 Beers criteria and the EU(7)-PIM list, in a cohort of Brazilian community-dwelling older adults in terms of specificity and sensitivity for presence of falls, hospitalizations, and cognitive impairment [31]. They found that the EU(7)-PIM list had a higher sensitivity (75.3 to 60.0%) but a lower specificity (41.1 to 46.9%) for all outcomes compared to the 2015 Beers criteria (53.0 to 56.9% and 51.6 to 53.8%). For the PRISCUS list, Wallerstedt et al. reported a very high specificity (97%) but a low sensitivity (29%) for detecting suboptimal drug treatment in a sample of Swedish hip fracture inpatients aged ≥ 65 years [33]. Therefore, the choice of the PIM criterion depends on the physician's objective. If he/she wants to detect all potentially inappropriate drugs among a patient's medication and accepts that many of the identified PIMs would actually not cause any harm, then he/she should choose an assessment tool with high sensitivity but low specificity, such as the EU(7)-PIM list. However, if the physician prefers to detect as few PIMs as possible, which are most likely harmful, and accepts that some inappropriate drugs might be overseen, he/she should apply a tool with a low sensitivity but a high specificity, like the PRISCUS list. The Beers criteria could be regarded as a compromise between these two approaches with similar sensitivity and specificity.

Our finding of a decline in PIM prevalence over the 6 years of FUP time is consistent with most other longitudinal studies [11, 34–37] but not all [12–14]. A possible explanation for the decrease could be that the physicians' awareness of PIM might have increased during the course of the study. An argument in favor of this hypothesis is that the first explicit PIM list specifically developed for Germany (PRISCUS list) was published towards the end of the baseline assessments and may have increased the physician's awareness for PIM in the following years. Another explanation could be a higher dropout rate of PIM users during FUP because study dropout and PIM use are both associated with the health status of study participants.

Risk factors and protective parameters for PIM use

Sociodemographic characteristics

In agreement with previous studies conducted in Germany, the prevalence of PIM use was higher in women [27, 38, 39]. We also identified female sex as a risk factor for current (all PIM definitions) and future PIM exposure (EU(7) PIM only). This is likely due to the fact that some of the PIM classes with the highest relative intake frequencies are used exclusively (e.g., sex hormones) or more frequently (e.g., antidepressants, benzodiazepines, urologic drugs) by women because associated diseases like depressive disorders, anxiety disorders, and urinary incontinence are more common among them [40]. However, it is uncertain whether female sex is an independent risk factor for PIM use as other studies report inconsistent results regarding the association with current PIM use [10, 27, 41] or change in PIM use [11–14].

We found that the unadjusted PIM prevalence generally increased with age. However, in the longitudinal multivariable analysis, a statistically significant association of age and PIM use was only observed for PRISCUS PIM. Presumably, adjusting for geriatric syndromes and diseases weakened the association with age. Similarly, findings in the literature are inconsistent [10–12, 14, 27, 41, 42]. Possibly, the applied PIM lists may explain the diverging findings. In line with the results of our study, Zimmermann et al. [11] found a significant association for age and PRISCUS PIM, but not for age and Beers PIM in their longitudinal analysis. In the PRISCUS list, drug classes that are particularly often prescribed for the oldest old, defined as adults aged 80 years and older (e.g., cardiac preparations, psychostimulants, urologic drugs, and peripheral vasodilators), have a higher relative weight compared to the other two criteria (Figs. 2 to 4, Appendix). This may explain the cross-sectional and longitudinal association of age and PRISCUS PIM prescriptions.

Diseases and biomarkers of the metabolic syndrome

All four conditions of the metabolic syndrome (obesity, hypertension, diabetes mellitus, and dyslipidemia) were identified as risk factors for current or future PIM use of at least one PIM list, though associations were weaker in the longitudinal analysis. This was not surprising because certain antihypertensive drugs and glucose-lowering drugs are part of the PIM lists.

Other diseases and disease events

Heart failure, CHD, and history of ulcer, depressive episodes, hip fracture, or any cancer were associated with the overall use of PIM (according to at least one list) in the longitudinal model. The associations with CHD, heart failure, and depressive episodes can be explained by the high relative frequency of use of PIMs that are used to treat these diseases (Figs. 2 to 4, Appendix). The current study also identified diseases preventing the use of PIM in the future, namely history of hip fracture and any kind of past cancer diagnosis. An explanation might be found in the fact that one of the most common causes of hip fractures in older adults are falls. Physicians are probably aware that benzodiazepines and Z-substances increase the risk of falling in older adults and avoid them for patients with a history of hip fracture. The negative association of cancer and future Beers PIM use may be explained by the contraindication of female sex hormones (which is the second most frequently used Beers drug class) in breast cancer patients in Germany and a closer surveillance by specialists [43].

Geriatric syndromes

In this study, unadjusted PIM prevalences were about two times higher in patients with at least one geriatric syndrome compared to those without any. The association of geriatric syndromes and PIM use was also confirmed in the multivariable cross-sectional analysis. There are two probable explanations for such a finding. Either the geriatric symptom leads to the prescription of a PIM or vice versa the geriatric symptom is a result of taking PIM. Therefore, it was important to address this research question in a longitudinal study design. The analysis showed that frailty, co-morbidity, and functional impairment but not cognitive impairment were also longitudinally associated with the use of Beers PIM. Associations with other PIM definitions were not significant. This is an argument for the causal direction of frailty, co-morbidity, and functional impairment towards future Beers PIM prescriptions. Other studies are required to allow inferences regarding the opposite causal direction, namely whether the geriatric symptom is a result of PIM use. In the following, we discuss the results of the four geriatric syndromes in detail.

Cognitive impairment was significantly associated with current PIM use, and ORs were similarly high for all criteria. This was in line with a recent systematic review, which reported overall higher prevalences of PIM use in inpatients with cognitive impairments compared to those without cognitive decline [44]. A large proportion of PIM should be avoided because they might affect cognitive performance in older adults, e.g., benzodiazepines or anticholinergic drugs, such as antihistamines, antidepressants, and antipsychotics. In a prospective cohort study, Koyama et al. [45] examined if baseline use of 2003 Beers PIM to avoid in cognitively impaired patients had an influence on cognitive decline in older women. The authors reported significant differences between PIM user and non-user in various cognitive tests. Consistently, the authors of a retrospective cohort study of claims data found a significant association between new 2003 Beers PIM

prescriptions and cognitive impairment after 30 days [46]. In summary, there is evidence from observational studies for the hypothesis that anticholinergic PIM consumption can affect cognitive performance, which may explain the strong cross-sectional association in our study. Additionally, our longitudinal analysis showed that persons who are cognitively impaired and do not yet receive PIM are not at increased risk for future PIM prescriptions.

Frailty and pre-frailty were strongly and statistically significantly associated with the current use of EU(7) and PRISCUS PIM, as well as the future use of Beers PIM. However, associations with the respective other PIM definitions in both the cross-sectional and longitudinal analysis cannot be ruled out since risk estimates were usually slightly increased without reaching statistical significance. This overall picture may be explained as follows: All three PIM lists might affect components of the frailty phenotype such as weakness, slow walking speed, or low physical activity because they are sedating and/or muscle relaxing (e.g., benzodiazepines, Z-substances, muscle relaxants) [19]. However, the relative weight of these drug classes in the overall PIM definition is highest in the PRISCUS list and lowest in the Beers criteria (Figs. 2 to 4, Appendix). Since the biological response to sedating and muscle relaxing drugs is immediate, a stronger cross-sectional association of EU(7) and PRISCUS PIM use could be explained by the induction of frailty by these drug classes. However, to the best of our knowledge, no study investigated the influence of PIM use on frailty in a prospective manner yet.

The lacking longitudinal association of frailty with PRISCUS PIM may indicate that most German physicians have been aware of the PRISCUS list during the later ESTHER FUP contacts and might have been cautious with such prescriptions for frail patients. This explanation can also be transferred to the EU(7)-PIM list, which includes almost all drugs of the PRISCUS list (Table A6). The US American Beers list, however, has little overlap with the PRISCUS list (Table A5) and is less well known in Germany. Particularly the 2015 version of the Beers criteria could not be known during the course of our study.

The associations between co-morbidity and PIM use showed a similar pattern as observed for frailty with significant cross-sectional associations with all PIM criteria and a significant longitudinal association with Beers PIM only. However, differences between PIM definitions were not large, and lack of statistical significance could simply origin from limited statistical power. In line with our findings, Renom-Guitera et al. [47], who investigated factors associated with use of EU(7) PIMs in a cohort of older adults with dementia, found that higher co-morbidity was associated with prescription of two or more PIMs. In addition, Di Giorgio et al. [48] found a significant correlation between the number of co-morbidities and PIMs defined with different criteria in a retrospective cohort study. Moriarty et al. [12] reported that the number of chronic conditions was not associated with a change in PIM prevalence in a prospective cohort study, but the result was on the border to statistical significance (OR [95%CI] 1.05 [0.99, 1.11]). In our opinion, it is unquestionable that the number of co-morbidities is associated with the current and future risk of PIM use, as the likelihood of PIM increases with the number of prescribed drugs, which in turn increases with the number of diseases. However, if models are additionally adjusted for multiple diseases with an indication for PIM (as done in our study with depression, hypertension, diabetes, CHD, heart failure, etc.) or the number of drugs (as done in the study of Moriarty et al. [12]), the co-morbidity score loses its predictive value. This may explain the weak and in some circumstances not statistically significant findings for co-morbidity in our study.

Finally, functional impairment was also associated with PIM use if only statistically significant with EU(7) PIM in the cross-sectional and Beers PIM in the longitudinal analysis. Several other studies are in line with these findings. A cross-sectional study among older people with dementia reported that a higher dependency in ADL was associated with prescription of two or more EU(7) PIM [47]. Three prospective studies [45, 49, 50] observed strong associations between Beers PIM and functional decline albeit only one reported statistically significant findings [45].

Strengths and limitations

The study has some limitations. Results are based on a German sample, aged 60 to 84 years, and generalization to other populations should be done with caution. In addition, it is known that the ESTHER study participants who agreed to the 3-h home visit by a GP are generally healthier than their peers in the general population [51]. Furthermore, a small number of the Beers and EU(7) PIM criteria had to be excluded because the information necessary for coding them were not available (Table A1). Therefore, prevalences may be slightly underestimated. Finally, the Barthel score was assessed by self-report, and this may have resulted in overly positive values [52]. The study's limitations are outweighed by its strengths, such as the large sample size, the long-term FUP, the detailed assessment of four major geriatric syndromes, and the comprehensive information on the participants' actual use and dosage of prescription and non-prescription drugs. Finally, the analysis of three different PIM criteria provides a uniquely comprehensive and contemporary overview of PIM use in Germany.

Conclusion

Depending on the criteria used, prevalences of PIM use differed. However, irrespective of the PIM criterion, the

prevalence decreased slightly over the FUP time of 6 years. Although not statistically significant for all PIM criteria, the general picture emerged that participants with the geriatric syndromes frailty, co-morbidity, functional, and/or cognitive impairment had increased odds of both taking a PIM and getting PIM prescriptions in the future (exception: cognitive impairment). Physicians should be particularly vigilant when prescribing drugs for patients with geriatric syndromes because these vulnerable persons are presumably more likely to experience adverse effects from PIM [53]. Caution is also needed when prescribing new drugs for patients with clinical conditions that were further identified as risk factors for future PIM use, namely depression, heart failure, CHD, the metabolic syndrome, and history of an ulcer. In addition, interventional studies are needed to show that avoidance of Beers, EU(7), and PRISCUS PIM leads to better health outcomes than regular care in the identified risk groups for PIM prescriptions.

Author contributions D.C.M. and B.S. designed the research; W.E.H. and H.B. developed the study and supervised the data collection; D.C.M. analyzed the data and drafted the manuscript, B.S. revised it; L.K.H., C.S., W.E.H., and H.B. contributed important intellectual content to the discussion. All authors were involved in the interpretation and discussion of results.

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Compliance with ethical standards

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 and is being 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.

Conflict of interest All authors declare that they have no conflict of interest.

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