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Optimization of Medication in Older Adults

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List of Abbreviations

ACE	Angiotensin-converting-enzyme
AM	Appropriate medication
ATC	Anatomical Therapeutic Chemical
ASA	Acetylsalicylic acid
BHP	Benign prostatic hypertrophy
BI	Basic intervention in three-armed trial
BMI	Body mass index
CG	Control group
CI	Confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DUFSS-5	Duke-UNC Functional Social Support Questionnaire, 5-item version
EI	Extended intervention in three-armed trial
EORCT	European Organisation for Research and Treatment of Cancer
eGFR	Estimated glomerular filtration rate
FORTA	Fit fOR The Aged
FDR	False discovery rate
GDS	Geriatric Depression Scale
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA_{1c}	Hemoglobin A_{1c}
HDL	High-density lipoprotein
HR	Hazard ratio
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IG	Intervention group
IQR	Interquartile range
LDL	Low-density lipoprotein
MCAR	Missing completely at random
MET	Metabolic equivalent of task

NAKO	German National Cohort
NSAIDs	Non-steroidal anti-inflammatory drugs
OPTIMAL	Optimization of polypharmacy in geriatric oncology
OR	Odds ratio
PHQ-9	Patient Health Questionnaire-9
PIM	Potentially inappropriate medication
PPIs	Proton pump inhibitors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAPA	Rapid Assessment of Physical Activity
RCT	Randomized controlled trial
RoB	Cochrane risk-of-bias tool for randomised trials
RECORD-PE	The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology
Ref	Reference
RR	Risk ratio
RSV	Respiratory syncytial virus
SSRIs	Selective serotonin reuptake inhibitors
UK	United Kingdom
Unkn.	Unknown
QLQ-C30	Quality of life C30 questionnaire
QoL	Quality of life

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1 Introduction

1.1 Optimization of medication in older adults

How to ensure optimal pharmacotherapy for older adults is a critical question facing clinicians in our ageing and increasingly multimorbid (Crimmins 2015) society, especially as reducing medication-related harm has become a priority of the third WHO Global Patient Safety Challenge launched in 2017 (World Health Organization, 2017, 2023). Since the proportion of people aged over 60 years is expected to double by 2050 (World Health Organization 2024), the subsequent increase in disease prevalences coupled with advances in treatments prolong the lives of affected (chronically) ill individuals (Crimmins 2015) and may, at the same time, also necessitate polypharmacy in older adults (Wastesson et al. 2018), which is commonly defined as the concurrent intake of five or more medications (Pazan et al. 2021).

Hence, the focus of medication optimization has shifted away from merely reducing medication quantity to improving medication quality. This encompasses addressing three types of medication problems: medication overuse and underuse, as well as so-called potentially inappropriate medications (PIM) with an expected poor benefit-to-harm ratio in geriatric patients (O'Mahony et al. 2023; Pazan et al. 2022b; Wauters et al. 2016). Accumulating evidence has linked these medication problems to poor health outcomes, such as functional impairments, hospitalizations, and premature death (Chen et al. 2022; Chen et al. 2021b; Meid et al. 2016; Pazan et al. 2019a), and reinforces the pressing need for effective medication optimization strategies for older adults.

Several medication assessment tools aiming to improve medication quality in older adults have been developed (American Geriatrics Society Beers Criteria® Update Expert Panel 2023; Laroche et al. 2007; Mann et al. 2023; McLeod et al. 1997; O'Mahony et al. 2023; Renom-Guiteras et al. 2015; Zhan et al. 2001), and a comprehensive, validated (Wehling et al. 2016) tool tailored to the German drug market is the Fit fOR The Aged (FORTA) list (Pazan et al. 2019b; Pazan et al. 2022b; Pazan et al. 2025). Based on regularly updated evidence and expert opinions, the FORTA classes A (indispensable) to D (avoid) help identify all three types of medication problems across various non-cancer and cancer indications and inform about appropriate medications (AM) to solve them. Additionally, underuse of vaccines recommended for older adults can be assessed, and all medication problems can be combined into the total FORTA score, a measure of overall medication quality (Pazan et al. 2022b).

1.2 Medication reviews in hospitalized patients to reduce rehospitalization and all-cause mortality

A recent meta-analysis of 100 observational studies revealed an overall prevalence of preventable medication-related harm of 5 % (95 % confidence interval (CI): 4–6%) in patients receiving healthcare, with 23 % being severe or potentially life-threatening (95% CI: 17–30%). Notably, medication-related harm predominantly occurred during the ordering and prescribing processes (53 %, 95 % CI: 42–65 %), and most of the evidence was obtained from inpatient settings (World Health Organization 2023).

Hospitalized patients are particularly prone to medication-related harm due to acute health conditions, frequent medication changes (Harris et al. 2013), and the use of complex medication regimens (World Health Organization 2017). Furthermore, PIM and polypharmacy, two major risk factors for medication-related harm (Chen et al. 2021a; Chen et al. 2022; Clark et al. 2020; Wastesson et al. 2018), are very common in hospitalized older patients, with prevalences of 44.6 % for PIM (Bories et al. 2021) and over 96.5 % for polypharmacy (Pazan et al. 2021). Thus, there is need for interventions that improve medication safety in clinical settings.

One strategy to address these targets is through medication reviews, the structured evaluation of an individual's medication to improve drug therapy and health outcomes (Griese-Mammen et al. 2018). Increasing efforts have been made to implement them in inpatient settings (Bülow et al. 2023; Cole et al. 2023). However, trials often yielded null-results in terms of clinical outcomes such as rehospitalization and all-cause mortality (Bülow et al. 2023; Dautzenberg et al. 2021; Huiskes et al. 2017). Although multiple published principles and tools aimed to standardize medication reviews (American Geriatrics Society Beers Criteria® Update Expert Panel, 2023; Pazan et al., 2022; Vaffis et al., 2023; O'Mahony et al., 2023; Mann et al., 2023), the substantial variability in medication review processes, trial characteristics, and methodology applied in previous randomized controlled trials (RCTs) complicates the drawing of meaningful conclusions about the effectiveness of medication reviews on clinical outcomes (Leendertse et al. 2010).

Up to the commencement of this investigation, few investigations on methodological aspects of medication reviews had been published, and they were either outdated (Leendertse et al. 2010), involved outpatients (Abrahamsen et al. 2020; Dautzenberg et al. 2021), or did not evaluate the impact of key aspects such as the frequency of medication reviews (Abrahamsen et al. 2020;

Bülow et al. 2023; Dautzenberg et al. 2021; Leendertse et al. 2010). Therefore, it was timely to investigate existing medication review RCTs from a methodological perspective.

1.3 Associations of PIM use in older adults with mortality and hospitalizations and methodological challenges in pharmacoepidemiology

The various PIM assessment tools (American Geriatrics Society Beers Criteria® Update Expert Panel 2023; Laroche et al. 2007; Mann et al. 2023; McLeod et al. 1997; O'Mahony et al. 2023; Pazan et al. 2022b; Pazan et al. 2023; Renom-Guiteras et al. 2015; Zhan et al. 2001) differ greatly in structure and content. For instance, negative lists, such as Beers criteria (American Geriatrics Society Beers Criteria® Update Expert Panel 2023), specifically define medications that should be avoided, whereas tools such as the FORTA list (Pazan et al. 2022b) and its European version EURO-FORTA (Pazan et al. 2023), also provide suggestions for AM. However, all these tools were commonly developed using expert opinions and consensus-driven processes such as Delphi rounds.

To investigate the risks associated with PIM use, RCTs would ideally compare new PIM prescriptions with new AM prescriptions. However, it would be difficult to conduct such trials, not only for ethical reasons. The available RCTs aimed to reduce prevalent PIM use but have not shown clear improvements in clinical outcomes (Cole et al. 2023). The likely explanation is that the included trial participants with PIM tolerated them well. Otherwise, they would have switched to other medications before. Previous observational studies aiming to provide evidence for hospitalization and mortality rate reductions by avoiding PIM in older individuals yielded inconsistent results (Muhlack et al. 2017; Xing et al. 2019; Zhou et al. 2024).

Observational studies are essential for deriving evidence on drug safety from real-world settings. Nonetheless, specific methodological challenges in pharmacoepidemiology, such as immortal time bias, depletion of susceptibles, healthy-adherer bias, and confounding by indication, have been observed to affect the judgment of the risk and benefit profiles associated with certain medications in the past (Criner et al. 2014; Glynn et al. 2006; Hernán et al. 2008; Suissa 2014; Suissa 2017; Suissa et al. 2012; Suissa et al. 1997). Given that such findings may influence treatment strategies, policymaking, and subsequent research efforts, minimizing these biases is crucial.

The meta-analysis by Muhlack et al., which addressed time-dependent biases, revealed a statistically significant 1.6-fold increased risk for all-cause mortality among PIM users in n=3 observational studies with a new user design. However, in their meta-analysis of n=10 studies with prevalent user design, no increased mortality among PIM users was detected (Muhlack et al. 2017). Given the methodological challenges of pharmacoepidemiologic studies and the large implications for medication use among vulnerable older patients, evidence on PIM safety that avoids typical biases and methodological challenges present in prior pharmacoepidemiologic research is needed.

1.4 Factors associated with PIM use, medication underuse, and overuse in older adults in the German National Cohort

Despite the pressing need for medication optimization strategies (Chen et al. 2021a; Chen et al. 2022; Degen et al. 2025; Meid et al. 2016; Pazan et al. 2019a), PIM use remains common, with a proportion exposed ranging from 10.8% to 37.4% in the general older German population (de Vries et al. 2021; Endres et al. 2018; Muhlack et al. 2018; Zimmermann et al. 2013). Furthermore, underuse and overuse of medications have received little attention in previous research. Additionally, it should be noted that efficient future medication optimization strategies will require effective identification of priority groups for medication reviews

The German National Cohort (NAKO) represents the largest German epidemiologic cohort study with nationwide recruitment. Its wide scope of available data, including self-reported data, medical and functional assessments, as well as blood-based biomarkers (Peters et al. 2022), enables the investigation of potential factors associated with PIM use, underuse, and overuse of medications more comprehensively than in any previous study (Boehlen et al. 2019; Endres et al. 2018; Fiss et al. 2011; Fiss et al. 2013; Muhlack et al. 2018; Pfefferle et al. ; Zimmermann et al. 2013).

1.5 Medication reviews for improved cancer and co-medication quality in older patients with polypharmacy

Evidence from the German DACHS study demonstrated a particularly high need for effective and feasible medication optimization strategies for older cancer patients: approximately half of the colorectal cancer patients aged 65 years or older were exposed to polypharmacy and even

more than 9 out of 10 experienced medication problems (all assessed with the FORTA list), which were statistically significantly inversely associated with overall and cancer-specific survival (Chen et al. 2021a; Chen et al. 2022).

FORTA-based medication reviews hold potential promise as a feasible, effective strategy to optimize cancer and co-medication quality (and mitigate associated risks) for older cancer patients in clinical practice. This hypothesis is not only based on evidence from the aforementioned DACHS study (Chen et al. 2021a; Chen et al. 2022) but is further strengthened by the VALFORTA RCT, which demonstrated the applicability and effectiveness of the freely accessible FORTA list in general geriatric hospital wards (Wehling et al. 2016). However, high-level evidence for older cancer patients with polypharmacy, who are particularly vulnerable, is lacking.

The 3-week inpatient rehabilitation, which is part of usual care shortly after completion of the primary oncologic therapy in Germany (Rick et al. 2017), represents an ideal context to conduct a comprehensive medication review as several changes have usually been made to the cancer and co-medication in hospitals or specialist practices during cancer treatment, the general practitioner (GP) may not (yet) be aware of.

1.6 Aims of the dissertation

Given the pressing need for effective medication optimization strategies for older adults, the overall aim of this dissertation was to generate evidence for medication optimization that is translatable and implementable into clinical practice in Germany. This encompassed assessing risks associated with PIM use, identifying potential target groups for medication reviews, and effective medication review strategies for the older (cancer) population in Germany.

The specific objectives included:

I. To systematically summarize the available evidence from RCTs on medication reviews in hospitalized patients regarding rehospitalization and all-cause mortality, and to explore potential components of effective interventions and study designs through detailed meta-analyses and meta-regressions with a focus on methodological study differences.

II. To assess the association of PIM use with the risks for hospitalization and all-cause mortality in community-dwelling older individuals who participated in the United Kingdom (UK) Biobank, avoiding typical bias and methodological challenges present in

prior pharmacoepidemiologic research, and to elucidate how common previous study designs might have under- or overestimated the risks associated with PIM use in prior studies.

III. To assess the frequency and factors associated with PIM use, underuse, and overuse of medications among community-dwelling older adults who participated in the NAKO.

IV. To evaluate the superiority of an advisory letter with the results from a FORTA-based, pharmacist-led, medication review sent to the treating rehabilitation physician compared to usual care with respect to the medication quality of older cancer patients with polypharmacy undergoing inpatient rehabilitation.

2 Material and Methods

2.1 Systematic review, meta-analysis, and meta-regression of RCTs investigating the effect of a medication review on rehospitalization and all-cause mortality in hospitalized patients

This systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, and the protocol was registered with PROSPERO in advance (CRD42024495896).

2.1.1 Inclusion and exclusion criteria

I included two-arm and multi-arm RCTs investigating medication reviews performed by healthcare professionals in hospitalized adults (≥ 18 years), which were followed by a medication change or an according advice, compared to usual care. Rehospitalization, defined as either all-cause or unplanned readmission as a dichotomous outcome without considering multiple hospital readmissions, and all-cause mortality were the outcomes of interest.

I excluded trials involving patients who were aged < 18 years or not admitted to the hospital, as well as interventions that did not result in medication changes or corresponding advice, and interventions restricted to certain medications. Furthermore, I excluded trials that lacked data on the two outcomes of interest or did not report results for these outcomes in sufficient detail to calculate risk ratios (RRs) usable for meta-analyses.

2.1.2 Literature search

I conducted a three-step literature search. I based the literature search on the Cochrane review by Bülow et al. (Bülow et al. 2023), with literature search until January 2022, as this review covered the type of trials I aimed for. Firstly, I included the RCTs also included in the Cochrane review by Bülow et al. (Bülow et al. 2023). Secondly, I screened trials excluded from the Cochrane review to determine whether they met my inclusion criteria. Thirdly, I utilized the same search strings used in the Cochrane review (Bülow et al. 2023), with adapted operators for EMBASE since I used a different database provider, to update the literature search by two years from 01 January 2022 to 17 January 2024. The search strings are detailed in **Appendix 1–**

Appendix 4 for the following four databases: MEDLINE (Ovid), Embase (Elsevier), the Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOhost), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. I imposed no restrictions on the publication language.

2.1.3 Study selection and data extraction

I imported all records obtained through the literature search into Rayyan (Ouzzani et al. 2016), removed duplicate articles, and excluded ineligible publication types such as systematic reviews. In the following step, I screened titles and abstracts and excluded non-relevant records. Based on my predefined inclusion and exclusion criteria, I subsequently assessed publications eligible for full-text screening. Any uncertainties were discussed with a second reviewer (Li-Ju Chen) until consensus was reached.

The study data were independently extracted by me and a second reviewer (Li-Ju Chen) using predetermined standardized data extraction forms. If important data from trials published before 2022, which were included in the Cochrane review, could not be found in the original articles, they were extracted from the Cochrane review because Bülow et al. obtained this information through author contacts. Any discrepancies between the second reviewer and me were resolved through consultation with a third reviewer (Ben Schöttker).

2.1.4 Data synthesis

Based on the methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins J. P. T. et al. 2023), I calculated RRs and 95% CIs for all trials not reporting a full intention-to-treat result. This approach ensured comparability between the results included in the meta-analysis. Consistent with the Cochrane review, I only included patients alive after discharge from their initial hospitalization in the meta-analysis on rehospitalization (Bülow et al. 2023). In three-armed trials, I calculated RRs and 95% CIs for both intervention arms combined versus usual care, and additionally, I calculated separate RRs and 95% CIs for each intervention arm versus usual care. I used these separate RRs and 95% CIs from the same trial for subgroup meta-analyses and meta-regressions to assess methodological differences between the intervention arms (e.g., one single medication review was conducted in the basic intervention (BI), whereas repeated medication reviews were conducted in the extended intervention (EI)).

2.1.5 Risk of bias assessment

In line with the methods applied by Bülow et al. (Bülow et al. 2023), I categorized trials as being at low, high, or unclear risk of selection, performance, detection, attrition, reporting, and other biases according to the Cochrane risk-of-bias tool for randomized trials (RoB) (Higgins J. P. T. et al. 2011a). To explore reporting bias, I compared trial reports with available study protocols and trial registry information. Furthermore, I evaluated contamination bias (Cochrane Effective Practice and Organisation of Care (EPOC) 2017) and additional study design-specific domains for cluster-randomized trials and cross-over trials (Higgins J. P. T. et al. 2011b).

To assess overall publication bias, I used funnel plots (Sterne et al. 2005) for visual and Egger's test (Egger et al. 1997) for statistical evaluation.

The bias assessment was performed independently by me and a second reviewer (Li-Ju Chen). Potential discrepancies were resolved through discussions, if necessary, in consultation with a third reviewer (Ben Schöttker).

2.1.6 Assessment of the strength of evidence

I applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al. 2008) to assess the strength of evidence for the main meta-analyses including all trials on rehospitalization and all-cause mortality.

2.1.7 Statistical analyses

I estimated pooled RRs with 95% CIs and determined the number needed to treat for meta-analyses according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann H. J. et al. 2023). To account for trial heterogeneity, a random-effects model was used.

All statistical tests were two-sided with a significance level set at $\alpha = 0.05$. The results of the two main meta-analyses, which included all trials for the endpoints "rehospitalization" and "all-cause mortality", were regarded as confirmatory. Statistical heterogeneity was assessed via I^2. All analyses were performed using Comprehensive Meta-Analysis 3.0 (Biostat, Englewood, NJ).

2.1.7.1 Subgroup analyses

Subgroup analyses were conducted for 15 predefined subgroups in order to explore potential effect modification by methodological study differences: length of the follow-up period (*30 days, 3 months, 6 months, ≥ 1 year*), setting (*Middle/Western Europe, Northern Europe, North America*), mean/median age (*< 70, ≥ 70 years of age*), mean/median number of medications (*< 7, ≥ 7-10, > 10*), number of medications as inclusion criterion (*≥ 4-5 medications, no or other inclusion criteria*), eligible diagnoses (*any, limited to certain diagnoses*), aim of the intervention (*deprescribing, optimisation of medication*), involvement of pharmacists in the intervention team (*yes, no*), recommendations per patient (*≤ 5, > 5*), method of data collection on mortality (*registries, relatives, primary care*), reason for the initial hospitalization (*acute admission, acute and elective admissions*), implementation of medication changes (*during in-hospital stay, after discharge*), frequency of medication review (*repeatedly, once*), number of patient contacts (*none, 1, ≥ 2*), patient contact after discharge (*yes, no*).

Trials that did not report relevant information were classified as *unknown*. Trials that did not meet the criteria for any subgroup were summarized as *other.* This approach ensured inclusion of all trials from the main meta-analysis for an outcome in one of the stratified meta-analyses for a methodological aspect.

Due to multiple testing, all subgroup meta-analyses were regarded as exploratory.

2.1.7.2 Meta-regression

I performed meta-regression to evaluate effect modification by the 15 methodological aspects stated above using log RRs, random-effects models, and the restricted maximum likelihood method. Firstly, I created univariate meta-regression models for each methodological aspect as a single covariate. Secondly, I created multivariate meta-regression models with forward selection, using $p < 0.05$ as the entry criterion.

Length of the follow-up period, age, recommendations per patient, and number of patient contacts were treated as continuous variables. Unknown values were imputed through mean imputation. Three-armed trials were considered as two separate trials, always comparing one intervention arm to the complete control group.

Where appropriate, I combined subgroups to mitigate issues arising from low sample sizes. Specifically, I summarized mortality assessments via primary care and registries due to their

comparably complete and unbiased outcome ascertainment. I summarized *other* and *unknown* mortality assessments for equivalent reasons. Similarly, I assigned the single trial for which eligible diagnoses were categorized as *unknown* to *any diagnoses* since this trial included a broad range of diagnoses.

2.2 Associations of PIM use in older adults with mortality and hospitalizations and methodological challenges in pharmacoepidemiology

This investigation is reported in line with the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE) (Langan et al. 2018).

2.2.1 Data source

Data were derived from the UK Biobank, which is a comprehensive prospective cohort that recruited over 500,000 participants aged 40 to 69 years from England, Scotland, and Wales between 2006 and 2010 (UK Biobank 2017). During the baseline visit at one of the 22 assessment centers, participants provided electronically signed consent, participated in touchscreen questionnaires, a brief interview, and multiple physical and functional assessments (Elliott et al. 2008; UK Biobank 2017). Information on prescription medications was collected by nurse-led verbal interviews. Participants were asked to bring their medications to the assessment centers, and those taken regularly (e.g., daily, weekly, monthly, or three-monthly) were recorded (Nevado-Holgado et al. 2016). Over-the-counter medications, as well as vitamins and supplements, were documented in the touch-screen questionnaire (UK Biobank 2011).

Linked electronic health records encompassed the UK National Health Service (NHS) data, primary care records with GP prescription data (available for approximately half of the cohort), hospital inpatient records, and death registries (Sudlow et al. 2015).

The study adhered to the Declaration of Helsinki. The UK Biobank was approved by the North West Multi-center Research Ethics Committee (approval ID 2016: #16/NW/027; renewed in 2021: 21/NW/0157).

2.2.2 Study population

Out of 502,366 UK Biobank participants, I excluded N=284,905 who were younger than 60 years and N=350 without available medication information at the baseline assessment, leaving N=217,111 individuals, of whom the majority (98.9%) was 60-69 years old, and only a small minority was aged up to 73 years. In the main analysis, I excluded participants without primary care linkage, leaving N=95,187 individuals for the longitudinal medication assessment.

2.2.3 Definition of potentially (in-)appropriate medication

I defined PIM and AM according to the EURO-FORTA list version 2 (Pazan et al. 2023), which accounts for differences in medication availability and prescribing practices in European countries. The EURO-FORTA list categorizes the safety, appropriateness, and efficacy of medications for frequent geriatric indications into the classes A (indispensable), B (beneficial), C (questionable), and D (avoid). I used this medication assessment tool because it defines PIM and also refers to AM for each indication, aligning with consensus recommendations. AM served as the active comparator in my study. EURO-FORTA classes A and B were defined as AM, whereas classes C and D were defined as PIM.

Read v2 codes assigned to the prescription data in the UK Biobank were translated into Anatomical Therapeutic Chemical (ATC) codes. The ATC codes used to code PIM and AM in this study are listed in **Appendix 5**. Short-term use of glucocorticoids in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) could not be coded as AM, and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) could not be coded as PIM because the duration of drug use is not available in the UK Biobank. Hence, the main PIM/AM assessment did not consider these two drug classes, but I explored the impact of excluding NSAIDs on the results in a sensitivity analysis.

Cancer indications of the EURO-FORTA list were not used in this population-based cohort. Furthermore, the main analysis was restricted to the 14 FORTA indications, for which both study participants who use PIM and participants who use AM could be identified in the UK Biobank.

For some medications, it was possible to assign them to more than one FORTA indication. For instance, angiotensin-converting-enzyme (ACE) inhibitors might be indicated in arterial hypertension, heart failure, acute coronary syndromes, and after myocardial infarction. The common co-occurrence of these diseases and the overlapping indicated treatments make it

difficult to assign the identified medication to one single EURO-FORTA indication. However, to perform the indication-wise matching of PIM and AM users, it was necessary to limit the assignment of each drug to one single FORTA indication. Therefore, the following rules were specified:

1. Arterial hypertension: included participants receiving a medication which was clearly assigned to treat arterial hypertension because
    a. there was no other possible cardiovascular indication for the relevant drug (e.g., Aliskiren); *or*
    b. the patient was diagnosed with arterial hypertension but not with any other potential indication for the treatment. For instance, this criterion was met if the ACE inhibitor ramipril was prescribed for a participant who was diagnosed with arterial hypertension, but not with the other potential cardiovascular indications (heart failure, acute coronary syndromes, or myocardial infarction).
2. Cardiovascular diseases: included participants if their medication
    a. was assigned to one of the following indications: heart failure, myocardial infarction, atrial fibrillation, acute coronary syndromes, or stroke due to the broad overlap of potential treatments and the frequent coincidence of diagnoses; *or*
    b. was indicated to treat arterial hypertension *and* at least one additional cardiovascular disease, as outlined in 2a), *and* the patient was diagnosed with multiple overlapping conditions. For instance, this criterion was met if Ramipril was prescribed in a participant diagnosed with both heart failure and arterial hypertension.
3. Medications to treat dementia and dementia-associated syndromes were pooled together.
4. In cases of overlap between indications and treatments, the medication was assigned to the more relevant indication. For instance, in participants diagnosed with epilepsy and chronic pain, antiepileptics were assigned to epilepsy.

2.2.4 Outcome ascertainment

Hospitalization dates were ascertained through linkage to hospital inpatient data (data fields “41280” and “41281”, which refer to the first date of inpatient diagnosis (International

Classification of Diseases, 10th (ICD-10) or 9th revision (ICD-9)). Information about vital status and date of death was obtained through linkage with national death registries. Both linkages were available for all participants. Follow-up data were completely available for mortality until 19/12/2022 and for hospitalizations until 31/05/2022. This covers more than the needed, up to 4-year follow-up period from the last recruited UKB participant (01/10/2010) plus the 2-year window after baseline recruitment for prescription of a new PIM or AM (i.e., the last theoretical cohort entry for the new user design analysis was 01/10/2012). Participants alive at the end of each follow-up period used in this investigation were censored.

2.2.5 Covariates ascertainment

I accounted for potential confounders (Glynn et al. 2006; Shrank et al. 2011) by incorporating n=41 covariates, which I listed in **Appendix 6**. These covariates comprised sociodemographic and economic factors, lifestyle factors, diseases (e.g., depression, cancer), functional assessments (e.g., grip strength, systolic blood pressure), and blood-based biomarkers (e.g., high-density lipoprotein (HDL), hemoglobin A_{1c} (HbA_{1c})).

Sociodemographic (e.g., average household income) and lifestyle (e.g., alcohol consumption, smoking status) information were obtained through touchscreen questionnaires (UK Biobank 2011). Self-reported medical history was gathered through touchscreen questionnaires and verbal interviews (UK Biobank 2011; UK Biobank 2012) and was complemented by diagnoses obtained through linkage to primary care records and hospital inpatient data. Physical examinations (e.g., anthropometric measurements) and laboratory methods for blood-based biomarkers are detailed elsewhere (Fry et al. 2019; UK Biobank 2014).

2.2.6 Statistical analyses

2.2.6.1 General remarks

I used SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC, USA) to perform the statistical analyses and tested the assumption of proportional hazards through Schoenfeld residuals. Only previous smoking violated the assumption for mortality outcomes, thus its interaction term with follow-up time was incorporated into the model. To assess hospitalization, I used cause-specific Cox regression models to account for the competing risk of death. All statistical tests were two-tailed, with a significance level set at $\alpha = 0.05$. I imputed missing covariate data through multiple imputation with the fully conditional specification method (van

Buuren 2007). Proportions of missing values before imputation are detailed in **Appendix 6**. Only three variables had missing value proportions > 4.1% (physical activity (25.9%), income (19.4%), and years since quitting smoking (13.3%)). Prior to imputation, I explored potential sources of non-random missingness, revealing a lower proportion of participants with higher incomes and a higher proportion of women among those with missing physical activity data compared to the total study population. Since income and sex were incorporated in the imputation model, missing values can be assumed to be missing at random. I generated 10 imputed datasets and aggregated analytical outcomes from them using the SAS procedure "PROC MIANALYZE".

2.2.6.2 The association of PIM with the study outcomes

The primary outcomes were 1-month hospitalization and 1-year all-cause mortality since these were the shortest follow-up times at which ≥ 100 events could be included in the main analysis. Longer observation periods (up to 4 years) were explored in sensitivity analyses. This approach addressed two competing needs: the study outcomes were acute events which predominantly occur during the early treatment period, requiring short-term follow-ups. On the other hand, restricting the follow-up period may reduce statistical power due to fewer observed events.

I applied three distinct study designs, as visualized in **Figure 1** (Schneeweiss et al. 2019).

In the main analysis, I compared new PIM and new AM users, identified via GP prescription data, utilizing a new user design with active comparator matching per indication (**Figure 1A**). Therefore, I assessed prescriptions from day 1 after the baseline assessment center visit until 2 years after baseline, with the first date of a new PIM/AM prescription being the index date. The exposure assessment window was restricted to two years after baseline because covariate accuracy could not be assumed over a longer period. I verified new PIM/AM by implementing a 6-month washout window. This means that medications taken at baseline, as reported during the baseline assessment center visit, or prescribed in the six months leading up to the baseline assessment visit, were not considered new medications. To ascertain possible PIM/AM indications, I used self-reported information gathered at the baseline assessment center visit and completed them with medical diagnoses from primary care and hospital inpatient records. Since these were mainly chronic conditions, I reviewed all available medical diagnoses from before the baseline assessment center visit through the end of the 2-year exposure assessment window. Participants who were simultaneously prescribed with new AM and new PIM were excluded.

Depending on the indication for the new PIM or new AM, I assigned the participant to the relevant indication-specific cohort. In brief, I calculated distinct propensity scores per indication for receiving new PIM versus new AM and matched new PIM and new AM users of the same indication in a 1:1 ratio using the SAS procedure "PROC PSMATCH". More specifically, in indication-specific cohorts with a large number of new AM users and few new PIM users, optimal fixed ratio matching was applied. Conversely, greedy nearest neighbor matching was used in indication-specific cohorts including fewer new AM compared to new PIM users, as well as in cohorts with little overlap in propensity scores. **Appendix 7** provides an overview of the propensity score matching procedure per indication. Caliper ≤ 0.2 was used and stepwise increased by 0.1 if optimal matching was not possible for an indication. To assess the balance produced by matching, I calculated standardized mean differences for all covariates. Standardized differences < 0.25 were considered well-balanced. In the next step, the well-balanced, indication-specific matched pairs were pooled into one analytical dataset that included all indications. Hence, this pooled, matched dataset included new PIM and new AM users with well-balanced covariates (**Appendix 7**). I analyzed the pooled matched dataset using Cox proportional hazards regression without any adjustment, as confounding was controlled for by the propensity score matching.

In *bias demonstration analysis I*, I utilized a new user design without appropriate active comparator selection (**Figure 1B**). I ascertained new PIM and new AM users using the same identification procedure as in the main analysis. In contrast to the main analysis, I did not distinguish between the different indications for PIM/AM use and included all identified new PIM/AM users in the same analytical dataset. Therefore, this dataset was much larger (N=36,354) than the main analysis with active comparator design (N=11,812).

I used two distinct multivariable Cox proportional hazards regression models to assess the associations of new PIM versus new AM use with the study outcomes. Model 1 was adjusted for age and sex. Model 2 was adjusted for a propensity score. Therefore, I calculated one single propensity score for the whole study population with the ß coefficients obtained from a logistic regression model with receiving new PIM versus new AM of any indication as the dependent variable and all n=41 covariates as independent variables. The propensity score was fairly distributed between new PIM and new AM users **(Appendix 8-Appendix 12)**, and all covariates were well-balanced after propensity score adjustment (**Appendix 13**).

In *bias demonstration analysis II*, I applied a prevalent PIM user versus non-user approach (**Figure 1C**). Therefore, I identified PIM users (≥ 1 PIM) and non-users (no PIM) by assessing

baseline medication information gathered at the baseline assessment center visit. To identify possible PIM indications, I used self-reported information gathered at the baseline assessment center visit and diagnoses identified through primary care and hospital inpatient records from the full available period prior to baseline.

I used two distinct multivariable Cox proportional hazards regression models to assess the associations of PIM use versus non-use with the study outcomes. Model 1 was adjusted for age and sex, and model 2 was adjusted for all n=41 covariates. As no matching was performed, the total cohort (N=217,111) was included.

All analyses applied an intention-to-treat principle, assuming adherence to the assigned treatment group, since the data did not allow me to measure adherence, which also aligns with the nature of prescribing in primary care.

2.2.6.3 Sensitivity analysis including NSAIDs

Following the EURO-FORTA list, only chronic intake of NSAIDs is classified as PIM (Pazan et al. 2023). However, the duration of the use of each drug was not recorded in the UK Biobank dataset. Since this relevant information was not available, I decided not to include NSAIDs use in the main analysis. Instead, a sensitivity analysis including NSAIDs was conducted. As the baseline interview information about NSAIDs use was required to ascertain the chronicity of NSAIDs use (NSAIDs are usually used as over-the-counter medications, and therefore often not recorded in prescription data), this sensitivity analysis could only be conducted for the prevalent PIM user analysis (*Bias demonstration analysis II*). In this sensitivity analysis, I assumed that NSAIDs were used regularly, and subsequently only coded them as PIM if participants reported NSAID use in the baseline interview and additionally met at least one of the following 3 criteria:

1. The participant replied “Yes” to the interview question about regular use of ibuprofen or aspirin.
2. The participant had received at least one NSAID prescription within 60 days prior to baseline according to the primary care prescription data.
3. The participant had received at least two NSAID prescriptions within 120 days before baseline according to the primary care prescription data.

2.2.6.4 Subgroup analyses

Subgroup analyses were conducted by age (*< 65*, *≥ 65 years of age*), sex (*female*, *male*), polypharmacy (*yes*, *no*), and prevalent PIM use at baseline (*yes*, *no*). I repeated the matching process used in the main analysis for each subgroup and used the shortest follow-up period at which it was possible to include ≥ 100 events in all subgroups. However, this number of events was not available for the outcome "all-cause mortality" because the maximum follow-up period should not exceed one year. Therefore, subgroup analyses were only performed for the outcome "6-month all-cause hospitalization".

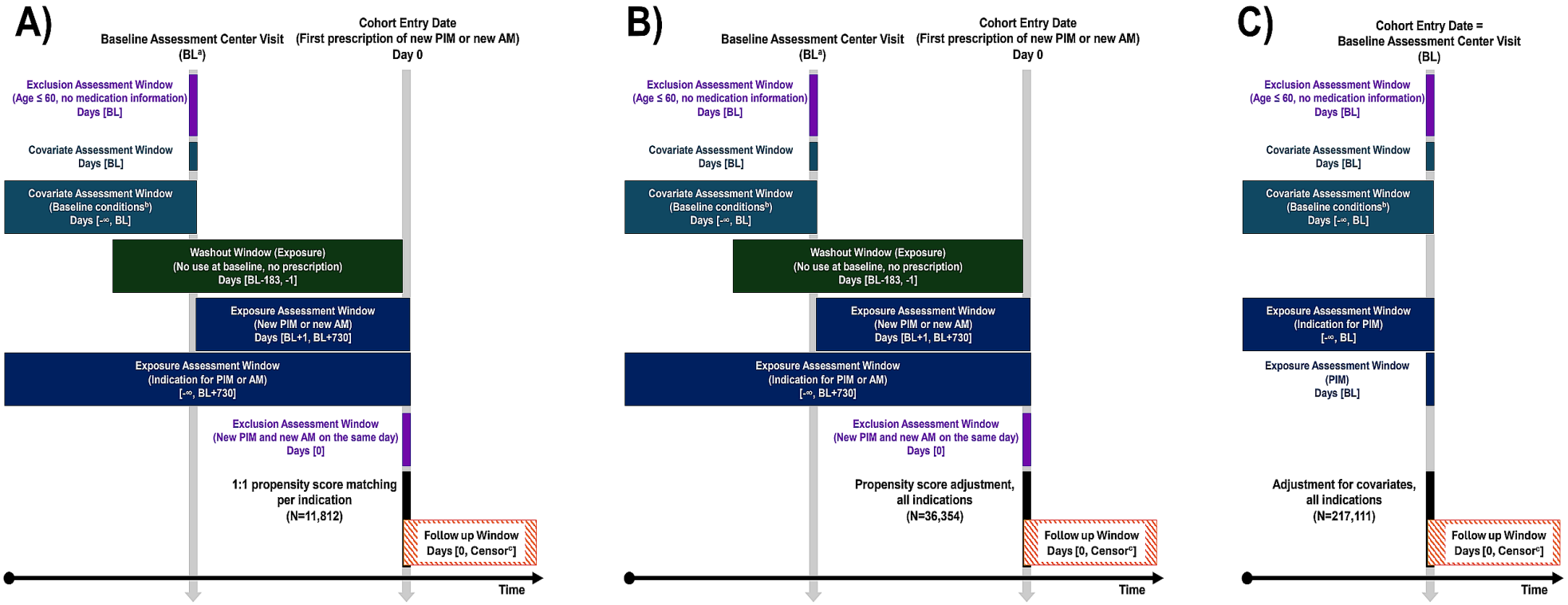

Figure 1. Visualization of the three study designs. Main analysis: active comparator propensity score matching per indication (A), bias demonstration analysis I: new user design with propensity score adjustment instead of matching by indication (B), bias demonstration analysis II: prevalent user design (C)

Abbreviations: AM, appropriate medication; BL, baseline assessment center visit; PIM, potentially inappropriate medication.

[a] Maximum time between baseline assessment center visit and cohort entry: 730 days.

[b] Diagnoses from hospital and primary care records were added to achieve complete information.

[c] At earliest of outcome or end of the follow-up period.

2.3 Factors associated with PIM use, medication underuse, and overuse in older adults in the German National Cohort

2.3.1 Data source

I conducted a cross-sectional study based on data from the baseline assessment visit of the NAKO, a large national, multi-center, population-based, prospective cohort study which recruited approximately 205,000 participants aged 19 to 74 years in 18 assessment centers between 2014 and 2019. Detailed methods have been published in another publication (Peters et al. 2022).

2.3.2 Study population

Out of 204,666 participants with available baseline data, I included those aged 60 to 74 years with available information on medication use, resulting in N=54,296 participants eligible for the main analysis (**Appendix 14**). Thereof, N=5,575 participants who properly and fully completed the NAKO vaccination data module without any warnings were included in the analysis on vaccination underuse. The upper age cut-off was determined by the inclusion criteria of the NAKO, and the lower age cut-off was chosen as a trade-off between fit of the population and sample size. Although the age cut-off of 65 years is more commonly applied, 60 years has also been used in previous research on medication quality among older adults (Degen et al. 2025; Xing et al. 2019; Zhou et al. 2024).

2.3.3 Data collection and variable definition

Socio-demographic information and lifestyle factors were collected through interviews and touchscreen questionnaires. Information about diseases was based on self-reported data, in which participants were asked whether they had ever been diagnosed with a specific condition by a physician. The Patient Health Questionnaire-9 (PHQ-9) was utilized to assess moderate to severe depressive symptoms (PHQ-9 sum scores 15-19 and ≥ 20, respectively). During physical examinations, functional assessments (e.g., blood pressure measurement) were conducted, and blood samples were collected.

Medication use was assessed by computer-assisted, face-to-face interviews. Participants were asked to bring packages of the medications they had used in the past seven days, and if they forgot to bring their packages, they were called by telephone after the study center visit. In the interview, additional information was collected for each medication regarding the type of prescription (prescribed, recommended by a physician, or not prescribed) and the type of use (regular or as needed).

Vaccination coverage was assessed through documented administered vaccinations according to the participants' vaccination booklets and additional questionnaires.

2.3.4 Assessment of medication problems: overuse, underuse, and PIM use

The three medication problems PIM use, underuse, and overuse were assessed as dichotomized exposures based on the 2024 version of the FORTA list, which classifies medications into four categories, encompassing A (indispensable), B (beneficial), C (questionable), and D (avoid) (Pazan et al. 2025).

Specifically, the medication problems were defined as follows:

1. Overuse: Any FORTA medication without an appropriate indication.
2. Underuse: Any untreated FORTA indication. To determine the need for pharmacotherapy, I also incorporated clinical biomarkers (e.g., HbA_{1c} levels in participants with diabetes), as detailed in **Appendix 15**.
3. PIM: Any medication classified as C or D taken by participants with the corresponding FORTA indication.

Out of 23 common geriatric indications listed in the FORTA list (Pazan et al. 2025), I included 17 indications, predominantly based on self-reported lifetime history of diagnoses and occasionally complemented by additional criteria such as diagnostic tools. **Appendix 15** lists the detailed definitions and assessments in the NAKO. Acute bacterial infections, constipation, nausea, and vomiting were not included since these are no chronic diseases requiring long-term medication. Anemia, bipolar disorder, behavioral/psychological symptoms of dementia, and urinary incontinence were not included because relevant information about these conditions was not available. Insomnia requiring medical treatment could not be distinguished from other types of insomnia and was therefore also excluded from the underuse assessment. To mitigate the risk of misclassification of over- and underuse, I additionally considered possible alternative

medications and indications not included in the FORTA list. **Appendix 16** provides the full list of potential medications for these 17 indications, as well as the assessed vaccinations.

Only pneumococcal and annual influenza vaccinations were included in the vaccination assessment, since Herpes zoster, coronavirus disease 2019 (COVID-19), and respiratory syncytial virus (RSV) vaccines were not part of national vaccination recommendations for older adults during the entire recruitment period (2014-2019). The recommendations for Herpes zoster, COVID-19, and RSV vaccinations were announced later in 12/2018, 12/2020, and 04/2025, respectively (Falman et al. 2025; Ständige Impfkommission (STIKO) 2018; Vygen-Bonnet et al. 2021). Given the small proportion of participants with complete available vaccination information (10.3%), the underuse of vaccines was reported separately from underuse of other medications. I explored the representativeness of this subpopulation with available vaccination data by comparing the baseline characteristics of the included subsample with the baseline characteristics of those not included and observed no major differences (**Appendix 17)**.

2.3.5 Statistical analyses

Multivariable logistic regression models were used to identify factors associated with PIM use, underuse, and overuse of medications as dependent variables. Results were presented as odds ratios (ORs) with 95% CIs. Overall, 32 factors encompassing sociodemographic/-economic factors, study center, lifestyle factors, and diseases were selected based on subject-matter knowledge. I assessed multicollinearity and model stability with the variance inflation factor. After exclusion of self-perceived general health status, no variable had a variance inflation factor ≥ 8. Therefore, the full model was adjusted for 31 independent variables, which are listed in **Appendix 17**. Additionally, I computed models only adjusted for age, sex, and study center.

To handle missing covariates, I utilized multiple imputation with the fully conditional specification method (van Buuren 2007) with 20 burn-in iterations and created 5 imputed datasets. Indications for medication use were not imputed. Instead, the absence of the indication was assumed if this information was missing. No covariate had more than 30% of missing values. The proportions of missing values for imputed covariates (**Appendix 18**) and medical indications (**Appendix 19**) are shown in the appendix.

In detail, missing patterns were explored visually prior to imputation. Since the grid display yielded an arbitrary missing pattern and potential sources of deviations from a missing completely at random (MCAR) occurrence, I subsequently utilized an expanded imputation model under the missing at random assumption which explicitly incorporated identified sources for non-MCAR (sex, income, and grip strength) and additional auxiliary variables (e.g., HDL blood levels as proxy for metabolic health) to mitigate potential risks of bias due to deviations from MCAR. Specifically, the following variables were included in the imputation model: age, sex, study center, income, years of education, social network index, body-mass index, daily alcohol consumption, smoking status and age at smoking cessation, self-perceived general health status, fractures since aged 50 years, pain in last four weeks, headache, gout, arthritis, osteoarthritis, self-reported lifetime history of depression, stroke, coronary heart disease, myocardial infarction, asthma, COPD, peripheral vascular disease, lifetime history of cancer, heart failure, atrial fibrillation, cardiac arrhythmia, epilepsy, Parkinson's disease, self-perceived memory difficulties, planned or prior physician consultation for cognitive impairment, reflux, peptic ulcer, insomnia, osteoporosis, diabetes, hypertension, HDL, creatinine, HbA_{1c}, systolic blood pressure, diastolic blood pressure, grip strength.

The goodness of fit of the imputation model was thoroughly assessed through trace plots and comparison of distributions before and after imputation, in accordance with recommended practice (Abayomi et al. 2008; van Buuren 2018), indicating adequate model performance. To derive analytical outcomes, I aggregated all 5 imputed datasets using the SAS procedure "PROC MIANALYZE".

I used SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC, USA) for the statistical analyses. All statistical tests were two-tailed, with a significance level set at $\alpha = 0.05$. P-values were adjusted for multiple testing using the false discovery rate (FDR) (Benjamini et al. 1995) per model and outcome.

2.4 Cancer co-medication quality in older patients with polypharmacy: a large randomized trial testing a medication review versus usual care

2.4.1 Trial registration and reporting

This investigation was reported according to the Consolidated Standards of Reporting Trials (CONSORT) guideline (Hopewell et al. 2025) and follows the published protocol of the

"Optimization of polypharmacy in geriatric oncology" (OPTIMAL) trial (Schöttker et al. 2023), which had additionally been registered in the German Clinical Trials Register (no. DRKS00031024).

2.4.2 Trial design, inclusion, and exclusion criteria

The parallel-group, randomized, controlled OPTIMAL trial assesses the efficacy of a pharmacist-led medication review in older cancer patients exposed to polypharmacy during inpatient rehabilitation. The study is single-blinded, as only patients were fully blinded to the allocation. The study was approved by the Ethics Committee of the Medical Faculty, Heidelberg University (08/02/2023) and adhered to the Declaration of Helsinki.

Individuals aged ≥ 65 years, exposed to polypharmacy (≥ 5 regularly used drugs), with a cancer diagnosis or recurrence (22 common cancer sites) within 5 years before the beginning of their rehabilitation, and an expected inpatient stay of 3 weeks in one out of 10 collaborating German rehabilitation clinics were eligible for inclusion. Exclusion criteria encompassed no written informed consent, no medication-related problem at baseline (FORTA score = 0), insufficient mental and physical capabilities to fill out questionnaires, insufficient knowledge of the German language, and missing information needed to conduct the medication review or to assess the participant's quality of life at admission. Specifically for this investigation, I further excluded trial participants without information from a checklist about medication changes made by the rehabilitation physician. This checklist was introduced approximately 5 months after the start of recruitment (on 26/10/2023), when the study team noticed that the routine discharge documentation was insufficiently detailed.

2.4.3 Recruitment and randomization

A randomization list with 1:1 allocation to the medication review and usual care group was prepared by the principal investigator in the coordinating center (Division of Clinical Epidemiology of Early Cancer Detection, German Cancer Research Center, Heidelberg, Germany) before the start of the study with *randomizer.at*, using permuted blocks of random sizes stratified by rehabilitation clinic. Study materials were labeled with the randomization IDs

and shipped to the rehabilitation clinics. Between June 2023 and September 2025, rehabilitation physicians recruited participants recently after their admission to the rehabilitation clinic and randomized them by picking the pre-labeled study materials. Except for the study pharmacists in the coordinating center, no study personnel or participant had access to the allocation sequence.

2.4.4 First study visit and collection of baseline information

During the first medical appointment with their treating rehabilitation physician, participants provided written informed consent and received a baseline questionnaires about socio-demographic information, lifestyle factors, medical history (including over-the-counter medication), current symptoms (e.g., pain, insomnia, nausea), medication use, and validated questionnaires for social support (Duke-UNC Functional Social Support Questionnaire (DUFSS-5) (Saracino et al. 2015)), physical activity (Rapid Assessment of Physical Activity (RAPA) tool (Topolski et al. 2006)), frailty (FRAIL scale (Morley et al. 2012)), depression (Geriatric Depression Scale (GDS) (Stiles et al. 1998)), and quality of life (QLQ, European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Aaronson et al. 1993)).

Additionally, the study physicians provided relevant cancer-related factors (ICD-10 code, stage, and primary treatment), medication use, and medical diagnoses through a checklist and/or copies of electronic health records. All study documents were sent to the coordinating center.

2.4.5 FORTA-based medication review

After receiving the study documents, a study pharmacist in the coordinating center created a complete list of medical diagnoses and medication use, compiling the information from physicians and patients. The pharmacist subsequently conducted the medication review for the intervention group using the 4th version of the FORTA list (Pazan et al. 2022b), which was the most recent version at the time of study initiation (last updated in 2021).

The medication review identified the three types of medication problems and assigned points as follows:

1. PIM (2 points per drug): Medications classified as C (questionable) or D (avoid) for a specific indication of the 30 FORTA indications were recorded as PIM.

2. Overuse (1 point per drug): For all remaining medications, the pharmacist reviewed whether the medication was indicated to treat an additional indication not included in the 30 FORTA indications. Appropriate use for medications not listed in the FORTA list was determined according to clinical guidelines. Each medication in the absence of an appropriate indication was recorded as overuse.

3. Underuse (1 point per untreated indication or vaccination underuse): Each untreated FORTA indication was recorded as medication underuse. In addition, I assessed underuse of vaccines for Herpes zoster, pneumococcus, influenza (in the last 12 months), and COVID-19 (vaccination or infection in the last 12 months) by self-reported information.

The total FORTA score combines the points for PIM, underuse, and overuse. I calculated it both with and without points for vaccination underuse. For participants allocated to the medication review, the pharmacist created an advisory letter with recommendations to switch PIM to AM for the respective indication classified as A (indispensable) or B (beneficial) by the FORTA list. Moreover, recommendations to initiate AM (with FORTA classification A or B) for untreated indications, to conduct missing vaccinations, and to discontinue medications classified as "overuse" were listed in the letter.

All proposed new drugs were checked for potential drug-drug interactions and contraindications, and recommendations were adapted as needed. Additional advice was included where appropriate (e.g., dosage adjustments, monitoring of specific parameters).

The entire process of medication review and recommendation letter creation was automated with a SAS code. As the study pharmacist, I checked the automatically generated recommendation letters for plausibility, contraindications, and potential drug-drug interactions. I used mistakes made by the initial SAS code to improve it over the course of the study. After about 100 medication reviews were performed, the SAS code was not changed anymore.

For participants allocated to the usual care group, I created a sham advisory letter stating that no medication recommendations were suggested.

The final version of the SAS code was used to automatically calculate the FORTA score and its sub-scores at rehabilitation admission and discharge for both the intervention and control groups.

2.4.5.1 Second study visit and documentation of medication changes in the checklist

Study physicians were free to decide which recommendations they would like to accept and/or to discuss with the patient during the 2nd study visit, which took place in the last week of rehabilitation. Accepted changes could be implemented directly by the rehabilitation physician or communicated to the patient's GP via the discharge letter. Each accepted and not accepted recommendation of the advisory letter needed to be documented in a checklist, along with updated information on medical diagnoses and medication use at rehabilitation discharge.

Rehabilitation physicians were allowed to make medication changes as part of usual care for all trial participants. This fact was used to blind the study participants. Physicians informed the participants about possible medication changes, explaining that any of these could result either from their own medical judgment as part of usual care or from allocation to the intervention group of the OPTIMAL trial. However, the true reason was not revealed. Not discussing medication changes could imply either optimal medication quality or assignment to the usual care group. The exact wording for the discussion with the patients was specified in the advisory letter and sham letter to avoid accidental unblinding of participants. The physicians were instructed to conduct a second study visit with all study participants, even if they received the sham letter, and to document that the meeting took place. This should ensure that all study participants were treated equally by study physicians and remained blinded to the intervention.

2.4.5.2 After rehabilitation clinic discharge

The pharmacist in the coordinating center used the medication and diagnoses information from the checklist to calculate the FORTA score at rehabilitation discharge. If the GP was asked to make the medication changes or to administer vaccinations in the discharge letter, these were treated as implemented recommendations for the FORTA score calculation at discharge.

I also calculated the FORTA score in the usual care group to assess potential learning effects of physicians, as specified in the trial protocol (Schöttker et al. 2023). However, these were not observed.

2.4.5.3 Outcomes analyzed in this investigation

As the follow-up of the OPTIMAL study is still ongoing, the primary endpoint "Quality of life at 8-month follow-up" will be published later. This investigation addresses the predefined

secondary endpoints of medication quality until rehabilitation discharge. The main outcome of interest is the change in total FORTA score points from rehabilitation admission to discharge. Further secondary endpoints include changes in FORTA sub-scores for and proportions of PIM use, underuse, overuse, and any of the aforementioned medication problems.

The frequency and acceptance rates of recommendations to reduce overuse and PIM use per medication class and to reduce underuse per indication in the intervention group were calculated based on the returned checklists. Specifically for overuse and underuse, patients sometimes forgot to mention a previous disease or a medication at baseline, which turned out while discussing medication changes during the second study visit. Such resolved medication problems were not directly attributable to the intervention. Therefore, I only counted resolved medication problems attributable to the intervention (accepted switch, drug initiation, or discontinuation) as accepted.

2.4.6 Statistical analysis

Since the FORTA (sub-)scores at discharge appeared to be not normally distributed (**Appendix 20**) and the changes in the FORTA (sub-)scores between admission and discharge were approximately normally distributed (**Appendix 21**), I used the Wilcoxon rank sum test as the primary test statistic for FORTA (sub-)scores at discharge and the t-test for changes in FORTA (sub-)scores. To compare the proportions of patients exposed to PIM, medication overuse, underuse, and any of these three medication problems at discharge, Chi^2 tests were used. If counts for an exposure were < 5, I used Fisher's exact test instead of the Chi^2 test. A significance level of $\alpha = 0.05$ was applied for all statistical tests. As the outcomes investigated in my project were secondary endpoints of the OPTIMAL trial, the results should be regarded as exploratory rather than confirmatory.

In a sensitivity analysis, I estimated β coefficients with 95% CIs for the treatment group allocation with respect to the change in FORTA (sub-)scores from admission to discharge using a multivariable adjusted linear regression model. Linearity, independence, homoscedasticity, and multicollinearity were assessed prior to the analysis, with no violation detected. I adjusted the model for 38 covariables, including the baseline FORTA score or the respective sub-score, age, sex, education, partnership, social support, body mass index (BMI), alcohol consumption, physical activity, smoking status, cancer site, cancer stage, previous cancer therapies, frailty,

global quality of life, depressive symptoms, and 20 common indications as single covariates (as listed in **Appendix 22**). I assessed multicollinearity and model stability through the VIF, and no variable had a VIF > 3.8.

I used SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC, USA) for the statistical analyses. I applied multiple imputation with the Markov Chain Monte Carlo method to impute missing covariate and endpoint values stratified by trial group, creating 20 imputed datasets, which were subsequently aggregated using the SAS procedure "PROC MIANALYZE". The FORTA score at discharge was missing for N=25 (5.6%) of the study participants. The cancer stage was unknown for 12.4% of study participants, and no other covariate had more than 2.5% of missing values (**Appendix 22**). All variables of the multivariable linear regression model were used for the imputation model, and it was extended for the rehabilitation clinic and the FORTA sub-scores at baseline.

This investigation was analyzed with an intention-to-treat approach, with every patient who was correctly included in the trial analyzed according to the group to which they were randomized. Additional per-protocol analyses were conducted, excluding all participants without a documented 2nd study visit and all participants assigned to the intervention group who did not return a discharge checklist. Subgroup analyses were conducted by rehabilitation clinic, sex, and age groups (65-74 and ≥ 75 years). Clinics that recruited fewer than 50 patients were combined. All statistical analyses were prespecified in the statistical analysis plan. No interim analyses were conducted.

2.4.7 Patient involvement of potential contamination bias

Relevance and appropriateness of the study have been discussed with and confirmed by a representative of a patient advocacy group (Deutsche ILCO e.V.) prior to study initiation.

3 Results

3.1 Systematic review, meta-analysis, and meta-regression of RCTs investigating the effect of a medication review on rehospitalization and all-cause mortality in hospitalized patients

3.1.1 Study selection

The PRISMA flow chart describing the study selection process is depicted in **Appendix 23**.

Out of the 25 RCTs included in the Cochrane Review (Bülow et al. 2023), which covered the literature search up to 17 January 2022, I included publications and database entries of 19 trials in my systematic review and meta-analysis (Adam et al. 2019; Alassaad et al. 2014; Alassaad et al. 2015; Bladh et al. 2011; Blum et al. 2021; Bonetti et al. 2018; Bonnerup et al. 2020; Crowley et al. 2020; Curtin et al. 2020; Curtin et al. 2019b; Dalleur et al. 2014; Farris et al. 2014; Gallagher et al. 2011; Gillespie et al. 2009; Graabæk et al. 2015; Graabæk et al. 2019; Graabæk et al. 2014; Gustafsson et al. 2017; Gustafsson et al. 2018; Lea et al. 2020; Lenssen et al. 2018; Lisby et al. 2018; Lisby et al. 2010; Lovheim 2021; Mowe 2020; Nielsen et al. 2013; Nielsen et al. 2017; O'Mahony et al. 2020; Rasmussen et al. 2019; Ravn-Nielsen 2019; Ravn-Nielsen et al. 2018; RWTH Aachen University 2017; Sallevelt et al. 2022; Scullin et al. 2007; Sjölander et al. 2019; University Hospital of Zurich 2022; Wallerstedt 2015; Zerah et al. 2021). Additionally, I evaluated 5 trials excluded from the previous review in the full-text screening and identified one eligible trial for my review (Pope et al. 2011).

Finally, I screened 1,922 records obtained from four databases published between 01 January 2022 and 17 January 2024. After removal of duplicates and ineligible publication types, I included 1,131 records in the title and abstract screening. Thereof, 86 articles were eligible for full-text screening, and publications related to 6 trials met the inclusion criteria (DTB Team 2023; Ferro-Uriguen et al. 2023; Ferro-Uriguen et al. 2022; Grischott et al. 2023; Johansen et al. 2022a; Johansen et al. 2022b; Kim et al. 2023; Robinson et al. 2023; Schapira et al. 2022; Shah et al. 2022; Vasilevskis et al. 2023; Visade et al. 2022). In total, 26 trials were included in this

systematic review and meta-analysis. The full list of trials excluded during the full-text screening, along with the reasons for exclusion, is provided in **Appendix 24**.

3.1.2 Description of included studies

The trials included in my review and meta-analyses were published between 2007 and 2023. Out of the 26 included trials, 22 trials with a total of 12,350 participants contributed to the meta-analyses on all-cause mortality, and 24 trials including 12,539 participants contributed to the meta-analyses on rehospitalization. The follow-up period lasted from 30 days to 20 months. **Table 1** summarizes the characteristics of the included trials and presents the RRs calculated for the outcomes of interest. Additional trial characteristics used for the subgroup meta-analyses are provided in **Appendix 25–Appendix 26**.

3.1.3 Risk of bias assessment

Appendix 27 presents the results of the risk of bias assessment. All trials except one (Grischott et al. 2023) exhibited a high risk of performance bias due to a lack of blinding of participants and personnel. Furthermore, in all except two trials (Blum et al. 2021; Grischott et al. 2023), a high risk of contamination bias due to potential improvements in drug prescribing quality in the control group through learning effects was observed. Other sources of bias were rare.

The funnel plots yielded no evidence for publication bias in trials on all-cause mortality (Egger's test: p=0.303) (**Appendix 28)** or rehospitalization (Egger's test: p=0.465) (**Appendix 29**).

Table 1. Study characteristics of all studies included in the systematic review and meta-analysis

First author, year (References)	Country	Follow-up time[a]		Number of participants[b]	Deaths[c]	Age[d,e]	Sex	Risk ratio (95% CI)	
		Mortality	Rehospitalization				% male	Mortality	Rehospitalization
Bladh 2011 (Bladh et al. 2011; Wallerstedt 2015)	Sweden	6 months	6 months	400 (199; 201)	15 (10; 5)	IG: 81 (72-87), CG: 82 (75-86)[d]	39	1.52 (0.89; 2.58)	0.96 (0.76; 1.20)
Blum 2021 (Adam et al. 2019; Blum et al. 2021; Crowley et al. 2020; Insel Gruppe AG and University Hospital Bern 2020; Sallevelt et al. 2022; Zerah et al. 2021)	Switzerland, Netherlands, Ireland, Belgium	12 months	12 months	2,008 (936; 1,045)	28 (7; 21)	79 (74-84)[d]	56	0.91 (0.75; 1.13)	0.94 (0.85; 1.04)
Bonetti 2018 (Bonetti et al. 2018)	Brazil	30 days	30 days	133 (66; 67)	7 (4; 3)	IG: 65 (10), CG: 65 (13)[e]	Unkn.	0.68 (0.20; 2.29)	0.59 (0.18; 1.92)
Bonnerup 2014 (Bonnerup et al. 2020; University of Aarhus 2013)	Denmark	3 months	-	375 (188; 187)	Unkn.	IG: 72.4, CG: 72.8[e]	Unkn.	1.17 (0.60; 2.30)	-
Curtin 2020 (Curtin et al. 2020; Curtin et al. 2019b; O'Mahony 2018)	Ireland	3 months	3 months	130 (65; 65)	10 (4; 6)	IG: 84.5 (5.6), CG: 85.7 (5.9)[e]	38	0.67 (0.35; 1.27)	1.74 (0.62; 4.89)
Dalleur 2014 (Dalleur et al. 2014)	Belgium	12 months	-	158 (77; 81)	0	IG: 84 (81-87), CG: 86 (81-89)[d]	37	1.05 (0.42; 2.66)	
Farris 2014 (Farris et al. 2014)	USA	3 months	3 months	945 (629; 316)[f]	Unkn.	61 (12.2)[e]	Unkn.	1.22 (0.51; 2.91)	1.07 (0.78; 1.47)
Ferro-Uriguen 2022 (Ferro-Uriguen 2022; Ferro-Uriguen et al. 2023; Ferro-Uriguen et al. 2022)	Spain	-	3 months	114 (57; 57)	33 (18; 15)	87.7 (5.7)[e]	42		0.91 (0.46; 1.79)

First author, year (References)	Country	Follow-up time[a]		Number of participants[b]	Deaths[c]	Age[d,e]	Sex	Risk ratio (95% CI)	
		Mortality	Rehospitalization				% male	Mortality	Rehospitalization
Gallagher 2011 (Gallagher et al. 2011)	Ireland	6 months	6 months	400 (200; 200)	18 (10; 8)	IG: 74.5 (71-80), CG: 77 (71-82)[d]	47	0.91 (0.51; 1.61)	1.04 (0.78; 1.37)
Gillespie 2009 (Alassaad et al. 2014; Alassaad et al. 2015; Gillespie et al. 2009)	Sweden	12 months	12 months	400 (199; 201)	27 (13; 14)	IG: 86.4 (4.2), CG: 87.1 (4.1)[e]	41	0.94 (0.73; 1.22)	0.95 (0.80; 1.13)
Graabaek 2019 (Graabæk et al. 2019; Graabæk et al. 2014)	Denmark	6 months	30 days	600 (400; 200)[g]	7 (6; 1)[h]	IG: 74 (69-80), CG: 75 (70-82)[d]	51	0.75 (0.41; 1.38)	0.79 (0.61; 1.02)
Grischott 2018 (Grischott et al. 2023; Grischott et al. 2018; University Hospital of Zurich 2022)	Switzerland	6 months[i]	6 months	609 (304; 305)	0	IG: 77.77 (8.88), CG: 77.12 (8.31)[e]	51	-[j]	1.07 (0.82; 1.40)[k]
Gustafsson 2017 (Gustafsson et al. 2017; Gustafsson et al. 2018; Lovheim 2021; Sjölander et al. 2019)	Sweden	6 months	6 months	460 (230; 230)	31 (18; 13)	83.1 (6.6)[e]	36	1.32 (0.95; 1.84)	0.94 (0.74; 1.19)
Johansen 2018 (Johansen et al. 2022a; Johansen et al. 2022b; Johansen et al. 2018; University of Tromso 2021)	Norway	12 months	12 months[l]	516 (257; 259)	13 (5; 8)	IG: 83.3 (6.4), CG: 83.0 (6.3)[e]	IG: 38, CG: 46	0.97 (0.69; 1.37)	0.77 (0.48; 1.25)
Lea 2020 (Lea et al. 2020; Mowe 2020)	Norway	20 months	12 months	399 (200; 199)	11 (5; 6)	79[d]	45	0.69 (0.53; 0.91)	0.88 (0.76; 1.03)
Lenssen 2018 (Lenssen et al. 2018; RWTH Aachen University 2017)	Germany	-	12 months	61 (31; 30)	0	IG: 75.9 (6.9), CG: 79.5 (8.6)[e]	40	-	0.91 (0.55; 1.49)
Lisby 2010 (Lisby et al. 2010)	Denmark	3 months	3 months	100 (50; 50)	0	IG: 80.2, CG: 78.2[e]	39	1.60 (0.56; 4.56)	1.00 (0.59; 1.69)
Lisby 2015 (Lisby et al. 2018)	Denmark	3 months	3 months	108 (53; 55)	1 (0; 1)	80.5[e]	29	1.04 (0.22; 4.91)	1.27 (0.66; 2.46)

First author, year (References)	Country	Follow-up time[a]		Number of participants[b]	Deaths[c]	Age[d,e]	Sex	Risk ratio (95% CI)	
		Mortality	Rehospitalization				% male	Mortality	Rehospitalization
Nielsen 2017 (Nielsen et al. 2017)	Denmark	12 months	12 months	593 (202; 391)[m]	Unkn.	73.1 (12.7)[e]	48	1.09 (0.71; 1.69)	0.98 (0.79; 1.21)
O'Mahony 2020 (Dalton et al. 2020a; Dalton et al. 2020b; Lavan et al. 2019; O'Mahony et al. 2020)	Belgium, Ireland, Spain, Italy, Scotland, Iceland	3 months	3 months	1,537 (772; 765)	Unkn.	78 (72-84)[d]	53	1.05 (0.73; 1.52)	1.04 (0.90; 1.21)
Pope 2011 (Pope et al. 2011)	Ireland	6 months	6 months	225 (110; 115)	Unkn.	IG: 83.3, CG: 82.5[e]	35	1.62 (0.79; 3.29)	1.74 (0.66; 4.63)
Ravn-Nielsen 2018 (Rasmussen et al. 2019; Ravn-Nielsen 2019; Ravn-Nielsen et al. 2018)	Denmark	6 months	6 months	1,467 (995; 503)[n]	Unkn.	BI: 72 (63-87), EI: 71 (63-79), CG: 83 (65-80)[e]	54	0.97 (0.70; 1.34)	0.88 (0.78; 0.99)
Schapira 2022 (Schapira et al. 2022)	Argentina	6 months	30 days	249 (120; 120)	0	IG: 85.9 (6.6), CG: 85.4 (6.7)[e]	28	0.65 (0.44; 0.95)	0.52 (0.33; 0.82)
Scullin 2007 (Scullin et al. 2007)	Northern Ireland	12 months	12 months	762 (371; 391)	Unkn.	70.1[e]	47	0.93 (0.69; 1.25)	0.86 (0.73; 1.03)
Vasilevskis 2019 (DTB Team 2023; Kim et al. 2023; Shah et al. 2022; Vasilevskis et al. 2023; Vasilevskis et al. 2019)	USA	3 months[o]	3 months[o]	372 (186; 186)	1 (0; 1)[p]	76.2 (10.7)[e]	38	0.90 (0.39; 2.08)	0.78 (0.64; 0.95)
Visade 2022 (Lille Catholic University 2019; Visade et al. 2022)	France	-	30 days	108[q] (54; 54)	4 (3; 1)	IG: 87.5, CG: Unkn.[e]	25	-	1.87 (0.67; 5.18)

Abbreviations: BI, basic intervention in three-armed trial; CG, control group; CI, confidence interval; EI, extended intervention in three-armed trial; IG, intervention group; Unkn., unknown.

[a] Maximum follow-up period.
[b] Number of participants randomized: total (IG; CG).
[c] Number of participants died during index hospitalization: total (IG; CG).
[d] Median (interquartile range, if reported).
[e] Mean (standard deviation, if reported).
[f] BI: 1,077; EI: 2,220 (Farris et al. 2014).
[g] BI: 200; EI: 200 (Graabæk et al. 2019).
[h] BI: 1; EI: 5 (Graabæk et al. 2019).
[i] The reported data were not usable for meta-analysis.
[j] Number of cases not reported.
[k] Adjusted for cluster randomization with an intra-cluster coefficient (ICC) = 0.02. A sensitivity analysis with an ICC = 0.0103 did not change the RR and had a negligible impact on the 95% CI (0.80; 1.36).
[l] Rehospitalization was not reported as a dichotomous outcome at 12 months follow-up, and hence, the data were not usable for meta-analysis. The reported data from the 30-day follow-up were usable for meta-analysis.
[m] Prospective period: 404 participants randomized (202; 202). Retrospective period: 1,142 participants randomized (189 to CG, 953 to no enrolment) (Nielsen et al. 2013).
[n] BI: 498; EI: 497 (Ravn-Nielsen et al. 2018).
[o] After discharge from the post-acute care facility, where participants stayed for 1-90 days (Vasilevskis et al. 2023).
[p] During the initial hospitalization (Vasilevskis et al. 2023).
[q] Initially, 109 patients were randomized. One patient withdrew consent after randomization, but it is not reported whether this patient was allocated to IG or CG (Visade et al. 2022).

3.1.4 Effect of a medication review on all-cause mortality in hospitalized patients

In the meta-analysis including all trials, I found a pooled RR of 0.95 (95% CI: 0.86; 1.04), p=0.244), indicating no significant decrease in all-cause mortality. The forest plot is depicted in **Figure 2**. I observed no statistical heterogeneity (I^2=0.0%). The certainty of evidence was moderate (**Table 2**).

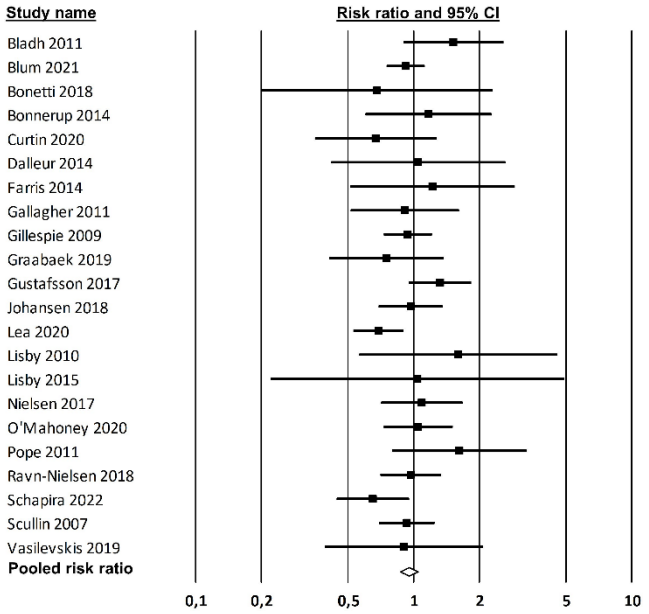

Figure 2. Random-effects meta-analysis of all included RCTs testing the effect of a medication review vs. usual care on all-cause mortality

However, I observed statistically significant effects in four subgroup meta-analyses (**Figure 4**). Statistically significant 14%, 19%, 13%, and 31% reductions in mortality were found in 9 trials with at least two patient contacts, in 10 trials with registry or primary care-based outcome assessment, in 7 trials with ≥ 4 medications as an inclusion criterion, and in 3 trials with patients taking less than 7 medications, respectively.

Close to statistical significance were a 10% and 9% reduction in mortality in meta-analyses including 7 trials with at least one year of follow-up (p=0.059) and 18 trials without restriction to specific diagnoses (p=0.051), respectively.

In univariate meta-regression models, four factors were statistically significantly associated with stronger results with respect to reduced mortality (p<0.05): medication reviews with a higher

number of recommendations per patient, mortality assessment via registries or primary care, a longer follow-up period, and no restriction of the study population to specific diagnoses (**Appendix 30**). Forward selection resulted in a multivariate model for the meta-regression of the two factors "mortality assessment method" and "number of recommendations per patient". In the multivariate model, the ß coefficients of both factors were slightly attenuated and narrowly missed statistical significance (p=0.073 and p=0.072, respectively) (**Appendix 31**).

3.1.5 Effect of a medication review on rehospitalization

The meta-analysis of all 24 trials demonstrated a statistically significant 8% reduced risk for rehospitalization through medication reviews compared to usual care (RR [95% CI]: 0.92 [0.88; 0.97], p=0.002), corresponding to a number needed to treat of 25 and 19 in a high-risk and very high-risk population, respectively. The forest plot is shown in **Figure 3**. I found no evidence for statistical heterogeneity (I^2=1.8%). The certainty of evidence was moderate (**Table 2**).

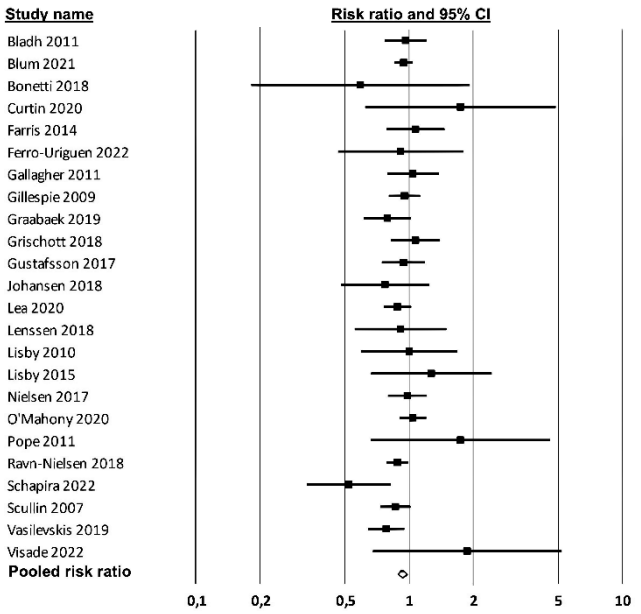

Figure 3. Random-effects meta-analysis of all included RCTs testing the effect of a medication review vs. usual care on rehospitalization

Compared with the main meta-analysis of all trials, a total of nine subgroup meta-analyses revealed stronger, similarly statistically significant effect estimates (**Figure 5**). However, only four subgroups showed a risk reduction >10%: 11 trials with ≥ 2 patient contacts (15% risk reduction), 3 trials involving patients with mean or median age of 70 to < 75 (12% risk

reduction), 9 trials with repeated medication reviews (11% risk reduction), and 5 trials with a follow-up period of up to 30 days (26% risk reduction). It is important to note that trials with 1 year of follow-up and trials with a mean or median age of 75 or older also yielded a statistically significant effect on the rehospitalization rate, but the magnitude of risk reduction was lower (8% and 7%, respectively).

Moreover, it should be noted that trials with only a single medication review, those conducted without pharmacists, and those including participants with a mean or median age below 70 years did not reduce the risk for rehospitalization.

Two factors were statistically significantly ($p<0.05$) associated with stronger results with respect to a lower rehospitalization rate in univariate meta-regression models: a higher number of patient contacts and involving pharmacists (**Appendix 30**). The multivariate model including both effect modifiers remained statistically significant for the number of patient contacts ($p=0.045$) but not for the involvement of pharmacists ($p=0.282$) (**Appendix 32**). These two factors were strongly entangled. All 12 trials in which the intervention comprised at least two patient contacts also involved pharmacists (**Appendix 33**).

Table 2. Strength of evidence (GRADE)

Outcome	Certainty assessment							Summary of findings		
	Participants (studies)	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95% CI)	Number needed to treat[b] High-risk	Number needed to treat[b] Very high-risk
Rehospitalization	12,539 (24 RCTs)	Some concerns[c]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	0.92 (0.88; 0.97)	25	19
Mortality (all-cause)	12,350 (22 RCTs)	Some concerns[d]	Not serious	Not serious	Serious[e]	None	⨁⨁◯◯ Low	0.95 (0.86; 1.04)	100	50

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, randomized controlled trials.

[a] Consistent with the Cochrane review by Bülow et al., the overall risk of bias was defined as the combination of selection, detection, and selective reporting bias. In cluster-randomized trials, additional design-specific biases were also considered (Bülow et al. 2023).

[b] The number needed to treat was calculated for a high-risk and a very high-risk population. Consistent with the Cochrane review by Bülow et al., the assumed risk with usual care based on published trial data and included the trials with the lowest and highest risk in the control group for both outcomes at 12-month follow-up (Bülow et al. 2023).

[c] Out of 24 trials, 10 trials had an overall low risk of bias. I assessed an overall high risk of bias in 14 trials. Thereof, 11 trials had an unclear risk of bias regarding at least one of the relevant domains. Downgraded once.

[d] Out of 22 trials, 11 trials had an overall low risk of bias. I assessed an overall high risk of bias in 11 trials. Notably, the categorization was based on unclear risk of biases due to insufficient information in all except one trial. Downgraded once.

[e] No statistically significant result. Downgraded once.

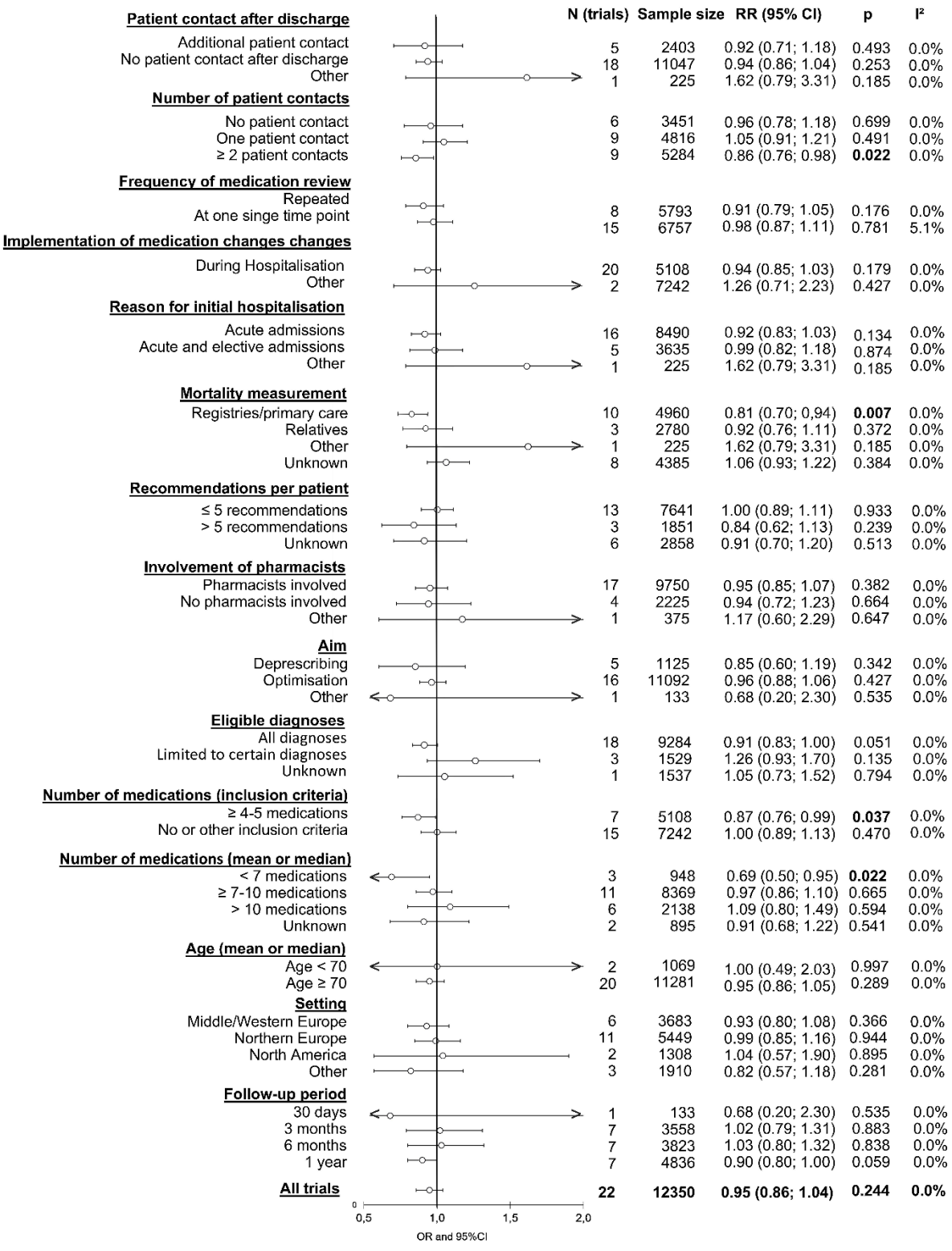

Figure 4. Subgroup random-effects meta-analyses according to methodological study differences for the effect of a medication review vs. usual care on all-cause mortality

Values printed in bold are statistically significant ($p<0.05$).

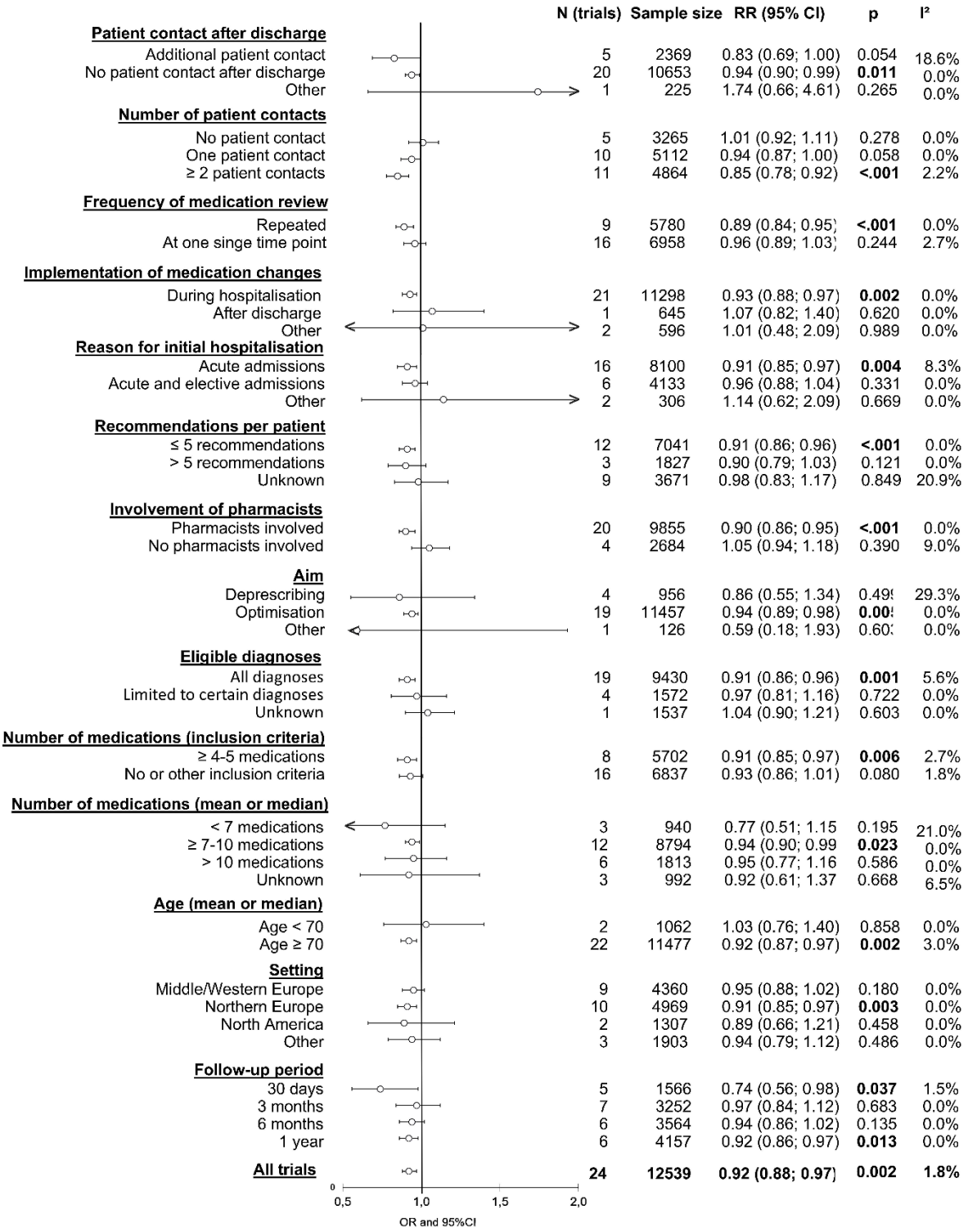

Figure 5. Subgroup random-effects meta-analyses according to methodological study differences for the effect of a medication review vs. usual care on rehospitalization

Values printed in bold are statistically significant ($p<0.05$).

3.2 Associations PIM use in older adults with mortality and hospitalizations and methodological challenges in pharmacoepidemiology

3.2.1 Characteristics of the study population

Table 3 presents the baseline characteristics of the study population (N=217,111). The median age was 64 (interquartile range (IQR): 62-66) years, slightly more participants were female (52.8%), and 43,307 (19.9%) participants used at least one PIM at baseline. Pain (70.4%), arterial hypertension (38.3%), and gastrointestinal symptoms (28.8%) were the most frequent conditions.

Out of 95,187 participants with available primary care data linkage, 9,351 (9.8%) received new PIM and 29,219 (30.7%) received new AM prescriptions within two years after baseline. After exclusion of 1,108 participants who were simultaneously prescribed with both new PIM and new AM on the same day, 8,243 new PIM and 28,111 new AM users were eligible for the propensity score matching. The main analysis included 11,812 participants, encompassing 5,906 new PIM and 5,906 new AM users matched in a 1:1 ratio (**Figure 6**). The comparison of patient characteristics between these two groups is shown in **Appendix 32,** and all were well balanced.

Table 3. Baseline characteristics of the analyzed UK Biobank population (N=217,111)

Characteristics	N (%)[a]	Median (IQR)[a]
Sociodemographic/ -economic factors		
Sex	-	-
Female	114,535 (52.8)	
Male	102,576 (47.2)	
Age		64 (62; 66)
Income[b]	-	-
Very low	77,606 (35.7)	
Low	70,875 (32.6)	
Middle	43,366 (20.0)	
High	20,417 (9.4)	
Very high	4,874 (2.2)	
Years of schooling	-	
≤ 10	114,282 (52.6)	

Characteristics	N (%)[a]	Median (IQR)[a]
11 – < 14	32,055 (14.8)	
≥ 14	70,774 (32.6)	
Lifestyle factors		
BMI *(kg/m²)*		27.0 (24.5; 30.0)
Physical activity *(MET-min/week)*		2,085 (1,036; 4,230)
Alcohol consumption *(g/day)*		15.0 (0.0; 31.6)
Smoking status	-	-
Never smoker	108,966 (50.1)	
Former smoker, years since quit		
< 5 years	72,868 (33.6)	
5-10 years	1,689 (0.8)	
11-15 years	1,387 (0.6)	
16-20 years	1,716 (0.8)	
> 20 years	12,597 (5.8)	
Current smoker[c]		
Regular	13,385 (6.2)	
Occasional	4,503 (2.1)	
Comorbidities	-	-
Diabetes		
No	201,703 (92.9)	
Untreated	4,345 (2.0)	
Treated with oral antidiabetics[d]	8,102 (3.7)	
Treated with insulin	2,961 (1.4)	
Arterial hypertension	83,050 (38.3)	
Stroke	6,090 (2.8)	
Myocardial infarction	14,591 (6.7)	
Heart failure	2,167 (1.0)	
Acute coronary syndromes	261,77 (12.1)	
Atrial fibrillation	5,573 (2.6)	
Asthma	27,876 (12.8)	
COPD	13,090 (6.0)	
Arthritis	38,406 (17.7)	
Osteoporosis	10,323 (4.8)	
History of fractures[e]	21,340 (9.8)	
Pain[f]	152,811 (70.4)	
Parkinson's disease	828 (0.4)	
Dementia	2,051 (0.9)	
Depression	25,383 (11.7)	
Bipolar disorder	802 (0.4)	
Insomnia	66,866 (30.8)	
Epilepsy	1,478 (0.7)	
Gastrointestinal symptoms[g]	62,429 (28.8)	
Incontinence	2,487 (1.1)	
Anemia	4,153 (1.9)	
History of cancer	28,003 (12.9)	
Overall health rating[h]	-	

Characteristics	N (%)[a]	Median (IQR)[a]
Excellent	3,2697 (15.0)	
Good	128,214 (59.1)	
Fair	47,051 (21.7)	
Poor	9,149 (4.2)	
Functional assessments	-	-
Systolic blood pressure *(mmHg)*		145.9 (19.8)
Diastolic blood pressure *(mmHg)*		82.4 (10.6)
Grip strength *(kg)*		30.0 (22.0; 39.0)
eGFR[i] *(ml/min/1.73m²)*		2 (1; 5)
Blood-based biomarkers	-	-
CRP *(mg/L)*		1.5 (0.8; 3.0)
HDL *(mmol/L)*		1.4 (1.2; 1.7)
LDL *(mmol/L)*		3.5 (2.9; 4.2)
HbA_{1c} *(mmol/L)*		36.3 (33.9; 39.0)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic equivalent of task; NSAIDs, non-steroidal anti-inflammatory drugs; UK, United Kingdom.

[a] Calculated from first imputed dataset.
[b] Average total household income before tax. Categories: very low: < 18,000£, low: 18,000-30,999£, middle: 31,000-51,999£, high: 52,000-100,000£, very high: > 100,000£.
[c] Regular smoking was defined as a minimum of one cigarette, cigar, pipe, etc. per day.
[d] Including parenteral formulations of glucagon-like-peptide-1 receptor agonists.
[e] Fractures in last five years.
[f] Combination of pain-related diagnoses (including migraine, other headache syndromes, facial pain, chronic back pain, chronic pain syndromes, arthritis, osteoarthritis, urinary tract stones, and gout) and self-reported pain in the last month.
[g] Including regular use of NSAIDs.
[h] Self-reported.
[i] Calculated based on the CKD-EPI equation.

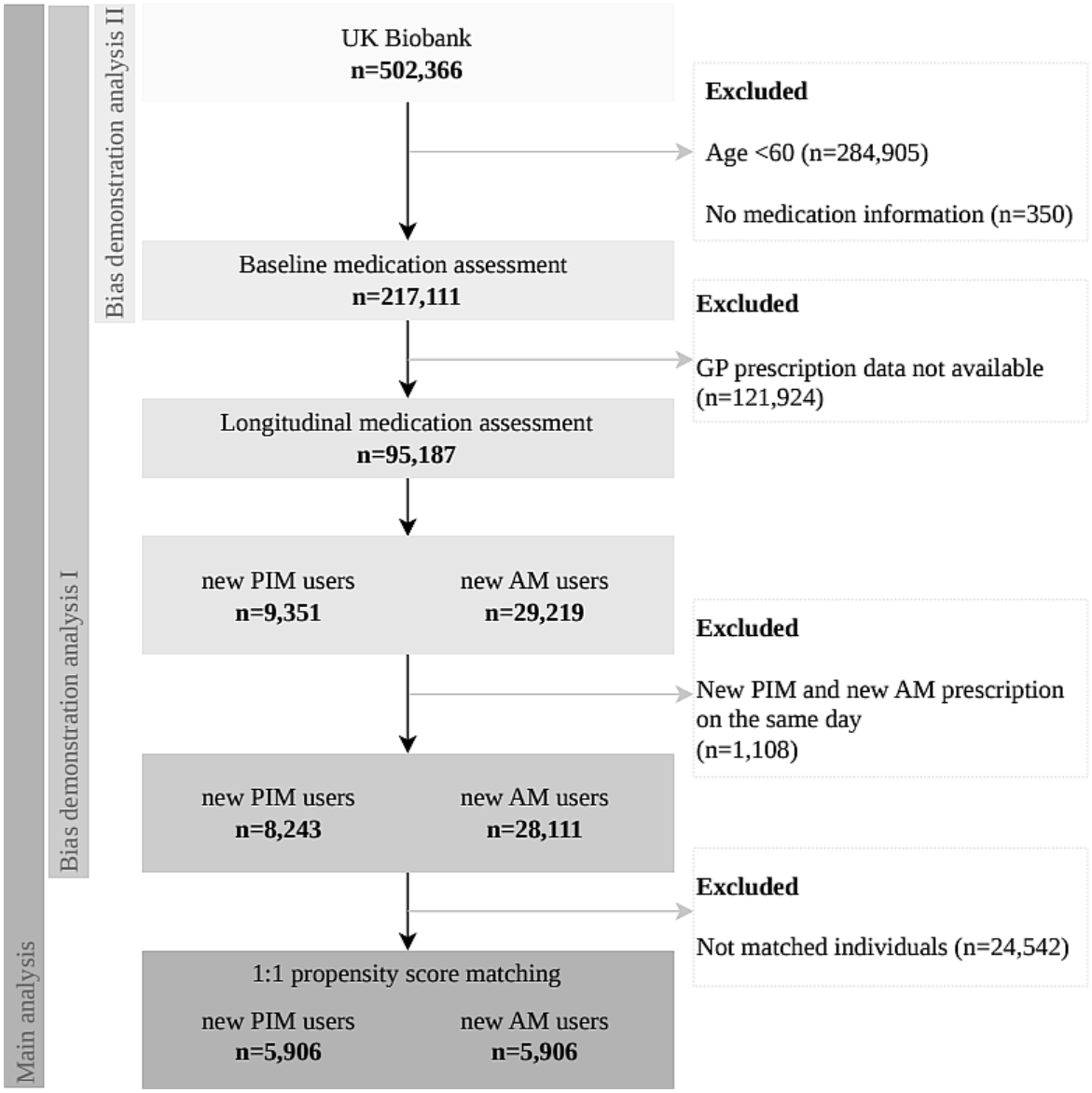

Figure 6. Flow chart describing the inclusion of the study population from the UK Biobank

Abbreviations: AM, appropriate medication; GP, general practitioner; PIM, potentially inappropriate medication; UK, United Kingdom.

3.2.2 Main analysis: 1:1 new user design with active comparator propensity score matching per indication

The associations of new PIM use versus new AM use with hospitalization and all-cause mortality are shown in **Table 4**. Within one month after cohort entry, 106 participants (0.9%) had a hospitalization and 132 patients (1.1%) died during the 1-year follow-up period. The risk for 1-month hospitalization was non-significantly increased by 20% (hazard ratio (HR) [95% CI]: 1.20 [0.76; 1.90]) and remained stable with 3 months of follow-up time. However, it decreased afterward: with follow-up times of one year or more, I observed no association. Similarly, I observed a non-significant 23% increased risk for 1-year all-cause mortality (HR [95% CI]: 1.23 [0.80; 1.89]) but detected no association between new PIM use and mortality with follow-up times of two years or more.

Table 4. *Main analysis*: The associations of new PIM use versus new AM use with hospitalization and all-cause mortality in 1:1 propensity-score matched population (N_{total}=11,812)

Outcome	N_{Event} (%)[a] PIM vs. AM users	HR (95% CI)[b]	p
Hospitalization			
1 month	55 (0.9) vs. 51 (0.9)	1.20 (0.76; 1.90)	0.439
3 months	102 (1.7) vs. 91 (1.5)	1.20 (0.88; 1.62)	0.247
6 months	247 (4.2) vs. 219 (3.7)	1.10 (0.90; 1.34)	0.344
1 year	422 (7.1) vs. 411 (7.0)	1.03 (0.87; 1.22)	0.748
2 years	764 (12.9) vs. 735 (12.4)	1.03 (0.91; 1.16)	0.678
3 years	1,130 (19.1) vs. 1,052 (17.8)	1.03 (0.92; 1.16)	0.550
4 years	1,486 (25.2) vs. 1,415 (24.0)	1.02 (0.91; 1.14)	0.722
All-cause mortality[c]			
1 year	69 (1.2) vs. 63 (1.1)	1.23 (0.80; 1.89)	0.347
2 years	106 (1.8) vs. 116 (2.0)	1.00 (0.72; 1.39)	0.998
3 years	153 (2.6) vs. 165 (2.8)	1.00 (0.76; 1.31)	0.985
4 years	202 (3.4) vs. 219 (3.7)	0.98 (0.78; 1.22)	0.866

Values in bold are statistically significant ($p<0.05$).
Abbreviations: AM, appropriate medication; CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication.

[a] First imputed dataset.
[b] New AM and new PIM users were matched based on a propensity score (1:1 ratio), including age, sex, income, years of education, body mass index, physical activity, alcohol consumption, smoking status, number of medications, comorbidities

(including arterial hypertension, diabetes, stroke, asthma, COPD, arthritis, heart failure, myocardial infarction, atrial fibrillation, acute coronary syndrome, epilepsy, depression, bipolar disorder, Parkinson's disease, dementia, chronic pain, osteoporosis, anemia, history of cancer), fractures in last 5 years, eGFR, HDL, LDL, HbA1c, CRP, systolic blood pressure, diastolic blood pressure, and grip strength.
[c] Three- and six-month mortality is not shown because the total number of events was < 100.
Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

Subgroup analyses were conducted for 6-month hospitalization since this was the shortest follow-up duration with ≥ 100 events in each subgroup. Although no subgroup analysis revealed statistically significant findings, I observed higher HR point estimates among females, participants aged 65 years or older, using PIM at baseline, and exposed to polypharmacy (**Table 5**).

Table 5. ***Main analysis in subgroups*****: The associations of new PIM versus new AM use with 6-month all-cause hospitalization in 1:1 propensity-score matched population stratified by age, sex, PIM use, and polypharmacy at baseline**

Subgroup	N_{total}	N_{Event} (%)[a] PIM vs. AM users	HR (95% CI)[b]	p
Age	11,212			
60-64	5,226	92 (3.5) vs. 94 (3.6)	1.01 (0.53; 1.91)	0.984
65-72	5,986	140 (4.7) vs. 117 (3.9)	1.27 (0.81; 1.99)	0.299
Sex	11,132			
Female	6,448	125 (3.9) vs. 101 (3.1)	1.14 (0.75; 1.73)	0.547
Male	4,684	108 (4.6) vs. 107 (4.6)	0.97 (0.55; 1.70)	0.914
PIM use at baseline	11,066			
Yes	3,476	80 (4.6) vs. 52 (3.0)	1.38 (0.67; 2.85)	0.372
No	7,590	150 (4.0) vs. 152 (4.0)	1.00 (0.72; 1.38)	0.983
Polypharmacy at baseline	10,992			
Yes	4,640	89 (3.8) vs. 73 (3.1)	1.34 (0.80; 2.25)	0.255
No	6,352	143 (4.5) vs. 133 (4.2)	1.08 (0.75; 1.56)	0.671

Values in bold are statistically significant (p<0.05).
Abbreviations: AM, appropriate medication; CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication.

[a] First imputed dataset.
[b] New AM and new PIM users were matched based on a propensity score (1:1 ratio), including age, sex, income, years of education, physical activity, body-mass-index, alcohol consumption, smoking status, number of medications, comorbidities (including arterial hypertension, diabetes, stroke, asthma, COPD, arthritis, heart failure, myocardial infarction, atrial fibrillation, acute coronary syndrome, epilepsy, depression, bipolar disorder, Parkinson's disease, dementia, chronic pain, osteoporosis, anemia, history of cancer), fractures in last 5 years, overall health ranking, eGFR, HDL, LDL, HbA1c, CRP, systolic blood pressure, diastolic blood pressure, and grip strength.
Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

3.2.3 Bias demonstration analysis I: new user design with propensity score adjustment instead of matching by indication

The associations of new PIM versus new AM use with the study outcomes are presented in **Table 6**. Within one month after cohort entry, 308 participants (0.8%) were hospitalized, and 326 patients (0.9%) died during the 1-year follow-up period.

Table 6. *Bias demonstration analysis I*: The associations of new PIM (N=8,243) versus new AM (N=28,111) use with hospitalization and all-cause mortality (N=36,354) without propensity score matching per indication

Outcome	N_{Event} (%)[a]	Model 1[b]	Model 2[c]	
	PIM users vs. AM users	HR (95% CI)	HR (95% CI)	p
Hospitalization				
1 month	82 (1.0) vs. 226 (0.8)	1.28 (1.00; 1.65)	1.24 (0.95; 1.61)	0.107
3 months	145 (1.8) vs. 440 (1.6)	1.15 (0.95; 1.40)	1.15 (0.95; 1.39)	0.156
6 months	347 (4.2) vs. 1,097 (3.9)	1.11 (0.98 1.25)	1.08 (0.95; 1.22)	0.222
1 year	589 (7.1) vs. 1,976 (7.0)	1.04 (0.95; 1.14)	1.02 (0.92; 1.12)	0.739
2 years	1,049 (12.7) vs. 3,487 (12.4)	1.04 (0.97; 1.12)	1.02 (0.95; 1.09)	0.672
3 years	1,572 (19.1) vs. 5,092 (18.1)	**1.07 (1.01 1.13)**	1.05 (0.99; 1.11)	0.106
4 years	2,053 (24.9) vs. 6,843 (24.3)	1.04 (0.99; 1.09)	1.02 (0.97; 1.07)	0.479
All-cause mortality[d]				
6 months	53 (0.6) vs. 115 (0.4)	**1.76 (1.27; 2.43)**	**1.55 (1.11; 2.17)**	**0.011**
1 year	104 (1.3) vs. 222 (0.8)	**1.77 (1.40; 2.24)**	**1.57 (1.24; 2.00)**	**<.001**
2 years	163 (2.0) vs. 438 (1.6)	**1.39 (1.16; 1.67)**	**1.27 (1.05; 1.52)**	**0.013**
3 years	224 (2.7) vs. 630 (2.2)	**1.32 (1.13; 1.54)**	**1.21 (1.04; 1.42)**	**0.015**
4 years	281 (3.4) vs. 870 (3.1)	**1.20 (1.05; 1.37)**	1.08 (0.95; 1.25)	0.225

Values in bold are statistically significant ($p<0.05$).
Abbreviations: AM, appropriate medication; CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication.

[a] First imputed dataset.
[b] Adjusted for age and sex.
[c] Adjusted for a propensity score, including age, sex, income, years of education, body mass index, physical activity, alcohol consumption, smoking status, number of medications, comorbidities (including arterial hypertension, diabetes, stroke, asthma, COPD, arthritis, heart failure, myocardial infarction, atrial fibrillation, acute coronary syndrome, epilepsy, depression, bipolar disorder, Parkinson's disease, dementia, chronic pain, osteoporosis, anemia, history of cancer), fractures in last 5 years, overall health ranking, eGFR, HDL, LDL, HbA1c, CRP, systolic blood pressure, diastolic blood pressure, and grip strength.
[d] Three-month mortality is not shown because the total number of events was < 100.
Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

In the age and sex adjusted model, the risk for hospitalization was statistically non-significantly increased by 28% (HR [95% CI]: 1.28 [1.00; 1.65]) at one month after the index prescription. The risk for hospitalization attenuated with longer follow-up time. After propensity score adjustment, the point estimates remained similar for 1-month hospitalization (HR [95% CI]: 1.24 [0.95; 1.61]) and the longer follow-up periods.

Furthermore, I observed a statistically significantly 77% increased risk for 1-year all-cause mortality (HR [95% CI]: 1.77 [1.40; 2.24]) in the age and sex adjusted model. In the model adjusted for the propensity score, the risk was still statistically significantly increased by 56% (HR [95% CI]: 1.57 [1.24; 2.00]). The risk attenuated over time: at 4-year follow-up, no statistically significant association was observed.

3.2.4 Bias demonstration analysis II: prevalent user design

The associations of prevalent PIM use versus non-use at the baseline visit with the study outcomes are shown in **Table 7**. Within 1 month after baseline, 644 (0.3%) patients had a hospitalization, and 635 (0.3%) patients died during the 1-year follow-up period.

In the age and sex adjusted model, I observed a 9-13% increased risk for hospitalization . However, there was no clear trend with increasing follow-up time from 1 month to 4 years. With an increasing number of events, the HRs became statistically significant from the 6-month follow-up on. Moreover, I observed a statistically significantly, more than 2-fold increased risk for 6-month mortality in the age and sex adjusted model (HR [95% CI]: 2.15 [1.66; 2.78]), which decreased over the 4-year follow-up period but remained statistically significant. However, the associations between PIM use and both outcomes diminished after full adjustment, with point estimates close to one (1-month hospitalization: HR [95% CI]: 1.04 [0.83; 1.31]; 1-year mortality: HR [95% CI]: 1.01 [0.83; 1.24]). At very long follow-up times, the associations even got reversed.

The inclusion of 17,096 additional PIM users with chronic NSAID use in a sensitivity analysis (**Appendix 35**) did not alter the results of the fully adjusted model (HR [95% CI] for 1-month hospitalization: 1.06 [0.86; 1.31]; HR [95% CI] for 1-year mortality: 1.00 [0.82; 1.22]).

Table 7. ***Bias demonstration analysis II*****: The associations of prevalent PIM use (N=43,307) versus non-use (N=173,804) with hospitalization and all-cause mortality (N=217,111)**

Outcome	N_{Event} (%)[a]	Model 1[b]	Model 2[c]	
	PIM users vs. non-users	HR (95% CI)	HR (95% CI)	p
Hospitalization				
1 month	137 (0.3) vs. 507 (0.3)	1.09 (0.90; 1.31)	1.04 (0.83; 1.31)	0.736
3 months	285 (0.7) vs. 1,041 (0.6)	1.10 (0.97; 1.26)	1.01 (0.86; 1.19)	0.879
6 months	949 (2.2) vs. 3,373 (1.9)	**1.13 (1.05 1.21)**	0.94 (0.86 1.03)	0.184
1 year	2,044 (4.7) vs. 7,265 (4.2)	**1.13 (1.07; 1.18)**	0.95 (0.89; 1.00)	0.071
2 years	4,252 (9.8) vs. 15,204 (8.7)	**1.12 (1.09; 1.16)**	**0.94 (0.90; 0.98)**	**0.002**
3 years	6,550 (15.1) vs. 23,593 (13.6)	**1.12 (1.09 1.15)**	**0.93 (0.90; 0.97)**	**<.001**
4 years	8,975 (20.7) vs. 32,673 (18.8)	**1.11 (1.09; 1.14)**	**0.94 (0.91; 0.97)**	**<.001**
All-cause mortality[d]				
6 months	91 (0.2) vs. 161 (0.1)	**2.15 (1.66; 2.78)**	0.96 (0.69; 1.32)	0.791
1 year	219 (0.5) vs. 416 (0.2)	**2.00 (1.69; 2.35)**	1.01 (0.83;1.24)	0.895
2 years	531 (1.2) vs. 1,119 (0.6)	**1.80 (1.62; 2.00)**	0.92 (0.81; 1.05)	0.219
3 years	919 (2.1) vs. 2,000 (1.2)	**1.75 (1.62; 1.89)**	0.92 (0.83; 1.01)	0.085
4 years	1,342 (3.1) vs. 3,008 (1.7)	**1.70 (1.59; 1.81)**	**0.92 (0.85; 1.00)**	**0.039**

Values in bold are statistically significant ($p<0.05$).
Abbreviations: CI, confidence interval; HR, hazard ratio; PIM, potentially inappropriate medication.

[a] First imputed dataset.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, income, years of education, body mass index, physical activity, alcohol consumption, smoking status, number of medications, comorbidities (including arterial hypertension, diabetes, stroke, asthma, COPD, arthritis, heart failure, myocardial infarction, atrial fibrillation, acute coronary syndrome, epilepsy, depression, bipolar disorder, Parkinson's disease, dementia, chronic pain, osteoporosis, anemia, history of cancer), fractures in last 5 years, overall health ranking, eGFR, HDL, LDL, HbA1c, CRP, systolic blood pressure, diastolic blood pressure, and grip strength.
[d] Three-month mortality is not shown because the total number of events was < 100.
Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

3.3 Factors associated with PIM use, medication underuse, and overuse in older adults in the German National Cohort

3.3.1 Characteristics of the study population

Table 8 provides the baseline characteristics of the study population (N=54,296). The median age was 65 years (IQR: 62-67), and half of the population was female (50.1%). The proportion

exposed to PIM use, underuse, and overuse in the total study population was 26.1%, 19.1%, and 23.6%, respectively. **Table 8** also shows how these proportions vary by baseline characteristics.

3.3.2 Frequency of and factors associated with PIM use

For the participants (N=14,182 (26.1%)) using at least one PIM, the ranking of the proportions according to FORTA indication is shown in **Table 9**. The largest proportions of individuals taking a PIM to treat the specific indication were identified among patients with Parkinson's disease (59.9%), epilepsy (39.9%), arterial hypertension (27.1%), atrial fibrillation (23.4%), and a history of depression (22.4%).

For the potential factors associated with PIM use, the results from the age, sex, and study center adjusted logistic regression models are provided in **Appendix 36**. **Table 10** shows the results of the full model. Among the sociodemographic/-economic factors, 12% and 14% lower odds for PIM use were observed in males compared to females and among participants with ≥ 13 years compared to < 13 years of education. In participants aged 65-69 and ≥ 70 years, I observed 10% and 17% higher odds for PIM use, respectively, compared to those aged 60-64 years. Moreover, participants with middle and high income had 11% and 19% lower odds for using PIM relative to participants with low income. Furthermore, I observed differences in the identified PIM rates in the 21 study centers. Compared to Augsburg, which was the largest study center and recruited 10.2% of the study participants, 8 study centers had statistically significantly higher or lower odds for PIM use. This ranged 13% lower odds in Hamburg to 49% increased odds in Neubrandenburg.

Obesity (defined BMI ≥ 30; 38% increased odds compared to normal BMI) and alcohol abstinence (29% increased odds compared to low alcohol consumption) were the lifestyle risk factors with the strongest association with PIM use. I additionally identified overweight (BMI 25 to 29.9) and current smoking as further associated factors, with 12% and 16% increased odds for PIM use. In contrast, participants with sufficient physical activity had 16% lower odds for PIM use relative to participants with insufficient physical activity.

I detected 18 out of 21 assessed morbidities as being statistically significantly associated with PIM use. The strongest associations with PIM use (OR ≥ 2.1) were observed among participants with Parkinson's disease, arterial hypertension, epilepsy, and depression, with 16.2-fold, 4.5-fold, 4.3-fold, and 2.1-fold increased odds, respectively. Acute coronary syndromes were the only diseases that were inversely associated with PIM use, with 39% lower odds.

Table 8. Distribution of potential factors associated with PIM use, medication underuse, and overuse in the analyzed study population of the NAKO (N=54,296)

Characteristics	N (%)[a]	Proportion (%)[a] of PIM users	Proportion (%)[a] of individuals with underuse	Proportion (%)[a] of individuals with overuse
Sociodemographic/ -economic factors				
Sex	-			
Female	27,189 (50.1)	27.4%	21.0%	26.1%
Male	27,107 (49.9)	24.8%	17.2%	22.0%
Age group, years	-			
60 – 64	25,853 (47.6)	24.0%	19.3%	21.7%
65 – 69	24,121 (44.4)	27.6%	18.8%	24.8%
≥ 70	4,322 (8.0)	30.6%	19.5%	28.1%
Study center				
Augsburg	5,513 (10.2)	25.6%	20.6%	23.5%
Regensburg	2,678 (4.9)	28.6%	18.5%	27.6%
Mannheim	2,558 (4.7)	24.8%	18.7%	25.8%
Freiburg	2,654 (4.9)	20.2%	21.9%	21.3%
Saarbrücken	2,723 (5.0)	25.5%	20.3%	26.4%
Essen	2,670 (4.9)	27.5%	21.8%	25.7%
Münster	2,557 (4.7)	21.3%	19.3%	24.2%
Düsseldorf	2,364 (4.4)	24.5%	19.4%	27.4%
Halle	2,807 (5.2)	34.3%	17.4%	24.5%
Leipzig	2,840 (5.2)	32.6%	20.1%	20.9%
Berlin North	2,684 (4.9)	24.5%	18.7%	20.4%
Central Berlin	2,772 (5.1)	23.8%	19.7%	22.6%
Berlin South	2,718 (5.0)	21.9%	19.0%	23.4%

Characteristics	N (%)[a]	Proportion (%)[a] of PIM users	Proportion (%)[a] of individuals with underuse	Proportion (%)[a] of individuals with overuse
Hannover	2,866 (5.3)	24.0%	18.6%	22.7%
Hamburg	2,595 (4.8)	20.5%	19.0%	23.2%
Bremen	2,753 (5.1)	21.8%	18.6%	19.0%
Kiel	2,511 (4.6)	25.4%	17.8%	23.7%
Neubrandenburg	3,401 (6.3)	33.3%	16.6%	23.2%
Neustrelitz	809 (1.5)	31.9%	18.9%	21.3%
Waren (Müritz)	1,125 (2.1)	33.0%	13.0%	23.3%
Demmin	698 (1.3)	36.5%	17.2%	25.8%
Income[b]	-			
Low	30,479 (56.1)	30.4%	20.4%	24.7%
Middle	16,866 (31.1)	22.0%	17.8%	22.1%
High	6,951 (12.8)	17.3%	16.6%	22.1%
Years of education	-			
< 13	2,251 (4.1)	35.1%	23.4%	27.6%
≥ 13	52,045 (95.9)	25.7%	18.9%	23.4%
Social network index[c]	-			
I+II	29,454 (54.2)	27.6%	20.0%	24.2%
III+IV	24,842 (45.8)	24.3%	18.0%	22.7%
Lifestyle factors				
BMI *(kg/m²)*	-			
< 20	1,177 (2.2)	16.4%	21.5%	22.9%
20 – 24.9	14,569 (26.8)	17.5%	19.5%	22.0%
25 – 29.9	22,728 (41.9)	24.2%	18.7%	22.5%
≥ 30	15,822 (29.1)	37.6%	19.2%	26.6%
Physical activity level[d]	-			
Insufficient	6,896 (12.7)	32.1%	19.0%	26.1%
Sufficient	47,400 (87.3)	25.2%	19.1%	23.2%
Alcohol consumption[e]	-			

Characteristics	N (%)[a]	Proportion (%)[a] of PIM users	Proportion (%)[a] of individuals with underuse	Proportion (%)[a] of individuals with overuse
Abstainer	5,126 (9.4)	35.8%	22.2%	29.8%
Low	43,113 (79.4)	25.1%	18.7%	22.7%
Moderate to high	6,057 (11.2)	25.3%	19.2%	24.3%
Smoking status	-			
Never smoker	23,614 (43.5)	25.3%	18.5%	22.2 %
Former smoker, years since quit				
> 20 years	12,799 (23.6)	25.3%	18.8%	22.3%
≤ 20 years	8,810 (16.2)	27.9%	20.3%	26.9%
Current smoker	9,073 (16.7)	27.7%	19.9%	25.7%
Comorbidities	-			
Diabetes	6,684 (12.3)	47.4%	20.9%	30.6%
Arterial hypertension	26,961 (49.7)	40.8%	21.4%	25.1 %
Atrial fibrillation/arrhythmia	8,235 (15.2)	38.5%	47.0%	22.7%
Stroke	1,879 (3.5)	45.1%	26.4%	29.9%
Myocardial infarction	2,234 (4.1)	36.6%	17.8%	25.7%
Heart failure	2,976 (5.5)	43.1%	31.2%	30.3%
Acute coronary syndrome	4,391 (8.1)	34.4%	20.5%	24.8%
Asthma	3,944 (7.3)	31.8%	27.7%	25.3%
COPD	4,069 (7.5)	38.7%	35.0%	27.8%
Osteoporosis	3,955 (7.3)	36.7%	61.1%	24.9%
Thyroid disease/hypothyroidism[f]	14,951 (27.5)	30.5%	21.8%	26.7%
History of fractures[g]	9,703 (17.9)	27.6%	24.6%	23.7%
Pain[h]	36,887 (67.9)	29.8%	21.7%	23.9%
Parkinson's disease	197 (0.4)	80.2%	38.6%	31.0%
Cognitive impairment/dementia[i]	2,234 (4.1)	41.0%	30.2%	24.1%
History of depression[j]	8,531 (15.7)	42.1%	26.2%	32.5%

Characteristics	N (%)[a]	Proportion (%)[a] of PIM users	Proportion (%)[a] of individuals with underuse	Proportion (%)[a] of individuals with overuse
Epilepsy	396 (0.7)	60.1%	22.0%	34.1%
Insomnia	13,836 (25.5)	29.1%	22.3%	23.5%
Gastrointestinal symptoms[k]	16,540 (30.5)	34.1%	26.4%	24.6%
History of cancer	7,612 (14.0)	29.3%	20.9%	26.5%
Renal impairment[l]	2,728 (5.0)	41.5%	18.3%	33.4%

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; NAKO, German National Cohort; PIM, potentially inappropriate medication.

[a] Calculated from first imputed dataset.
[b] Average total household income before tax. Categories: low: < 2900€; middle: 2900 – < 5000€; high: ≥ 5000€.
[c] Categories: I (isolated) to IV (least isolated).
[d] Adherence to WHO recommendations following the Global Physical Activity Questionnaire (GPAQ). Categories: sufficient: ≥ 600 metabolic equivalent of task (MET)–min/week; insufficient: < 600 MET–min/week.
[e] Alcohol consumption, g ethanol per day. Categories: abstainer: 0 g/day; low: women 0-19.99g/d or man 0-39.99g/d; moderate – high: women ≥ 20g/d or man ≥ 40g/d.
[f] Lifetime history of thyroid disease, self-reported. Underuse for the indication hypothyroidism was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list)
[g] Fractures since aged 50 years.
[h] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[i] Based on the interview question “Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?”.
[j] Lifetime history of depression, self-reported.
[k] Combination of self-reported information on reflux, peptic ulcer (“Have you ever been diagnosed with this condition by a physician?”), and regular intake of NSAIDs (ATC M01A). Underuse for this indication was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment, and in participants regularly taking NSAIDs.
[l] Estimated glomerular filtration rate < 60ml/min/1.73m², calculated based on CKD-EPI equation.

Table 9. Ranking of proportion of participants with PIM use per indication in NAKO participants aged 60-74 years (N=54,296)

Indication	$N_{indication}$ (%)	N (%) with PIM use for specific indication
Parkinson's disease	197 (0.4)	118 (59.9)
Epilepsy	396 (0.7)	158 (39.9)
Arterial hypertension	26,961 (49.7)	7,295 (27.1)
Atrial fibrillation/arrhythmia	8,235 (15.2)	1,931 (23.4)
History of depression[a]	8,745 (16.1)[b]	1,963 (22.4)
Heart failure	2,976 (5.5)	398 (13.4)
Cognitive impairment/dementia[c]	2,234 (4.1)	250 (11.2)
Pain[d]	36,887 (67.9)	3,838 (10.4)
Myocardial infarction	2,234 (4.1)	203 (9.1)
Diabetes	6,684 (12.3)	571 (8.5)
Osteoporosis	3,955 (7.3)	268 (6.8)
COPD	4,069 (7.5)	257 (6.3)
Acute coronary syndrome	4,391 (8.1)	273 (6.2)
Insomnia	13,836 (25.5)	814 (5.9)
Gastrointestinal symptoms[e]	16,540 (30.5)	101 (0.6)
Stroke	1,879 (3.5)	11 (0.6)
Thyroid disease/hypothyroidism[f]	14,951 (27.5)	*n.a.*[f]

Abbreviations: COPD, chronic obstructive pulmonary disease; n.a., not available; NAKO, German National Cohort; PIM, potentially inappropriate medication.

[a] Lifetime history of depression, self-reported.
[b] Including 8,531 participants with self-reported history of depression and 214 additional participants with moderate to severe depressive symptoms according to the patient health questionnaire-9 (PHQ-9).
[c] Based on the interview question "Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?".
[d] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[e] Combination of self-reported information on reflux, peptic ulcer ("Have you ever been diagnosed with this condition by a physician?"), and regular intake of NSAIDs (ATC M01A).
[f] Lifetime history of thyroid disease, self-reported. No PIM defined for this indication.
Note: PIM exposure was defined according to the "Fit fOR The Aged" (FORTA) list 2024.

Table 10. Results of the full logistic regression model of potential factors associated with PIM use, medication underuse, and overuse in the NAKO study (N=54,296)

Variables	PIM, full model			Underuse, full model			Overuse, full model		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Sociodemographic/-economic factors									
Sex									
Female	Ref			Ref			Ref		
Male	**0.88 (0.84; 0.92)**	**<.001**	**<.001**	**1.08 (1.02; 1.14)**	**0.010**	**0.026**	**0.75 (0.71; 0.78)**	**<.001**	**<.001**
Age group, years									
60 – 64	Ref			Ref			Ref		
65 – 69	**1.10 (1.06; 1.16)**	**<.001**	**<.001**	**0.84 (0.80; 0.89)**	**<.001**	**<.001**	**1.21 (1.16; 1.27)**	**<.001**	**<.001**
≥ 70	**1.17 (1.08; 1.27)**	**<.001**	**<.001**	**0.75 (0.68; 0.83)**	**<.001**	**<.001**	**1.46 (1.35; 1.57)**	**<.001**	**<.001**
Study center									
Augsburg	Ref			Ref			Ref		
Regensburg	**1.15 (1.02; 1.29)**	**0.020**	**0.031**	**0.85 (0.75; 0.97)**	**0.019**	**0.044**	**1.21 (1.09; 1.35)**	**0.001**	**0.001**
Mannheim	0.96 (0.85; 1.09)	0.534	0.585	**0.85 (0.74; 0.97)**	**0.018**	**0.043**	1.10 (0.99; 1.23)	0.080	0.138
Freiburg	**0.85 (0.75; 0.96)**	**0.009**	**0.015**	1.13 (0.99; 1.28)	0.067	0.112	0.91 (0.81; 1.02)	0.090	0.147
Saarbrücken	0.99 (0.88; 1.12)	0.884	0.899	0.88 (0.78; 1.00)	0.056	0.097	**1.20 (1.08; 1.34)**	**0.001**	**0.002**
Essen	1.08 (0.96; 1.22)	0.173	0.225	0.99 (0.87; 1.13)	0.876	0.892	1.12 (1.00; 1.24)	0.049	0.094
Münster	0.97 (0.86; 1.10)	0.665	0.702	0.94 (0.83; 1.08)	0.386	0.468	1.10 (0.99; 1.23)	0.086	0.145
Düsseldorf	0.96 (0.85; 1.09)	0.515	0.575	0.87 (0.76; 1.00)	0.048	0.086	**1.20 (1.07; 1.34)**	**0.001**	**0.003**
Halle	**1.42 (1.27; 1.59)**	**<.001**	**<.001**	**0.67 (0.58; 0.76)**	**<.001**	**<.001**	1.04 (0.94; 1.16)	0.445	0.539
Leipzig	**1.33 (1.19; 1.48)**	**<.001**	**<.001**	0.86 (0.76; 0.98)	0.023	0.051	**0.87 (0.78; 0.97)**	**0.016**	**0.036**
Berlin North	0.93 (0.82; 1.05)	0.221	0.274	**0.80 (0.70; 0.91)**	**0.001**	**0.003**	**0.87 (0.78; 0.98)**	**0.019**	**0.043**
Central Berlin	0.89 (0.79; 1.00)	0.050	0.073	0.87 (0.76; 0.98)	0.028	0.057	0.93 (0.84; 1.04)	0.229	0.326
Berlin South	0.88 (0.78; 1.00)	0.045	0.067	0.86 (0.76; 0.98)	0.025	0.054	0.95 (0.85; 1.07)	0.411	0.521
Hannover	1.01 (0.89; 1.13)	0.928	0.928	**0.85 (0.75; 0.97)**	**0.016**	**0.040**	0.97 (0.86; 1.08)	0.524	0.621
Hamburg	**0.87 (0.77; 0.98)**	**0.026**	**0.040**	0.93 (0.82; 1.06)	0.304	0.400	0.97 (0.87; 1.09)	0.621	0.708
Bremen	0.97 (0.86; 1.09)	0.604	0.650	0.95 (0.84; 1.08)	0.467	0.544	**0.78 (0.69; 0.87)**	**<.001**	**<.001**
Kiel	1.07 (0.95; 1.21)	0.292	0.354	**0.77 (0.67; 0.88)**	**<.001**	**0.001**	1.03 (0.92; 1.15)	0.655	0.732

Variables	PIM, full model			Underuse, full model			Overuse, full model		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Neubrandenburg	**1.49 (1.34; 1.66)**	**<.001**	**<.001**	**0.74 (0.65; 0.84)**	**<.001**	**<.001**	1.02 (0.92; 1.13)	0.758	0.822
Neustrelitz	1.13 (0.95; 1.36)	0.167	0.222	0.81 (0.65; 1.00)	0.047	0.086	0.90 (0.75; 1.08)	0.262	0.355
Waren (Müritz)	**1.28 (1.10; 1.50)**	**0.002**	**0.003**	**0.51 (0.41; 0.62)**	**<.001**	**<.001**	1.00 (0.86; 1.17)	0.998	0.998
Demmin	**1.47 (1.22; 1.77)**	**<.001**	**<.001**	**0.61 (0.48; 0.77)**	**<.001**	**<.001**	1.12 (0.93; 1.35)	0.242	0.337
Income[c]									
Low	Ref			Ref			Ref		
Middle	**0.89 (0.84; 0.94)**	**<.001**	**<.001**	0.95 (0.90; 1.01)	0.102	0.161	1.00 (0.95; 1.05)	0.837	0.867
High	**0.81 (0.74; 0.87)**	**<.001**	**<.001**	0.97 (0.89; 1.05)	0.426	0.506	1.07 (1.00; 1.15)	0.067	0.123
Years of education									
< 13	Ref			Ref			Ref		
≥ 13	**0.86 (0.77; 0.95)**	**0.004**	**0.007**	0.92 (0.82; 1.04)	0.188	0.274	1.00 (0.91; 1.10)	0.994	0.998
Social network index[d]									
I+II	Ref			Ref			Ref		
III+IV	0.98 (0.93; 1.03)	0.437	0.509	0.99 (0.92; 1.06)	0.688	0.740	0.98 (0.92; 1.04)	0.534	0.621
Lifestyle factors									
BMI, kg/m²									
< 20	1.09 (0.91; 1.30)	0.336	0.399	1.02 (0.86; 1.21)	0.843	0.874	1.02 (0.88; 1.18)	0.784	0.827
20 – 24.9	Ref			Ref			Ref		
25 – 29.9	**1.12 (1.05; 1.19)**	**<.001**	**<.001**	0.96 (0.90; 1.02)	0.196	0.279	1.02 (0.97; 1.08)	0.373	0.494
≥ 30	**1.38 (1.30; 1.47)**	**<.001**	**<.001**	**0.82 (0.76; 0.88)**	**<.001**	**<.001**	**1.14 (1.07; 1.21)**	**<.001**	**<.001**
Physical activity level[e]									
Insufficient	Ref			Ref			Ref		
Sufficient	**0.84 (0.79; 0.90)**	**<.001**	**<.001**	1.04 (0.96; 1.13)	0.341	0.423	**0.89 (0.84; 0.95)**	**<.001**	**0.001**
Alcohol consumption[f]									
Abstainer	**1.29 (1.20; 1.40)**	**<.001**	**<.001**	0.98 (0.90; 1.06)	0.591	0.647	**1.28 (1.20; 1.38)**	**<.001**	**<.001**

Variables	PIM, full model			Underuse, full model			Overuse, full model		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Low	Ref			Ref			Ref		
Moderate – high	1.03 (0.96; 1.10)	0.475	0.542	1.04 (0.96; 1.13)	0.272	0.369	1.07 (1.00; 1.14)	0.044	0.086
Smoking									
Never	Ref			Ref			Ref		
Former smoker, years since quit									
> 20 years	1.04 (0.98; 1.10)	0.201	0.254	1.02 (0.96; 1.08)	0.584	0.647	1.06 (1.01; 1.12)	0.024	0.051
≤ 20 years	1.05 (0.98; 1.12)	0.150	0.209	1.05 (0.98; 1.13)	0.187	0.274	**1.31 (1.23; 1.39)**	**<.001**	**<.001**
Current smoker	**1.16 (1.08; 1.25)**	**<.001**	**<.001**	1.03 (0.95; 1.10)	0.508	0.580	**1.24 (1.17; 1.32)**	**<.001**	**<.001**
Comorbidities									
Diabetes	**1.79 (1.69; 1.90)**	**<.001**	**<.001**	1.04 (0.96; 1.12)	0.309	0.400	**1.35 (1.27; 1.44)**	**<.001**	**<.001**
Arterial hypertension	**4.50 (4.28; 4.72)**	**<.001**	**<.001**	**1.29 (1.22; 1.36)**	**<.001**	**<.001**	**1.08 (1.03; 1.13)**	**0.001**	**0.002**
Atrial fibrillation/arrhythmia	**1.52 (1.44; 1.61)**	**<.001**	**<.001**	**6.13 (5.79; 6.49)**	**<.001**	**<.001**	**0.82 (0.77; 0.87)**	**<.001**	**<.001**
Stroke	**1.40 (1.26; 1.56)**	**<.001**	**<.001**	1.14 (1.01; 1.28)	0.037	0.073	**1.23 (1.11; 1.37)**	**<.001**	**<.001**
Myocardial infarction	**1.54 (1.33; 1.77)**	**<.001**	**<.001**	0.88 (0.75; 1.05)	0.151	0.232	1.10 (0.96; 1.27)	0.183	0.268
Heart failure	**1.19 (1.09; 1.31)**	**<.001**	**<.001**	1.02 (0.92; 1.12)	0.759	0.801	**1.36 (1.25; 1.49)**	**<.001**	**<.001**
Acute coronary syndromes	**0.61 (0.55; 0.68)**	**<.001**	**<.001**	**0.67 (0.59; 0.75)**	**<.001**	**<.001**	**0.86 (0.78; 0.96)**	**0.007**	**0.017**
Asthma	0.93 (0.85; 1.01)	0.072	0.103	1.08 (0.99; 1.18)	0.085	0.139	0.99 (0.91; 1.07)	0.764	0.822
COPD	**1.37 (1.26; 1.48)**	**<.001**	**<.001**	**2.02 (1.86; 2.20)**	**<.001**	**<.001**	1.06 (0.98; 1.15)	0.117	0.185
Osteoporosis	**1.47 (1.36; 1.60)**	**<.001**	**<.001**	**9.51 (8.80; 10.29)**	**<.001**	**<.001**	0.93 (0.86; 1.01)	0.076	0.135
Thyroid disease/hypothyroidism[g]	1.04 (0.99; 1.09)	0.160	0.218	0.94 (0.89; 1.00)	0.048	0.086	**1.10 (1.05; 1.15)**	**<.001**	**<.001**
History of fractures[h]	1.00 (0.94; 1.08)	0.884	0.899	1.04 (0.96; 1.11)	0.332	0.421	0.97 (0.91; 1.04)	0.381	0.494
Pain[i]	**1.40 (1.33; 1.47)**	**<.001**	**<.001**	**1.39 (1.31; 1.47)**	**<.001**	**<.001**	**0.91 (0.87; 0.95)**	**<.001**	**<.001**
Parkinson's disease	**16.23 (11.01; 23.91)**	**<.001**	**<.001**	**2.60 (1.85; 3.64)**	**<.001**	**<.001**	1.26 (0.92; 1.72)	0.151	0.232
Cognitive impairment/dementia[j]	**1.76 (1.59; 1.94)**	**<.001**	**<.001**	**1.50 (1.34; 1.67)**	**<.001**	**<.001**	0.89 (0.81; 0.99)	0.031	0.063
History of depression[k]	**2.11 (1.99; 2.23)**	**<.001**	**<.001**	**1.12 (1.05; 1.19)**	**0.001**	**0.003**	**1.62 (1.54; 1.71)**	**<.001**	**<.001**
Epilepsy	**4.29 (3.40; 5.43)**	**<.001**	**<.001**	0.83 (0.63; 1.10)	0.202	0.281	**1.50 (1.21; 1.86)**	**<.001**	**0.001**
Insomnia	**1.16 (1.10; 1.22)**	**<.001**	**<.001**	**1.14 (1.08; 1.21)**	**<.001**	**<.001**	0.97 (0.92; 1.02)	0.183	0.268
Gastrointestinal symptoms[l]	**1.37 (1.31; 1.43)**	**<.001**	**<.001**	**1.57 (1.49; 1.65)**	**<.001**	**<.001**	0.98 (0.94; 1.03)	0.428	0.530

Variables	PIM, full model			Underuse, full model			Overuse, full model		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
History of cancer	**1.10 (1.04; 1.17)**	**0.002**	**0.003**	1.00 (0.94; 1.07)	0.939	0.939	**1.14 (1.07; 1.20)**	**<.001**	**<.001**
Renal impairment[m]	**1.57 (1.43; 1.72)**	**<.001**	**<.001**	**0.75 (0.67; 0.84)**	**<.001**	**<.001**	**1.43 (1.31; 1.56)**	**<.001**	**<.001**

Values in bold are statistically significant with FDR (p<0.05).
Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDR, false discovery rate; NAKO, German National Cohort; OR, odds ratio; PIM, potentially inappropriate medication; Ref, reference.

[a] Unadjusted for multiple testing.
[b] P values adjusted for multiple testing using the FDR (Benjamini-Hochberg method).
[c] Average total household income before tax. Categories: low: < 2900€; middle: 2900 – < 5000€; high: ≥ 5000€.
[d] Categories: I (isolated) to IV (least isolated).
[e] Adherence to WHO recommendations following the Global Physical Activity Questionnaire (GPAQ). Categories: sufficient: ≥ 600 metabolic equivalent of task (MET) –min/week; insufficient: < 600 MET-min/week.
[f] Alcohol consumption, g ethanol per day. Categories: abstainer: 0 g/day; low: women 0-19.99g/d or man 0-39.99g/d; moderate – high: women ≥ 20g/d or man ≥ 40g/d.
[g] Lifetime history of thyroid disease, self-reported. Underuse was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list).
[h] Fractures since aged 50.
[i] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[j] Based on the interview question “Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?”.
[k] Self-reported lifetime history.
[l] Combination of self-reported information on reflux, peptic ulcer (“Have you ever been diagnosed with this condition by a physician?”), and regular intake of NSAIDs (ATC M01A). Underuse was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment, and in participants regularly taking NSAIDs.
[m] Estimated glomerular filtration rate < 60 ml/min/1.73m², calculated based on CKD-EPI equation.
Note: PIM exposure was defined according to the “Fit fOR The Aged” (FORTA) list 2024.

3.3.3 Frequency of and factors associated with medication underuse

Medication underuse was detected in 10,371 (19.1%) participants.

The results from the age, sex, and study center adjusted logistic regression model of potential factors associated with underuse are shown in **Appendix 36**. In the fully adjusted model (**Table 10**), males had 8% higher odds for underuse compared to females. Compared to participants aged 60-64 years, those aged 65-69 and ≥ 70 years had 16% and 25% lower odds for medication underuse, respectively. Furthermore, participants in 9 out of 21 study centers had statistically significantly lower odds for underuse compared with participants at the study center in Augsburg. The lowest odds for underuse (49% lower odds) were observed in Waren (Müritz).

In contrast to other lifestyle factors, only obesity was statistically significantly associated with underuse, with 18% lower odds for underuse among obese participants compared to those with a normal BMI.

Overall, 12 out of the 21 tested diseases were statistically significantly associated with underuse. Thereof, osteoporosis (9.5-fold increased odds), atrial fibrillation (6.1-fold increased odds), Parkinson's disease (2.6-fold increased odds), and COPD (2.0-fold increased odds) were identified as particularly strongly associated with underuse (OR ≥ 2.0). **Table 11** shows the ranked proportions of participants with underuse per indication. More than half of the participants with osteoporosis (51.7%) and more than a third (38.7%) of the participants with atrial fibrillation had medication underuse for the specific indication. Parkinson's disease ranked 4th with 15.7%, and COPD ranked 6th with 11.2% of individuals with underuse.

Conversely, a lifetime history of acute coronary syndromes and renal impairment were inversely associated with underuse, with 33% and 25% lower odds.

Table 11. Ranking of proportion of participants with underuse of medication per indication in NAKO participants aged 60-74 years (N=54,296)

Indication	$N_{indication}$	N (%) with underuse for specific indication
Osteoporosis	3,955 (7.3)	2,046 (51.7)
Atrial fibrillation/arrhythmia	8,235 (15.2)	3,187 (38.7)
Heart failure	2,976 (5.5)	498 (16.7)
Parkinson's disease	197 (0.4)	31 (15.7)
Stroke	1,879 (3.5)	267 (14.2)
COPD	4,069 (7.5)	457 (11.2)
Arterial hypertension	26,961 (49.7)	1,990 (7.4)
Gastrointestinal symptoms[a]	16,540 (30.5)	1,110 (6.7)
Acute coronary syndrome	4,391 (8.1)	265 (6.0)
Diabetes	6,698 (12.3)	336 (5.0)
Cognitive impairment/dementia[b]	2,234 (4.1)	105 (4.7)
Myocardial infarction	2,234 (4.1)	103 (4.6)
Pain[c]	36,887 (67.9)	1,620 (4.4)
History of depression[d]	8,531 (15.7)	89 (1.0)[e]
Thyroid disease/hypothyroidism[f]	14,951 (27.5)	12 (0.1)
Epilepsy	396 (0.7)	0 (0.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; NAKO, German National Cohort.

[a] Combination of self-reported information on reflux, peptic ulcer ("Have you ever been diagnosed with this condition by a physician?"), and regular intake of NSAIDs (ATC M01A). Underuse was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment, and in participants regularly taking NSAIDs.
[b] Based on the interview question "Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?".
[c] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[d] Lifetime history of depression, self-reported.
[e] Underuse was only assessed in untreated individuals with severe depression according to the patient health questionnaire-9 (PHQ-9, sum score ≥ 20).
[f] Lifetime history of thyroid disease, self-reported. Underuse was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list).
Note: Exposure was defined according to the "Fit fOR The Aged" (FORTA) list 2024.

3.3.4 Frequency and factors associated with medication overuse

Medication overuse was observed in 12,787 (23.6%) participants.

The most frequently overused medication classes are ranked in **Table 12**. No indication for low-dose acetylsalicylic acid (ASA), hormone replacement therapy (HRT), proton pump inhibitors (PPIs), and antidepressants use could be detected in 5.1%, 3.6%, 3.3%, and 2.2% of the total

study population, respectively. All other drug classes were identified as being overused in less than 2% of the total study population.

The results from the age, sex, and study center adjusted logistic regression model of potential factors associated with overuse are provided in **Appendix 36**. In the fully adjusted model (**Table 10**), 25% lower odds for overuse were observed in males compared to females, and 21% and 46% increased odds were observed in participants aged 65-69 and ≥ 70 years compared to those aged 60-64 years. Moreover, participants at 6 study centers had statistically significantly lower or higher odds for overuse. This ranged from statistically significantly 22% lower odds for overuse in Bremen to 21% increased odds in Regensburg compared to the study center in Augsburg. After adjustment for multiple testing, no other socioeconomic or demographic factors were statistically significantly associated with overuse.

All assessed lifestyle factors were associated with overuse. Obesity, alcohol abstinence, and current as well as ≤ 20 years since quitting smoking were positively associated with overuse, whereas sufficient physical activity was inversely associated with it.

After adjustment for multiple testing, 12 out of the 21 assessed diseases were statistically significantly associated with overuse. Thereof, the strongest associations (OR ≥ 1.5) were observed with a lifetime history of depression (1.6-fold increased odds) and epilepsy (1.5-fold increased odds). In contrast, atrial fibrillation, acute coronary syndromes, and pain were inversely associated with overuse, with 18%, 14%, and 9% lower odds for overuse.

3.3.5 Frequency of vaccination underuse

In the subsample with complete available information on administered vaccinations, 90.6% and 62.7% of study participants did not have the recommended pneumococcal and annual influenza virus vaccinations, respectively.

Table 12. Ranking of medication classes classified as overuse in NAKO study participants aged 60-74 years (N=54,296)

Medication	N (%) among total study population (N=54,296)
ASA, low-dose	2,769 (5.1)
Hormone replacement therapy	1,953 (3.6)
Proton-pump inhibitors	1,799 (3.3)
Antidepressants	1,195 (2.2)
Antidementia drugs[a]	774 (1.4)
Antihypertensives	785 (1.4)
Anticoagulants	725 (1.3)
Betablockers	531 (1.0)
Drugs used in obstructive airway diseases[b]	531 (1.0)
Ginkgo and ginseng preparations	519 (1.0)
Expectorants, mucolytics[c]	485 (0.9)
Benzodiazepines, z-drugs	467 (0.9)
Levothyroxine	455 (0.8)
Antiparkinson medications	440 (0.8)
Systemic glucocorticoids	390 (0.7)
Diuretics	338 (0.6)
Statins	264 (0.5)
Antipsychotics	171 (0.3)
Sedative antihistamines	167 (0.3)
NSAIDs for long-term use	154 (0.3)
Paracetamol	143 (0.3)
Antiplatelet drugs except ASA	130 (0.2)
Antiepileptics	125 (0.2)
Antidiabetics	119 (0.2)
Metamizole	117 (0.2)
Antiarrhythmics	77 (0.1)
Nitrates[d]	73 (0.1)
Opioids	72 (0.1)
Bisphosphonates	66 (0.1)
Lipid modifying agents except statins	64 (0.1)
H2 receptor antagonists	43 (0.1)
Other	68 (0.1)

Abbreviations: ASA, acetylsalicylic acid; NAKO, German National Cohort; NSAIDs, non-steroidal anti-inflammatory drugs.

[a] Excluding ginkgo and ginseng preparations.
[b] Including theophylline, roflumilast, inhalative corticosteroids, inhalative anticholinergics, and inhalative beta 2 mimetic agents.
[c] Including mucolytic agents and antitussives.
[d] Including molsidomine.
Note: Exposure was defined according to the "Fit fOR The Aged" (FORTA) list 2024.

3.4 Cancer co-medication quality in older patients with polypharmacy: a large randomized trial testing a medication review versus usual care

3.4.1 Characteristics of the study population

Figure 7 depicts the study flow chart. Out of N=561 individuals randomized between 05/06/2023 and 08/09/2025, N=542 were correctly included in the trial because they met the inclusion criteria and did not withdraw consent during the trial. N=443 ($N_{intervention}$=234; $N_{control}$=209) of these participants were eligible for inclusion in the ITT analysis of this investigation because they were recruited after 26/10/2023, when the discharge checklist was implemented. Thereof, I excluded N=17 with a missing discharge checklist and N=8 with completely missing documentation of the 2nd study visit (consideration of the intervention with the advisory/sham letter by study physician is unlikely) for the per-protocol analysis, leaving N=418 participants ($N_{intervention}$, n=212; $N_{control}$, 206).

In the total study population, the mean age was 73.3 years (standard deviation (SD): 5.9), and 68.2% of the population was female. **Table 1** presents the baseline characteristics of the study population separately for the control and intervention groups. Except for a history of depression and frailty, which were more common in the control group, baseline characteristics were well balanced between the study arms.

3.4.2 Medication quality at admission to the rehabilitation clinics

In the total study population at admission, the median (interquartile range (IQR)) FORTA score was 6 (4; 8) with and 4 (3; 6) without counting vaccine underuse (**Appendix 37**). The median FORTA sub-scores indicate that study participants had, on average, 1 PIM, used 1 drug without an indication (overuse), 1 drug was missing for a FORTA indication (medication underuse), and 2 recommended vaccinations were missing (vaccination underuse). The proportions of patients exposed to PIM, medication overuse, and medication underuse were 66.1%, 58.9%, and 71.1%, respectively. There were no relevant differences between the trial arms (**Table 13**).

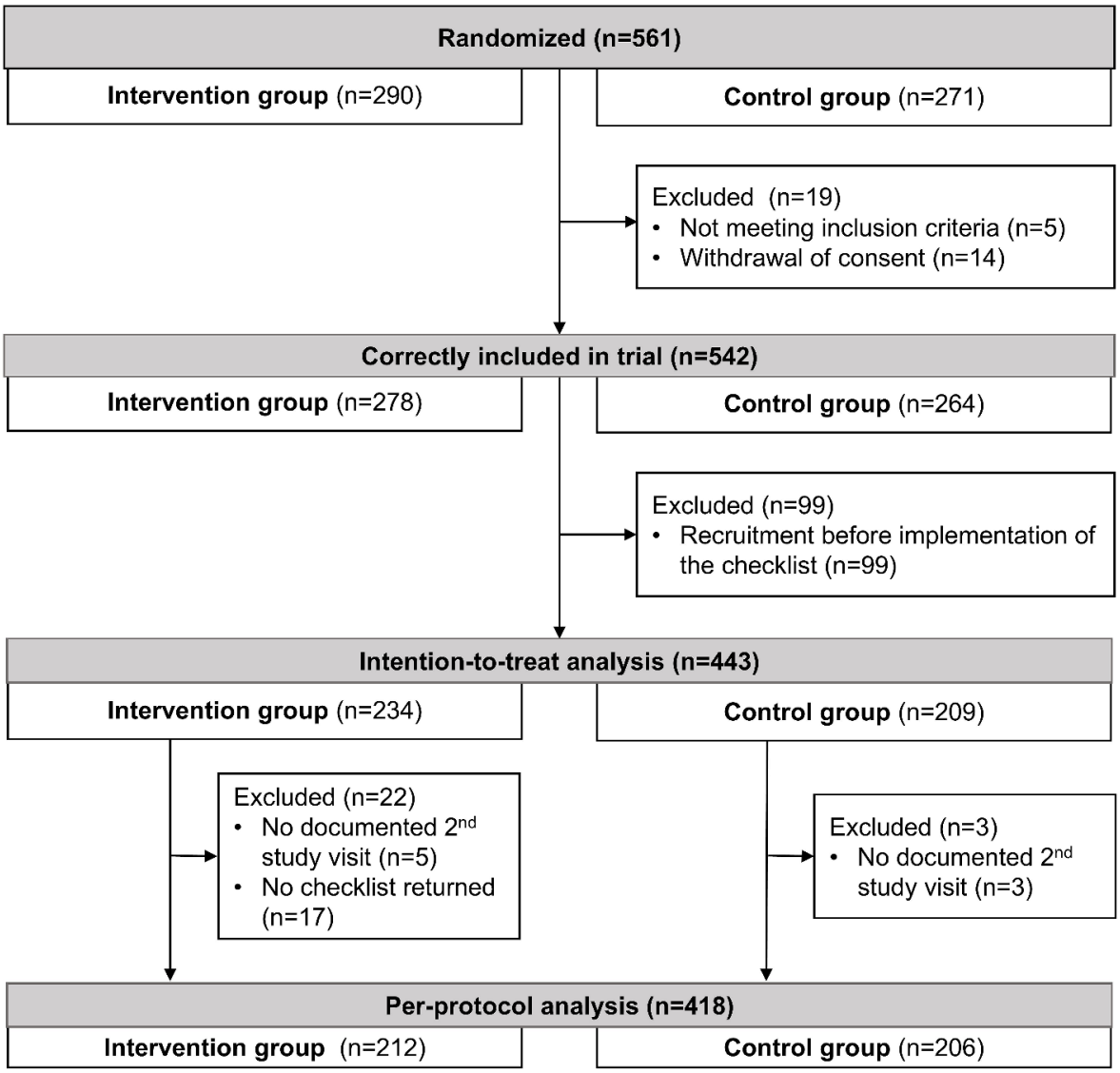

Figure 7. CONSORT flow chart describing the OPTIMAL trial population

Table 13. Baseline characteristics of the OPTIMAL intention-to-treat population (N=443)

Characteristics	Control (N=209)		Intervention (N=234)	
	N (%)[a]	Mean (SD)[a]	N (%)[a]	Mean (SD)[a]
Socio-demographic factors				
Sex				
Female	147 (70.3)		155 (66.2)	
Male	62 (29.7)		79 (33.8)	
Age		73.5 (6.0)		73.2 (5.7)
Years of schooling				
≤ 9	83 (39.7)		83 (35.5)	
10-11	87 (41.6)		94 (40.2)	
≥ 12	39 (18.7)		57 (24.4)	
Partnership				
Yes	129 (61.7)		157 (67.1)	
No	80 (38.3)		77 (32.9)	
Social support[b]		16.0 (5.0)		16.0 (5.3)
Lifestyle factors				
BMI *(kg/m²)*		28.2 (5.8)		27.7 (5.2)
Alcohol consumption[c] *(g/day)*				
Abstainer	79 (37.8)		83 (35.5)	
WHO class I	126 (60.3)		143 (61.1)	
WHO class II-III	4 (1.9)		8 (3.4)	
Physical activity[d]				
Sedentary or underactive	19 (9.1)		25 (10.7)	
Regular underactive, light activities	54 (25.8)		51 (21.8)	
Regular underactive	61 (29.2)		88 (37.6)	
Regular active	75 (35.9)		71 (30.3)	
Smoking status				
Never smoker	117 (56.0)		124 (53.0)	
Former				
< 20 years	52 (24.9)		55 (23.5)	
≥ 20 years	27 (12.9)		38 (16.2)	
Current	13 (6.2)		18 (7.7)	
Cancer-related factors				
Cancer site[e]				
Breast	111 (53.1)		117 (50.0)	
Prostate	31 (14.8)		40 (17.1)	
Other	67 (32.1)		77 (32.9)	
Stage				
I	91 (43.5)		108 (46.2)	
II	55 (26.3)		59 (25.2)	
III	52 (24.9)		40 (17.1)	
IV	13 (6.2)		30 (12.8)	
Previous cancer therapy				
Surgery	183 (87.6)		201 (85.9)	

Characteristics	Control (N=209)		Intervention (N=234)	
	N (%)[a]	Mean (SD)[a]	N (%)[a]	Mean (SD)[a]
Chemotherapy	69 (33.0)		75 (32.1)	
Radiotherapy	114 (54.5)		128 (54.7)	
Comorbidities				
Diabetes	67 (32.1)		70 (29.9)	
Arterial hypertension	188 (90.0)		204 (87.2)	
Stroke	25 (12.0)		30 (12.8)	
Myocardial infarction	34 (16.3)		32 (13.7)	
Heart failure	31 (14.8)		42 (17.9)	
Acute coronary syndromes	28 (13.4)		35 (15.0)	
Atrial fibrillation	59 (28.2)		51 (21.8)	
Asthma, COPD	43 (20.6)		43 (18.4)	
Osteoporosis	53 (25.4)		50 (21.4)	
Chronic pain[f]	165 (78.9)		172 (73.5)	
History of depression	44 (21.1)		26 (11.1)	
Insomnia	47 (22.5)		63 (26.9)	
Gastrointestinal symptoms[g]	29 (13.9)		33 (14.1)	
Incontinence	54 (25.8)		75 (32.1)	
Anemia[h]	29 (13.9)		39 (16.7)	
Constipation	15 (7.2)		12 (5.1)	
Hypothyroidism	80 (38.3)		97 (41.5)	
Chronic kidney disease	39 (18.7)		47 (20.1)	
Dyslipidemia	37 (17.7)		36 (15.4)	
Peripheral vascular disease	12 (5.7)		16 (6.8)	
Frailty[i]				
No	66 (31.6)		82 (35.0)	
Pre-frail	86 (41.1)		117 (50.0)	
Frail	57 (27.3)		35 (15.0)	
Quality of life (QoL)				
Global QoL score[j]		52.4 (18.2)		53.8 (17.0)
Symptoms				
Depressive symptoms[k]	79 (37.8)		78 (33.3)	
Exposure[l]				
Total FORTA score				
Incl. vaccine underuse	209 (100.0)	6.6 (2.9)	234 (100.0)	6.2 (3.0)
Without vaccine underuse	209 (100.0)	4.6 (2.6)	224 (95.7)	4.3 (2.8)
FORTA score sub-categories				
PIM	150 (71.8)	2.6 (2.6)	143 (61.1)	2.3 (2.6)
Overuse	123 (58.9)	0.9 (1.0)	138 (59.0)	0.9 (1.0)
Underuse				
Incl. vaccine underuse	195 (93.3)	3.1 (1.7)	224 (95.7)	3.0 (1.6)
Without vaccine underuse	152 (72.7)	1.1 (0.9)	163 (69.7)	1.1 (1.0)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FORTA, Fit fOR The Aged List Version 4; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; QoL, quality of life; WHO, World Health Organization.

[a] Calculated from first imputed dataset.
[b] According to DUFSS-5 (Saracino et al. 2015).
[c] In 12 months before cancer diagnosis.
[d] According to the RAPA tool (Topolski et al. 2006).
[e] Primary cancer according to the inclusion criteria.
[f] Combination of self-reported pain in the last week and pain-related diagnoses (including migraine, other headache, chronic pain syndromes, arthritis, osteoarthritis, gout, and dorsopathies).
[g] Including regular use of NSAIDs.
[h] Due to iron or vitamin B12 deficiency.
[i] According to FRAIL scale (Morley et al. 2012).
[j] According to the EORTC QLQ-C30 global health status /quality of life scale (Aaronson et al. 1993).
[k] According to the GDS (Stiles et al. 1998).
[l] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
Note: Proportions in certain categories do not sum up to 100.0% due to rounding issues.

3.4.3 Change in medication quality from admission to discharge

The box and scatter plots depicting the distribution of the total FORTA (sub-)scores at admission and discharge (**Appendix 38**) as well as their changes from admission to discharge (**Appendix 39**) are provided in the appendix. The median (IQR) total FORTA score in the control group (6 (4; 9)) was statistically significantly higher at discharge compared to the mean in the intervention group (2 (0; 4)), corresponding to a median difference (95% CI) of -4 (-4.8; -3.2) score points (**Table 14**). Consequently, I observed a similar, statistically significant mean difference (95% CI) in change in total FORTA score of -3.7 (-4.2; -3.3) score points from admission to discharge in the intervention compared to the control group ($p<.001$). Not considering vaccines would lead to an about 1-point lower change in the mean (95% CI) difference of the total FORTA score (-2.6 [-3.0; -2.2]), which was statistically significant as well. The FORTA sub-scores for PIM, overuse, and underuse (including or excluding vaccines) were also statistically significantly reduced (all $p<0.001$). The sensitivity analysis with a multivariate linear regression model obtained almost identical results (**Appendix 40**), and the results were consistent in the per-protocol analysis (**Appendix 41**).

Table 14. Median difference in FORTA (sub-)score scales between intervention and control group at discharge and mean difference in changes from admission to discharge in OPTIMAL intention-to-treat analysis (N=443)

FORTA score[a]	At Discharge				Change from Admission to Discharge			
	Control (N=209) Median (IQR)	Intervention (N=234) Median (IQR)	Median Difference (95% CI)[b]	p[b]	Control (N=209) Mean (95% CI)	Intervention (N=234) Mean (95% CI)	Difference Mean (95% CI)	p
Total								
Incl. vaccine underuse	6 (4; 9)	2 (0; 4)	**-4 (-4.8; -3.2)**	**<.001**	-0.1 (-0.3; 0.1)	**-3.9 (-4.3; -3.5)**	**-3.7 (-4.2; -3.3)**	**<.001**
Without vaccine underuse	4 (3; 6)	1 (0; 3)	**-3 (-3.6; -2.4)**	**<.001**	0.2 (0.1; 0.4)	**-2.3 (-2.7; -2.0)**	**-2.6 (-3.0; -2.2)**	**<.001**
Sub-categories								
PIM	2 (0; 4)	0 (0; 2)	**-2 (-2.0; -2.0)**	**<.001**	0.0 (-0.1; 0.1)	**-1.4 (-1.7; -1.1)**	**-1.4 (-1.8; -1.1)**	**<.001**
Overuse	1 (0; 1)	0 (0; 1)	**-1 (-1.0; -1.0)**	**<.001**	0.1 (0.1; 0.2)	**-0.5 (-0.6; -0.4)**	**-0.6 (-0.8; -0.5)**	**<.001**
Underuse								
Incl. vaccine underuse	3 (1; 4)	1 (0; 2)	**-2 (-2.5; -1.5)**	**<.001**	-0.3 (-0.4; -0.1)	**-2.0 (-2.2; -1.7)**	**-1.7 (-2.0; -1.4)**	**<.001**
Without vaccine underuse	1 (0; 2)	0 (0; 1)	**-1 (-1.0; -1.0)**	**<.001**	0.1 (0.0; 0.2)	**-0.4 (-0.6; -0.3)**	**-0.6 (-0.7; -0.4)**	**<.001**

Values in bold are statistically significant ($p<0.05$).
Abbreviations: FORTA, Fit fOR The Aged List Version 4; CI, confidence interval; PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
[b] The p-value was obtained by the Wilcoxon rank sum test. The confidence interval of the median difference was estimated with quantile regression with resampling.

At the individual participant level, the proportion of study participants exposed to any medication problem was statistically significantly (p<.001) 25.2 percentage points lower at discharge in the intervention group compared to the control group, in which all participants (100.0%) remained exposed (**Table 15**). The highest absolute exposure difference at discharge was observed for PIM (-41.3 percent points), followed by underuse including vaccines (-35.5 percent points), and overuse (-30.7% percent points), which were all highly statistically significant (p<0.001). In the per-protocol analysis, the reduction was approximately 2 percentage points greater in each category (**Appendix 42**)

Table 15. Proportions of study participants exposed to medication problems at discharge in the OPTIMAL intention-to-treat population (N=443)

Medication problems[a]	Control (N=209) N (%)[b]	Intervention (N=234) N (%)[b]	Absolute difference (95% CI)[c]	p
Any (FORTA score > 0)				
Incl. vaccine underuse	209 (100.0)	175 (74.8)	**-25.2 (-30.9; -19.5)**	**<.001[d]**
Without vaccine underuse	209 (100.0)	172 (73.5)	**-26.6 (-32.4; -20.8)**	**<.001[d]**
FORTA sub-categories				
PIM	148 (70.8)	70 (29.9)	**-41.3 (-50.1; -32.6)**	**<.001**
Overuse	134 (64.1)	80 (34.2)	**-30.7 (-39.7; -21.7)**	**<.001**
Underuse				
Incl. vaccine underuse	187 (89.5)	127 (54.3)	**-35.5 (-43.5; -27.6)**	**<.001**
Without vaccine underuse	153 (73.2)	105 (44.9)	**-26.7 (-35.8; -17.6)**	**<.001**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval; FORTA, Fit fOR The Aged List Version 4; PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
[b] Rounded values from first imputed dataset.
[b] In proportions exposed to the relevant medication problem.
[b] Tested with Fisher's exact test as all participants of the control group were exposed.

3.4.4 Frequency and acceptance rates of recommendations

Out of 218, 191, and 610 recommendations made to reduce PIM, overuse, and underuse in the intervention group, respectively, the acceptance rates attributable to the intervention were 77.1% for switching PIM, 77.0% for withdrawal of overused drugs, and 75.1% for underuse-specific recommendations. The latter included 52.4% accepted new drug initiations and 89.9% vaccinations, respectively.

Table 16 shows that most recommendations (≥ 50) regarding changes of PIM were made for analgesics and beta blockers, and that they were accepted in > 75% of cases. Antidepressants, antipsychotics/sedatives, and drugs for obstructive airway diseases were identified as PIM ≥ 20 times, and acceptance rates varied from 65% to 80%. All other PIM drug groups were rather rare (≤10 recommendations).

Table 16. Proportions of accepted recommendations from the advisory letter regarding PIM in the intervention group per medication group (N=212; per-protocol population)

Medication group	Recommendations[a]	Proportion accepted[b]
	n	n (%)
Analgesics[c]	54	43 (79.6)
Betablockers	50	38 (76.0)
Antidepressants	23	17 (73.9)
Antipsychotics and sedatives[d]	20	16 (80.0)
Drugs for obstructive airway diseases	20	13 (65.0)
Spironolactone	10	8 (80.0)
Antidiabetics	8	8 (100.0)
Antithrombotic agents	6	3 (50.0)
Antihypertensives[e]	4	3 (75.0)
Anti-incontinence drugs	4	3 (75.0)
Antiarrhythmics	3	3 (100.0)
Antiepileptics	3	3 (100.0)
Corticosteroids, systemic use	3	2 (66.7)
Expectorants, cough suppressants	3	3 (100.0)
Drugs for bone diseases[f]	2	1 (50.0)
Drugs for constipation	2	2 (100.0)
Antiemetics	1	1 (100.0)
Antiparkinson drugs	1	1 (100.0)
Endocrine antineoplastic therapy	1	0 (0.0)
Total	**218**	**168 (77.1)**

Abbreviations: AM, appropriate medication; NSAIDs, non-steroidal anti-inflammatory drugs; PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
[b] The recommendation to switch a PIM to a recommended AM was accepted. The medication change was either initiated directly by the study physician or communicated to the patient's GP. All accepted switches were considered attributable to the intervention.
[c] Including NSAIDs.
[d] Including anxiolytics, hypnotics, and antihistamines for systemic use (psycholeptics).
[e] Excluding beta blockers.
[f] Including hormone replacement therapy in participants diagnosed with osteoporosis.

Table 17 presents the proportions of accepted recommendations from the advisory letter on overuse in the intervention group per medication group. PPIs were the most common drug group classified as overuse (n=41 recommendations), followed by lipid-modifying agents, antithrombotic agents, analgesics, and antipsychotics/sedatives, with 14 to 28 recommendations each. The acceptance rate to discontinue these drug classes ranged from 71 to 88%. All other drug classes were rarely classified as overuse (< 10 recommendations).

Table 18 shows the proportions of accepted recommendations from the advisory letter regarding underuse in the intervention group. Frequent indications for underuse were chronic pain, incontinence, and insomnia, with 66, 57, and 38 recommendations, respectively, whereas all other indications showed medication underuse in less than 15 study participants. Recommended initiation of treatment was accepted in more than half of the study participants for chronic pain and insomnia, whereas physicians only followed about 1 out of 3 recommendations for incontinence treatment.

All four recommended vaccinations for older adults were very commonly missing, with the annual COVID-19 vaccination most frequently missing (in 110 out of 212 participants (52%)), and the annual influenza vaccination least commonly missing (in 65 out of 212 participants (31%)). The acceptance rate for all vaccination recommendations was greater than 80%.

Table 17. Proportions of accepted recommendations from the advisory letter regarding overuse in the intervention group per medication group (N=212; per-protocol population)

Medication group	Recommendations[a]	Proportion accepted[b]
	n	n (%)
PPIs	41	35 (85.4)
Lipid-modifying agents	28	22 (78.6)
Antithrombotic agents	24	21 (87.5)
Analgesics[c]	20	16 (80.0)
Antipsychotics and sedatives[d]	14	10 (71.4)
Antiglaucoma drugs	8	6 (75.0)
Drugs for BHP	8	6 (75.0)
Drugs for constipation	7	1 (14.3)
Iron supplements	7	5 (71.4)
Antiparkinson drugs	5	3 (60.0)
Mineral supplements	4	3 (75.0)
Antidepressants	4	3 (75.0)
Drugs for obstructive airway diseases	4	3 (75.0)
Thyroid preparations	3	2 (66.7)
Antidiabetics	3	2 (66.7)
Drugs for bone diseases	3	2 (66.7)
Organic nitrates	3	3 (100.0)
Diuretics	2	1 (50.0)
Antidementia drugs	1	1 (100.0)
Antiepileptics	1	1 (100.0)
Corticosteroids, systemic use	1	1 (100.0)
Total	**191**	**147 (77.0)**

Abbreviations: BHP, benign prostatic hypertrophy; NSAIDs, non-steroidal anti-inflammatory drugs;PIM, potentially inappropriate medication; PPIs, proton pump inhibitors.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4". Recommendations were not counted if a previously undocumented but clinically appropriate indication for the specific medication was identified until the discharge visit.

[b] The recommendation to withdraw a medication rated as overuse was accepted. The medication was either stopped directly by the study physician or the recommendation was communicated to the patient's GP.

[c] Including NSAIDs.

[d] Including anxiolytics, hypnotics, and antihistamines for systemic use (psycholeptics).

Table 18. Proportions of accepted recommendations from the advisory letter regarding underuse in the intervention group per medication group or vaccine (N=212; per-protocol population)

Indication for underuse	Recommendations[a]	Proportion accepted[b]
	n (%)	n (%)
Underuse of medications		
Chronic pain	66	43 (65.2)
Incontinence	57	17 (29.8)
Insomnia	38	20 (52.6)
Hypothyroidism	14	7 (50.0)
Diabetes	10	4 (40.0)
Osteoporosis	9	8 (88.9)
COPD	8	4 (50.0)
Gastrointestinal symptoms	8	6 (75.0)
Stroke	5	1 (20.0)
Arterial hypertension	4	3 (75.0)
Constipation	4	2 (50.0)
Nausea and vomiting	2	1 (50.0)
Neutropenia	1	1 (100.0)
Atrial fibrillation	1	1 (100.0)
Anemia, tumor-related	1	1 (100.0)
Anemia, Vitamin B12 or iron-related	1	1 (100.0)
Bipolar disorder	1	1 (100.0)
Heart failure	1	0 (0.0)
Total, medication-related	231	121 (52.4)
Underuse of vaccinations		
COVID-19 vaccination	110	104 (94.5)
Herpes zoster vaccination	104	91 (87.5)
Pneumococcal vaccination	100	89 (89.0)
Influenza vaccination	65	53 (81.5)
Total, vaccination-related	379	337 (89.9)
Total, overall	**610**	**458 (75.1)**

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4". Recommendations were not counted if a previously undocumented medication for the specific indication was identified during the discharge visit.
[b] The recommendation to initiate a new medication for an untreated indication was accepted by the study physician. The new medication was either initiated directly by the study physician or the recommendation was communicated to the patient's GP.

4 Discussion

4.1 Systematic review, meta-analysis, and meta-regression of RCTs investigating the effect of a medication review on rehospitalization and all-cause mortality in hospitalized patients

4.1.1 Summary of findings and comparison with the Cochrane review of Bülow et al.

This systematic review with meta-analysis and meta-regression comprises evidence from 26 RCTs testing a medication review compared to usual care in hospitalized patients on rehospitalization and all-cause mortality. Compared with the Cochrane review by Bülow et al. (Bülow et al. 2023), n=7 additional studies were included, and I focused on detailed methodological aspects.

The findings from the main meta-analyses marginally changed the effect estimates of the full intention-to-treat meta-analyses reported by Bülow et al. (Bülow et al. 2023): for rehospitalization, the RR point estimate slightly decreased from 0.93 to 0.92 and remained statistically significant. With respect to all-cause mortality, the point estimate remained the same (RR: 0.95), and although the confidence interval narrowed slightly, this outcome still lacked statistical significance. However, six interesting methodological study aspects were identified, which were statistically significant effect modifiers in univariate meta-regression analyses: number of patient contacts, involvement of pharmacists, number of recommendations per patient, diseases of the study population, length of the follow-up, and the method of mortality assessment. I will discuss their roles in detail in the following. Moreover, I observed that medication reviews were particularly effective in trials involving patients aged 70 years or older (mean or median), and I will also elucidate the role of aging in greater detail.

4.1.2 Relevance of methodological study differences in RCTs with medication review vs. usual care for observed effects on rehospitalization and all-cause mortality

This investigation did not only demonstrate a statistically significant 15% reduced risk for

rehospitalization (RR [95% CI]: 0.85 [0.78; 0.92], p<0.001) and a 14% mortality reduction (RR [95% CI]: 0.86 [0.76; 0.98], p=0.022) in trials providing two or more patient contacts. It also identified the number of patient contacts as the most important effect modifier in multivariate meta-regression analysis on rehospitalization (p=0.045). The number of patient contacts was closely linked to pharmacists' involvement in the medication reviews, as pharmacists were involved in all trials that provided multiple patient contacts. Hence, the pharmacist's expertise in medication optimization and pharmacology might have contributed as well to the favorable effects of multiple patient contacts. The scope of these contacts varied across the trials and encompassed patient empowerment (Bonetti et al. 2018; Gillespie et al. 2009; Ravn-Nielsen et al. 2018), discharge counselling (Bonetti et al. 2018; Farris et al. 2014; Gillespie et al. 2009; Lea et al. 2020; Lenssen et al. 2018; Ravn-Nielsen et al. 2018) and tailored patient counselling (Graabæk et al. 2019; Lenssen et al. 2018; Scullin et al. 2007) as well as patient (Farris et al. 2014; Gillespie et al. 2009; Schapira et al. 2022) and family education (Schapira et al. 2022), medication reconciliation (Lea et al. 2020), and shared decision making (Ferro-Uriguen et al. 2023; Johansen et al. 2022b). The narrow, patient-centered healthcare conveyed through this approach enhances patient satisfaction and adherence (Rathert et al. 2013) and may reduce mortality (Ruppar et al. 2016). Additionally, a network meta-analysis including 24 trials and 11,677 participants reported a decrease in readmission when medication reviews were complemented by medication reconciliation, patient or healthcare professional education, and transitional care (RR [95% CI]: 0.82 [0.74; 0.91]) (Dautzenberg et al. 2021), which strongly supports my finding that multiple patient contacts are a key aspect for medication reviews to effectively reduce hospital readmission. Interestingly, most studies providing multiple patient contacts (6 out of 9 for the outcome mortality and 5 out of 11 for the outcome rehospitalization) also used such contacts for a repeated medication review.

The role of the follow-up time varied by outcome. With respect to mortality, the univariate meta-regression confirmed the hypothesis that long-term effects are more likely than short-term effects (p=0.032). However, the subgroup analysis of 7 trials with 1-year follow-up narrowly missed statistical significance (RR [95% CI]: 0.90 [0.80; 1.00], p=0.059). This aligns with the findings from a large cohort study comparing 5,033 study participants who participated in an interprofessional medication management program in primary care with 10,039 propensity-score-matched controls (Meid et al. 2023): a statistically significantly 16% reduced all-cause mortality was observed within a relatively long follow-up time of 2 years (HR [95% CI]: 0.84 [0.76; 0.94]). In contrast, I observed the strongest effect of a medication review on

rehospitalization (26% reduced risk) within 30 days after discharge. Medication changes during the hospitalization represent a plausible explanation. Whilst they were optimized in the intervention group, patients of the usual care group quickly experienced adverse events that may result in another readmission after discharge.

The findings from subgroup analyses yielding that medication reviews reduced mortality by 19% (RR [95% CI]: 0.81 [0.70; 0.94], p=0.007) in trials with outcome assessment via registries or primary care data, raises the question of whether other previous trials might have underestimated the effect on mortality due to poor methodology, particularly since 8 trials did not report how death cases were ascertained. The meta-regression confirmed that the method of mortality ascertainment had a relevant effect on the medication review effects observed in the trials (p=0.014).

I also identified a higher number of recommendations per patient and the inclusion of individuals with any rather than certain specified diagnoses as effect modifiers for the outcome mortality that facilitated stronger inverse associations between mediation reviews and mortality. A plausible explanation for the role of both aspects might be the inclusion of multimorbid participants, for whom more recommendations were provided due to a higher number of severe conditions requiring medication adjustments. These patients have the greatest need for medication reviews and likely benefit more than patients with a few medications. This hypothesis is supported by the result from the subgroup analysis on the number of medications as an inclusion criterion: only in trials that included patients with ≥ 4 drugs, a statistically significant effect of medication reviews was detected.

4.1.3 Relevance of the study participant's age in RCTs with medication review vs. usual care

Age was not a significant effect modifier in the meta-regression, which might be explained by the fact that there were few variations in the age of the included trial populations. Except for two trials, all trials included patients aged 70 years or older on average. Noteworthy, no effect on mortality (RR [95% CI]: 1.00 [0.49; 2.03], p=0.997) and rehospitalization (RR [95% CI]: 1.03 [0.76; 1.40], p=0.858) was observed in meta-analyses of these two trials, which included populations with a mean or median age below 70 years. This emphasizes geriatric patients as

priority group for medication reviews. In terms of drug safety, older patients are particularly vulnerable, which is rooted in an increased prevalence of multimorbidity, age-related physiological changes, and an increased risk of adverse drug events (Mangoni et al. 2004; Shi et al. 2011).

4.1.4 Strengths and limitations

This systematic review was grounded in an extensive review of the published literature on medication reviews in hospitalized patients. The inclusion of 26 RCTs provided robust statistical power and enabled me to explore detailed methodological study differences in several subgroup analyses and meta-regression.

I only included RCTs, as they are considered the gold standard in evidence hierarchy. However, it is important to acknowledge limitations with respect to the quality of the included RCTs. Firstly, I detected contamination bias in 24 of the 26 included trials. In these trials, randomization occurred at the individual patient level, resulting in the same healthcare professionals being involved in both the treatment and control arms. This bias may underestimate the true effect of the intervention. Secondly, the nature of the intervention challenges blinding of participants and personnel, which led to an overall high risk of performance bias. However, imperfect blinding has likely a minimal impact on endpoints such as rehospitalization and mortality. Thirdly, some trials deviated from the protocol, notably discharging patients before completing the full intervention. However, this is a common occurrence in hospital settings, which I addressed through a full intention-to-treat analysis.

Finally, I did not adjust for multiple testing. Hence, the findings from the subgroup meta-analyses should be interpreted cautiously.

4.2 Associations of PIM use in older adults with mortality and hospitalizations and methodological challenges in pharmacoepidemiology

4.2.1 Summary of findings

This large-scale study of 11,812 1:1 propensity score matched new PIM and new AM users aged 60-69 participating in the UK Biobank indicated that new PIM might be associated with a 20% increased risk for 1-month hospitalization (HR [95% CI]: 1.20 [0.76; 1.90) and a 23% increased

risk for 1-year all-cause mortality (HR [95% CI]: 1.23 [0.80; 1.89]). However, the results for both outcomes did not meet statistical significance.

Bias demonstration analyses including 36,354 and 217,111 individuals, respectively, demonstrated the impact of common methodological challenges in pharmacoepidemiologic research on PIM: a new user design with adjustment for one common propensity score instead of matching by multiple indication-specific propensity scores (*bias demonstration analysis I*) led to a marginally overestimated risk for 1-month hospitalization (HR [95% CI]: 1.24 [0.95; 1.61]) and a substantially overestimated risk for 1-year all-cause mortality (HR [95% CI]: 1.57 [1.24; 2.00]). In contrast, the prevalent user design (*bias demonstration analysis II*) resulted in null-findings for both outcomes (HRs [95% CIs]: 1-month hospitalization: 1.04 [0.83; 1.31]; 1-year mortality: 1.01 [0.82; 1.23]).

4.2.2 Comparison with previous studies including a bias assessment

This was the first study utilizing the new user design with active comparator propensity score matching per indication. Hence, it is not possible to directly compare the results of the main analysis from the UK Biobank with results from previous studies. Whilst most of these studies reported ORs or RRs, the HRs from my analyses cannot be directly compared to their results. Nevertheless, the comparison of my main analysis with my two bias demonstration analyses may inform about the magnitude of over- or underestimation of the risks associated with PIM reported by previous studies. In this context, it was interesting to note that compared to my main analysis, the most recent meta-analyses on PIM use in individuals aged 60 or older, namely the meta-analyses by Xing et al. (Xing et al. 2019) and Zhou et al. (Zhou et al. 2024), yielded statistically significant associations. Specifically, they reported a 27% increased risk for hospitalization (14 cohort studies including N_{total}=288,835 participants; OR [95% CI]: 1.27 [1.20; 1.35]) (Xing et al. 2019) and 28% increased risk for mortality (44 cohort studies including N_{total}=2,191,651 participants; OR [95% CI]: 1.28 [1.20; 1.36]) (Zhou et al. 2024), respectively. These meta-analyses pooled studies that might have either under- or overestimated the risk due to the absence of appropriate comparators and time-dependent biases. This might have averaged out the bias quite well, since the pooled effect estimates are not far from the effect estimates of my two main analyses.

The relevance of time-dependent biases has previously been explored by the meta-analysis by Muhlack et al., which revealed a statistically significant 1.6-fold increased risk for mortality among three studies (Dedhiya et al. 2010; Lau et al. 2005; Pugh et al. 2013) that applied a new user design (RR [95% CI]: 1.59 [1.45; 1.75]) (Muhlack et al. 2017). However, the studies included in this meta-analysis lacked appropriate active comparators. Therefore, this meta-analysis resembles my *bias demonstration analysis I* which yielded a quite similar result (1-year mortality in UK Biobank: HR [95% CI]: 1.57 [1.24; 2.00]). More specifically, the meta-analysis included a retrospective database study of 1,807,404 veterans aged at least 65 years and older, which reported a 1.6-fold increased odds for 1-year mortality (OR [95% CI]: 1.62 [1.56; 1.68]) among individuals with a new PIM prescription compared to those without (Pugh et al. 2013) and two studies of nursing home residents aged 65 years or older (Dedhiya et al. 2010; Lau et al. 2005). In the study by Dedhiya et al. (Dedhiya et al. 2010), new non-PIM users served as comparators, and their finding on 1-year mortality (OR [95% CI]: 1.46 [1.31; 1.62]) was close to the result from my *bias demonstration analysis I*. In contrast, Lau et al. (Lau et al. 2005) selected non-users as comparators, and the association with mortality within the same or the following month was less pronounced (OR [95% CI]: 1.28 (1.05; 1.55]). However, their findings for 1-month hospitalization (OR [95% CI]: 1.27 [1.09; 1.47]) were consistent with the results from my *bias demonstration analysis I* (HR [95% CI]: 1.24 [0.95; 1.61).

The main detriment of my *bias demonstration analyses I* and studies following this approach is that inappropriate comparators facilitate unmeasured confounding that can only be handled by the correct study design, but not by statistical adjustment (D'Arcy et al. 2018; Lund et al. 2017; Psaty et al. 2010; Yoshida et al. 2015). Hence, propensity score adjustments based on a single common propensity score, irrespective of the PIM indications, are insufficient, as different PIM indications also have distinct underlying risks for hospitalization and mortality. Thus, comparing PIM and AM from different indications is like comparing apples and oranges. Furthermore, PIM and AM users of six different indications could not be matched as their baseline characteristics were not sufficiently balanced or their propensity scores did not overlap (**Appendix 7**). The main analysis did therefore not include quite rare indications like dementia with safety concerning PIM classes such as benzodiazepines and antipsychotics. On the other hand, more common indications (e.g., arterial hypertension, COPD) with less safety concerning PIM, such as beta blockers and inhalative corticosteroids, were included. Therefore, the strong associations of PIM with clinical outcomes reported by prior studies might result from residual confounding, where they relate more to the users' risk profiles than to the medications themselves. This unresolved

confounding may lead to an overestimation of risks, as demonstrated through the comparison between *bias demonstration analyses I* and my *main analysis*. In the main analysis, I addressed this methodological pitfall through the comprehensive active comparator propensity score matching per indication.

The majority of previous studies investigated PIM use compared to non-user and reported no significant association with mortality (Barnett et al. 2011; Bo et al. 2018; Cross et al. 2017; Espino et al. 2006; Haerig et al. 2023; Hanlon et al. 2002; Mekonnen et al. 2022; Muhlack et al. 2017; Pasina et al. 2014; Pozzi et al. 2010; Wauters et al. 2016) and hospitalization (Bo et al. 2018; Gillespie et al. 2013; Pasina et al. 2014; Pozzi et al. 2010; Wauters et al. 2016). I replicated this approach in *bias demonstration analysis II* and produced consistent results (1-year mortality: HR [95% CI]: 1.01 [0.82; 1.23]; 1-month hospitalization: HR [95% CI]: 1.04 [0.83; 1.31]), which were further corroborated by the meta-analysis by Muhlack et al. of n=10 studies with a prevalent user design for the outcome mortality (RR [95% CI]: 1.01 [0.97; 1.04]) (Muhlack et al. 2017). This is not surprising since time-dependent biases, such as immortal time bias (Suissa 2007; Suissa 2008), healthy adherer bias (Shrank et al. 2011), and depletion of susceptibles (Renoux et al. 2017), may lead to an underestimation of risk. Nevertheless, falsely strong associations can still be found if the statistical models are not sufficiently adjusted. For instance, the 2-fold increased risk for 1-year mortality (HR [95% CI]: 2.00 [1.69; 2.35]) yielded in the age and sex adjusted model of my *bias demonstration analysis II* sharply contrasted with the null result after full adjustment (HR [95% CI]: 1.01 [0.83; 1.24]), which underscores the magnitude of potential misjudgment. This may explain the strong associations of prevalent PIM use with all-cause mortality (OR [95% CI]: 2.34 [1.61; 3.40]) reported by a cohort study of 1,117 long-term residents in Georgian nursing homes (Perri et al. 2005), as they did not adjust for key risk factors such as disease severity and smoking.

Some studies yielded results that were less consistent with my *bias demonstration analyses*. However, these studies exhibited different additional methodological challenges, and their effects were hard to disentangle. More precisely, immortal time biases were introduced in studies with a longitudinal medication assessment that included both prevalent and new users (Albert et al. 2010; Brown et al. 2016; Fick et al. 2008), whereas this type of bias was avoided in my *bias demonstration analysis I*. Moreover, I noted misalignment between eligibility and assignment to the study arm by using future information (Fick et al. 2008; Hsu et al. 2024; Pugh et al. 2013),

which violates key principles of pharmacoepidemiology and may cause immortal time bias, selection bias, and unpredictable effects (Hernán et al. 2016; Hernán et al. 2025; Lund et al. 2017).

4.2.3 Association of new PIM with early and later hospitalization and mortality risks

Whilst the point estimates of the main analysis yielded statistically non-significantly increased early hospitalization and mortality risks after the prescription of new PIM, I did not observe an association with long-term follow-ups (HRs [95% CIs] 1-year hospitalization: 1.03 [0.87; 1.22]; 2-year mortality: 1.00 [0.72; 1.39]). This reflects the time-varying risks for adverse drug events, which typically peak during the early therapy period and decrease later, commonly also resulting from the withdrawal of this PIM after the adverse event was treated. Thus, the number of person-years at risk for both study outcomes does not equal the number of person-years of PIM exposure (Kramer et al. 1987; Renoux et al. 2017). This underscores the necessity of short-term follow-ups when evaluating PIM safety, even though the limited number of events may affect the statistical power.

4.2.4 Subgroup analyses

When I conducted my main analyses stratified by subgroups, I observed higher HR point estimates among females, participants aged 65 years or older, with previous PIM use, and exposed to polypharmacy. The stronger effect estimates are plausible, as these are known risk factors for adverse drug events (Fried et al. 2014; Martin et al. 1998) and drug-related hospitalizations (Pouyanne et al. 2000). Thus, the results emphasize the importance of careful prescribing practices and comprehensive checks for potential drug interactions when new medications are being prescribed for these particularly vulnerable populations.

The subgroup analysis of new PIM users who were already taking at least one additional PIM at baseline indicated a stronger association with 6-month hospitalization (HR [95% CI]: 1.38 [0.67; 2.85]) than in the subgroup of individuals without PIM exposure at baseline (HR [95% CI]: 1.00 [0.72; 1.38]). This finding is strengthened by the prospective cohort study of Weir et al., who observed that the risk for a combined endpoint of emergency department visits, rehospitalizations, and death within 30 days after hospital discharge increased by 13% (HR [95% CI]: 1.13 [1.03; 1.26]) per each newly prescribed PIM and only by 5% (HR [95% CI]: 1.05 [1.01; 1.10]) per each new non-PIM (Weir et al. 2020).

Similarly, my subgroup analysis suggested that new PIM users who were exposed to polypharmacy at baseline had a higher risk for 6-month hospitalization (HR [95% CI]: 1.34 [0.80; 2.25]) than those without polypharmacy (HR [95% CI]: 1.08 [0.75; -1.56]). This may be attributed to the pharmacologic profile of many PIMs, which are known for their potential to cause drug-drug interactions (Motter et al. 2018). In consequence, the risk for drug-drug interactions increases with the number of co-medications, and it is especially high among participants with polypharmacy.

Moreover, a non-significantly 23% increased risk for 6-month hospitalization was observed in the subgroup analysis of individuals aged 65-72 years (HR [95% CI]: 1.27 [0.81; 1.99]), but no increased risk in those aged 60-64 years (HR [95% CI]: 1.01 [0.53; 1.91]), which supports the widely used age cut-off of 65 years for defining PIM. An older study population may generally lead to stronger associations observed between PIM use and hospitalizations, as studies involving very old participants (e.g., mean ages of 73 to 80 years) reported much higher hospitalization risks than I observed in my study with a mean age of 64 years (Fick et al. 2008; Haerig et al. 2023; Mekonnen et al. 2022), which is a relatively young study population for PIM research. However, the results are not directly comparable due to the different methodological approaches.

A potentially higher risk for 6-month hospitalization among female PIM users (HR [95% CI]: 1.14 [0.75; 1.73]) compared to male PIM users (HR [95% CI]: 0.97 [0.55; 1.70]) might be explained by the underrepresentation of females in clinical trials and women's higher susceptibility to certain adverse drug reactions, including severe events such as cardiac arrythmias (Franconi et al. 2014; Rivero et al. 2010).

4.2.5 Strengths and limitations

This was not only one of the largest studies assessing the association of PIM with clinical outcomes in a general older population, but it was also the first study applying a new user/active comparator approach, the gold standard in pharmacoepidemiology that minimizes unmeasured confounding and typical biases (Acton et al. 2023; Hernán et al. 2016; Yoshida et al. 2015). Nonetheless, it should be underscored that unmeasured confounding can never be entirely ruled out. However, this gold standard approach also had the major detriment that the propensity score matching by indication substantially reduced the study population and hence the statistical

power. As primary care linkage was only available for approximately half of the cohort, this unfortunately led to statistically non-significant results in the main analysis. To verify the approximately 20% increased risk for hospitalization and mortality among new PIM users, an even larger sample size than the N=95,187 UK Biobank participants with longitudinal medication data will be needed. However, I am confident that such studies will be conducted in the future based on large claims data sets that include millions of individuals (e.g., Medicare data from the United States or the Clinical Practice Research Datalink (CPRD) from the UK). Such larger studies could investigate cause-specific mortality, which was not possible in my dataset due to event number restrictions, and additionally distinguish between unplanned and elective hospitalizations.

A strength of using the UK Biobank instead of claims data was the availability of important confounders, such as lifestyle factors, which are usually not available in claims data sets. However, my data set also had limitations. I cannot rule out misclassification arising from non-adherence since this was not assessed. Additionally, the data did not allow me to account for the treatment durations and changes within the two-year follow-up period. I addressed these limitations by applying an intention-to-treat principle with short-term follow-ups as primary outcomes. The "healthy volunteer" bias of the UK Biobank population (Batty et al. 2020) and the relatively young age of the participants are further limitations. The UK Biobank mainly recruited individuals up to age 69. Therefore, my results cannot be generalized to older populations. Given that the oldest age groups might be at a particularly high risk for adverse outcomes due to PIM, and approximately half of my study population was even younger than 65 years, future studies including even older individuals will likely obtain stronger effect estimates for the risks of PIM use with hospitalization and mortality. Generalizability to other countries may also be limited, as physicians' prescribing patterns vary largely in different health care systems. Lastly, it is important to note that PIM lists, such as the EURO-FORTA list, are expert consensus-based, resembling low evidence in the evidence-based medicine hierarchy.

4.2.6 Implications for bias assessment guidelines in pharmacoepidemiology

Interestingly, recent systematic reviews about PIM use judged 12 out of 16 studies on hospitalization (Xing et al. 2019) and 39 out of 44 studies on all-cause mortality (Zhou et al. 2024) as having a low risk of bias according to the Newcastle Ottawa Scale. Although reporting guidelines for pharmacoepidemiology are now available (Langan et al. 2018; Wang et al. 2023), current bias assessment tools do not sufficiently cover the specific methodological challenges of

pharmacoepidemiologic research. Given that these challenges have been insufficiently recognized in prior research, I encourage the development of tailored bias assessment tools to enhance the quality of future studies on this research topic.

4.3 Factors associated with PIM use, medication underuse, and overuse in older adults in the German National Cohort

4.3.1 Summary of findings

This study summarized real-world data of N=54,296 individuals aged 60-74 years participating in the NAKO, and showed that PIM use, underuse, and overuse of medications according to the 2024 version of the FORTA list (Pazan et al. 2025) were very common, with 26.1%, 19.1%, and 23.6% exposed individuals. Moreover, 90.6% and 62.7% of the participants with completely available vaccination information had not received the recommended pneumococcal and annual influenza virus vaccinations, respectively. Additionally, I identified multiple factors associated with PIM use, overuse, and underuse in the areas of sociodemographic/-economic factors, lifestyle factors, and morbidities.

4.3.2 Comparison of frequencies of FORTA-based medication quality estimates with those from previous studies

Multiple other explicit medication assessment tools aimed at improving pharmacotherapy for geriatric patients (Curtin et al. 2019a; Reeve 2020). Given that each tool addresses different medication classes and aspects of medication quality, I will not go into detail on studies utilizing other lists.

Although the FORTA list has been applied in previous studies (Chen et al. 2022; Dreischulte et al. 2023; Greten et al. 2021; Krüger et al. 2021; Michalek et al. 2014; Nguyen et al. 2021; Pazan et al. 2022a; Pazan et al. 2018; Pazan et al. 2019a; Rabenberg et al. 2019; Rieg et al. 2020; Schulze Westhoff et al. 2022; Stenmanns et al. 2024; Wehling et al. 2016; Wickop et al. 2016), my study was the first to assess the frequency of all three medication problems contributing to poor medication quality, including PIM use, underuse, and overuse in a general older population.

Proportions reported by previous studies (Chen et al. 2022; Dreischulte et al. 2023; Greten et al. 2021; Krüger et al. 2021; Michalek et al. 2014; Nguyen et al. 2021; Pazan et al. 2022a; Pazan et al. 2018; Pazan et al. 2019a; Rabenberg et al. 2019; Rieg et al. 2020; Schulze Westhoff et al. 2022; Stenmanns et al. 2024; Wehling et al. 2016; Wickop et al. 2016) ranged from 52.6% to 76.5% (Chen et al. 2022; Dreischulte et al. 2023; Krüger et al. 2021; Wickop et al. 2016) for PIM use and from 48.7% (Chen et al. 2022) to 62.8% (Dreischulte et al. 2023) for underuse. Only one study (Chen et al. 2022) reported a prevalence for overuse, and two out of three participants (66.7%) were exposed.

All these studies included participants who had a mean age of 74 years or older. In contrast, with a median age of 65 years, my study population was relatively young. Moreover, the morbidity was lower in the population-based NAKO sample, whereas high-risk populations were included in the previous studies. Thus, it was not surprising that all previous studies observed higher proportions of exposed individuals (Chen et al. 2022; Dreischulte et al. 2023; Greten et al. 2021; Krüger et al. 2021; Michalek et al. 2014; Nguyen et al. 2021; Pazan et al. 2022a; Pazan et al. 2018; Pazan et al. 2019a; Rabenberg et al. 2019; Rieg et al. 2020; Schulze Westhoff et al. 2022; Stenmanns et al. 2024; Wehling et al. 2016; Wickop et al. 2016). Furthermore, a “healthy volunteer” bias is apparent in the NAKO study population, which precludes estimating medication use or disease prevalences in the German population without using weights. Therefore, I report frequencies rather than prevalences and recommend treating them with caution. Nevertheless, although my observations likely underestimated the prevalences of PIM use, underuse, and overuse of medication in the “true” older general German population, they are still quite high, underscoring the need for measures to reduce them.

4.3.3 Factors associated with PIM use

Given that no previous study has investigated factors associated with PIM use based on the FORTA list, I cautiously refer to studies that applied other tools (Endres et al. 2018; Fiss et al. 2011; Fiss et al. 2013; Muhlack et al. 2018; Zimmermann et al. 2013). Prior research has reported inconsistent results on potential associations of PIM use with age and sex (Endres et al. 2018; Fiss et al. 2011; Fiss et al. 2013; Muhlack et al. 2018; Zimmermann et al. 2013). However, my observation that older age and female sex were statistically significantly associated with PIM use is supported by three previous studies (Fiss et al. 2013; Muhlack et al. 2018; Zimmermann et al. 2013).

The higher risk of PIM use among individuals with low income, obesity, and insufficient physical activity as well as among alcohol abstainers and current smokers has not yet been shown by previous German studies (Endres et al. 2018; Zimmermann et al. 2013) but they are consistent with international research findings (Doheny et al. 2023; Hwang et al. 2023; Paust et al. 2024), suggesting that individuals with lower socioeconomic status and less healthy lifestyles might be more likely to receive PIM. Alcohol abstinence might appear to be an indicator of a healthy lifestyle. However, in the context of population-based studies, abstainers are usually less healthy than low alcohol consumers, since they also include previous alcoholics and individuals who quit drinking due to diseases or interactions with their medication (Rehm et al. 2008; Shaper et al. 1988).

It was not surprising that most of the assessed diseases (18 out of 21) were statistically significantly associated with PIM use, given that most of them are also FORTA indications. All cardiovascular diseases were among these factors, but arterial hypertension stood out with a particularly high 4.5-fold increased odds for PIM use. However, all second- and third-line antihypertensives are classified as FORTA C (questionable) or D (avoid) (Pazan et al. 2025). Thus, simply switching these drugs to potentially more appropriate alternatives is not feasible in many cases and may partly explain the high PIM rate for this indication.

I also observed three neurological diseases among the factors exhibiting the strongest associations with PIM use: Parkinson's disease, epilepsy, and depression with 16.2-fold, 4.3-fold, and 2.1-fold increased odds for PIM use. The varying response rates and pharmacologic profiles of antiparkinson medications, antiepileptics, and antidepressants are likely the challenging aspects for optimizing the pharmacotherapy for these indications. For instance, it would be crucial to consider the differing pharmacological profiles of antidepressants, since all classes, except selective serotonin reuptake inhibitors (SSRIs), are categorized as PIMs according to the FORTA list (Pazan et al. 2025).

4.3.4 Factors associated with medication underuse

Prior studies (Boehlen et al. 2019; Gage et al. 2000; Hsu et al. 2016) investigating factors associated with medication underuse have been based on guidelines for specific indications or the START criteria (Meid et al. 2016). My finding that older age groups had higher odds of medication underuse resulted from the comprehensive adjustment for morbidities. In the model

only adjusted for age, sex, and study center, no association between age and underuse was observed. This would align with a previous study from Germany, which detected no association between age and underuse (Meid et al. 2016). Furthermore, the identified 8% higher odds for underuse among males compared to females might be explained by sex differences with respect to symptom awareness, preventive health behaviors, and subsequent numbers of physician contacts (Golinelli et al. 2025).

Obesity was the only lifestyle factor exhibiting an inverse association with underuse in the fully adjusted model. This was also not observed in the model only adjusted for age, sex, and study center, but appeared after adjustment for the diseases. Maybe individuals with obesity as a comorbidity have a higher number of physician visits and get more medications prescribed.

With respect to the diseases, osteoporosis, atrial fibrillation, Parkinson's disease, and COPD appeared to be most relevant since they were associated with more than 2.0-fold increased odds for underuse. Over half (51.7%) of the participants with osteoporosis did not receive the indicated medication, which is consistent with previous studies (Michalek et al. 2014; Pazan et al. 2018; Stenmanns et al. 2024). Given the well-established associations of osteoporosis-related hip fractures with higher mortality (Konnopka et al. 2009; Rapp et al. 2010) and greater economic burden (Duclos et al. 2010; Konnopka et al. 2009), undertreatment of osteoporosis has been recognized as an important national (Fülling et al. 2021; Hadji et al. 2024; Kanis et al. 2021; Sing et al. 2023) and global (Kanis et al. 2021; Sing et al. 2023) (Conley et al. 2020; Harvey et al. 2017; Kanis et al. 2014; Khosla et al. 2017) concern. As FORTA-based prescribing has been proven to statistically significantly reduce underuse of osteoporosis medications in two RCTs (Michalek et al. 2014; Pazan et al. 2018), there is sufficient evidence to implement such interventions in usual care.

The observed 6.1-fold increased odds for underuse among participants with atrial fibrillation point to another area that requires clinical attention. Although it was not feasible to examine previous successful treatments through ablation or cardioversion, the 38.7% of medication underuse in individuals with atrial fibrillation aligns with the 19% to over 50% underuse of anticoagulation among high-risk patients identified by prior studies (Gage et al. 2000; Hsu et al. 2016; Schnabel et al. 2015). However, given the increasing prevalence of atrial fibrillation with age, along with the complexity of bleeding risks, optimal stroke prevention, and rhythm management in the oldest patient group (Go et al. 2001; Parks et al. 2024), the detected high medication underuse rate should receive attention in clinical care.

For some diseases with considerably high rates for indication-specific underuse (e.g., Parkinson's disease and COPD), a lack of efficacy of the first-line drugs could be an explanation for underuse, as well as early-stage diseases, for which the pharmacotherapy had not yet been initiated.

4.3.5 Factors associated with medication overuse

Only one previous study investigated factors associated with medication overuse, and this study only focused on antidepressants based on the START criteria (Boehlen et al. 2019). In my study, I observed 25% lower odds for overuse among men compared to women. This sex difference was likely driven by hormone replacement therapy (HRT), which ranked second among all overused drug classes. The FORTA list classifies HRT as overuse for individuals without osteoporosis if it is not used within three years of menopause (Pazan et al. 2022b; Pazan et al. 2025), which typically occurs between the ages of 50 and 51 in Europe (Schoenaker et al. 2014). Given that my study population was 60 years and older, HRT was subsequently classified as overuse in all study participants without osteoporosis. Periodically re-evaluating the need for HRT and the individual risk profile is also recommended by the European clinical practice guideline (Lumsden et al. 2025).

With respect to lifestyle factors, the clear pattern emerged that individuals leading unhealthy lifestyles appeared to be more likely to overuse medications. Maybe physicians tend to treat these patients with medications rather than recommending lifestyle changes, which would be identified as overuse if there is no clear indication. Moreover, patients with unhealthy lifestyles are commonly the most morbid and often receive polypharmacy. With an increasing number of diseases, the medication also becomes more complex, posing challenges for the physicians to maintain an overview of all drugs (still) needed.

Compared to PIM use and underuse, diseases were less prominent factors associated with overuse. However, a history of depression and epilepsy (1.6 and 1.5-fold increased odds) appeared to be most relevant. A large proportion of overuse among participants with depression may be explained by relapse prophylaxis or maintenance therapy (Kishi et al. 2023; Machmutow et al. 2019; National Institute for Health and Care Excellence (NICE) 2022) since 11.2% of the participants with a lifetime history of depression received antidepressants but reported no moderate or severe symptoms, which I applied to define an indication for antidepressants. Given

that prior research recommended maintenance therapy for at least 6 months after remission to effectively prevent relapse (Kato et al. 2021; Kishi et al. 2023), the absence of at least moderate depressive symptoms could also reflect the effectiveness of an appropriate and indicated treatment. Distinguishing appropriate maintenance therapy from "true" overuse requires regular review of each individual's treatment in clinical practice. However, I had no information on whether these evaluations took place. Antidepressants and antiepileptics used to treat pain could not have been a driver of overuse, as I also considered pain an alternative indication.

When further exploring underlying sources of overuse among patients with epilepsy or a history of depression, I detected considerable overuse of low-dose ASA and PPIs among participants with these indications. Regarding epilepsy, the high proportions of low-dose ASA overuse might be explained by appropriate secondary stroke prevention, given that stroke is the most common cause of epilepsy in older individuals (Lühdorf et al. 1986). If these participants did not report their history of stroke, overuse would be detected. With respect to PPI, these medications might have been initiated due to gastrointestinal side effects caused by antiepileptic drugs (Nevitt et al. 2022) or somatic depressive symptoms (Zamani et al. 2023). However, if these symptoms were not severe, the medications to treat them appear to be overused. Regarding low-dose ASA and depression, associations of depression with cardiovascular disease have also been established (Triolo et al. 2024). However, the low-dose ASA appears as overuse if no cardiovascular disease has yet been diagnosed.

The finding that low-dose ASA was the most frequently overused drug (in 5.1% of the study population) warrants attention in clinical practice. The observed frequency was supported by an observational study from Spain, which found overuse of low-dose ASA among 7% of the participants (Candela Marroquín et al. 2012). In light of the associated bleeding risks, current guidelines have become very conservative regarding its use in primary prevention (US Preventive Services Task Force 2022; Visseren et al. 2021). The US guidelines even recommend against initiating low-dose ASA for primary prevention in adults aged over 60 years (US Preventive Services Task Force 2022).

In addition to the identified associated factors, an interesting finding was that 3.3% of the study population overused PPIs. Concerns about their appropriate use have been progressively emphasized and addressed through specific deprescribing guidelines (Bytzer 2018; Farrell et al. 2017). A previous drug utilization study using German claims data revealed a notable rise in PPI prescriptions between 2010 and 2016, and 52% of the new PPI users lacked a documented on-label indication (Rückert-Eheberg et al. 2022).

4.3.6 Underuse of vaccinations

The low vaccination rates for pneumococcal (90.6% underuse) and annual influenza (62.7% underuse) vaccines observed in this study were consistent with recent data from the German vaccination monitoring. Specifically, 88.2% and 68.6% of the citizens aged 60-64 and 65-69 years, respectively, had not received pneumococcal vaccinations. Moreover, 61.8% of those aged 60 years or older were not vaccinated against influenza (Robert Koch-Institut 2025). Implementing regular vaccination checks, ideally through easily accessible opportunities outside standard physician visits, could help reduce underutilization of vaccines.

4.3.7 Regional differences

Regional social inequalities between rural and urban German regions have been previously recognized, highlighting better accessibility to primary and specialist care in urban regions (Bauer et al. 2018; Hansen et al. 2017; Schäfer et al. 2020). My results might reflect these disparities by showing differences in the odds for all three medication problems by study center. For instance, the odds for PIM use were particularly low in Hamburg, which is the second largest city in Germany and has a higher average socioeconomic status and a higher ratio of physicians per residents compared to most other German rural regions. Consequently, participants attending study centers in rural eastern German regions, such as Neubrandenburg and Demmin, had the highest odds for PIM use. Interestingly, these rural regions additionally had the lowest odds for underuse. With respect to overuse, the pattern was less clear, since urban regions were among the study centers with the highest (Regensburg) and lowest (Bremen) odds for overuse. Collectively, I consider these potential regional differences as interesting signals warranting further investigation.

4.3.8 Strengths and limitations

To the best of my knowledge, this was the first study to examine the frequency of and factors associated with all three medication problems that contribute to poor medication quality in the general older population. The availability of a wealth of data enabled me to investigate potential associations of a broad range of factors. Incorporating diagnostic and physical assessments as

well as blood-based biomarkers into the indication assessment was a unique strength that helped minimize potential misclassification of diagnoses. Furthermore, the comprehensive brown-bag review ensured a high level of completeness and reliability of the medication assessment. Finally, the large sample size (N=54,296) provided sufficient statistical power to address numerous potentially associated factors (n=31) with correction for multiple testing. While the identified associated factors provide a clinically relevant foundation for effectively identifying target populations for medication reviews, it is important to note that the cross-sectional design primarily reflects correlations but does not imply causal inference.

The main detriment of this study is the "healthy volunteer" bias and a relatively young sample of older adults (60-74 years). Thus, the results cannot be extrapolated to older populations or all German adults aged 60 years and older.

Another important limitation is the risk of information bias, encompassing both under- and overreporting of indications (e.g., through recall bias or undiagnosed conditions) and (over-the-counter) medications. This was accounted for by comprehensive statistical adjustment and completing indications with information from medications, physical/diagnostic assessments, and biomarkers.

This study was based on the 2024 version of the FORTA list, while the NAKO baseline data was collected between 2014 and 2019. The minimal changes in the FORTA list during this time did likely not affect the results to a relevant extent. However, the German study population and the application of the Germany-specific FORTA list might restrict the generalizability to other countries. Notably, the European version of the FORTA list (Pazan et al. 2023) is largely consistent with the Germany-specific version. A future study across European countries, ideally with available linkage to validated diagnoses (e.g., claims data), would be desirable.

4.3.9 Clinical implications

My findings highlight critical areas that clinical practice may need to address, such as untreated osteoporosis and low vaccination uptake. Additionally, the factors associated with the three medication problems can be used to assign resources for comprehensive FORTA-based medication reviews to those patients with the highest odds for PIM use, underuse, or overuse, which were individuals with arterial hypertension, Parkinson's disease, epilepsy, depression, osteoporosis, COPD, and atrial fibrillation. Given that arterial hypertension has a very high prevalence in older adults (49.7% in this study sample), and all second- and third-line

antihypertensives are classified as PIM, making changes in antihypertensive medication would be difficult. Thus, I recommend focusing on the other six named, less common, indications. As "only" 0.4%, 0.7%, 15.7%, 7.3%, 7.5%, and 15.2% of the older German NAKO study population were affected by Parkinson's disease, epilepsy, depression, osteoporosis, COPD, and atrial fibrillation, respectively, and since they are also usually documented in electronic health records, they could be used to quickly identify a high-risk population for medication problems. If resources for comprehensive medication reviews with the FORTA list are limited, this disease-defined high-risk population could be prioritized. However, it should be noted that this suggested priority group is not based on evidence from RCTs demonstrating greater benefit of comprehensive medication reviews in these patient populations compared to others. Such RCTs are still needed. In addition, further research could establish effective strategies that help clinicians address poor medication quality in hard-to-reach groups, such as patients with lower socioeconomic status, with unhealthy lifestyles, or those living in rural regions with barriers to healthcare access. Finally, the application of the FORTA list should only be regarded as a screening tool to help detect medication problems. It cannot replace clinical judgment, and the final decisions regarding (de-)prescribing should also be guided by patient preferences and treatment goals.

4.4 Cancer co-medication quality in older patients with polypharmacy: a large randomized trial testing a medication review versus usual care

4.4.1 Summary of findings

This RCT demonstrated that an advisory letter containing the results of a comprehensive FORTA-based medication review sent to the treating rehabilitation physician was highly feasible and statistically significantly reduced the total FORTA score of older cancer patients with polypharmacy from admission to discharge by approximately 4 score points compared to usual care. A reduction of 4 FORTA score points translates, for example, to the switch of 2 PIM to AM, the withdrawal of 4 drugs labeled as overuse, or new treatments for 4 indications with drug underuse. The acceptance rates by rehabilitation physicians for recommendations to reduce PIM use, overuse, medication and vaccine underuse were comparably high, and led to statistically

significant reductions in the proportion of subjects exposed to all these highly common medication problems among older cancer patients during oncological rehabilitation.

4.4.2 Comparison with previous studies

My findings confirm the results from the two previous FORTA-based RCTs in general older hospitalized patients, the VALFORTA trial (Wehling et al. 2016) and its feasibility-oriented pilot RCT (Michalek et al. 2014). They demonstrated the clinical applicability of the FORTA list, the acceptability of the recommendations across different indications, and a significant reduction in the FORTA score by (median) 3 points in the intervention group vs. 1 point in the control group (Michalek et al. 2014; Wehling et al. 2016). Their median group difference of 2 points was slightly lower than the 3 points in the OPTIMAL trial (without vaccine underuse, which was not part of the first version of the FORTA list used in the VALFORTA trial). The difference can best be explained by the study populations. The older cancer patients in the OPTIMAL intervention group had a median FORTA score of 4 (without vaccine underuse), and the older hospitalized patients in the VALFORTA study's intervention group had a median FORTA score of 3. There was simply a greater need for improvements in the medication quality of geriatric cancer patients, and the OPTIMAL study showed that it was possible to achieve this goal through the pharmacist-led counseling of rehabilitation physicians. In the VALFORTA study, the physicians conducted the medication reviews themselves.

Vaccine underuse was added to the FORTA list in 2021. OPTIMAL was the first RCT to evaluate the underuse of 4 recommended vaccinations in older cancer patients in Germany. The high acceptance rate (89.9%) for vaccine-related recommendations observed in the OPTIMAL intervention group was in line with the one reported by a US-American RCT with older cancer patients (Nipp et al. 2019).

Furthermore, the statistically significant reductions in PIM and medication underuse align with previous evidence from RCTs across diverse clinical populations and medication assessment tools summarized in the systematic review by Cole et al. (Cole et al. 2023). However, few RCTs with rather small sample sizes (N=60 to N=147) tested the feasibility and effectiveness of medication reviews in reducing medication problems in older cancer patients (Dürr et al. 2021; Lund et al. 2021; Nipp et al. 2019; Vega et al. 2016), and their results are not directly comparable with others because the methods of the medication reviews differed.

4.4.3 Acceptance of recommendations

The high acceptance rates of recommendations for PIM, overuse, and underuse of vaccinations (all > 75%) by the rehabilitation physicians demonstrated the effectiveness of the FORTA list not only in detecting relevant medication problems but also in suggesting solutions that are mostly acceptable for clinicians. I consider the lower acceptance rate of recommendations for underused drugs (52%) as less clinically relevant. Among the top 5 FORTA indications, for which at least 10 underuse-specific recommendations were given, three displayed indications, which can be treated non-pharmacologically: type 2 diabetes by lifestyle interventions, insomnia by sleep hygiene and behavioral therapy, and incontinence by bladder training (American Diabetes Association 2021; Riemann et al. 2023; Russo et al. 2021).

4.4.4 Implications for clinical practice

4.4.4.1 Clinical relevance of the total medication quality measured by the FORTA score

The OPTIMAL trial provides robust evidence for the effectiveness of FORTA-based medication reviews in optimizing cancer and co-medication quality for older cancer patients. The effect size is clinically relevant because the recorded reduction in the total FORTA score by approximately 4 score points (rounded) in the intervention compared to the control group translates to, for instance, the withdrawal of 4 drugs labeled as overuse, the new initiation of 4 drugs for indications not yet treated, or the switch of 2 PIM to more appropriate alternatives. Evidence for the clinical relevance of treating medication overuse and underuse is rather weak (Meid et al. 2015; Omuya et al. 2023), but the evidence for the clinical relevance of reducing PIM is quite strong because PIM use has been linked to hospitalizations and premature death (Chen et al. 2021a; Chen et al. 2022; Degen et al. 2025).

4.4.4.2 Clinical relevance of PIM use

Thus, I advise physicians to critically review prescriptions for the most common PIM groups, including analgesics, beta blockers, antidepressants, antipsychotics, and sedatives, and to exploit appropriate alternative medications.

NSAIDs deserve particular attention as they accounted for almost two-thirds (63%) of the pain-related PIM. The recently published German guideline for pain management in geriatric patients also recommends the FORTA list to guide treatment selection and emphasizes the importance of carefully weighing the risks associated with NSAID use in older patients (Deutsche Schmerzgesellschaft e.V. et al. 2025), which include cardiovascular events, renal toxicity, and gastrointestinal bleeding (Bhala et al. 2013; Calvo et al. 2025; Sostres et al. 2011). As this has often been underacknowledged in clinical practice (Scholle et al. 2020), I encourage physicians to give greater consideration to recommended alternatives such as paracetamol, metamizole, and different opioids (Pazan et al. 2022b; Pazan et al. 2025).

To minimize inappropriate beta blocker use, I recommend that physicians first evaluate if patients have any indication beyond arterial hypertension for their use, such as atrial fibrillation, heart failure, or previous acute coronary syndromes. For these indications, beta blockers would be classified as AM (Pazan et al. 2022b; Pazan et al. 2025). However, in isolated arterial hypertension, it is advisable to prioritize ACE inhibitors, angiotensin II receptor blockers, diuretics, and dihydropyridine calcium channel blockers, given the inferiority of beta blockers on clinical outcomes (Wright et al. 2018) and their more than 7-fold increased odds for orthostatic hypotension (OR [95% CI]: 7.76 [2.51; 24.03]) [36] that may increase the risk for falls (Colón-Emeric et al. 2024).

Anticholinergic antidepressants, antipsychotics, and sedatives are further common PIM groups that are associated with an elevated risk for falls (Bhanu et al. 2021; Colón-Emeric et al. 2024) as well as cognitive impairment (Taylor-Rowan et al. 2021). Optimal treatment selection is essential to prevent these adverse drug events, and the FORTA list can help identify suitable alternatives depending on the underlying indication (e.g., depression, dementia-related symptoms, sleep disorders). While PIM may be deemed necessary in individual cases, such as benzodiazepines in terminally ill cancer patients, the high acceptance rates for the recommended alternatives reflect that these PIM are not necessary in most cases.

4.4.4.3 Clinical relevance of medication underuse

Analgesics, prolonged-release melatonin against insomnia, and drugs against incontinence were among the most common underused medications. I identified most of these cases by frequent and severe symptoms reported by patients in the self-administered questionnaire. It can be assumed that the physicians were often not aware of this symptom burden, as previous research demonstrated that pain and insomnia remain frequently undisclosed during medical consultations

(Paskins et al. 2018), and reporting incontinence can be a source of embarrassment. It is advisable for physicians to proactively ask about these symptoms because they have a large impact on the patient's quality of life. However, I acknowledge that it is worth exploring non-pharmacological options first for insomnia and incontinence.

4.4.4.4 Clinical relevance of vaccination underuse

On average, two of the four vaccinations recommended for subjects 65 years or older in Germany were missing. Given that older cancer patients are an especially vulnerable patient group for infections, closing this gap is of high clinical relevance (Zheng et al. 2021). I recommend incorporating vaccination assessments into medication reviews. Furthermore, I encourage oncologists to proactively ask about vaccination status and not to leave this care only in the hands of the GP. The high acceptance rate of vaccine-related recommendations by the physicians and their patients in the OPTIMAL trial showed that it is possible to catch up on missing vaccinations in most cases.

4.4.4.5 Clinical relevance of medication overuse

PPIs and antithrombotic drugs were the most and third most common overused medication classes. Frequently, they are "leftovers" from hospital stays, where PPIs were prescribed to temporarily prevent medication-induced upper gastrointestinal bleeding (e.g., through NSAIDs) and antithrombotic drugs to prevent major cardiovascular events for immobilized patients. They are usually not intended to be continued after hospital discharge (Ahrens et al. 2012; Steinsdóttir et al. 2024). I recommend physicians in rehabilitation clinics or the outpatient setting to deprescribe these drugs in the absence of a clear indication (Targownik et al. 2022). Deprescribing PPIs is of special relevance for cancer patients as they may severely interact with antineoplastic agents, including proven loss of efficacy for certain tyrosine kinase inhibitors (Raoul et al. 2023). The second most frequent drug group with overuse was lipid-lowering drugs, and in 79% of cases, physicians discontinued their use when notified about the overuse in the recommendation letter. The rehabilitation physicians had measurements of the lipids and triglycerides from the admission blood samples available to base their decision on. It is advisable to always consider the potential discontinuation of lipid-lowering drugs in clinical routine when these biomarkers are measured as part of routine check-ups.

4.4.4.6 Application of the FORTA list in clinical practice

The FORTA list alone is not meant to replace clinical judgment and consideration of individual treatment goals. However, in combination with these standard medical procedures, no harm is expected from using it as a tool for guidance. The FORTA list is free of charge, easy to apply (via smartphone app or web-based list), and available for many countries (Pazan et al. 2020; Pazan et al. 2023). These structural benefits would also support a potential large-scale implementation into standard (rehabilitation) care in the future. Decentralized medication reviews, e.g., communicated through advisory letters as conducted in this trial, represent a feasible strategy, especially when resources for medical and pharmaceutical personnel in the clinics are limited. Alternatively, implementing an automated PC-based program could be a viable, cost-effective option.

4.4.5 Strengths and limitations

To my knowledge, this was the first RCT to assess a medication review in the oncologic rehabilitation setting and the first to use the FORTA criteria in cancer patients. By combining physician and patient-reported information, I achieved a comprehensive overview of medical history (including untreated symptoms, such as pain, insomnia, incontinence, and constipation) and medication use (including over-the-counter medication use).

I am confident that the rigorous methodological approach mitigated common biases (e.g., contamination bias by monitoring potential learning effects and sending sham recommendation letters for participants in the control group, or selection bias by using an intention-to-treat approach as the main analysis).

Although oncological rehabilitation may be organized differently in other countries, I am confident that results are generalizable to other developed countries, which have similar oncological care programs. The multi-center study design with 10 rehabilitation clinics across Germany and the subgroup analysis by rehabilitation clinic ensured that the results are robust and translatable to clinical practice in Germany.

The main limitation of this investigation is that clinicians could not be blinded because they could correctly guess the control group allocation for study participants for whom they received the sham advisory letter.

4.5 Conclusion

Based on original data analyses of two large-scale, population-based, national cohort studies, summarized evidence from existing RCTs, and the new OPTIMAL RCT, this dissertation generated high-level evidence for effective strategies to optimize medication use in older adults in Germany.

My systematic review, meta-analysis, and meta-regression of RCTs investigating medication reviews in hospitalized patients provided insights into methodological aspects that may explain why some trials observed a higher efficacy of medication reviews in reducing rehospitalization and mortality rates than others. Incorporating multiple patient contacts, involving pharmacists, and multi-morbid patients as priority target groups are recommended key components for effective interventions. The current evidence is strong for a reduction in hospital readmissions by medication reviews among patients aged 70 years and older, which is a particularly vulnerable population regarding drug safety. Moreover, a complete mortality ascertainment with at least 1 year of follow-up is required for trials aiming to improve mortality outcomes. Therefore, I recommend implementing medication reviews as part of standard hospital care, preferably considering the identified key components.

My original data analysis assessing the risks for hospitalization and mortality associated with PIM use was the first study to utilize the gold standard methodology and demonstrated that all previous studies on PIM have either under- or overestimated these risks by overlooking typical methodological pitfalls in pharmacoepidemiology. Future research should overcome these limitations by using the new user/active comparator approach. Very large data sets, ideally including older adults, will be needed to detect moderately increased risks of approximately 20% with statistical significance.

In my original data analysis of older adults participating in the large, population-based NAKO, PIM use, medication underuse, and overuse were very common. Arterial hypertension, Parkinson's disease, epilepsy, depression, osteoporosis, COPD, and atrial fibrillation were identified as diseases with the highest odds of these medication problems. Patients with the latter six diseases could be prioritized for medication reviews if resources are limited, as they had prevalences < 16%.

The pharmacist-led comprehensive medication review with the FORTA score to counsel physicians in oncological rehabilitation wards was highly feasible and substantially improved the medication quality of older cancer patients with polypharmacy. Clinicians may draw on the freely available FORTA list as a guiding resource in their daily clinical practice. In light of the proven efficacy of medication reviews in reducing rehospitalizations and their potential to reduce mortality, there is sufficient evidence to consider integrating FORTA-based medication reviews into standard oncologic rehabilitation.

5 Summary

5.1 English summary

Previous research has linked common medication problems, including medication underuse and overuse, as well as the use of potentially inappropriate medications (PIM) in older adults, to hospitalizations and premature death. The freely accessible Fit fOR The Aged (FORTA) list helps to identify and to solve these medication problems. However, the evidence for effective medication optimization strategies was limited by methodological shortcomings of prior research. Hence, the overall aim of this dissertation was to generate robust evidence for medication optimization strategies in older adults that can be translated into clinical practice.

My systematic review, meta-analysis, and meta-regression demonstrated an 8% reduced risk for rehospitalizations in 24 randomized controlled trials (RCTs) (RR [95% confidence interval (CI)]: 0.92 [0.88; 0.97], p=0.002) testing medication reviews compared to usual care in hospitalised patients, and 19% reduced mortality (RR [95% CI]: 0.81 [0.70; 0.94], p=0.007) in 10 RCTs with complete mortality ascertainment via registries or primary care data. Investigating potential sources for heterogeneous trial results, multiple patient contacts, involving pharmacists, and multi-morbid target groups were identified as key components for effective interventions.

My data analysis of 217,111 United Kingdom Biobank participants aged 60–69 years assessed the risks for hospitalizations and mortality associated with PIM use. I introduced the 1:1 propensity-score stratified by indication matching of new PIM users and new appropriate medication users (assessed with the European version of the FORTA list) as a novel method. Although this yielded biologically plausible, approximately 20% increased risks for both outcomes (hazard ratios (HRs) [95% CIs]: 1-month hospitalization: 1.20 [0.76; 1.90]; 1-year mortality: 1.23 [0.80; 1.89]) in 11,812 propensity score-matched individuals identified through primary care linkage, effect estimates were not statistically significant. I also demonstrated that previous studies have either under- or overestimated the risk profile of PIM by overlooking typical methodological pitfalls of pharmacoepidemiology.

My original data analysis of 54,296 German National Cohort (NAKO) participants aged 60–74 years showed a high need for medication optimization in the general older population in Germany, with 26.1%, 19.1%, and 23.6% exposed to PIM use, medication underuse, and

overuse, respectively. I found that Parkinson's disease, arterial hypertension, epilepsy, and depression were strongly associated with PIM use (all ≥ 2.1-fold increased odds), osteoporosis, atrial fibrillation, Parkinson's disease, and chronic obstructive pulmonary disease were particularly strongly associated with underuse (all ≥ 2.0-fold increased odds), and depression and epilepsy were the most prominent factors associated with overuse (1.6 and 1.5-fold increased odds).

In the randomized controlled OPTIMAL trial, I conducted FORTA-based medication reviews for 433 cancer patients aged ≥ 65 years with polypharmacy (≥ 5 medications) undergoing rehabilitation and tested the superiority of an advisory letter with their results sent to the treating physician compared to usual care on the FORTA score until discharge in 10 collaborating rehabilitation clinics. At admission, 66.1%, 94.6%, and 58.9% of 443 trial participants included in the intention-to-treat analysis were exposed to PIM, medication underuse, or overuse, respectively, and the median total FORTA score was 6. At discharge, participants of the intervention group (N=234) had a statistically significantly greater reduction in the mean total FORTA score than the control group (N=209): mean difference [95% CI]: -3.7 [-4.2; -3.3] score points. This translates, for example, to the withdrawal of 2 PIM or 4 drugs labeled as overuse or the initiation of 4 underused drugs. Furthermore, the proportions exposed to PIM, underuse, and overuse were statistically significantly reduced by the intervention by 41.3, 35.5, and 30.7 percentage points (all $p<.001$).

As medication reviews have proven efficacy in reducing hospital readmissions in hospitalized patients and may also reduce mortality, this dissertation provides sufficient evidence to implement them into usual hospital care. The OPTIMAL RCT also demonstrated that a pharmacist-led medication review with the FORTA list was highly feasible and substantially improved the medication quality of older cancer patients with polypharmacy, among whom medication problems were even more prevalent compared to the general older population. I recommend that physicians draw on the FORTA list in their daily clinical practice to optimize medications for older patients, as the prescription of a new PIM is associated with approximately 20% increased risk for hospitalization and mortality. Patients with Parkinson's disease, epilepsy, depression, osteoporosis, COPD, and atrial fibrillation represent suggested priority groups if the resources are limited, since these diseases have prevalences < 16% in the older German population.

5.2 Deutsche Zusammenfassung

Frühere Studien haben Zusammenhänge zwischen bestimmten Medikationsproblemen bei älteren Personen mit Hospitalisierungen und vorzeitigem Tod gezeigt. Diese Medikationsprobleme umfassen den Über- und Untergebrauch von Medikamenten sowie potenziell ungeeignete Medikamente (PIM), die mithilfe der Fit fOR The Aged (FORTA)-Liste identifiziert und durch geeignetere Medikamente gelöst werden können. Die Evidenz für Medikationsoptimierungsstrategien war allerdings beschränkt, insbesondere durch methodische Schwächen vorangegangener Studien. Diese Dissertation hatte daher das übergeordnete Ziel, robuste Evidenz für die Medikationsoptimierung bei älteren Erwachsenen in der klinischen Praxis zu gewinnen.

Meine systematische Übersichtsarbeit mit Meta-Analyse randomisierter, kontrollierter Studien (RCTs) demonstrierte, dass hospitalisierte Erwachsene, die eine Medikationsanalyse erhalten hatten, ein statistisch signifikant 8% niedrigeres Risiko für Rehospitalisierungen hatten als diejenigen, die die übliche Versorgung ohne Medikationsanalyse erhielten (24 RCTs; relatives Risiko (RR) [95% Konfidenzintervall (KI)]: 0.92 [0.88; 0.97], p=0.002). In den 10 RCTs mit vollständiger Todesfallerfassung anhand von Register- oder Primärversorgungsdaten hatten Patient*innen, die eine Medikationsanalyse erhalten hatten, zudem ein um 19% geringeres Mortalitätsrisiko (RR [95% KI]: 0.81 [0.70; 0.94], p=0.007). In Subgruppenanalysen und Meta-Regressionen identifizierte ich wiederholte Patient*innenkontakte, pharmazeutische Beteiligung sowie multimorbide Zielgruppen als Schlüsselkomponenten für effektive Medikationsanalysen.

Meine Datenanalyse von insgesamt 217.111 älteren (60–69 Jahre) Teilnehmenden der United Kingdom Biobank untersuchte, ob PIM-Gebrauch mit erhöhten Hospitalisierungs- und Mortalitätsrisiken verbunden ist. Dafür verwendete ich ein indikationsstratifiziertes 1:1 *Propensity Score Matching* von Personen, die innerhalb von 2 Jahren nach der Rekrutierung in prospektiven Verschreibungsdaten eine neue PIM- oder geeignetere Medikamentenverordnung (gemäß der europäischen Version der FORTA-Liste) erhielten. Obwohl die Analyse der 11.812 gematchten Personen biologisch plausible, circa 20% höhere Risiken für beide Endpunkte ergab (*Hazard Ratios* (HRs) [95% KIs]: 1-Monats-Hospitalisierungen: 1.20 [0.76; 1.90]; 1-Jahres-Mortalität: 1.23 [0.80; 1.89]), waren die Effektschätzer statistisch nicht signifikant. Zudem zeigte ich, dass frühere Studien aufgrund typischer methodischer Fallstricke der Pharmakoepidemiologie die mit PIM verbundenen Risiken über- oder unterschätzt haben.

Meine Datenanalyse von 54.296 älteren (60–74 Jahre) Teilnehmenden der NAKO Gesundheitsstudie zeigte den hohen Bedarf für Medikationsoptimierung in der älteren Allgemeinbevölkerung in Deutschland: 26,1%, 19,1% und 23,6% waren von PIM-Gebrauch, Medikationsunter- und -überversorgung betroffen. Morbus Parkinson, arterielle Hypertonie, Epilepsie und Depressionen waren stark mit PIM-Gebrauch assoziiert (≥ 2,1-fach erhöhte *Odds*). Osteoporose, Vorhofflimmern, Morbus Parkinson und chronisch obstruktive Lungenerkrankungen waren besonders stark mit Medikationsunterversorgung assoziiert (≥ 2,0-fach erhöhte *Odds*). Depressionen und Epilepsie waren die Faktoren, die die stärkste Assoziation mit Medikationsüberversorgung aufwiesen (1,6- bzw. 1,5-fach erhöhte *Odds*).

In der OPTIMAL RCT habe ich untersucht, ob eine Medikationsanalyse die Art und Anzahl der Medikationsprobleme (zusammengefasst als FORTA Score) von älteren (≥ 65 Jahre) Krebspatient*innen mit Polypharmazie (≥ 5 Medikamente) von der Aufnahme bis zur Entlassung aus zehn onkologischen Rehakliniken stärker verbessert als die übliche Versorgung. Dazu habe ich für 443 Teilnehmende Medikationsanalysen mit der FORTA-Liste durchgeführt und einen Beratungsbrief (oder Scheinbrief) an die behandelnden Reha-Ärzt*innen gesendet. Bei Aufnahme waren 66,1%, 94,6% sowie 58,9% der *Intention-to-Treat*-Population von PIM-Gebrauch, Medikationsunter- sowie -überversorgung betroffen. Der mediane FORTA-Score betrug 6. Bei Entlassung hatten Patient*innen der Interventionsgruppe (N=234) eine statistisch signifikant größere Reduktion des FORTA-Scores als Kontrollgruppenpatient*innen (N=209): mittlere Differenz [95% KI]: -3.7 [-4.2; -3.3]. Das entspricht dem Absetzen von 2 PIM oder 4 übergebrauchten Medikamenten oder dem Ansetzen von Medikamenten für 4 unbehandelte Indikationen. Verglichen mit der Kontrollgruppe war der Anteil der Teilnehmenden mit PIM-Gebrauch, Medikationsunter- und -überversorgung bei Entlassung statistisch signifikant um 41,3, 35,5 sowie 30,7 Prozentpunkte ($p<.001$) geringer.

Diese Dissertation liefert robuste Evidenz für die Implementierung von Medikationsanalysen in die Standardversorgung. Medikationsanalysen verbessern die Medikationsqualität sowie die damit verbundenen klinischen Endpunkte Rehospitalisierung und Mortalität bei hospitalisierten Erwachsenen. Die frei verfügbare FORTA-Liste ist ein geeignetes Hilfsmittel, auf das Ärzt*innen auch bei komplexen Patientenkollektiven wie älteren Krebspatient*innen mit Polypharmazie zurückgreifen können. Sollten die Ressourcen beschränkt sein, könnten Patienten mit Morbus Parkinson, Epilepsie, Depressionen, Osteoporose, Vorhofflimmern und chronisch obstruktiver Lungenerkrankung priorisiert werden, da diese Erkrankungen in der älteren Bevölkerung in Deutschland Prävalenzen von < 16% aufweisen.

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7 Own Publications and Contributions

All results, including texts, tables, figures, and appendices presented in this dissertation are part of the following 4 publications, of which the first 3 have already been published in international, peer-reviewed journals with high impact factors:

1. Degen, M., Chen, L. J. and Schöttker, B. (2025). **Medication reviews in hospitalised patients for reduced hospital readmission and mortality. Systematic review, meta-analysis and meta-regression of RCTs.** Ageing Res Rev 104, 102661, doi: 10.1016/j.arr.2025.102661.

2. Degen, M. and Schöttker, B. (2025). **Associations of potentially inappropriate medications in older adults with mortality and hospitalizations: methodological challenges in pharmacoepidemiology.** Eur J Epidemiol 40(9), 1067-1082, doi: 10.1007/s10654-025-01294-x.

3. Degen, M., Haug, U., Scholle, O. H. F., Awuku-Larbi, Y., Carlsson, S., Ebert, N., Harth, V., Hauri, A. M., Heier, M., Herrmann, A., Leitzmann, M., Linseisen, J., Meinke-Franze, C., Obi, N., Pendt, P., Reinhold, T., Thorand, B., Brenner, H. and Schöttker, B. (2026). **Factors associated with potentially inappropriate medication use, medication underuse and overuse in older adults in the German National Cohort.** J Intern Med, doi: 10.1111/joim.70097 [Online ahead of print].

4. Degen, M., Kopp-Schneider, A., Vlaski, T., Carlsson, S., Hallermann, P., Jewlanowa, L., Barinoff, J., Goede, V., Lüders, C., Kiefer-Trendelenburg, T., Lüftner, D., Doll, J., Wagner, J., Leibbrand, B., Brenner, H. and Schöttker, B. (202X). **Cancer co-medication quality in older patients with polypharmacy: a large randomized trial testing a medication review versus usual care.** [submitted to journal]

In this dissertation, Chapters 1.1, 1.2, 1.6 (aim I), 2.1, 3.1, 4.1, and 4.5 are based on **publication 1**. I contributed 50% to the conceptualization and methodology. I conducted the literature search (including screening of trials previously included and excluded by a previous Cochrane review as well as an updated literature search of two years using search strings developed by the authors of the previous Cochrane review with minor changes in operators used for one out of four

databases because I used a different database provider). I conducted 100% of the title-/abstract screening. The full-text screening, the data extraction, and the risk of bias assessment were performed independently by me and a second reviewer (Dr. Li-Ju Chen) in the framework of a four-eye-principle. I conducted the meta-analyses and meta-regressions and drafted the manuscript. My supervisor, Prof. Dr. Ben Schöttker, was involved in the conceptualization and methodology and made significant contributions to the revision of the manuscript. Dr. Li-Ju Chen commented critically on the manuscript in its advanced stage.

Chapters 1.1, 1.6 (aim II), 2.2, 3.2, 4.2, and 4.5 originate from **publication 2**. I contributed 60% of the conceptualization and methodology, 100% of the literature review, 100% of the data analyses, and 80% of the interpretation of the results. I drafted the manuscript and my supervisor, Prof. Dr. Ben Schöttker, revised it.

Chapters 1.1, 1.6 (aim III), 2.3, 3.3, 4.3, and 4.5 stem from **publication 3**. I contributed 60% of the conceptualization and methodology, 100% of the literature review, 100% of the data analyses, and 80% of the interpretation of the results. I drafted the manuscript and my supervisor, Prof. Dr. Ben Schöttker, revised it. The co-authors commented critically on the manuscript in its advanced stage. Dr. Margit Heier and Prof. Dr. Jakob Linseisen were furthermore responsible for the NAKO modules for the initial registration.

Chapters 1.1, 1.6 (aim IV), 2.4, 3.4, 4.4, and 4.5 originate from **publication 4**. Prof. Dr. Ben Schöttker designed the OPTIMAL trial, wrote its protocol, and obtained funding (together with Prof. Dr. Hermann Brenner and Dr. Li-Ju Chen) to conduct if. I conducted 90% of the medication reviews (including creation of the advisory letter or sham letter) and was involved in the trial as study coordinator. The initial SAS codes to perform the medication reviews and to calculate the FORTA scores were prepared by Dr. Li-Ju Chen and throughout the course of the trial, I modified and improved them. Together with the medical documentarist Dr. Thomas Heger, I was involved in the creation of the baseline datasets. Additionally, I created the dataset to analyze the discharge checklists. Based on the study protocol, I authored the statistical analysis plan, which was reviewed and approved by Prof. Dr. Ben Schöttker. I performed 100% of the statistical analyses, contributed 80% of the interpretation of the results, and drafted the manuscript. My supervisor, Prof. Dr. Ben Schöttker, revised it. The co-authors commented critically on the manuscript in its advanced stage.

Further own and co-authored publications

Sha, S., Degen, M., Vlaski, T., Fan, Z., Brenner, H. and Schöttker, B. (2024). **The Safety Profile of Vitamin D Supplements Using Real-World Data from 445,493 Participants of the UK Biobank: Slightly Higher Hypercalcemia Prevalence but Neither Increased Risks of Kidney Stones nor Atherosclerosis.** Nutrients 16(14), doi: 10.3390/nu16142251.

Jungreithmayr, V., Bittmann, J. A., Wurmbach, V. S., Degen, M., Dierkes, T., Obersteiner, S., Bruns, B., Estel, S., Bugaj, T. J. and Seidling, H. M. (2025). **A Novel Screening Method to Prioritise Cardiovascular Patients Receiving a Pharmaceutical Care Intervention and the Effects on Patients' Difficulties with Managing Their Drug Treatment.** Patient Prefer Adherence 19, 3807-3818, doi: 10.2147/ppa.S543261.

Presentations at scientific conferences:

European Drug Utilisation Group (EuroDURG) Conference 2025,
International Society for Pharmacoepidemiology (ISPE)
July 1-4, 2025, Uppsala, Sweden
Short oral communication: “Prevalence and determinants of potentially inappropriate medication use in the German National Cohort (NAKO)”

Annual workshop of the pharmacoepidemiology working group,
Deutsche Gesellschaft für Epidemiologie and Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie
November 11-12, 2024, Berlin, Germany
Talk: “Potentially inappropriate medications and mortality – insights from the German National Cohort (NAKO) and UK Biobank”

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Appendix 1. Search string applied in Ovid (MEDLINE)

#	Search string	Results
1	(medication adj2 (review? or reconcil* or counsel*)).ti,ab,kf.	6127
2	((inappropriate or appropriate or improve* or optim* or quality) adj5 (pharmacotherapy or medication* or medicine* or prescri*)).ti,ab,kf.	58725
3	(deprescrib* or deprescript* or de-prescrib* or de-prescript*).ti,ab,kf.	2261
4	((beer* or shan? or mcleod?) adj3 criter*).ti,ab,kf.	1028
5	integrated medicine? management.ti,ab,kf.	22
6	("fit for the aged" adj3 (criter* or list? or instrument or classif*)).ti,ab,kf.	39
7	((forta or rasp or priscus) adj3 (criter* or list? or instrument)).ti,ab,kf.	141
8	(stopp criter* or stopp list?).ti,ab,kf.	262
9	inappropriate prescribing/	4717
10	potentially inappropriate medication list/	1080
11	medication reconciliation/	1577
12	pharmacy service, hospital/og	3819
13	hospital*.ti,ab,kf,hw.	2010335
14	or/1-11	66884
15	13 and 14	16199
16	12 or 15	19600
17	exp randomized controlled trial/	608635
18	controlled clinical trial.pt.	95530
19	randomi#ed.ti,ab.	817076
20	placebo.ab.	244852
21	randomly.ti,ab.	426123
22	Clinical Trials as topic.sh.	201612
23	trial.ti.	300946
24	or/17-23	1633108
25	exp animals/ not humans/	5187831
26	24 not 25	1506716
27	16 and 26	2181
28	(2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	3693284
29	27 and 28	**403**

Appendix 2. Search string applied in Embase (Elsevier)

#	Search string	Results
1	(medication NEAR/2 (review$ OR reconcil* OR counsel*)):ti,ab,kw	12,216
2	((inappropriate OR appropriate OR improv* OR optim* OR quality) NEAR/5 (pharmacotherapy OR medication* OR medicine* OR prescri*)):ti,ab,kw	100,389
3	deprescrib*:ti,ab,kw OR deprescript*:ti,ab,kw OR de-prescrib*:ti,ab,kw OR de-prescript*:ti,ab,kw	3,369
4	((beer* OR shan$ OR mcleod$) NEAR/3 criter*):ti,ab,kw	1,873
5	'integrated medicine$ management':ti,ab,kw	69
6	('fit for the aged' NEAR/3 (criter* OR list$ OR instrument OR classif*)):ti,ab,kw	59
7	((forta OR rasp OR priscus) NEAR/3 (criter* OR list$ OR instrument)):ti,ab,kw	217
8	'stopp criter*':ti,ab,kw OR 'stopp list$':ti,ab,kw	567
9	'inappropriate prescribing'/de	6,107
10	'potentially inappropriate medication'/de	2,898
11	'medication therapy management'/de	15,403
12	hospital*:ti,ab,kw	2,652,720
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	122,876
14	#12 AND #13	31,319
15	'hospital pharmacy'/de	16,772
16	'organization and management'/de	428,958
17	#15 AND #16	2,283
18	#14 OR #17	33,513
19	random*:ti,ab	2,016,599
20	factorial*:ti,ab	48,677
21	crossover:ti,ab OR 'cross over':ti,ab	126,502
22	((doubl* NEAR/2 blind*):ti,ab) OR ((singl* NEAR/2 blind*):ti,ab)	281,847
23	assign*:ti,ab OR allocat*:ti,ab OR voluntee*:ti,ab OR placebo*:ti,ab	1,290,648
24	'crossover procedure'/de	76,433
25	'single blind procedure'/de	53,215
26	'randomized controlled trial'/de	803,373
27	'double blind procedure'/de	215,015
28	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	2,981,758
29	'animals'/exp NOT 'humans'/de	6,223,759
30	#28 NOT #29	2,679,037
31	#18 AND #30	4,673
32	#31 AND [embase]/lim	4,167
33	#32 AND [2022-2024]/py	**651**

Appendix 3. Search string applied in CINAHL (EBSCOhost)

#	Search string	Results
S40	S39	255
S39	S15 AND S38	892
S38	S37 NOT S36	987,657
S37	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	1,035,913
S36	S34 NOT S35	215,146
S35	MH (human)	2,754,058
S34	S31 OR S32 OR S33	249,488
S33	TI (animal model*)	3,856
S32	MH (animal studies)	155,677
S31	MH animals+	102,850
S30	AB (cluster W3 RCT)	505
S29	MH (crossover design) OR MH (comparative studies)	486,840
S28	AB (control W5 group)	147,155
S27	PT (randomized controlled trial)	154,671
S26	MH (placebos)	13,936
S25	MH (sample size) AND AB (assigned OR allocated OR control)	4,461
S24	TI (trial)	188,175
S23	AB (random*)	403,887
S22	TI (randomised OR randomized)	146,763
S21	MH cluster sample	5,405
S20	MH pretest-posttest design	54,618
S19	MH random assignment	82,933
S18	MH single-blind studies	16,105
S17	MH double-blind studies	54,407
S16	MH randomized controlled trials	141,144
S15	S13 AND S14	10,416
S14	TI hospital* OR AB hospital* OR MW hospital*	670,805
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	42,639
S12	(MH "Pharmacy Service")	8,325
S11	(MH "Medication Management")	1,822
S10	(MH "Medication Reconciliation")	2,146
S9	(MH "Inappropriate Prescribing")	3,618
S8	TI (stopp criter* or stopp list?) OR AB (stopp criter* or stopp list?)	237
S7	TI ((forta or rasp or priscus) N3 (criter* or list? or instrument)) OR AB ((forta or rasp or priscus) N3 (criter* or list? or instrument))	52
S6	TI ("fit for the aged" N3 (criter* or list? or instrument or classif*)) OR AB ("fit for the aged" N3 (criter* or list? or instrument or classif*))	20
S5	TI (integrated medicine? management) OR AB (integrated medicine? management)	49
S4	TI ((beer* or shan? or mcleod?) N3 criter*) OR AB ((beer* or shan? or mcleod?) N3 criter*)	**611**

S3	TI (deprescrib* or deprescript* or de-prescrib* or de-prescript*) OR AB (deprescrib* or deprescript* or de-prescrib* or de-prescript*)	1,314
S2	TI ((inappropriate or appropriate or improve* or optim* or quality) N5 (pharmacotherapy or medication* or medicine* or prescri*)) OR AB ((inappropriate or appropriate or improve* or optim* or quality) N5 (pharmacotherapy or medication* or medicine* or prescri*))	27,078
S1	TI (medication N2 (review? or reconcil* or counsel*)) OR AB (medication N2 (review? or reconcil* or counsel*))	4,938

Abbreviations: CINAHL, Cumulative Index to Nursing & Allied Health Literature.

Appendix 4. Search string applied in the Cochrane Central Register of Controlled Trials (CENTRAL)

#	Search string	Results
#1	(medication near/2 (review? or reconcil* or counsel*)):ti,ab	1,577
#2	((inappropriate or appropriate or improve* or optim* or quality) near/5 (pharmacotherapy or medication* or medicine* or prescri*)):ti,ab	11,730
#3	(deprescrib* or deprescript* or de-prescrib* or de-prescript*):ti,ab	330
#4	((beer* or shan? or mcleod?) near/3 criter*):ti,ab	79
#5	(integrated next medicine? next management):ti,ab	5
#6	("fit for the aged" near/3 (criter* or list? or instrument or classif*)):ti,ab	3
#7	((forta or rasp or priscus) near/3 (criter* or list? or instrument)):ti,ab	37
#8	((stopp next criter*) or (stopp next list?)):ti,ab	41
#9	[mh "inappropriate prescribing"]	247
#10	[mh "potentially inappropriate medication list"]	61
#11	[mh "medication reconciliation"]	128
#12	[mh "pharmacy service, hospital"/OG]	51
#13	hospital*:ti,ab,kw	239,075
#14	(77-#11)	13,053
#15	#13 and #14	3,555
#16	#12 or #15 with Cochrane Library publication date Between Jan 2022 and Jan 2024, in Trials	**613**

Appendix 5. ATC codes of the assessed medications and classification and according to EURO-FORTA list version 2

Medication	Class	ATC codes
Arterial hypertension		
ACE-inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09DA, C09DB, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX14, C10BX15, C10BX17, C10BX18, C10BX21, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C10BX10, C10BX16, C10BX19, C10BX20
Long-acting calcium antagonists, dihydropyridine type	A	C08CA, C08GA, C09DB, C09BB, CO7FB, C10BX03, C10BX07, C10BX09, C10BX11, C10BX18, C10BX19, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08,
Indapamide	A	C03BA11, C09BX01, C09BX06, C10BX13
Other diuretics	B	C03A, C03B, C03C, C03E, C03DB, C09BA, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C09BX01, C09BX03, C09BX06, C10BX13
Alpha receptor antagonists	C	C02CA; C02LE
Spironolactone	C	C03DA01, C03EA13, C03EA07, C03EA01, C03EA02
Moxonidine	C	C02AC05, C02LC05
Aliskiren	C	C09XA02, C09XA53, C09XA52, C09XA54, C09DX02
Betablockers[a]	C	C07A
Atenolol[a]	D	C07AB03, C07AB11
Clonidin	D	C02AC01, C02LC01,C02LC51
Minoxidil	D	C02DC01
Calcium antagonists, verapamil type	D	C08D, C09BB10
Cardiac insufficiency		
ACE-inhibitors, angiotensin receptor antagonists	A	C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX14, C10BX15, C10BX17, C10BX18, C10BX21, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C10BX10, C10BX16, C10BX19, C10BX20, C09DX04
Betablockers	A	C07A; excluding (C07AA07), pindolol (C07AA03), propranolol (C07AA05), and carteolol (C07AA15)
Diuretics	A	C03A, C03B, C03C, C03E, C03DB, C09BA, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C09BX01, C09BX03, C09BX06, C10BX13
SGLT2 inhibitors	B	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27, A10BD29
Spironolactone	B	C03DA01, C03EA13, C03EA07, C03EA01, C03EA02
Digitalis preparations	C	C01AA, C01AA02, C01AA52, C01AA08, C01AA04, C01AA01
Ivabradine	C	C01EB17, C07FX06, C07FX05
Acute coronary syndromes		
ACE-inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09DA, C09DB, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX14, C10BX15, C10BX17, C10BX18, C10BX21, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C10BX10, C10BX16, C10BX19, C10BX20
Low-dose ASA	A	B01AC06, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02, B01AF51
Heparin	A	B01AB

Medication	Class	ATC codes
Betablockers[b]	A	C07A; excluding sotalol (C07AA07)
Atorvastatin	A	C10AA05, C10BX08, C10BX03, C10BA05, C10BA08, C10BX15, C10BX12, C10BX06, C10BX19, C10BX11, C10BX18
Nitroglycerin spray, on demand	A	C01DA02[c]
Clopidogrel, prasugrel[d]	B	B01AC04, B01AC22
Thrombolytics, especially rTPA	B	B01AD
Nitrates, long term	C	C01DA02,[e] C01DA08,[f] C01DA14, C01DA05
Glycoprotein IIb/IIIa antagonist	C	B01AC13, B01AC16, B01AC17
Ivabradine	C	C01EB17, C07FX06, C07FX05
Myocardial infarction		
ACE-inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09DA, C09DB, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX14, C10BX15, C10BX17, C10BX18, C10BX21, C09DX01, C09DX03, C09DX06, C09DX07, C09DX08, C10BX10, C10BX16, C10BX19, C10BX20
Low dose ASA	A	B01AC06, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02, B01AF51
Clopidogrel[g, h]	A	B01AC04
Nitroglycerin spray, on demand	A	C01DA02[c]
Statins	A, B[i]	C10AA, C10BA, C10BX
Betablockers	A,[b] C[j]	C07; excluding sotalol (C07AA07)
Nitrate, long-term use	C	C01DA02,[e] C01DA08,[f] C01DA14, C01DA05
Ezetimibe	C	C10AX09, C10BA05, C10BA10, C10BA11, C10BA12, C10BA06, C10BA02
Fibrates	C	C10AB
Amiodarone	C	C01BD01
Other class-I/III antiarrhythmic agents	D	C01BA, C01BB, C01BC, C01BG, C01BD02, C01BD03, C01BD04, C01BD05, C01BD06, C01BD07, C07AA07, C07FX02, C07BA07
Dihydropyridine antagonists[k]	D	C08CA, C08GA, C10BX03, C10BX09, C10BX11, C10BX14, C10BX18, C10BX19
Niacin	D	C10AD
Stroke		
Low dose ASA	A	B01AC06, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02, B01AF51
Statins	A	C10AA, C10BA, C10BX
r-TPA	A	B01AD
Clopidogrel	A	B01AC04
Anticoagulants, including NOACs	A	B01AA, B01AE, B01AF
Dipyridamole plus ASA	B	B01AC07
Atrial fibrillation		
Betablockers	A	C07; excluding sotalol (C07AA07)
Oral vitamin K antagonists	B	B01AA03
Digoxin	B	C01AA05
NOACs except Dabigatran	B	B01AF
Dabigatran	C	B01AE07
Heparin[l]	C	B01AB
Digitoxin	C	C01AA04
Diltiazem, verapamil	C	C08DB01, C08DA01, C09BB10, C08DA51
Amiodarone	C	C01BD01

Medication	Class	ATC codes
Other class I or III antiarrhythmic agents	D	C01BA, C01BB, C01BC, C01BG, C01BD02, C01BD03, C01BD04, C01BD05, C01BD06, C01BD07, C07AA07, C07FX02, C07BA07
Low dose ASA[m]	D	B01AC06, B01AC56, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02
COPD		
Inhalative long-acting parasympatholytics	A	R03BB02, R03BB03, R03BB04, R03BB05, R03BB06, R03BB07, R03BB54, R03AL03, R03AL04, R03AL05, R03AL06
Antibiotics except fluoroquinolones	A	J01A, J01B, J01C, J01D, J01F, J01G, J01XA, J01XB, J01XC, J01XD, J01XX02, J01XX03, J01XX04, J01XX05, J01XX06, J01XX08, J01XX09, J01XX10, J01XX11, J01XX12
Inhalative beta 2 mimetic agents	B	R03AC
Systemic glucocorticoids	A, D[n]	H02
Inhalative glucocorticoids[o]	C	R03BA, R03AK06, R03AK07, R03AK08, R03AK09, R03AK10, R03AK11, R03AK12, R03AK13, R03AK14, R03AL08, R03AL09, R03AL11, R03AL12
Mucolytic agents	C	R05CB
Roflumilast	C	R03DX07
Theophylline	D	R03DA04, R03DB04, R03DA54, R03DA74
Antitussives	D	R05DA, R05DB
Osteoporosis		
Calcium and vitamin D	A	A12A, A11CC05, A11CC55
Bisphosphonates	A, B[p]	M05BA
Raloxifene	B	G03XC01
Denosumab	B	M05BX04
Alfacalcidol	C	M05BB06, A11CC03, A11CC04
Parathormone, teriparatide	C	H05AA
Strontium ranelate	D	M05BX03, M05BX53
Nandrolone decanoate	D	A14AB01
Fluoride	D	A12CD
Hormone replacement therapy	D	G03C, G03F, G03AA, G03AB
Diabetes		
Metformin	A	A10BA02, A10BD17, A10BD13, A10BD16, A10BD15, A10BD20, A10BD23, A10BD22, A10BD18, A10BD11, A10BD26, A10BD05, A10BD14, A10BD03, A10BD10, A10BD07, A10BD02, A10BD28, A10BD08, A10BD27, A10BD25
DPP-4 inhibitors	B	A10BH, A10BD07, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD14, A10BD25, A10BD27, A10BD28
Insulin	B	A10A
GLP-1-RAs	B	A10BJ
Acarbose	C	A10BF01, A10BD17
SGLT2-inhibitors[q]	C	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27
Glinides	C	A10BX02, A10BX03, A10BX05, A10BX08, A10BD14
Sulfonylureas	C, D[r]	A10BB12, A10BB31, A10BB06, A10BB02, A10BB10, A10BB05, A10BB03, A10BB01, A10BB04, A10BB09, A10BB07, A10BB08, A10BB11, A10BD01, A10BD02, A10BD06

Medication	Class	ATC codes
PPARγ ligands	C, D[s]	A10BG, A10BD09, A10BD12, A10BD04, A10BD03, A10BD05, A10BD06, A10BD26
Dementia		
Acetylcholinesterase inhibitors	B	N06DA
Memantine	C	N06DX01
Ginkgo biloba	D	N06DA53, N06DX02, N06DX30
Statins[t]	D	C10AA, C10BX, C10BA01, C10BA02, C10BA03, C10BA04, C10BA05, C10BA06, C10BA07, C10BA08, C10BA09, C10BA11, C10BA12
Piracetam	D	N06BX03
Antioxidants: vitamin E, selenium, vitamin C	D	A11G, A11EB, A11HA03, A11CB
Ginseng	D	A13AP02
Hormone preparations[u]	D	G03
Selegiline[v]	D	N04BD01
Nimodipine	D	C08CA06
Ergoline derivates	D	C04AE
Pyritinol	D	C08CA06
Antiphlogistics, e.g. indomethacin	D	M01AB01, M01AB51
Desferrioxamine	D	V03AC01
Dementia-associated depression		
SSRIs	C	N06AB
Mirtazapine	C	N06AX11
SNRIs	C	N06AX16, N06AX23, N06AX21, N06AX17, N06AX28
Dementia-associated paranoia, hallucination		
Risperidone	C	N05AX08
Melperone	C	N05AD03
Quetiapine	C	N05AH04
Aripiprazol	C	N05AX12
Haloperidol	C	N05AD01
Clozapin	D	N05AH02
Dementia-associated insomnia		
Melatonin	C	N05CH01
Mirtazapine	C	N06AX11
Doxepin	D	N06AA12
Z-drugs	C	N05CF
Dementia-associated restlessness, agitation		
Trazodon		N06AX05
Risperidone	C	N05AX08
Melperone	C	N05AD03
Quetiapine	C	N05AH04
Citalopram[w]	C	N06AB04, N06AB10
Clomethizole	D	N05CM02
Pipamperone	D	N05AD05
Depression		

Medication	Class	ATC codes
SSRIs	B	N06AB
Tricyclic antidepressants	C	N06AA,[x] N06CA01
Mirtazapine	C	N06AX11
SNRIs	C	N06AX16, N06AX23, N06AX21, N06AX17, N06AX28
Bupropion	C	N06AX12
Quetiapine[y]	C	N05AH04
Vortiotexine	C	N06AX26
Trazodone	C	N06AX05
Olanzapine	C	N05AH03
Moclobemide	D	N06AG
Benzodiazepines[z]	D	N05CD, N05BA, N03AE
St. Johns Wort	D	N06AX25
Agomelatine	D	N06AX22
Reboxetine	D	N06AX18
Bipolar disorder		
Lithium	B	N05AN
Quetiapin	B	N05AH04
Valproic acid	C	N03AG01
Lamotrigine[z]	C	N03AX09
Carbamazepine	D	N03AF01
Insomnia		
Melatonin[aa]	B	N05CH01
Z-drugs	C	N05CF
Pipamperone	C	N05AD05
Melperone	C	N05AD03
Mirtazapine	C	N06AX11
Doxepin	D	N06AA12
Benzodiazepines[z]	D	N05CD, N05BA, N03AE
Opipramol	D	N06AA05
Sedative antihistamines	D	R06AA02, R06AA52, R06AC01, R06AC03, R06AC53, R06AX05, R06AC04, R06AA08, R06AA09, R06AA59, R06AA01, R06AA04, R06AA54, R06AA11, R06AA61, R06AB05, R06AB04, R06AB54, R06AB02, R06AB52, R06AB06, R06AB56, R06AB01, R06AB51, R06AX07, R06AE03, R06AE53, R06AE04, N05BB01, N05BB51, R06AE05, R06AE55, R06AD02, R06AD52, R06AD01, R06AX02, N05CM27, N05CM20
Pain		
Paracetamol	A	N02BE01, N02BE51, N02AJ06, N02AJ13
Opioids, e.g. Buprenorphine, oxycodone, hydromorphone, fentanyl	B	N02AB03, N02AE01, N02AA05, N02AA03
Morphine	C	N02AA01, N02AA51, N02AG01
Opioid agonist/antagonist combinations	C	N02AX51, N02AA55, N02AA53, N02AA56
Metamizole	C	N02BB02, N02BB52
Tramadol	C	N02AX02, N02AJ14, N02AJ15, N02AJ13, N02AJ16

Medication	Class	ATC codes
SSRIs[ab]	C	N06AB
SNRIs	C	N06AX16, N06AX23, N06AX21, N06AX17, N06AX28
Antiepileptics[z, ac]	C, D[ad]	N03AF02, N03AF04, N03AX15, N03AB02, N03AB52, N03AA02, N03AD01, N03AD51, N02BF01, N03AG01, N03AF01
Tricyclic antidepressants	D	N06AA,[x] N06CA01
NSAIDs for long-term use[ae]	D	M01AA, M01AB, M01AC, M01AD, M01AE01, M01AE02, M01AE03, M01AE04, M01AE05, M01AE06, M01AE07, M01AE08, M01AE09, M01AE10, M01AE11, M01AE12, M01AE13, M01AE14, M01AE15, M01AE16, M01AE17, N02BA51, N02BA71, M01BA01, M01BA03, N02BA01
Epilepsy		
Levetiracetam	B	N03AX14
Lamotrigine	B	N03AX09
Gabapentin	B	N02BF01
Topiramat	B	N03AX11
Lorazepam	B, D[af]	N05BA06, N05BA56
Pregabalin	C	N02BF02
Valproic acid	C	N03AG01
Carbamazepine	C	N03AF01
Eslicarbamazepine	C	N03AF04
Oxcarbamazepine	C	N03AF02
Zonisamide	C	N03AX15
Lacosamide	C	N03AX18
Diazepam	C, D[ag]	N05BA01
Midazolam	C, D[ag]	N05CD08
Phenytoin	D	N03AB02, N03AB52
Phenobarbital	D	N03AA02
Ethosuximide	D	N03AD01, N03AD51
Parkinsons disease		
Levodopa	A	N04BA01, N04BA02, N04BA03
COMT inhibitors	B	N04BX02, N04BX04, N04BA03
Ropinirole	B	N04BC04
Piribedil	B	N04BC08
Quinagolide	B	G02CB04
Rotigotine	B	N04BC09
Pramipexole	C	N04BC05
MAO-B inhibitors	C	N04BD02, N04BD01, N04BD03
Bromocriptine	D	N04BC01
Cabergoline	D	N04BC06
Amantadine	D	N04BB01
Anticholinergics	D	N04A
Incontinence		
Fesoterodine	B	G04BD11
Tolterodine	C	G04BD07
Trospium chloride	C	G04BD09
Oxybutynin	C, D[ah]	G04BD04
Gastrointestinal symptoms		

Medication	Class	ATC codes
PPIs	B	A02BC
H_2 receptor antagonists	C	A02BA

Abbreviations: ASA, acetylsalicylic acid; ATC, Anatomical Therapeutic Chemical Classification; COMT, catechol-O-methyltransferase; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1-RA, Glucagon-like peptide-1 receptor agonists; MAO, monoamine oxidase; NOACs, new oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPARγ, peroxisome proliferator-activated receptor gamma; PPIs, proton pump inhibitors; SGLT2, sodium glucose linked transporter 2; SNRIs, serotonin-noradrenalin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a] In participants without a diagnosis of acute coronary syndrome, myocardial infarction, atrial fibrillation, and cardiac insufficiency.
[b] In participants with a history of myocardial infarction, beta blockers are only considered AM if the date of the last myocardial infarction was ≤ 3 years before the prescription.
[c] Only considered as AM if identified as an immediate-release preparation. Glyceryl trinitrate patches were not considered.
[d] If prescribed within 1 year after diagnosis of myocardial infarction.
[e] Patches.
[f] Preparations with extended release.
[g] Up to 12 months after diagnosis or in case of ASA intolerance.
[h] Participants receiving ASA prescriptions after their clopidogrel prescription were not considered as being ASA intolerant.
[i] In participants aged > 85 years.
[j] Only considered as PIM if the last diagnosis of myocardial infarction was > 3 years ago. Not considered as PIM in participants with cardiac insufficiency or atrial fibrillation.
[k] Only considered as PIM in participants without arterial hypertension.
[l] Only considered as PIM in patients without a diagnosis of acute coronary syndromes.
[m] Only considered as PIM in participants without acute coronary syndrome, cardiac insufficiency, and stroke.
[n] A: acute, short-term use (5-7 days) in cases of exacerbation. D: chronic use. Not considered in the analyses since it was not possible to assess exacerbations and the duration of use from prescription data.
[o] Not considered as PIM in participants with asthma.
[p] A: preparations for intravenous use. B: preparations for oral intake.
[q] Not considered as PIM in participants with cardiac or renal insufficiency.
[r] 1st generation sulfonylureas are classified as D.
[s] Rosiglitazone.
[t] Not considered as PIM in participants with acute coronary syndrome, myocardial infarction, and stroke.
[u] Only considered as PIM in participants without osteoporosis.
[v] In participants without Parkinson's disease.
[w] Including escitalopram.
[x] Doxepin (N06AA12) only in participants without insomnia.
[y] Only considered as PIM in participants without bipolar disorder.
[z] Only considered as PIM in participants without epilepsy.
[aa] In participants without dementia.
[ab] In participants without depression.
[ac] Valproic acid (N03AG01) and carbamazepine (N03AF01) were only considered as PIM in participants without bipolar disorder.
[ad] C: antiepileptics excluding carbamazepine. D: carbamazepine.
[ae] If regular use was verified through primary care prescription data or if the participant reported regular use of ibuprofen or aspirin in the baseline questionnaire.
[af] B: emergency use. D: long-term use. Not relevant since no participants with epilepsy and lorazepam use were identified.
[ag] C: emergency use. D: long-term use.
[ah] C: extended release. D: immediate release.

Appendix 6. Percentages of missing data of covariates prior to imputation in analyzed UK Biobank population (N=217,111)

Characteristics	Proportion missing (%)
Sociodemographic/ -economic factors	-
Sex	0
Age	0
Income[a]	19.4
Years of schooling	1.1
Lifestyle factors	-
BMI *(kg/m²)*	0.1
Physical activity *(MET-min/week)*	25.9
Alcohol consumption *(g/day)*	0.2
Smoking status	0.1
Years since quit	13.3
Comorbidities	-
Diabetes	0
Arterial hypertension	0
Stroke	0
Myocardial infarction	0
Heart failure	0
Acute coronary syndromes	0
Atrial fibrillation	0
Asthma	0
COPD	0
Arthritis	0
Osteoporosis	0
History of fractures[b]	0
Pain[c]	0
Parkinson's disease	0
Dementia	0
Depression	0
Bipolar disorder	0
Insomnia	0
Epilepsy	0
Gastrointestinal symptoms[d]	0
Incontinence	0
Anemia	0
History of cancer	0
Overall health rating[e]	0.5
Number of medications	0
Functional assessments	-
Systolic blood pressure *(mmHg)*	<0.1
Diastolic blood pressure *(mmHg)*	<0.1
Grip strength *(kg)*	0.1
eGFR[f] *(ml/min/1.73m²)*	2.1

Characteristics	Proportion missing (%)
Blood-based biomarkers	-
CRP *(mg/L)*	2.2
HDL *(mmol/L)*	4.1
LDL *(mmol/L)*	2.2
HbA_{1c} *(mmol/L)*	2.3

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task; NSAIDs, non-steroidal anti-inflammatory drugs; UK, United Kingdom.

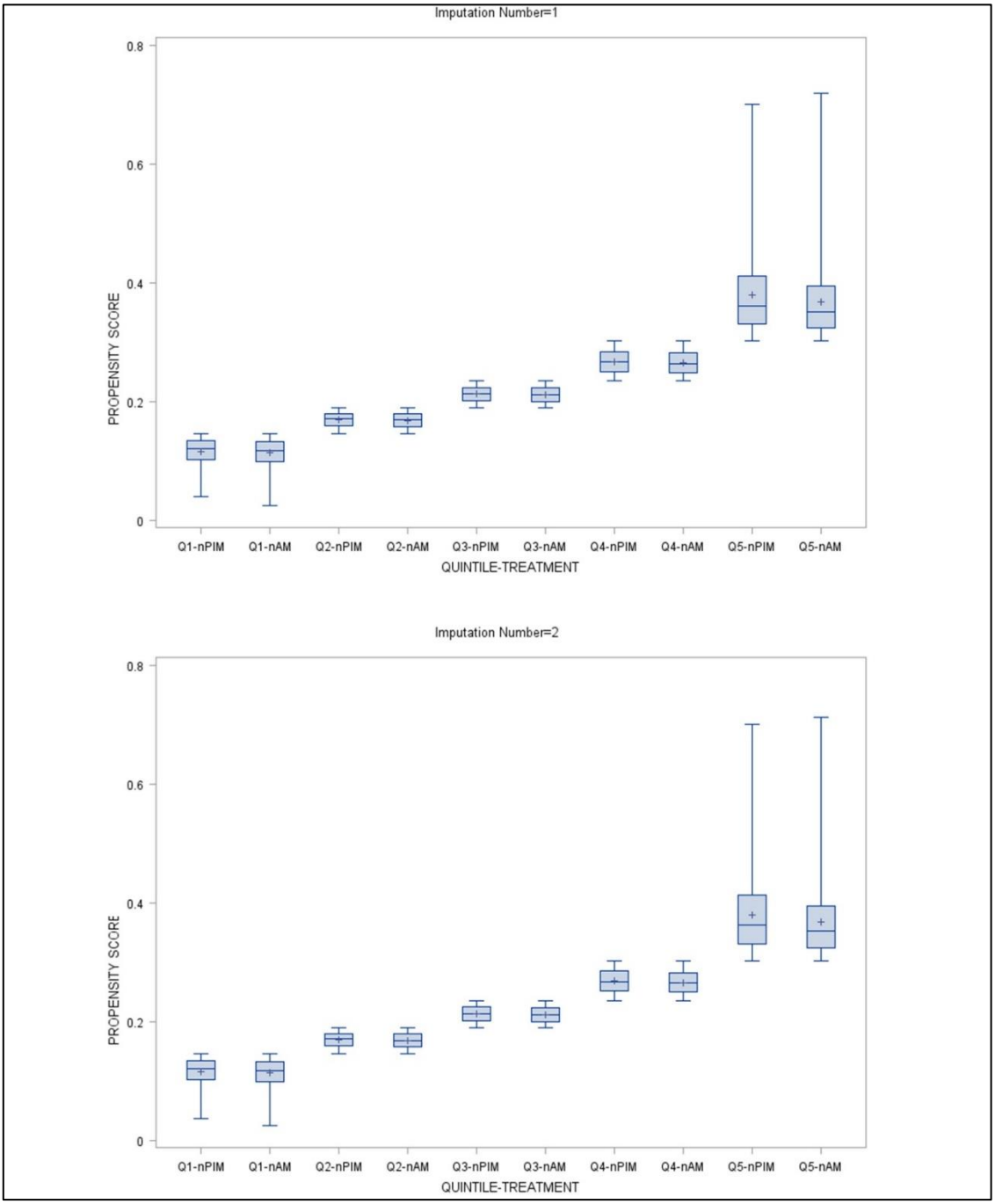
[a] Average total household income before tax.
[b] Fractures in the last five years.
[c] Combination of pain-related diagnoses (including migraine, other headache syndromes, facial pain, chronic back pain, chronic pain syndromes, arthritis, osteoarthritis, urinary tract stones, and gout) and self-reported pain in the last month.
[d] Including regular use of NSAIDs.
[e] Self-reported.
[f] Calculated based on CKD-EPI equation.

Appendix 7. Overview of 1:1 propensity score matching of new PIM and new AM users per indication (N_{total}=36,534)

Indication	N_{total} (N_{PIM}; N_{AM})[a]	Matched pairs[a]	PS_{PIM}[a,b]	PS_{AM}[a,b]	Matching method[c]	Caliper	Standardized differences[d]
1. Arterial hypertension	4,810 (582; 4,228)	581	0.0275-0.5063	0.000-0.4318	OFR	0.3	**<0.25**
2. Cardiovascular diseases[e]	4,225 (501; 3,724)	501	0.0099-0.6819	0.0028-0.6711	OFR	0.3	**<0.25**
3. COPD	5,857 (391; 5,466)	390	0.0119-0.2823	0.0084-0.2397	OFR	0.1	**<0.25**
4. Osteoporosis	740 (174; 566)	170	0.0332-0.7784	0.0000-0.6445	GNN[f]	0.3	**<0.25**
5. Diabetes	954 (360; 594)	244	0.0288-1.0000	0.0093-0.9213	GNN[g]	0.3	**<0.25**
6. Dementia[h]	127 (114; 13)	0[i]	0.9971-1.0000	0.0000-0.0025	-	-	**-**
7. Depression	1,244 (714; 530)	461	0.0989-1.0000	0.0738-0.9069	GNN	0.3	**<0.25**
8. Bipolar disorder	14 (6; 8)	0[i]	0.9999-0.9999	0.0001-0.0001	-	-	**-**
9. Insomnia	1,584 (1,563; 21)	0[j]	0.8001-1.0000	0.7429-0.9991	-	-	>0.25[j]
10. Chronic pain	11,937 (3,213; 8,724)	3,212	0.0505-0.8685	0.0422-0.7719	OFR	0.2	**<0.25**
11. Epilepsy	57 (41; 16)	0[i]	0.9995-1.0000	0.0000-0.0006	-	-	**-**
12. Parkinson's disease	113 (41; 72)	0[j]	0.0389-1.0000	0.0000-0.6519	-	-	>0.25[j]
13. Incontinence	212 (194; 18)	0[j]	0.3348-1.0000	0.0000-0.9842	-	-	>0.25[j]
14. Gastrointestinal symptoms[k]	4,480 (349; 4,131)	347	0.0238-0.5693	0.0000-0.3939	OFR	0.3	**<0.25**

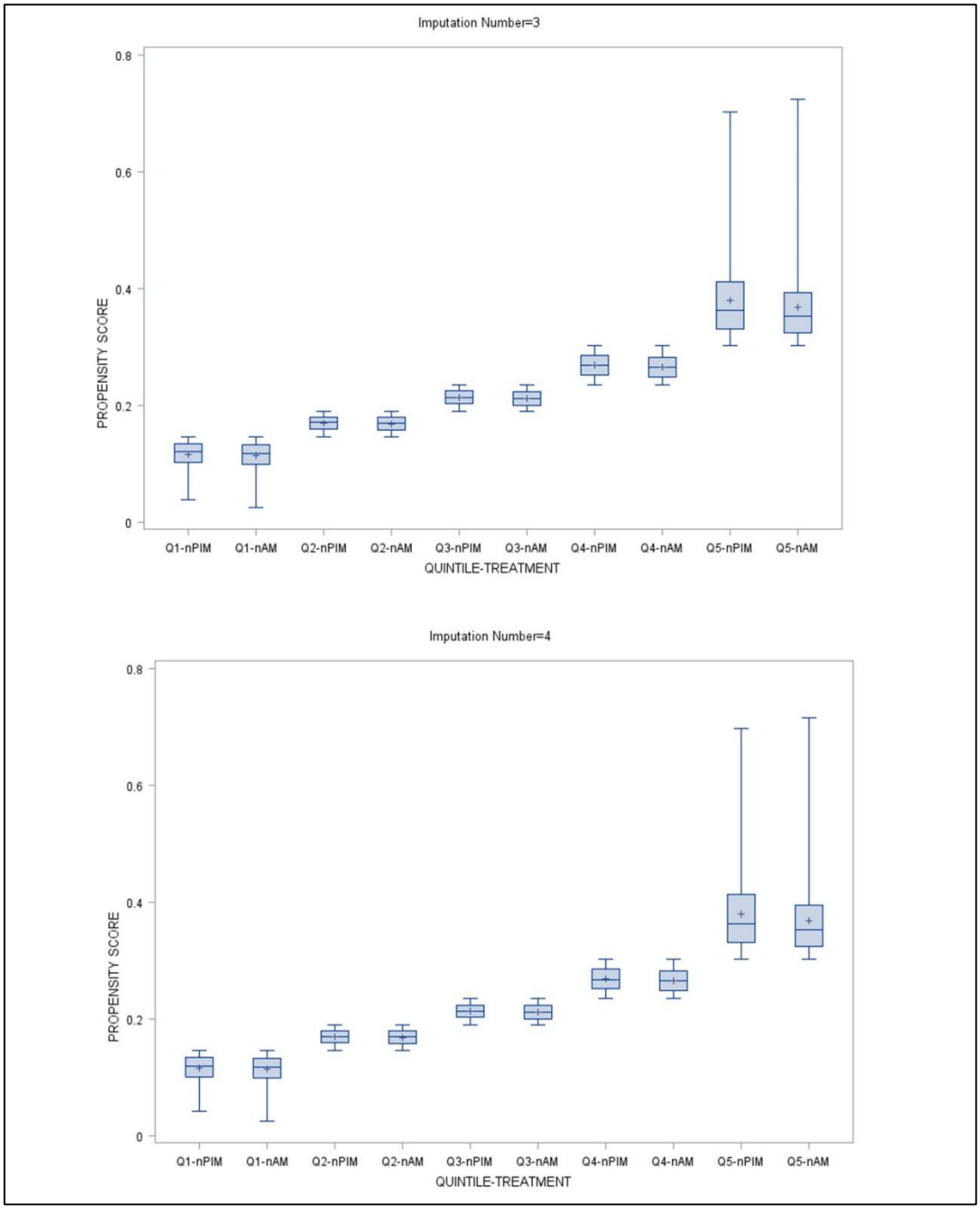
Values in bold indicate well-balanced covariates.
Abbreviations: AM, appropriate medication; COPD, chronic obstructive pulmonary disease; GNN, greedy nearest neighbor; NSAIDs, non-steroidal anti-inflammatory drugs; OFR, optimal fixed ratio; PIM, potentially inappropriate medication; PS, propensity score.

[a] First imputed dataset.
[b] Range, all observations before matching.
[c] Applied in the extended common support region.
[d] Standardized differences were calculated for all covariates used in propensity score matching. Standardized differences <0.25 after propensity score matching indicate well-balanced covariates.
[e] Including heart failure, acute coronary syndromes, chronic therapy after myocardial infarction, stroke, and atrial fibrillation.
[f] GNN was used because OFR matching was only possible with a caliper > 0.6.
[g] Exact matching on treatment of diabetes at baseline (no diabetes, untreated diabetes, diabetes treated with oral antidiabetics, diabetes treated with insulin) was applied.
[h] Including dementia-associated behavioral and psychological syndromes, e.g., hallucination, agitation, aggressiveness, depression, and insomnia.
[i] Matching was not possible because the propensity scores of PIM and AM users did not overlap.
[j] Matching was not applied because it was not possible to produce well-balanced groups despite different methods and calipers tested.
[k] Including regular use of NSAIDs.
Note: PIM and AM exposure were defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".



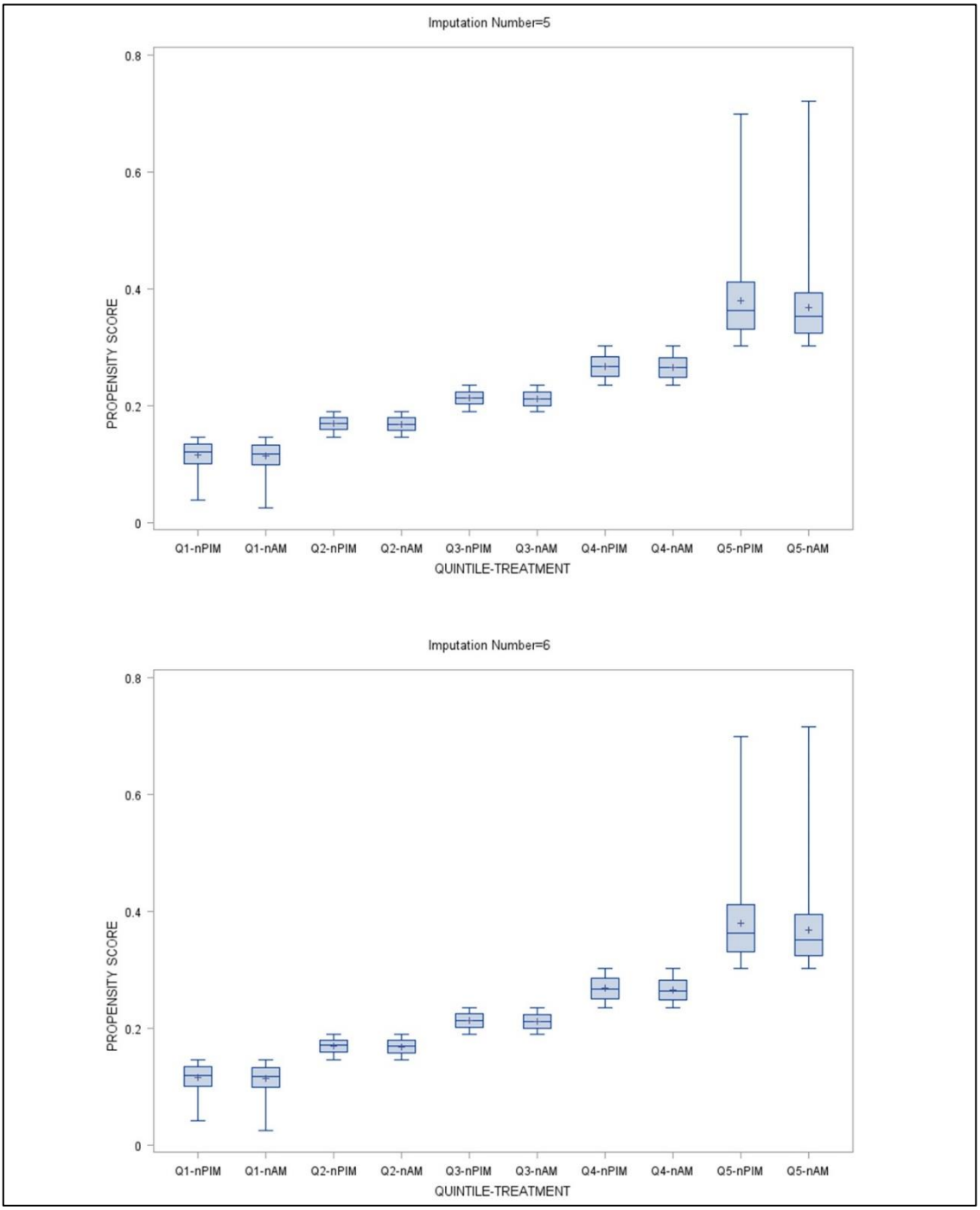
Appendix 8. Distribution of propensity scores for receiving new PIM versus new AM within two years after baseline by quintile and treatment (N=36,534) in 1st and 2nd imputed dataset

Abbreviations: nAM, newly prescribed appropriate medication; nPIM, newly prescribed potentially inappropriate medication; Q, quintile.



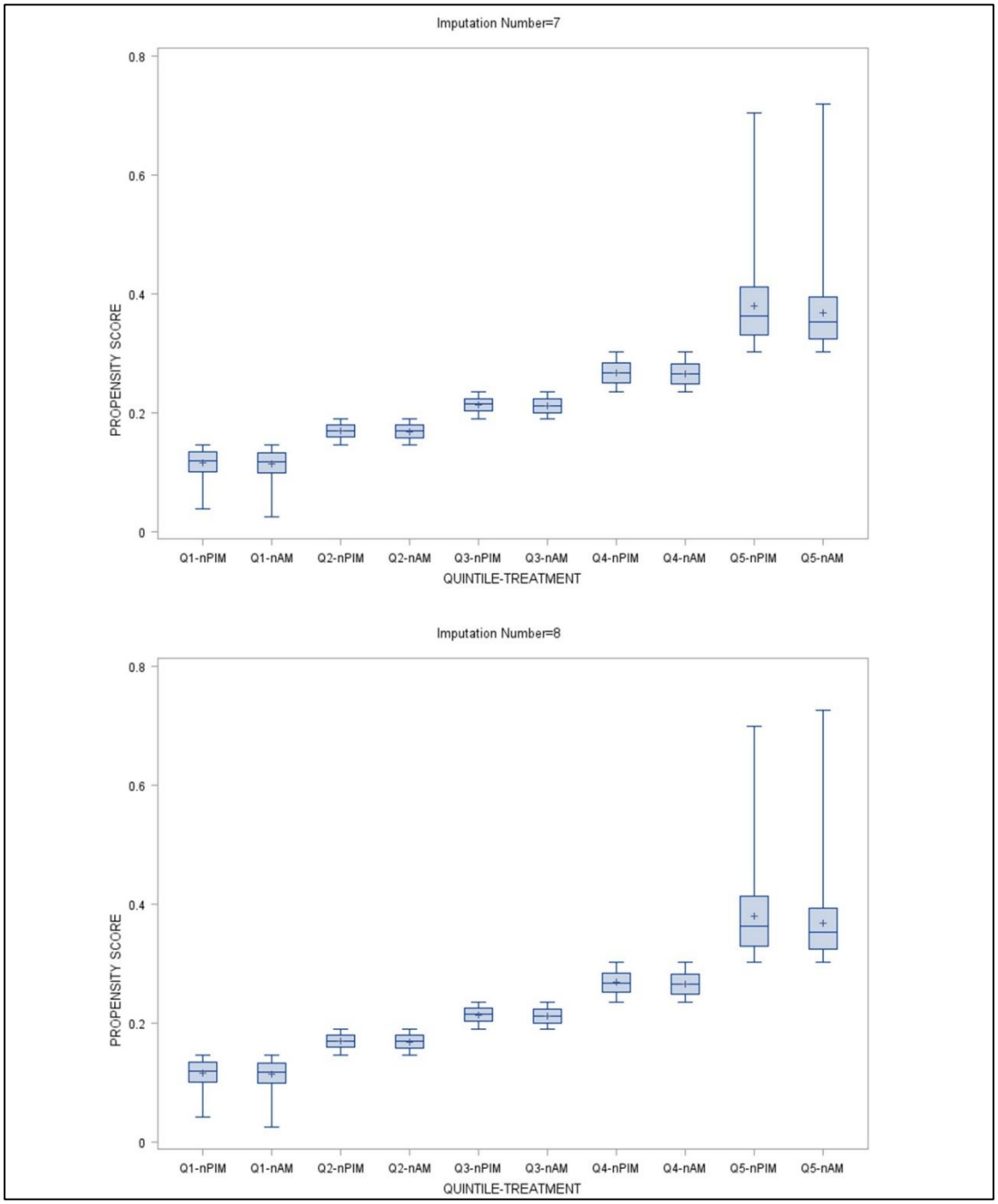
Appendix 9. Distribution of propensity scores for receiving new PIM versus new AM within two years after baseline by quintile and treatment (N=36,534) in 3rd and 4th imputed dataset

Abbreviations: nAM, newly prescribed appropriate medication; nPIM, newly prescribed potentially inappropriate medication; Q, quintile.



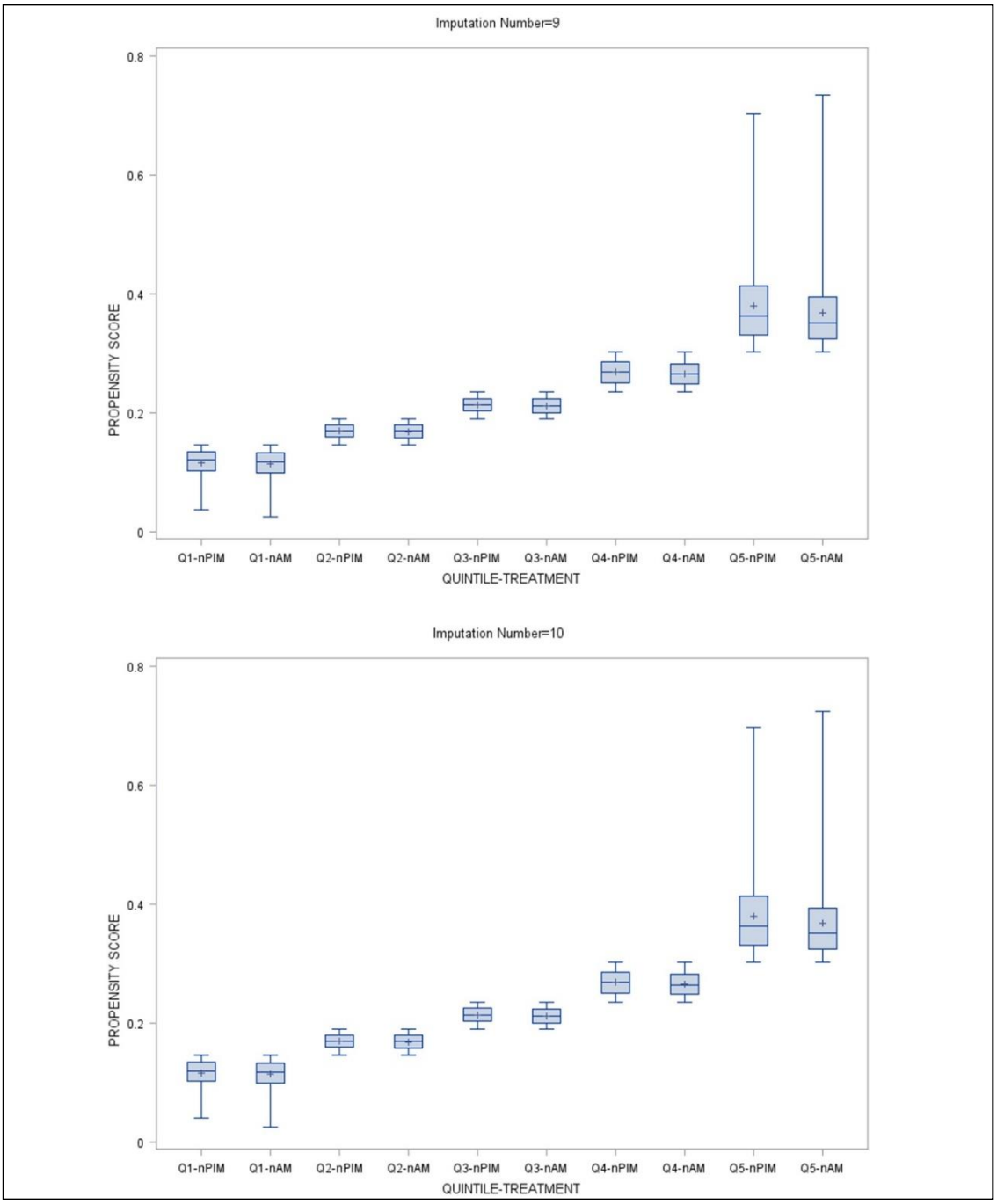
Appendix 10. Distribution of propensity scores for receiving new PIM versus new AM within two years after baseline by quintile and treatment (N=36,534) in 5th and 6th imputed dataset

Abbreviations: nAM, newly prescribed appropriate medication; nPIM, newly prescribed potentially inappropriate medication; Q, quintile.



Appendix 11. Distribution of propensity scores for receiving new PIM versus new AM within two years after baseline by quintile and treatment (N=36,534) in 7th and 8th imputed dataset

Abbreviations: nAM, newly prescribed appropriate medication; nPIM, newly prescribed potentially inappropriate medication; Q, quintile.



Appendix 12. Distribution of propensity scores for receiving new PIM versus new AM within two years after baseline by quintile and treatment (N=36,534) in 9th and 10th imputed dataset

Abbreviations: nAM, newly prescribed appropriate medication; nPIM, newly prescribed potentially inappropriate medication; Q, quintile.

Appendix 13. Assessment of the balance of baseline covariates between new PIM and new AM users after propensity score adjustment (N=36,354)

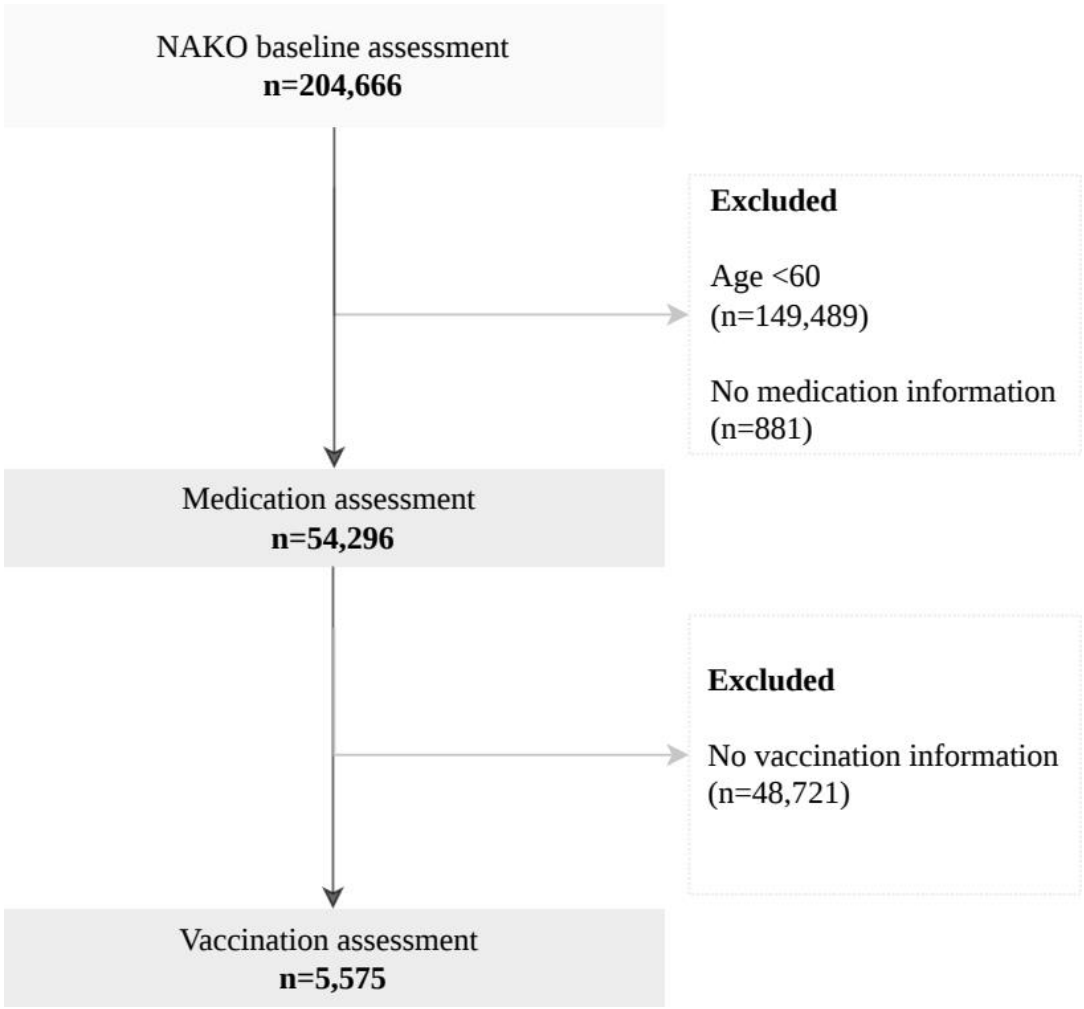
Baseline covariates	Standardized difference (mean)[a,b]
Sociodemographic/ -economic factors	**-**
Sex	**-**
Female	**0.03**
Male	**-**
Age	**0.02**
Income[c]	**-**
Very low	**0.02**
Low	**0.01**
Middle	**0.00**
High	**0.01**
Very high	**0.01**
Years of schooling	**-**
≤ 10	**0.02**
11 - < 14	**0.00**
≥ 14	**0.02**
Lifestyle factors	**-**
BMI *(kg/m²)*	**0.01**
Physical activity (MET-h/week) *median (IQR)*	**<.01**
Alcohol consumption, g ethanol/d	**0.04**
Smoking status	**-**
Never smoker	**0.01**
Former smoker, years since quit	**-**
< 5 years	**0.01**
5-10 years	**0.02**
11-15 years	**<.00**
16-20 years	**0.01**
> 20 years	**0.02**
Current smoker[d]	
Regular	**0.01**
Occasional	**<.01**
Comorbidities	**-**
Type II diabetes mellitus	**-**
No	**0.02**
Untreated	**0.02**
Treated with oral antidiabetics[e]	**0.06**
Treated with insulin	**0.02**
Arterial hypertension	**0.01**
Stroke	**0.01**
Myocardial infarction	**0.04**
Heart failure	**0.01**
Acute coronary syndromes	**0.03**

Baseline covariates	**Standardized difference (mean)[a,b]**
Atrial fibrillation	**0.03**
Asthma	**0.03**
COPD	**0.01**
Arthritis	**0.03**
Osteoporosis	**0.03**
History of fractures[f]	**<.01**
Pain[g]	**0.05**
Parkinson's disease	**<.01**
Dementia	**0.02**
Depression	**0.04**
Bipolar disorder	**0.01**
Insomnia, sleep disorder	**0.10**
Epilepsy	**0.01**
Incontinence	**0.02**
Gastrointestinal symptoms[h]	**0.04**
Anemia	**0.01**
History of cancer	**0.01**
Number of medications	**0.02**
Overall health rating[i]	**-**
Excellent	**0.01**
Good	**0.01**
Fair	**0.02**
Poor	**0.03**
Functional assessments	**-**
Systolic blood pressure *(mmHg)*	**0.04**
Diastolic blood pressure *(mmHg)*	**0.03**
Grip strength *(kg)*	**0.04**
eGFR[j] *(ml/min/1.73m²)*	**<.01**
Blood-based biomarkers	**-**
CRP *(mg/L)*	**0.02**
HDL *(mmol/L)*	**<.01**
LDL *(mmol/L)*	**0.01**
HbA_{1c} *(mmol/L)*	**0.01**

Values in bold indicate well-balanced covariates.
Abbreviations: AM, appropriate medication; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task; NSAIDs, non-steroidal anti-inflammatory drugs; PIM, potentially inappropriate medication.

[a] Calculated from first imputed dataset.
[b] Standardized differences <0.25 after propensity score adjustment indicate well-balanced covariates.
[c] Average total household income before tax. Categories: very low: < 18,000£, low: 18,000-30,999£, middle: 31,000-51,999£, high: 52,000-100,000£, very high: > 100,000£.
[d] Regular smoking was defined as minimum one cigarette, cigar, pipe, etc. per day.

[e] Including parenteral formulations of glucagon-like-peptide-1 receptor agonists.
[f] Fractures in last five years.
[g] Combination of pain-related diagnoses (including migraine, other headache syndromes, facial pain, chronic back pain, chronic pain syndromes, arthritis, osteoarthritis, urinary tract stones, and gout) and self-reported pain in the last month.
[h] Including regular use of NSAIDs.
[i] Self-reported.
[j] Calculated based on CKD-EPI equation.



Appendix 14. Flow chart describing the selection of the study population based on the NAKO baseline assessment

Abbreviations: NAKO, German National Cohort.

Appendix 15. Definitions of FORTA indications applied to assess medication problems in the NAKO

FORTA Indication	Description	Additional information
Diabetes	Combination of self-reported information and use of diabetes medication (ATC A10), use of oral antidiabetics and/or GLP-1-RAs (ATC A10B, A10X), and use of insulin (ATC A10A). Categories: No, untreated, treated with oral antidiabetics, treated with insulin.	Underuse was only considered in untreated individuals with HbA_{1c} > 48 mmol/mol
Arterial hypertension	Combination of self-reported information and use of antihypertensives (ATC C02, C03, C04, C08CA, C09)	Underuse was only considered in untreated individuals with systolic blood pressure > 140 mmHg
Atrial fibrillation	S.r.	Note: interview question covered any type of cardiac arrhythmia and was not specific to atrial fibrillation
Stroke	S.r.	
Myocardial infarction	S.r.	
Heart failure	S.r.	
Acute coronary syndromes	Combination of self-reported information on history of coronary heart disease and myocardial infarction	
COPD	S.r.	Note: also included chronic bronchitis. Underuse was only considered in individuals with Tiffenau Index < 0.7
Osteoporosis	S.r.	
Thyroid disease/ hypothyroidism	S.r.	Interview question covered any thyroid disease and was not specific to hypothyroidism. Underuse was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list)
Pain	Combination of self-reported moderate, severe, or very severe pain during the last 4 weeks (“How severe has your pain been in the past 4 weeks?”) and pain-related diagnoses. Pain-related diagnoses included certain or likely migraine or tension headaches in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.	
Parkinson’s disease	S.r.	

FORTA Indication	Description	Additional information
Cognitive impairment/dementia	Subjective cognitive impairment, combination of interview questions: "How would you evaluate your memory at the moment?" – Five categories: very good to very bad; and: "Have you ever talked to a physician about your memory difficulties, or do you plan to talk to a physician about this?"	The full model was adjusted for a binary variable indicating bad or very bad subjective cognitive impairment. The same variable was used as diagnosis in the PIM assessment; underuse was only considered in untreated individuals indicating having the worst category of memory; overuse was not considered in individuals that indicated very bad or bad memory or that indicated moderate memory and consulted a physician or planned to consult a physician due to memory issues
Depression	Combination of self-reported information ("Have you ever been diagnosed with this condition by a physician?") and PHQ-9 sum score (0-14: no or mild depression, 15-19: moderate to severe depression, ≥ 20: severe depression)	Self-reported lifetime history of depression was used for statistical adjustment; PIM: self-reported depression or moderate to severe depression according to PHQ-9 (sum score ≥ 15); overuse assessment: moderate to severe depression according to PHQ-9 (sum score ≥ 15); underuse was only considered in untreated individuals with severe depression according to or PHQ-9 (sum score ≥ 20).
Epilepsy	Classified as certain, possible, or no diagnosis, based on an algorithm created by the NAKO expert group neurological and psychiatric disorders, considering self-reported information on ever being diagnosed and time since first diagnosis, treatment during the last 12 months, and current use of antiepileptics.	The model was adjusted for a binary variable (no/certain or possible); PIM assessment: considered possible and certain diagnosis; underuse was only considered in untreated individuals with certain diagnosis; overuse was not considered in participants with possible or certain diagnosis
Insomnia	Difficulties falling asleep ≥ 3 days per week or difficulty staying asleep ≥ 3 times per week	Underuse was not assessed due to the large proportion (94.7%) of individuals with underuse for this indication
Gastrointestinal symptoms	Combination of self-reported information on reflux, peptic ulcer ("Have you ever been diagnosed with this condition by a physician?"), and regular intake of NSAIDs (ATC M01A)	Underuse was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment and in participants regularly taking NSAIDs

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; COPD, chronic obstructive pulmonary disease; FORTA, Fit for the aged; GLP-1-RA, Glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A_{1c}; NAKO, German National Cohort; NSAIDs, non-steroidal anti-inflammatory drugs; PHQ-9, patient health questionnaire; PIM, potentially inappropriate medication; s.r., self-reported previous diagnosis; TSH, thyroid stimulating hormone.

Appendix 16. Classification and ATC codes of assessed medications according to FORTA list version 5

Medication	Class[a]	ATC codes[b]
Arterial hypertension		
ACE-inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX10, C09DX04
Long-acting calcium antagonists, dihydropyridine type	A	C08CA
Indapamide	A	C03BA11, C09BX01, C09BX06, C09BA54, C10BX13, C08GA22
Other diuretics	B	C03
Hypertensives	n.l.	*Summarized as C02, C03, C04, C05, C06, C07, C08, C09*
Alpha receptor antagonists	C	C02CA, C02LE
Spironolactone	C	C03DA01, C03EC41, C03ED01, C03EC21, C03EC01
Moxonidine	C	C02AC05, C02LC05
Aliskiren	C	C09XA02, C09XA53, C09XA52, C09XA54, C09DX02
Betablockers[c]	C	C07
Atenolol[c]	D	C07AB03, C07FX18, C07DB01, C07DB03, C07DB53, C07DB23, C07DB03, C07BB03
Clonidine	D	C02AC01, C02LC01, C02LC51
Minoxidil	D	C02DC01
Calcium antagonists, verapamil type	D	C08D, C09BB10, C08GA53, C08GA23
Cardiac insufficiency		
ACE inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX10, C09DX04
Betablockers	A	C07
Diuretics	B	C03A, C03B, C03C, C03E, C03DB, C09BA, C09DX01, C09DX03, C09BX01
Iron substitution	A	B03A
Sacubitril/Valsartan	A	C09DX04
SGLT2 inhibitors	B	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27, A10BD29, A10BD30
Mineralocorticoid antagonists	C	C03DA01, C03EC41, C03ED01, C03EC21, C03EC01, C03DA03, C03DA05, C03DA04
Digitalis preparations	C	C01AA
Ivabradine	C	C01EB17, C07FX06, C07FX05
Acute coronary syndromes		
ACE inhibitors, angiotensin receptor antagonists[d]	A	C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX10, C09DX04
Low-dose ASA[e]	A	B01AC34, B01AC36, C07FX03, C10BX02, B01AF51, C10BX05, C10BX01, C10BX04, C07FX02, B01AC06, B01AC56, B01AC86, C10BX12, C10BX06, C10BX08, C10FX04
Heparin	A	B01AB
Beta blockers[f]	A	C07

Medication	Class[a]	ATC codes[b]
Atorvastatin	A	C10AA05, C10BX08, C10BX03, C10BA05, C10BX12, C10BX06, C10BX11
Nitroglycerin spray, acute single use on demand	A	C01DA02[g]
Clopidogrel, prasugrel	A	B01AC04, B01AC22, B01AC34
Thrombolytics, especially rTPA	B	B01AD
Antithrombotic agents	n.l.	*B01A*
Nitrates, long-acting	C	C01DA02,[g] C01DA52,[g] C01DA08,[g] C01DA58,[g] C01DA14, C01DA05, C01DA55
Glycoprotein IIb/IIIa antagonist	C	B01AC13, B01AC16, B01AC17
Ivabradine	C	C01EB17, C07FX06, C07FX05
Molsidomine	D	C01DX12
Myocardial infarction		
ACE inhibitors, angiotensin receptor antagonists	A	C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX10, C09DX04
Low-dose ASA	A	B01AC06, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02, B01AF51
Clopidogrel	A	B01AC04, B01AC34
Ezetimibe	B	C10AX09, C10BA05, C10BA06, C10BA02
Statins	A, B	C10AA, C10BA, C10BX, A10BH51
Antithrombotic agents	n.l.	*B01A*
Betablockers	B, C[f]	C07
Nitroglycerin spray	A, C[h]	C01DA02[g]
Bempedoic acid	C	n.a.
Fibrates	C	C10AB, C10BB02, C10BB01, C10BA03, C10BA04
Ranolazine	C	C01EB18
Amiodarone	C	C01BD01
Other class-I/III antiarrhythmic agents	D	C01BA, C01BB, C01BC, C01BG, C01BD02, C01BD03, C01BD04, C01BD05, C01BD06, C01BD07, C07AA07, C07FX02, C07BA07
Dihydropyridine antagonists[i]	D	C08CA, C08GA, C10BX03, C10BX09, C10BX11
Niacin	D	C10AD
PCSK9 inhibitors	D	C10AX13, C10AX14
Stroke		
Low-dose ASA	A	B01AC34, B01AC36, C07FX03, C10BX02, B01AF51, C10BX05, C10BX01, C10BX04, C07FX02, B01AC06, B01AC56, B01AC86, C10BX12, C10BX06, C10BX08, C10FX04
Statins	A	C10AA, C10BA, C10BX, A10BH51
r-TPA	A	B01AD
Clopidogrel	A	B01AC04, B01AC34
Antithrombotic agents	n.l.	B01A
Dipyridamole plus ASA	C	B01AC36
Atrial fibrillation		
Betablockers	A	C07
NOACs	A, B[j]	B01AE, B01AF
Warfarin	B	B01AA03
Heparin[k]	C	B01AB
Digoxin, digitoxin	C	C01AA

Medication	Class[a]	ATC codes[b]
Phenprocoumon	C	B01AA04
Amiodarone	C	C01BD01
Other class I or III antiarrhythmic agents	D	C01BA, C01BB, C01BC, C01BG, C01BD02, C01BD03, C01BD04, C01BD05, C01BD06, C01BD07, C07AA07, C07FX02, C07BA07
Diltiazem, verapamil	D	C08DB01, C08DA01, C09BB10, C08DA51, C08DA81, 08GA53, C08DA51, C08GA23
Low-dose ASA[l]	D	B01AC06, B01AC56, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02
COPD		
Antibiotics except fluoroquinolones	A	Not assessed
Inhalative long-acting parasympatholytics	A	R03BB02, R03BB04, R03BB05, R03BB06, R03BB07, R03BB54, R03AL03, R03AL04, R03AL05, R03AL06, R03AL07, R03AL09
Inhalative beta 2 mimetic agents	B	R03AC, R03AL, R03AK03, R03AK04, R03AK05, R03AK06, R03AK07, R03AK08, R03AK09, R03AK10, R03AK11, R03AK12, R03AK13
Inhalative glucocorticoids	B	R03BA, R03AK06, R03AK07, R03AK08, R03AK09, R03AK10, R03AK11, R03AK12, R03AK13, R03AL09
Drugs for obstructive airway diseases	n.l.	*Summarized as R03*
Systemic glucocorticoids	A, D[m]	H02
Mucolytic agents	C	R05CB
Roflumilast	C	R03DX07
Theophylline	D	R03DA04, R03DB04, R03DA54, R03DA74
Antitussives	D	R05DA, R05DB
Osteoporosis		
Calcium and vitamin D[n]	A	A12A, A11CC05, A11CC80
Bisphosphonates	A, B	M05BA, M05BB
Raloxifene	A	G03XC01
Denosumab	A	M05BX04
Alfacalcidol	B, C[o]	M05BB06, A11CC03
Romosozumab	B	n.a.
Teriparatide	B	H05AA02
Parathormone	C	H05AA03
Nandrolone decanoate	D	A14AB01
Fluoride	D	A12CD
Hormone replacement therapy	D	G03C, G03F, G03AA, G03AB
Diabetes		
DPP-4 inhibitors	A	A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD19, A10BD21
GLP-1-RAs	B	A10BJ
Insulin	B	A10A
Metformin	B	A10BA02, A10BD17, A10BD13, A10BD20, A10BD18, A10BD11, A10BD05, A10BD14, A10BD03, A10BD10, A10BD07, A10BD02, A10BD08, A10BD31, A10BD10

Medication	Class[a]	ATC codes[b]
SGLT2-inhibitors	B	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27
Acarbose	C	A10BF01, A10BD17
Glinides	C	A10BX02, A10BX03, A10BX08, A10BD14
Sulfonylureas	C, D	A10BB, A10BD01, A10BD02, A10BD04, A10BD06
PPARγ ligands	C, D	A10BG, A10BD09, A10BD12, A10BD04, A10BD03, A10BD05, A10BD06
Cognitive impairment/dementia		
Acetylcholinesterase inhibitors	B	N06DA
Memantine	B	N06DX01, N06DA52, N06DA53
Ginkgo biloba	C	N06DA53, N06DP01
Aducanumab	D	n.a.
Antioxidants: vitamin E, selenium, vitamin C	D	A11G, A11EB, A11HA03, A11CB, A12CE
Ginseng	D	A13AP02
Hormone preparations	D	G03
Lecanemab	D	n.a.
Piracetam	D	N06BX03
Statins[p]	D	C10AA, C10BA, C10BX, A10BH51
Depression		
SSRIs	B	N06AB
Antidepressants	n.l.	*Summarized as N06A*
Mirtazapine	C	N06AX11
SNRIs	C	N06AX16, N06AX23, N06AX21, N06AX17
Bupropion	C	N06AX12
Quetiapine	C	N05AH04
Tianeptin	C	N06AX14
Benzodiazepines[q]	C, D	N05CD, N05BA, N03AE
Agomelatine	D	N06AX22
MAO-A inhibitors	D	N06AG
St. John's Wort	D	N06AP01
Reboxetine	D	N06AX18
Trazodone	D	N06AX05
Tricyclic antidepressants	D	N06AA, N06CA01
Insomnia		
Melatonin	B	N05CH01
Daridorexant	C	n.a.
Z-drugs	C	N05CF
Pipamperone	C	N05AD05
Melperone	C	N05AD03
Mirtazapine	C	N06AX11
Trazodone	C	N06AX05
Doxepin	C, D	N06AA12
Benzodiazepines[q]	D	N05CD, N05BA, N03AE
Opipramol	D	N06AA05

Medication	Class[a]	ATC codes[b]
Sedative antihistamines	D	R06AA02, R06AA52, R06AC01, R06AC03, R06AC53, R06AX05, R06AC04, R06AA08, R06AA09, R06AA59, R06AA01, R06AA04, R06AA54, R06AA11, R06AB05, R06AB04, R06AB54, R06AB02, R06AB52, R06AB06, R06AB56, R06AB01, R06AB51, R06AX07, R06AE03, R06AE53, R06AE04, N05BB01, N05BB51, R06AE05, R06AE55, R06AD02, R06AD52, R06AD01, R06AX02, N05CM20, N05CM21, N05CM22
Pain		
Paracetamol	A	N02BE01, N02BE51, N02AJ06, N02AJ13, N02BE61, N02BE71
Metamizole	B	N02BB02, N02BB52
Opioids, e.g., Buprenorphine, oxycodone, hydromorphone	B	N02AE01, N02AA05, N02AA03
Analgesics	n.l.	*Summarized as N02*
Morphine, fentanyl	C	N02AA01, N02AA51, N02AG01, N02AB03
Opioid agonist/antagonist combinations	C	N02AX51, N02AA55
SSRIs[r]	C	N06AB
SNRIs	C	N06AX16, N06AX23, N06AX21, N06AX17
Tapentadol	C	N02AX06
Tramadol	C	N02AX02, N02AJ14, N02AJ15, N02AJ13
Antiepileptics[s]	C, D	N03AF02, N03AF04, N03AX15, N03AB02, N03AB52, N03AD01, N03AD51, N03AG01, N03AF01, N03AX12, N03AX16
Tricyclic antidepressants	D	N06AA, N06CA01
NSAIDs for long-term use[t]	D	M01AA, M01AB, M01AC, M01AD, M01AE, M01BA01, M01BA03, N02BA51, N02BA71, N02BA01
Epilepsy		
Levetiracetam	B	N03AX14
Lamotrigine	B	N03AX09
Gabapentin	B	N03AX12
Topiramate	B	N03AX11
Lacosamide	B	N03AX18
Antiepileptics	n.l.	*Summarized as N03A*
Lorazepam	B, D[t]	N05BA06, N05BA56
Pregabalin	C	N03AX16
Valproic acid	C	N03AG01
Carbamazepine	C	N03AF01
Eslicarbamazepine	C	N03AF04
Oxcarbamazepine	C	N03AF02
Zonisamide	C	N03AX15
Diazepam	C, D	N05BA01
Midazolam	C, D	N05CD08
Phenytoin	D	N03AB02, N03AB52
Phenobarbital	D	N03AA02
Ethosuximide	D	N03AD01, N03AD51
Parkinsons disease		

Medication	Class[a]	ATC codes[b]
Levodopa	A	N04BA01, N04BA03, N04BA10, N04BA11, N04BA13, N04BA14
COMT inhibitors	B	N04BX01, N04BX02, N04BA03, N04BX04
Ropinirole	B	N04BC04
Rotigotine	B	N04BC09
Antiparkinson drugs	n.l.	*Summarized as N04*
MAO-B inhibitors	C, D	N04BD02, N04BD01, N04BD03
Pramipexole	C	N04BC05
Piribedil	C	N04BC08
Bromocriptine	D	N04BC01
Cabergoline	D	N04BC06
Amantadine	D	N04BB01
Anticholinergics	D	N04A
Gastrointestinal symptoms		
PPIs	B	A02BC
Drugs for acid-related disorders	n.l.	*Summarized as A02*
H_2 receptor antagonists	C	A02BA
Hypothyroidism		
L-Thyroxin	A[u]	H03
Vaccinations		
Annual influenza vaccination	A	Interview question[v] and vaccines administered according to the vaccination booklet
Pneumococcal vaccination	A	Administered vaccines according to the vaccination booklet
Herpes zoster vaccine	A	Not assessed
RSV vaccine	A	Not assessed

Abbreviations: ACE, angiotensin-converting-enzyme; ASA, acetylsalicylic acid; ATC, Anatomical Therapeutic Chemical Classification; COMT, catechol-O-methyltransferase; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; GLP-1-RA, Glucagon-like peptide-1 receptor agonists; MAO, monoamine oxidase; n.l., not listed in FORTA list; n.a., not available at time of baseline assessment; NOACs, new oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARγ, peroxisome proliferator-activated receptor gamma; PPIs, proton pump inhibitors; RSV, respiratory syncytial virus; rTPA, recombinant tissue plasminogen activator; SGLT2, sodium glucose linked transporter 2; SNRIs, serotonin-noradrenalin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a] Classes: A: indispensable; B: beneficial; C: questionable; D: avoid.
[b] According to the German modification of ATC codes version 2018.
[c] Only considered as PIM in participants without a diagnosis of acute coronary syndrome, myocardial infarction, atrial fibrillation, and cardiac insufficiency.
[d] FORTA only explicitly lists ACE inhibitors. Angiotensin receptor antagonists were also considered.
[e] Not identified as overuse in participants with atrial fibrillation, peripheral vascular disease, history of myocardial infarction, stroke, angina pectoris, and other acute coronary syndromes.
[f] In participants with a history of myocardial infarction, beta blockers are only considered PIM if the date of the last myocardial infarction was > 3 years ago and in the absence of other indications (atrial fibrillation, acute coronary syndromes, cardiac insufficiency).
[g] Immediate-release glyceryl trinitrate formulations used on demand were not defined as PIM (e.g., spray, solution, bite capsules). Patches were identified as PIM.
[h] A: on-demand use. B: long-term use.
[i] Only considered as PIM in participants without arterial hypertension.
[j] A: Apixaban, B: other NOACs.
[k] Not identified as PIM in participants with acute coronary syndromes.
[l] Not identified as PIM in participants with myocardial infarction, acute coronary syndromes, or stroke.
[m] Only identified as PIM if regularly used. Not identified as PIM in patients diagnosed with one of the following conditions: arthritis, leukemia, lymphoma, breast cancer, prostate cancer, colorectal cancer, lung cancer, multiple sclerosis, eczema,

psoriasis, Crohn's disease, ulcerative colitis, and after organ transplantation.
[n] Not counted as overuse in participants without osteoporosis.
[o] B: in participants with eGFR < 30 ml/min/1.73m². C: in participants with eGFR ≥ 30 ml/min/1.73m². Only identified as PIM if eGFR was not missing prior to imputation.
[p] Not identified as PIM in participants with one of the following conditions: dyslipidemia, acute coronary syndromes, myocardial infarction, and stroke.
[q] Not identified as PIM in participants with a certain or possible diagnosis of epilepsy.
[r] Not identified as PIM in participants with self-reported depression or moderate to severe depression according to PHQ-9.
[s] Antiepileptics classified as FORTA B were not identified as PIM in participants with a certain or possible diagnosis of epilepsy.
[t] Only identified as PIM if used regularly.
[u] Only identified as underuse in participants with TSH > 8 mU/L.
[v] Interview question: "How often do you get an influenza vaccination?".

Appendix 17. Comparison of baseline characteristics of NAKO study participants included in the subsample with complete vaccination information (N=5,575) and those excluded from it (N=48,721)

Characteristics	N (%)[a]	
	Vaccination subsample (N=5,575)	Study population not included in vaccination subsample (N=48,721)
Sociodemographic/ -economic factors		
Sex		
Female	2,884 (51.7)	24,305 (49.9)
Male	2,691 (48.3)	24,416 (50.1)
Age group, years		
60 – 64	2,661 (47.7)	23192 (47.6)
65 – 69	2,432 (43.6)	21689 (44.5)
≥ 70	482 (8.7)	3,840 (7.9)
Study center		
Augsburg	688 (12.3)	4,825 (9.9)
Regensburg	120 (2.2)	2,558 (5.3)
Mannheim	729 (13.1)	1,829 (3.8)
Freiburg	373 (6.7)	2,281 (4.7)
Saarbrücken	324 (5.8)	2,399 (4.9)
Essen	249 (4.5)	2,421 (5.0)
Münster	23 (0.4)	2,534 (5.2)
Düsseldorf	10 (0.2)	2,354 (4.8)
Halle	229 (4.1)	2,578 (5.3)
Leipzig	886 (15.9)	1,954 (4.0)
Berlin North	244 (4.4)	2,440 (5.0)
Central Berlin	199 (3.6)	2,573 (5.3)
Berlin South	23 (0.4)	2,695 (5.5)
Hannover	769 (13.8)	2,097 (4.3)
Hamburg	99 (1.8)	2,496 (5.1)
Bremen	296 (5.3)	2,457 (5.0)
Kiel	50 (0.9)	2,461 (5.1)
Neubrandenburg	166 (3.0)	3,235 (6.6)
Neustrelitz	98 (1.8)	711 (1.5)
Waren (Müritz)	0 (0.0)	1,125 (2.3)
Demmin	0 (0.0)	698 (1.4)
Income[b]		
Low	3,211 (57.6)	27,268 (56.0)
Middle	1,681 (30.2)	15,185 (31.2)
High	683 (12.3)	6,268 (12.9)
Years of education		
< 13	195 (3.5)	2,056 (4.2)
≥ 13	5,380 (96.5)	46,665 (95.8)
Social network index[c]		

Characteristics	N (%)[a]	
	Vaccination subsample (N=5,575)	**Study population not included in vaccination subsample (N=48,721)**
I+II	2,881 (51.7)	26,573 (54.5)
III+IV	2,694 (48.3)	22,148 (45.5)
Lifestyle factors		
BMI *(kg/m²)*		
< 20	104 (1.9)	1073 (2.2)
20 – 24.9	1,494 (26.8)	13,075 (26.8)
25 – 29.9	2,423 (43.5)	20,305 (41.7)
≥ 30	1,554 (27.9)	14,268 (29.3)
Physical activity level[d]		
Insufficient	725 (13.0)	6,171 (12.7)
Sufficient	4,850 (87.0)	42,550 (87.3)
Alcohol consumption[e]		
Abstainer	455 (8.2)	4,671 (5.6)
Low	4,460 (80.0)	38,653 (79.3)
Moderate to high	660 (11.8)	5,397 (11.1)
Smoking status		
Never smoker	2,622 (47.0)	20,992 (43.1)
Former smoker, years since quit		
> 20 years	1,342 (24.1)	11,457 (23.5)
≤ 20 years	834 (15.0)	7,976 (16.4)
Current smoker	777 (13.9)	8,296 (17.0)
Comorbidities		
Diabetes	635 (11.4)	6,049 (12.4)
Arterial hypertension	2,787 (50.0)	24,174 (49.6)
Atrial fibrillation/arrhythmia	830 (14.9)	7,405 (15.2)
Stroke	162 (2.9)	1,717 (3.5)
Myocardial infarction	158 (2.8)	2,076 (4.3)
Heart failure	298 (5.3)	2,678 (5.5)
Acute coronary syndrome	349 (6.3)	4,042 (8.3)
Asthma	395 (7.1)	3,549 (7.3)
COPD	428 (7.7)	3,641 (7.5)
Osteoporosis	409 (7.3)	3,546 (7.3)
Thyroid disease/hypothyroidism[f]	1,667 (29.9)	13,284 (27.3)
History of fractures[g]	983 (17.6)	8,720 (17.9)
Pain[h]	3,679 (66.0)	33,208 (68.2)
Parkinson's disease	14 (0.3)	183 (0.4)
Cognitive impairment/dementia[i]	190 (3.4)	2,044 (4.2)
History of depression[j]	835 (15.0)	7,696 (15.8)
Epilepsy	35 (0.6)	361 (0.7)
Insomnia	1,494 (26.8)	12,342 (25.3)

Characteristics	N (%)[a]	
	Vaccination subsample (N=5,575)	**Study population not included in vaccination subsample (N=48,721)**
Gastrointestinal symptoms[k]	1,718 (30.8)	14,822 (30.4)
History of cancer	814 (14.6)	6,798 (14.0)
Renal impairment[l]	235 (4.2)	2,493 (5.1)

Values in bold are statistically significant ($p<0.05$).
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; NAKO, German National Cohort; PIM, potentially inappropriate medication.

[a] Calculated from first imputed dataset.
[b] Average total household income before tax. Categories: low: < 2900€; middle: 2900 – < 5000€; high: ≥ 5000€.
[c] Categories: I (isolated) to IV (least isolated).
[d] Adherence to WHO recommendations following Global Physical Activity Questionnaire (GPAQ). Categories: sufficient: ≥ 600 metabolic equivalent of task (MET)–min/week; insufficient: < 600 MET–min/week.
[e] Alcohol consumption, g ethanol per day. Categories: abstainer: 0 g/day; low: women 0-19.99g/d or man 0-39.99g/d; moderate – high: women ≥ 20g/d or man ≥ 40g/d.
[f] Lifetime history of thyroid disease, self-reported. Underuse for the indication hypothyroidism was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list)
[g] Fractures since aged 50 years.
[h] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[i] Based on the interview question “Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?”.
[j] Lifetime history of depression, self-reported.
[k] Combination of self-reported information on reflux, peptic ulcer (“Have you ever been diagnosed with this condition by a physician?”), and regular intake of NSAIDs (ATC M01A). Underuse for this indication was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment, and in participants regularly taking NSAIDs.
[l] Estimated glomerular filtration rate < 60ml/min/1.73m², calculated based on CKD-EPI equation.

Appendix 18. Percentages of missing data of covariates prior to imputation in analyzed NAKO population (N=54,296)

Characteristics	Proportion of missing (%)
Sociodemographic/ -economic factors	
Sex	0.0
Age	0.0
Study center	0.0
Income[a]	7.3
Years of education	0.2
Social network index	26.7
Lifestyle factors	
BMI *(kg/m²)*	3.7
Physical activity level *(MET-min/week)*	8.8
Alcohol consumption *(g/day)*	7.6
Smoking status	5.3
Quitage	0.2
Comorbidities	-
History of fractures[b]	26.8
History of cancer	0.4
Renal impairment[c]	4.6

Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; NAKO, German National Cohort.

[a] Average total household income before tax. Categories: low: < 2900€; middle: 2900 – < 5000€; high: ≥ 5000€.
[b] Fractures since aged 50.
[c] Estimated glomerular filtration rate < 60 ml/min/1.73m², calculated based on the CKD-EPI equation.

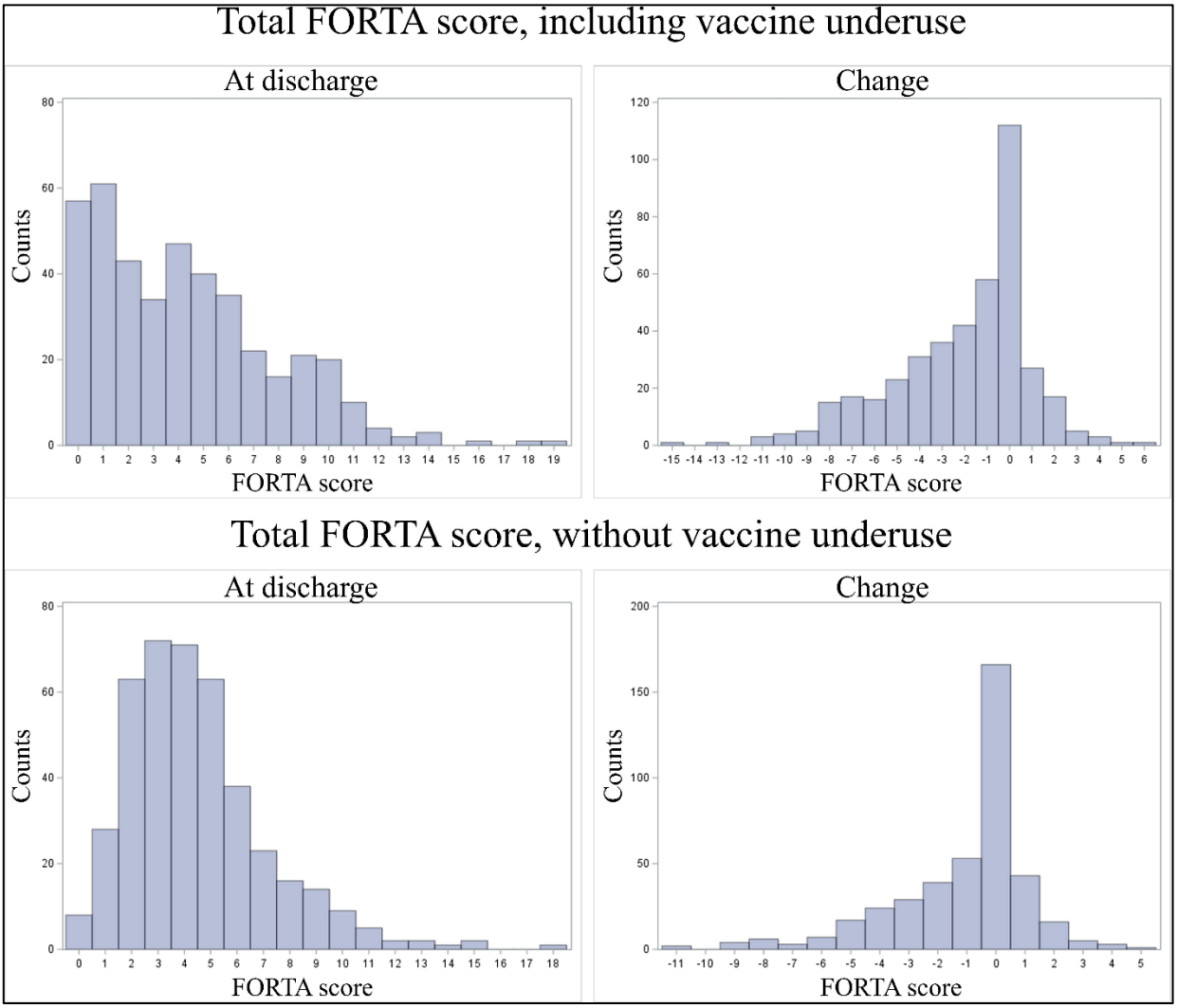
Appendix 19. Percentages of missing data of indications for medication use prior to imputation in analyzed NAKO population (N=54,296)

FORTA Indication	Proportion of missing (%)
Diabetes	0.3
Arterial hypertension	0.4
Atrial fibrillation/arrhythmia	1.0
Stroke	0.4
Myocardial infarction	0.3
Heart failure	1.2
Acute coronary syndrome	0.8
Asthma	0.5
COPD	0.6
Tiffeneau index[a]	29.1
Osteoporosis	0.9

FORTA Indication	Proportion of missing (%)
Thyroid disease/hypothyroidism[b]	0.5
TSH[c] *(mU/l)*	48.0
Pain[d]	4.6
Parkinson's disease	0.2
Cognitive impairment/dementia[e]	0.4
History of depression	0.6
PHQ-9[f]	12.5
Epilepsy	0.3
Insomnia	24.7
Gastrointestinal symptoms[g]	0.5

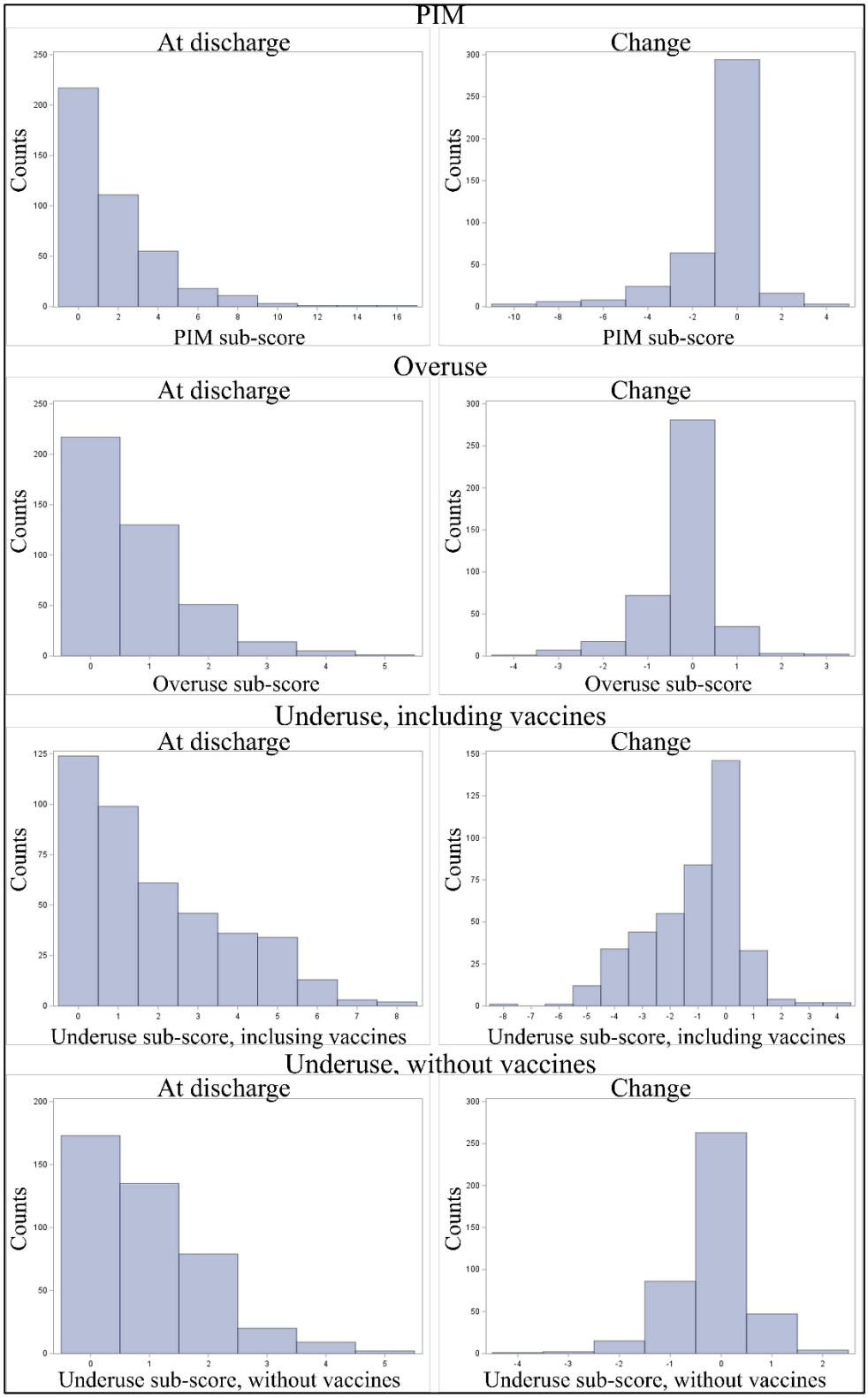
Abbreviations: COPD, chronic obstructive pulmonary disease; NAKO, German National Cohort; PHQ-9, Patient Health Questionnaire; TSH, thyroid stimulating hormone.

[a] Proportion of missing values among participants with COPD: 20.5%. Participants with self-reported lifetime history of COPD but missing Tiffeneau Index were not classified as underusers for this specific indication.
[b] Lifetime history of thyroid disease, self-reported. Underuse was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list).
[c] Proportion of missing values among participants with self-reported history of thyroid disease: 46.7%. Participants with a lifetime history of thyroid diseases but missing TSH blood levels were not classified as underusers for this specific indication.
[d] Combination of self-reported pain in the last 4 weeks and pain-related diagnoses (including certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout).
[e] Self-reported bad or very bad memory based on the interview question "How would you evaluate your memory at the moment?" – five categories: very good to very bad.
[f] PHQ-9 sum scores were used to determine the indication for depression treatment: PIM and overuse were considered in participants with self-reported lifetime history of depression or moderate to severe depression according to PHQ-9 (sum score ≥ 15). Underuse was only considered in untreated individuals with severe depression according to or PHQ-9 (sum score ≥ 20). Proportion of missing values among participants with a lifetime history of depression: 13.9%. Missing values were treated as PHQ-9 sum score < 15.
[g] Combination of self-reported information on reflux, peptic ulcer ("Have you ever been diagnosed with this condition by a physician?"), and regular intake of NSAIDs (ATC M01A).



Appendix 20. Distributions of total FORTA score at discharge and change in total FORTA score between admission and discharge, per-protocol population (N=418)

Abbreviations: FORTA, Fit fOR The Aged List Version 4.



Appendix 21. Distributions of FORTA sub-scores at discharge and change in FORTA (sub-)scores between admission and discharge, per-protocol population (N=418)

Abbreviations: FORTA, Fit fOR The Aged List Version 4.

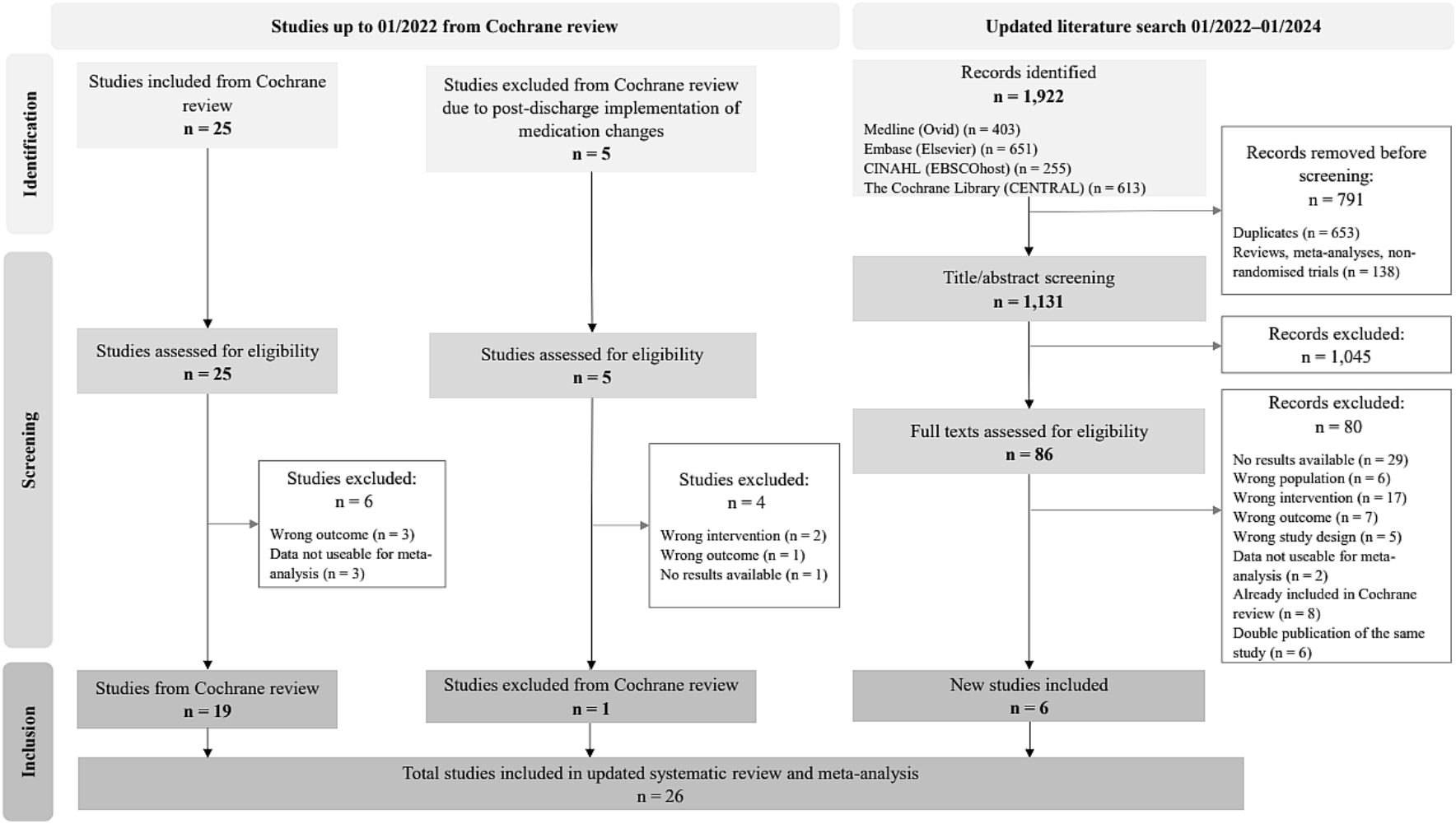
Appendix 22. Proportion of missing data in OPTIMAL intention-to-treat population (N=443)

Variable	N (data)	Proportion missing (%)
Sociodemographic/ -economic factors		
Sex	443	0.0
Age	443	0.0
Years of schooling	440	0.7
Partnership	443	0.0
Social support[a]	438	1.1
Lifestyle factors		
BMI *(kg/m²)*	440	0.7
Alcohol consumption *(g/day)*	432	2.5
Physical activity[b]	440	0.7
Smoking status	440	0.7
Cancer		
Cancer site	443	0.0
Stage	388	12.4
Cancer therapy		
Chemotherapy	435	1.8
Radiotherapy	436	1.6
Surgery	436	1.6
Comorbidities		
Diabetes	443	0.0
Arterial hypertension	443	0.0
Stroke	443	0.0
Myocardial infarction	443	0.0
Heart failure	443	0.0
Acute coronary syndromes	443	0.0
Atrial fibrillation	443	0.0
Asthma, COPD	443	0.0
Osteoporosis	443	0.0
Chronic pain	443	0.0
Depression	443	0.0
Insomnia	443	0.0
Gastrointestinal symptoms	443	0.0
Incontinence	443	0.0
Anemia, iron or B12-related	443	0.0
Constipation	443	0.0
Hypothyroidism	443	0.0
Chronic kidney disease	443	0.0
Dyslipidemia	443	0.0
Gout	443	0.0

Variable	N (data)	Proportion missing (%)
Peripheral vascular disease	443	0.0
Physical/diagnostic assessments		
Depressive symptoms[c]	440	0.7
Frailty[d]	432	2.5[e]
Global quality of life score[f]	441	0.2

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

[a] According to DUFSS-5 (Saracino et al. 2015).
[b] According to the RAPA tool (Topolski et al. 2006).
[c] According the GDS (Stiles et al. 1998).
[d] According to FRAIL scale (Morley et al. 2012).
[e] Comprised 5 domains which were imputed separately. Maximum proportion of missing values: 2.5%. Minimum proportion of missing values: 0.0%.
[f] According to the EORTC QLQ-C30 global health status /quality of life scale (Aaronson et al. 1993).



Appendix 23. PRISMA flow chart

If trials were excluded due to multiple reasons, I only reported the most relevant exclusion criterion.

Appendix 24. Trials excluded in the full-text screening and reason for exclusion

Trial reference	Reason for exclusion
DTB Team (2023). **A deprescribing intervention from hospital to postacute community care**. Drug Ther Bull *61(12)*, 181, doi: 10.1136/dtb.2023.000061.	Double publication of Vasilevskis 2019
Basger, B. (2014). **Application of a prescribing indicators tool to assist in identifying and resolving drug-related problems in older Australians - a randomized controlled trial.** Australian New Zealand Clinical Trials Registry (ANZCTR) identifier: ACTRN12611000995976. URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=347487 [last accessed 18.02.2024].	Wrong outcome (difference in the number of prescribing indicators, health-related quality of life)
Etherton-Beer, C. (2018). **The Australian Team Approach to Polypharmacy Evaluation and Reduction (AusTAPER) study for older hospital inpatients**. Australian New Zealand Clinical Trials Registry (ANZCTR) identifier: ACTRN12618000979257. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12618000979257 [last accessed 18.02.2024].	No results available (ongoing study)
Hilmer, S. (2022). **The Effects of an Intervention to Optimise Quality Use Of Medicines In Older People in Hospital**. Australian New Zealand Clinical Trials Registry (ANZCTR) identifier: ACTRN12622000374763. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12622000374763 [last accessed 18.02.2024].	No results available (ongoing study); wrong study design (not considered to be an RCT due to stepped wedge design)
Penm, J. (2023). **Timely post-discharge medication reviews to Improve Continuity – the Transitions Of Care stewardship (TIC TOC) study in rural and regional Australia**. Australian New Zealand Clinical Trials Registry (ANZCTR) identifier: ACTRN12623000727640. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12623000727640 [last accessed 18.02.2024].	No results available (not yet recruiting); wrong outcome (medication-related readmissions or emergency department visits, cost-effectiveness, quality of life, patient experiences with the intervention)
Adam, L., Baretella, O., Feller, M., Blum, M. R., Papazoglou, D. D., Boland, B., Aujesky, D., Baggio, S. and Rodondi, N. (2023). **Statin therapy in multimorbid older patients with polypharmacy- a cross-sectional analysis of the Swiss OPERAM trial population**. Front Cardiovasc Med *10*, 1236547, doi: 10.3389/fcvm.2023.1236547.	Trial was already included in Cochrane review as Blum 2021
Ahmad, A., Nijpels, G., Dekker, J. M., Kostense, P. J. and Hugtenburg, J. G. (2012). **Effect of a pharmacist medication review in elderly patients discharged from the hospital**. Arch Intern Med *172(17)*, 1346-1347, doi: 10.1001/archinternmed.2012.2816.	Wrong intervention (medication review was conducted post-discharge)
Aubert, C. E., Blum, M. R., Gastens, V., Dalleur, O., Vaillant, F., Jennings, E., Aujesky, D., Thompson, W., Kool, T., Kramers, C., Knol, W., O'Mahony, D. and Rodondi, N. (2023). **Prescribing, deprescribing and potential adverse effects of proton pump inhibitors in older patients with multimorbidity: an observational study**. CMAJ Open *11(1)*, E170-e178, doi: 10.9778/cmajo.20210240.	Trial was already included in Cochrane review as Blum 2021
Boxer, R. S., Dolansky, M. A., Chaussee, E. L., Campbell, J. D., Daddato, A. E., Page, R. L., 2nd, Fairclough, D. L. and Gravenstein, S. (2022). **A Randomized Controlled Trial of Heart Failure Disease Management in Skilled Nursing Facilities**. J Am Med Dir Assoc *23(3)*, 359-366, doi: 10.1016/j.jamda.2021.05.023.	Wrong intervention (medication review was restricted to heart failure medication)

Trial reference	Reason for exclusion
Chang, C. T., Teoh, S. L., Cheah, W. K., Lee, P. J., Azman, M. A., Ling, S. H., Chuah, A. S. C., Sabki, N. H., George, D., Oh, H. L., Goh, J. Y., Lee, S. H., Foong, W. K., Lee, J. C. Y., Chan, H. K., Teoh, L. R., Lim, X. J., Rajan, P. and Lee, S. W. H. (2023). **Impact of deprescribing intervention on potentially inappropriate medications and clinical outcomes among hospitalized older adults in Malaysia: a randomized controlled trial (REVMED RCT) protocol**. J Pharm Policy Pract *16(1)*, 113, doi: 10.1186/s40545-023-00621-5.	No results available (ongoing study)
Chen, J. Z., Hoang, H. L., Yaskina, M., Kabbani, D., Doucette, K. E., Smith, S. W., Lau, C., Stewart, J., Remtulla, S., Zurek, K., Schultz, M., Koriyama-McKenzie, H. and Cervera, C. (2023). **Efficacy and safety of antimicrobial stewardship prospective audit and feedback in patients hospitalised with COVID-19 (COVASP): a pragmatic, cluster-randomised, non-inferiority trial**. Lancet Infect Dis *23(6)*, 673-682, doi: 10.1016/s1473-3099(22)00832-5.	Wrong intervention (medication review was restricted to antibiotics)
Choi, J. Y., Lee, J. Y., Shin, J., Kim, C. O., Kim, K. J., Hwang, I. G., Lee, Y. G., Koh, S. J., Hong, S., Yoon, S. J., Kang, M. G., Kim, J. W., Kim, J. H. and Kim, K. I. (2022). **COMPrehensive geriatric AsseSSment and multidisciplinary team intervention for hospitalised older adults (COMPASS): a protocol of pragmatic trials within a cohort**. BMJ Open *12(8)*, e060913, doi: 10.1136/bmjopen-2022-060913.	No results available (ongoing study)
Colucciello, N., Kowalkowski, M., Wardi, G., Kooken, M. and Taylor, S. (2023). **A SEPSIS TRANSITION PROGRAM IMPROVES CARE DELIVERY TO SEPSIS SURVIVORS DISCHARGED TO POST-ACUTE CARE**. Crit Care Med *51(1)*, 585, doi: 10.1097/01.ccm.0000910432.08079.42.	Wrong intervention (transition and recovery intervention including antibiotic stewardship (restricted to antibiotic medications), discharge order review for certain high-risk drugs (not considered to be a full medication review), post-discharge medication review (wrong setting/population: outpatient)); IMPACTS trial
Colucciello, N., Parks Taylor, S., Kowalkowski, M. A. R. C. and Wardi, G. (2022). **Passing the SNF Test: A Secondary Analysis of a Sepsis Transition Intervention Trial Among Patients Discharged to Post-Acute Care**. Chest *162(4)*, A909, doi: 10.1016/j.chest.2022.08.718.	Wrong intervention (transition and recovery intervention including antibiotic stewardship (restricted to antibiotic medications), discharge order review for certain high-risk drugs (not considered to be a full medication review), post-discharge medication review (wrong setting/population: outpatient)); Secondary analysis of the excluded IMPACTS trial
Cossette, B., Éthier, J. F., Joly-Mischlich, T., Bergeron, J., Ricard, G., Brazeau, S., Caron, M., Germain, O., Payette, H., Kaczorowski, J. and Levine, M. (2017). **Reduction in targeted potentially inappropriate medication use in elderly inpatients: a pragmatic randomized controlled trial**. Eur J Clin Pharmacol *73(10)*, 1237-1245, doi: 10.1007/s00228-017-2293-4.	Data was not suitable for meta-analysis due to methodological issues (hospitalizations)[a]

Trial reference	Reason for exclusion
de Wildt, K. K., van de Loo, B., Linn, A. J., Medlock, S. K., Groos, S. S., Ploegmakers, K. J., Seppala, L. J., Bosmans, J. E., Abu-Hanna, A., van Weert, J. C. M., van Schoor, N. M. and van der Velde, N. (2023). **Effects of a clinical decision support system and patient portal for preventing medication-related falls in older fallers: Protocol of a cluster randomized controlled trial with embedded process and economic evaluations (ADFICE_IT)**. PLoS One *18(9)*, e0289385, doi: 10.1371/journal.pone.0289385.	No results available (ongoing study); wrong outcome (time to first injurious fall, number of falls, time to first fall, quality of life, cost effectiveness, feasibility); wrong population (outpatients)
Demirci, M. Y., Okuyan, B., Sancar, M. and Mutlu, B. (2023). **Impact of clinical pharmacist led theory-based discharge counselling service on clinical outcomes of patients with acute coronary syndrome: preliminary results of a randomized controlled study**. Eur J Cardiovasc Nurs *22*, i134, doi: 10.1093/eurjcn/zvad064.151.	Data not useable for meta-analysis
Donzé, J., John, G., Genné, D., Mancinetti, M., Gouveia, A., Méan, M., Bütikofer, L., Aujesky, D. and Schnipper, J. (2023). **Effects of a Multimodal Transitional Care Intervention in Patients at High Risk of Readmission: The TARGET-READ Randomized Clinical Trial**. JAMA Intern Med *183(7)*, 658-668, doi: 10.1001/jamainternmed.2023.0791.	Wrong intervention (medication reconciliation in order to resolve and detect discrepancies, patient education)
Schöttker, B. (2023). **Optimization of polypharmacy in geriatric oncology**. German Clinical Trials Register (DRKS) identifier: DRKS00031024. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02572929/full [last accessed 18.02.2024].	No results available (ongoing study)
Farhat, A., Al-Hajje, A., Lang, P. O. and Csajka, C. (2022). **Impact of Pharmaceutical Interventions with STOPP/START and PIM-Check in Older Hospitalized Patients: A Randomized Controlled Trial**. Drugs Aging *39(11)*, 899-910, doi: 10.1007/s40266-022-00974-7.	Wrong study design (comparison of two types of medication reviews, but not compared to usual care)
Ferro-Uriguen, A., Beobide-Telleria, I., Gil-Goikouria, J., Peña-Labour, P. T., Díaz-Vila, A., Herasme-Grullón, A. T. and Echevarría-Orella, E. (2023). **Effectiveness of a Person-Centered Prescription Model in Hospitalized Older People at the End of Life According to Their Disease Trajectories and Frailty Index**. Int J Environ Res Public Health *20(4)*, doi: 10.3390/ijerph20043542.	Double publication of Ferro-Uriguen 2022
Forman, D. E., Racette, S. B., Toto, P. E., Peterson, L. R., Glynn, N. W., Pruskowski, J., Byard, T., Delligatti, A., Lolley, R., Mulkareddy, V., Allsup, K., Perera, S., Lenze, E. J. and Rich, M. W. (2022). **Modified Application of Cardiac Rehabilitation in Older Adults (MACRO) Trial: Protocol changes in a pragmatic multi-site randomized controlled trial in response to the COVID-19 pandemic**. Contemp Clin Trials *112*, 106633, doi: 10.1016/j.cct.2021.106633.	No results available (ongoing study)
Geneletti, L., Chanoine, S., Lugosi, M., Allenet, B., Bouilet, L., Bedouch, P. and Deroux, A. (2019). **Impact of hospital-city communication based on the multiprofessional and collaborative development of the discharge letter on the continuity of patients' medication management-city study**. Eur J Hosp Pharm *26(Suppl 1)*, A172-A172, doi: 10.1136/ejhpharm-2019-eahpconf.370.	Wrong intervention (the intervention was not a medication review)
Ghazi, L., Desai, N. R., Simonov, M., Yamamoto, Y., O'Connor, K. D., Riello, R. J., Huang, J., Olufade, T., McDermott, J., Inzucchi, S. E., Velazquez, E. J., Wilson, F. P. and Ahmad, T. (2022). **Rationale and design of a cluster-randomized pragmatic trial aimed at improving use of guideline directed medical therapy in outpatients with heart failure: PRagmatic trial of messaging to providers about treatment of heart failure (PROMPT-HF)**. Am Heart J *244*, 107-115, doi: 10.1016/j.ahj.2021.11.010.	Wrong intervention (medication review was restricted to heart failure medication); wrong population (outpatients: the trial was conducted in outpatient clinics)

Trial reference	Reason for exclusion
Giger, A. W., Ditzel, H. M., Jørgensen, T. L., Ditzel, H. J., Mohammadnejad, A., Ewertz, M., Pfeiffer, P., Lund, C. M. and Ryg, J. (2022). **Predictive value of geriatric oncology screening and geriatric assessment of older patients with cancer: A randomized clinical trial protocol (PROGNOSIS-RCT)**. J Geriatr Oncol *13(1)*, 116-123, doi: 10.1016/j.jgo.2021.07.005.	Wrong population (outpatients: the trial was conducted in outpatient clinics)
Göhner, A., Dreher, E., Kentischer, F., Maurer, C., Farin-Glattacker, E., von der Warth, R., Brühmann, B. A., Maun, A., Minin, V., Salm, C., Ritzi, A., Engelhardt, G., Sofroniou, M. and Voigt-Radloff, S. (2022). **Reduction of care-relevant risks to older patients during and after acute hospital care (ReduRisk) - study protocol of a cluster randomized efficacy trial in a stepped wedge design**. BMC Geriatr *22(1)*, 754, doi: 10.1186/s12877-022-03442-4.	Wrong study design (not considered to be an RCT due to stepped wedge design)
Gouveia, A., Mancinetti, M., Genné, D., Méan, M., John, G., Bütikofer, L., Aujesky, D., Schnipper, J. L. and Donzé, J. (2023). **Effectiveness of Transition Care Intervention Targeted to High-Risk Patients to Reduce Readmissions: Study Protocol for the TARGET-READ Multicenter Randomized-Controlled Trial**. Healthcare (Basel) *11(6)*, doi: 10.3390/healthcare11060886.	No results available (not yet recruiting)
Hias, J., Hellemans, L., Laenen, A., Walgraeve, K., Liesenborghs, A., De Geest, S., Luyten, J., Spriet, I., Flamaing, J., Van der Linden, L. and Tournoy, J. (2022). **The effect of a trAnSitional Pharmacist Intervention in geRiatric inpatients on hospital visits after dischargE (ASPIRE): Protocol for a randomized controlled trial**. Contemp Clin Trials *119*, 106853, doi: 10.1016/j.cct.2022.106853.	No results available (ongoing study)
Hill, R. R., Willett, E. C., Manuel, J. D. and Delate, T. (2022). **Impact of Palliative Care Clinical Pharmacists in an Inpatient Care Setting on Total Health Care Expenditures**. J Palliat Med *25(10)*, 1518-1523, doi: 10.1089/jpm.2021.0642.	Wrong study design (retrospective longitudinal cohort study)
Huibers, C. J. A., Sallevelt, B., Heij, J., O'Mahony, D., Rodondi, N., Dalleur, O., van Marum, R. J., Egberts, A. C. G., Wilting, I. and Knol, W. (2022). **Hospital physicians' and older patients' agreement with individualised STOPP/START-based medication optimisation recommendations in a clinical trial setting**. Eur Geriatr Med *13(3)*, 541-552, doi: 10.1007/s41999-022-00633-5.	Trial was already included in Cochrane review as Blum 2021
University of Leicester (2023). **A study evaluating an intervention for doctors and pharmacists working in older people's medicine wards in hospitals in England, to review and stop medicines no longer needed or where the risk of harm outweighs the benefit**. The UK's Clinical Study Registry (ISRCTN) identifier: ISRCTN13248281. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN13248281 [last accessed 18.02.2024].	No results available (ongoing study); wrong study design (not considered to be an RCT due to stepped wedge design)
Johansen, J. S., Halvorsen, K. H., Havnes, K., Wetting, H. L., Svendsen, K. and Garcia, B. H. (2022a). **Intervention fidelity and process outcomes of the IMMENSE study, a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients**. J Clin Pharm Ther *47(5)*, 619-627, doi: 10.1111/jcpt.13581.	Double publication of Johansen 2018

Trial reference	Reason for exclusion
Juanes, A., Garin, N., Mangues, M. A., Herrera, S., Puig, M., Faus, M. J. and Baena, M. I. (2018). **Impact of a pharmaceutical care programme for patients with chronic disease initiated at the emergency department on drug-related negative outcomes: a randomised controlled trial**. Eur J Hosp Pharm *25(5)*, 274-280, doi: 10.1136/ejhpharm-2016-001055.	Outcomes did not meet inclusion criteria
Juanes, A., Ruíz, J., Puig, M., Blázquez, M., Gilabert, A., López, L., Baena, M. I., Guiu, J. M. and Antònia Mangues, M. (2023). **The Effect of the Drug-Related Problems Prevention Bundle on Early Readmissions in Patients From the Emergency Department: A Randomized Clinical Trial**. Ann Pharmacother *57(9)*, 1025-1035, doi: 10.1177/10600280221143237.	Wrong population (patients not admitted to the hospital were included; the intervention was conducted in the ED)
Kim, K. I. (2022b). **Establishment of comprehensive geriatric assessment based multidisciplinary team approach for hospitalized frail patients**. The Clinical Research Information Service (CRIS) identifier: KCT0006270. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0006270 [last accessed 18.02.2024].	No results available (ongoing study)
Kim, C. O. (2022a). **Establishment of comprehensive geriatric assessment based multidisciplinary team approach for hospitalized frail patients**. The Clinical Research Information Service (CRIS) identifier: KCT0007968. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02524932/full [last accessed 18.02.2024].	No results available (ongoing study)
Kempen, T. G. H., Bertilsson, M., Hadziosmanovic, N., Lindner, K. J., Melhus, H., Nielsen, E. I., Sulku, J. and Gillespie, U. (2021). **Effects of Hospital-Based Comprehensive Medication Reviews Including Postdischarge Follow-up on Older Patients' Use of Health Care: A Cluster Randomized Clinical Trial**. JAMA Netw Open *4(4)*, e216303, doi: 10.1001/jamanetworkopen.2021.6303.	Data not usable for meta-analysis due to the high risk of bias caused by the cross-over design
Khadela, A., Bhikadiya, V. and Vyas, B. (2022). **Impact of oncology pharmacist services on humanistic outcome in patients with breast cancer**. J Oncol Pharm Pract *28(2)*, 302-309, doi: 10.1177/1078155220988333.	Wrong outcome (quality of life); wrong study design (not an RCT: pre-post-study design)
Kim, K. I. (2022c). **Information technology-supported integrated health service for older adults in long-term care settings: A cluster randomized controlled study**. International Society for Gerontechnology 13th World Conference, October 24-26, 2022, Daegu, South Korea. Gerontechnology *21*, 1.	Wrong outcome (PIM use, diabetes control)
Kim, J. L., Lewallen, K. M., Hollingsworth, E. K., Shah, A. S., Simmons, S. F. and Vasilevskis, E. E. (2023). **Patient-Reported Barriers and Enablers to Deprescribing Recommendations During a Clinical Trial (Shed-MEDS)**. Gerontologist *63(3)*, 523-533, doi: 10.1093/geront/gnac100.	Double publication of Vasilevskis 2019
Klopotowska, J. E., Kuks, P. F. M., Wierenga, P. C., Stuijt, C. C. M., Arisz, L., Dijkgraaf, M. G. W., de Keizer, N., Smorenburg, S. M. and de Rooij, S. E. (2022). **The effect of structured medication review followed by face-to-face feedback to prescribers on adverse drug events recognition and prevention in older inpatients - a multicenter interrupted time series study**. BMC Geriatr *22(1)*, 505, doi: 10.1186/s12877-022-03118-z.	Wrong outcome (rate and change in the rate of serious hospital-acquired preventable and unrecognized adverse drug events, change in the rate of hospital-acquired preventable adverse drug events); wrong study design (not an RCT: interrupted time series study with quasi-experimental approach)

Trial reference	Reason for exclusion
Kowalkowski, M., Rios, A., Murphy, S., McWilliams, A., Hetherington, T., Rossman, W., Chou, S. and Taylor, S. (2022). **The Effect of a Sepsis-Specific Transitional Care Intervention on 12-Month Outcomes After Sepsis Hospitalization**. Am J Respir Crit Care Med *205(1)*, doi: 10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A2372.	Wrong intervention (transition and recovery intervention including antibiotic stewardship (restricted to antibiotic medications), discharge order review for certain high-risk drugs (not considered to be a full medication review), post-discharge medication review (wrong setting/population: outpatient)); IMPACTS trial
Lee, V., Kowalski, J., Liu, M. and Thayer, B. (2022). **Impact of Discharge Medication Reconciliation Across a Five-Hospital Health System**. J Healthc Qual *44(4)*, 194-200, doi: 10.1097/jhq.0000000000000335.	Wrong study design (not an RCT: pre-post-study design)
Linkens, A., Milosevic, V., van Nie, N., Zwietering, A., de Leeuw, P. W., van den Akker, M., Schols, J., Evers, S., Gonzalvo, C. M., Winkens, B., van de Loo, B. P. A., de Wolf, L., Peeters, L., de Ree, M., Spaetgens, B., Hurkens, K. and van der Kuy, H. M. (2022). **Control in the Hospital by Extensive Clinical rules for Unplanned hospitalizations in older Patients (CHECkUP); study design of a multicentre randomized study**. BMC Geriatr *22(1)*, 36, doi: 10.1186/s12877-021-02723-8.	Wrong intervention (medication review was conducted by a CDSS instead of a healthcare professional)
Logan, B., Viecelli, A. K., Johnson, D. W., Aquino, E. M., Bailey, J., Comans, T. A., Gray, L. C., Hawley, C. M., Hickey, L. E., Janda, M., Jaure, A., Jose, M. D., Kalaw, E., Kiriwandeniya, C., Matsuyama, M., Mihala, G., Nguyen, K. H., Pascoe, E., Pole, J. D., Polkinghorne, K. R., Pond, D., Raj, R., Reidlinger, D. M., Scholes-Robertson, N., Varghese, J., Wong, G. and Hubbard, R. E. (2023). **Study protocol for The GOAL Trial: comprehensive geriatric assessment for frail older people with chronic kidney disease to increase attainment of patient-identified goals-a cluster randomised controlled trial**. Trials *24(1)*, 365, doi: 10.1186/s13063-023-07363-4.	No results available (ongoing study); wrong population (outpatients: the trial was conducted in outpatient clinics)
Moreau, L. A., Holloway, I., Fylan, B., Hartley, S., Cundill, B., Fergusson, A., Alderson, S., Alldred, D. P., Bojke, C., Breen, L., Ismail, H., Gardner, P., Mason, E., Powell, C., Silcock, J., Taylor, A., Farrin, A. and Gale, C. (2022). **Using routine healthcare data to evaluate the impact of the Medicines at Transitions Intervention (MaTI) on clinical outcomes of patients hospitalised with heart failure: protocol for the Improving the Safety and Continuity Of Medicines management at Transitions of care (ISCOMAT) cluster randomised controlled trial with embedded process evaluation, health economics evaluation and internal pilot**. BMJ Open *12(4)*, e054274, doi: 10.1136/bmjopen-2021-054274.	Wrong intervention (not a medication review: patient education and enhanced discharge communication between the hospital and the patient's community pharmacy, the community pharmacy is asked to invite the patient for a discussion about the medication)
Morley, C., Donaldson, M., Kowalkowski, M., Samuel, P., Noorali, A., Sutaria, N., Reed, N. and Taylor, S. (2023). **QUANTIFYING MEDICATION ERRORS MITIGATED BY AN EFFECTIVE POST-SEPSIS TRANSITION PROGRAM**. Crit Care Med *51(1)*, 609, doi: 10.1097/01.ccm.0000910624.86471.b1.	Wrong intervention (transition and recovery intervention including antibiotic stewardship (restricted to antibiotic medications), discharge order review for certain high-risk drugs (not considered to be a full medication review), post-discharge medication review (wrong setting/population: outpatient)); Secondary analysis of the excluded IMPACTS trial

Trial reference	Reason for exclusion
Forman, M. (2023). **Modified Application of Cardiac Rehabilitation for Older Adults (MACRO)**. ClinicalTrials.gov identifier: NCT03922529. URL: https://clinicaltrials.gov/study/NCT03922529?tab=history [last accessed 18.02.2024].	No results available (ongoing study)
Davidson, G. (2022). **Preventing Medication-Related Problems in Care Transitions to Skilled Nursing Facilities**. ClinicalTrials.gov identifier: NCT05241951. URL: https://clinicaltrials.gov/study/NCT05241951?tab=study [last accessed 18.02.2024].	No results available (ongoing study)
O'Mahony, D. (2022). **OPTImization of Medication by Transdisciplinary Assessment of Drug Treatment in Elderly Hospitalized Patients**. ClinicalTrials.gov identifier: NCT05387096. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02405233/full [last accessed 18.02.2024].	No results available (ongoing study)
Mahidol University (2022). **Impact of Pharmaceutical Care on Drug-related Problems in Patients With Parkinson's Disease**. ClinicalTrials.gov identifier: NCT05410210. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02402305/full [last accessed 18.02.2024].	Wrong outcome (change in the number of drug-related problems and affecting factors, change in Movement Disorder Society-Unified Parkinson's Disease Rating Scale Score, Patient Global Impression of Change and affecting factors, change in quality of life)
Hospices Civils de Lyon (2022). **RhEumatoid Arthritis MEDIcation Adherence**. ClinicalTrials.gov identifier: NCT05413759. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02405890/full [last accessed 18.02.2024].	No results available (ongoing study); wrong outcome ((disease activity score, rheumatoid arthritis-related hospitalizations, hospitalizations due to adverse drug events, Functional and quality of life criteria, criteria for patient behavior in relation to their disease-modifying antirheumatic drugs, economic criteria, implementation and acceptability-related criteria)
Bekaty, M. Y. (2022). **Development and Evaluation of Clinical Pharmacy Services in Respiratory Diseases**. ClinicalTrials.gov identifier: NCT05564156. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02475124/ful [last accessed 18.02.2024].	No results available (not published yet)
Eriksson, T. (2023). **Correct Medication List at and After Hospital Discharge**. ClinicalTrials.gov identifier: NCT05784194. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02538147/full [last accessed 18.02.2024].	No results available (ongoing study); wrong outcome (correct medication list, clinical consequences associated with errors, health economic evaluation)
Abebe, K. (2023). **A Patient-centered Trial of a Process-of-care Intervention in Hospitalized AKI Patients: the COPE-AKI Trial**. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02542368/full [last accessed 18.02.2024].	No results available (ongoing study); wrong outcome (hospital-free days, rate of major adverse kidney events, recurrent acute kidney injury hospitalization, quality of life, interactions with providers, social support)
Lee, S. W. H. (2023). **Impact of Medications Review on Potentially Inappropriate Medications and Clinical Outcomes Among Hospitalized Older Adults**. ClinicalTrials.gov identifier: NCT05875623. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02563426/full [last accessed 18.02.2024].	No results available (ongoing study); wrong outcomes (number of PIMs, number of chronic medications)

Trial reference	Reason for exclusion
Radboud University Medical Center (2023). **Less Is More: optimized Pharmacotherapy With Improved coNtinuity of CarE in hospitaLized oLder peOple**. ClinicalTrials.gov identifier: NCT05899114. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02573119/full [last accessed 18.02.2024].	No results available (ongoing study)
University of New Mexico (2023). **Impact of Clinical Pharmacy Services on Medication Cost and Hospitalization Rates in Hemodialysis Patients**. ClinicalTrials.gov identifier: NCT05952388. URL: https://clinicaltrials.gov/ct2/show/NCT05952388 [last accessed 18.02.2024].	No results available (ongoing study); wrong outcome (reduction in at-home medication); wrong population (outpatients)
National Taiwan University Hospital (2023). **Using SMART HOME Strategy to Reduce the Incidence of Delirium in the Intensive Care Unit**. ClinicalTrials.gov identifier: NCT06030453. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02597610/full [last accessed 18.02.2024].	No results available (ongoing study)
Cliniques universitaires Saint-Luc- Université Catholique de Louvain (2023). **Concordance : a New Concept for Clinical Pharmacy in Partnership With Patients at a Geriatric Day Clinic (COPAPI-G)**. ClinicalTrials.gov identifier: NCT06059235. URL: https://clinicaltrials.gov/ct2/show/NCT06059235 [last accessed 18.02.2024].	No results available (ongoing study)
Sancar, M. (2023). **Effects of Pharmaceutical Care in Stroke Patients**. ClinicalTrials.gov identifier: NCT06129318. URL: https://clinicaltrials.gov/study/NCT06129318 [last accessed 18.02.2025].	Wrong outcome (adherence, quality of life, drug-related problems, stroke recurrence, National Institutes of Health Stroke Scale, blood pressure, HbA_{1c}, LDL cholesterol, triglyceride)
Nguyen, H. N., Nguyen, C. V., Nguyen, D. T., Le, T. D. and Bui, Q. T. H. (2023). **Impact of pharmacist-led interventions on heart failure medication adherence: a prospective cohort study**. J Pharm Health Serv Res *14(2)*, 205-211, doi: 10.1093/jphsr/rmad008.	Wrong intervention (patient education)
Nymoen, L. D., Flatebø, T. E., Moger, T. A., Øie, E., Molden, E. and Viktil, K. K. (2022). **Impact of systematic medication review in emergency department on patients' post-discharge outcomes-A randomized controlled clinical trial**. PLoS One *17(9)*, e0274907, doi: 10.1371/journal.pone.0274907.	Wrong population (patients not admitted to the hospital were included; the intervention was conducted in the ED)
Nymoen, L. D., Flatebø, T. E., Øie, E., Molden, E. and Viktil, K. K. (2023). **How to tailor pharmacist-led interventions to the emergency department setting**. Int J Clin Pharm *45(2)*, 528, doi: 10.1007/s11096-023-01576-y.	Wrong population (patients not admitted to the hospital were included; the intervention was conducted in the ED)
Ogilvie, M., Nissen, L., Kyle, G. and Hale, A. (2022). **An evaluation of a collaborative pharmacist prescribing model compared to the usual medical prescribing model in the emergency department**. Res Social Adm Pharm *18(10)*, 3744-3750, doi: 10.1016/j.sapharm.2022.05.005.	Wrong outcome (prescribing errors, omissions, discrepancies, documentation of adverse drug reactions, appropriate risk assessment, prescribing of thromboembolism prophylaxis)
Paudel, N., Shrestha, S., Marasine, N. R., Khanal, P., Aryal, S., Erku, D. and Poudel, A. (2023). **Impact of hospital pharmacist-delivered individualised pharmaceutical service intervention on clinical and patient-reported outcomes in patients with hypertension: a randomised controlled trial**. Eur J Hosp Pharm *30(6)*, 316-321, doi: 10.1136/ejhpharm-2020-002512.	Wrong intervention (intervention was not a systematic review: patient education intervention; intervention did not result in change of the medication or in an according advice; restricted to antihypertensive medication); wrong outcome (change in blood pressure, adherence, quality of life)

Trial reference	Reason for exclusion
Rantsi, M., Pitkälä, K. H., Kautiainen, H., Hyttinen, V. and Kankaanpää, E. (2022). **Cost-effectiveness of an educational intervention to reduce potentially inappropriate medication**. Age Ageing *51(5)*, doi: 10.1093/ageing/afac112.	Wrong population (residents of assisted living facilities)
Rapp, T., Sicsic, J., Tavassoli, N. and Rolland, Y. (2023). **Do not PIMP my nursing home ride! The impact of Potentially Inappropriate Medications Prescribing on residents' emergency care use**. Eur J Health Econ *24(7)*, 1085-1100, doi: 10.1007/s10198-022-01534-x.	Wrong intervention (not a medication review: systematic dementia screening with interdisciplinary team meetings; the article was on an investigation on the relationship between PIM use and ED visit risks in study participants); wrong outcome (ED visits, economic outcomes); wrong population (included outpatients: nursing home residents visiting the ED)
Coutinho Ribeiro, L. (2022). **Evaluation of the pharmacist's performance in the care of hospital discharge patients in the cardiology unit of a teaching hospital in Espírito Santo**. Registro Brasileiro de Ensaios Clínicos (REBEC) identifier: RBR-10hdj2bg. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02475976/full [last accessed 18.02.2024].	No results available (not yet recruiting)
Oliveira, T. Z. (2023). **The impacts of Pharmaceutical Care in an emergency unit of a teaching hospital**. Registro Brasileiro de Ensaios Clínicos (REBEC) identifier: RBR-7s755rt. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02570645/full [last accessed 18.02.2024].	No results available (ongoing study)
Fundação Universidade Federal de Sergipe (2023). **Intervenções Farmacêuticas sobre o tratamento medicamentoso dos idosos com Doença de Risco Cardiovascular**. Registro Brasileiro de Ensaios Clínicos (REBEC) identifier: RBR-8dvw5zp. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02513341/full [last accessed 18.02.2024].	No results available (not yet recruiting)
Robinson, E. G., Gyllensten, H., Johansen, J. S., Havnes, K., Granas, A. G., Bergmo, T. S., Småbrekke, L., Garcia, B. H. and Halvorsen, K. H. (2023a). **A Trial-Based Cost-Utility Analysis of a Medication Optimization Intervention Versus Standard Care in Older Adults**. Drugs Aging *40(12)*, 1143-1155, doi: 10.1007/s40266-023-01077-7.	Wrong outcome (cost-effectiveness); only parts of the IMMENSE trial population included
Robinson, E. G., Pham, S., Gyllensten, H., Granas, A. G., Havnes, K., Bergmo, T., Garcia, B. H. and Halvorsen, K. H. (2023b). **Health-Related Quality of Life Among Acutely Hospitalized Older Adults: Data From the IMMENSE Trial**. Int J Clin Pharm *45(1)*, 268-269, doi: 10.1007/s11096-023-01537-5.	Double publication of Johansen 2018
Rovner, B. W., Casten, R., Chang, A. M., Hollander, J. E., Leiby, B. E., Nightingale, G., Pizzi, L., Herres, J., White, N., Kelley, M. and Rising, K. (2023). **Interprofessional Intervention to Reduce Emergency Department Visits in Black Individuals with Diabetes**. Popul Health Manag *26(1)*, 46-52, doi: 10.1089/pop.2022.0216.	Wrong population (patients not admitted to the hospital were included; the intervention was conducted in the ED)
Rubin, D. J., Gogineni, P., Deak, A., Vaz, C., Watts, S., Recco, D., Dillard, F., Wu, J., Karunakaran, A., Kondamuri, N., Zhao, H., Naylor, M. D., Golden, S. H. and Allen, S. (2022). **The Diabetes Transition of Hospital Care (DiaTOHC) Pilot Study: A Randomized Controlled Trial of an Intervention Designed to Reduce Readmission Risk of Adults with Diabetes**. J Clin Med *11(6)*, doi: 10.3390/jcm11061471.	Wrong intervention (not a medication review: patient education, optimization of diabetes medication)
Rudawsky, N. and Patel, H. U. (2022). **Impact of a Transition of Care Pharmacist in a Community Hospital Discharge Model**. J Healthc Qual *44(6)*, 347-353, doi: 10.1097/jhq.0000000000000348.	Wrong study design (not a randomised controlled trial: pre-post-study design)

Trial reference	Reason for exclusion
Salari, P., O'Mahony, C., Henrard, S., Welsing, P., Bhadhuri, A., Schur, N., Roumet, M., Beglinger, S., Beck, T., Jungo, K. T., Byrne, S., Hossmann, S., Knol, W., O'Mahony, D., Spinewine, A., Rodondi, N. and Schwenkglenks, M. (2022). **Cost-effectiveness of a structured medication review approach for multimorbid older adults: Within-trial analysis of the OPERAM study**. PLoS One *17(4)*, e0265507, doi: 10.1371/journal.pone.0265507.	Trial was already included in Cochrane review as Blum 2021
Sallevelt, B., Huibers, C. J. A., Heij, J., Egberts, T. C. G., van Puijenbroek, E. P., Shen, Z., Spruit, M. R., Jungo, K. T., Rodondi, N., Dalleur, O., Spinewine, A., Jennings, E., O'Mahony, D., Wilting, I. and Knol, W. (2022). **Frequency and Acceptance of Clinical Decision Support System-Generated STOPP/START Signals for Hospitalised Older Patients with Polypharmacy and Multimorbidity**. Drugs Aging *39(1)*, 59-73, doi: 10.1007/s40266-021-00904-z.	Trial was already included in Cochrane review as Blum 2021
Schnipper, J. L., Kirwin, J. L., Cotugno, M. C., Wahlstrom, S. A., Brown, B. A., Tarvin, E., Kachalia, A., Horng, M., Roy, C. L., McKean, S. C. and Bates, D. W. (2006). **Role of pharmacist counseling in preventing adverse drug events after hospitalization**. Arch Intern Med *166(5)*, 565-571, doi: 10.1001/archinte.166.5.565.	Wrong outcome (all and preventable adverse drug events, patient satisfaction, healthcare utilization, adherence, medication discrepancies)
Scott, S., Atkins, B., Martin-Kerry, J. M., Pritchard, M., Alldred, D. P., Clark, A. B., Colles, A., Hammond, A., Murphy, K., Keevil, V. L., Kellar, I., Patel, M., Sims, E., Taylor, J., Turner, D., Witham, M., Wright, D. and Bhattacharya, D. (2023). **CompreHensive geriAtRician-led MEdication Review (CHARMER): protocol for a feasibility study of a hospital deprescribing behaviour change intervention**. BMJ Open *13(8)*, e075795, doi: 10.1136/bmjopen-2023-075795.	No results available (not published yet); wrong study design (not considered to be an RCT due to purposive allocation)
Shah, A. S., Hollingsworth, E. K., Shotwell, M. S., Mixon, A. S., Simmons, S. F. and Vasilevskis, E. E. (2022). **Sources of medication omissions among hospitalized older adults with polypharmacy**. J Am Geriatr Soc *70(4)*, 1180-1189, doi: 10.1111/jgs.17629.	Double publication of Vasilevskis 2019
Sibille, F. X., de Saint-Hubert, M., Henrard, S., Aubert, C. E., Goto, N. A., Jennings, E., Dalleur, O., Rodondi, N., Knol, W., O'Mahony, D., Schwenkglenks, M. and Spinewine, A. (2023). **Benzodiazepine Receptor Agonists Use and Cessation Among Multimorbid Older Adults with Polypharmacy: Secondary Analysis from the OPERAM Trial**. Drugs Aging *40(6)*, 551-561, doi: 10.1007/s40266-023-01029-1.	Trial was already included in Cochrane review as Blum 2021
Song, Y. K., Jeong, S., Han, N., Na, H., Jang, H. Y., Sohn, M., Kim, Y. S., Joo, K. W., Oh, K. H., Kim, D. K., Lee, H., Oh, J. M. and Drug, T. S. G. (2021). **Effectiveness of Clinical Pharmacist Service on Drug-Related Problems and Patient Outcomes for Hospitalized Patients with Chronic Kidney Disease: A Randomized Controlled Trial**. J Clin Med *10(8)*, doi: 10.3390/jcm10081788.	Wrong outcome (drug-related problems at discharge, adherence, acute care utilization, change in medication discrepancies, drug-related problems during in-hospital stay, and resolution rate)
de Boer, M., Ramrattan, M. A., Kiewiet, J. J., Boeker, E. B., Gombert-Handoko, K. B., van Lent-Evers, N. A., Kuks, P. F., Dijkgraaf, M. G., Boermeester, M. A. and Lie, A. H. L. (2011). **Cost-effectiveness of ward-based pharmacy care in surgical patients: protocol of the SUREPILL (Surgery & Pharmacy In Liaison) study**. BMC Health Serv Res *11*, 55, doi: 10.1186/1472-6963-11-55.	Data not usable for meta-analysis

Trial reference	Reason for exclusion
Syversen, M. O., Shah, S. F., Mathiesen, L., Mowé, M. and Lea, M. (2023). **Effect of integrated medicines management on the quality of drug treatment in hospitalised multimorbid patients - a secondary endpoint analysis of a randomised controlled trial**. Int J Pharm Pract *31(3)*, 314-320, doi: 10.1093/ijpp/riad007.	Trial was already included in Cochrane review as Lea 2020
Tan, S. L., Xiao, J., Yuan, H. Y., Chen, L., Wang, Q., Xiang, D. X., Li, X., Zhou, Y. G., Guo, Y., Huang, H. Y., Zhao, D. H., Li, Y., Wang, L., Li, Q., Liu, J. and Xu, P. (2022). **Establishing and evaluating physician-pharmacist collaborative clinics to manage patients with type 2 diabetes in primary hospitals in Hunan province: study protocol of a multi-site randomized controlled trial in the era of COVID-19 pandemic**. BMC Health Serv Res *22(1)*, 299, doi: 10.1186/s12913-022-07653-8.	Wrong intervention (not a medication review: patient education, identification, and treatment of adverse drug reactions; intervention was restricted to diabetes medication); wrong population (outpatients: the trial was conducted in outpatient clinics)
Tasseff, N., Axtell, S. and Nixon, B. (2024). **Effect of extended pharmacist involvement in discharge transitions of care on hospital readmission rates: Prospective, randomized, parallel arm design trial**. J Am Coll Clin Pharm *7(1)*, 8-14, doi: 10.1002/jac5.1887.	Data not usable for meta-analysis
Taylor, S. P., Murphy, S., Rios, A., McWilliams, A., McCurdy, L., Chou, S. H., Hetherington, T., Rossman, W., Russo, M., Gibbs, M. and Kowalkowski, M. A. (2022). **Effect of a Multicomponent Sepsis Transition and Recovery Program on Mortality and Readmissions After Sepsis: The Improving Morbidity During Post-Acute Care Transitions for Sepsis Randomized Clinical Trial**. Crit Care Med *50(3)*, 469-479, doi: 10.1097/ccm.0000000000005300.	Wrong intervention (transition and recovery intervention including antibiotic stewardship (restricted to antibiotic medications), discharge order review for certain high-risk drugs (not considered to be a full medication review), post-discharge medication review (wrong setting/population: outpatient)); IMPACTS trial
Thevelin, S., Pétein, C., Metry, B., Adam, L., van Herksen, A., Murphy, K., Knol, W., O'Mahony, D., Rodondi, N., Spinewine, A. and Dalleur, O. (2022). **Experience of hospital-initiated medication changes in older people with multimorbidity: a multicentre mixed-methods study embedded in the OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM) trial**. BMJ Qual Saf *31(12)*, 888-898, doi: 10.1136/bmjqs-2021-014372.	Trial was already included in Cochrane review as Blum 2021
Yap, D. F. S., Khairudin, N. A., Sabarudin, N. D. A. and Wong, S. W. (2022). **COMPARING SERVICE MODELS: PHARMACIST-ASSISTED TRANSITION OF CARE (TOC) VERSUS STANDARD OF CARE (SOC) TOWARDS EFFECT ON HEALTHCARE RESOURCE UTILIZATION AMONG PATIENTS FROM MEDICAL WARDS**. Journal of Health and Translational Medicine *25(1)*, 18-26, doi: 10.22452/jummec.vol25no1.5.	Wrong intervention (not a medication review: medication reconciliation, patient education)

Abbreviations: RCT, randomized controlled trial.

Appendix 25. Trial characteristics – Number of medications, eligible diagnoses, reason for the initial hospitalization, aim, involvement of pharmacists, number of recommendations, mortality assessment, and implementation of medication changes

First author, year (References)	Number of medications		Eligible diagnoses	Reason for initial admission	Aim	Involvement of Pharmacists	Number of recommendations	Outcome assessment	Implementation[a]	
	Mean or median	Inclusion criteria						Mortality	DH	AD
Bladh 2011	7[b]	No[c]	All	All	O[d]	Yes	133	Unkn.	X	
Blum 2021	IG: 10 (7-13), CG: 9 (7-12)[b]	≥ 5	All	All	O[d,e]	Yes	2,331	Relatives[f]	X	
Bonetti 2018	Unkn.[g]	No[c]	Lim.[h]	All	Other[i]	Yes	Unkn.	Unkn.	X	
Bonnerup 2014	11[j]	Other[k]	All	Acute	O[d]	Other[l]	123	Registry	X	
Curtin 2020	11[j]	≥ 5	All	Acute	D[m]	Yes	Unkn.	PC[n]	X	
Dalleur 2014	7[b]	No[c]	All	All	D[o]	Yes	68	PC[p]	X	
Farris 2014	11[j]	No[c]	Lim.[q]	All	O[d]	Yes	3,297[r]	PC[s]	X	
Ferro-Uriguen 2022	IG: 9.0 (3.2), CG: 8.2 (3.5)[j]	No[c]	Lim.[t]	Other[u]	O[v]	Yes	Unkn.	Unkn.[w]	X	
Gallagher 2011	7.7	No[c]	All	Acute	O[x]	No	183	Relatives[f]	X	
Gillespie 2009	8[j]	No[c]	All	Acute	O[y]	Yes	476	Unkn.	X	
Graabaek 2019	6[j]	No[c]	All	Acute	O[d]	Yes	920	Registry	X	
Grischott 2018	IG: 9.54 (4.00), CG: 9.74 (4.37)[j]	≥ 5	All	All	O[z]	No	Unkn.	PC[p]		X[aa]
Gustafsson 2017	IG: 8.4, CG: 8.3[j]	No[c]	Lim.[bb]	Acute	O[d]	Yes	310	Unkn.	X	
Johansen 2018	IG: 8 (5-12), CG: 9 (6-13)[b]	No[c]	All	Acute	O	Yes	> 5 per patient[cc]	Registry	X	
Lea 2020	8[b]	≥ 4	All	Acute	O	Yes	1651	Registry	X	
Lenssen 2018	16.8[j]	Other[k]	All	All	O[y]	Yes	100	NA	X	

First author, year (References)	Number of medications		Eligible diagnoses	Reason for initial admission	Aim	Involvement of Pharmacists	Number of recommendations	Outcome assessment	Implementation[a]	
	Mean or median	Inclusion criteria						Mortality	DH	AD
Lisby 2010	10.2[j]	Other[k]	All	Acute	O[d]	Yes	187	Unkn.	X	
Lisby 2015	6.7[j]	≥ 4	All	Acute	O[d]	Yes	222	Registry	X	
Nielsen 2017	8[b]	≥ 4	All	Acute	O[y]	Yes	Unkn.	Unkn.	X	
O'Mahony 2020	10 (8-13)[b]	Other[dd]	Unkn.[ee]	Acute	O[d,e]	No	Unkn.	Unkn.	X	
Pope 2011	IG: 11.64, CG: 11.07[j]	No[c]	All	Other[ff]	D[gg]	Yes	Unkn.[hh]	Other[ii]		Other[jj]
Ravn-Nielsen 2018	IG: 10, CG: 9 (7-12)[b]	≥ 5	All	Acute	O[d]	Yes	946	Registry	X	
Schapira 2022	IG: 5.5 (2.7), CG: 5.6 (2.8)[j]	No[c]	All	Acute	D[kk]	Yes	Unkn.	PC[ll]	X	
Scullin 2007	Unkn.	Other[mm]	All	Acute	O[y]	Yes	1628[nn]	Unkn.	X	
Vasilevskis 2019	16 (12-20)[b]	≥ 5	All	Acute	D[oo]	Yes	883[pp]	Relatives		Other[qq]
Visade 2022	Unkn.	No	All	Acute	O	Yes	Unkn.	NA	X	

Abbreviations: AD, after discharge; CG, control group; D, deprescribing; DH, during hospitalization; IG, intervention group; Lim., limited; NA, not assessed; PC, primary care; Unkn., unknown.

[a] Implementation of medication changes.
[b] Median (interquartile range, if reported).
[c] No medication-related
[d] Underuse was assessed.
[e] The intervention was based on a clinical decision support system based on START/STOP criteria.
[f] Telephone call with patients and their proxies.
[g] At discharge: IG: 7, CG: 8 (mean). The number of medications at admission was not reported.
[h] Stable angina, acute coronary syndrome, congestive heart failure, valvular diseases, arrhythmias or hypertension.
[i] The pharmaceutical intervention was limited to discharge medication, and no clear aim could be identified.
[j] Mean (standard deviation).
[k] At least one medication required.
[l] The intervention encompassed a risk screening to decide whether the medication review would be conducted by either a pharmacologist or a pharmacist.
[m] The intervention was based on STOPFrail criteria.
[n] The patient's nursing home was contacted.
[o] The intervention was based on STOP criteria and aimed at discontinuation or dose reduction of potentially inappropriate medications.

[p] The patient's GP was contacted.
[q] Asthma, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, heart failure, coronary artery disease, myocardial infarction, stroke or transient ischemic attack.
[r] Basic intervention: 1,077; extended intervention: 2,220.
[s] Not specified, but follow-up data included information from the patient's GP and the community pharmacy.
[t] Non-oncological advanced chronic disease with an indication for palliative care.
[u] Geriatric convalescence unit.
[v] Deprescribing criteria (Beers, STOPFrail) were applied, but sufficient symptom control was also assessed (underuse) and the medication was adapted accordingly.
[w] This trial was not included in the meta-analysis on all-cause mortality: it was not possible to calculate risk ratios usable for meta-analysis from the reported data.
[x] The intervention based on START/STOP criteria.
[y] Advice on drug selection after a thorough review and assessment of each patient's condition and medication was given.
[z] Determination of main complaint and treatment goals. The appropriateness of medications and the availability of alternatives with a more favorable risk-harm balance were assessed.
[aa] Discharge intervention: medication changes and the corresponding rationale were explained in the discharge letter.
[bb] Dementia or cognitive impairment.
[cc] 437 medication discrepancies were identified. Thereof, 92.9% were discussed with the physician.
[dd] At least three chronic conditions requiring pharmacotherapy.
[ee] Multimorbid patients with ≥ 3 chronic conditions, but several diagnoses were excluded: liver failure, patients with renal failure receiving dialysis treatment, solid organ transplant graft, non-accidental overdose/self-harm, admission to geriatric medicine, clinical pharmacology, clinical oncology, hematology, psychiatry, palliative medicine, emergency medicine, and intensive care.
[ff] Patients receiving hospital continuing care: only patients of the highest dependency requiring expert nursing care.
[gg] Deprescribing tools (e.g., Beers) were used. The trial aimed at reducing medications (primary endpoints: number of medications, costs).
[hh] At least one medication change was recommended in 102 (92.7%) patients. The total number of recommendations is not reported.
[ii] The trial was conducted in continuing-care wards in hospitals. Mortality was likely assessed by the medical treatment team.
[jj] The recommendations were made to the GP, but the patients resisted in a continuing care ward of a hospital.
[kk] Identification of potentially inappropriate medication (PIM) via Beers criteria. A medication list was created in which PIMs were deprescribed.
[ll] Electronic health records were used.
[mm] One of the following criteria: 1. ≥ 4 medications, 2. intravenous antibiotics on day 1 of admission, 3. taking a predefined high-risk drug, 4. taking antidepressants, 5. ≥ 65 years 6. previous hospitalization within the last 6 months.
[nn] Number of clinical interventions.
[oo] Deprescribing intervention with 6 possible recommendations on dose reduction or discontinuation of medications. Deprescribing tools (Beers, STOPP, and RASP) were used to identify potentially inappropriate medications. Underuse was not assessed.
[pp] Number of medications identified as PIM, and the patients agreed to deprescribe them.
[qq] One of 6 deprescribing recommendations was assigned to each identified medication issue. The recommendation included instructions on when (before/after discharge) and how (stop/dose reduction/monitoring) to deprescribe the relevant medication.

Appendix 26. Trial characteristics – Frequency of medication review, number of patient contacts, and patient contact after discharge of all included trials

First author, year	Frequency of MR		Patient contacts[a]			Patient contact after discharge	
	1	≥ 2	0	1	≥ 2	Yes	No
Bladh 2011		X		X			X
Blum 2021		X		X			X
Bonetti 2018	X				X	X	
Bonnerup 2014	X			X			X
Curtin 2020	X		X				X
Dalleur 2014	X		X				X
Farris 2014[b]							
Farris 2014 (BI)		X			X		X
Farris 2014 (EI)		X			X	X	
Ferro-Uriguen 2022	X				X		X
Gallagher 2011	X		X				X
Gillespie 2009	X				X	X	
Graabaek 2019[b]							
Graabaek 2019 (BI)	X			X			X
Graakaek 2019 (EI)		X			X		X
Grischott 2023	X						X
Gustafsson 2017	X			X			X
Johansen 2018		X			X		X
Lea 2020		X			X		X
Lenssen 2018		X			X		
Lisby 2010	X			X			X
Lisby 2015	X			X			X
Nielsen 2017	X			X			X
O'Mahony 2020	X		X				X
Pope 2011						Other[c]	
Ravn-Nielsen 2018[b]							
Ravn-Nielsen 2018 (BI)	X		X				X
Ravn-Nielsen 2018 (EI)	X				X	X	
Schapira 2022	X				X	X	
Scullin 2007	X				X		X
Vasilevskis 2019		X		X			X
Visade 2022	X			X			X

Abbreviations: BI, basic intervention; EI, extended intervention; MR, medication review.

[a] Patient contacts were defined by the number of patient contacts within the intervention, e.g. shared decision-making with the patient before recommended medications were implemented, patient education, or medication counseling. Patient contacts provided as part of usual care were not counted.

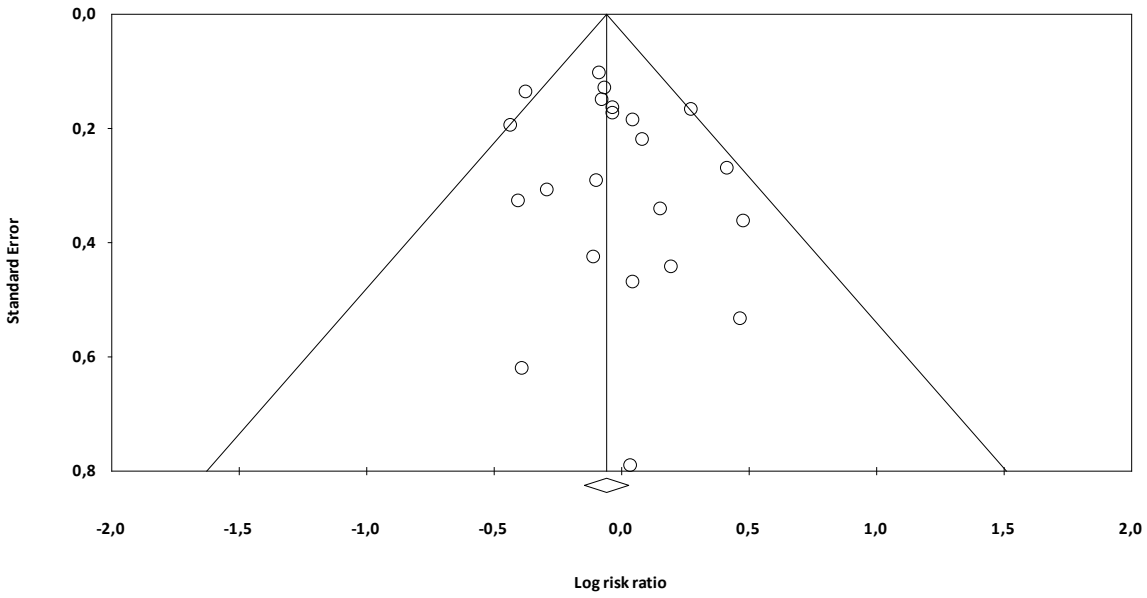
[b] Three-armed trials were split into basic and extended interventions and assigned separately if major differences were observed regarding the considered methodological aspect.

[c] Patients were not discharged: the trial was conducted in continuing care wards.

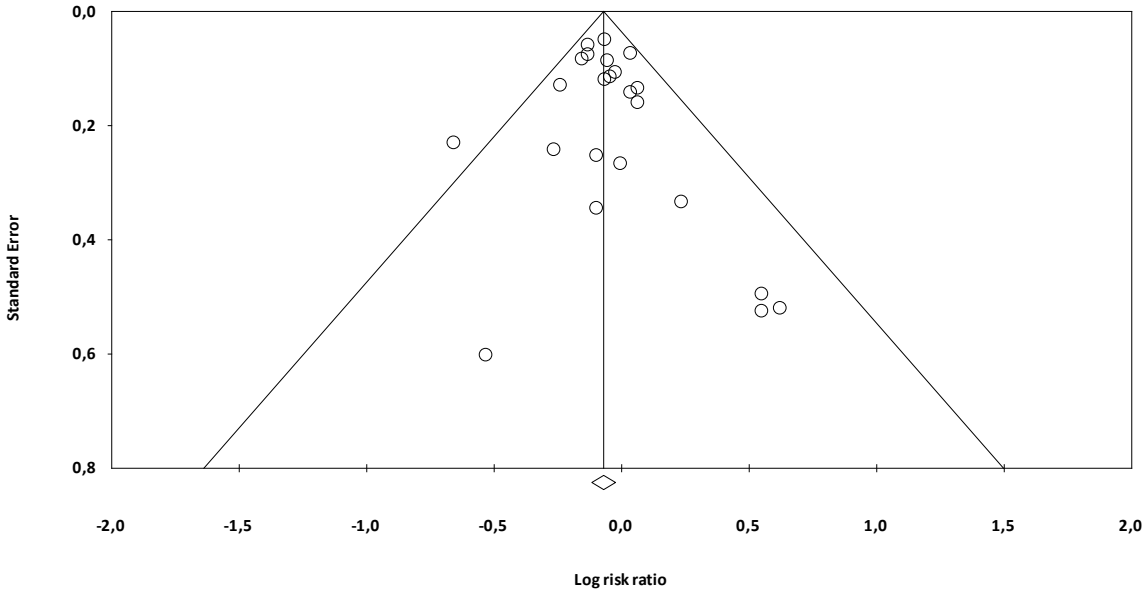
Appendix 27. Risk of bias assessment

Trial	RS	AC	BP	BOA		IOD		SR	CB	OB
				M	R	M	R			
Bladh 2011	+	+	-	+	+	+	+	+	-	+
Blum 2021	+	+	-	+	+	+	+	+	+	+
Bonetti 2018	+	?	-	+	+	-	-	?	-	+
Bonnerup 2014	+	+	-	+	+	+	+	+	-	?
Curtin 2020	+	+	-	+	+	+	+	+	-	
Dalleur 2014	?	-	-	+		-		?	-	-
Farris 2014	+	+	-	+	+	?	?	+	-	+
Ferro-Uriguen 2022	?	?	-		+		+	?	-	?
Gallagher 2011	+	+	-	+	+	+	+	+	-	+
Gillespie 2009	+	+	-	+	+	+	+	+	-	+
Graabaek 2019	+	+	-	+	+	+	+	?	-	+
Grischott 2023	-	?	+		+		-	+	+	?
Gustafsson 2017	+	+	-	+	+	+	+	+	-	+
Johansen 2018	+	+	-	+	+	+	+	?	-	?
Lea 2020	+	+	-	+	+	+	+	-	-	+
Lenssen 2018	+	-	-		+		+	+	-	+
Lisby 2010	+	?	-	+	+	+	+	+	-	+
Lisby 2015	+	?	-	+	+	+	+	+	-	+
Nielsen 2017	+	+	-	+	+	+	+	+	-	+
O'Mahony 2020	+	+	-	+	+	+	+	+	-	+
Pope 2011	+	?	-	+	+	+	+	?	-	?
Ravn-Nielsen 2018	+	+	-	+	+	+	+	?	-	+
Schapira	+	+	-	+	+	+	+	?	-	+
Scullin 2007	+	?	-	+	+	?	-	+	-	-
Vasilevskis 2019	+	+	-	+		+		+	-	+
Visade 2022	?	?	-		+		?	?	-	-

Abbreviations: AC, allocation concealment (selection bias); BP, blinding of participants and personnel (performance bias); BOA, blinding of outcome assessment (detection bias); CB, contamination bias; IOD, incomplete outcome data (attrition bias); M, mortality (all-cause); OB, other bias; R, rehospitalization (all-cause/unplanned); RS, random sequence generation (selection bias); SR, selective reporting (reporting bias).
Note: Results of studies included from the previous Cochrane review of Bülow et al. were taken over from this review.



Appendix 28. Assessment of publication bias: funnel plot for studies reporting on all-cause mortality



Appendix 29. Assessment of publication bias: funnel plot on rehospitalization

Appendix 30. Univariate meta-regression results for the outcomes mortality and rehospitalization testing the factors one by one

Factor	Mortality		Rehospitalization	
	β coefficient[a] (95% CI)	**p-value**	**β coefficient[a] (95% CI)**	**p-value**
Follow-up time (per month)	**-0.02 (-0.03; 0.00[b])**	**0.032**	0.00 (-0.01; 0.02)	0.695
Setting				
Middle/Western Europe	-0.04 (-0.29; 0.20)	0.727	0.06 (-0.06; 0.19)	0.323
Northern Europe	Ref.		Ref.	
North America	0.09 (-0.49; 0.67)	0.773	-0.01 (-0.20; 0.18)	0.933
Other	-0.18 (-0.52; 0.16)	0.304	0.03 (-0.15; 0.22)	0.720
Mean/Median age (per year)	0.00 (-0.02; 0.01)	0.762	0.00 (-0.01; 0.01)	0.863
Mean/Median number of medications (per drug)[c]	0.03 (-0.03; 0.01)	0.306	0.00 (-0.02; 0.02)	0.992
Number of medications as inclusion criterion				
≥ 4	-0.14 (-0.34; 0.06)	0.163	-0.03 (-0.13; 0.07)	0.622
No or other inclusion criterion	Ref.		Ref.	
Eligible diagnoses				
Any[d]	Ref		Ref.	
Restricted to certain diagnoses	**0.31 (0.01; 0.62)**	**0.045**	0.08 (-0.11; 0.26)	0.416
Aim				
Deprescribing	-0.17 (-0.48; 0.13)	0.265	-0.16 (-0.35; 0.02)	0.084
Optimisation	Ref.		Ref.	
Other	-0.35 (-1.59; 0.88)	0.573	-0.46 (-1.64; 0.73)	0.450
Involvement of pharmacists				
Yes	Ref.		Ref.	
No	-0.02 (-0.34; 0.30)	0.913	**0.15 (0.02; 0.28)**	**0.017**
Other	0.21 (-0.51; 0.93)	0.567	-	

Factor	Mortality		Rehospitalization	
	β coefficient[a] (95% CI)	**p-value**	**β coefficient[a] (95% CI)**	**p-value**
Number of recommendations per patient[c]	**-0.02 (-0.04; 0.00[b])**	**0.013**	0.00 (-0.01; 0.0)	0.664
Mortality assessment				
Registries or primary care	**-0.26 (-0.46; -0.05)**	**0.014**	-	
Relatives	-0.17 (-0.43; 0.09)	0.204	-	
Other or unknown	Ref.		-	
Reason for initial hospitalization				
Acute	Ref.		Ref.	
Acute and elective	0.11 (-0.16; 0.38)	0.415	0.08 (-0.04; 0.19)	0.194
Other	0.56 (-0.19; 1.32)	0.144	0.22 (-0.34; 0.79)	0.438
Implementation of medication changes				
During hospitalization	Ref.		Ref.	
After hospitalization	0.29 (-0.27; 0.86)	0.311	0.15 (-0.13; 0.43)	0.300
Other	-		-0.13 (-0.34; 0.07)	0.201
Frequency of medication review				
Repeated	-0.07 (-0.27; 0.13)	0.486	-0.06 (-0.16; 0.04)	0.237
At one single time point	Ref.		Ref.	
Number of patient contacts[e]	-0.08 (-0.20; 0.05)	0.235	**-0.09 (-0.14; -0.03)**	**0.003**
Patient contact after discharge				
Yes	-0.04 (-0.28; 0.21)	0.765	-0.11 (-0.22; 0.01)	0.070
No	Ref.		Ref.	
Other	0.53 (-0.22; 1.29)	0.165	0.62 (-0.36; 1.59)	0.214

Values in bold are statistically significant ($p<0.05$).
Abbreviations: CI, confidence interval.

[a] Beta coefficient tested for each aspect alone in a model.
[b] Exact values: follow-up time: -0.0016; number of recommendations: Number of recommendations per patient: -0.0046
[c] Unknown values were imputed through mean imputation.
[d] The trial categorized as “unknown” was assigned to the group of trials including any diagnoses.
[e] Used as a continuous covariate. If two or more patient contacts were provided, the value was set to two.

Appendix 31. Multivariate model of the meta-regression on all-cause mortality

Factors	ß coefficient (95% CI)	p-value
Mortality assessment		
Registry or primary care	-0.19 (-0.39; 0.02)	0.073
Relatives	-0.17 (-0.40; 0.06)	0.154
Other or unknown	Ref	Ref
Number of recommendations per patient[a]	-0.02 (-0.04; 0.00[b])	0.072

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval.

[a] Unknown values were imputed through mean imputation.
[b] Exact value: 0.0016.

Appendix 32. Multivariate model of the meta-regression on rehospitalization

Factors	ß coefficient (95% CI)	p-value
Involvement of pharmacists		
Yes	Ref	Ref
No	0.08 (-0.07; 0.23)	0.282
Number of patient contacts	**-0.07 (-0.13; 0.00[a])**	**0.045**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval.

[a] Exact value: -0.0014.

Appendix 33. Contingency table of number of patient contacts and involvement of pharmacists in trials on rehospitalization

Number of patient contacts	Involvement of pharmacists		Total, n (%)
	No, n (%)	Yes, n (%)	
0, n (%)	3 (11.1)	2 (7.4)	**5 (18.5)**
1, n (%)	1 (3.7)	9 (33.3)	**10 (37.0)**
≥ 2, n (%)	0 (0.0)	12 (44.4)	**12 (44.4)**
Total, n (%)	**4 (14.8)**	**23 (85.2)**	**27 (100.0)**

Abbreviations: CI, confidence interval.
Note: Three-armed trials were split and considered as two separate studies.

Appendix 34. Baseline characteristics of propensity score matched new PIM and AM users

Characteristics	New AM users (N=5,906)		New PIM users (N=5,906)	
	N (%)[a]	Median (IQR)[a]	N (%)[a]	Median (IQR)[a]
Sociodemographic/ -economic factors				
Sex	-	-	-	-
Female	3,365 (57.0)		3,419 (57.9)	
Male	2,541 (43.0)		2,587 (42.1)	
Age[b]		65 (62; 67)		65 (63; 67)
Income[c]	-	-	-	-
Very low	2,668 (45.2)		2,601 (44.0)	
Low	1,921 (32.5)		1,959 (33.2)	
Middle	861 (14.6)		916 (15.5)	
High	391 (6.6)		363 (6.1)	
Very high	65 (1.1)		67 (1.1)	
Years of schooling	-	-	-	-
≤ 10	3,667 (62.1)		3,669 (62.1)	
11 – < 14	738 (12.5)		727 (12.3)	
≥ 14	1,501 (25.4)		1,510 (25.6)	
Lifestyle factors				
BMI *(kg/m²)*		27.8 (25.1; 31.1)		27.7 (25.0; 30.9)
Physical activity *(MET-min/week)*		2,000 (996; 4,066)		2,000 (989; 4,260)
Alcohol consumption *(g/day)*		11.3 (0.0; 28.3)		11.3 (0; 27.6)
Smoking status	-	-	-	-
Never smoker	2,692 (45.6)		2,730 (46.2)	
Former smoker, years since quit				
< 5 years	2,274 (38.5)		2,248 (38.1)	
5-10 years	49 (0.8)		46 (0.8)	
11-15 years	38 (0.6)		38 (0.6)	
16-20 years	49 (0.8)		43 (0.7)	
> 20 years	270 (4.6)		262 (4.4)	
Current smoker[d]				
Regular	385 (6.5)		403 (6.8)	
Occasional	149 (2.5)		136 (2.3)	
Comorbidities				
Diabetes	-	-	-	-
No	5,156 (87.3)		5,175 (87.6)	
Untreated	164 (2.8)		150 (2.5)	
Treated with oral antidiabetics[e]	447 (7.6)		441 (7.5)	
Treated with insulin	139 (2.4)		140 (2.4)	
Arterial hypertension	2,825 (47.8)		2,843 (48.1)	
Stroke	271 (4.6)		251 (4.2)	
Myocardial infarction	679 (11.5)		662 (11.2)	
Heart failure	116 (2.0)		108 (1.8)	

Characteristics	New AM users (N=5,906)		New PIM users (N=5,906)	
	N (%)[a]	Median (IQR)[a]	N (%)[a]	Median (IQR)[a]
Acute coronary syndromes	1,338 (22.7)		1,362 (23.1)	
Atrial fibrillation	307 (5.2)		322 (5.5)	
Asthma	1,055 (17.9)		1,031 (17.5)	
COPD	963 (16.3)		964 (16.3)	
Arthritis	1,747 (29.6)		1,776 (30.1)	
Osteoporosis	495 (8.4)		470 (8.0)	
History of fractures[f]	697 (11.8)		664 (11.2)	
Pain[g]	5,485 (92.4)		5,439 (92.1)	
Parkinson's disease	23 (0.4)		21 (0.4)	
Dementia	43 (0.7)		46 (0.8)	
Depression	1,146 (19.4)		1,100 (18.6)	
Bipolar disorder	25 (0.4)		34 (0.6)	
Insomnia	2,349 (39.8)		2,320 (39.3)	
Epilepsy	44 (0.7)		51 (0.9)	
Gastrointestinal symptoms[h]	2,749 (46.6)		2,758 (46.7)	
Incontinence	159 (2.7)		154 (2.6)	
Anemia	320 (5.4)		294 (5.0)	
History of cancer	964 (16.3)		951 (16.1)	
Overall health rating[i]	-	-	-	-
Excellent	438 (7.4)		417 (7.1)	
Good	2,988 (50.6)		3,020 (51.1)	
Fair	1,943 (32.9)		1,944 (32.9)	
Poor	537 (9.1)		525 (9.0)	
Functional assessments				
Systolic blood pressure *(mmHg)*		144 (132; 158)		144 (132; 158)
Diastolic blood pressure *(mmHg)*		82 (75; 89)		82 (75; 89)
Grip strength *(kg)*		28.0 (21.0; 37.0)		28.0 (21.0; 36.0)
eGFR[j] *(ml/min/1.73m²)*		87.7 (75.9; 94.1)		88.1 (76.8; 94.0)
Blood-based biomarkers				
CRP *(mg/L)*		1.7 (0.9; 3.5)		1.8 (0.9; 3.5)
HDL *(mmol/L)*		1.4 (1.1; 1.6)		1.4 (1.1; 1.6)
LDL *(mmol/L)*		3.4 (2.7; 4.1)		3.4 (2.7; 4.1)
HbA_{1c} *(mmol/L)*		36.7 (34.2; 39.9)		36.8 (34.2; 40.0)

Abbreviations: AM, appropriate medication; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein, MET, metabolic equivalent of task; NSAIDs, non-steroidal anti-inflammatory drugs; PIM, potentially inappropriate medication.

[a] Calculated from first imputed dataset.
[b] At index prescription.
[c] Average total household income before tax. Categories: very low: < 18,000£, low: 18,000-30,999£, middle: 31,000-51,999£, high: 52,000-100,000£, very high: > 100,000£.
[d] Regular smoking was defined as a minimum of one cigarette, cigar, pipe, etc. per day.

[e] Including parenteral formulations of glucagon-like-peptide-1 receptor agonists.
[f] Fractures in last five years.
[g] Combination of pain-related diagnoses (including migraine, other headache syndromes, facial pain, chronic back pain, chronic pain syndromes, arthritis, osteoarthritis, urinary tract stones, and gout) and self-reported pain in the last month.
[h] Including regular use of NSAIDs.
[i] Self-reported.
[j] Calculated based on CKD-EPI equation.
Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

Appendix 35. The associations of prevalent PIM use including chronic use of NSAIDs (N=60,403) versus non-use (N=156,708) with hospitalization and all-cause mortality (N=217,111) in the UK Biobank

Outcome	N_{Event} (%)[a]	Model 1[b]	Model 2[c]	
	PIM users vs. non-users	HR (95% CI)	HR (95% CI)	p
Hospitalization				
1 month	193 (0.3) vs. 451 (0.3)	1.12 (0.94; 1.32)	1.06 (0.86; 1.31)	0.581
3 months	389 (0.6) vs. 937 (0.6)	1.08 (0.96; 1.22)	0.98 (0.85; 1.14)	0.882
6 months	1,306 (2.2) vs. 3,016 (1.9)	**1.12 (1.05 1.20)**	0.97 (0.89; 1.05)	0.393
1 year	2,805 (4.6) vs. 6,504 (4.2)	**1.12 (1.07; 1.17)**	0.95 (0.90; 1.01)	0.080
2 years	5,857 (9.7) vs. 13,599 (8.7)	**1.12 (1.09; 1.16)**	0.95 (0.91; 0.99)	0.008
3 years	9,069 (15.0) vs. 21,074 (13.5)	**1.12 (1.10 1.15)**	0.96 (0.93; 0.99)	0.006
4 years	12,405 (20.5) vs. 29,243 (18.7)	**1.11 (1.09; 1.13)**	**0.96 (0.93; 0.98)**	**0.001**
All-cause mortality[d]				
6 months	110 (0.2) vs. 142 (0.1)	**1.97 (1.53; 2.52)**	1.05 (0.77; 1.43)	0.779
1 year	262 (0.43) vs. 373 (0.2)	**1.77 (1.52; 2.08)**	1.00 (0.82; 1.22)	0.962
2 years	657 (1.1) vs. 993 (0.6)	**1.67 (1.51; 1.84)**	0.92 (0.81; 1.03)	0.164
3 years	1,141 (1.9) vs. 1,778 (1.1)	**1.62 (1.51; 1.75)**	0.93 (0.84; 1.02)	0.106
4 years	1,668 (2.8) vs. 2,682 (1.7)	**1.57 (1.48; 1.67)**	0.94 (0.87; 1.02)	0.137

Values in bold are statistically significant ($p<0.05$).

Abbreviations: CI, confidence interval; HR, hazard ratio; NSAIDs, non-steroidal anti-inflammatory drugs; PIM, potentially inappropriate medication.

[a] First imputed dataset.

[b] Adjusted for age and sex.

[c] Adjusted for a propensity score, including age, sex, income, years of education, body mass index, physical activity, alcohol consumption, smoking status, number of medications, comorbidities (including arterial hypertension, diabetes, stroke, asthma, COPD, arthritis, heart failure, myocardial infarction, atrial fibrillation, acute coronary syndrome, epilepsy, depression, bipolar disorder, Parkinson's disease, dementia, chronic pain, osteoporosis, anemia, history of cancer), fractures in last 5 years, overall health ranking, eGFR, HDL, LDL, HbA1c, CRP, systolic blood pressure, diastolic blood pressure, and grip strength.

[d] Three- and six-month mortality are not shown because the total number of events was < 100.

Note: PIM exposure was defined according to "The EURO-FORTA (Fit fOR The Aged) List Version 2".

Appendix 36. Potential factors associated with PIM, medication underuse, and overuse in the NAKO study - Results of the logistic regression model adjusted for age, sex, and study center (N=54,296)

Variables	PIM			Underuse			Overuse		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Sociodemographic/-economic factors									
Sex									
Female	Ref			Ref			Ref		
Male	**0.86 (0.83; 0.90)**	**<.001**	**<.001**	**0.79 (0.75; 0.82)**	**<.001**	**<.001**	**0.75 (0.72; 0.78)**	**<.001**	**<.001**
Age group, years									
60 – 64	Ref			Ref			Ref		
65 – 69	**1.22 (1.17; 1.27)**	**<.001**	**<.001**	0.97 (0.93; 1.01)	0.140	0.190	**1.20 (1.15; 1.25)**	**<.001**	**<.001**
≥ 70	**1.43 (1.33; 1.54)**	**<.001**	**<.001**	1.01 (0.93; 1.10)	0.797	0.826	**1.43 (1.33; 1.54)**	**<.001**	**<.001**
Study center									
Augsburg	Ref			Ref			Ref		
Regensburg	**1.15 (1.04; 1.28)**	**0.008**	**0.010**	**0.87 (0.77; 0.98)**	**0.017**	**0.031**	**1.13 (1.02; 1.26)**	**0.023**	**0.035**
Mannheim	0.96 (0.86; 1.07)	0.456	0.473	0.88 (0.78; 0.99)	0.040	0.061	**0.88 (0.79; 0.99)**	**0.029**	**0.042**
Freiburg	**0.74 (0.66; 0.82)**	**<.001**	**<.001**	1.08 (0.96; 1.21)	0.191	0.241	**1.18 (1.07; 1.32)**	**0.002**	**0.004**
Saarbrücken	1.00 (0.90; 1.11)	0.971	0.988	0.98 (0.87; 1.10)	0.696	0.735	**1.14 (1.02; 1.26)**	**0.021**	**0.033**
Essen	1.11 (1.00; 1.24)	0.043	0.051	1.07 (0.95; 1.19)	0.265	0.322	1.06 (0.95; 1.18)	0.336	0.420
Münster	**0.80 (0.71; 0.89)**	**<.001**	**<.001**	0.92 (0.82; 1.03)	0.159	0.211	**1.23 (1.10; 1.37)**	**<.001**	**0.001**
Düsseldorf	0.94 (0.84; 1.05)	0.284	0.311	0.92 (0.81; 1.04)	0.173	0.224	1.05 (0.95; 1.17)	0.330	0.420
Halle	**1.52 (1.38; 1.68)**	**<.001**	**<.001**	**0.81 (0.72; 0.91)**	**<.001**	**0.001**	**0.86 (0.77; 0.96)**	**0.008**	**0.014**
Leipzig	**1.41 (1.28; 1.56)**	**<.001**	**<.001**	0.96 (0.86; 1.08)	0.501	0.549	**0.85 (0.76; 0.95)**	**0.005**	**0.009**
Berlin North	0.96 (0.86; 1.06)	0.408	0.431	0.88 (0.78; 0.99)	0.034	0.056	0.94 (0.85; 1.05)	0.290	0.393
Central Berlin	0.90 (0.81; 1.00)	0.049	0.057	0.94 (0.84; 1.06)	0.318	0.370	0.96 (0.86; 1.07)	0.446	0.541
Berlin South	**0.79 (0.71; 0.88)**	**<.001**	**<.001**	0.89 (0.79; 1.00)	0.051	0.074	0.95 (0.85; 1.06)	0.339	0.420
Hannover	0.91 (0.82; 1.01)	0.088	0.100	**0.87 (0.78; 0.98)**	**0.019**	**0.032**	0.97 (0.87; 1.08)	0.574	0.654
Hamburg	**0.74 (0.66; 0.83)**	**<.001**	**<.001**	0.90 (0.80; 1.01)	0.081	0.116	**0.77 (0.68; 0.86)**	**<.001**	**<.001**
Bremen	**0.81 (0.73; 0.91)**	**<.001**	**<.001**	**0.88 (0.78; 0.98)**	**0.025**	**0.042**	1.02 (0.92; 1.14)	0.690	0.764

Variables	PIM			Underuse			Overuse		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Kiel	1.00 (0.90; 1.11)	0.990	0.990	**0.83 (0.74; 0.94)**	**0.004**	**0.006**	1.00 (0.9; 1.10)	0.924	0.975
Neubrandenburg	**1.47 (1.34; 1.62)**	**<.001**	**<.001**	**0.76 (0.68; 0.85)**	**<.001**	**<.001**	0.90 (0.75; 1.08)	0.246	0.341
Neustrelitz	**1.39 (1.19; 1.63)**	**<.001**	**<.001**	0.90 (0.74; 1.08)	0.249	0.296	1.00 (0.86; 1.16)	0.975	0.992
Waren (Müritz)	**1.44 (1.25; 1.66)**	**<.001**	**<.001**	**0.57 (0.48; 0.69)**	**<.001**	**<.001**	1.10 (0.92; 1.32)	0.304	0.402
Demmin	**1.71 (1.45; 2.02)**	**<.001**	**<.001**	0.80 (0.65; 0.99)	0.036	0.057	**1.13 (1.02; 1.26)**	**0.023**	**0.035**
Income[c]									
Low	Ref			Ref			Ref		
Middle	**0.70 (0.67; 0.73)**	**<.001**	**<.001**	**0.84 (0.80; 0.89)**	**<.001**	**<.001**	**0.90 (0.86; 0.95)**	**<.001**	**<.001**
High	**0.55 (0.51; 0.59)**	**<.001**	**<.001**	**0.79 (0.73; 0.85)**	**<.001**	**<.001**	**0.92 (0.86; 0.98)**	**0.023**	**0.035**
Years of education									
< 13	Ref			Ref			Ref		
≥ 13	**0.63 (0.57; 0.69)**	**<.001**	**<.001**	**0.63 (0.57; 0.69)**	**<.001**	**<.001**	**0.63 (0.57; 0.69)**	**<.001**	**<.001**
Social network index[d]									
I+II	Ref			Ref			Ref		
III+IV	**0.83 (0.79; 0.86)**	**<.001**	**<.001**	**0.89 (0.84; 0.94)**	**<.001**	**<.001**	**0.91 (0.86; 0.97)**	**0.003**	**0.007**
Lifestyle factors									
BMI, kg/m²									
< 20	0.92 (0.78; 1.08)	0.292	0.314	1.09 (0.94; 1.27)	0.236	0.293	1.03 (0.89; 1.19)	0.697	0.764
20 – 24.9	Ref			Ref			Ref		
25 – 29.9	**1.50 (1.43; 1.59)**	**<.001**	**<.001**	1.00 (0.95; 1.06)	0.898	0.898	**1.07 (1.02; 1.13)**	**0.006**	**0.012**
≥ 30	**2.77 (2.62; 2.92)**	**<.001**	**<.001**	1.02 (0.96; 1.08)	0.576	0.619	**1.32 (1.25; 1.39)**	**<.001**	**<.001**
Physical activity level[e]									
Insufficient	Ref			Ref			Ref		
Sufficient	**0.71 (0.67; 0.75)**	**<.001**	**<.001**	**0.71 (0.67; 0.75)**	**<.001**	**<.001**	**0.71 (0.67; 0.75)**	**<.001**	**<.001**
Alcohol consumption[f]									

Variables	PIM			Underuse			Overuse		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Abstainer	**1.67 (1.57; 1.79)**	**<.001**	**<.001**	**1.21 (1.12; 1.30)**	**<.001**	**<.001**	**1.42 (1.33; 1.52)**	**<.001**	**<.001**
Low	Ref			Ref			Ref		
Moderate to high	1.05 (0.99; 1.12)	0.126	0.142	1.03 (0.97; 1.11)	0.340	0.388	**1.09 (1.02; 1.17)**	**0.008**	**0.014**
Smoking									
Never	Ref			Ref			Ref		
Former smoker, years since quit									
> 20 years	**1.09 (1.03; 1.14)**	**0.001**	**0.001**	1.06 (1.00; 1.12)	0.048	0.072	**1.07 (1.02; 1.13)**	**0.011**	**0.018**
≤ 20 years	**1.28 (1.20; 1.35)**	**<.001**	**<.001**	**1.16 (1.09; 1.24)**	**<.001**	**<.001**	**1.40 (1.32; 1.48)**	**<.001**	**<.001**
Current smoker	**1.26 (1.19; 1.34)**	**<.001**	**<.001**	**1.12 (1.05; 1.29)**	**<.001**	**<.001**	**1.31 (1.23; 1.39)**	**<.001**	**<.001**
Comorbidities									
Diabetes	**2.93 (2.78; 3.09)**	**<.001**	**<.001**	**1.19 (1.12; 1.27)**	**<.001**	**<.001**	**1.55 (1.46; 1.64)**	**<.001**	**<.001**
Arterial hypertension	**5.21 (4.98; 5.44)**	**<.001**	**<.001**	**1.40 (1.34; 1.46)**	**<.001**	**<.001**	**1.20 (1.15; 1.25)**	**<.001**	**<.001**
Atrial fibrillation/arrhythmia	**1.98 (1.89; 2.08)**	**<.001**	**<.001**	**5.54 (5.26; 5.83)**	**<.001**	**<.001**	**0.93 (0.88; 0.98)**	**0.012**	**0.020**
Stroke	**2.40 (2.18; 2.63)**	**<.001**	**<.001**	**1.62 (1.46; 1.80)**	**<.001**	**<.001**	**1.43 (1.29; 1.58)**	**<.001**	**<.001**
Myocardial infarction	**1.72 (1.57; 1.88)**	**<.001**	**<.001**	0.99 (0.88; 1.11)	0.835	0.850	**1.22 (1.11; 1.35)**	**<.001**	**<.001**
Heart failure	**2.17 (2.01; 2.34)**	**<.001**	**<.001**	**2.10 (1.93; 2.28)**	**<.001**	**<.001**	**1.45 (1.34; 1.57)**	**<.001**	**<.001**
Acute coronary syndromes	**1.55 (1.45; 1.65)**	**<.001**	**<.001**	**1.18 (1.09; 1.28)**	**<.001**	**<.001**	**1.13 (1.05; 1.22)**	**0.001**	**0.003**
Asthma	**1.39 (1.29; 1.49)**	**<.001**	**<.001**	**1.65 (1.53; 1.77)**	**<.001**	**<.001**	1.08 (1.00; 1.16)	0.057	0.081
COPD	**1.90 (1.78; 2.03)**	**<.001**	**<.001**	**2.46 (2.29; 2.63)**	**<.001**	**<.001**	**1.24 (1.15; 1.33)**	**<.001**	**<.001**
Osteoporosis	**1.60 (1.49; 1.71)**	**<.001**	**<.001**	**8.61 (8.02; 9.23)**	**<.001**	**<.001**	0.98 (0.90; 1.05)	0.508	0.591
Thyroid disease/hypothyroidism[g]	**1.31 (1.25; 1.37)**	**<.001**	**<.001**	**1.17 (1.12; 1.23)**	**<.001**	**<.001**	**1.15 (1.10; 1.21)**	**<.001**	**<.001**
History of fractures[h]	**1.10 (1.03; 1.16)**	**0.003**	**0.004**	**1.46 (1.37; 1.55)**	**<.001**	**<.001**	0.98 (0.92; 1.04)	0.468	0.555
Pain[i]	**1.85 (1.76; 1.93)**	**<.001**	**<.001**	**1.76 (1.67; 1.85)**	**<.001**	**<.001**	1.00 (0.96; 1.04)	0.999	0.999
Parkinson's disease	**11.72 (8.24; 16.68)**	**<.001**	**<.001**	**2.74 (2.06; 3.66)**	**<.001**	**<.001**	**1.46 (1.08; 1.98)**	**0.015**	**0.024**
Dementia[j]	**2.10 (1.93; 2.30)**	**<.001**	**<.001**	**1.87 (1.70; 2.05)**	**<.001**	**<.001**	1.02 (0.92; 1.12)	0.748	0.805
Depression[k]	**2.56 (2.44; 2.69)**	**<.001**	**<.001**	**1.58 (1.49; 1.67)**	**<.001**	**<.001**	**1.69 (1.60; 1.77)**	**<.001**	**<.001**
Epilepsy	**4.45 (3.63; 5.46)**	**<.001**	**<.001**	1.21 (0.95; 1.54)	0.118	0.164	**1.75 (1.42; 2.15)**	**<.001**	**<.001**
Insomnia	**1.26 (1.20; 1.31)**	**<.001**	**<.001**	**1.28 (1.22; 1.34)**	**<.001**	**<.001**	1.00 (0.95; 1.05)	0.962	0.992

Variables	PIM			Underuse			Overuse		
	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]	OR (95% CI)	p[a]	FDR[b]
Gastrointestinal symptoms[l]	**1.78 (1.71; 1.86)**	**<.001**	**<.001**	**1.89 (1.80; 1.97)**	**<.001**	**<.001**	**1.07 (1.02; 1.12)**	**0.002**	**0.005**
History of cancer	**1.18 (1.11; 1.24)**	**<.001**	**<.001**	**1.12 (1.06; 1.19)**	**<.001**	**<.001**	**1.16 (1.10; 1.22)**	**<.001**	**<.001**
Renal impairment[m]	**2.33 (2.15; 2.54)**	**<.001**	**<.001**	0.95 (0.86; 1.05)	0.353	0.395	**1.61 (1.47; 1.75)**	**<.001**	**<.001**

Values in bold are statistically significant with FDR (p<0.05).
Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDR, false discovery rate; NAKO, German National Cohort; OR, odds ratio; PIM, potentially inappropriate medication; Ref, reference.

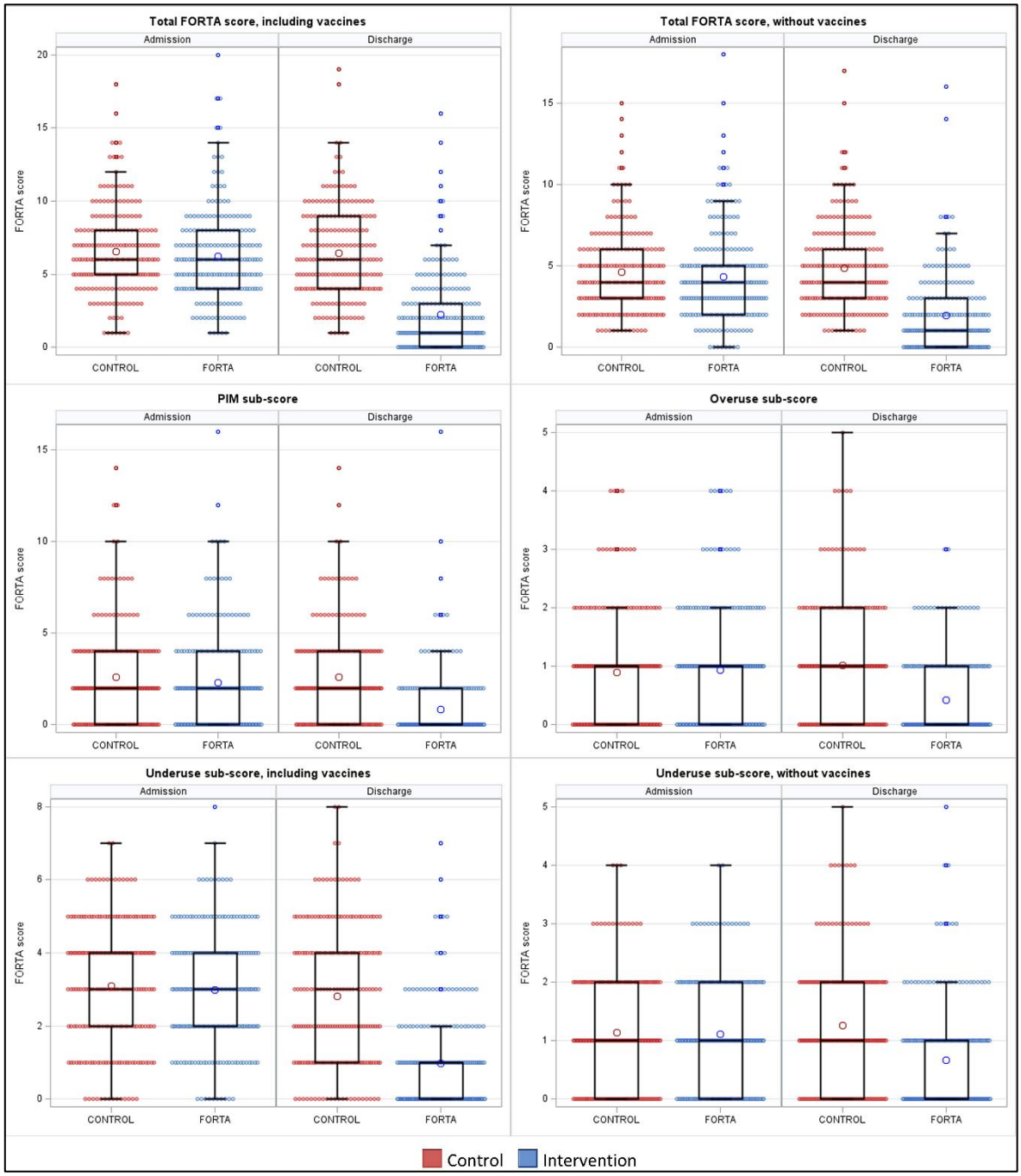
[a] Unadjusted for multiple testing.
[b] P values adjusted for multiple testing using the FDR (Benjamini-Hochberg method).
[c] Average total household income before tax. Categories: low: < 2900€; middle: 2900 – < 5000€; high: ≥ 5000€.
[d] Categories: I (isolated) to IV (least isolated).
[e] Adherence to WHO recommendations following the Global Physical Activity Questionnaire (GPAQ). Categories: sufficient: ≥ 600 metabolic equivalent of task (MET) –min/week; insufficient: < 600 MET–min/week.
[f] Alcohol consumption, g ethanol per day. Categories: abstainer: 0 g/day; low: women 0-19.99g/d or man 0-39.99g/d; moderate – high: women ≥ 20g/d or man ≥ 40g/d.
[g] Lifetime history of thyroid disease, self-reported. Underuse was only considered in individuals with TSH > 8.0 mU/L (cut-off for treatment of older patients suggested by FORTA list).
[h] Fractures since aged 50.
[i] Pain-related diagnoses included certain or likely migraine or tension headache in the last 12 months (following the 3rd edition of The International Classification of Headache Disorders), and self-reported information on arthritis, osteoarthritis, and gout.
[j] Based on the interview question “Have you ever contacted a physician due to memory difficulties or are you planning to speak to a physician about it?”.
[k] Lifetime history of depression, self-reported.
[l] Combination of self-reported information on reflux, peptic ulcer (“Have you ever been diagnosed with this condition by a physician?”), and regular intake of NSAIDs (ATC M01A). Underuse was only considered if the participant was diagnosed with reflux or peptic ulcer in the year of their baseline assessment, and in participants regularly taking NSAIDs.
[m] Estimated glomerular filtration rate < 60 ml/min/1.73m², calculated based on CKD-EPI equation.
Note: PIM exposure was defined according to the “Fit fOR The Aged” (FORTA) list 2024.

Appendix 37. FORTA (sub-)scores and proportions exposed to medication problems at rehabilitation clinic admission in OPTIMAL intention-to-treat (N=443) and per-protocol population (N=418)

Exposure	Intention-to-treat population (N=443)		Per-protocol population (N=418)	
	Score	Exposed	Score	Exposed
	Median (IQR)	N (%)[a]	Median (IQR)	N (%)[a]
Total FORTA score[a]				
Incl. vaccine underuse	6 (4; 8)	443 (100.0)	6 (4; 8)	418 (100.0)
Without vaccine underuse	4 (3; 6)	433 (97.7)	4 (3; 6)	410 (98.1)
FORTA score sub-categories				
PIM	2 (0; 4)	293 (66.1)	2 (0; 4)	277 (66.3)
Overuse	1 (0; 1)	261 (58.9)	1 (0; 1)	248 (59.3)
Underuse				
Incl. vaccine underuse	3 (2; 4)	419 (94.6)	3 (2; 4)	394 (94.3)
Without vaccine underuse	1 (0; 2)	315 (71.1)	1 (0; 2)	298 (71.3)

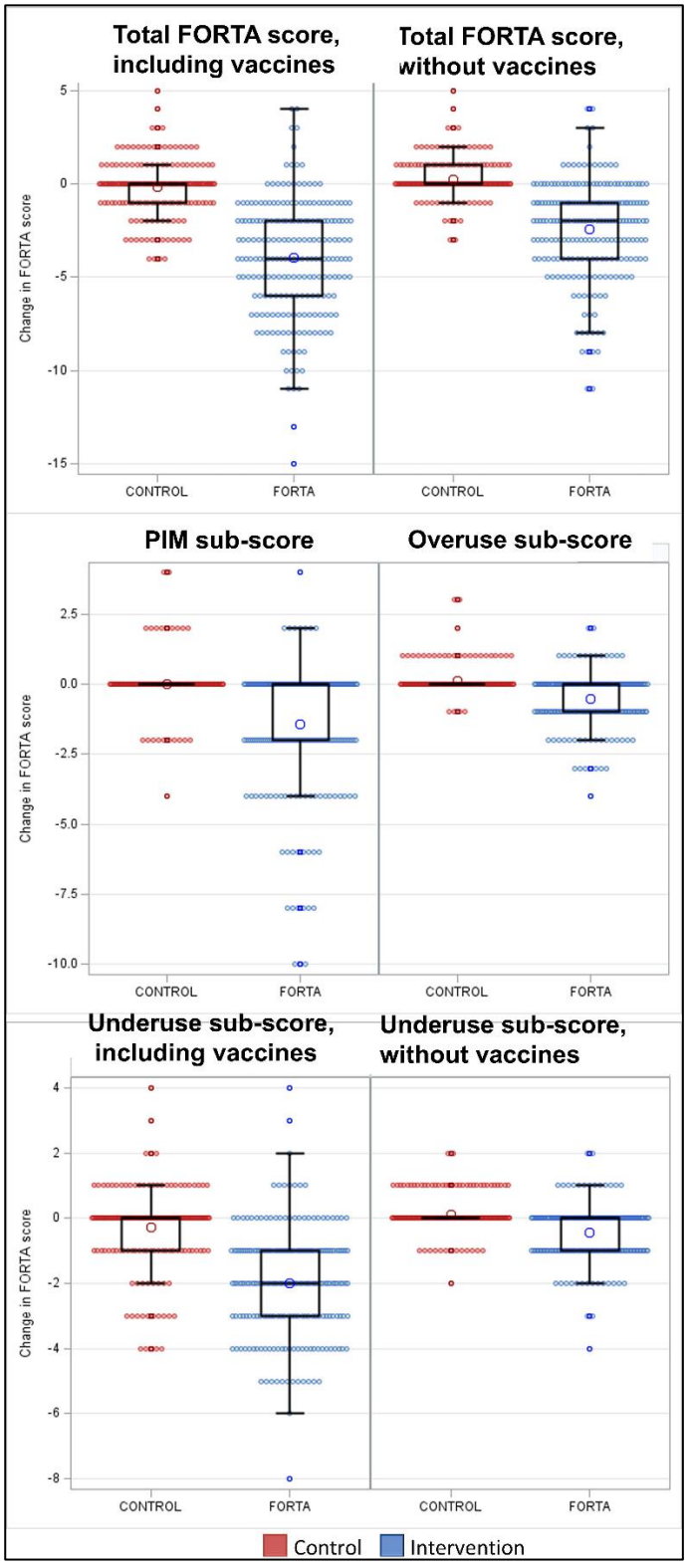
Abbreviations: CI, confidence interval; FORTA, FORTA, Fit fOR The Aged List Version 4; IQR, interquartile range; PIM, potentially inappropriate medication.

[a] Recommendations according to the “The FORTA (Fit fOR The Aged) List Version 4”.



Appendix 38. Distribution of FORTA score and sub-scores at admission and discharge, per-protocol population (N=418)

Abbreviations: PIM, potentially inappropriate medication; FORTA, Fit fOR The Aged List Version 4.



Appendix 39. Distribution of change in FORTA score and sub-scores from admission to discharge, per-protocol population (N=418)

Abbreviations: PIM, potentially inappropriate medication; FORTA, Fit fOR The Aged List Version 4.

Appendix 40. Results of the multivariate linear regression model with group allocation as independent and changes in mean difference in FORTA (sub-)score scales between intervention and control group from admission to discharge as the dependent variable. OPTIMAL intention-to-treat population (N=443)

FORTA score change[a]	ß coefficient (95% CI)[b]	p
Total		
Incl. vaccines	**-3.8 (-4.2; -3.3)**	**<.001**
Without vaccines	**-2.6 (-3.0; -2.3)**	**<.001**
Sub-scores		
PIM	**-1.5 (-1.8; -1.2)**	**<.001**
Overuse	**-0.6 (-0.7; -0.5)**	**<.001**
Underuse		
Underuse incl. vaccines	**-1.7 (-1.9; -1.4)**	**<.001**
Underuse without vaccines	**-0.5 (-0.7; -0.4)**	**<.001**

Values in bold are statistically significant ($p<0.05$).
Abbreviations: CI, confidence interval; FORTA, Fit fOR The Aged List Version 4; PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
[b] Model adjusted for baseline FORTA score or the respective FORTA sub-score, age, sex, education, partnership, social support, body mass index, alcohol consumption, physical activity, smoking status, cancer site, cancer stage, previous cancer therapy, comorbidities as single covariates (including diabetes, arterial hypertension, stroke, myocardial infarction, heart failure, acute coronary syndromes, atrial fibrillation, asthma/COPD, osteoporosis, chronic pain, depression, insomnia, gastrointestinal symptoms, incontinence, anemia, constipation, hypothyroidism, chronic kidney disease, dyslipidemia, peripheral vascular disease), frailty, global quality of life, and depressive symptoms.

Appendix 41. Median difference in FORTA (sub-)score scales between intervention and control group at discharge and mean difference in changes from admission to discharge in the per-protocol population (N=418)

FORTA score[a]	At Discharge				Change from Admission to Discharge			
	Control (N=206) Median (IQR)	Intervention (N=212) Median (IQR)	Median Difference (95% CI)[b]	p[b]	Control (N=206) Mean (95% CI)	Intervention (N=212) Mean (95% CI)	Difference Mean (95% CI)	p
Total								
Incl. vaccines	6 (4; 9)	1 (0; 3)	**-5 (-5.7; -4.3)**	**<.001**	-0.1 (-0.3; 0.1)	**-4.0 (-4.4; -3.5)**	**-3.8 (-4.3; -3.4)**	**<.001**
Without vaccines	4 (3; 6)	1 (0; 3)	**-3 (-3.3; -2.7)**	**<.001**	0.2 (0.1; 0.4)	**-2.4 (-2.8; -2.1)**	**-2.7 (-3.0; -2.3)**	**<.001**
Sub-scores								
PIM	2 (0; 4)	0 (0; 2)	**-2 (-2.0; -2.0)**	**<.001**	0.0 (-0.1; 0.1)	**-1.5 (-1.8; -1.1)**	**-1.5 (-1.8; -1.1)**	**<.001**
Overuse	1 (0; 2)	0 (0; 1)	**-1 (-1.0; -1.0)**	**<.001**	0.1 (0.1; 0.2)	**-0.5 (-0.6; -0.4)**	**-0.6 (-0.8; -0.5)**	**<.001**
Underuse								
Incl. vaccine underuse	3 (1; 4)	1 (0; 1)	**-2 (-2.8; -1.2)**	**<.001**	-0.3 (-0.4; -0.1)	**-2.0 (-2.2; -1.6)**	**-1.7 (-2.0; -1.4)**	**<.001**
Without vaccine underuse	1 (0; 2)	0 (0; 1)	**-1 (-1.0; -1.0)**	**<.001**	0.1 (0.0; 0.2)	**-0.4 (-0.6; -0.3)**	**-0.6 (-0.7; -0.4)**	**<.001**

Values in bold are statistically significant ($p<0.05$).

Abbreviations: CI, confidence interval; FORTA, Fit fOR The Aged List Version 4; IQR, interquartile range; PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4."

[a] The p-value was obtained by the Wilcoxon rank sum test. The confidence interval of the median difference was estimated with quantile regression with resampling.

Appendix 42. Proportions of study participants exposed to medication problems at discharge in the OPTIMAL per-protocol population (N=418)

Medication problems[a]	Control (N=206) N (%)	Intervention (N=212) N (%)	Absolute difference[b] (95% CI)	p
Any (FORTA score > 0)				
Incl. vaccines	206 (100.0)	155 (73.1)	**-26.9 (-32.9; -20.9)**	**<.001[c]**
Without vaccines	206 (100.0)	152 (71.7)	**-28.3 (-34.4; -22.2)**	**<.001[c]**
FORTA sub-categories				
PIM	145 (70.4)	56 (26.4)	**-44.0 (-52.6; -35.4)**	**<.001**
Overuse	133 (64.6)	68 (32.1)	**-32.5 (-41.6; -23.4)**	**<.001**
Underuse				
Incl. vaccines	184 (89.3)	110 (51.9)	**-37.4 (-45.4; -29.5)**	**<.001**
Without vaccines	150 (72.8)	95 (44.8)	**-28.0 (-37.0; -19.0)**	**<.001**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval; FORTA, Fit fOR The Aged List Version 4, PIM, potentially inappropriate medication.

[a] Recommendations according to the "The FORTA (Fit fOR The Aged) List Version 4".
[b] In proportions exposed to the relevant medication problem.
[c] Tested with Fisher's exact test, as all participants of the control group were exposed.

Appendix 43. Subgroup analysis by rehabilitation clinic for mean difference FORTA (sub-)score change from admission to discharge, OPTIMAL intention-to-treat population (N=443)

Subgroups	Control		Intervention		Difference	p
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Clinic in Ückeritz	68	-0.4 (-0.7; 0.0)	76	-5.3 (-6.0; -4.6)	**-4.9 (-5.7; -4.1)**	**<.001**
Clinic in Durbach	65	0.2 (-0.1; 0.6)	68	-4.5 (-5.1; -4.0)	**-4.7 (-5.4; -4.1)**	**<.001**
Clinic in Rüdersdorf	41	-0.5 (-0.9; -0.1)	40	-2.4 (-3.2; -1.6)	**-1.9 (-2.8 -1.0)**	**<.001**
Other clinics[a]	36	0.0 (-0.6; 0.6)	49	-2.0 (-2.9; -1.1)	**-2.0 (-3.1; -0.9)**	**<.001**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval; FORTA, Fit fOR The Aged List Version 4, PIM, potentially inappropriate medication.

[a] Clinics with < 50 participants were summarized. Clinic ($n_{control;}$ $n_{intervention}$): clinic in Bad Neuenahr-Ahrweiler (17; 18); clinic in Blankenburg (0; 0); clinic in Cologne (4; 3); clinic in Buckow (1; 3); clinic in Bad Salzuflen (13; 12); clinic in Bad Wildungen (0; 1); and clinic in Bad Lippenspringe (1; 12).

Appendix 44. Subgroup analysis by sex for mean difference FORTA (sub-)score change from admission to discharge, OPTIMAL intention-to-treat population (N=443)

Subgroups	Control		Intervention		Difference	p
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Females	147	-0.2 (-0.4; 0.0)	155	-4.0 (-4.5; -3.5)	**-3.8 (-4.4; -3.2)**	**<.001**
Males	62	0.0 (-0.4; 0.3)	79	-3.6 (-4.2; -3.0)	**-3.6 (-4.3; -2.8)**	**<.001**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval.

Appendix 45. Subgroup analysis by age for mean difference FORTA (sub-)score change from admission to discharge, OPTIMAL intention-to-treat population (N=443)

Subgroups	Control		Intervention		Difference	p
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
65 – 74 years	124	-0.2 (-0.5; 0.1)	147	-4.1 (-4.7; 3.6)	**-3.9 (-4.5; -3.3)**	**<.001**
75 – 92 years	85	0.0 (-0.3; 0.2)	87	-3.4 (-4.0; -2.8)	**-3.4 (-4.1; -2.7)**	**<.001**

Values in bold are statistically significant (p<0.05).
Abbreviations: CI, confidence interval.

Appendix 46. Information on AI-based electronic tools used in German

ZIELE, FÜR DIE KI-BASIERTE HILFSMITTEL IN DER VORLIEGENDEN ARBEIT EINGESETZT WURDEN:

Literaturverwaltung im Rahmen des Titel-/Abstract Screenings des systematischen Reviews.

Überprüfung von Rechtschreibung und Grammatik.

DOKUMENTATION DER VERWENDUNGSWEISE DER KI-BASIERTEN HILFSMITTEL

Rayyan wurde zur Literaturverwaltung im Rahmen des Titel-/Abstract-Screenings des systematischen Reviews verwendet.

Rechtschreibung und Grammatik wurden mithilfe von Grammarly überprüft.

NENNUNG DER KAPITEL UND ABSCHNITTE, IN DENEN KI-BASIERTE HILFSMITTEL EINGESETZT WURDEN, UM INHALTE ZU ERZEUGEN

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Curriculum Vitae

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Eidesstattliche Versicherung

1. Bei eingereichten Dissertation zu dem Thema
   „Optimization of Medication in Older Adults“
   handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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