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Comparison of FORTA, PRISCUS and EU(7)-PIM lists on identifying potentially inappropriate medication and its impact on cognitive function in multimorbid elderly German people in primary care: a multicentre observational study

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ABSTRACT

Objectives Our study aimed to assess the frequency of potentially inappropriate medication (PIM) use (according to three PIM lists) and to examine the association between PIM use and cognitive function among participants in the MultiCare cohort.

Design MultiCare is conducted as a longitudinal, multicentre, observational cohort study.

Setting The MultiCare study is located in eight different study centres in Germany.

Participants 3189 patients (59.3% female).

Primary and secondary outcome measures The study had a cross-sectional design using baseline data from the German MultiCare study. Prescribed and over-the-counter drugs were classified using FORTA (Fit fOR The Aged), PRISCUS (Latin for 'time-honoured') and EU(7)-PIM lists. A mixed-effect multivariate linear regression was performed to calculate the association between PIM use patients' cognitive function (measured with (LDST)).

Results Patients (3189) used 2152 FORTA PIM (mean 0.9±1.03 per patient), 936 PRISCUS PIM (0.3±0.58) and 4311 EU(7)-PIM (1.4±1.29). The most common FORTA PIM was phenprocoumon (13.8%); the most prevalent PRISCUS PIM was amitriptyline (2.8%); the most common EU(7)-PIM was omeprazole (14.0%). The lists rate PIM differently, with an overall overlap of 6.6%. Increasing use of PIM is significantly associated with reduced cognitive function that was detected with a correlation coefficient of −0.60 for FORTA PIM (p=0.002), −0.72 for PRISCUS PIM (p=0.025) and −0.44 for EU(7)-PIM (p=0.005).

Conclusion We identified PIM using FORTA, PRISCUS and EU(7)-PIM lists differently and found that PIM use is associated with cognitive impairment according to LDST, whereby the FORTA list best explained cognitive decline for the German population. These findings are consistent with a negative impact of PIM use on multimorbid elderly patient outcomes.

Trial registration number ISRCTN89818205.

Strength and limitations of this study

- From 3189 multimorbid elderly patients, medication was recorded using brown bag review, taking into account not only prescription medicines but also over-the-counter medicines.
- Drugs were categorised independently of dose according to PRISCUS and EU(7)-potentially inappropriate medication (PIM) lists because the daily dose and the frequency were not sufficiently documented.
- Since the FORTA list does not differentiate between drugs on demand or drugs taken regularly, all drugs were included in the analysis to allow comparability between the three PIM lists.
- The multivariate analysis and the multilevel models allow cluster effects.

INTRODUCTION

Medication management in multimorbid elderly patients is becoming more and more relevant because of ageing populations worldwide. Due to alterations in pharmacokinetics and pharmacodynamics, the risk for adverse drug events (ADEs) in older adults is increased.[1 2] In addition, elderly patients often suffer from multiple chronic conditions leading to a higher risk of hospitalisation.[3 4] Another risk factor in elderly patients

is multimedication that is associated with multimorbidity.[5 6] Multimedication, also known as 'polypharmacy', is defined as the coprescription of at least five drugs[7 8] and leads to a higher risk of drug–drug-interactions, drug–disease interactions and medication errors.[9–11] Moreover, elderly patients are especially vulnerable to potentially inappropriate medication (PIM), which is associated with decreased cognitive skills, frailty and falls.[12] The identification of PIM is an important step to improve medication safety and to optimise prescribing and also deprescribing in multimorbid elderly patients. Since the first PIM list was published by Beers, several tools from different countries have been published.[13] In our study, we decided to compare the following three screening tools, all of which are well suited for the German pharmaceutical market: FORTA (Fit fOR The Aged), PRISCUS (Latin for 'time-honoured') and EU(7)-PIM lists.[14–16] We wanted to compare a well-established, but 10-year-old, German national PIM list (PRISCUS) with a more currently updated and more comprehensive European PIM list (EU(7)-PIM list). As both lists are explicit tools and do not focus on individual patient's needs, we decided to include FORTA list as an implicit national PIM list in our analysis. The PIM lists provide a broad heterogeneity of the PIM included, which poses the question of whether they rate drugs similarly.

Although studies are examining PIM use in Germany using PRISCUS and EU(7)-PIM list, only a few offer large data from community-dwelling patients, and they do not investigate the association of PIM use on the cognitive function.[17–19] In addition, large studies often only use health insurance data and do not include over-the-counter (OTC) medication.[20] To the best of our knowledge, no study compares FORTA as an implicit PIM list with the two explicit PIM lists PRISCUS and EU(7)-PIM list for the same patient collective, especially concerning the association with a decrease in cognitive function. Since the risk of developing ADEs is even higher in patients with cognitive impairments.[21]

The prospective German cohort study MultiCare was conducted to investigate the consequences of multimorbidity in elderly patients in primary care. As part of MultiCare, general practitioners (GPs) and patients were interviewed about prescribed and OTC medications as well as health and functional status, thus enabling the present study.[22] The aims of the current study were (1) to examine and compare the frequency of PIM use identified via three different lists—FORTA list, PRISCUS list and EU(7)-PIM list; and (2) to examine and compare associations between PIM use according to each PIM list and to identify the PIM list that has the most impact on cognitive function.

METHODS

Study design

MultiCare—a multicentre, observational longitudinal cohort—recruited multimorbid patients from a total of 158 general practices in eight study centres in Germany (Universities of Bonn, Düsseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich). Patients were randomly selected from the electronic files of GPs. Patient inclusion criteria were:at least three diagnosed chronic diseases and age between 65 and 85 years. Patients were excluded if they were nursing home residents; were blind and deaf; could not provide consent, particularly patients with dementia; had an expected life expectancy of fewer than 3 months; had insufficient ability to read and speak German; participated in other studies; and were poorly known by the physician. Out of 50 786 patients from the GP's electronic files, a random sample of 7172 were contacted for informed consent after screening for inclusion and exclusion criteria because of an estimated positive response rate of 40%–50%. Of those contacted, a total of 3317 (46.2%) responded and were willing to participate. A total of 128 patients were excluded retrospectively because they died before the baseline interview or due to other reasons. A total of 3189 patients were therefore included in our analyses. Morbidity was assessed in standardised GP interviews. Gender, age, education and income were collected in standardised patient interviews, which also comprised cognitive testing, using the letter digit substitution test (LDST). A brown bag review—gaining information about product name, German national drug code, pharmaceutical form, partly dosage, frequency and medication on demand or daily use—was performed at the patients' home, collecting information about OTC and prescription drugs used by the patients within the last 3 months. The analyses presented here are based on the baseline assessment, which took place between 21 July 2008 and 6 November 2009. Detailed information on the study design has been published previously by Schäfer *et al*[22 23] in the study protocol (online supplemental material 1).

FORTA list

The FORTA list, recently updated in 2018, includes 296 drugs used in the treatment of 30 diagnoses or indications. For each indication, the drugs were categorised by an expert Delphi panel into four categories: A (absolute), B (beneficial), C (careful) and D (don't). FORTA categories A and B are designed to detect potential undertreatment, whereas categories C and D signify drugs with questionable safety and effectiveness and can be used to identify PIM.[14]

PRISCUS list

The German PRISCUS list (last updated in 2011) includes 83 drugs from 18 drug classes. The list provides advice on treatment alternatives and necessary actions if the PIM use is unavoidable. The PRISCUS list was developed following a structured expert survey in a two-round Delphi process.[15]

EU(7)-PIM list

The EU(7)-PIM list is a European list for PIM based on different national PIM lists (German PRISCUS list, PIM lists from USA, France and Canada) published in 2015. The EU(7)-PIM list contains 282 drugs from 34 drug classes. The list comprises restrictions to dose and duration for some drugs and gives therapeutic alternatives and advice on dose adjustment. Two Delphi survey rounds with 30 experts were performed.[16]

PIM classification

Data on prescription and OTC drugs were gathered via brown bag review. The drugs were classified according to the anatomical therapeutic classification (ATC) system.[24]

Excel V.2016 and QlikView V.11.20 (QlikTech, Radnor, USA) were used to identify PIM according to the three different PIM lists.

Drugs were classified as potentially inappropriate according to PRISCUS and EU(7)-PIM list dose-independently. As the FORTA list does not differentiate between medication on demand or daily use, we decided to include all drugs into the analysis to enable comparability between the three lists. With FORTA, we screened patients' medication for FORTA A–D drugs. In contrast to the other two lists, FORTA classification depends on the diagnosis, so that several drugs are classified differently according to their indication. When there was no documented indication for the drug and the drug only occurred once in the FORTA list, we assumed the drug was taken for that indication. Where a drug has multiple entries, we only rated the drug as PIM (C and D), if an indication was documented.

Descriptive analysis of PIM use and subgroup analyses

Data analysis was conducted using Excel V.2016 and Stata V.15.1. Subgroups were selected according to gender, age (<80 years and ≥80 years) and the number of drugs used (median split: 0–7 drugs and 8–29 drugs). For each subgroup, we considered the number of PIMs used per person. To examine differences in PIM use by gender, age and the number of drugs used, a two-sample t-test with equal variances was performed.

Association of PIM use with cognitive function

A multivariate mixed-effect linear regression was performed to examine the associations between each of the three different PIM lists with cognitive function. The cognitive skills were determined via LDST.[25] The LDST is a speed-dependent cognitive task where patients have to replace letters by numbers in a specified time, as processing speed is an important cognitive ability for normal cognitive development and aging.[26] To account for regional variation between the eight different study centres (Bonn, Düsseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich) and personal prescribing habits of the 158 general practices, we conducted a multilevel linear regression analysis adjusted for random effects on the study centre and GP practice with study centre level. We included gender, age, number of drugs used, number of diseases weighted by severity, highest education degree in the three groups according to the international CASMIN (**C**omparative **A**nalysis of **S**ocial **M**obility in **I**ndustrial **N**ations) classification and household net adjusted disposable income as independent variables into the model.[27] The missing values in LDST, number of diseases weighted by severity, education standard and the income data sets were imputed via hot-deck imputation. This procedure has been described in detail elsewhere.[22] Analyses were performed with the imputed data sets. To determine which PIM list has the most impact on the cognitive decline, the described model was extended to all three PIM lists. An alpha level of 5% ($p \leq 0.05$) was defined as statistically significant. All statistical tests were conducted using Stata V.15.1.

Patient and public involvement statement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

Characterisation of the study cohort

Table 1 describes the sociodemographic data of the patients. In the MultiCare cohort (3198 patients aged 65–85 years), 24 535 drugs, thereof 24.2% (5935) OTC, were identified and related to an ATC code (mean 7.7±3.9 drugs; median 7 drugs, range 0–29 drugs).

As shown in table 2, patients used PIM according to FORTA with a prevalence of 55.9%. In average, they used 0.9 (±1.0) FORTA PIM with a range of 0–7 PIMs per

Table 1 Sociodemographic data of 3189 patients at baseline

Age (years) (mean±SD)	74.4±5.2
Male (years) (mean±SD)	74.0±5.1
Female (years) (mean±SD)	74.7±5.3
Gender (%)	
Male	40.7
Female	59.3
Education (in CASMIN grade) (%)	
Low (grade 1)	62.3
Medium (grade 2)	26.8
High (grade 3)	10.9
Household-size adjusted net income per month (€) (mean±SD)	1412±704
Number of chronic conditions (mean±SD)	7.0±2.5
Number of taken drugs (mean±SD)	7.7±3.9

Table 2 Comparison of the descriptive results from FORTA, PRISCUS and EU(7)-PIM list

	FORTA PIM	PRISCUS PIM	EU(7)-PIM
Medication			
Total number (%) of drugs used	24 535	24 535	24 535
Prescribed	18 600 (75.8)	18 600 (75.8)	18 600 (75.8)
OTC	5935 (24.2)	5935 (24.2)	5935 (24.2)
Total number (%) of PIM	2852 (11.6)	963 (3.9)	4311 (17.6)
Prescribed	2474 (86.7)	939 (97.5)	3919 (90.9)
OTC	378 (13.3)	24 (2.5)	392 (9.1)
Median number of PIM (range)	1 (0–7)	0 (0–4)	1 (0–8)
Mean number of PIM (SD)	0.9 (±1.0)	0.3 (±0.6)	1.4 (±1.3)
Patients (%)			
Patients with at least one PIM	55.9	24.7	70.1
Patients with one PIM	1048 (32.9)	656 (20.6)	1020 (32.0)
Patients with two PIMs	496 (15.6)	123 (3.9)	678 (21.3)
Patients with three PIMs	168 (5.3)	15 (0.5)	320 (10.0)
Patients with four PIMs	47 (1.5)	4 (0.1)	140 (4.4)
Patients with five PIMs	19 (0.6)	–	50 (1.6)
Patients with six PIMs	3 (0.1)	–	19 (0.6)
Patients with seven PIMs	1 (0.03)	–	5 (0.2)
Patients with eight PIMs	–	–	2 (0.1)

FORTA, Fit fOR The Aged; OTC, over-the-counter; PIM, potentially inappropriate medication.

patient. PRISCUS PIMs were detected with a prevalence of 24.7%, and patients used PRISCUS PIM with a mean of 0.3 (±0.58) and with a range of 0–4. According to the EU(7)-PIM list, patients used 1.4 (±1.29) with a range of 0–8 PIMs. We detected EU(7)-PIM with a prevalence of 70.1%.

Regarding FORTA, we detected 2852 category C or D PIM in total and thereof 13.3% (378) OTC drugs. Divided by category, we identified a mean of 0.7 in category C FORTA PIM and 0.2 in category D FORTA PIM per patient. The most common category C PIM is phenprocoumone for the treatment of atrial fibrillation (441 patients, 13.8%), followed by ginkgo leaf preparations for the treatment of dementia (152, 4.8%), glimepiride for the treatment of diabetes mellitus (144, 4.5%) and verapamil for the treatments of hypertension and atrial fibrillation (116, 3.6%). The most common category D drugs are acetylic salicylic acid as antiplatelet agent for atrial fibrillation with 3.1% (100 patients), molsidomine (76, 2.4%), glibenclamide (69, 2.2%) and tocopherol (63, 2.0%).

We detected 963 PRISCUS PIM in total with a proportion of 2.5% (24) OTC drugs. The most common drugs were amitriptyline (88 patients, 2.8%), acetyldigoxin (60 patients, 1.9%), nifedipine (53 patients, 1.7%) and zopiclone (47 patients, 1.5%).

We identified 4311 drugs (17.6%) as EU(7)-PIM, and thereof 9.1% (392) were classified as OTC drugs. The most common drugs are omeprazole (448 patients, 14.0%), diclofenac (390 patients, 12.2%), ibuprofen (335 patients, 10.5%) and acetyl salicylic acid as analgesic (191, 6.0%).

Figure 1 illustrates the overlap between the three different PIM lists. Of the detected PIMs, 384 (6.7%) were identified within all three lists, while nearly all PRISCUS PIMs were also detected by EU(7)-PIM (97.9 %). Moreover, the summary of the top 20 PIMs used by the patients points out the small grade of overlap between the three PIM lists (table 3).

Subgroup analysis: age, gender and number of used drugs

Results of the subgroup analysis are described in table 4. Women were using significantly more PIM according to PRISCUS and EU(7)-PIM list (both p<0.001). Furthermore, patients who are 80 years old and older used more PIM according to FORTA and PRISCUS list (p=0.005 and p<0.001). In addition, we detected that patients using more than seven drugs at the same time used significantly more PIM according to all three PIM lists (all lists p<0.001). This effect was also detectable—in all three PIM lists—continuously with a growing number of used drugs (FORTA: 0.130, 95% CI 0.122 to 0.138, p<0.001; PRISCUS: 0.050, 95% CI 0.045 to 0.055, p<0.001; EU(7): 0.190, 95% CI 0.181 to 0.200, p<0.001).

Association with cognitive function

In table 5, the results of the LDST are shown. On average, patients achieved a mean score of 23 (±7.1) with a range

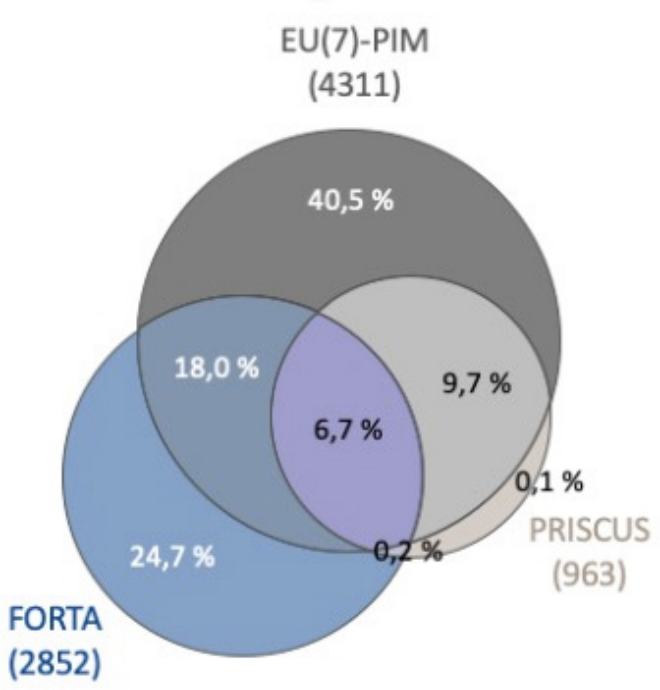

Figure 1 Venn diagram showing the overlap between FORTA, PRISCUS and EU(7)-PIM lists in terms of PIM (percentages sum up to 100%). FORTA, Fit fOR The Aged; PIM, potentially inappropriate medication.

of 0–50 in LDST. More than half of the patients (51.9%) scored between 20 and 29 in LDST.

We found that patients who used PIM scored significantly worse values in LDST than patients who used less or none PIM. This is true for all three PIM lists in a multivariate approach, with each PIM list analysed separately in the same regression model: FORTA-PIM (−0.397, 95% CI −0.644 to −0.150, p=0.002), PRISCUS (−0.464, 95% CI − 0.870 to −0.058, p=0.025) and EU(7)-PIM (−0.300, 95 CI% −0.508 to −0.092, p=0.005) (table 6).

By including all three PIMs in one regression model, the impact of FORTA (−0.306, 95% CI −0.567 to −0.044, p=0.022), PRISCUS (−0.118, 95% CI −0.652 to 0.276, p=0.428) and EU(7)-PIM list (−0.188, 95% CI −0.416 to 0.072, p=0.168) on the cognitive decline is shown (table 7). It appears that the association between PIM use and the patient's ability to complete the LDST is best depicted in the FORTA list.

DISCUSSION

Statement of principal findings

With the help of the three PIM lists, different numbers of PIM within the multimorbid elderly patients were detected. We identified that the use of PIM is associated with reduced cognitive function in multimorbid elderly patients. This was demonstrated for FORTA, PRISCUS and EU(7)-PIM lists. However, the FORTA list seems to be most suitable to reveal the association between PIM use and decreased cognitive function in multimorbid elderly patients.

Table 3 Top 20 drugs most commonly resulting in inappropriate prescribing according to FORTA, PRISCUS and EU(7)-PIM (drugs analysed in total 24 535)

PIM	FORTA	PRISCUS	Eu(7)-PIM
Omeprazole	–	–	448
Phenprocoumon	441	–	–
Diclofenac	–	–	390
Ibuprofen	–	–	335
Acetyl salicylic acid (analgesic)	–	–	191
Glimepiride	144	–	144
Pantoprazole	–	–	157
Ginkgo biloba leaves	152	–	–
Glimepiride	144	–	144
Verapamil	116	–	116
Moxonidine	114	–	114
Spironolactone	–	–	107
Tramadol	105	–	105
Theophylline	104	–	104
Acetyl salicylic acid (antiplatelet agent)	100	–	–
Amitriptyline	80	88	88
Digitoxin	32	–	93
Amitriptyline	80	88	88
Molsidomine	76	–	–
Tilidin	76	–	–

FORTA, Fit fOR The Aged.

PIM classification

In general, our data are in good accordance with recently published data. Other studies detected EU(7)-PIM with a prevalence of 57.2%–72.8%.[1 28 29] This seems to be comparable with our findings (70.1%). None of the three studies included OTC drugs, and in addition, Wauters *et al* included only patients 80 years and older.

The German ESTHER cohort detected PIM according to PRISCUS with a prevalence of 13.7% and according to the EU(7)-PIM list of 37.4%.[19] As they have a much younger patient collective—50 years–75 years—it is explainable that we found a higher prevalence in the MultiCare cohort (24.7% prevalence of PRISCUS PIM). Another reason for the higher observed PIM prevalences in detected EU(7)-PIM and PRISCUS PIM might be that only patients with at least three chronic diseases were included in our study. This is also apparent in a study including only patients with multimedication (five or more drugs) where the authors detected even higher prevalences of 45% PRISCUS PIM and 61% FORTA PIM (prevalence of FORTA PIM in our study: 55.9%).[30] The observed prevalence for PRISCUS PIM is quite lower than for FORTA and EU(7)-PIM. This is also following

Table 4 Difference between gender (male and female), the two different age groups (<80 years and ≥80 years) and between patients with zero to seven drugs at the same time and patients using more than seven drugs (8–29) at the same time measured with FORTA, PRISCUS and EU(7)-PIM list (significant p values marked in bold)

			PIM absolute					
		Patients (n)	(PIM (n)/drugs (n) (%))	Mean per patient	SD	Range	95% CI	P value
FORTA PIM	Male	1271	1126 (4.6)	0.89	1.00	0–5	0.83 to 0.94	
	Female	1876	1726 (7.0)	0.92	1.05	0–7	0.87 to 0.97	
								0.362
PRISCUS PIM	Male	1271	336 (1.4)	0.26	0.55	0–4	0.23 to 0.29	
	Female	1876	627 (2.6)	0.33	0.60	0–4	0.31 to 0.36	
								<0.001
EU (7)-PIM	Male	1271	1538 (6.3)	1.21	1.22	0–7	1.14 to 1.28	
	Female	1876	2773 (11.3)	1.48	1.33	0–8	1.42 to 1.54	
								<0.001
FORTA PIM	<80 years	2601	2293 (9.3)	0.88	1.02	0–7	0.84 to 0.92	
	≥80 years	546	559 (2.3)	1.02	1.08	0–6	0.93 to 1.11	
								0.005
PRISCUS PIM	<80 years	2601	744 (3.0)	0.29	0.57	0–4	0.27 to 0.31	
	≥80 years	546	219 (0.9)	0.40	0.62	0–3	0.34 to 0.45	
								<0.001
EU (7)-PIM	<80 years	2601	3519 (14.3)	1.35	1.29	0–8	1.30 to 1.40	
	≥80 years	546	792 (3.2)	1.44	1.31	0–8	1.33 to 1.55	
								0.145
FORTA PIM	0–7 drugs	1646	857 (3.5)	0.52	0.70	0–3	0.49 to 0.55	
	8–29 drugs	1501	1995 (8.1)	1.32	1.16	0–7	1.27 to 1.39	
								<0.001
PRISCUS PIM	0–7 drugs	1646	271 (1.1)	0.16	0.41	0–2	0.14 to 0.18	
	8–29 drugs	1501	692 (2.8)	0.46	0.69	0–4	0.43 to 0.50	
								<0.001
EU (7)-PIM	0–7 drugs	1646	1334 (5.4)	0.81	0.87	0–4	0.77 to 0.85	
	8–29 drugs	1501	2977 (12.1)	1.98	1.39	0–8	1.91 to 2.05	
								<0.001

FORTA, Fit fOR The Aged; PIM, potentially inappropriate medication.

Table 5 Descriptive results of LDST (imputed data: missing value 255 from 3189 patients) to measure the cognitive function of patients and the number of boxes patients were able to fill out correctly

	LDST
Mean (SD)	23.0 (±7.1)
Median (range)	23 (0–50)
Results LDST	**Patients (n)**
≤10 (relative)	78 (2.4%)
10 up to <20 (relative)	879 (27.6%)
20 up to <30 (relative)	1656 (51.9%)
30 up to <40 (relative)	533 (16.7%)
≥40 (relative)	43 (1.3%)

LDST, letter digit substitution test.

the aforementioned literature. These differences in the detected prevalences might occur due to the smaller number of drugs included in the PRISCUS list.

Moreover, the three PIM lists evaluate the drugs quite differently. For example, the PRISCUS list comprises more 'classic inappropriate' substances like antidepressants (18.2%), antihypertensives (5.7%) and hypnotics/sedatives (13.5%), which is also in good accordance with findings described in literature.[3 17 31] It is described that the prescriptions of sedatives, hypnotics, neuroleptics, antipsychotics and antihypertensives are risk factors for falls in elderly patients.[32] On the contrary, in addition to the classic potentially inappropriate substances, the FORTA list also identified as PIM those whose effectiveness had not been proven, for example, *Ginkgo biloba* and tocopherol. In addition, phenprocoumon is only listed in FORTA but not in PRISCUS or EU-(7) PIM, and it was the most common FORTA PIM. In V.2015 of FORTA,

Table 6 Multivariate linear regression model—impact of FORTA or PRISCUS or EU(7)-PIM use on cognitive function measured by LDST

LDST	Correlation coefficient	P value	95% CI
FORTA PIM per patient	−0.397	0.002	−0.644 to −0.150
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.538	<0.001	2.072 to 3.004
CASMIN3_2	2.348	<0.001	1.813 to 2.883
CASMIN3_3	3.791	<0.001	3.007 to 4.575
Income	2.407	<0.001	1.869 to 2.945
Number of diseases weighted by severity	−0.121	<0.001	−0.169 to −0.072
Number of taken drugs	−0.034	0.340	−0.105 to 0.036
PRISCUS PIM per patient	−0.464	0.025	−0.870 to −0.058
Age	−0.340	<0.001	−0.383 to −0.296
Sex	2.560	<0.001	2.093 to 3.026
CASMIN3_2	2.366	<0.001	1.831 to 2.901
CASMIN3_3	3.776	<0.001	2.992 to 4.561
Income	2.423	<0.001	1.885 to 2.961
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.060	0.079	−0.127 to 0.007
EU(7)-PIM per patient	−0.300	0.005	−0.508 to −0.092
Age	−0.344	<0.001	−0.387 to −0.300
Sex	2.597	<0.001	2.130 to 3.065
CASMIN3_2	2.351	<0.001	1.815 to 2.886
CASMIN3_3	3.772	<0.001	2.998 to 4.556
Income	2.409	<0.001	1.871 to 2.947
Number of diseases weighted by severity	−0.127	<0.001	−0.176 to −0.079
Number of taken drugs	−0.025	0.507	−0.101 to 0.050

Dependent variable: results from LDST; *independent variables*: FORTA PIM or PRISCUS PIM or EU(7)-PIM; *covariables* included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard; casmin3_3: comparison between high and low educational standard), number of diseases weighted by severity, income and number of taken drugs. Every PIM list is analysed separately in the same regression model.
FORTA, Fit fOR The Aged; LDST, letter digit substitution test; PIM, potentially inappropriate medication.

phenprocoumon was listed as a class B drug. However, with the availability of newer anticoagulants that do not require INR (international normalized ratio) monitoring, it has been recategorised as a FORTA C PIM in the updated version from 2018. Nevertheless, in most guidelines, phenprocoumon is still recommended.[33]

In addition to the substances detected with the PRISCUS list mentioned previously, proton pump inhibitors (PPIs) (15.7%) and NSAIDs (non-steroidal anti-inflammatory drug) (18.7%) were found to be the most common PIM in the EU(7)-PIM list. The high use of PPIs and NSAIDs is shown by some other studies as well.[1 28] But interestingly, in most studies, hypnotics and sedatives were found to be the most commonly prescribed EU(7)-PIM. We detected only 3.6% benzodiazepines, whereas other studies detected 4.2%–18.1% benzodiazepines, and therefore some studies presented only single substances.[1 28 34] Strikingly, there was only a small overlap between all three PIM lists. Although all three lists were developed for the German or European drug market, there is—besides some classic drugs—a broad heterogeneity in detected PIM. That raises the question of whether the use of only one PIM list is sufficient for the identification of PIM, leading to the assumption that already existing PIM lists need to be improved or even questioned to simplify and standardise this process. We need valid tools for identifying PIM because medication management in elderly multimorbid patients is highly complex. Detecting PIM and showing alternatives are still an important step to improve medication safety in multimorbid elderly patients.[12]

Risk factors for PIM use

To minimise the amount of prescribed PIM, we need to find out and, if possible, reduce risk factors for prescribing PIM. For example, we could demonstrate that multimedication is a risk factor for prescribing PIM in multimorbid elderly patients by pointing out that patients using seven drugs and more at the same time used significantly more

Table 7 Multivariate linear regression model—impact of FORTA, PRISCUS and EU(7)-PIM use on cognitive skills measured by LDST

LDST	Correlation coefficient	P value	95% CI
FORTA PIM per patient	−0.306	0.022	−0.567 to −0.044
PRISCUS PIM per patient	−0.118	0.428	−0.652 to 0.276
EU(7)-PIM per patient	−0.188	0.168	−0.416 to 0.072
Age	−0.172	<0.001	−0.384 to −0.296
Sex	−0.340	<0.001	2.114 to 3.050
CASMIN3_2	2.334	<0.001	1.799 to 2.869
CASMIN3_3	3.784	<0.001	3.000 to 4.567
Income	2.406	<0.001	1.868 to 2.943
Number of diseases weighted by severity	−0.121	<0.001	−0.170 to −0.073
Number of taken drugs	−0.004	0.921	−0.081 to 0.073

Dependent variable: results from LDST; *independent variables*: FORTA PIM, PRISCUS PIM, EU(7)-PIM; *covariables* included in the regression model: sex, age, education standard (casmin3_2: comparison between medium and low educational standard, casmin3_3: comparison between high and low educational standard), number of diseases weighted by severity, income and number of taken drugs.
All three PIM lists are included in one regression model.
FORTA, Fit fOR The Aged; LDST, letter digit substitution test; PIM, potentially inappropriate medication.

PIM. As multimedication is a well-described risk factor for prescribing PIM and is also associated with a higher risk of falls and hip fractures in multimorbid elderly patients, we must have the goal of rational prescribing.[31 35 36] Furthermore, the association between age and PIM use is inconsistent between the three PIM lists. Previous publications also showed different results.[21] We were also able to demonstrate that women are at higher risk of receiving PIM according to PRISCUS and EU(7)-PIM list but not according to FORTA. The observed gender differences in PIM use are in good accordance with the literature.[19 31] Moreover, Toepfer *et al* indicate that the female sex is at a greater risk of PIM use due to higher use of antidepressants, sleep-inducing drugs, analgesics and the use of oestrogens.[17]

Association of the use of PIM with the cognitive function

The relation between PIM use and the reduction of the cognitive function was based on poorer scores in a LDST, as determined by multivariate analysis. Other studies described that age, educational standard and gender influence LDST test results, so we decided—among others—to include those variables in our regression model.[25 37] In addition, the prescribing bias due to regional effects and the GPs were minimised by performing a multilevel regression. Muhlack *et al*[19] showed a strong cognitive impairment that is associated with PIM use according to EU(7), PRISCUS and Beers list. Beyond that, most studies that revealed the influence of PIM on cognitive function included patients with dementia.[21 38] Patients with dementia already have cognitive impairments due to their illness. In the MultiCare study, we excluded patients with all forms of dementia. Even though we cannot completely exclude the presence of already cognitively impaired patients in our study, we can show an effect of PIM use on the cognitive decline with less interference due to already cognitively impaired patients. Interestingly, in our model, the FORTA list best explained the decrease in cognitive function in multimorbid elderly patients. A possible explanation is that the FORTA list—in contrast to the PRISCUS and EU(7)-PIM lists—rates drugs based on indications as an implicit PIM list. Most other PIM lists are explicit tools and do not address the individual differences in patient needs. Furthermore, the FORTA list was developed for the German drug market and in contrast to the also German PRISCUS list, the FORTA list was recently updated in 2018. Another advantage is that the FORTA list is basically a positive and negative list because of the different categories. Also, the VALFORTA study points out the benefits of the FORTA list by showing that the use of the FORTA list reduced the occurrence of ADE and revealed overtreatment and undertreatment in elderly patients.[39]

Strength and limitations

There are some limitations with the present study. The PIM use according to the PRISCUS and EU(7)-PIM lists might have been overestimated in our study because we did not differentiate between medication on demand and regularly used medication. For example, omeprazole is inappropriate if it is used at maximum dosage for longer than 8 weeks without a clear indication. Furthermore, the daily dose was not documented consequently during the brown bag review. Due to this fact, it was not possible to categorise PIM—for the PRISCUS and EU(7)-PIM lists—according to their dosing.

The medication review was conducted at the patients' homes, via brown bag review. Additionally, patients were asked how the GPs told them to take their medication. It is therefore possible that a daily used NSAID, hypnotic, or PPIs has been labelled as medication on demand. As we did not want to underestimate the use of critical drugs

like PPIs, NSAIDs or hypnotics, we decided to count every drug that is documented as a PIM according to one of the three lists. In addition, almost all studies using large data analysed PIM irrespective of the dose, that is why we believe that this procedure is suitable for our patient collective.[17–20] However, this may lead to an overestimation of PIM use according to the PRISCUS and EU(7)-PIM lists. Therefore, we conducted a sensitivity analysis, excluding all medication on demand for PRISCUS and EU(7)-PIM. Both analyses still showed that there is an association between PIM according to the PRISCUS (−0.497, 95% CI −0.942 to −0.051, p=0.029) and EU(7)-PIM (−0.391, 95% CI −0.610 to −0.172, p<0.001) lists and a decreased cognitive function. Including all three PIM lists without medication on demand in one model, besides FORTA also the EU(7)-PIM list shows a significant association on patients' cognitive functions (FORTA: CC −0.269, 95% CI −0.534 to −0.003, p=0.047; EU(7)-PIM: - 0.275, 95% CI −0.536 to −0.014, p=0.039), while PRISCUS does not (−0.124, 95% CI −0.631 to 0.382, p=0.631).

FORTA PIM was analysed strictly indication-based, so it is possible that we even underestimated the sensitivity of the FORTA list. A strength of the data presented is that we included OTC drugs. Among the detected FORTA PIM and EU(7)-PIM, we had a high proportion of OTC drugs (13.3% and 9.1%). In addition, the number of OTC drugs might even have been underestimated because we counted NSAIDs and PPIs as prescription drugs because as they are prescribable for some indications due to the German medicines law. An additional strength consists of multivariate analyses, multilevel models allowing for cluster effects and advanced treatment of missing values.

Taken together, we were able to show that decreased cognitive function was apparent within all three PIM lists and that the FORTA list illustrates the cognitive decline most clearly. Besides that, the association between decreased cognitive function and the use of PIM underlines the importance of reducing the amount of PIM in elderly patients.

CONCLUSION

The supply of multimorbid elderly patients is a huge challenge we are facing, and therefore, we need to improve the medication safety of those patients. By identifying PIM with FORTA, PRISCUS and EU(7)-PIM lists and revealing that cognitive impairment is associated with PIM use, we can highlight the negative association of PIM use on elderly patients' outcomes and emphasise the importance of reducing the amount of PIM in elderly patients. To improve drug safety, it is important to have tools to identify PIM. However, the broad heterogeneity of detected PIM with the different tools also reflects that we still need to improve the already existing PIM lists.

Although we identified a high use of PIM among elderly multimorbid patients with different PIM lists, a longitudinal analysis is needed.

In summary, we identified PIM using FORTA, PRISCUS and EU(7)-PIM lists and revealed that PIM use is related to a decreased cognitive function. For the German population, the use of PIM detected by the FORTA list best explained the cognitive decline.

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Study protocol

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The German MultiCare-study: Patterns of multimorbidity in primary health care – protocol of a prospective cohort study

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Abstract

Background: Multimorbidity is a highly frequent condition in older people, but well designed longitudinal studies on the impact of multimorbidity on patients and the health care system have been remarkably scarce in numbers until today. Little is known about the long term impact of multimorbidity on the patients' life expectancy, functional status and quality of life as well as health

care utilization over time. As a consequence, there is little help for GPs in adjusting care for these patients, even though studies suggest that adhering to present clinical practice guidelines in the care of patients with multimorbidity may have adverse effects.

Methods/Design: The study is designed as a multicentre prospective, observational cohort study of 3.050 patients aged 65 to 85 at baseline with at least three different diagnoses out of a list of 29 illnesses and syndromes. The patients will be recruited in approx. 120 to 150 GP surgeries in 8 study centres distributed across Germany. Information about the patients' morbidity will be collected mainly in GP interviews and from chart reviews. Functional status, resources/risk factors, health care utilization and additional morbidity data will be assessed in patient interviews, in which a multitude of well established standardized questionnaires and tests will be performed.

Discussion: The main aim of the cohort study is to monitor the course of the illness process and to analyse for which reasons medical conditions are stable, deteriorating or only temporarily present. First, clusters of combinations of diseases/disorders (multimorbidity patterns) with a comparable impact (e.g. on quality of life and/or functional status) will be identified. Then the development of these clusters over time will be analysed, especially with regard to prognostic variables and the somatic, psychological and social consequences as well as the utilization of health care resources. The results will allow the development of an instrument for prediction of the deterioration of the illness process and point at possibilities of prevention. The practical consequences of the study results for primary care will be analysed in expert focus groups in order to develop strategies for the inclusion of the aspects of multimorbidity in primary care guidelines.

Background

Multimorbidity is a highly frequent condition in older people that is supposed to significantly affect the patients' quality of life, functional status and life expectancy. But multimorbidity also is a complex phenomenon with an almost endless number of possible disease combinations of unclear implications. Therefore, it is not surprising that there is only marginal evidence on the causes and impact of multimorbidity today. To make things even more complex, there is a wide diversity in definitions and criteria of multimorbidity and there are many different measurement instruments and considerable differences in populations investigated [1].

Findings on the prevalence of multimorbidity are not consistent. A recent review by Marengoni of 33 population based studies published between 1989 and 2007 found prevalence rates in older people ranging from 21% to 98% [2]. Another review by Fortin et al. found rates of multimorbidity between 50 to 100% [3]. In both reviews, the ranges were due to differences in data sources, age groups investigated and the definitions of multimorbidity used.

In contrast to a larger number of cross-sectional epidemiological data, well designed longitudinal studies on the impact of multimorbidity on patients and the health care system have been remarkably scarce in numbers. The effect of multimorbidity was investigated in a review by Gijsen et al. [4]. According to these autors, multimorbidity was significantly associated with higher mortality, increased disability, a decline of functional status and a lower quality of life. Multimorbidity was also associated with an increase in health care utilization, i.e. number of physician encounters, rate of hospitalization, length of hospital stay, drug intake and costs [4,5]. Several studies also suggest an interrelation between mental and somatic disorders in multimorbidity clusters [6] and a protective effect of psychosocial resources of the patient [7].

There is a widespread consensus that actual health care delivery may not correspond to the needs of patients with multimorbidity. The central medical professional for the care and management of multiple chronic diseases is the GP. This is related to his broad expertise but also to the usually long-standing relationship to older patients. However, there is little help for the GP concerning the treatment of patients with multimorbidity. At present, clinical practice guidelines are mostly focussed on one disease only. Although adhering to current clinical practice guidelines in the treatment of multimorbidity may therefore even have adverse effects, the GP is widely left alone in adjusting the care for these patients [8]. In general, the diversity of results in studies on multimorbidity is not sufficient to provide robust evidence for the care of patients with multimorbidity [9].

In summary, the specific elements and processes in multimorbidity, the interactions and possible synergies of the diseases within multimorbidity clusters are basically a black box up to today. It remains unclear to which extent single disease combinations and to which extent a generalizable influence of multimorbidity contribute to the var-

ious outcomes [4]. Also, how multimorbidity develops over time is largely unknown.

The wide variety of possible disease combinations with diverse impacts on the patient makes it difficult to tackle the phenomenon of multimorbidity. In our approach, we will try to discern a limited number of groups of disease combinations ("multimorbidity patterns") with comparable impact (e.g. on quality of life and/or functional status). The statistical analyses will take the different multimorbidity patterns into account.

As a result of these considerations, the aims of the study are to:

- identify clusters of combinations of diseases/disorders (multimorbidity patterns) in the elderly general practice population and to determine their frequency and severity in relation to each other;
- investigate the development of these clusters over time (12 years), especially with regard to the internal interaction between the diseases within the cluster (addition, synergism, buffer, protection);
- analyse the relationship of mental and somatic disorders in these patterns;
- identify prognostic variables for the course of specific multimorbidity patterns;
- investigate the somatic, psychological and social consequences of multimorbidity (patterns) for the patient's quality of life and functional status; and
- describe the utilization of health care resources and the costs of care of multimorbidity (patterns).

Methods/Design

Design of the study

The study is designed as a multicentre, prospective, observational cohort study of 3.050 patients from general practice. The patients will be recruited from GP surgeries in 8 study centers distributed across Germany (Bonn, Düsseldorf, Frankfurt/Main, Hamburg, Jena, Leipzig, Mannheim and Munich). In each surgery, 50 eligible patients will be contacted and asked to participate in the study. All contacted patients who are willing to participate will be included in the study. As we estimate a rate of positive responses between 40 and 50%, approx. 120 to 150 GP surgeries have to be recruited consecutively. Each study center will recruit 435 patients with the exception of Frankfurt/Main and Jena, which will recruit 220 patients each. This equates to 18 GP surgeries with 24 patients each in every study center (9 GP surgeries in Frankfurt and Jena respectively).

The study centers began to recruit GPs in July 2008. Subsequently patient recruitment and data collection at baseline started in the same month. It is projected to perform a total of 9 waves of data collection by means of both GP and patient interviews. Each wave will take 15 months to be accomplished.

Sample Size

Due to the investigation of multiple outcomes and the observational character of the study, there is no issue of statistical power to be considered. Nevertheless, we can derive from our experience with the similarly designed AgeCoDe-study that a sample size of 3.050 patients can be managed well in 8 study centres and will allow valid multivariate data analysis [10]. We expect a drop-out rate of 10% from baseline to first follow-up and a drop-out rate of 5% for all other consecutive waves.

Inclusion of participants

Participating GPs will retrieve a list of all patients born between 1.7.1923 and 30.6.1943 who have consulted them within the last completed quarter (i.e. 3 month period). Out of all eligible patients from this list 50 patients will be selected at random (using random number tables) and invited to participate in the study by a letter from their GP. In case of interest, the patient will consult the GP and receive written and oral information. The information covers aims and procedures of the study, selection of participants, data collection, processing and storage as well as possibilities for cancellation. In case of acceptance, participants will have to sign an informed consent form to participate in the study. For each surgery, recourse and number of excluded patients per exclusion criteria will be documented. We will estimate the actual selection bias from age, gender and morbidity data.

Participants will be interviewed at all follow-ups by the same interviewer, if possible. This personal relationship is supposed to reduce the possibility of loss to follow-up. From follow-up 1 on, each participant will be asked to designate a contact person allowed to give information in the case the participant cannot be contacted. In case of drop out we will register the reason why (e.g. death, relocation, cancellation of participation in study etc.).

Exclusion criteria

- Residence in a nursing home (inappropriateness for longitudinal studies because of an average life expectancy of 6 months after institutionalization).
- Severe illness probably lethal within three months according to the GP.

- Insufficient ability to speak and read German.
- Insufficient ability to consent (e.g. dementia).
- Insufficient ability to participate in interviews (e.g. blindness, deafness).
- Poorly known patients to the GP because of accidental consultation.
- Participation in other studies at the present time.

Definition of multimorbidity

Multimorbidity is usually defined as the presence of two or more chronic diseases at the same time. Two chronic diseases are present in almost all people aged 65 years or older. In order to enrich the sample, we therefore decided to include only patients with at least three chronic conditions. Furthermore, single diseases are unequally distributed within the multimorbidity spectrum. For example, hypertension, hyperlipidemia and low back pain are present in between 50 and 75% of these age groups according to our (unpublished) analysis of the data of the Gmünder ErsatzKasse, a German statutory health insurance with 1.5 million members.

An unselected application of the three-disease-criterion would have resulted in an overrepresentation of these very frequent diseases in the study population. This would have led to little interest of the medical community in the results, as practical conclusions would have been limited to a very small number of patterns.

In order to ensure a wide range of diseases and syndromes, those with a prevalence of more than 25% were not used for inclusion into the sample. Nevertheless, these highly prevalent entities are frequently combined with the relatively lower prevalent ones and therefore still part of the sample. All diseases (including those not used for patient inclusion, e.g. hypertension) are registered in the morbidity spectrum of the patients and accounted for in the pattern analysis in order to obtain a complete picture of the diseases/syndromes in a patient.

Disease list for inclusion (ICD10 Codes in brackets)

- alcohol abuse; alcoholic liver disease (F10;K70;K76);
- anaemia (D63-D64);
- anxiety disorders (F40-F41);
- arthrosis (excludes: osteoarthritis of spine) (M15-M19);
- atherosclerosis; intermittent claudication (I70;I73.9);
- cardiac arrhythmia (I44-I49);
- chronic ischemic heart disease; angina pectoris (I20;I25);
- chronic lower respiratory diseases (J40-J47);
- chronic stroke; transient cerebral ischemic attack; impaired cerebral blood flow (I60-I64;I67;I69;G45);
- chronic thyroid disorders; goitre (E01-E05;E06.1-E06.3;E06.5;E06.9;E07);
- depressive disorders (F32-F33);
- diabetes mellitus (E10-E14);
- disorders of vestibular function; dizziness and giddiness (H81;R42);
- diverticular intestinal disease (K57);
- hearing loss (H90-H91);
- heart failure (I50);
- malignant tumours (C00-C26;C30-C41;C43-C58;C60-C97;D00-D09;D37-D48);
- migraine (G43);
- neuropathies (G50-G64);
- non-rheumatic mitral valve or aortic valve disorders (I34-I35);
- osteoporosis (M80-M82);
- parkinson's disease (G20);
- psoriasis (L40);
- renal failure (N18-N19);
- rheumatoid arthritis; other soft tissue disorders (M05-M06;M79);
- somatoform disorders (F45);
- urinary incontinence (N39.3-N39.4;R32);
- varicose veins of lower extremities (I83);

- visual disturbances (H25-H26;H28;H33-H36;H40;H43;H47;H53-H54).

Documentation of multimorbidity

The morbidity of the patients will be registered via chart review, GP-interviews and patient interviews.

Chart review

For the last quarter, all ICD10 diagnoses from patients' charts in the GP documentation system will be retrieved for all recruited patients.

GP interview

The GP will provide the disease spectrum of the patient by means of a standardized documentation instrument which covers:

1. all diseases described above (amended during follow-up data collection for chronic indications frequently mentioned in the open questions in previous waves);

2. neoplasms under 14 ICD10 subject headings;

3. mental and behavioral disorders under 11 ICD10 subject headings;

4. two open questions regarding further chronic and acute conditions not mentioned in the chronic diseases list.

For each illness, the GP will indicate duration (presence since how many years) and severity (regarding prognosis and subjective burden) on a Likert-type scale ranging from 0 = marginal to 4 = very severe.

Patient interview

A similar list of diseases will be used in patient interviews, with the following modifications:

- due to the lack of comparison possibilities for the patient, the severity of the single diseases will not be rated by the patient;

- ICD-based psychic diseases are not included in the patient list. Assessment of the psychic situation of the patient from his/her view will be done with the following screening tests:

  1. a culturally adapted version of the Four Dimensional Symptom Questionnaire (4DSQ) [11] for depression, anxiety, somatization and distress in primary care patients;

  2. the Geriatric Depression Scale (GDS) [12];

  3. the presence of cognitive disorders is assessed with the Clinical Dementia Rating (CDR) [13].

As a part of the patient interview a complete medication survey will be performed. The interviewer will collect data on all pharmaceutical products used by the patient within the last three months. The data include product name, pharmaceutical form, German national drug code ("Pharmazentralnummer" – PZN-), periodic or prn (pro re nata) medication, dosage and frequency (for periodic medication). The interviewer will ask the patient to show the packages of the pharmaceuticals to get the most valid information. If product name and drug code are not available, the patient will be asked for the medical indication of the drugs.

The total burden of morbidity will be measured by several multimorbidity indices, which will be automatically calculated from the disease data collected in the GP interviews and data on medication from patient interviews respectively:

- the count of the number of chronic conditions [14], without taking the disease severity in account (Unweighted Disease Count);

- the total number of chronic conditions weighted by disease severity as rated in GP interview (Weighted Disease Count);

- the diagnosis-related comorbidity score developed by Charlson et al. (Charlson Index) [15];

- the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [16], a multimorbidity index based on disease severity grouped at organ system levels;

- the medication-based chronic disease score developed by Von Korff et al. (Von Korff Index) [17].

The different indices will be compared regarding their predictive values.

The interviewers will also collect the following data about the attending GPs and GP surgeries:

- number of attending doctors in surgery;

- number of patients per doctor;

- location of surgery;

- age, gender and specialty of attending doctor;

- date of setting up of the surgery.

The patient interviews will contain an assessment of health care utilization. The questionnaire was developed on the basis of cost diaries used in earlier studies [18]. A random sample of 1/3 of the patients will be asked to give extensive information about the following data, whereas the other 2/3 will receive a short version:

- number of hospitalizations and of hospital days;
- number of contacts with GPs, specialists and dentists;
- prescriptions of therapeutic measures (e.g. physiotherapy);
- stage of nursing needs (according to the Statutory Nursing Insurance);
- utilization of nursing services.

Variables under study

The variables under study belong to four groups: morbidity (as described above), functional status, resources/risk factors and socio-demographic data. The domain of functional status includes activities and instrumental activities of daily living, motor skills, senses (i.e. hearing and vision), cognition, pain and health-related quality of life. Resources include physical activity, balanced nutrition, social support, general self-efficacy, utilization of medical services and the quality of medical care according to the Chronic Care Model [19]. Risk factors include physical inactivity, malnutrition, alcohol abuse, smoking, body-mass-index and waist-to-hip-ratio. Socio-demographic variables include age, gender, migrant status, marital status, living conditions, household size, education, former occupation, income and wealth.

Table 1 gives an overview of the variable groups, and the measuring instruments and data sources for the variables. The instruments were chosen according to comprehensiveness, established reliability and validity, appropriateness for the age group ≥ 65 years, understandability and ease of administration in face-to-face interviews.

Visual aids with possible response options will guide interviewees in the different standardized questionnaires. For each interviewer, age, gender, experience, and professional background will be documented to assess (and statistically control for) interviewer effects.

Quality assurance

Procedures for prevention of insufficient data quality, detection of inaccurate or incomplete data and actions to improve data quality will be performed, e.g. user reliability trainings, automatic plausibility and integrity checks and data error reports to the collaborating centers. The centers will receive feedback by quality reports for which the indicators of the national guidelines of the TMF-project ("telematics platform for medical research networks") for data quality will be applied. These quality controls will be conducted by the Institute for Biometry of Hannover Medical School. For every survey wave, the Institute will conduct a source data validation of a 1% random sample of all questionnaires to calculate input data errors.

Data security

The interviews will be performed by trained scientists and study nurses at the patients' homes and for the GPs in their surgeries using printed forms. Regular training sessions will be performed twice each year. An email list server will be used for clarification of not anticipated assessment problems. Survey sheets and patient contact sheets will be stored in separate lockers in the study centers. Data will be entered in the local centers via an internet based remote data entry system. The data are transferred via 128 bit SSL encryption. The data will be stored in a central database in the Institute for Biometry of Hannover Medical School. The access to the internal database and web server is controlled by two consecutive firewall systems. A pseudonym will be automatically created when the identification data are entered and a printed copy with the pseudonym and the identification data will be archived by an officiating notary ("data trustee"). The identification data will neither be electronically transferred nor stored. The members of the study group will have access to the electronic data entry system according a detailed concept of roles and rights. An audit trail will ensure an automatic protocol of all data entries, changes and deletions.

Description of risks

It is not expected that participation in the study will expose the patients to any risks. Nevertheless, monitoring of the impact of the study on patients will be performed by the interviewers and counseling given in case participants experience any discomfort or harm.

Ethics approval

The study is conducted in compliance with the Helsinki Declaration. The study protocol was approved by the Ethics Committee of the Medical Association of Hamburg in February 2008 and amended in November 2008 (Approval-No. 2881).

Data Analysis

Cross-sectional analysis

Recruitment and baseline data will be used to develop statistical models that relate the independent variables to the dependents:

Table 1: Variables, measuring instruments and data sources

Morbidity	Measuring instrument	Data source
Diagnoses	ICD-10 codes	chart review
Diseases	self-developed questionnaire	GP interview
	self-developed questionnaire	patient interview
	Four-Dimensional Symptom Questionnaire (4DSQ) [11]	patient interview
	Geriatric Depression Scale (GDS) [12]	patient interview
	Clinical Dementia Rating (CDR) [13]	rated by interviewer
Functional Status		
Activities of daily living	Barthel Index [22]	patient interview
	Instrumental Activities of Daily Living (IADL) Scale [23]	patient interview
Motor skills	FFB-Mot [24]	patient interview
Vision and hearing	2 items rated on a 4 point scale	patient interview
Cognitive impairment	CERAD [25] subtests word list and animal naming	cognitive tests by interviewer
	Letter Digit Substitution Test (LDST) [26]	cognitive tests by interviewer
Pain	Graded Chronic Pain Scale (GCPS) [27]	patient interview
Health-related quality of life	EuroQoL (EQ-5D) Scale [28]	patient interview
Resources/Risk Factors		
Physical risk factors	Body-Mass-Index and Waist-to-Hip-Ratio	physical checkup by GP
Physical activity	International Physical Activities Questionnaire (IPAQ) [29]	patient interview
Nutrition	12 items for frequency and portion size of nutriments	patient interview
Alcohol use	AUDIT-C [30]	patient interview
	total amount of alcohol consumption per week	patient interview
Smoking behavior	9 items indicating current smoking status and pack years	patient interview
General self-efficacy	General Self-efficacy Scale [31]	patient interview
Social support	F-SOZU K14 [32]	patient interview
Medical care	Patient Assessment of Chronic Illness Care (PACIC) [33]	patient interview at baseline
	age and gender of GP/size and location of surgery	GP interview
Utilization of medical services (incl. medication)	15 items (short form), respectively 91 items (long form)	patient interview
Sociodemographic Data		
Age and gender	age and gender	chart review
Migrant status	standardised indicators for mapping migrant status [34]	patient interview at baseline
Marital status	marital status	patient interview
Living conditions	independent or assisted living	patient interview
Household size	household size/household members under 15 years	patient interview
Education	CASMIN classification [35]	patient interview at baseline
Former occupation	German epidemiological standard questionnaire [36]	patient interview at baseline
Income	household size adjusted net income	patient interview
Wealth	home ownership	patient interview

• Multimorbidity patterns of similar severity will be identified by methods of supervised learning (methods of recursive partitioning like CART [Classification and Regression Trees], logistic regression).

• We will conduct different regression modelling strategies [20]. The basic model for each dependent will contain the independents as regressors, and interactions between them.

• Mixed models will be applied allowing to take the GP-induced cluster structure into account.

• The correspondence of GP-rated and patient-rated data will be analysed using inter-rater-reliability (Cohen's kappa).

Longitudinal analysis

• Based on the results of the cross-sectional analysis, hypotheses will be formulated as far as the individual outcomes (dependents) at the end of the follow-up period are concerned. Predictive scores will be calculated [21].

• As soon as the follow-up data are available, mixed models which include the baseline variables will be

fitted for the follow-up data or the changes from baseline, respectively.

• Structural equation modeling will be applied to map causal chains between dependents.

• A classification system will be derived which groups patients as they are comparable with respect to intensity of care and costs.

Discussion

The project will be the first large scale and longitudinal investigation of multimorbidity in Germany based on a cohort of multimorbid patients randomly selected from general practice data bases. The project will help to discern distinct multimorbidity patterns and identify variables associated with these patterns. A better understanding of the individual variability in the process of multimorbidity is necessary for a better quality of medical care, better support of patients' self management and a more effective and efficient allocation of resources.

Therefore, the main aim of the cohort study is to monitor the course of the illness process and to analyse for which reasons medical conditions are stable, deteriorating or only temporarily present. The results will allow the development of an instrument for prediction of the deterioration of the illness process and point at possibilities of prevention.

The practical consequences of the study results for primary care will be analysed in expert focus groups of GPs and nurses, supplemented by further experts (e.g. geriatricians). The aim is to develop strategies for the inclusion of the aspects of multimorbidity in primary care guidelines. This will include:

• rating of existing guidelines with regard to their (in)appropriateness for primary care;

• prioritization of multimorbidity patterns according to the needs for specific guidelines;

• needs for special services for patients with multimorbidity (e.g. improvement of the existing education programs; possibilities and limits of multimorbidity oriented disease management programs).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HvdB, IS, HK, ME, KW and BW conceived the study. AA, KB, HB, MB, AF, JG, FMG, HH, SH, HHK, ML, WM, JJP, JP, SRH, AR, GS, SS, OvdK, JW and SW participated in implementing the study. IS, HvdB and HH drafted the manuscript. All authors commented on the draft and approved the final version of the manuscript.

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