Anticholinergic burden: Prevalence in the German general population, current evidence regarding the risk of fractures and usefulness for prediction of fractures in older adults

Kumulative Dissertation

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2 SYNOPSIS

English

Anticholinergic medications antagonize the effect of the neurotransmitter acetylcholine in the central and peripheral nervous system as well as in neuromuscular junctions, leading to desired and undesired anticholinergic effects. Use of anticholinergic medication can lead to anticholinergic burden, which is commonly measured with anticholinergic burden scales. However, as there is neither a consensus in regards to which medications are considered anticholinergic, nor what anticholinergic potency they exhibit, differences exist between anticholinergic burden scales. Anticholinergic burden has been associated with adverse effects, including fractures. Information regarding (i) the association between anticholinergic burden and risk of fractures, (ii) the prevalence of anticholinergic burden and (iii) the usefulness of anticholinergic burden for the prediction of fractures in the German population, is scarce. In the context of this dissertation, a systematic review was conducted and showed that a majority of included studies report an increased risk of fractures. In a sub-group of studies which use the same anticholinergic burden scale, a dose-response relationship between increasing anticholinergic burden and the risk of fractures was observed. The studies were heterogenous in regard to their methodology and use of anticholinergic burden scales, and few studies were of high quality. In a second study, the prevalence of use of anticholinergic medication and anticholinergic burden was assessed in a sample of the German population, based on claims data. Use of anticholinergic medication and anticholinergic burden increased steadily with age. In general, women had higher prevalences of anticholinergic burden. A third study showed that the usefulness of anticholinergic burden as a predictor of the risk of fractures in German was comparable to other measures of (cumulative) use of medication. Overall, the performance of models, which used German claims data to predict the risk of fractures in older adults, was moderate. The usefulness of anticholinergic burden as a predictor of fractures was small. More studies are needed to assess the association between anticholinergic burden and

fractures. However, inherent limitations of the concept of anticholinergic burden hamper its usefulness in research.

German

Anticholinerge Arzneimittel sind Antagonisten des Neurotransmitters Acetylcholin im zentralen und peripheren Nervensystem sowie in motorischen Endplatten. Ihre Wirkung hat gewollte und ungewollte anticholinerge Effekte zur Folge. Die Nutzung von anticholinergen Arzneimitteln kann zu anticholinerger Last führen, die durch Skalen erfasst wird. Da es jedoch weder einen Konsensus gibt, welche Arzneimittel anticholinerg sind, noch welche anticholinerge Potenz diese besitzen, bestehen Unterschiede zwischen den Skalen. Anticholinerge Last wurde mit unerwünschten Ereignissen assoziiert, unter anderem Knochenbrüchen. Es bestehen noch Wissenslücken bezüglich (i) der Assoziation zwischen anticholinerger Last und dem Risiko für Knochenbrüche, (ii) der Prävalenz von anticholinerger Last sowie (iii) der Nutzbarkeit der anticholinergen Last zur Prädiktion von Knochenbrüchen in der Deutschen Bevölkerung. Im Zuge dieser Dissertation wurde ein systematisches Review durchgeführt, in dem ein Großteil der eingeschlossenen Studien ein erhöhtes Risiko für Knochenbrüche berichtet. In einer Subgruppe von Studien, die dieselbe Skala zur Erfassung der anticholinergen Last nutzen, wird eine Dosis-Wirkungs-Beziehung zwischen anticholinerger Last und dem Risiko für Knochenbrüche beobachtet. Insgesamt sind die Studien bezüglich der Methodik und der genutzten Skalen heterogen. In einer zweiten Studie wurde die Nutzung von anticholinergen Arzneimitteln und die anticholinerge Last in deutschen Versichertendaten erfasst. Nutzung von anticholinergen Arzneimitteln steigt mit dem Alter stetig an. Frauen haben höhere Prävalenzen anticholinerger Last als Männer. Eine dritte Studie zeigt, dass die anticholinerge Last als Prädiktor für Knochenbrüche mit anderen Methoden zur Erfassung der (kumulativen) Nutzung von Arzneimitteln vergleichbar ist. Grundsätzlich zeigt sich eine mäßige Fähigkeit der Modelle, das Risiko von Knochenbrüchen in

Versichertendaten vorherzusagen. Die Nützlichkeit der anticholinergen Last als Prädiktor von Knochenbrüchen ist gering. Die Durchführung von weiteren Studien zur Assoziation zwischen anticholinerger Last und Knochenbrüchen ist notwendig. Inhärente Limitationen des Konzepts der anticholinergen Last verringern seinen Nutzen für die Forschung.

3 ABBREVIATIONS

AAS	Anticholinergic activity scale
ACB	Anticholinergic cognitive burden
ADS	Anticholinergic drug scale
ARS	Anticholinergic risk scale
AUC	Area under the curve
COPD	Chronic obstructive pulmonary disease
CrAS	Clinician-rated anticholinergic score
DBI	Drug burden index
FRIDs	Fall risk increasing drugs
GABS	German anticholinergic burden scale
GePaRD	German pharmacoepidemiological research database
KABS	Korean anticholinergic Burden Scale
SAA	Serum radioreceptor anticholinergic activity assay

4 INTRODUCTION

Anticholinergic agents have been used for centuries for their therapeutic, hallucinogenic, cosmetic and toxic effects (1). They work by antagonizing the effect of acetylcholine through competitive binding to muscarinic receptors, thus causing anticholinergic effects, due to the inhibition of parasympathetic nerve impulses in the central and peripheral nervous system (2). Today, more than 600 medications or medicinal products are considered to have anticholinergic effects (3). This includes many commonly used medication such as medication for overactive bladder, asthma, chronic obstructive pulmonary disease (COPD) and Parkinson's disease as well as antipsychotics, antidepressants, antihistamines and mydriatics (4). Some anticholinergic medications are used specifically for their anticholinergic effect, while others exhibit anticholinergic effects in addition to their primary therapeutic mechanisms (5). For example, in patients with overactive bladder, anticholinergic effects reduce the activity of the bladder detrusor muscle through inhibition of the peripheral muscarinic receptors (6). In contrast, tricyclic antidepressants have a number of undesired anticholinergic effects such as sedation, psychomotor and memory impairment, dry mouth and blurred vision, in addition to their intended antidepressive effects (7).

Overdose and cumulative use of anticholinergic medication can lead to anticholinergic toxicity (8). In order to quantify the cumulative use of anticholinergic medication in clinical practice, the concept of anticholinergic burden was established (9). Different methods for the measurement of anticholinergic burden have been developed. As of now, the most commonly used methods in clinical practice and research are anticholinergic burden scales (10). Depending on their personal anticholinergic burden score, patients are classified into different risk categories (1). However, as there is neither a consensus regarding which medications are considered anticholinergic, nor what anticholinergic potency they exhibit, differences exist between anticholinergic burden scales (11-13). Nevertheless, studies on anticholinergic burden have reported associations with adverse outcomes such as dementia and cognitive impairment (14), delirium (15), functional

impairment, hospitalization (10, 16-22), increased risk of mortality (23) as well as increased risk of falls (24) and fractures (20, 25-30). As a consequence of age-related processes, older adults are particularly vulnerable to adverse outcomes associated with anticholinergic burden (31). However, the risk of adverse effects associated with anticholinergic burden is not exclusive to older adults (32-38). Due to the widespread use of anticholinergic medication, anticholinergic burden is a potential public health concern. As the concept of anticholinergic burden is still relatively novel, population-based studies assessing parameters such as prevalence of use of anticholinergic medication and anticholinergic burden on population level are lacking. Moreover, the majority of studies have been conducted in highly selected populations e.g., nursing home residents, psychiatric patients and hospitalized persons (39-45). Among potential adverse events associated with anticholinergic burden, fractures are of high public health relevance owing to their association with subsequent adverse outcomes such as (long-term) hospitalization, disability and mortality, particularly among older adults (46). Additionally, fractures are responsible for high costs for the healthcare system which are predicted to increase in the future due to aging populations, for example in Germany (47). As evidence on this topic is scarce, more studies investigating the association between anticholinergic burden and fractures are needed. New evidence could potentially contribute to measures for the prevention of fractures as well as raise awareness in regards to risks regarding the occurrence of fractures associated with use anticholinergic medication and anticholinergic burden. Initially, however, the existing evidence on the risk of fractures associated with use of anticholinergic medication and anticholinergic burden has to be evaluated.

5 BACKGROUND AND CURRENT STATE OF RESEARCH

5.1 Pharmacological mechanism of anticholinergic medication in the cholinergic system

Acetylcholine is an essential neurotransmitter found in synaptic vesicles of presynaptic cholinergic neurons, which are present in the central and peripheral nervous system as well as in neuromuscular junctions (3). It regulates parasympathetic nerve impulses in the central and peripheral nervous system (2). Upon stimulation of the presynaptic neuron, vesicles containing acetylcholine are transported out of the neuron and into the synaptic cleft where acetylcholine acts on receptors present on postsynaptic neurons and thus excite or inhibit functions in the central and peripheral nervous system. Any process that reduces acetylcholine at the postsynaptic receptor is defined as an anticholinergic effect. This can occur through (i) increased activity of acetylcholinesterase, an enzyme in the synaptic cleft with the function to degrade acetylcholine and decrease its concentration, or (ii) by inhibition of the postsynaptic receptor (3). The effect of anticholinergic medication is based on mechanism (ii), and more specifically on the inhibition of muscarinic postsynaptic receptors through competitive binding, of which five subtypes (M1-M5) exist throughout the body (1, 48). In the central nervous system, muscarinic receptors are associated with functions such as learning, memory, attention, and sensorimotor processing as well as lower-level functions such as sleep-wake cycles and arousal. Furthermore, in the peripheral nervous system they are associated with contractility of the bladder detrusor muscle, saliva production, gastrointestinal motility, cardiac function as well as contractility and dilation of the eye (48). Most anticholinergic medication, however, are non-selective and do not discriminate between muscarinic receptor subtypes and therefore have the potential to inhibit acetylcholine-mediated responses in the entire body, thus affecting a wide range of mechanisms (1). The over 600 medications and medicinal products known to have anticholinergic effects include commonly used prescription medication as well as some commonly used over-the-counter medications and medicinal products, such as St.

John's Wort (49). Adverse effects of anticholinergic medication, also called anticholinergic toxicity, are often the result of the cumulative anticholinergic burden of several anticholinergic medications rather than the effect of a single medication. Due to the ubiquity of anticholinergic medication, persons using a large number of medications (e.g., persons with chronic illnesses and/or older adults) are at high risk of anticholinergic burden and anticholinergic toxicity (9). Clinicians employ a mnemonic to remember the typical signs of anticholinergic toxicity: "Mad as a hatter, blind as a bat, dry as a bone, hot as a hare, bloated as a toad, the heart runs alone, full as a flask and red as a beet" referring to symptoms in different organ systems: brain: delirium, cognitive impairment, sedation, and confusion; eye: improperly-timed pupillary dilation (mydriasis) and blurred vision; salivary glands: decreased salivation and dry mouth with difficulty of swallowing; sweat glands: decreased ability to sweat; heart: sinus tachycardia and increased contractility; gastrointestinal system: reduced motility resulting in constipation; bladder: urinary retention due to inability to contract the bladder; skin: flush (48, 50). Due to age-related changes to pharmacokinetic and pharmacodynamic processes, older adults as well as persons with chronic diseases, particularly neurodegenerative disorders, are more susceptible to adverse effects of anticholinergic burden (51). This includes reduced renal and hepatic clearance, which in turn lead to prolonged elimination half-life and the potential accumulation of anticholinergic medication and their metabolites (2). Furthermore, with increasing age, pharmacodynamical sensitivity to the blockade of muscarinic receptors in the central nervous system and the vulnerability to effects of anticholinergic medication increase (52). Additionally, a lower binding affinity for acetylcholine, a reduction in the activity of the pre-synaptic enzyme choline acetyltransferase (responsible for the synthesis of acetylcholine) and a lower muscarinic receptor density in the brain has been reported in older adults (1). Finally, permeability of the blood-brain barrier increases with age and is further increased in patients with vascular dementia or Alzheimer's disease (51, 53) as well as diabetes mellitus, multiple sclerosis, brain tumors, ischemic episodes and meningitis (51, 54).

5.2 Assessment of anticholinergic burden

Two different methods for the assessment of anticholinergic burden have been established: (i) serum radioreceptor anticholinergic activity assay (SAA), and (ii) expert-based scales of medication with anticholinergic activity, also called anticholinergic burden scales (1). SAA is a method for measurement of anticholinergic activity in a person's serum, based on the assessment of the binding of compounds to muscarinic receptors (55). However, studies have shown that SAA is not capable to reflect the concentration of anticholinergic medication in the central nervous system (1). Furthermore, studies failed to confirm an association between high SAA and impaired cognitive performance (56) and concerns arose that endogenous substances other than anticholinergic medication and related metabolites may affect the results of the SAA (57). Thus, currently, anticholinergic burden scales are routinely used to assess anticholinergic burden in clinical practice and research (10). Anticholinergic burden scales are score models, based on expert opinion or affinity of medications to the muscarinic receptor, developed to determine the anticholinergic burden of an individual person (1, 11). The aim of these scales is to allow clinicians to measure the anticholinergic burden in their patients and to give guidance how it can be decreased in order to reduce the risk of anticholinergic-induced adverse effects as well as to give researchers a tool to investigate the prevalence and the risk of the anticholinergic burden (1). Various anticholinergic burden scales have been developed with differences regarding the underlying assumptions and the sources of information required for their application (58). Most scales score anticholinergic medications, either according to potency i.e. the probability and severity of the expected anticholinergic effect or according to the prescribed dose. Typically, anticholinergic medications with mild anticholinergic effects are scored with one point and medications with moderate or high anticholinergic potency receive a score of two or three (11). Medications are scored differently across scales as they have been designed to capture different elements of anticholinergic activity or anticholinergic effects as well as due to country-specific

differences in availability of medications and prescribing practices (58). A patient's anticholinergic burden is then calculated by adding the scores of all medications, classified as anticholinergic by the respective scale, that are used by the patient at a point in time or within a time period. The resulting estimation of anticholinergic burden is often expressed in four or five categories 0, 1, 2, 3 or 0, 1, 2, 3, 4 in which a score of 0 means no anticholinergic burden and a higher score is associated with higher anticholinergic burden. If a patient's score exceeds the scale-specific threshold, he or she is considered to be at risk for adverse effects related to anticholinergic burden (59-64).

As of now, there are 11 anticholinergic burden scales that do not take the prescribed dose into account (59-69) (Table 1). Furthermore, three scores exist that incorporate dose of anticholinergic medication (5, 70, 71) (Table 2). Some studies have created lists of anticholinergic medication and graded them according to their anticholinergic potency (55) or potential for adverse effects (72, 73), without creating a scale (Table 3) and other studies have combined and harmonized existing lists from different sources (74) as well as created country specific adaptations of existing scales (75-78), for example for Germany (79).

5.3 Limitations of the assessment of anticholinergic burden through anticholinergic burden scales

Assessment of anticholinergic burden through anticholinergic burden scales has a number of limitations. First of all, there is no consensus in regards to which medication are considered anticholinergic or what anticholinergic potency they exhibit (1). The definition of anticholinergic medication and classification according to anticholinergic potency is based on affinity of the medication to muscarinic receptors, a method whose limitations has already been discussed earlier, as well as expert opinion or a combination of both methods (74). Due to the low reproducibility of the methods used for the creation of anticholinergic burden scales (11), the medications included differ considerably. Consequently, concordance between anticholinergic burden scales is low: Naples et al.

(80) conducted a study in community-dwelling older adults and found large differences between the included scales, due to variations in the medications-lists on which the scales were based on; only 20 medications were common to all five investigated scales. Another study found that the five investigated anticholinergic burden scales considered between 27–520 medications (81). Therefore, in the assessment of prevalence of anticholinergic medication, scales that define a higher number of medications as anticholinergic as well as those that consider more commonly used medications as anticholinergic, could result in higher prevalences of use of anticholinergic medication and anticholinergic burden. Additionally, the ranking of anticholinergic medication according to anticholinergic potency is inconsistent and varies between scales (1). For example, quetiapine was considered to have high anticholinergic activity in the anticholinergic cognitive burden (ACB) scale (59), moderate in the clinician-rated anticholinergic score (CrAS) (63) and low anticholinergic activity in both the anticholinergic risk scale (ARS) (61) and the anticholinergic activity scale (AAS) (64). Secondly, anticholinergic burden scales tend to simplify the complexity of the underlying pharmacological mechanism of anticholinergic toxicity through the assumption of a linear additive model of anticholinergic burden and by disregarding biological differences influencing drug metabolism within individual persons (1, 10). For example, anticholinergic burden scales do not consider that medications could have actions on multiple muscarinic receptor subtypes or have potential synergistic or antagonistic effects (1). Moreover, individual differences between persons such as renal impairment, or tolerance to anticholinergic medication (e.g., tolerance through cumulative exposition to anticholinergic medication, genetic polymorphism at the muscarinic receptor level or cholinergic degeneration caused by ageing or by the presence of dementia) are not considered (1, 10). The division of anticholinergic medication into categories is, by definition, a simplification as the relative anticholinergic activities as well as the potentially resulting adverse effects are not likely to be proportional to the 0,1,2,3 ratio proposed by many anticholinergic burden scales. Moreover, the aspect of dose is not

considered in many anticholinergic risk scales in favor of easier application in practice and research. This is problematic, as adverse effects of anticholinergic medication are often dose-dependent (10). Finally, the route of administration is considered inconsistently, some scales excluded topical, ophthalmic, otologic or inhaled preparations, while others do not (82).

5.4 Prevalence of anticholinergic burden

Many studies have assessed anticholinergic burden in selected populations, such as persons with dementia or nursing home residents (83-85). However, assessments of anticholinergic burden that include an entire population are scarce. So far, only one study has assessed anticholinergic burden on a population level. Cebron Lipovec et al. (86) conducted a study, using the ACB score, based on all outpatient prescriptions of 2018 from the Slovenian nationwide health claims database. Approximately a third (29.8%) of the 1,474,864 included persons with at least one outpatient prescription of any medication had at least one prescription of anticholinergic medication (ACB≥1) and 7.6% were exposed to clinically significant anticholinergic burden of ACB≥3. Anticholinergic medications were most frequently prescribed to older adults (≥65 years) (ACB≥1: 43.1%, ACB≥3: 12.1%), followed by adults (19-64 years) (ACB≥1: 25.8, ACB≥3: 7.3%). However, 20.7% of children (≤18 years) had ACB≥1 and 1.2% ACB≥3. Among medications with possible anticholinergic activity (ACB=1) systemic antihistamines were most frequently prescribed. Antiepileptics were the most common drug class among medication with definite anticholinergic activity (ACB=2) and among medications with ACB=3 antipsychotics, urologicals and antidepressants were most frequently prescribed (86). As of spring of 2023, seven studies have assessed the use of anticholinergic medication and/or anticholinergic burden in Germany. These studies were not population based and were restricted to older adults with specific indications e.g., hospitalized persons or nursing home residents with dementia (39-45). Prevalences for use of ≥1 anticholinergic medication ranged between 16% (44) and 53.7% (45).

5.5 Risk of fractures associated with use of anticholinergic medication and anticholinergic burden

In older adults, fractures, particularly hip fractures, are associated with an increased short- and long-term risk of death (87). Furthermore, patients with fractures have a higher likelihood of subsequent fractures (88), and fractures are associated with loss of mobility, limitations in activities of daily living, ability for self-care, societal participation as well as reduced quality of life (89). Costs of treatment of fractures as well as fracture-related long-term disability costs in Germany are high, representing approximately 3.7% of total healthcare spending, which is expected to increase in the future due to Germany's rapidly aging population (47). A number of studies have suggested an association between anticholinergic burden and increased risk of fractures (20, 26, 28) and falls (24), the main cause of fractures in older adults (90). The pathway between use of anticholinergic medications and anticholinergic burden and increased risk of fractures is hypothesized to be associated with their central and peripheral adverse effects, discussed in section 5.1. Among these, cognitive (91) and visual impairment (92), delirium and confusion (93) as well as drowsiness and sedation (94) have been shown to be independent risk factors of falls. There are only a limited number of studies that have investigated the association between anticholinergic burden and fractures, and so far, no systematic review has been conducted. The available studies were conducted in different countries and heterogeneous populations using various methods for the assessment of anticholinergic burden and use of anticholinergic medication. Some studies reported an increased risk of fractures associated with anticholinergic burden and/or use of anticholinergic medication (20, 25-29), while others did not find an association (95, 96).

6 RESEARCH QUESTIONS

The aim of this dissertation is to provide insight on the use of anticholinergic medication and the utility of the concept of anticholinergic burden for research by assessing the anticholinergic burden in a sample of the German population using claims data as well

as by assessing and enhancing the current evidence on the association between anticholinergic burden and the risk of fractures. Consequently, the research questions of this dissertation are defined as follows:

1. What is the current evidence regarding the risk of fractures associated with anticholinergic burden and what is the methodological quality of published studies?
2. What is the prevalence of anticholinergic burden and use of anticholinergic medication in German health claims data?
3. Is anticholinergic burden a useful predictor of fractures based on German health claims data?

7 METHODS AND DEFINITIONS

Three studies were conducted to answer the research questions of this dissertation. To supplement the description of methodology in the respective studies, this chapter will give additional details in regards to the selection of an anticholinergic burden scale and the assessment of fractures in the German Pharmacoepidemiological Research Database (GePaRD) as well as the rationale for the selection of study populations in the three studies.

7.1 Assessment of anticholinergic burden in GePaRD

For research questions 2 and 3 it was necessary to assess use of anticholinergic medication and anticholinergic burden in GePaRD. For this, a list of anticholinergic medication which were approved and used in Germany, including information regarding the respective anticholinergic potency of these medications was needed. Moreover, an anticholinergic burden scale had to be selected that could be applied with the information available in German claims data, i.e. a scale that was not reliant on the physician prescribed dose, as this information is not available in GePaRD (97). The list and scale developed by Kiesel et al. (79) fulfilled these criteria. In the literature this scale is often called the German Anticholinergic Burden Scale (GABS). Using different sources, the

authors, a multidisciplinary team of geriatricians and clinical pharmacists, compiled a list of anticholinergic medications available in Germany including information in regards to their anticholinergic potency. As a result 104 medications were defined to have a weak (ACB=1), 18 to have a moderate (ACB=2) and 29 to have a strong anticholinergic effects (ACB=3) (79). The scale was closely based on the ACB scale (59) and defined clinically relevant anticholinergic burden as a score of ≥3 (79). This scale was selected for use in the studies based on GePaRD as (i) the physician prescribed dose was not necessary for its application and (ii) comparison to results of other studies was expected to be easier due to the widespread use of the ACB scale (10).

7.2 Study population

For research question 1, in order not to exclude relevant studies, no restrictions regarding the demographic characteristics of the study population or setting were applied. For research question 2, use of anticholinergic medication and anticholinergic burden was assessed in the general population without any restriction to age to give a complete overview of the use of anticholinergic medication and anticholinergic burden in the entire population of GePaRD as well as to put the prevalence of use in each age group into context with the prevalence of use in other age groups. For research question 3, only older adults aged ≥65 years were included in the study population as they are the population at highest risk for fractures and thus the population of interest for prevention of fractures (98).

7.3 Assessment of fractures in GePaRD

For research question 3, the outcome any fractures, which included hip/femur fractures, pelvis fractures, vertebral fractures, wrist, hand and shoulder fractures and other fractures, was assessed. Only fractures that required a hospitalization and were recorded as main discharge diagnoses were included. This resulted in a sensitive outcome definition, as it was expected that any fracture requiring hospitalization in older adults could represent a debilitating injury.

8 OWN STUDIES CONDUCTED IN THE CONTEXT OF THE DISSERTATION

Three studies were conducted in order to answer the proposed research questions. In this chapter the publications written for this cumulative dissertation are briefly summarized

Jonas Reinold, Wiebke Schäfer, Lara Christianson, Francesco Barone−Adesi, Oliver Riedel, Federica Edith Pisa. Anticholinergic Burden and Fractures: A Systematic Review with Methodological Appraisal. Drugs & Aging 37, 885–897 (2020). https://doi.org/10.1007/s40266-020-00806-6

This study was the first systematic assessment of results and methodological quality of studies investigating the risk of fractures as well as predictors of fractures, such as reduced bone mineral density, associated with anticholinergic burden. Observational studies, which assessed the association between anticholinergic burden and any type of bone fracture, osteoporosis or reduced bone mineral density, were included. Exposure had to be defined as anticholinergic burden assessed through an anticholinergic burden scale, and crude or adjusted measure of association between the exposure and the outcome as well as the corresponding confidence interval, or sufficient data for its calculation, had to be reported. No restrictions regarding the study population or setting were applied. No articles were excluded based on language. Studies published up to August 2020 were included from relevant literature databases. Nine studies were included for the association anticholinergic burden and fractures and two studies for anticholinergic burden and reduced bone mineral density. The included studies were heterogeneous in regards to methods, particularly in the choice of anticholinergic burden scale, and only a few were of high quality. Seven out of the nine studies on anticholinergic burden and fractures found a positive association and within a sub-group of four studies that used the ARS, a dose-response relationship between increasing anticholinergic burden and the risk of fractures could be observed. One of the two studies included for the association between anticholinergic burden and reduced bone mineral density reported an association at one skeletal site, while the other study did not find any association between anticholinergic burden and reduced bone mineral density.

Jonas Reinold, Malte Braitmaier, Oliver Riedel, Ulrike Haug. Anticholinergic burden: First comprehensive analysis using claims data shows large variation by age and sex. PLoS One. 2021;16(6):e0253336. https://doi.org/10.1371/journal.pone.0253336

The aim of the study was to assess prevalence of anticholinergic burden and to identify the classes of medication contributing to the cumulative anticholinergic burden, stratified by age and sex. A cross-sectional study was conducted using 2016-data from GePaRD. Persons were included who had ≥1 day of insurance in 2016, preceded by ≥365 days of continuous insurance. Persons were excluded who were not resident in Germany, had invalid information regarding age or sex, or were hospitalized for ≥90 days. Use of anticholinergic medication and anticholinergic burden was assessed through the GABS scale (79). Cumulative anticholinergic burden was calculated as described by Campbell et al. (99). The study population included 16,470,946 persons. The prevalence of ACB=1 was 17.6% in men and 19.7% in women, while the prevalence of ACB=2 was 6.7% in men and 8.2% in women, and the prevalence of ACB≥3 was 7.2% in men and 10.4% in women. There was a steady increase of prevalence of anticholinergic burden with age, but the prevalence of ACB≥3 was higher in persons aged ≤18 years than in persons aged 19-49 years. High prevalences of morbidities and use of medication were associated high ACB. Persons with ACB≥3 were, on average, more frequently hospitalized, remained hospitalized for longer periods, had a higher prevalence of nursing home residency and obesity. Analyses based on cumulative anticholinergic burden showed that there were differences by age and sex regarding the medications contributing to the cumulative anticholinergic burden, e.g., while in younger women antidepressants were the largest contributor, in older ages group the proportion of cardiovascular medication and diuretics increased.

Jonas Reinold, Malte Braitmaier, Oliver Riedel, Ulrike Haug. Potential of health insurance claims data to predict fractures in older adults: A prospective cohort study. Clin Epidemiol. 2022;14:1111-1122. https://doi.org/10.2147/CLEP.S379002

Older adults are at high risk for fractures, a risk that further increases with age. Use of certain medications, anticholinergic burden and other factors such as age, sex, prior fractures and chronic diseases, have been shown to be associated with an increased risk of fractures. Strategies for the prevention of fractures are needed; however, this requires knowledge regarding predictors of fractures and their relevance. Due to their availability, population coverage and low cost, claims data could be a useful tool for the prediction of fractures. Thus, the aim of this study was to assess the potential of German claims data to predict fractures in older adults. Based on GePaRD, persons aged ≥65 years with ≥365 days of continuous insurance coverage and no fractures prior to January 1st 2017 (baseline) were included. The study population was randomly divided into a training (80%) and a test sample (20%) and logistic regression and random forest models were used to predict the risk of fractures within one year after baseline based on different combinations of potential predictors including anticholinergic burden. In total, 2,997,872 persons (56% women) were included. Based on the logistic regression and random forest models, the maximum predictive performance as measured by the area under the curve (AUC) across models was 0.63 in men and 0.60 in women and was achieved by combining information on medication and morbidities. AUCs were lowest in age group ≥85 years. Overall, the performance of the models was moderate. As a predictor of fractures in older adults, anticholinergic burden on its own or in combination with other predictors did not bring a marked benefit compared with other measures of (cumulative) use of medications such as number of medications used or use of fall risk increasing drugs (FRIDs).

9 DISCUSSION

The aim of this dissertation was to provide insights into the association between anticholinergic burden and fractures as well as the prevalence of anticholinergic burden and the usefulness of anticholinergic burden as a predictor of fracture risk in German claims data. In this chapter, the results and implications of the individual publications (P1-P3) are discussed.

9.1 Discussion of P1

P1 was the first systematic review to investigate the association between anticholinergic burden and risk of fractures. Most studies included in P1 reported an increased risk of fractures associated with anticholinergic burden. Moreover, in a sub-group of studies that used the ARS, a dose-response relationship between increasing anticholinergic burden and the risk of fracture was observed. Studies were heterogenous in regards to their methodology and use of anticholinergic burden scales and few studies were of high quality (e.g., included studies had only small sample sizes, only three used longitudinal study designs and many were conducted in selected populations such as hospitalized persons or nursing home residents).

Soon after the publication of P1, a systematic review with a similar aim was published by Ogawa et al. (100). The authors reported increased risk of fractures associated with anticholinergic burden measured through ARS and ACB scales. While there was a substantial overlap between both reviews regarding the inclusion of studies, of the 10 studies found eligible by Ogawa et al., five were also included in P1, this was mainly due to the use of less stringent eligibility criteria in regards to exposure by Ogawa et al.. In P1, studies were only included if they used an anticholinergic burden scale in the assessment of exposure. In the study by Ogawa et al., in addition to studies using anticholinergic burden scales for the assessment of exposure, studies were also included if there was an assessment of risk of fractures associated with anticholinergic medication even if no anticholinergic burden scale was used in the original study (100). For example, a study was included in the systematic review which compared the risk of fractures

between users of paroxetine and other selective serotonin reuptake inhibitors. The results of this study were then included in the meta-analysis for the ACB, ARS and anticholinergic drug scale (ADS) based on the respective classification of the anticholinergic potency of paroxetine in each scale (101). In addition to the ACB, ARS and ADS, Ogawa et al. also performed meta-analyses on studies using the drug burden index (DBI) to assess exposure, or on studies whose exposure of interest was included in one of the scales. Moreover, one analysis combined results of studies using ACB and ARS. The study by Ogawa et al. comes to similar conclusions as P1 in regards to the ARS, reporting an association between higher categories of ARS and an increased risk of fractures. Additionally, Ogawa et al. report increased risks of fractures associated with higher DBI, ACB and ADS. These results were, however, only based on a limited number of studies. In both studies, interpretation of results is difficult due to the heterogeneity of the methodology of the included studies. The study of Ogawa et al. has several limitations, of which the small number of included studies is shared with P1. Furthermore, one of the included studies was judged to have a high risk of bias and meta-analyses were performed on a very small number of studies (100). Moreover, the inclusion of studies that originally did not use anticholinergic burden as an exposure of interest but a subset or a selection of certain anticholinergic medication might have led to the inclusion of even more heterogenous studies, severely limiting the interpretability of the results of the systematic review.

After the publication of P1, two other studies have reported increased risk of fractures associated with anticholinergic burden. In a large cohort study based on Taiwanese claims data, Hsu et al. (102) report increased risk of fracture-specific hospitalizations with increasing anticholinergic burden in older adults assessed through ARS and ACB. Shmuel et al. (103) conducted a self-controlled study in older adults with Medicare coverage, in which exposure to anticholinergic and sedative medications was assessed based on an US-adaptation of the DBI (104). The results suggest a short-term

association between anticholinergic and sedative medication and risk of fall-related fractures within hazard periods of 7, 14 and 21 days (103).

Even with the newly published studies which are in line with the results from P1 and the systematic review by Ogawa et al. (100), the number of high-quality longitudinal studies remains low. Moreover, due to differences in prescribing behavior and availability of anticholinergic medication between countries as well as the use of different scales for the assessment of anticholinergic burden, considerable heterogeneity remains. Therefore, the results of the studies by Hsu et al. (102) and Shmuel et al. (103) as well as the systematic reviews P1 and the study by Ogawa et al. (100) should be interpreted carefully. More information from high quality studies is needed. In the future, the conduct of high-quality studies which enable the drawing of causal conclusions, e.g., studies with target trial emulation design, could potentially provide results that allow for a more certain interpretation.

9.2 Discussion of P2

P2 was the first study in which anticholinergic burden was assessed on population level in Germany. The prevalence of any use of anticholinergic medication was between 17.6–19.7% and the prevalence of clinically relevant anticholinergic burden was between 6.7%–8.2%. Anticholinergic burden increased steadily with age. Generally, women had higher prevalences of anticholinergic burden than men. The results of P2 showed that clinically relevant anticholinergic burden is present among all age groups of the German population and that across age groups and sexes, different types of medication are contributing to anticholinergic burden.

It is difficult to put the results of P2 into context with other research due to the lack of comparable studies. Only in the study by Cebron Lipovec et al. (86), based on the Slovenian nationwide health claims database, the prevalence of anticholinergic burden has been assessed based on a similar sample of the general population. Briefly, the overall prevalence of ACB≥3 in the Slovenian population was 7.6%, while in P2 it was 10.4% in women and 7.2% in men. In Slovenian older adults the prevalence of use of at

least one anticholinergic medication was 43.1% compared to P2 where the prevalence was 62.7%–76.0% in women and 59.0%–71.1% in men. In the Slovenian population prevalence of ACB≥3 was 12.1% and compared to 21.9%–26.3% in women and 17.2%–22.7% in men in Germany (86).

Two other studies have used population-based data sources but restricted the study population to older adults. The study from Jun et al. (105) was based on a sample of 20% of Korean older adults and included 1,292,323 persons aged ≥65 years. Similar to P2, the study design was cross-sectional and assessed prevalence of anticholinergic burden during 2016. Prevalence of clinically relevant anticholinergic burden (KABS≥3) was 25.5% (105), assessed using the Korean Anticholinergic Burden Scale (KABS) (75). In P2, the prevalence of clinically relevant anticholinergic burden (ACB≥3), assessed among persons aged ≥70 years, was 22–32% in women, 17–26% in men. In the Korean study, the prevalence of older adults exposed to at least one anticholinergic medication was 81.5–90.2%, compared to 62.7–76.0% of women and 59.0–71.1% of men in Germany. As in P2, anticholinergic burden was associated with a higher risk of comorbidities, which in the study of Jun et al., was based on the Charlson's comorbidity index (105).

The study from Salahudeen et al. (106) included 537,387 persons aged ≥65 years and was based on the Pharmaceutical Claims Data Mart (Pharms), which covered almost the entire population of older adults in New Zealand. Exposure to anticholinergic medication was assessed through eight anticholinergic burden scales using medication available in New Zealand. The prevalences of exposure to anticholinergic medication differed according to the used scale and were between 22.8% (ARS) and 55.9% (ACB), while the prevalence of use of at least one anticholinergic medication in Germany among older adults aged ≥70 years was between 62.7–76.0% in women and between 59.0–71.1% in men (106). The comparison of the results of P2 to the three other population-based studies illustrates the difficulty of comparing measures of anticholinergic burden assessed through anticholinergic burden scales across different countries and health

care systems. A source of uncertainty is that the number of anticholinergic medications included in the studies varied considerably; the GABS (79), used in P2, included 151 anticholinergic medications, ACB, as used by Cebron Lipovec et al. (86) included 37, the KABS (75), used by Jun et al. (105), included 137 and the ACB as used by Salahudeen et al. (106) included 74 anticholinergic medications (Table 4). The overlap of included anticholinergic medication between GABS (79) and the other scales was 49% (compared to KABS (75)), 30% (compared to ACB in Salahudeen et al. (106)) and 20% (compared to ACB in Cebron Lipovec et al. (86)). Moreover, for a total of 14 medications there were conflicting categorizations in regards to anticholinergic potency between the scales (e.g., low vs. high potency, medium vs. high or low vs. medium potency). A recent systematic review, aiming to analyze the degree of agreement among different anticholinergic burden scales, also reported large differences in the prevalence of anticholinergic burden when different scales were used. The authors concluded that due to the differences in the included anticholinergic medications, anticholinergic burden scales are not interchangeable (13). Thus, it is difficult to interpret the assessments of prevalence of both the exposure to at least one anticholinergic medication based on the differences in included medications, and the exposure to clinically relevant anticholinergic medication due to the differences in classification of anticholinergic potency. Consequently, comparisons of study results on international level are extremely difficult and even the comparison of results on national level are potentially difficult to interpret if different anticholinergic burden scales are used. It is unclear whether the prevalence of anticholinergic burden in Germany, in comparison to other countries, is higher, lower or similar. The comparisons between P2 and the three population-based studies illustrate the limitations of assessment of anticholinergic burden using anticholinergic burden scales and have to be interpreted very carefully, if at all, due to the differences between anticholinergic burden scales.

9.3 Discussion of P3

The results of P3 indicate that the usefulness of anticholinergic burden as a predictor of fractures in older adults based on German claims data is similar to other measures of (cumulative) use of medication and less useful than predictors based on morbidity. Analogous to P2, the results of P3 are difficult to put into perspective as there are currently no comparable studies that predict the risk of fractures that have included anticholinergic burden as a predictor in multivariate models. Other studies have also used claims or national registry data to predict the occurrence of fractures without including anticholinergic burden assessed through an anticholinergic burden scale as a predictor. The most relevant of these studies are the studies of Engels et al. (107) and Kruse et al. (108), which had better model performance compared to P3 due to the higher availability of clinical information and a higher risk of fractures in the populations. The results of P3 are quite interesting as the expectation from P1 was that clinically relevant anticholinergic burden could potentially be a useful predictor for the occurrence of fractures. Moreover, the results of the univariate analysis of P3, stratified by sex and age groups, show odds ratios between 1.4 and 2.1 in men and 1.1 and 1.7 in women for ACB≥3. However, the risk estimates decreased with increasing age and were smaller than the univariate results for predictors such as Parkinson's disease, dementia, use of antipsychotics and hyper polypharmacy, which is defined as the use of 10 or more different medications (109) and has been shown to be associated with an increased risk for fractures (110). Furthermore, in the multivariate analyses, the model which only included predictors related to morbidity, lifestyle factors and nursing home residency, resulted in AUCs very similar to those of another model in which anticholinergic burden, FRIDs and polypharmacy were included. For context, FRIDs are a diverse list of medication that are associated with an increased risk of falls identified through systematic reviews (111-113). This indicates that the risk of fractures in this population was mediated rather through morbidity than (cumulative) use of medication. Moreover, as Parkinson's disease and dementia are associated with frailty, it is possible that frailty

or morbidities closely associated with frailty might be more useful predictors of fractures in claims data than anticholinergic burden. Indeed, in other studies frailty has been shown to be a predictor of fractures (114, 115). However, the majority of these studies were based on primary data with smaller sample sizes and thus less statistical power.

The discrepancy in regards to the strength of the risk of fractures associated with anticholinergic burden between P1 and P3 invites the question whether the results of the studies included in P1 were subject to confounding by indication due to frailty or morbidities associated with frailty. Indeed, 6 of the 9 studies included in P1 were conducted in persons aged ≥60 years (20, 25, 27-30), one in persons aged ≥50 years (95), one in women aged 50-79 years (96), and one in persons aged ≥40 years (26). In three studies the population was selected from the general population (20, 27, 30), another three were selected from community dwelling persons (28, 95, 96), one study was conducted in hospitalized persons with Parkinson's disease or paralysis agitans (26), one in nursing home residents with depression (25) and one in hospitalized persons without history of fractures or osteoporosis (29). While the populations are heterogenous, most studies included persons aged ≥60 years and some included populations that could have a high prevalence of frailty, such as nursing home residents (116) or hospitalized persons with Parkinson's disease (117). Frail persons use more medication and are more likely to be affected by polypharmacy and anticholinergic burden (118). Consequently, there is debate whether increased use of medication reflects the accumulation of morbidities associated with the transition to frailty, if the medications themselves are responsible for the transition, or if both factors are contributing to the transition to frailty (118, 119). Studies have suggested that at least in some patients the prescription of high-risk medication, including anticholinergic medication, can exacerbate the transition to frailty and thus be a risk factor for frailty (120) and consequently also for fractures. However, considering the results from P3, there might be more potential in using predictors related to morbidity, particularly frailty, to predict the occurrence of fractures in GePaRD. Additionally, if the cumulative use of medication can be included,

the use of a complex tool such as anticholinergic burden assessed through an anticholinergic burden scale might not be necessary. Instead, methods that are easier to implement such as FRIDs (111-113) or polypharmacy could be used (121, 122). Particularly, as these tools also include anticholinergic medication either partially (FRIDs) or completely (polypharmacy). In addition to being more easily implemented, polypharmacy in particular has the potential to facilitate easier comparison with international studies.

10 CONCLUSION AND OUTLOOK

Overall, the studies conducted for this dissertation have illustrated the challenges of using anticholinergic burden assessed through anticholinergic burden scales for research, particularly in claims data. The lack of consensus in regards to which medications are defined as anticholinergic and what their anticholinergic potency is, the lack of a gold standard for the assessment of anticholinergic burden, and the considerable differences in use of anticholinergic medication across different countries limit the comparability of study results. These limitations make it difficult to put results into context and to come to a meaningful conclusion regarding their clinical significance. In the context of this dissertation, the usefulness of anticholinergic burden for the prediction of fractures in German claims data was small and comparable to other measures of (cumulative) use of medication. More studies are needed to assess if this result was due to the used methodology and if the finding can be reproduced. More high-quality studies are needed to clarify the contribution of both anticholinergic burden and frailty to the risk of fractures. The inherent limitations of the concept of anticholinergic burden, the challenges in comparison of results as well as the existence of alternative measures based on (cumulative) burden of medication for the assessment of risk of fractures make a case against the use of anticholinergic burden it in research. However, the concept in its originally intended form, as a tool for the assessment of individual risk of adverse outcomes of a patient in clinical practice, is still valid. Particularly, in the

context of medication review and deprescribing efforts, anticholinergic burden scales have shown to be useful (123).

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12 APPENDIX

12.1 Own contributions to the publications

Own contributions to the publications

As requested in § 6 paragraph 2 number 2 of the Promotionsordnung for Dr. rer. nat. at Faculty 11, University of Bremen, an overview of the candidate's own contribution to the publications with first authorship is provided in the table below

Step	**P1**	**P2**	**P3**
Conceptualization and research question	Equally	Equally	Equally
Literature search	Predominantly	Entirely	Entirely
Study plan	Predominantly	Predominantly	Equally
Data collection*	Predominantly	-	-
Data analysis	Entirely	Equally	Equally
Discussion and interpretation	Predominantly	Predominantly	Predominantly
Drafting of manuscript	Entirely	Entirely	Entirely
Revision	Predominantly	Predominantly	Predominantly

* as publications P2 and P3 are based on pseudonymous secondary data, no collection of data was performed. Data management, (supervision of) programming of analysis datasets and statistical programming are included in "data analysis".
Entirely: all steps performed independently in frequent exchange with colleagues
Predominantly: the majority of steps performed independently
Equally: in equal parts by candidate and colleagues

12.2 Versicherung an Eides Statt gem. § 65 Absatz 5 BremH

Versicherung an Eides Statt

Ich, Jonas Reinold, [redacted]

(Vorname, Name, Anschrift, Matr.-Nr.)

versichere an Eides Statt durch meine Unterschrift, dass ich die vorstehende Arbeit selbständig und ohne fremde Hilfe angefertigt, meine Eigenleistung und Beiträge der Koautorinnen und Koautoren im Falle einer kumulativen Dissertation entsprechend richtig ausgewiesen habe.

Ich versichere an Eides Statt, dass ich alle Stellen, die ich wörtlich dem Sinne nach aus Veröffentlichungen entnommen habe, als solche kenntlich gemacht habe, mich auch keiner anderen als der angegebenen Literatur oder sonstiger Hilfsmittel bedient habe.

Ich versichere an Eides Statt, dass ich die vorgenannten Angaben nach bestem Wissen und Gewissen gemacht habe und dass die Angaben der Wahrheit entsprechen und ich nichts verschwiegen habe.

Die Strafbarkeit einer falschen eidesstattlichen Versicherung ist mir bekannt, namentlich die Strafandrohung gemäß § 156 StGB bis zu drei Jahren Freiheitsstrafe oder Geldstrafe bei vorsätzlicher Begehung der Tat bzw. gemäß § 161 Absatz 1 StGB bis zu einem Jahr Freiheitsstrafe oder Geldstrafe bei fahrlässiger Begehung.

Bremen, 4.4.23
Ort, Datum

Unterschrift

12.3 Tables

Table 1. Anticholinergic burdens scales that do not include dose in the assessment of anticholinergic burden

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
CrAS	Clinician-rated Anticholinergic score	Canada / 2001	340	0-3	Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Archives of internal medicine*. Apr 23 2001;161(8):1099-105.
ADS	Anticholinergic drug scale	USA / 2006	117	0-3	Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. Journal of clinical pharmacology. Dec 2006;46(12):1481-6. doi:10.1177/0091270006292126
ABC	Anticholinergic burden classification	France / 2006	27	0-3	Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ (Clinical research ed)*. Feb 25 2006;332(7539):455-9. doi:10.1136/bmj.38740.439664.DE

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
ACB	Anticholinergic cognitive burden scale	USA / 2008	88	0-3	Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4(3):311-320. doi:10.2217/1745509x.4.3.311
ARS	Anticholinergic risk scale	USA / 2008	49	0-3	Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Archives of internal medicine*. Mar 10 2008;168(5):508-13. doi:10.1001/archinternmed.2007.106
CABS	Cancelli's anticholinergic burden scale	Italy / 2009	17	0-3	Cancelli I, Beltrame M, D'Anna L, Gigli GL, Valente M. Drugs with anticholinergic properties: a potential risk factor for psychosis onset in Alzheimer's disease? *Expert opinion on drug safety*. 2009/09/01 2009;8(5):549-557. doi:10.1517/14740330903099636
AAS	Anticholinergic activity scale	Norway / 2010	99	0-4	Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *Journal of neurology, neurosurgery, and psychiatry*. Feb 2010;81(2):160-5. doi:10.1136/jnnp.2009.186239
ALS	Anticholinergic loading scale	Australia / 2011	49	0-3	Sittironnarit G, Ames D, Bush AI, et al. Effects of anticholinergic drugs on

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
					cognitive function in older Australians: results from the AIBL study. *Dementia and geriatric cognitive disorders*. 2011;31(3):173-8. doi:10.1159/000325171
AEC	Anticholinergic effect on cognition scale	UK / 2017	165	0-3	Bishara D, Harwood D, Sauer J, Taylor DM. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. *International journal of geriatric psychiatry*. Jun 2017;32(6):650-656. doi:10.1002/gps.4507
AIS	Anticholinergic impregnation scale	France / 2017	128	1-3	Briet J, Javelot H, Heitzmann E, et al. The anticholinergic impregnation scale: Towards the elaboration of a scale adapted to prescriptions in French psychiatric settings. *Therapie*. Sep 2017;72(4):427-437. doi:10.1016/j.therap.2016.12.010
ATS	Anticholinergic toxicity scale	USA / 2017	25	0-5	Xu D, Anderson HD, Tao A, et al. Assessing and predicting drug-induced anticholinergic risks: an integrated computational approach. *Therapeutic advances in drug safety*. Nov 2017;8(11):361-370. doi:10.1177/2042098617725267

Table 2. Anticholinergic burdens scales that include dose in the assessment of anticholinergic burden

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
DBI	Drug burden index	USA / 2007	No list of medication reported	Continuous scale; no cut off reported	Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. *Archives of internal medicine*. Apr 23 2007;167(8):781-7. doi:10.1001/archinte.167.8.781
DBI-WHO	Drug burden index - WHO	2014 / France	No list of medication reported	Continuous scale; no cut off reported	Dauphinot V, Faure R, Omrani S, et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. *Journal of clinical psychopharmacology*. Oct 2014;34(5):565-70. doi:10.1097/jcp.0000000000000195
MARANTE	Muscarinic acetylcholinergic Receptor antagonist exposure scale	2017 / Belgium, Netherlands	Based on list from Duran et al.	Continuous scale; no cut off reported	Klamer TT, Wauters M, Azermai M, et al. A Novel Scale Linking Potency and Dosage to Estimate Anticholinergic Exposure in Older Adults: the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale. *Basic & clinical pharmacology & toxicology*. Jun 2017;120(6):582-590. doi:10.1111/bcpt.12699

Table 3. Lists of anticholinergic medication and/or country specific adaptations of existing lists and/or scales

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
Chew's scale	n.A.	USA / 2008	22	n.A., categorization of medication according to anticholinergic potency	Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *Journal of the American Geriatrics Society*. Jul 2008;56(7):1333-41. doi:10.1111/j.1532-5415.2008.01737.x
DL	Duran's list	Ecuador /2013	225	n.A. (high / low potency)	Duran CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *European journal of clinical pharmacology*. Jul 2013;69(7):1485-96. doi:10.1007/s00228-013-1499-3
GABS	German anticholinergic burden scale	Germany / 2018	504	0-3	Kiesel EK, Hopf YM, Drey M. An anticholinergic burden score for German prescribers: score development. *BMC geriatrics*. Oct 11 2018;18(1):239. doi:10.1186/s12877-018-0929-6
mACB (AUS)	Modified anticholinergic burden score - Australia	Australia / 2019	82	1-3	Kable A, Fullerton A, Fraser S, et al. Comparison of Potentially Inappropriate Medications for People with Dementia at Admission and Discharge during An Unplanned Admission to Hospital: Results from the SMS Dementia Study. *Healthcare (Basel)*. Jan 9 2019;7(1)doi:10.3390/healthcare7010008

Acronym	Full Name	Country / Year	Number of medications	Scoring level	Citation
KABS	Korean anticholinergic burden scale	Korea / 2019	494	0-3	Jun K, Hwang S, Ah YM, Suh Y, Lee JY. Development of an Anticholinergic Burden Scale specific for Korean older adults. *Geriatrics & gerontology international*. Jul 2019;19(7):628-634. doi:10.1111/ggi.13680
BAADS	Brazilian anticholinergic activity drug scale	Brazil / 2019	125	1-3	Nery RT, Reis AMM. Development of a Brazilian anticholinergic activity drug scale. *Einstein (Sao Paulo, Brazil)*. Apr 1 2019;17(2):eAO4435. doi:10.31744/einstein_journal/2019AO4435
CALS	CRIDECO anticholinergic load scale	Spain / 2022	2017	1-3	Ramos H, Moreno L, Pérez-Tur J, Cháfer-Pericás C, García-Lluch G, Pardo J. CRIDECO Anticholinergic Load Scale: An Updated Anticholinergic Burden Scale. Comparison with the ACB Scale in Spanish Individuals with Subjective Memory Complaints. *J Pers Med*. Feb 3 2022;12(2)doi:10.3390/jpm12020207

Table 4. Comparison of anticholinergic burden scales GABS, KABS, ACB Slovenia, ACB New Zealand

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
Aclidinium	1	1	0	0	0	
Alimemazine	1	0	1	0	1	
Alprazolam	1	1	1	1	0	
Alprazolam	1	0	0	0	1	
Amisulpride	1	0	1	0	0	
Ampicillin	1	1	0	0	0	
Aripiprazole	1	1	1	1	0	
Asenapine	1	1	0	0	0	
Atenolol	1	1	0	0	1	
Azathioprine	1	1	0	0	0	
Baclofen	1	1	1	0	0	
Benazepril	1	1	0	0	0	
Betaxolol	1	1	0	0	0	
Bisacodyl	1	1	0	0	0	
Blonanserin	1	0	1	0	0	
Bromperidol	1	0	1	0	0	
Bromocriptine	1	1	0	0	0	
Brompheniramine maleate	1	0	0	0	1	
Bupropion	1	1	1	1	1	
Captopril	1	1	0	1	1	
Carbamazepine	1	0	1	0	0	KABS considers this as Potency=1, GABS as Potency=2
Celecoxib	1	1	0	0	0	
Cetirizine	1	1	1	1	0	
Chlordiazepoxide	1	1	1	0	0	
Chlorthalidone	1	1	0	0	1	
Ciclosporin	1	1	0	0	0	
Cimetidine	1	0	0	0	1	ACB NZ considers this as Potency=1, GABS and KABS as Potency=2
Cinnarizine	1	0	1	0	0	
Citalopram	1	1	1	0	0	
Clindamycin	1	1	0	0	0	
Clonazepam	1	1	1	0	0	
Clorazepate	1	1	1	0	1	
Codeine	1	1	1	0	1	
Colchicine	1	0	0	0	1	
Coumadin	1	0	0	0	1	
Desloratadine	1	1	1	1	0	
Desvenlafaxine	1	0	1	0	0	
Dexamethasone	1	1	0	0	0	
Dextromethorphan	1	1	1	0	0	
Diazepam	1	1	1	1	1	
Digitoxin	1	1	0	0	0	
Digoxin	1	1	1	0	1	

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
Diltiazem	1	1	0	0	0	
Dimetindene	1	1	0	0	0	
Dipyridamole	1	1	0	0	1	
Disopyramide phosphate	1	0	0	0	1	
Domperidone	1	1	0	0	0	
Doxylamine	1	1	0	0	0	KABS considers this Potency=3, GABS as Potency=1
Emedastine	1	0	1	0	0	
Entacapone	1	1	0	0	0	
Escitalopram	1	1	1	0	0	
Estazolam	1	0	1	0	0	
Etoricoxib	1	1	0	0	0	
Famotidine	1	1	0	0	0	
Fentanyl	1	1	1	1	1	
Fexofenadine	1	1	0	0	0	
Flunitrazepam	1	1	1	0	0	
Fluoxetine	1	1	1	0	0	
Flupentixol	1	0	1	0	0	
Fluphenazine	1	1	0	0	0	
Flurazepam	1	1	1	0	0	
Fluvoxamine	1	1	1	0	1	
Furosemide	1	1	1	1	1	
Gentamicin	1	1	0	0	0	
Glycopyrronium	1	1	0	0	0	
Guaifenesin	1	1	1	0	0	
Haloperidol	1	0	1	1	1	ACB Slovenia, ACB NZ and KABS considers this as Potency=1, GABS as Potency=2
Hydralazine	1	1	1	0	1	
Hydrocodone	1	0	1	0		
Hydrocortisone	1	1	1	0	1	
Ipratropium	1	1	0	0		
Isosorbide dinitrate	1	1	0	0	1	
Isosorbide mononitrate	1	1	0	1	0	
Ketorolac	1	1	0	0	0	
Ketotifen	1		1	0	0	
Lansoprazole	1	1	0	0	0	
Levocetirizine	1	1	1	1	0	
Levodopa	1	1	0	0	0	
Lithium	1	1	0	0	0	
Loperamide	1	0	1	0	1	KABS and ACB NZ considers this as Potency=1, GABS as Potency=2
Loratadine	1	1	1	1	0	
Lorazepam	1	1	1	0	0	
Metformin	1	1	0	0	0	

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
Methocarbamol	1	1	1	0	0	
Methotrexate	1	1	0	0	0	
Methylprednisolone	1	1	0	0	0	
Metoclopramide	1	1	0	0	0	
Metoprolol	1	1	0	1	1	
Midazolam	1	1	1	0	0	
Mirtazapine	1	1	1	0	0	
Morphine	1	1	1	0	1	
Naratriptan	1	1	0	0	0	
Nifedipine	1	1	0	1	1	
Oxazepam	1	1	0	0	0	
Oxycodone	1	1	1	0	0	
Paliperidone	1	1	1	0	0	
Pancuronium	1	1	0	0	0	
Perphenazine	1	1	0	0	0	KABS considers this as Potency=2, GABS as Potency=1
Phenobarbital	1	1	0	0	0	
Piperacillin	1	1	0	0	0	
Pramipexole	1	1	0	0	0	
Prednisolone	1	1	1	0	0	
Prednisone	1	1	0	0	1	
Promethazine	1	1	0	0	0	GABS considers this as Potency=1, ACB NZ as Potency=3
Pseudoephedrine	1	1	0	0	0	
Quinidine	1	1	0	0	1	
ranitidine	1	0	0	1	1	ACB Slovenia and ACB NZ considers this as Potency=1, GABS as Potency=2
Risperidone	1	1	1	1	1	
Rotigotine patch	1	1	0	0	0	
Selegiline	1	1	0	0	0	
Sertraline	1	1	0	0	0	
Sumatriptan	1	1	0	0	0	
Temazepam	1	1	1	0	0	
Theophylline	1	0	1	0	1	KABS and ACB NZ considers this as Potency=1, GABS as Potency=2
Thiothixene	1	0	1	0	0	
Tiotropium	1	1	0	0	0	
Trandolapril	1	1	0	0	0	
Trazodone	1	1	1	1	0	
Triamcinolone	1	1	0	0	0	
Triamterene	1	1	0	0	1	
Triazolam	1	1	1	0	0	
Valproic acid	1	1	0	0	0	
Vancomycin	1	1	0	0	0	
Venlafaxine	1	1	1	1	0	
Warfarin	1	1	0	1	0	

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
Ziprasidone	1	1	1	0	0	
Zolmitriptan	1	1	0	0	0	
Amantadine	2	1	1	1	1	
Carbamazepine	2	1	0	1	1	KABS considers this as Potency=1, GABS, ACB Slovenia and ACB NZ as Potency=2
Cyclobenzaprine	2	0	1	0	1	
Cyproheptadine	2	0	1	0	1	KABS and ACB NZ considers this as Potency =2, GABS as Potency=3
Cimetidine	2	1	1	0	0	ACB NZ considers this as Potency=1, GABS and KABS as Potency=2
Clidinium	2	0	1	0	0	
Cloperastine	2	0	1	0	0	
Empracet	2	0	0	0	0	
Difenidol	2	0	1	0	0	
Glycopyrrolate	2	0	1	0	0	
Haloperidol	2	1	0	0	0	
Levomepromazine	2	0	1	1	0	ACB Slovenia and KABS considers this as Potency=2, GABS as Potency=3
Loperamide	2	1	0	0	0	KABS and ACB NZ considers this as Potency=1, GABS as Potency=2
Loxapine	2	1	1	0	1	
Maprotiline	2	1	0	0	0	
Mebeverine	2	0	1	0	0	
Methadone	2	1	0	0	0	
Methotrimeprazine	2	0	0	0	1	
Molindone	2	0	1	0	0	
Nefopam	2	0	1	0	0	
Olanzapine	2	1	0	0	0	ACB Slovenia, ACB NZ and KABS considers this as Potency=3, GABS as Potency=2
Opipramol	2	1	0	0	0	
Oxcarbazepine	2	1	1	1	1	
Paroxetine	2	1	1	0	0	ACB NZ and ACB Slovenia consider this as Potency=3, GABS and KABS as Potency=2
Pethidine	2	1	1	0	1	
Pimozide	2	1	1	0	1	
Perphenazine	2	0	1	0	0	KABS considers this as Potency=2, GABS as Potency=1
Quetiapine	2	1	1	0	0	ACB Slovenia nad ACB NZ consider this as Potency=3, GABS and KABS as Potency=2
Ranitidine	2	1	1	0	0	
Theophylline	2	1	0	0	0	KABS and ACB NZ considers this as Potency=1, GABS as Potency=2
Tizanidine	2	0	1	0	0	
Tramadol	2	1	1	0	0	
Trimebutine	2	0	1	0	0	

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
Triprolidine	2	0	1	0	0	
Zotepine	2	0	1	0	0	
Zuclopenthixol	2	0	1	0	0	
Amitriptyline	3	1	1	1	1	
Amoxapine	3	0	1	0	1	
Atropine	3	1	1	1	1	
Belladone alkaloids	3	0	1	0	0	
Benzatropine	3	0	1	0	1	
Biperiden	3	0	1	0	0	
Brompheniramine	3	0	1	0	1	
Carbinoxamine	3	0	1	0	0	
Cimetropium	3	0	1	0	0	
Chlorpheniramine	3	1	1	0	1	
Chlorpromazine	3	0	1	0	1	
Chlorprothixene	3	0	1	0	0	
Clemastine	3	1	1	0	0	
Clomipramine	3	1	1	0	1	
Clozapine	3	1	1	1	1	
Cyproheptadine	3	1	0	0	0	KABS and ACB NZ considers this as Potency =2, GABS as Potency=3
Darifenacin	3	1	0	1	0	
Desipramine	3	0	0	0	0	
Dexbrompheniramine	3	0	1	0	0	
Dexchlorpheniramine	3	0	1	0	0	
Dicyclomine	3	0	1	0	1	
Difemerine	3	0	1	0	0	
Dimenhydrinate	3	1	1	0	1	
Diphenhydramine	3	1	1	0	1	
Doxepin	3	1	1	0	1	
Doxylamine	3	0	1	0	0	KABS considers this Potency=3, GABS as Potency=1
Fesoterodine	3	1	1	1	0	KABS calls this Festerodine
Flavoxate	3	1	1	0	0	
Homochlorcyclizine	3	0	1	0	0	
Hydroxyzine	3	1	1	0	1	
Hyoscyamine	3	0	1	0	0	
Imidafenacin	3	0	1	0	0	
Imipramine	3	1	1	0	1	
Levomepromazine	3	1	0	0	0	
Meclizine	3	0	1	0	1	
Mequitazine	3	0	1	0	0	
Nortriptyline	3	1	1	0	1	
Octylonium bromide	3	0	1	0	0	
Olanzapine	3	0	1	1	1	ACB Slovenia, ACB NZ and KABS considers this as

Medication	Score/ Potency	GABS	KABS	ACB (Slovenia)	ACB (New Zealand)	Comments
						Potency=3, GABS as Potency=2
Orphenadrine	3	1	1	0	1	
Oapium iodide	3	0	1	0	0	
Oxybutynin	3	1	1	0	1	
Paroxetine	3	0	0	1	1	ACB NZ considers this as Potency=3, GABS and KABS as Potency=2
Pheniramine	3	0	1	0	0	
Piprinhydrinate	3	0	1	0	0	
Pridinol	3	0	1	0	0	
Procyclidine	3	1	1	0	1	
Promazine	3	0	0	0	1	
Promethazine	3	0	0	0	1	
Propentheline	3	0	0	0	1	
Propiverine	3	1	1	0	0	
Pyrilamine	3	0	1	0	1	
Quetiapine	3	0	0	1	1	ACB Slovenia and ACB NZ consider this as Potency=3, GABS and KABS as Potency=2
Scopolamine	3	1	1	1	1	
Scopolamine butylbromide	3	0	0	0	0	
Scopolia extract	3	0	1	0	0	
Solifenacin	3	1	1	1	0	
Tamsulosin and solifenacin	3	0	0	1	0	
Thioridazine	3	1	1	0	1	
Tiemonium	3	0	1	0	0	
Timepidium	3	0	1	0	0	
Tiquizium	3	0	1	0	0	
Tizanidine	3	1	0	0	0	
Tolterodine	3	1	1	1	1	
Trifluoperazine	3	0	0	0	1	
Trihexyphenidyl	3	1	1	0	0	
Trimipramine	3	1	0	0	1	
Trospium	3	1	1	1	0	
Valethamate bromide	3	0	1	0	0	

12.4 P1: Systematic review on the risk of fractures associated with anticholinergic burden

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SYSTEMATIC REVIEW

Anticholinergic Burden and Fractures: A Systematic Review with Methodological Appraisal

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Abstract

Introduction Medications with anticholinergic activity (MACs) are used to treat diseases common in older adults. Evidence on the association between anticholinergic burden (AB) and increased risk of fractures and osteoporosis or reduced bone mineral density (BMD) is inconsistent. Our aim was to conduct a systematic review of observational studies on AB with fractures and osteoporosis or reduced BMD and provide methodological appraisal of included studies.

Methods We searched MEDLINE, EMBASE, Science Citation Index and CENTRAL as well as grey literature from database inception up to August 2020. Eligibility criteria were: observational design, AB-exposure measured through a scale, fracture of any type or osteoporosis or reduced BMD as outcome, and reported measure of association between exposure and outcome. No restrictions related to time, language or type of data were applied. Eligibility and risk of bias assessment as well as data extraction were performed independently by two reviewers. Risk of bias of the included studies was assessed using the Newcastle–Ottawa Scale and the RTI Item Bank.

Results The majority of the nine included studies had low risk of bias but heterogeneous methodology. No study used a new user design. Seven studies reported an increased risk of fractures associated with AB. In four studies using the Anticholinergic Risk Scale (ARS), adjusted risk of fractures was increased by 2–61% for ARS = 1, by 0–97% for ARS = 2, by 19–84% for ARS = 3, and by 56–96% for ARS ≥ 4; in three studies the ARS was aggregated, risk increased by 39% for ARS = 1–2 and 17% for ARS = 2–3. Two studies reported increased risk of fractures of 14 and 52% in the highest AB-category and one study reported that change in ARS of ≥ 3 during hospitalization was associated with a 321% increased risk in fractures. Two studies did not find an association between AB and fractures. The association between AB and osteoporosis or reduced BMD could only be assessed in two studies, one reporting increased risk of lower BMD at Ward's triangle, the other reporting no association between AB and BMD T-score change at the femoral neck.

Discussion Our study suggests an association between AB and increased risk of fractures with possible dose-exposure gradient in studies using the ARS. The low number of studies and heterogeneity of methods calls for the conduct of more studies.

Plain language summary We conducted a study investigating the risk of fractures associated with anticholinergic burden, which is the result of taking one or more medication with anticholinergic activity. The results of our study suggest that persons who experience anticholinergic burden might have a higher risk of fractures. However, since we were only able to include nine studies, more studies conducted in a similar way are needed.

1 Introduction

Medications with anticholinergic activity (MACs) are used for the treatment of various conditions including Parkinson's disease, depression, cardiovascular diseases, asthma, chronic obstructive pulmonary disease (COPD), allergies as well as incontinence and overactive bladder [1, 2]. Prevalence of use of MACs differs depending on the study population: in community dwelling or general populations aged 65 and older between 9 and 57%; [3–5] among nursing home residents between 55 and 77% [6–9].

Oliver Riedel and Federica Pisa share senior authorship.

At the time of study conception and coordination, FEP worked at the Leibniz Institute for Prevention Research and Epidemiology – BIPS. From 1st March 2020 she is working at Bayer AG. Her current affiliation has no relation with this paper.

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Extended author information available on the last page of the article

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Key Points

This systematic review suggests that the risk of fractures is increased in persons with high anticholinergic burden.

In studies using Anticholinergic Risk Scale (ARS), the risk increases with increasing anticholinergic burden, suggesting a dose exposure gradient.

We found that one study reported an increased risk of lower BMD at Ward's triangle in persons with high anticholinergic burden, however a second study did not find an association.

Overall, the studies used heterogeneous methods and few studies had high quality. This calls for conduct of more high quality studies.

Anticholinergic burden, often the result of concomitant use of multiple MACs [10], has been associated with adverse effects such as cognitive and functional impairment, reduced quality of life, impaired activities of daily living [2] as well as falls [11, 12] and fall-related injuries, particularly fractures [13–16]. These effects are usually associated with the person's total anticholinergic burden, rather than specific medications. Several scores have been proposed to summarize the anticholinergic burden of patients. However, they vary in their rationale, intended use and association with outcomes [12].

Fractures, especially in older adults, often result in permanent disability or death and have a high impact on the health care system and informal caregivers [17–20]. Approximately one in three older adults experience at least one fall each year; as a consequence, 5% of them will sustain a fracture and 1% a hip fracture [19]. Hip fractures are associated with high short- and long-term mortality, reduced life expectancy, increased risk of dependency and high costs for the health care system [17–19].

Despite the high public health relevance of fractures, their possible association with anticholinergic burden has not yet been addressed in a systematic review. Therefore, we aimed to conduct a systematic review on the association between anticholinergic burden and the risk of fractures. Moreover, since a recent study suggested an association between anticholinergic burden and reduced bone mineral density (BMD) [21], which along with osteoporosis is a major risk factor for fractures [22], we also aimed to conduct a systematic review on studies investigating this association. A special emphasis was put on the description of the methodological quality of the included studies for both outcomes.

2 Methods

This systematic review was conducted in accordance with the PRISMA [23] and MOOSE [24] guidelines as well as a guideline for the conduct of systematic reviews and meta-analyses in older adults [25]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42018116737) and published in a peer-reviewed journal [26]. As the protocol has already been published, we will only give a brief description of methods.

2.1 Sources of evidence and search strategy

Search strategies were developed by the project team under the guidance of an experienced medical librarian. To identify papers on the association between anticholinergic burden and risk of fractures, the search strategy included two concepts: anticholinergic (including medication and burden), and fractures. For the association between anticholinergic burden and osteoporosis or reduced BMD, the search strategy included the concepts anticholinergic (including medication and burden), and osteoporosis or reduced BMD. The appropriate controlled vocabulary representing these concepts in each database was used (see Online Resource 1).

The search strategies were applied in the following electronic databases and information resources: MEDLINE (1950 to July 2020), EMBASE (1947 to August 2020) and Science Citation Index (1900 to July 2020). Moreover, we searched in the Cochrane Controlled Register of Trials (CENTRAL), sources dedicated to grey literature (Open Grey, OSFPreprints, GreyLit and Google Scholar) and relevant open access repositories (Open DOAR) until July 2020.

Additionally, references of included studies, prior systematic reviews and meta-analyses and studies citing included studies were screened for eligible articles. Authors who have published in this field were contacted for articles that may have been missed or are unpublished.

2.2 Eligibility

To be eligible, studies had to be observational (i.e., cohort, case–control, case-crossover or self-controlled cohort studies) and conducted in humans without restrictions regarding demographics (i.e., age and sex) or setting (i.e., both population-based studies and studies including persons hospitalized or residents of nursing homes or other types of long-term care facility). They had to evaluate exposure to the anticholinergic burden through a scale (either previously published or newly developed) or cumulative exposure to MACs. Of note, studies evaluating exposure to one or more individual MACs were excluded.

Moreover, studies were eligible either if they addressed the outcome fractures without restriction to a defined site (that is, fractures of any site, e.g., of the hip, of the hip and the femur, of the wrist) or to a defined type (that is, any fractures for whichever reason, e.g., fall-related, fragility-related) or if they addressed the outcome osteoporosis or reduced BMD. A crude or adjusted measure of association between the exposure and the outcome (i.e., relative risk, odds ratio (OR), hazard ratio (HR) or rate ratio), and the corresponding 95% confidence interval (CI), or sufficient data for its calculation had to be reported. Neither time or language restrictions nor restrictions related to type of data (e.g., primary data or secondary data) were applied. Conference abstracts were not considered in the full-text analysis.

2.3 Selection, data extraction and risk of bias assessment

Eligibility assessment of titles, abstracts and full-text articles as well as data extraction were performed independently by two reviewers (OR and JR). Discrepancies were solved by consensus. In case consensus could not be reached, an expert researcher (FEP) resolved the discrepancy.

The risk of bias for each included study was assessed using two quality assessment tools: the Newcastle–Ottawa Quality Assessment Scale (NOS) [27] and the RTI item bank [28]. We chose to use both quality assessment tools since the NOS provides a concise evaluation of study quality and is widely used, and the RTI item bank provides a detailed evaluation of aspects of the studies that are specifically relevant for studies addressing exposure to medications. Each included study was independently assessed by each reviewer (OR and JR) using both tools. For each item of each tool, disagreement between the ratings of reviewers was solved by consensus. Again, if consensus could not be reached, an expert researcher (FEP) resolved the discrepancy.

2.4 Deviations from protocol

Due to the heterogeneity among the included studies and the low number of included studies overall we decided not to conduct quantitative assessment and to do a qualitative assessment instead.

3 Results

3.1 Study selection

For anticholinergic burden and fractures 1100 articles were identified, leaving 978 potentially eligible articles after duplicates had been removed. Eligibility was assessed based on title and abstract, leading to the exclusion of 929 articles (Fig. 1). Of the 49 articles eligible for full-text assessment, 40 were excluded, as they did not use an anticholinergic burden scale ($N=17$), did not assess fractures as an outcome ($N=10$), did not report a measure of association ($N=4$), or were only published as conference abstracts ($N=9$). Nine studies fulfilled all eligibility criteria and were included into the systematic review, corresponding to six cohort [14–16, 29–31] and three case–control studies [13, 32, 33].

We identified a total of 621 articles on the association between anticholinergic burden and osteoporosis or reduced BMD, leaving 590 articles after removal of duplicates. After screening of title and abstract, 587 were excluded and 3 articles were included into full-text review. One article was excluded as it was only published as a conference abstract. Two full-text articles fulfilled the eligibility criteria and were included in the systematic review [21, 30].

3.2 Anticholinergic burden and fractures

3.2.1 Study population and data source

The characteristics of the included studies are shown in Table 1. The studies included a total of 610,862 persons, 74% ($N=452,659$) of which were women [13–16, 29–33]. Sample sizes ranged from 601 [32] to 202,260 persons [13]. The study population was mainly drawn from North America ($N=363,723$; 60%) [13, 29–31] and East Asia ($N=175,686$; 29%) [14, 16, 32]. The remaining two studies included persons from New Zealand [15] and Colombia [33]. Three studies evaluated persons treated with MACs during the 2010s [15, 32, 33], four studies during the 2000s [13, 14, 16, 29] and two studies during the 1990s [30, 31].

Study participants were mostly older adults. Five studies included persons aged ≥ 65 years [13–16, 32], one study included persons aged ≥ 60 years [33] and another one persons aged ≥ 50 years [30]. One study was restricted to women between 50 and 79 years [31] and one study included persons with Parkinson's disease aged ≥ 40 years [29]. The study population was directly drawn from the general population in three studies [14, 16, 33], while three other studies were conducted in cohorts of community dwelling persons [15, 30, 31]. Two studies included only hospitalized patients [29, 32] and another one only nursing home residents [13].

Most studies were based on electronic claims or other administrative data and used prescription or dispensation records to assess the exposure to anticholinergic burden [13, 14, 16, 29, 33]. Two studies were based on primary data and used self-reported use of MACs for exposure assessment [30, 31]. The study of Jamieson et al. [15] was based on both primary and administrative data but used records from a national prescription register for exposure assessment. Kose et al. [32] used inpatient medical records for exposure assessment.

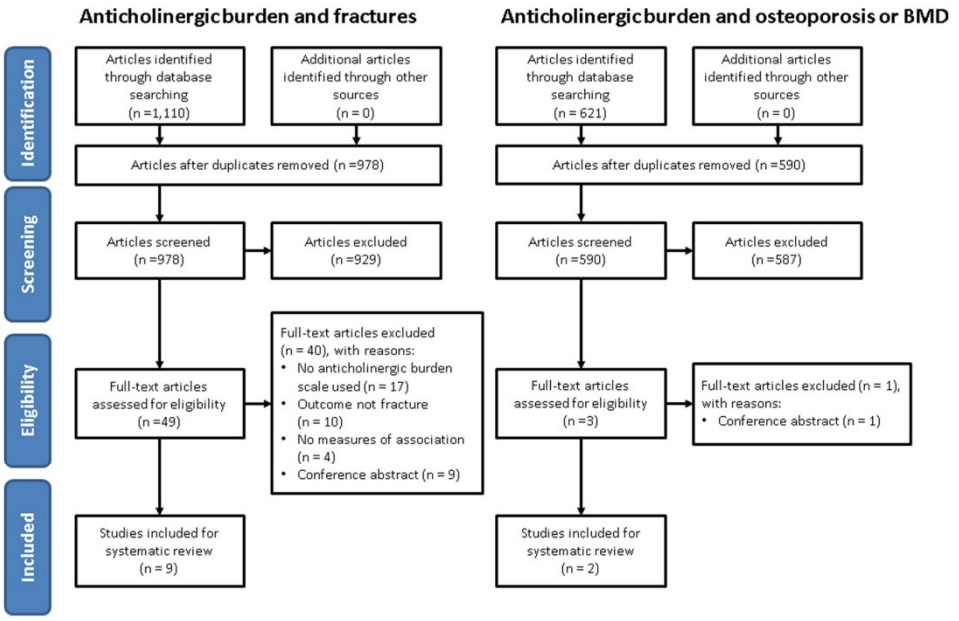


Fig. 1 PRISMA flow diagram of literature search and selection process for the association between anticholinergic burden and fractures and anticholinergic burden and osteoporosis or reduced bone mineral density

3.2.2 Assessment of Exposure

The most common tool to measure the exposure was the Anticholinergic Risk Scale (ARS), applied in four studies exclusively [16, 29, 32, 33]; Marcum et al. [31] used the Anticholinergic Drug Scale (ADS) and Jamieson et al. [15] used the Drug Burden Index (DBI) [34]. Two studies used more than one scale: the ARS, Anticholinergic Cognitive Burden (ACB) scale and the DBI [14] and the ADS and ACB scale [13]. Finally, Fraser et al. [30] developed a specific tool including the medications with score 2 and 3 from the ARS and those with high anticholinergic effects listed by Ancelin et al. [35].

In four studies, exposure was based on assessment of anticholinergic burden either at baseline or at multiple time points during follow-up. In the study of Crispo et al. [29], anticholinergic burden was assessed using the Anticholinergic Risk Scale (ARS) [36] based on all medication prescribed at the baseline hospital encounter. Fraser et al. [30] assessed exposure to MACs at baseline and at visits after 5 and 10 years. A last-value-carried-forward approach was used and exposure to MACs was assumed to be continuous between visits [30]. Kose et al. [32] evaluated change in ARS scores between hospital admission and discharge and occurrence of hip fracture. Marcum et al. [31] assessed self-reported exposure to MACs during the past two weeks, at baseline and after three years using the Anticholinergic Drug Scale (ADS) [37].

Two studies assessed exposure to MACs during a defined assessment period of 30 days before the occurrence of the outcome among cases and corresponding date controls [13, 33]. Within this assessment period, Chatterjee et al. [13] assessed whether a patient was exposed to at least one level 2 or 3 medication from the ADS. They also conducted sensitivity analyses extending the assessment period to 60 and 90 days and applied the Anticholinergic Cognitive Burden (ACB) scale [38] as a second exposure measurement tool. Conversely, Machado-Duque et al. [33] summed up ARS scores of all prescribed MACs.

The exposure was assessed longitudinally in three studies. In two, cumulative anticholinergic burden scores for each study participant were calculated on a quarterly [16] or monthly [14] basis during the up to 10-year follow-up periods. Jamieson et al. [15] calculated participant's cumulative anticholinergic burden on a 90-days interval basis, during the up to three-year long follow-up period.

Exposure categories were defined differently across the included studies: While Fraser et al. [30] and Marcum et al. [31] defined exposure simply as use of at least one MAC, levels of anticholinergic burden were distinguished in the

Table 1 Characteristics of included studies

Study	Country	Data source and study period	Study population	Number of included persons	Measurement of anticholinergic burden	Baseline prevalence of anticholinergic burden	Outcome	Results
Anticholinergic burden and fractures								
Cohort studies								
Fraser et al. [30]	Canada	Primary data (1995–1997)	≥ 50 years, community dwelling	7753 persons, 1189 cases 5566 women 2187 men	Medication with score 2 or 3 from ARS and Medication with high anticholinergic effects described in Ancelin et al	8%	Any fractures	aHR = 0.99 (0.79—1.24)
Lu et al. [16]	Taiwan	Claims data (2002–2011)	(General population) ≥ 65 years, without chronic disease	59,042 persons, 8220 cases 28,838 women 30,204 men	ARS	13%	Any fractures	ARS: 1–2: aOR 1.39 (1.31–1.48) ARS: ≥ 3: aOR 1.53 (1.41–1.66)
Marcum et al. [31]	USA	Primary data (Woman's health initiative) (1993–1998)	Community dwelling women 50–79 years	137,408 persons, 14,702 cases 137,408 women 0 men	ADS (with revised medication list)	11%	Hip, lower arm/wrist and total fractures	Hip fracture a HR 1.08 (0.89–1.30) Lower arm/wrist aHR 1.01 (0.91–1.13) Total fracture a HR 1.03 (0.98–1.09)
Crispo et al. [29]	USA	Electronic medical records (2000–2011)	Hospitalized persons ≥ 40 years with Parkinson's or paralysis agitans	16,302 persons, 1452 cases 7730 women 8572 men	ARS	85%	Any fractures	ARS 1: aOR 1.15 (0.95–1.39) ARS 2–3: aOR 1.17 (0.97–1.42) ARS 4+: aOR 1.56 (1.29–1.88)

Table 1 (continued)

Study	Country	Data source and study period	Study population	Number of included persons	Measurement of anticholinergic burden	Baseline prevalence of anticholinergic burden	Outcome	Results
Hsu et al. [14]	Taiwan	Claims data (2002–2011)	(General population) ≥ 65 years, without chronic disease	116,043 persons, 19,267 cases 57,523 women 58,520 men	ARS, ACB and DBI-Ach	ARS: 37% ACB: 60% DBI-Ach: 37%	Any fractures	Aged 65–74 ARS 1: aOR 1.61 (1.47–1.76) ARS 2: aOR 1.64 (1.48–1.81) ARS 3: aOR 1.64 (1.49–1.81) ARS4 + : aOR 1.96 (1.72–2.23) Aged 75–84 ARS1: aOR 1.49 (1.33–1.66) ARS2: aOR 1.56 (1.37–1.79) ARS3: aOR 1.64 (1.43–1.87) ARS 4 + : aOR 1.73 (1.44–2.07) Aged ≥ 85 ARS 1: aOR 1.02 (0.75–1.39) ARS 2: aOR 0.99 (0.63–1.55) ARS 3: aOR 1.19 (0.79–1.78) ARS4 + : aOR 1.65 (1.03–2.66) Aged 65–74 ACB 1: aOR 1.10 (1.02–1.18) ACB 2: aOR 1.13 (1.04–1.23) ACB 3: aOR 1.34 (1.23–1.46) ACB 4 + : aOR 1.71 (1.57–1.86) Aged 75–84 ACB 1: aOR 1.17 (1.07–1.28) ACB 2: aOR 1.18 (1.05–1.31) ACB 3: aOR 1.37 (1.22–1.54) ACB 4 + : aOR 1.62 (1.45–1.82) Aged ≥ 85 ACB 1: aOR 1.00 (0.84–1.20) ACB 2: aOR 1.18 (0.94–1.48) ACB 3: aOR 1.28 (0.98–1.67) ACB 4 + : aOR 1.18 (0.89–1.58) Aged 65–74 DBI 0 < score ≤ 0.5: aOR 1.45 (1.38–1.53) DBI 0.5 < score ≤ 1: aOR 1.67 (1.52–1.84) Aged 75–84 DBI 0 < score ≤ 0.5: aOR 1.43 (1.34–1.52) DBI 0.5 < score ≤ 1: aOR 1.48 (1.30–1.68) Aged ≥ 85 DBI 0 < score ≤ 0.5: aOR 1.13 (0.94–1.37) DBI 0.5 < score ≤ 1: aOR 1.60 (1.15–2.23)

Table 1 (continued)

Study	Country	Data source and study period	Study population	Number of included persons	Measurement of anticholinergic burden	Baseline prevalence of anticholinergic burden	Outcome	Results
Jamieson et al. [15]	New Zealand	Primary and claims data (2012–2015)	Community dwelling persons ≥ 65 years	70,553 persons, 2249 cases 43,048 women* 27,501 men*	DBI	57%	Hip fractures	DBI 0 <—≤ 1 aSHR 1.12 (1.01–1.24) DBI 1 <—≤ 3 aSHR 1.32 (1.18–1.47) DBI > 3 aSHR 1.52 (1.28–1.81)
Case–control studies								
Chatterjee et al. [13]	USA	Medicare Minimum Data Set (2008–2010)	≥ 65 years, nursing home resident with depression, no fall or fracture in 2007	202,260 persons (40,452 cases, 161,808 controls) 171,513 women 30,747 men	ADS and ACB score	66% of cases, 62% of controls	Hip or femur fractures	ADS 2: aOR 1.15 (1.11–1.19) ADS 3: aOr 1.10 (1.07–1.15) ADS 2/3: aOR 1.14 (1.11–1.17
Kose et al. [32]	Japan	Primary data (2010–2016)	Hospitalized persons ≥ 65 years, no steroid therapy or history of osteoporosis or fracture	601 persons (68 cases, 533 controls) 391 women 210 men	ARS	9%	Hip fractures	ARS change 0: OR = 1.0 (reference) ARS change + 1: OR = 1.57 (0.68–3.33) ARS change + 2: OR = 2.86 (0.94–6.85) ARS change ≥ 3: OR = 4.21 (2.81–7.56)
Machado-Duque et al. [33]	Colombia	Claims data (Pharmacy dispensing data) (2015)	(General population) ≥ 60 years	900 persons (300 cases, 600 controls) 642 women 258 men	ARS	62%	Hip fractures	ARS 0: aOR 1.0 (ref.) ARS 1: aOR 1.08 (95% CI: 0.7–1.6) ARS 2: aOR 1.97 (95% CI: 1.19–3.27) ARS ≥ 3: aOR 1.84 (95% CI: 1.13–2.97)
Anticholinergic burden and osteoporosis or reduced BMD								
Cohort studies								
Ablett et al. [21]	UK	Primary data (Baseline 1990–1993; follow up 1997–2000)	Women aged 45–54 (at baseline)	3883 women	ACB	15%	Lowest quintile total hip, trochanter, neck of femur, Ward's triangle or lumbar spine BMD	Lowest 20% of Ward's triangle BMD ACB ≥ 1 aOR 2.56 (95% CI 1.25–5.23)

Table 1 (continued)

Study	Country	Data source and study period	Study population	Number of included persons	Measurement of anticholinergic burden	Baseline prevalence of anticholinergic burden	Outcome	Results
Fraser et al. [30]	Canada	Primary data (1995–1997)	≥ 50 years, community dwelling	7753 persons, 1189 cases 5566 women 2187 men	Medication with score 2 or 3 from ARS and Medication with high anticholinergic effects described in Ancelin et al	8%	Mean change in BMD T-score at the femoral neck	Mean [SD] = −0.60 [0.63] vs −0.49 [0.45]; P = 0.086

MAC Medication with anticholinergic activity, *ARS* Anticholinergic Risk Scale, *ADS* Anticholinergic Drug Scale, *ACB* Anticholinergic Cognitive Burden (Scale), *DBI-Ach* Drug Burden Index; Anticholinergic component, *BMD* Bone Mineral Density

studies of Lu et al. (ARS 1–2, ≥ 3) [16], Crispo et al. (ARS 1, 2–3, ≥ 4) [29], Hsu et al. (ARS/ACB 1, 2, 3, ≥ 4; DBI 0 <—≤ 0.5, 0.5 <—≤ 1) [14], Chatterjee et al. (ADS 2, 3 2/3) [13] and Machado-Duque et al. (ARS 1, 2, ≥ 3) [33]. Exposure in the study of Kose et al. was categorized as change of anticholinergic burden of ARS 1, 2 and ≥ 3 [32].

Reference category in eight studies was either non-use of MACs or no anticholinergic burden [13–16, 29–31, 33]. One study used no change in anticholinergic burden during hospitalization as reference category [32]. None of the studies used a new-user design or applied criteria to prevent the inclusion of prevalent users of MACs.

3.2.3 Assessment of outcome

The most commonly assessed outcome was any fracture (4 studies) [14, 16, 29, 30], followed by hip fracture (3 studies) [15, 32, 33], hip/femur fracture (1 study) [13] as well as hip, lower arm/wrist and total fracture (1 study) [31]. The outcome was mostly assessed based on secondary data, that is, diagnostic codes recorded in databases (6 studies) [13–16, 29, 33], hospital medical records (1 study) [32] or self-reports of fractures adjudicated through medical or radiology records (2 studies) [30, 31]. Three studies excluded patients who had a prior history of fall or fracture [13, 31, 32] and six studies did not [14–16, 29, 30, 33].

3.2.4 Baseline prevalence of anticholinergic burden

Baseline prevalence of use of MACs ranged from 8% [30] to 85% [29]. With the exception of Lu et al. [16], baseline use of MACs was lower in studies that were based on primary data [30–32] compared to studies that were based on administrative and/or claims data [13–15, 29, 33].

Association between anticholinergic burden and fractures.

All nine studies reported adjusted risks [13–16, 29–33], including known risk factors for fractures. Of these, three studies adjusted for time-varying covariates [14, 15, 32] but one study adjusted only for age and time-varying according to the Charlson Comorbidity Index [14].

Seven studies reported increased risk of fractures associated with anticholinergic burden [13–16, 29, 32, 33], while two studies did not find an association if factors related to health status and risk factors for fractures were adjusted for [30, 31]. Four studies using the ARS showed a dose-exposure gradient [14, 16, 29, 33] (Fig. 2). In these studies, adjusted risk estimates in the exposure categories of ARS 1 were associated with 2–61% increased risk (compared with ARS = 0) for the respective outcomes [14, 16, 29, 33]. Furthermore, ARS 1–2 was associated with increased risk of 39%, ARS 2 with risks of 0–97%, ARS 2–3 with risks of 17%, ARS 3 with risks of 19–84% and ARS ≥ 4 with risks of 56–96% [14, 16, 29, 33].

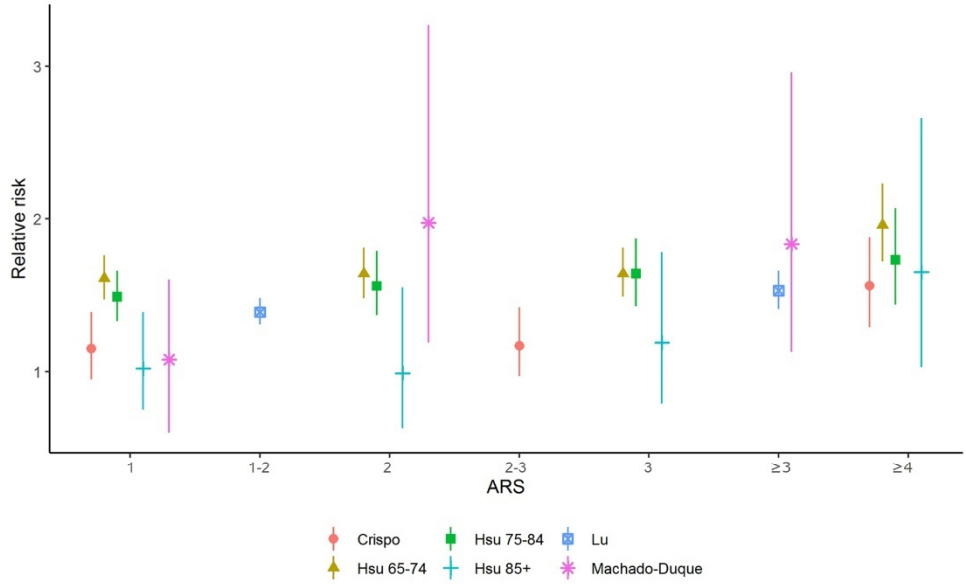


Fig. 2 Results of subset of studies that use the anticholinergic risk scale (ARS) for the assessment of the association between anticholinergic burden and fractures

3.2.5 Risk of bias assessment

Based on the Newcastle–Ottawa scale, the risk of bias was lowest in Jamieson et al. [15], followed by Lu et al. [16] and Chatterjee et al. [13], while it was highest in Machado-Duque et al. [33] (Table 2). Intermediate risk of bias was found in Hsu et al. [14], Fraser et al. [30], Marcum et al. [31] and Kose et al. [32].

Risk of bias assessments based on the RTI Item Bank showed that the majority of studies had a low risk of bias (Table 3): The risk of bias was low in 88–92% of the items for four studies [13–16] and in 58–71% of the items for another four studies [29, 31–33]. Fraser et al. [30] had a low risk of bias in only 25% of the items. Items 6 "Do the confidence intervals suggest lack of precision?" and 27 "Is the impact of unmeasured confounding important enough to affect the believability of results?" were the items most frequently rated as high risk of bias in the RTI Item Bank (five [15, 29, 30, 32, 33] and four studies, respectively [29, 30, 32, 33]). Item 7 "What is the level of detail in describing the intervention or exposure?" was most frequently rated as unclear risk of bias (five studies [13, 30–33]).

3.3 Anticholinergic burden and osteoporosis or reduced bone mineral density

The study of Ablett et al. [21], assessed the association between reduced BMD (through dual-energy X-ray absorptiometry) and the anticholinergic burden (ACB scale, based on self-reported use of MACs) among 3,883 UK women aged 45–54 years who participated in the Aberdeen Prospective Osteoporosis Study between 1997 and 2000. In total, 590 (15.2%) women used at least one MAC. Having adjusted for comorbidities (including age), women with ACB score of ≥ 2 had about three times the risk of having reduced BMD in the lowest quintile BMD at Ward's triangle [OR 2.81 (95% CI 1.16–6.79)], compared with women with ACB = 0, but not at other skeletal sites, such as hip, femur, trochanter or spine.

In addition to the association between anticholinergic burden and falls and fractures, Fraser et al. [30] also assessed change in BMD T-score at the femoral neck for a subgroup of $n = 194$ participants who reported being treated with MACs at study baseline and at the second assessment five years later. Change of BMD T-score was compared between baseline and the second assessment 10 years later using an independent t test. After adjustment for variables associated with BMD there was no significant association between use of MAC and change in BMD.

Both studies were rated as having an intermediate risk of bias based on the Newcastle–Ottawa scale; Ablett et al. had a low risk of bias in 81% and Fraser et al. in 80% of the items according to RTI Item Bank.

Table 2 Risk of bias in the included studies according to Newcastle–Ottawa risk assessment scale

Cohort studies	Selection[a]	Comparability[b]	Outcome[c]
Anticholinergic burden and fractures			
Crispo et al. [29]	3/4	1/1	2/3
Fraser et al. [30]	3/4	0/1	2/3
Hsu et al. [14]	4/4	0/1	2/3
Jamieson et al. [15]	4/4	1/1	3/3
Lu et al. [16]	3/4	1/1	3/3
Marcum et al. [31]	2/4	1/1	2/3
Case–Control studies	Selection[a]	Comparability[b]	Exposure[c]
Anticholinergic burden and fractures			
Chatterjee et al. [13]	3/4	1/1	3/3
Kose et al.[32]	3/4	0/1	2/3
Machado-Duque et al. [33]	2/4	0/1	3/3
Cohort Studies	Selection[a]	Comparability[b]	Outcome[c]
Anticholinergic burden and osteoporosis or BMD			
Ablett et al. [21]	3/4	1/1	2/3
Fraser et al. [30]	3/4	1/1	1/3

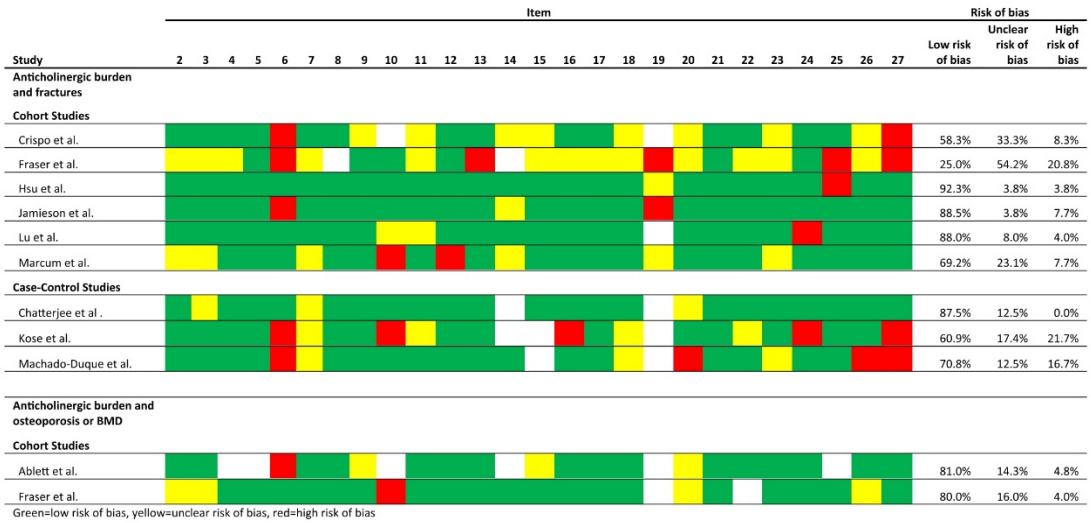
A lower score represents a higher risk of bias

[a]A maximum rating of four can be given for the category "selection"

[b]A maximum rating of one can be given for the category "comparability"

[c]A maximum rating of three can be given for the categories "outcome" and "exposure"

Table 3 Risk of bias in the included studies according to RTI Item bank



4 Discussion

In this first systematic review of studies assessing the risk of fractures associated with anticholinergic burden, seven out of the nine included studies found a positive association. Four studies that used the ARS showed a dose–response relationship. We also looked at studies that focused on osteoporosis or reduced BMD as an outcome. One of the two included studies reported an association of anticholinergic burden with lower BMD at Ward's triangle, but not at other

skeletal sites [21]. The other study did not find an association between use of MAC and change of BMD T-score at femoral neck [30].

In the included studies that assessed the risk of fractures associated with anticholinergic burden, the increased risk was consistent despite the large heterogeneity in terms of population and study design. Increased risks of fractures were reported in different geographical regions (e.g., North America [13, 29] and East Asia [14, 16, 32]); in the general population [14, 16, 33] as well as in nursing home residents [13], community dwellers [15] and hospitalized persons [29, 32]; in studies with longitudinal [14–16] and baseline assessment of anticholinergic burden [13, 29, 32, 33]. Interestingly, the studies that did not find an association between anticholinergic burden and fractures were studies that were based on primary data, assessed anticholinergic burden based on self-reported use of MACs and whose patients were recruited during the 1990s [30, 31].

The included studies differed in regards to the methods used to assess the anticholinergic burden: (i) four different anticholinergic burden scales were used (ARS, ADS, ACB, DBI) and among the five studies that used the ARS scale for the assessment of anticholinergic burden different definitions for MACs were used; (ii) not all studies distinguished between different levels of anticholinergic burden in their exposure assessments, which made dose response assessment difficult (iii) among the studies that used the ARS and distinguished between levels of anticholinergic burden, exposure assessment and categorization of the ARS into exposure categories differed considerably. For example, in their highest exposure category, Fraser et al. [30] included medication with ARS score 2 and 3 and medication with high anticholinergic effects defined by Ancelin et al. [35]. In contrast, the other four studies used the list of MACs from Rudolph et al. [36]. Finally, (iv) exposure assessment was not uniform across studies: Kose et al. [32] defined exposure as the magnitude of change in anticholinergic burden, whereas the other studies that used the ARS measured anticholinergic burden at certain points in time or within time frames.

To our knowledge, this is the first systematic review investigating the association between anticholinergic burden and fractures. Our findings are consistent with some, but not all, systematic reviews on the association between anticholinergic burden and falls [12, 39, 40]. The pathway from falls to fractures is plausible as falls are the main cause of fractures, particularly among older adults [41]. Welsh et al. [12] and Cardwell et al. [11] reported that the majority of studies consistently found an increased risk of falls associated with anticholinergic burden. However, Ruxton et al. [40] concluded that only some MACs (olanzapine and trazodone) were associated with an increased risk of falls while others (amitriptyline, paroxetine and risperidone) were not. In their narrative review, Collamati et al. [39] reported inconclusive evidence regarding increased risk of falls associated with anticholinergic burden.

Strengths of this systematic review include the search for eligible studies in the most relevant literature databases using a comprehensive and reproducible search strategy. Additionally, references of included studies, studies citing included studies as well as grey literature were searched. Evaluation of potentially eligible studies, data extraction as well as the risk of bias assessment were performed by two independent investigators. The review was performed according to the relevant guidelines [23–25] and the protocol was first registered in PROSPERO and subsequently published in an open access journal [26].

Limitations of this systematic review include the low number of included studies. We could not quantitatively summarize the risk across the included studies because of their high heterogeneity in particular due to differences in methods for the assessment of anticholinergic burden, specifically the use of different scales and individual modifications to the scale's lists of MACs. We also could not summarize the results of the subgroup of studies that used the ARS due to different definitions of exposure categories across these studies. Moreover, as prior studies showed only a low concordance between the scales for the assessment of anticholinergic burden [42, 43], we chose not to combine studies in which anticholinergic burden was assessed using different scales. Since none of the included studies used a new user design, the inclusion of prevalent users of MACs may have contributed to depletion of susceptible which may have led to an under ascertainment of fractures occurring early after start of treatment with MACs [44]. Moreover, only three studies used a longitudinal design. Most studies were either conducted in North America or East Asia and two studies were based on data that was collected in the 1990s. Evidence for Europe and other geographical regions is thus lacking.

This systematic review suggests an increased risk of fractures associated with anticholinergic burden and a dose response relationship in studies using the ARS. Physicians should be careful when prescribing MACs and consider all other medications the patient is taking in this regard. Furthermore, medication regimen with potential risk for high anticholinergic burden should be revised and substitutes without anticholinergic activity should be prescribed. If treatment with MACs is necessary, patients should be advised of adverse events including falls and fractures and be closely monitored.

The mixed methodological quality of included studies calls for the conduct of more studies with longitudinal assessment of anticholinergic burden or new user design. Standardization of the method for the assessment of anticholinergic burden would greatly improve the comparability of

studies as meta-analysis in this systematic review was not possible due to the differences in use of scales for the assessment and classification of anticholinergic burden. Furthermore, the lack of studies from other geographical areas such as Europe, Africa and South America calls for the conduct of studies in these regions.

We could only include two studies that investigated the association between anticholinergic burden and the risk of osteoporosis or reduced BMD. Therefore, more studies are needed on this outcome before a conclusion can be made.

Declarations

This systematic review was conducted in accordance with the PRISMA and MOOSE guidelines as well as a guideline for the conduct of systematic reviews and meta-analyses in older adults by Shenkin et al.

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Consent for publication All authors consented to the publication of this study.

Author contributions JR: Study design, conduct of study, bibliographic research, design of data entry forms, article evaluation and selection, data management, manuscript writing and review. WS: Study design, manuscript review. LC: Bibliographic research design and conduct, manuscript review. FBA: Study design, statistical analysis, scientific guidance/advice, manuscript writing and review. OR: Study conception and design, scientific coordination, article evaluation and selection, manuscript review. FEP: Study conception and design, scientific coordination, article evaluation and selection, manuscript writing and review. All authors contributed to and have approved the final manuscript.

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12.5 P2: Anticholinergic burden: first comprehensive analysis using claims data shows large variation by age and sex

PLOS ONE

RESEARCH ARTICLE

Anticholinergic burden: First comprehensive analysis using claims data shows large variation by age and sex

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Abstract

Purpose

The cumulative effect of medication inhibiting acetylcholine activity—also known as anticholinergic burden (AB)—can lead to functional and cognitive decline, falls, and death. Given that studies on the population prevalence of AB are rare, we aimed to describe it in a large and unselected population sample.

Methods

Using the German Pharmacoepidemiological Research Database (GePaRD) with claims data from ~20% of the German population we analyzed outpatient drug dispensations in 2016. Based on the Anticholinergic Cognitive Burden (ACB) scale, we classified persons into four categories and determined the cumulative AB as continuous variable.

Results

Among 16,470,946 persons (54% female), the prevalence of clinically relevant AB (ACB≥3) was 10% (women) and 7% (men). Below age 40 it was highest in persons ≤18 years (6% both sexes). At older ages (50–59 vs. 90–99 years), prevalence of ACB≥3 increased from 7% to 26% (men) and from 10% to 32% (women). Medication classes contributing to the cumulative AB differed by age: antihistamines, antibiotics, glucocorticoids (≤19 years), antidepressants (20–49 years), antidepressants, cardiovascular medication, antidiabetics (50–64 years), and additionally medication for urinary incontinence/overactive bladder (≥65 years). Medication dispensed by general physicians contributed most to the cumulative AB.

Conclusion

Although a clinically relevant AB is particularly common in older persons, prevalence in younger age groups was up to 7%. Given the risks associated with AB in older persons, targeted interventions at the prescriber level are needed. Furthermore, risks associated with AB in younger persons should be explored.

Law. Researchers have to apply for a project-specific permit from the statutory health insurance providers which then need an approval from their governing authorities. The use of the data on which this publication is based was only allowed for BIPS employees within the framework of the specified project and limited to a pre-defined time span. Researchers who want to access the data on which this publication is based need to ask for new approval by the statutory health insurance providers DAK-Gesundheit (service@dak.de), die Techniker (service@tk.de), hkk Krankenkasse (info@hkk.de) and AOK Bremen/Bremerhaven (info@hb.aok.de) which upon granting approval would have to ask their respective authorities for approval. Please contact gepard@leibniz-bips.de for help with this process. The authors confirm that they had no special access privileges to the data and that other researchers will be able to access the data in the same manner as the authors by following the instructions described above.

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Introduction

Medications with anticholinergic activity (MACs) inhibit the effect of the neurotransmitter acetylcholine [1]. They are used for the treatment of diseases such as depression, psychosis, cardiovascular diseases, asthma, overactive bladder, and COPD [1]. The cumulative effect of MACs, also called anticholinergic burden (AB), has been shown to be associated with adverse health outcomes such as functional [2, 3] and cognitive decline [2, 4, 5], delirium [6, 7], falls [3, 8], and death [9, 10].

Although the majority of studies on the adverse effects of AB focused on older adults, there are studies suggesting that younger populations might also be affected. In some of those studies, AB was associated with impaired cognitive ability and real-world functioning as well as a negative impact on the outcomes of psychosocial treatment programs in patients with schizophrenia or schizoaffective disorder [11]. Notably, many of the medications contributing to the AB had indications other than psychiatric diseases [11]. Some studies showed impairment of verbal learning and/or verbal memory associated with AB in persons with schizophrenia [12–14] and major depressive disorder [15]. Furthermore, studies have shown an association between AB and delirium in pediatric intensive care patients [16] and critically ill middle-aged adults [17]. These data suggest that already in younger patients, AB might be associated with adverse effects. So far, only a single study has provided a comprehensive overview of the prevalence of AB in all age groups of a population [18]. However, in this study, age categories were defined broadly and AB prevalences were not stratified by sex within age groups.

In our study, we aimed to characterize the prevalence of AB in a large and unselected sample of the German general population and to assess the classes of medication contributing to the total cumulative AB, stratified by age and sex.

Methods

Data source

We used the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. In Germany, about 90% of the general population are covered by statutory health insurance. The health care system is characterized by uniform access to all levels of care and free choice of providers.

In addition to demographic data, GePaRD contains information on outpatient drug dispensations as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. Information on medication includes the anatomical-therapeutic-chemical (ATC) code, the prescription and dispensation date, the specialty of the prescriber as well as the number of defined daily doses (DDDs). Diagnoses are coded according to the German modification of the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM).

Study design and study population

We conducted a cross-sectional study using data from the year 2016, the most recent data at the time of analysis, to assess the prevalence of AB. We included all persons with at least one day of insurance coverage during the observation period, i.e., between 1 January and 31 December 2016 preceded by at least 365 days of continuous insurance (pre-observation

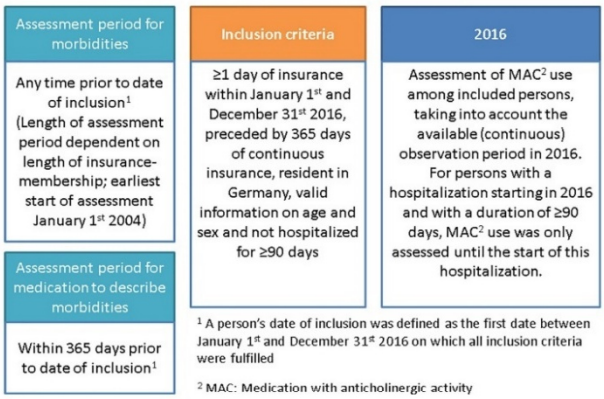

Fig 1. Graphical depiction of study design.

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period). We excluded persons with a place of residence outside of Germany, without valid information on age and sex as well as persons with a hospitalization of ≥90 days, which overlapped into this person's observation period. For all included persons, the available (continuous) observation period in 2016 was used to assess the use of MAC. For persons with a hospitalization starting in 2016 and with a duration of ≥90 days, MAC use was only assessed until the start of this hospitalization (Fig 1).

We identified morbidities and treatment with medication excluding MAC using sensitive identification algorithms: The coding of morbidities was assessed any time prior to observation period (starting from 2004) through records of ≥1 ICD-10-GM inpatient or outpatient diagnoses or records of ≥1 codes of relevant operations, procedures or outpatient services as well as participation in disease management plans. This approach, i.e. taking into account all information on morbidity available for a person before 2016, aims to compensate for the fact that with secondary data, a person cannot be asked if he or she ever had a certain disease, as it would be done in a study based on primary data. Treatment with medication excluding MAC was assessed within 365 days before start of observation period (excluding start of observation period) based on records of ≥1 outpatient dispensations.

Assessment of the anticholinergic burden

Exposure to MAC was assessed based on outpatient prescriptions dispensed during the observation period, i.e., in 2016. Treatment durations were estimated based on DDDs. In case MAC were dispensed before 1 January 2016 and the days of supply covered by this dispensation overlapped with the observation period, the DDDs overlapping with the observation period were also considered. We assumed lower DDDs for persons aged ≤18 and ≥65 years if recommended in the respective Summary of Product Characteristics. Moreover, we identified the specialty of the prescribing physician for each dispensation of MAC. To quantify the AB in individuals, we used a list of relevant MAC and a scoring system proposed by Kiesel et al. [19]. Kiesel et al. systematically reviewed published lists of MAC and corresponding scores, mainly developed in the US, UK or Australia, and adapted them to medications relevant for Germany [19]. Their categorization of AB [19] was based on the Anticholinergic Cognitive Burden (ACB) scale, which was developed by Boustani et al. to identify persons at risk for cognitive

impairment [20]. Based on this scoring system, MACs dispensed during the observation period were scored according to their anticholinergic effects: ACB score 1 (evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor), ACB score 2 (evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect) or ACB score 3 (evidence from literature, expert opinion, or prescriber's information that medication may cause delirium) [20, 21]. Boustani et al. considered dispensation of MAC with an ACB score 2 or 3 as well as a total ACB score of 3 or higher as clinically relevant [20]. For the interpretation of this study, we defined ACB≥3 as clinically relevant and additionally considered ACB categories ACB = 0, ACB = 1, ACB = 2, and ACB≥3 in order to assess borderline AB in the study population. For our study population, the AB was calculated for each person on a daily basis during the observation period by adding up the scores of all dispensed MACs. Prevalence of morbidities, treatment with medication other than MAC, and health care utilization were stratified by the highest category of AB reached during the observation period.

We also calculated a measure which we called "cumulative AB". We calculated this additional measure because it allowed us to assess the proportion of AB attributable to a certain class of MAC (e.g., antidepressants) or to a certain physician specialty. This measure was called "cumulative burden" because it takes into account all dispensations in the observation period (i.e. in 2016). This cumulative AB was calculated as follows for each person: We first multiplied the AB score of each MAC dispensed to the person during the observation period or overlapping the observation period with the length of supply (based on DDD) and then summed up the score points of all dispensations. Subsequently, these AB scores were summed up per person to calculate the cumulative AB. For example, a person receiving 200 DDDs of metformin (ACB score 1) and 30 DDDs of tramadol (ACB score 2) during the observation period had a cumulative AB of 260 (i.e., the result of 200 x 1 + 30 x 2). This method was proposed by Campbell et al. [5]. Campbell et al. further divided the cumulative AB by the number of days in the exposure period to transfer the total AB score into a mean score per person but this additional transformation was not relevant in the context of our study [5].

Data analysis

We calculated the period prevalence of AB for each of the four AB categories for the observation period. The prevalence was calculated as the number of persons in the respective AB category (numerator) divided by the number of included persons (denominator). Again, persons were allocated to the highest level of AB reached during the observation period.

In order to describe which proportion of the cumulative AB was attributable to a certain class of MAC (e.g., antidepressants) or physician specialty (e.g., general practitioners), the cumulative AB of a MAC class or physician specialty of each respective age and sex group was divided by the total cumulative AB in that age and sex group.

Data management and analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics and approvals

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to

the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

Results

The study population included a total of 16,470,946 persons (53.6% female) with a median age of 45 years (Q1–Q3: 26–61 years) (Fig 2).

For the majority of the study population, we observed no AB during the observation period, i.e., ACB = 0 in 68.5% of men and in 61.7% of women (Table 1). Prevalence of ACB = 1 was 17.6% in men and 19.7% in women, for ACB = 2, it was 6.7% in men and 8.2% in women, while a clinically relevant AB (ACB≥3) was observed in 7.2% of men and 10.4% of women (Fig 3).

Both in men and women, the prevalence of ACB≥3 was about 6% in persons aged ≤18 years and thus higher than in persons aged 19–49 years. At older ages, the prevalence of ACB≥3 steadily increased. In men, it increased from 7.2% (50–59 years) to 11.1% (60–69 years) and 17.2% (70–79 years). The same pattern was seen in women but the prevalences were about 3–4 percentage points higher (50–59 years: 10.6%, 60–69 years: 14.8%, 70–79 years: 21.9%).

For all morbidities and medications assessed prior to start of observation period, prevalences increased with increasing ACB score (S1 Table). For example, compared to persons with lower or no ACB, persons with ACB≥3, had higher prevalences of psychiatric and behavioral, musculoskeletal as well as endocrine and metabolic diseases. They were prescribed medications from a higher number of different prescribers and had higher prevalences of cardiovascular therapy, analgesics and psychiatric medication. Moreover, persons with ACB≥3 were, on average, more frequently hospitalized, remained hospitalized for longer periods and had a higher prevalence of nursing home residency and obesity.

Persons with ACB≥3 were more frequently users of antidepressants (45.3% vs. 8.8%), antihistamines (17.7% vs. 7.1%), and antipsychotics (13.9% vs. 1.3%) (Table 2). Individuals who used medications for urinary incontinence/overactive bladder had ACB≥3 by default (13.0%), since all of these medications have an ACB score of 3.

Median total cumulative burden increased with higher age, was highest among the age group 80–94 years, and decreased slightly in age group ≥95 years (Fig 4).

The contribution of the medication classes of MAC to the total cumulative AB differed between age groups (Table 3). In persons aged ≤19 years, antihistamines and antibiotics contributed most—with about 20–24% each—to the cumulative burden, followed by glucocorticoids with about 12–13%. In females, the contribution of antidepressants to the cumulative AB was twice as high as in males (16% vs. 8%). In persons aged 20–64 years, antidepressants

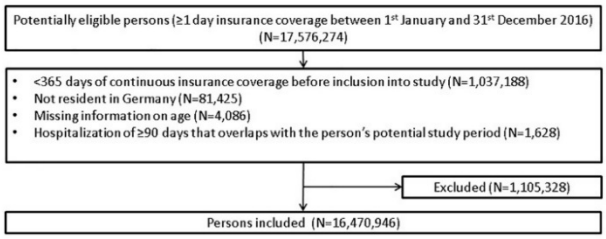

Fig 2. Flow chart illustrating the inclusion and exclusion of persons into the study.

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Table 1. Number and period prevalence of persons with and without anticholinergic burden measured through the Anticholinergic Cognitive Burden (ACB) scale during the observation period (2016), by sex and age.

		ACB score							
	Total	ACB = 0		ACB = 1		ACB = 2		ACB ≥ 3	
Sex	N[a]	N[b]	Prevalence (%)	N[b]	Prevalence (%)	N[b]	Prevalence (%)	N[b]	Prevalence (%)
Men	7,635,507	5,232,064	68.5	1,342,836	17.6	507,767	6.7	552,840	7.2
Age									
≤ 18	1,361,884	1,069,419	78.5	185,882	13.6	30,520	2.2	76,063	5.6
19 to 29	1,128,700	956,617	84.8	121,521	10.8	31,648	2.8	18,914	1.7
30 to 39	1,077,901	862,425	80.0	138,917	12.9	44,353	4.1	32,206	3.0
40 to 49	975,152	715,119	73.3	158,347	16.2	55,720	5.7	45,966	4.7
50 to 59	1,210,955	790,562	65.3	240,566	19.9	92,866	7.7	86,961	7.2
60 to 69	853,986	448,660	52.5	214,327	25.1	96,021	11.2	94,978	11.1
70 to 79	697,604	285,943	41.0	191,496	27.5	100,439	14.4	119,726	17.2
80 to 89	293,902	93,090	31.7	82,108	27.9	49,783	16.9	68,921	23.5
90 to 99	35,049	10,119	28.9	9,557	27.3	6,353	18.1	9,020	25.7
≥ 100	374	110	29.4	115	30.7	64	17.1	85	22.7
Women	8,835,439	5,447,201	61.7	1,741,731	19.7	728,329	8.2	918,178	10.4
Age									
≤ 18	1,286,334	1,017,119	79.1	167,010	13.0	28,592	2.2	73,613	5.7
19 to 29	1,120,182	867,427	77.4	175,136	15.6	47,879	4.3	29,740	2.7
30 to 39	1,154,740	850,292	73.6	194,824	16.9	62,185	5.4	47,439	4.1
40 to 49	1,214,399	804,947	66.3	236,844	19.5	87,472	7.2	85,136	7.0
50 to 59	1,516,942	888,755	58.6	329,169	21.7	138,788	9.1	160,230	10.6
60 to 69	1,086,934	531,914	48.9	264,899	24.4	128,807	11.9	161,314	14.8
70 to 79	923,303	344,264	37.3	238,524	25.8	138,632	15.0	201,883	21.9
80 to 89	429,269	117,652	27.4	109,445	25.5	76,061	17.7	126,111	29.4
90 to 99	100,998	24,229	24.0	25,221	25.0	19,451	19.3	32,097	31.8
≥ 100	2,338	602	25.7	659	28.2	462	19.8	615	26.3

[a] Denominator of the prevalence are persons insured for ≥1 day within the observation period and with ≥1 year continuous insurance before.

[b] Numerator of the prevalence, calculated as the number of persons with ACB = 0, ACB = 1, ACB = 2, and ACB ≥ 3, respectively. Persons will be allocated in the highest level of the ACB score ever reached during the observation period.

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contributed most to the cumulative AB, with proportions ranging between 25% in men aged 50–64 years to 48% in women aged 20–34 years. From age group 65–79 onwards, cardiovascular medication contributed to 24–26% of the AB in men and 21–23% in women. The proportion of diuretics increased particularly from age group 65–79 onwards and contributed to 6–19% of the cumulative AB in men and 6–17% in women. Also, the contribution of medication for urinary incontinence or overactive bladder increased with higher age to up to 14% (men aged 80–94 years). The contribution of antidiabetics to the cumulative AB was highest in men aged 50–79 years (17–19%). The contribution of medication for the treatment of respiratory diseases, gastrointestinal medications, and opioids increased slightly in persons aged ≥65 years, while the contribution of glucocorticoids to the AB decreased.

Prescriptions from general practitioners were the main contributors to the cumulative AB (Table 4). The proportion ranged between 40 and 41% in persons aged 20–34 years and increased to over 70% and more in persons aged 65 or older. In the age groups 20–49 years, prescriptions from physicians specializing in psychology and psychiatry contributed to about one fourth of the total cumulative AB. The number of different physician specialties that

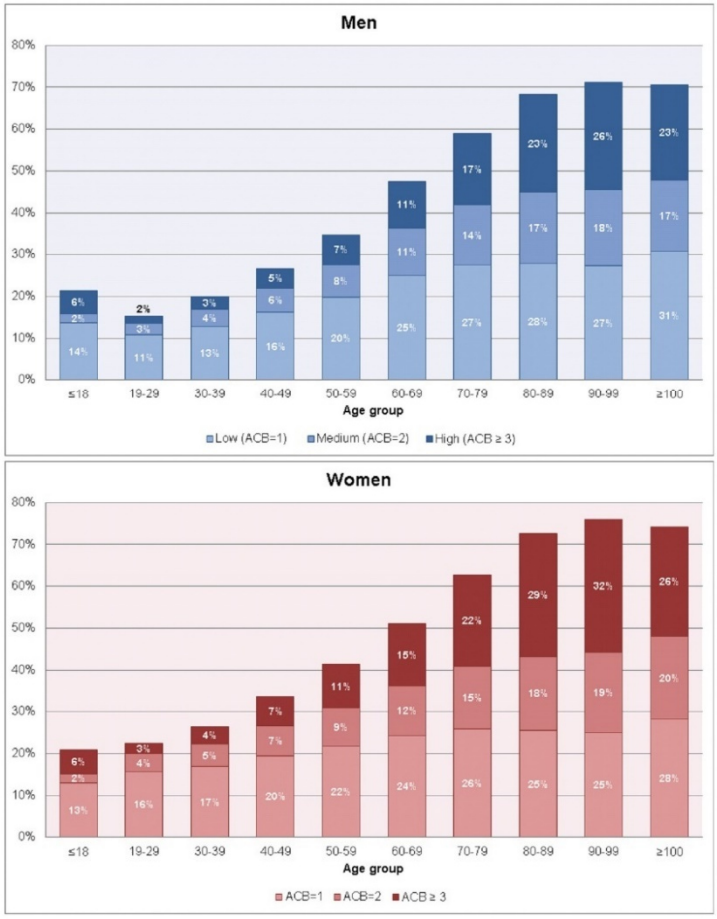

Fig 3. Proportion of anticholinergic burden measured through the Anticholinergic Cognitive Burden (ACB) scale (2016), by sex and age.

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contributed 5% or more to the cumulative AB was five in persons aged ≤19 years, 3–4 in persons aged 20–64 years, and 2–3 in persons aged ≥65 years.

Discussion

In our study, which included an unselected sample of 16 million persons of the German general population, about 7% of men and 10% of women had a clinically relevant AB (ACB≥3) based on prescriptions in 2016. The prevalence of ACB≥3 was higher in women than in men across all age groups and—even though increasing with age—already reached levels of 2–7% (men) and 3–11% (women) in persons younger than 60 years. The classes of medication contributing to the total cumulative AB differed greatly between sex and age groups: While antidepressants had a dominant share in age groups <60 years, their relative proportion decreased

Table 2. Prevalence of use of medications with anticholinergic activity (MACs) in persons with anticholinergic burden measured through the anticholinergic cognitive burden (ACB) scale during the observation period (2016).

	ACB score[a]		
MAC class	ACB = 1	ACB = 2	ACB ≥ 3
	N = 3,084,567[b]	N = 1,236,096[b]	N = 1,471,018[b]
Antidepressants	271,776 (8.8%)	272,488 (22.0%)	665,675 (45.3%)
Antihistamines	218,228 (7.1%)	63,216 (5.1%)	260,137 (17.7%)
Antipsychotics	40,943 (1.3%)	66,412 (5.4%)	204,098 (13.9%)
Benzodiazepines	66,391 (2.2%)	54,438 (4.4%)	143,152 (9.7%)
Cardiovascular medication	487,324 (15.8%)	276,345 (22.4%)	343,257 (23.3%)
Diuretics	58,088 (1.9%)	63,387 (5.1%)	111,202 (7.6%)
Gastrointestinal medication	8,208 (0.3%)	47,898 (3.9%)	90,185 (6.1%)
Opioids	200,374 (6.5%)	170,598 (13.8%)	275,654 (18.7%)
Medication for Parkinson's disease	32,517 (1.1%)	31,349 (2.5%)	91,838 (6.2%)
Medication for urinary incontinence/overactive bladder	0 (0.0%)	0 (0.0%)	191,768 (13.0%)
Medication for respiratory diseases	125,958 (4.1%)	85,436 (6.9%)	135,733 (9.2%)
Glucocorticoids	697,422 (22.6%)	332,459 (26.9%)	414,559 (28.2%)
Tropane alkaloids	0 (0.0%)	0 (0.0%)	9,131 (0.6%)
Immunosuppressants	10,696 (0.3%)	11,859 (1.0%)	14,953 (1.0%)
Muscle relaxants	123,733 (4.0%)	44,098 (3.6%)	99,581 (6.8%)
Antiemetics	203,433 (6.6%)	72,146 (5.8%)	133,709 (9.1%)
Antibiotics	444,014 (14.4%)	311,271 (25.2%)	215,548 (14.7%)
Antiepileptics	16,259 (0.5%)	29,071 (2.4%)	58,048 (3.9%)
Non-opioid analgesics	126,367 (4.1%)	68,198 (5.5%)	95,586 (6.5%)
Antidiabetics	233,543 (7.6%)	161,959 (13.1%)	179,913 (12.2%)
Other MAC	41,977 (1.4%)	40,833 (3.3%)	48,087 (3.3%)

[a] Categorization based on the highest level of the ACB score ever reached during the observation period.

[b] Denominator is the number of included persons who had ≥1 dispensation of MAC for ≥1 day during the observation period.

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among persons aged ≥60 years due to the increased prescribing of cardiovascular medication and antidiabetics with anticholinergic activity.

As of now, only one other study has assessed the prevalence of AB without limitations on age or certain patient groups. The study of Cebron Lipovec et al. [18] was based on Slovenian outpatient prescriptions in 2018 and used the ACB scale for the assessment of AB. Results were stratified by the age groups children (≤18 years), adults (19–64 years), and older adults (≥65 years) but not by sex within these groups. The overall prevalence of ACB≥3 in the Slovenian population was 7.6%, similar to our results (7.2% in men and 10.4% in women). Prevalence of use of at least one MAC in Slovenian children was 20.7% which was similar to our study (21.5% in boys and 20.9% in girls). However, prevalence of ACB≥3 was much lower in Slovenian children (1.2% vs. 5.6% in boys and 5.7% in girls). The prevalence of use of at least one MAC among adults in Slovenia was in the lower ranges of the German results (25.8% vs. 15.2%–47.5% in men and 22.6%–62.7% in women). However, the prevalence of ACB≥3 for adults was similar (7.3% vs. 1.7%–11.1% in men and 2.7%–14.8% in women). Interestingly, the prevalence of use of at least one MAC in Slovenian older adults was much lower than in Germany with 43.1% vs. 59.0%–71.1% in men and 62.7%–76.0% in women as was the prevalence of ACB≥3 with 12.1% vs. 17.2%–22.7% in men and 21.9%–26.3% in women. As the list of MACs used in our study is more extensive than the one used by Cebron Lipovec et al. it is not

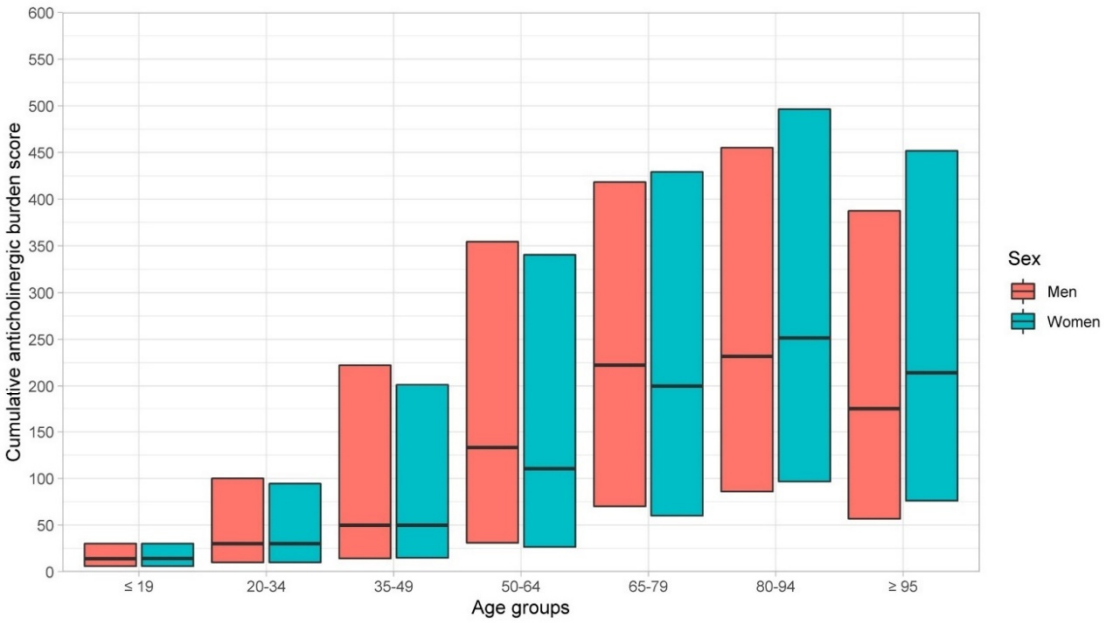

Fig 4. Median (Q1-Q3) cumulative anticholinergic burden, by sex and age.

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clear whether the differences in prevalence of AB are due to the prescription behavior regarding MACs or the definition of MACs. However, the much lower prevalence of ACB≥3 in Slovenian older adults compared to German older adults is notable.

Among studies conducted in Germany, the comparison to our findings is hampered given that they were typically restricted to older adults or patients with a certain indication: Pfistermeister et al. [22] conducted a study in a population of hospitalized geriatric patients (median age 82 years), Ivchenko et al. [23] in older adults with overactive bladder (median age 75 years), Lippert et al. [24] in patients with dementia (mean age 84.7 years), Mayer et al. [25] in community-dwelling older German adults (median age 72 years), Phillips et al. [26] in community-dwelling older adults aged 65 years and older (mean age 73.8), and Mueller et al. [7] in patients undergoing cancer surgery (mean age 71.8 years). In the studies of Pfistermeister et al. [22] and Ivchenko et al. [23], where AB was assessed through ACB scale and categorized in the same way as in our study, the AB was similar, ACB≥3 27% and 25%, respectively, to the results of our study where the prevalence of an ACB≥3 was above 20% from age 70 in women and from age 80 in men. The studies of Lippert et al. [24] and Mayer et al. [25] also used the ACB scale but assessed AB as use of ≥1 MAC. The AB prevalence in their populations, 50% and 46%, respectively, was slightly lower than in our study (59%–71% in men, 63%–76% in women in the age groups 70 to ≥100 years). The studies of Phillips et al. [26] and Mueller et al. [7] reported much lower prevalences of AB, 19% and 16%, respectively, than our study. However, comparisons with the results of our study are difficult as Phillips et al. [26] used the Drug Burden Index (DBI) [27] and Mueller et al. [7] the Anticholinergic Drug Scale (ADS) [28] for the assessment of AB, which use different lists of MACs (e.g., unlike the ACB scale, the DBI does not consider inhaled MAC) and calculate AB differently (the DBI also includes the prescribed

Table 3. Contribution of anticholinergic medication classes to cumulative anticholinergic burden[a] in men and women, with at least one dispensation of medication with anticholinergic activity (MAC) during the observation period (2016), by age group.

	Age group[b]													
	≤ 19		20–34		35–49		50–64		65–79		80–94		≥ 95	
Characteristics	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N = 306,894	N = 288,767	N = 260,776	N = 378,155	N = 372,387	N = 568,948	N = 627,682	N = 913,551	N = 609,698	N = 848,695	N = 221,985	N = 373,292	N = 4,021	N = 16,830
MAC class (%)[c]														
Antidepressants	8.1%	16.3%	38.7%	47.9%	35.9%	45.3%	25.6%	36.1%	11.8%	21.4%	10.3%	19.4%	11.2%	18.9%
Antihistamines	24.0%	20.7%	3.6%	4.4%	2.0%	2.8%	1.2%	1.7%	0.9%	1.2%	1.3%	1.7%	2.7%	2.4%
Antipsychotics	3.9%	3.1%	18.1%	8.3%	14.6%	9.1%	6.4%	6.2%	2.1%	2.8%	1.6%	2.4%	2.4%	3.5%
Benzodiazepines	0.6%	0.6%	1.0%	0.7%	1.0%	0.9%	0.8%	0.9%	0.6%	1.0%	0.8%	1.3%	1.6%	2.3%
Cardiovascular medication	0.9%	0.8%	2.5%	2.4%	7.6%	5.8%	16.5%	12.2%	23.8%	20.8%	25.4%	23.3%	26.0%	22.5%
Diuretics	0.2%	0.2%	0.3%	0.4%	1.1%	1.3%	2.9%	2.7%	5.6%	5.5%	9.8%	9.8%	19.0%	16.7%
Gastrointestinal medication	0.7%	0.9%	1.0%	1.2%	1.5%	1.3%	1.9%	1.7%	2.1%	2.0%	1.9%	1.8%	1.8%	1.6%
Opioids	0.4%	0.5%	2.0%	1.6%	3.1%	2.5%	2.9%	2.8%	2.5%	3.3%	3.0%	5.3%	4.5%	8.2%
Medication for Parkinson's disease	0.2%	0.1%	0.2%	0.3%	0.5%	0.5%	1.4%	1.0%	4.0%	2.5%	5.3%	2.9%	2.1%	1.7%
Medication for urinary incontinence/overactive bladder	8.9%	5.6%	2.8%	3.2%	2.4%	4.0%	3.4%	6.0%	8.9%	10.7%	13.5%	12.5%	12.1%	10.8%
Medication for respiratory diseases	2.9%	2.4%	1.6%	2.3%	2.9%	3.2%	5.0%	4.6%	6.4%	4.9%	6.2%	3.6%	4.9%	2.6%
Glucocorticoids	12.5%	12.3%	9.4%	10.7%	7.5%	8.5%	6.4%	7.1%	6.5%	6.8%	6.3%	5.4%	5.1%	3.6%
Tropane alkaloids	2.0%	1.9%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.1%	0.0%	0.1%	0.0%	0.1%	0.0%
Immunosuppressants	1.4%	1.1%	1.8%	1.3%	1.1%	0.8%	0.6%	0.5%	0.3%	0.3%	0.2%	0.1%	0.1%	0.1%
Muscle relaxants	0.8%	0.7%	1.4%	1.3%	1.4%	1.5%	1.0%	1.1%	0.5%	0.5%	0.3%	0.3%	0.1%	0.2%
Antiemetics	0.8%	1.1%	0.8%	1.1%	0.4%	0.6%	0.3%	0.5%	0.3%	0.5%	0.4%	0.7%	0.6%	0.9%
Antibiotics	20.1%	21.4%	4.6%	5.7%	2.1%	2.2%	1.1%	1.3%	1.1%	1.2%	1.1%	0.9%	1.1%	0.9%
Antiepileptics	9.9%	7.1%	7.0%	3.3%	5.0%	2.7%	2.9%	2.0%	1.5%	1.1%	1.0%	0.7%	0.8%	0.3%
Non-opioid analgesics	0.2%	0.5%	1.1%	1.2%	1.6%	1.8%	1.6%	2.1%	1.1%	1.7%	0.9%	1.3%	0.9%	0.9%
Antidiabetics	0.1%	0.3%	1.1%	1.3%	7.1%	3.4%	16.6%	7.4%	18.6%	10.3%	10.1%	6.0%	2.8%	1.8%

[a] The cumulative anticholinergic burden of a MAC is calculated by multiplying each MAC's anticholinergic cognitive burden (ACB) score by its duration (prescribed number of DDDs).

[b] The total anticholinergic burden per age group is calculated by summing up each person's cumulative anticholinergic burden during the observation period in the respective age group.

[c] Cumulative anticholinergic burden stratified by MAC class.

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Table 4. Contribution of prescriber specialty to cumulative anticholinergic burden[a] in men and women, with at least one dispensation of medication with anticholinergic activity (MAC) during the observation period (2016), by sex and age group.

Characteristics	Age group[b]													
	≤ 19		20–34		35–49		50–64		65–79		80–94		≥ 95	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N = 306,894	N = 288,767	N = 260,776	N = 378,155	N = 372,387	N = 568,948	N = 627,682	N = 913,551	N = 609,698	N = 848,695	N = 221,985	N = 373,292	N = 4,021	N = 16,830
Prescribers of MAC (%)[c]														
General practitioner	58.3%	54.1%	39.2%	41.0%	48.5%	47.0%	63.5%	56.5%	71.2%	68.5%	73.3%	78.2%	85.0%	86.3%
Anesthesiology	0.1%	0.1%	0.3%	0.4%	0.5%	0.8%	0.6%	1.0%	0.3%	0.6%	0.2%	0.3%	0.1%	0.1%
Ophthalmology	5.0%	5.5%	2.3%	2.5%	1.6%	1.5%	1.2%	1.3%	1.9%	2.2%	2.0%	1.6%	1.1%	0.6%
Surgery	0.8%	0.7%	1.0%	1.0%	1.2%	1.4%	1.0%	1.3%	0.6%	0.9%	0.4%	0.5%	0.2%	0.2%
Gynecology	0.0%	0.3%	0.0%	1.1%	0.0%	1.0%	0.0%	1.3%	0.0%	1.8%	0.0%	0.9%	0.0%	0.2%
Otorhinolaryngology	2.0%	1.7%	1.3%	1.4%	0.9%	0.8%	0.5%	0.4%	0.2%	0.2%	0.1%	0.1%	0.0%	0.0%
Dermatology	7.5%	8.7%	2.3%	3.2%	0.9%	1.1%	0.5%	0.6%	0.3%	0.3%	0.3%	0.2%	0.3%	0.3%
Internal medicine	1.6%	1.7%	4.2%	4.5%	4.5%	4.6%	6.1%	5.8%	7.3%	6.1%	5.7%	3.5%	2.5%	1.5%
Pediatrics	5.6%	4.8%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Psychology and psychiatry	5.9%	9.7%	27.7%	26.7%	25.3%	26.0%	15.9%	19.9%	6.8%	9.0%	5.2%	6.0%	2.9%	5.3%
Neurosurgery	0.0%	0.0%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%
Neurology	0.6%	0.9%	5.1%	5.3%	4.8%	5.2%	3.5%	4.0%	3.1%	2.9%	2.8%	2.2%	1.8%	1.6%
Radiology	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%
Physical medicine and rehabilitation	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.1%	0.0%	0.0%
Urology	3.3%	2.1%	1.6%	2.0%	1.5%	2.2%	2.4%	3.0%	6.4%	5.1%	8.7%	4.7%	5.1%	2.1%
Unknown specialty	9.8%	10.1%	15.6%	11.4%	11.1%	9.1%	5.6%	5.7%	2.4%	2.7%	1.6%	1.9%	1.2%	2.0%

[a] The cumulative anticholinergic burden of a MAC is calculated by multiplying each MAC's anticholinergic cognitive burden (ACB) score by its duration (prescribed number of DDDs).

[b] The total anticholinergic burden per age group is calculated by summing up each person's cumulative anticholinergic burden during the observation period in the respective age group.

[c] Cumulative anticholinergic burden stratified by prescribing physician's specialty.

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dose). Furthermore, in the study of Phillips et al. [26], there might have been a selection of healthier patients into the study population as suggested by their non-responder analysis.

Our study provides information on the use of MAC and AB across all age groups. This analysis showed that use of MAC in Germany can roughly be divided into four phases: (i) persons aged ≤19 years with a low cumulative AB mainly due to use of antihistamines, antibiotics, and glucocorticoids; (ii) persons aged 20–49 years with a low but steadily increasing cumulative AB with antidepressants as the main contributor to the cumulative AB; (iii) a transitional phase in persons aged 50–64 where the contribution of cardiovascular medication and antidiabetics starts to increase, which is higher in men than in women; and (iv) persons aged ≥65 years where the relative contribution of antidepressants decreases due to the increased contribution of medication for the treatment of cardiovascular disease, diabetes, and urinary incontinence/overactive bladder. The increased burden of chronic diseases is reflected in the high cumulative AB, which peaks in the age group 80–94 years.

MAC prescribed by general practitioners accounted for 39–86% of the total cumulative AB and thus had the highest share. In health systems with the general physician in the role of gatekeeper, this proportion might be even higher. In Germany, persons are free to choose which physician to see. There is no requirement of a referral from a general practitioner to access specialist care. In our study, there was an age gradient regarding the diversity of physician specialties contributing to the cumulative AB. In the oldest age groups, MACs were almost exclusively prescribed by general practitioners. In Germany, patients in these age groups are also treated by specialists but refills of medication are often prescribed by general practitioners. Therefore, this result is to be expected. These aspects are relevant if interventions to reduce the AB in specific patient groups or to increase the awareness of AB in general were to be designed. Our results suggest that general practitioners would be an important target group, particularly for older age groups but involvement of specialists, who often initiate prescriptions of a certain medication, may also be required.

Our study showed that there are persons with an AB considered to be clinically relevant in all age groups. This demonstrates the need to conduct studies on potentially harmful effects not only in older adults but also in children, adolescents, and the entire adult population. However, it has to be kept in mind that there are a lot of unanswered questions in regards to how AB can cause or contribute to clinically relevant adverse effects. For example, the time period over which the cumulative effects of anticholinergic burden may accrue and possibly produce harms are unclear. Also the role of type and dosage of single MACs and their overlap are not well understood. When planning a study on the risk of AB, this means that classifying persons as exposed or unexposed bears a high level of uncertainty, so robustness of findings would need to be assessed by comprehensive sensitivity analyses. Also in many other regards, studies on the risk of outcomes associated with AB are challenging, e.g. regarding issues such as confounding by indication, unmeasured confounding and time-varying exposure.

To our knowledge this is the first study in Germany providing a detailed description of the AB in an unselected population sample, i.e., without restrictions to a certain age or patient group. The large sample size allowed us to precisely estimate the prevalence of the AB stratified by age and sex. AB was estimated using the ACB scale—a widely used and validated tool—and a list of MACs created specifically for the German health care system. There are many scales for the assessment of AB and they have been shown to differ [29, 30]. Thus, direct comparisons with studies using other AB scales are difficult. Moreover, medications classified with an ACB score of 1 only have a possible anticholinergic effect based on in vitro affinity to muscarinic receptors without clinically relevant negative cognitive effects. It is not clear whether the cumulative use of several medications with a possible anticholinergic effect is equivalent to the AB induced through the use of medications with established and clinically relevant cognitive

anticholinergic effects (ACB scores 2 or 3). However, some studies have shown increased risks of adverse effects already for an ACB score of 1 [22, 31].

Our study was based on German claims data. Due to the nature of the data the study is not affected by recall or volunteer bias. Moreover, the study population was fairly stable: 91% of included persons were observable for the whole year of 2016, 98% were observable for 90 days or more and only 3.3% exited the study before the end of the observation period due to end of continuous insurance. Limitations of the data source include lack of information regarding the use of medication during hospitalization as well as lack of information on adherence—no information is available on whether dispensed medication was actually used by the patient. Furthermore, over-the-counter medication is not captured, thus dispensations of MACs, particularly of antihistamines, might have been underestimated. Treatment durations of MACs were estimated using DDDs as the prescribed dose is not available. However, for each MAC we reviewed summaries of product characteristics and, if applicable, adapted lower DDDs for persons aged <18 and ≥ 65 years. Nonetheless, this approach is not equivalent to other studies that had more information on dosage and used more sophisticated methods to take it into account. Finally, in our study we have not assessed AB in a longitudinal manner, which–in view of the aforementioned unanswered questions about clinically relevant AB levels–would be essential in a subsequent risk study to understand the potential link between AB exposure and negative health outcomes. Such risk studies are particularly needed in the younger population where it is even less clear if such a link exists at all.

In conclusion, this comprehensive overview showed that a clinically relevant AB is common in the German general population. This holds particularly true for older persons but there are also younger age groups with a prevalence of up to 7%. Among adults, prevalence of clinically relevant AB was consistently higher in women than in men. Given the known risks associated with AB in older persons, targeted interventions at the prescriber level are needed. Furthermore, studies exploring possible risks associated with AB in children, adolescents and the entire adult population are warranted.

Supporting information

S1 Table. Description of study population stratified by anticholinergic burden measured through Anticholinergic Cognitive Burden (ACB) score.
(DOCX)

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12.6 P3: Potential of health insurance claims data to predict fractures in older adults: A prospective cohort study

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ORIGINAL RESEARCH

Potential of Health Insurance Claims Data to Predict Fractures in Older Adults: A Prospective Cohort Study

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Purpose: In older adults, fractures are associated with mortality, disability, loss of independence and high costs. Knowledge on their predictors can help to identify persons at high risk who may benefit from measures to prevent fractures. We aimed to assess the potential of German claims data to predict fractures in older adults.

Patients and Methods: Using the German Pharmacoepidemiological Research Database (short GePaRD; claims data from ~20% of the German population), we included persons aged ≥65 years with at least one year of continuous insurance coverage and no fractures prior to January 1, 2017 (baseline). We randomly divided the study population into a training (80%) and a test sample (20%) and used logistic regression and random forest models to predict the risk of fractures within one year after baseline based on different combinations of potential predictors.

Results: Among 2,997,872 persons (56% female), the incidence per 10,000 person years of any fracture in women increased from 133 in age group 65–74 years (men: 71) to 583 in age group 85+ (men: 332). The maximum predictive performance as measured by the area under the curve (AUC) across models was 0.63 in men and 0.60 in women and was achieved by combining information on drugs and morbidities. AUCs were lowest in age group 85+.

Conclusion: Our study showed that the performance of models using German claims data to predict the risk of fractures in older adults is moderate. Given that the models used data readily available to health insurance providers in Germany, it may still be worthwhile to explore the cost–benefit ratio of interventions aiming to reduce the risk of fractures based on such prediction models in certain risk groups.

Keywords: fracture, older adults, claims data, prediction

Introduction

Older adults have a high risk of fractures that further increases with advancing age.[1–4] Fractures can be detrimental for older adults as they are associated with a high risk of death, disability and loss of independence.[5–7] In addition to age and sex, a number of other factors like prior fractures, chronic morbidities such as osteoporosis, Parkinson's disease, dementia as well as lifestyle-related factors such as alcohol and illicit drug abuse, heavy smoking and low Body Mass Index (BMI) have been shown to be associated with an increased risk of fractures.[8–15] Moreover, the use of certain medications has been linked to an increased risk of falls and fractures such as those included in the so-called list of fall risk increasing drugs (FRIDs) (loop diuretics, digitalis, antipsychotics, antidepressants, benzodiazepines, opioids and antiepileptics) as well as further drugs such as proton pump inhibitors and glucocorticoids.[16–20] Additionally, the number of used medications overall, which is associated with multimorbidity, as well as the cumulative effects of medications with anticholinergic activity, known as anticholinergic burden (AB), have been identified as potential risk factors for fractures.[21,22]

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Due to the effects of fractures on morbidity, mortality as well as healthcare costs,[23] risk-based prevention strategies directed at persons with a high risk of fractures are needed. However, in order to implement these strategies detailed knowledge regarding risk factors of fractures and their relevance is required. Information on some of the known predictors of fractures is available in claims data. Prediction of fractures based on claims data would be useful as the data is readily available, includes information from various settings (inpatient, outpatient, pharmacy) and the analysis is fairly cheap and often representative of entire populations. However, it is not clear to what extent the information available in (German) claims data is useful for predicting fractures, which of the available predictors are most useful and whether the predictive power differs by sex and age.

We therefore aimed to assess the potential of German claims data to predict fractures in older adults stratified by age group and sex.

Methods

Data Source

We used the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. In Germany, about 90% of the general population is covered by statutory health insurance. The healthcare system is characterized by uniform access to all levels of care and free choice of providers.

In addition to demographic data, GePaRD contains information on outpatient drug dispensations as well as outpatient (ie, from general practitioners and specialists) and inpatient services and diagnoses. Information on medication includes the anatomical-therapeutic-chemical (ATC) code, the prescription and dispensation date, the specialty of the prescriber as well as the number of defined daily doses (DDDs). Diagnoses are coded according to the German modification of the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM).

Study Design and Study Population

A cohort was established which included all persons from GePaRD with continuous insurance coverage from January 1, 2016 to January 1, 2017 (inclusion period) without missing information on sex and age. Further inclusion criteria were German residency, age 65 years or older during the inclusion period. Moreover, only persons with no record of a fracture between January 1, 2017 and the beginning of the individual lookback period (as early as January 1, 2004) were included to focus on persons most relevant for primary prevention of fractures. It is already known that persons with prior fractures are at high risk for subsequent fractures,[24–26] so measures to prevent a second fracture may already have been taken. Time before January 1, 2017 was defined as baseline period where information on potential predictors was assessed. The occurrence of fractures was assessed during the follow-up period from January 1 to December 31, 2017. Persons were followed until the first of the following criteria: death, occurrence of fractures, end of insurance or end of follow-up period.

Potential Predictors of Fractures and Study Outcome

We considered the following potential predictors of fractures, which were identified from literature and are available in claims data: (i) morbidities influencing the risk of fractures and falls: osteoporosis,[10] osteoarthrosis,[27] rheumatoid arthritis,[19,28] vitamin D deficiency,[19,29] Parkinson's disease,[11] dementia[30] and type 2 diabetes mellitus;[31–33] (ii) codes for lifestyle-related factors or morbidities relevant to the risk of fractures: alcohol abuse,[13] heavy smoking[14] and obesity (high BMI associated with lower risk of fractures);[15,34] (iii) codes indicating frailty:[35] nursing home residency; (iv) medications relevant to the risk of fractures: high-ceiling diuretics, cardiac glycosides, antidepressants, antipsychotics, benzodiazepines, opioids, antiepileptics,[16–18] glucocorticoids,[36] proton pump inhibitors,[19] AB[22] and polypharmacy[21] (Table 1). The study outcome fractures, including hip and femur fractures, vertebral fractures, wrist, hand and shoulder

Table 1 Included Models and Predictors

Model	Included Predictor(s)
A	AB
B	FRIDs
D	Polypharmacy
D	AB, FRIDs
E	AB, polypharmacy
F	FRIDs, polypharmacy
G	Glucocorticoids, proton pump inhibitors, osteoporosis medication, osteoporosis, osteoarthrosis, rheumatoid arthritis, vitamin D deficiency, obesity, heavy smoking, alcohol abuse, illicit drug abuse, Parkinson's disease, dementia, type 2 diabetes mellitus, nursing home residency
H	AB, FRIDs, glucocorticoids, proton pump inhibitors, osteoporosis medication, osteoporosis, osteoarthrosis, rheumatoid arthritis, vitamin D deficiency, obesity, heavy smoking, alcohol abuse, illicit drug abuse, Parkinson's disease, dementia, type 2 diabetes mellitus, nursing home residency, polypharmacy

Abbreviations: AB, anticholinergic burden; FRIDs, fall risk increasing drugs.

fractures, pelvis fractures and other fractures, were assessed based on ICD-10-GM codes recorded as inpatient main discharge diagnoses (see Appendix 1).

Definition of Study Variables

Information on medication and healthcare utilization was assessed between January 1 and December 31, 2016. We considered a person to be exposed to a medication of interest if the person had ≥1 dispensation in the outpatient setting of the respective medication. AB was assessed through the Anticholinergic Cognitive Burden (ACB) scale as described by Kiesel et al.[37]

Information on morbidities was assessed any time prior to January 1, 2017 (starting from database inception on January 1, 2004). Most morbidities were assessed through the presence of records of ≥1 ICD-10-GM inpatient or outpatient diagnoses. For some morbidities, also specific procedure (OPS) or service (EBM) codes relevant in the treatment of these conditions were considered (eg, hemodialysis in the case of renal failure). For type 2 diabetes, dementia and Parkinson's disease specific disease identification algorithms were used to minimize misclassification (see Appendix 2).

Statistical Analyses

Crude incidence rates were calculated by dividing the number of fractures observed in the study period by the sum of person-time under risk of any fractures. Exact confidence intervals were calculated using the relationship between the chi-squared and the Poisson distribution.[38] Univariate odds ratios (OR) were calculated to assess the association between the occurrence of fractures during follow-up (as binary variable) and selected pre-baseline predictor variable (with two or more categories). Estimation of univariate odds ratios and corresponding 95% confidence intervals was done non-parametrically.[39]

To develop and validate a prediction model, the data was split (8:2) into a training sample (n = 2,406,861) and a test sample (n = 591,011). The training sample was used to train a range of pre-specified models (Table 1) using both logistic regression and random forests. We considered models that used only information on medication (FRIDs, AB, polypharmacy), models that used only information on morbidities (including nursing home residency as indicator for frailty) as well as models that considered both. Given that glucocorticoids and proton pump inhibitors are mainly relevant due to their association with osteoporosis, these drugs were considered in the morbidity model rather than in the medication models. For random forests, 10-fold cross-validation was performed on the training sample. Threshold values for

predicting case vs non-case status were set using Youden's J (sensitivity + specificity − 1).[40] Predictive performance of all models was assessed on the test sample, using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). The selected models included combinations of potential predictors of fractures, namely AB, FRIDs, polypharmacy and morbidities, co-medication and nursing home residency in order to assess their usefulness as predictors of fractures alone and in combination with other predictors.

Data preparation, calculation of summary statistics, incidence rates and univariate OR were done in SAS 9.4. Statistical modelling (ie, logistic regression and random forests) was done in R version 4.0.2 (caret package version 6.0–86, ranger package version 0.12.1). No parameter tuning was applied for random forests due to computational limitations, using the default settings in ranger instead.

Ethics and Approvals

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen, studies based on GePaRD are exempt from institutional review board review.

Results

The study population comprised a total of 2,997,872 persons (56% women) with a median age of 74 years at baseline (interquartile range (IQR): 10 years). Crude incidence of any fracture across all age and sex groups was 176.1 per 10,000 person years. The incidence varied by sex and increased with age: While in age group 65–74 years, it was 133.1 in women and 70.6 in men, it was more than four times higher in age group ≥85 years (women: 583.1, men: 332.0). The highest incidence was observed for wrist, hand and shoulder fractures, followed by hip and femur fractures (Table 2). Compared to persons without fractures during follow-up, individuals with fractures had more chronic diseases at baseline (eg, dementia, Parkinson's disease or osteoporosis) and were prescribed more medication for the treatment of chronic diseases as well as FRIDs. Individuals with fractures were also more likely to have high AB (ACB≥3) and polypharmacy (Table 3).

Table 2 Incidence of Fractures (per 10,000 Person Years) in the Study Population by Age and Sex

	Age Groups						
	65–74 Years		75–84 Years		85+ Years		
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)	Total (N = 2,997,872)
Any fractures	70.6 (68.6–72.6)	133.1 (130.6–135.6)	126.3 (123.3–129.4)	249.9 (246.0–253.8)	332.0 (321.2–343.1)	583.1 (571.5–594.8)	176.1 (174.6–177.6)
Hip fractures/femur fractures	14.2 (13.3–15.1)	19.8 (18.8–20.8)	38.8 (37.1–40.5)	65.9 (63.9–67.9)	155.0 (147.7–162.6)	255.3 (247.7–263.0)	50.5 (49.7–51.3)
Vertebral fractures	10.4 (9.7–11.2)	17.0 (16.1–17.9)	26.2 (24.8–27.6)	48.3 (46.6–50.0)	66.3 (61.6–71.3)	108.4 (103.5–113.5)	31.1 (30.5–31.7)
Wrist, hand and shoulder fractures	20.2 (19.1–21.3)	63.0 (61.3–64.7)	25.0 (23.6–26.3)	88.5 (86.2–90.8)	41.3 (37.5–45.3)	133.3 (127.8–138.9)	55.4 (54.5–56.2)
Pelvis fractures	1.7 (1.4–2.0)	2.2 (1.9–2.6)	4.6 (4.0–5.2)	7.9 (7.2–8.6)	14.5 (12.3–16.9)	25.2 (22.9–27.7)	5.5 (5.3–5.8)
Other fractures	25.1 (23.9–26.4)	32.8 (31.6–34.0)	34.6 (33.1–36.3)	45.5 (43.8–47.1)	61.9 (57.3–66.8)	78.1 (73.9–82.4)	37.9 (37.2–38.6)

Table 3 Description of Study Population by Age, Sex and Fracture Status During Follow-Up

	Age Groups											
	65–74 Years				75–84 Years				85+ Years			
	Men		Women		Men		Women		Men		Women	
	Fracture (N = 4660)	No Fracture (N = 665,042)	Fracture (N = 10,991)	No Fracture (N = 827,139)	Fracture (N = 6622)	No Fracture (N = 531,150)	Fracture (N = 15,974)	No Fracture (N = 640,287)	Fracture (N = 3570)	No Fracture (N = 112,579)	Fracture (N = 9658)	No Fracture (N = 170,200)
AB												
None (ACB=0)	1930 (41.4%)	323,468 (48.6%)	4370 (39.8%)	376,507 (45.5%)	1887 (28.5%)	204,445 (38.5%)	4452 (27.9%)	221,747 (34.6%)	998 (28.0%)	36,055 (32.0%)	2516 (26.1%)	47,632 (28.0%)
Low (ACB=1)	1187 (25.5%)	177,390 (26.7%)	2635 (24.0%)	209,641 (25.3%)	1734 (26.2%)	150,370 (28.3%)	3854 (24.1%)	169,730 (26.5%)	983 (27.5%)	31,940 (28.4%)	2412 (25.0%)	44,450 (26.1%)
Medium (ACB=2)	604 (13.0%)	82,509 (12.4%)	1522 (13.8%)	106,863 (12.9%)	1181 (17.8%)	80,959 (15.2%)	2754 (17.2%)	101,986 (15.9%)	616 (17.3%)	19,229 (17.1%)	1844 (19.1%)	30,598 (18.0%)
High (ACB≥3)	939 (20.2%)	81,675 (12.3%)	2464 (22.4%)	134,128 (16.2%)	1820 (27.5%)	95,376 (18.0%)	4914 (30.8%)	146,824 (22.9%)	973 (27.3%)	25,355 (22.5%)	2886 (29.9%)	47,520 (27.9%)
Mean cumulative AB (SD)	244 (420.0)	161 (300.7)	232 (397.7)	166 (315.7)	303 (429.9)	205 (332.3)	293 (413.4)	222 (350.2)	277 (387.1)	236 (345.7)	290 (374.3)	269 (364.7)
Use of different medication												
0	617 (13.2%)	111,448 (16.8%)	1481 (13.5%)	141,058 (17.1%)	435 (6.6%)	49,117 (9.2%)	1023 (6.4%)	56,775 (8.9%)	172 (4.8%)	7121 (6.3%)	433 (4.5%)	9536 (5.6%)
1 to 4	1909 (41.0%)	316,735 (47.6%)	5127 (46.6%)	422,946 (51.1%)	2092 (31.6%)	217,861 (41.0%)	5707 (35.7%)	272,309 (42.5%)	1080 (30.3%)	37,719 (33.5%)	3061 (31.7%)	56,785 (33.4%)
5 to 9 (polypharmacy)	1472 (31.6%)	186,679 (28.1%)	3176 (28.9%)	209,699 (25.4%)	2720 (41.1%)	198,042 (37.3%)	6342 (39.7%)	232,815 (36.4%)	1645 (46.1%)	50,194 (44.6%)	4379 (45.3%)	75,872 (44.6%)
≥ 10 (hyper-polypharmacy)	662 (14.2%)	50,180 (7.5%)	1207 (11.0%)	53,436 (6.5%)	1375 (20.8%)	66,130 (12.5%)	2902 (18.2%)	78,388 (12.2%)	673 (18.9%)	17,545 (15.6%)	1785 (18.5%)	28,007 (16.5%)
FRIDs	1564 (33.6%)	140,213 (21.1%)	3801 (34.6%)	214,677 (26.0%)	3209 (48.5%)	167,949 (31.6%)	7917 (49.6%)	246,652 (38.5%)	2126 (59.6%)	55,749 (49.5%)	6009 (62.2%)	98,666 (58.0%)
High-ceiling diuretics	677 (14.5%)	54,239 (8.2%)	1101 (10.0%)	52,984 (6.4%)	1769 (26.7%)	86,007 (16.2%)	3140 (19.7%)	95,819 (15.0%)	1406 (39.4%)	36,518 (32.4%)	3447 (35.7%)	57,063 (33.5%)
Cardiac glycosides	81 (1.7%)	8096 (1.2%)	89 (0.8%)	6121 (0.7%)	189 (2.9%)	13,239 (2.5%)	426 (2.7%)	16,755 (2.6%)	153 (4.3%)	4711 (4.2%)	505 (5.2%)	10,318 (6.1%)
Antidepressants	576 (12.4%)	45,764 (6.9%)	1987 (18.1%)	109,522 (13.2%)	925 (14.0%)	42,319 (8.0%)	3583 (22.4%)	99,653 (15.6%)	509 (14.3%)	11,391 (10.1%)	2116 (21.9%)	31,872 (18.7%)
Antipsychotics	576 (12.4%)	45,764 (6.9%)	1987 (18.1%)	109,522 (13.2%)	925 (14.0%)	42,319 (8.0%)	3583 (22.4%)	99,653 (15.6%)	407 (11.4%)	7969 (7.1%)	1266 (13.1%)	17,534 (10.3%)
Benzodiazepines	106 (2.3%)	9915 (1.5%)	372 (3.4%)	20,893 (2.5%)	262 (4.0%)	11,600 (2.2%)	750 (4.7%)	23,689 (3.7%)	155 (4.3%)	3814 (3.4%)	523 (5.4%)	8347 (4.9%)
Opioids	431 (9.2%)	36,273 (5.5%)	1180 (10.7%)	57,826 (7.0%)	800 (12.1%)	40,987 (7.7%)	2561 (16.0%)	74,348 (11.6%)	495 (13.9%)	12,424 (11.0%)	1893 (19.6%)	30,442 (17.9%)
Antiepileptics	359 (7.7%)	26,781 (4.0%)	780 (7.1%)	34,558 (4.2%)	631 (9.5%)	31,230 (5.9%)	1475 (9.2%)	41,381 (6.5%)	270 (7.6%)	7887 (7.0%)	727 (7.5%)	12,649 (7.4%)
Other medication												
Glucocorticoids	628 (13.5%)	66,424 (10.0%)	1735 (15.8%)	102,501 (12.4%)	949 (14.3%)	62,657 (11.8%)	2659 (16.6%)	87,919 (13.7%)	435 (12.2%)	13,293 (11.8%)	1187 (12.3%)	19,421 (11.4%)
Proton pump inhibitors	1477 (31.7%)	165,777 (24.9%)	3,702 (33.7%)	233,182 (28.2%)	2427 (36.7%)	157,349 (29.6%)	6447 (40.4%)	220,256 (34.4%)	1361 (38.1%)	38,776 (34.4%)	3912 (40.5%)	66,408 (39.0%)
Morbidities												
Osteoporosis	425 (9.1%)	31,390 (4.7%)	3,622 (33.0%)	193,352 (23.4%)	1072 (16.2%)	46,675 (8.8%)	7823 (49.0%)	237,768 (37.1%)	673 (18.9%)	15,087 (13.4%)	5278 (54.6%)	80,721 (47.4%)
Osteoarthrosis	2753 (59.1%)	365,400 (54.9%)	7631 (69.4%)	542,637 (65.6%)	4435 (67.0%)	348,606 (65.6%)	12,730 (79.7%)	489,633 (76.5%)	2644 (74.1%)	81,813 (72.7%)	7854 (81.3%)	139,216 (81.8%)
Rheumatoid arthritis	1426 (30.6%)	182,086 (27.4%)	3262 (29.7%)	216,121 (26.1%)	2347 (35.4%)	167,866 (31.6%)	5486 (34.3%)	200,196 (31.3%)	1197 (33.5%)	37,900 (33.7%)	3249 (33.6%)	56,931 (33.4%)
Vitamin D deficiency	227 (4.9%)	26,120 (3.9%)	1049 (9.5%)	68,185 (8.2%)	485 (7.3%)	28,717 (5.4%)	1699 (10.6%)	60,139 (9.4%)	246 (6.9%)	7211 (6.4%)	938 (9.7%)	15,317 (9.0%)
Obesity	1524 (32.7%)	200,040 (30.1%)	3435 (31.3%)	264,319 (32.0%)	2027 (30.6%)	152,403 (28.7%)	5157 (32.3%)	213,926 (33.4%)	778 (21.8%)	26,972 (24.0%)	2442 (25.3%)	49,304 (29.0%)
Heavy smoking	957 (20.5%)	104,173 (15.7%)	1676 (15.2%)	102,782 (12.4%)	861 (13.0%)	46,642 (8.8%)	1279 (8.0%)	38,148 (6.0%)	193 (5.4%)	5403 (4.8%)	273 (2.8%)	4607 (2.7%)
Alcohol abuse	719 (15.4%)	52,633 (7.9%)	726 (6.6%)	29,372 (3.6%)	683 (10.3%)	30,059 (5.7%)	711 (4.5%)	17,291 (2.7%)	163 (4.6%)	3973 (3.5%)	207 (2.1%)	3206 (1.9%)
Parkinson's disease	170 (3.6%)	7705 (1.2%)	213 (1.9%)	6058 (0.7%)	521 (7.9%)	16,525 (3.1%)	674 (4.2%)	13,038 (2.0%)	241 (6.8%)	5375 (4.8%)	391 (4.0%)	5818 (3.4%)
Dementia	264 (5.7%)	13,598 (2.0%)	434 (3.9%)	14,395 (1.7%)	1169 (17.7%)	41,555 (7.8%)	2428 (15.2%)	48,387 (7.6%)	1103 (30.9%)	23,506 (20.9%)	3170 (32.8%)	43,175 (25.4%)
Type 2 diabetes mellitus	1076 (23.1%)	135,608 (20.4%)	1500 (13.6%)	109,770 (13.3%)	1809 (27.3%)	127,709 (24.0%)	3136 (19.6%)	118,810 (18.6%)	804 (22.5%)	25,923 (23.0%)	1835 (19.0%)	32,041 (18.8%)
Nursing home residence	532 (11.4%)	37,392 (5.6%)	903 (8.2%)	42,229 (5.1%)	1266 (19.1%)	56,603 (10.7%)	2728 (17.1%)	71,472 (11.2%)	1043 (29.2%)	24,712 (22.0%)	3077 (31.9%)	48,506 (28.5%)

Abbreviations: AB, anticholinergic burden; ACB, anticholinergic cognitive burden scale; FRIDs, fall risk increasing drugs.

Results of the univariate analysis showed an increased risk of fractures over all age and sex categories for persons with Parkinson's disease, dementia, polypharmacy, FRIDs (particularly antipsychotics and high-ceiling diuretics), alcohol abuse, osteoporosis and high AB. The highest ORs regarding any fractures were observed for persons with Parkinson's disease (age group 65–74 years: 3.2 for men, 2.7 for women; age group 75–84 years: 2.7 for men, 2.1 for women and age group 85+: 1.4 for men, 1.2 for women) and dementia (age group: 65–74 years: 2.9 in men, 2.6 in women; age group 75–84 years: 2.2 in men, 2.3 in women and age group 85+: 1.5 in men, 1.4 in women) (Table 4).

Table 4 Predictors of Any Fractures by Sex and Age (Univariate Model)

Predictors	Age Groups					
	65–74 Years		75–84 Years		85+ Years	
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)
AB						
None (ACB=0) (ref)	–	–	–	–	–	–
Low (ACB=1)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	1.2 (1.2–1.3)	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.0 (1.0–1.1)
Medium (ACB=2)	1.2 (1.1–1.3)	1.2 (1.2–1.3)	1.6 (1.5–1.7)	1.3 (1.3–1.4)	1.2 (1.0–1.3)	1.1 (1.1–1.2)
High (ACB≥3)	1.9 (1.8–2.1)	1.6 (1.5–1.7)	2.1 (1.9–2.2)	1.7 (1.6–1.7)	1.4 (1.3–1.5)	1.1 (1.1–1.2)
AB						
0 (ref)	–	–	–	–	–	–
1–25th percentile	1.1 (1.0–1.2)	1.0 (1.0–1.1)	1.3 (1.2–1.4)	1.1 (1.1–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.1)
26–50th percentile	1.2 (1.1–1.3)	1.2 (1.1–1.2)	1.4 (1.3–1.5)	1.2 (1.2–1.3)	1.1 (1.0–1.3)	1.0 (1.0–1.1)
51–75th percentile	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.5 (1.4–1.6)	1.4 (1.3–1.4)	1.2 (1.0–1.3)	1.1 (1.0–1.2)
76–100th percentile	1.9 (1.7–2.0)	1.7 (1.6–1.8)	2.1 (2.0–2.3)	1.8 (1.7–1.8)	1.4 (1.3–1.6)	1.2 (1.1–1.3)
Use of different medication						
0 (ref)	–	–	–	–	–	–
1 to 4	1.1 (1.0–1.2)	1.2 (1.1–1.2)	1.1 (1.0–1.2)	1.2 (1.1–1.2)	1.2 (1.0–1.4)	1.2 (1.1–1.3)
Polypharmacy (5 to 9 different medications)	1.4 (1.3–1.6)	1.4 (1.4–1.5)	1.6 (1.4–1.7)	1.5 (1.4–1.6)	1.4 (1.2–1.6)	1.3 (1.1–1.4)
Hyper-polypharmacy (≥ 10 different medications)	2.4 (2.1–2.7)	2.2 (2.0–2.3)	2.3 (2.1–2.6)	2.1 (1.9–2.2)	1.6 (1.3–1.9)	1.4 (1.3–1.6)
FRIDs	1.9 (1.8–2.0)	1.5 (1.4–1.6)	2.0 (1.9–2.1)	1.6 (1.5–1.6)	1.5 (1.4–1.6)	1.2 (1.1–1.2)
High-ceiling diuretics	1.9 (1.8–2.1)	1.6 (1.5–1.7)	1.9 (1.8–2.0)	1.4 (1.3–1.4)	1.4 (1.3–1.4)	1.1 (1.1–1.1)
Cardiac glycosides	1.4 (1.2–1.8)	1.1 (0.9–1.4)	1.1 (1.0–1.3)	1.0 (0.9–1.1)	1.0 (0.9–1.2)	0.9 (0.8–0.9)
Antidepressants	1.9 (1.7–2.1)	1.4 (1.4–1.5)	1.9 (1.7–2.0)	1.6 (1.5–1.6)	1.5 (1.3–1.6)	1.2 (1.2–1.3)
Antipsychotics	2.3 (2.0–2.6)	1.7 (1.6–1.9)	2.7 (2.4–2.9)	1.9 (1.8–2.0)	1.7 (1.5–1.9)	1.3 (1.2–1.4)
Benzodiazepines	1.5 (1.3–1.9)	1.4 (1.2–1.5)	1.8 (1.6–2.1)	1.3 (1.2–1.4)	1.3 (1.1–1.5)	1.1 (1.0–1.2)
Opioids	1.8 (1.6–2.0)	1.6 (1.5–1.7)	1.6 (1.5–1.8)	1.5 (1.4–1.5)	1.3 (1.2–1.4)	1.1 (1.1–1.2)
Antiepileptics	2.0 (1.8–2.2)	1.8 (1.6–1.9)	1.7 (1.6–1.8)	1.5 (1.4–1.6)	1.1 (1.0–1.2)	1.0 (0.9–1.1)
Other medication						
Glucocorticoids	1.4 (1.3–1.5)	1.3 (1.3–1.4)	1.3 (1.2–1.3)	1.3 (1.2–1.3)	1.0 (0.9–1.1)	1.1 (1.0–1.2)
Proton pump inhibitors	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.4 (1.3–1.4)	1.3 (1.2–1.3)	1.2 (1.1–1.3)	1.1 (1.0–1.1)
Morbidities and lifestyle factors						
Osteoporosis	2.0 (1.8–2.2)	1.6 (1.5–1.7)	2.0 (1.8–2.1)	1.6 (1.6–1.7)	1.5 (1.3–1.6)	1.3 (1.3–1.4)
Osteoarthrosis	1.2 (1.1–1.3)	1.2 (1.1–1.2)	1.1 (1.0–1.1)	1.2 (1.2–1.3)	1.1 (1.0–1.2)	1.0 (0.9–1.0)
Rheumatoid arthritis	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.1 (1.1–1.2)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Vitamin D deficiency	1.3 (1.1–1.4)	1.2 (1.1–1.3)	1.4 (1.3–1.5)	1.1 (1.1–1.2)	1.1 (0.9–1.2)	1.1 (1.0–1.2)
Obesity	1.1 (1.1–1.2)	1.0 (0.9–1.0)	1.1 (1.0–1.2)	1.0 (0.9–1.0)	0.9 (0.8–1.0)	0.8 (0.8–0.9)

(*Continued*)

Table 4 (Continued).

Predictors	Age Groups					
	65–74 Years		75–84 Years		85+ Years	
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)
Heavy smoking	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.6 (1.4–1.7)	1.4 (1.3–1.5)	1.1 (1.0–1.3)	1.0 (0.9–1.2)
Alcohol abuse	2.1 (2.0–2.3)	1.9 (1.8–2.1)	1.9 (1.8–2.1)	1.7 (1.6–1.8)	1.3 (1.1–1.5)	1.1 (1.0–1.3)
Parkinson's disease	3.2 (2.8–3.8)	2.7 (2.3–3.1)	2.7 (2.4–2.9)	2.1 (2.0–2.3)	1.4 (1.3–1.7)	1.2 (1.1–1.3)
Dementia	2.9 (2.3–3.6)	2.6 (2.2–3.1)	2.2 (2.0–2.5)	2.3 (2.1–2.5)	1.5 (1.3–1.7)	1.4 (1.3–1.6)
Type 2 diabetes mellitus	1.2 (1.1–1.3)	1.0 (1.0–1.1)	1.2 (1.1–1.3)	1.1 (1.0–1.1)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Nursing home residence	2.2 (2.0–2.4)	1.7 (1.6–1.8)	2.0 (1.9–2.1)	1.6 (1.6–1.7)	1.5 (1.4–1.6)	1.2 (1.1–1.2)

Abbreviations: AB, anticholinergic burden; ACB, anticholinergic cognitive burden scale; FRIDs, fall risk increasing drugs.

Predictive performance of the models, as measured by the AUC, is shown in Table 5 for men and in Table 6 for women. In models using medication and utilization of medication as predictors (models A–F), the range of AUC was 0.51–0.60 for both the random forest models and the logistic regression models. In model G, which included predictors related to morbidities and lifestyle, the AUC in the age group 65–74 years was 0.60 in men (logistic regression model: 0.60) and 0.59 in women (logistic regression model: 0.59). In the age group 75–84 years, the AUC for the random forest model was 0.61 in men (logistic regression model: 0.61) and 0.60 in women (logistic regression model: 0.60). In the age group ≥85 years, the AUC for the random forest model was 0.57 for men (logistic regression model: 0.57) and 0.54 in women (logistic regression model: 0.55). In model H, which included all predictors used in the previous models, the AUC in the age group 65–74 years, was 0.60 in men (logistic regression model: 0.61) and 0.58 in women (logistic regression model: 0.60). In the age group 75–84 years the AUC for the random forest model was 0.62 in men (logistic regression model: 0.63) and 0.59 in women (logistic regression model: 0.60). In the age group ≥85 years, the AUC for the random forest model was 0.56 for men (logistic regression model: 0.58) and 0.54 in women (logistic regression model: 0.55). Across all sex and age groups, models G and H had the highest AUCs in random forest and logistic regression models.

Discussion

Based on a large and unselected population sample including 2,997,872 persons aged 65 or older, we assessed the usefulness of information available in GePaRD for the prediction of fractures within up to one year after baseline, stratified by age and sex. In the univariate analysis, the predictors Parkinson's disease, dementia, hyper-polypharmacy, FRIDs, alcohol abuse, osteoporosis and AB showed the strongest association with fractures. In the multivariate analysis, models that included medication, morbidities and lifestyle-related factors achieved the highest predictive performance as measured by the AUC. AUCs were lowest in age group 85+. The performance of the random forest models was largely similar to the logistic regression models.

A study (n = 288,086) aiming to predict osteoporotic hip fractures based on German claims data using machine learning reported AUCs ranging from 0.65 to 0.70.[41] However, unlike in our study, this study did not exclude persons with prior fractures, so occurrence of the strong predictor "prior fracture" was included in the models, which likely explains the higher AUC compared to our study. Moreover, the study had information on the level of care (a higher level suggesting a higher frailty and thus a higher risk of falls and fractures) and the study population was based only on statutory health insurance data of persons working in agriculture and their families, ie, a study cohort with higher baseline risk for fractures. Indeed, the authors reported that 3% of the study population experienced a hip fracture during follow-up, which is much higher compared to our study in which 1.7% of the population had any fracture during follow-up. Compared to studies analyzing data with more clinical and laboratory information such as bone mineral density, vitamin D3, T-scores of the hip and lumbar spine as well as biochemical glucose measurements, the predictive performance of our model using only claims data is not as good. A recent study from the Netherlands reported

Table 5 Predictive Performance of All Models (Men)

Model	Age Group																					
	65–74 Years						75–84 Years						85+ Years									
	Random Forest				Logistic Model				Random Forest				Logistic Model				Random Forest				Logistic Model			
	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*
A	0.55	0.007	0.20	0.88	0.55	0.00697	0.20	0.88	0.58	0.0126	0.45	0.67	0.58	0.0126	0.45	0.67	0.53	0.0297	0.73	0.32	0.53	0.0297	0.73	0.32
B	0.57	0.007	0.35	0.79	0.57	0.00697	0.35	0.79	0.58	0.0126	0.48	0.69	0.58	0.0126	0.48	0.69	0.56	0.0296	0.61	0.51	0.56	0.0296	0.61	0.51
C	0.57	0.007	0.39	0.73	0.58	0.00697	0.39	0.73	0.58	0.0126	0.43	0.69	0.58	0.0126	0.43	0.69	0.53	0.0297	0.45	0.62	0.55	0.0296	0.37	0.7
D	0.57	0.007	0.35	0.79	0.57	0.00696	0.35	0.79	0.60	0.0126	0.55	0.63	0.60	0.0126	0.55	0.63	0.56	0.0296	0.61	0.51	0.55	0.0296	0.61	0.51
E	0.57	0.007	0.3	0.81	0.58	0.00697	0.39	0.74	0.59	0.0126	0.45	0.7	0.59	0.0126	0.42	0.72	0.54	0.0297	0.41	0.66	0.54	0.0297	0.41	0.67
F	0.58	0.007	0.4	0.74	0.59	0.00696	0.40	0.74	0.60	0.0126	0.51	0.66	0.60	0.0126	0.49	0.67	0.55	0.0296	0.61	0.5	0.56	0.0296	0.62	0.49
G	0.60	0.007	0.38	0.79	0.60	0.00696	0.37	0.80	0.61	0.0126	0.45	0.72	0.61	0.0126	0.43	0.74	0.57	0.0296	0.55	0.58	0.57	0.0296	0.57	0.57
H	0.60	0.007	0.43	0.75	0.61	0.00696	0.49	0.70	0.62	0.0127	0.62	0.57	0.63	0.0126	0.59	0.62	0.56	0.0297	0.49	0.61	0.58	0.0296	0.42	0.71

Note: *Youden (sensitivity and specificity are given at the optimal Youden value).
Abbreviations: AUC, area under the curve; MSPE, mean squared prediction error; Se, sensitivity; Sp, specificity.

Table 6 Predictive Performance of All Models (Women)

Model	Age Group																					
	65–74 years							75–84 Years						85+ Years								
	Random Forest				Logistic Model				Random Forest				Logistic Model				Random Forest				Logistic Model			
	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*
A	0.54	0.0129	0.36	0.71	0.54	0.01286	0.36	0.71	0.56	0.0233	0.48	0.61	0.56	0.0233	0.48	0.61	0.51	0.051	0.48	0.54	0.51	0.051	0.48	0.54
B	0.54	0.0129	0.34	0.74	0.54	0.01286	0.34	0.74	0.55	0.0233	0.49	0.61	0.55	0.0233	0.49	0.61	0.52	0.051	0.63	0.42	0.52	0.051	0.63	0.42
C	0.56	0.0129	0.32	0.77	0.56	0.01286	0.32	0.77	0.57	0.0233	0.49	0.61	0.57	0.0233	0.49	0.61	0.51	0.051	0.75	0.28	0.52	0.051	0.75	0.28
D	0.55	0.0129	0.39	0.70	0.55	0.01286	0.39	0.70	0.57	0.0233	0.55	0.56	0.57	0.0233	0.55	0.56	0.52	0.051	0.63	0.42	0.53	0.051	0.63	0.42
E	0.56	0.0129	0.65	0.43	0.56	0.01286	0.37	0.72	0.57	0.0233	0.59	0.52	0.57	0.0233	0.53	0.58	0.52	0.051	0.45	0.59	0.52	0.051	0.47	0.57
F	0.56	0.0129	0.44	0.65	0.56	0.01286	0.44	0.65	0.57	0.0233	0.62	0.50	0.57	0.0233	0.57	0.54	0.53	0.051	0.61	0.44	0.53	0.051	0.58	0.47
G	0.59	0.0129	0.48	0.67	0.59	0.01284	0.55	0.6	0.60	0.0233	0.60	0.54	0.60	0.0233	0.51	0.63	0.54	0.0509	0.56	0.52	0.55	0.0509	0.72	0.36
H	0.58	0.0129	0.46	0.67	0.60	0.01284	0.47	0.68	0.59	0.0233	0.54	0.60	0.60	0.0233	0.48	0.68	0.54	0.0511	0.61	0.45	0.55	0.0509	0.68	0.40

Note: *Youden (sensitivity and specificity are given at the optimal Youden value).
Abbreviations: AUC, area under the curve; MSPE, mean squared prediction error; Se, sensitivity; Sp, specificity.

a c-index of 0.70 (CI: 0.66–0.73) for the prediction of subsequent major osteoporotic fractures in patients with prior fractures,[42] and a Danish study reported an AUC of up to 0.92 (CI: 0.89–0.94) for the prediction of hip fractures in patients who had undergone bone mineral density measurement with dual-energy X-ray absorptiometry.[43] Again, however, patients included in both studies might be subject to higher fracture risk. In the Dutch study, 11% of patients sustained a fracture within a median time of 114 weeks, and in the Danish study, approximately 7% of patients sustained a hip fracture within five years.

The various models assessed in our study suggest that combining information on medication and morbidity is important to achieve at least an AUC of ≥0.60. In age group 85+, however, even models combining this information showed hardly any predictive performance. This may reflect the difficulty of capturing frailty in GePaRD, a factor that becomes increasingly important with age. Generally, it seems reasonable to judge the discriminatory power of a model based on the context and its intended use. If a model is intended to be used for diagnostic purposes in oncology, eg, to distinguish between persons with and without preclinical cancer, a model performance of 0.6 would likely be considered as poor because at acceptable levels of specificity a high proportion of cancer patients would remain undetected. The situation is different if a model is intended to predict future occurrence of a disease in order to narrow down, for example, the population at risk that may benefit from preventive measures. In the context of our study, the question is whether the prediction of fractures based on a model with an AUC of ~0.6 may still be of some practical use in Germany to screen for persons at high risk of fractures in older adults below the age of 85. Model H may serve as an example (see Table 1). If we select a cutoff level yielding a sensitivity of 0.62 and 0.54 in men and women, respectively, and a specificity of 0.57 and 0.60 and apply this to a theoretical population of 2000 older adults aged 74–85 years (1000 men, 1000 women), the screening tool has a positive predictive value of 2% in men and 3% in women. Among the 432 men and 403 women identified by the model to have a high risk of fractures, 8 men and 13 women would actually have a fracture within one year. Considering the high impact of fractures on health, life expectancy and quality of life in those afflicted and the fact that fall prevention measures have no harm, it seems plausible to assume a net benefit if the measures are effective. Evaluating whether such a program would be affordable requires a systematic assessment of costs saved due to prevented fractures versus costs of the intervention. An advantage regarding the costs of such an intervention is certainly the fact that the data are readily available at the statutory health insurance providers. It could be an option that statutory health insurance providers directly analyze their data in order to identify and inform groups of persons that may particularly benefit from preventive measures. The screening tool itself would thus not cause high additional costs; however, this would constitute only a part of the total costs of such an intervention.

Even though including persons with prior fractures would likely have increased the predictive performance of the models in our study, we consider it a strength that we excluded these persons. It is known that these persons are at high risk of subsequent fractures.[24–26] However, as they already experienced a fracture they or their caregivers are alerted and may already have taken measures, so this would not be the relevant target group for prevention of a first fracture. Mixing persons with and without prior fractures may thus overrate the value of such models in terms of preventing a first fracture, which is different from the question of preventing subsequent fractures.

Another strength of our study is the population-based setting and the large sample size, which made it possible to conduct analyses specific to sex and age group. Indeed, predictive performance in our model tended to differ by age and sex, therefore it seems logical not to combine these categories. Given the nature of claims data analysis, our study is free of non-responder and recall bias. In order to mitigate outcome misclassification and ensure a high specificity of the outcome definition, fractures were assessed based on ICD-10-GM main hospital discharge diagnoses as these are the most valid diagnoses in German claims data. This also means that we did not capture fractures treated conservatively outside the hospital, but from a public health perspective we think it is more relevant to predict the risk of fractures leading to hospitalization as these are likely the more severe kind.

Our study also has limitations. First, while inpatient diagnosis codes in German claims data have a very high validity, there is often an over-reporting of diagnoses in the outpatient setting. To minimize misclassification, it is therefore often advisable to use algorithms that consider outpatient diagnosis codes only, for example, if there is also a specific treatment for the respective disease. In our study, we used specific algorithms for type 2 diabetes, dementia and Parkinson's disease, which were developed in prior projects,[44–46] but considered any in- or outpatient diagnosis codes for the other morbidities. This corresponds to a sensitive but less specific definition of these other morbidities; consequently, the

prevalence of some predictors may have been overestimated. Second, information on medication in German claims data is limited to outpatient pharmacy records except for certain expensive medications (eg, monoclonal antibodies). As in most pharmacoepidemiological studies, no information on adherence was available, ie, whether dispensed medication was actually taken by the patient. Moreover, over-the-counter medication is not captured in GePaRD. Third, our findings may not be generalizable to all German claims databases. While we could only use codes indicating nursing home residency to capture "frailty", there may be databases with information on the level of care, as the study mentioned above,[41] or on the reimbursement of medical devices such as walkers.

In conclusion, our study showed that the performance of models using German claims data to predict the risk of fractures in older adults is moderate. Given that the models used data readily available to health insurance providers in Germany, it may still be worthwhile to explore the cost–benefit ratio of interventions aiming to reduce the risk of fractures based on such prediction models in certain risk groups.

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Disclosure

The authors report no conflicts of interest in this work.

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