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Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD013540.

DOI: [10.1002/14651858.CD013540.pub2](https://doi.org/10.1002/14651858.CD013540.pub2).

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[Prognosis Review]

Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome

Martin Taylor-Rowan¹, Sophie Edwards², Anna H Noel-Storr³, Jenny McCleery⁴, Phyo K Myint⁵, Roy Soiza⁶, Carrie Stewart⁷, Yoon Kong Loke⁸, Terry J Quinn¹

¹Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK. ²University of Glasgow, Glasgow, UK. ³Radcliffe Department of Medicine, University of Oxford, Oxford, UK. ⁴Oxford Health NHS Foundation Trust, Banbury, UK. ⁵Division of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK. ⁶Department of General Internal Medicine, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK. ⁷ACER, IAHS, University of Aberdeen, Aberdeen, UK. ⁸Norwich Medical School, University of East Anglia, Norwich, UK

Contact address: Terry J Quinn, Terry.Quinn@glasgow.ac.uk, tjq1t@clinmed.gla.ac.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.

Publication status and date: New, published in Issue 5, 2021.

Citation: Taylor-Rowan M, Edwards S, Noel-Storr AH, McCleery J, Myint PK, Soiza R, Stewart C, Loke YK, Quinn TJ. Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD013540. DOI: [10.1002/14651858.CD013540.pub2](https://doi.org/10.1002/14651858.CD013540.pub2).

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ABSTRACT

Background

Medications with anticholinergic properties are commonly prescribed to older adults. The cumulative anticholinergic effect of all the medications a person takes is referred to as the 'anticholinergic burden' because of its potential to cause adverse effects. It is possible that high anticholinergic burden may be a risk factor for development of cognitive decline or dementia. There are various scales available to measure anticholinergic burden but agreement between them is often poor.

Objectives

To assess whether anticholinergic burden, as defined at the level of each individual scale, is a prognostic factor for future cognitive decline or dementia in cognitively unimpaired older adults.

Search methods

We searched the following databases from inception to 24 March 2021: MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), CINAHL (EBSCOhost), and ISI Web of Science Core Collection (ISI Web of Science).

Selection criteria

We included prospective and retrospective longitudinal cohort and case-control observational studies with a minimum of one year' follow-up that examined the association between an anticholinergic burden measurement scale and future cognitive decline or dementia in cognitively unimpaired older adults.

Data collection and analysis

Two review authors independently assessed studies for inclusion, and undertook data extraction, assessment of risk of bias, and GRADE assessment. We extracted odds ratios (OR) and hazard ratios, with 95% confidence intervals (CI), and linear data on the association between anticholinergic burden and cognitive decline or dementia. We intended to pool each metric separately; however, only OR-based data were suitable for pooling via a random-effects meta-analysis. We initially established adjusted and unadjusted pooled rates for each available anticholinergic scale; then, as an exploratory analysis, established pooled rates on the prespecified association across scales. We examined variability based on severity of anticholinergic burden.

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Main results

We identified 25 studies that met our inclusion criteria (968,428 older adults). Twenty studies were conducted in the community care setting, two in primary care clinics, and three in secondary care settings. Eight studies (320,906 participants) provided suitable data for meta-analysis. The Anticholinergic Cognitive Burden scale (ACB scale) was the only scale with sufficient data for 'scale-based' meta-analysis. Unadjusted ORs suggested an increased risk for cognitive decline or dementia in older adults with an anticholinergic burden (OR 1.47, 95% CI 1.09 to 1.96) and adjusted ORs similarly suggested an increased risk for anticholinergic burden, defined according to the ACB scale (OR 2.63, 95% CI 1.09 to 6.29). Exploratory analysis combining adjusted ORs across available scales supported these results (OR 2.16, 95% CI 1.38 to 3.38), and there was evidence of variability in risk based on severity of anticholinergic burden (ACB scale 1: OR 2.18, 95% CI 1.11 to 4.29; ACB scale 2: OR 2.71, 95% CI 2.01 to 3.56; ACB scale 3: OR 3.27, 95% CI 1.41 to 7.61); however, overall GRADE evaluation of certainty of the evidence was low.

Authors' conclusions

There is low-certainty evidence that older adults without cognitive impairment who take medications with anticholinergic effects may be at increased risk of cognitive decline or dementia.

PLAIN LANGUAGE SUMMARY

The impact of medications with anticholinergic effects on future problems with memory and thinking

What was the aim of this review?

Medicines can be classified by their ability to block the action of a chemical signalling system in the body called the cholinergic system. Medicines that do this are said to have anticholinergic effects. There are various measurement scales to quantify the effects of anticholinergic medicines. The overall anticholinergic effect caused by all the anticholinergic medications a person is taking is referred to as 'anticholinergic burden.'

We aimed to investigate if older people who have no problems with memory or thinking are more likely to develop dementia when prescribed anticholinergic medicines than people who are not prescribed these medicines.

Anticholinergic burden ratings can vary with the scale used because different scales score medicines in different ways. Therefore, we also wanted to know if any particular anticholinergic burden measurement scale was more strongly associated with increased risk of dementia than other scales.

Key messages

There may be a link between anticholinergic medicine use and future risk of dementia. However, there are limitations in the published evidence, and we cannot say definitively if dementia is caused by the anticholinergic medicines themselves or by other factors. There were too few studies to allow us to compare the various anticholinergic measurement tools.

What was studied in the review?

There are more than 40 million older people worldwide living with dementia. These numbers are expected to rise to over 100 million by 2050 and at present there are very limited treatment options available. Therefore, it is important to identify factors that may increase the risk of dementia.

Because the cholinergic system in the brain plays an important role in learning and memory, there are theoretical reasons to believe that medications with anticholinergic effects could cause future dementia. Research has suggested that these medications may have unintended effects on memory and thinking, potentially resulting in dementia. If this is the case, one way to reduce the numbers of older people who develop dementia may be to avoid prescribing these medicines. Many commonly used medications have anticholinergic effects, for example medications for hay fever, insomnia (difficulty getting to sleep or staying asleep for long enough to feel refreshed), and depression.

In this review, we investigated the link between anticholinergic medicines, as measured by various measurement scales, and future dementia.

What were the main results of the review?

We found 25 studies, including 968,428 people aged 50 years or more. Despite the relatively large number of studies, differences in design and methods only allowed us to combine a few of them in analyses. We found that there is a consistent link between use of anticholinergic medicines and risk of future dementia. We cannot say if these medicines play a causal role; however, if they do, taking these medicines could potentially double a person's risk of dementia.

Of the anticholinergic measurement scales available, we could assess one commonly used tool – the 'Anticholinergic Cognitive Burden scale.' If this scale identified someone as having high anticholinergic burden, the risk of future dementia was more than two times higher than for someone with no anticholinergic burden.

The evidence included in this review was of a low quality overall and may have exaggerated the strength of the association between anticholinergic medicines and dementia. For example, anticholinergic medicines may be prescribed for the early symptoms of dementia. This would give a strong link but would not imply that the medicine caused the memory problems. Similarly, there is a risk that studies are only published when they show an association between anticholinergic medicines and future dementia. It may be that the only way to truly establish if anticholinergic medications are associated with future dementia would be to conduct a study where some people have their anticholinergic medications stopped or changed to an alternative and others continue their usual medications.

How up to date was this review?

We searched for studies published up to 24 March 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Older adults with anticholinergic burden compared with older adults with no anticholinergic burden for dementia

Older adults with anticholinergic burden compared with older adults with no anticholinergic burden for dementia

Patient or population: older adults without cognitive impairment at baseline

Settings: mixed

Intervention: older adults with an anticholinergic burden (defined according to the Anticholinergic Cognitive Burden scale)

Comparison: older adults with no anticholinergic burden

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cognitive decline or dementia	OR 2.63 (95% CI 1.09 to 6.29)	125,359 (4 studies) ^a	⊕⊕⊕⊕ Low ^{b,c,d,e}	Findings were restricted to studies included in our primary analysis evaluating the association between anticholinergic burden (as defined by the Anticholinergic Cognitive Burden scale) and risk of cognitive decline or dementia, independent of age, sex, and comorbidities. Evidence indicates anticholinergic burden may increase the odds of developing future cognitive decline or dementia.

CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a Campbell 2016; Hafdi 2020; Hsu 2017; Richardson 2018. Differences in design and methods restricted suitability of available studies for pooling in meta-analysis to these four studies.

^bTwo of four studies were at high risk of bias, with issues around reverse causation. The remaining two studies were at unclear risk of bias, one of which had unclear risk of bias due to reverse causation. Therefore, downgraded one level for serious risk of bias.

^cThe confidence intervals of our pooled odds ratio differed by more than five points. Downgraded one level for imprecision.

^dWe were unable to evaluate risk of bias via a funnel plot; however, risk of publication bias was assumed within this literature unless evidence was found to the contrary. Downgraded one level.

^eA trend of increasing risk based on severity of anticholinergic burden was apparent in subgroup analysis, with the odds ratios increasing linearly from 'low severity' to 'high severity.' Upgraded one level.

BACKGROUND

Description of the condition

Cognition (or cognitive function) is the mental process of acquiring knowledge and understanding through experience, senses, and thought. It includes the domains of memory, language, attention, executive functioning, and visuospatial processing. Cognitive impairment is the disruption of functioning of any one of these domains. Cognitive function may be assessed in detail using a battery of neuropsychological tests covering multiple domains; although in clinical practice, brief assessment tools such as the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) are often used (Folstein 1975; Nasreddine 2005).

Dementia is a syndrome of decline in cognitive function beyond that expected from normal ageing and to an extent that interferes with usual functioning. It may affect memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. There are a variety of internationally accepted diagnostic criteria for dementia, the most widely used of which are included in the World Health Organization International Classification of Diseases (ICD) and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM). The most recent iteration of the DSM (DSM-5) refers to 'major neurocognitive disorder' instead of dementia.

The labels of 'dementia' or 'major neurocognitive disorder' encompass a variety of pathologies, with specific diagnostic criteria also available for pathologically defined dementia subtypes, such as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for dementia due to Alzheimer's disease (McKhann 1984; McKhann 2011); McKeith criteria for Lewy body dementia (McKeith 2005); Lund criteria for frontotemporal dementias (McKhann 2001); and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (Román 1993).

An individual may experience a decline in cognition that is not enough to merit a label of dementia but that is more than would be expected as part of ageing. An objective cognitive impairment that is not severe enough to have a significant impact on daily activities is referred to as a mild cognitive impairment (MCI). This is a risk factor for future dementia as one in five may go on to develop dementia within five years (Petersen 2001).

Dementia and cognitive decline are major public health issues. There are currently more than 40 million people worldwide with dementia due to Alzheimer's disease – the most common subtype – and this number is projected to increase to more than 100 million by 2050 (Prince 2016). Dementia costs were estimated at USD 818,000 million in 2015, equivalent to 1.1% of global gross domestic product. It is estimated that by 2030, the global cost of dementia could grow to USD 2,000,000 million, which could overwhelm health and social care systems (Wimo 2017). The total cost of dementia to the UK alone is GBP 34,700 million, of which GBP 4,900 million is paid by the National Health Service (NHS) and GBP 15,700 million is paid by social care. The remainder is paid by those

living with dementia and their families, and is classified as unpaid social care or private care (Alzheimer's Society 2019).

A number of prognostic factors have been associated with the onset of dementia, including age, sex, premorbid intelligence, genetics, medical conditions (e.g. diabetes, hypertension), and lifestyle factors (e.g. physical inactivity) (Livingston 2017). Identification of prognostic factors could assist healthcare professionals in predicting outcomes for people with cognitive syndromes and help policymakers in planning for future population healthcare needs. Identification of modifiable prognostic factors are potential targets for preventing or delaying the onset of cognitive decline and dementia.

Description of the prognostic factor

A prognostic factor is any measure that is associated with a future clinical outcome. The prognostic factor of interest for this review is anticholinergic burden from medication use.

Numerous medications commonly used in older adults have anticholinergic properties. Some medications, such as oxybutynin (for overactive bladder), exert their intended action through their anticholinergic activity. For other medications, such as amitriptyline for depression, anticholinergic activity is probably incidental to their intended mechanism of action. It is common for older adults to be taking multiple medications with anticholinergic properties (Myint 2015).

Even medications that have low anticholinergic activity individually may contribute to a significant overall anticholinergic effect if a person is taking several of them. This can be quantified as the anticholinergic burden. There is a reported relationship between anticholinergic burden and various adverse health outcomes (Singh 2008). It has been suggested that exposure to high anticholinergic burden is associated with cognitive decline and dementia in older adults (Fox 2014). Anticholinergic burden measures are used in primary and secondary care as part of the medication review process. Such reviews are increasingly recommended for older adults. The quantification of anticholinergic burden is designed to assess risk of future adverse events. Based on the anticholinergic burden score, clinicians may recommend reducing or replacing certain medications. Use of measures of anticholinergic burden to guide treatment decisions is entering clinical practice. The most recent National Institute for Health and Care Excellence (NICE) dementia guideline recommends considering anticholinergic burden as a factor that may be contributing to cognitive impairment and suggests using a validated scale to measure anticholinergic burden (NICE 2018). To date, anticholinergic burden has been considered largely as a 'stand-alone' prognostic factor (not as part of a multifactorial prediction model).

Measures of anticholinergic burden

Anticholinergic burden can be measured using a variety of approaches. There is no consensus on which anticholinergic burden measures provide the most accurate and clinically useful prognostic information. Generally, anticholinergic burden measures use a person's medication list and assign a score to certain medications. A cumulative total based on all prescribed medications is then calculated. Although these measures should be

similar, overlap is limited; they include differing medications and assign differing scores to these medications.

Our literature scoping suggests that 18 tools to measure anticholinergic burden have been published. One large population cohort (UK Biobank) reported that anticholinergic burden was strongly associated with future adverse health outcomes regardless of which anticholinergic burden measure was used (Hanlon 2020). However, at the individual patient level, there was substantial variability in the anticholinergic burden score generated by each measure. Methodologies for developing respective scales vary significantly: where some incorporate expert clinical opinion in their development and are designed to measure both central and peripheral anticholinergic effects, others focus on serum radioreceptor anticholinergic activity assay or muscarinic receptor affinity measurements and may only capture peripheral anticholinergic effects. Therefore, any prognostic review should be completed at the individual scale level in addition to creating summary estimates for all anticholinergic burden measures.

Prior to adoption in clinical practice, there should be a comprehensive assessment of the available literature to describe whether anticholinergic burden is a true prognostic factor, particularly adjusting for other dementia risk factors that may also be associated with anticholinergic prescribing. The relationship may vary based on the duration of the drug exposure period or via differences in clinical and demographic characteristics in specific clinical or community-based settings. If anticholinergic burden is a prognostic factor, the strength of the association and the quality of the supporting evidence should also be described. Looking at the prognostic properties of each anticholinergic burden measure may assist in choosing a preferred scale.

Why is it important to do this review?

Increasing clinical interest in anticholinergic burden is accompanied by a growth in the research literature on anticholinergic burden as a prognostic factor. However, results from individual studies of anticholinergic burden and cognition or dementia are conflicting. Not all published papers have followed best practice in design, conduct, or reporting; and comparative strength of associations between respective scales and dementia has not been established. Thus, there is uncertainty around the clinical utility of anticholinergic burden and, consequently, inconsistency in clinical practice and guideline recommendations. In this systematic review, we aimed to estimate the prognostic utility (adjusted and unadjusted) of different anticholinergic burden measures for predicting cognitive decline or dementia in a cognitively healthy older adult population, and to assess the quality of the supporting evidence.

OBJECTIVES

Primary objective

- To assess whether anticholinergic burden, as defined at the level of each individual scale, is a prognostic factor for future cognitive decline or dementia in cognitively unimpaired older adults.

Secondary objectives

- To assess whether the strength of association between anticholinergic burden and future cognitive decline or dementia

differs in various settings (e.g. primary care, secondary care, or community settings).

- To compare the prognostic validity of different anticholinergic burden scales.
- To examine the effect of duration of exposure and duration of follow-up on the anticholinergic burden dementia risk association.

METHODS

We followed best practice in design, conduct, and reporting of our prognosis review as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The review was supported by the Cochrane Prognostic Methods Group, partners within the Cochrane Mental Health and Neuroscience Network, and the UK National Institute for Health Research Complex Reviews Support Unit (NIHR CRSU).

We used the PICOT (Patient/Problem; Intervention; Comparison; Outcome; Timing) system to design our review question (Schardt 2007) (Table 1). As recommended by the Cochrane Prognosis Methods Group, we followed guidelines suggested by Riley 2019, to ensure that our review was designed, conducted, and reported in keeping with best practice recommendations.

Criteria for considering studies for this review

Types of studies

We included prospective and retrospective longitudinal cohort and case-control observational studies. We did not include cross-sectional studies, as it is not possible to determine prognosis from this design. We did not include prospective case studies, defined here as having fewer than 20 participants. We excluded studies that were published only as abstracts or posters at conferences, as these have not undergone peer review.

Types of participants

We included any studies that recruited older adults (as defined by the authors, but with minimum median/mean age 50 years at baseline) who were free of any known cognitive diagnosis (MCI, dementia, delirium) at time of recruitment and at time of application of the anticholinergic burden measure. We did not exclude studies that did not assess cognition at baseline; however, where a mixed population was recruited, we only included the study if the prevalence of dementia was less than 7% in a community sample (similar to general population prevalence in unselected older adults). We also included studies that recruited mixed populations in a hospital setting, where the prevalence of dementia was higher, provided that it was conducted in an unselected (i.e. consecutive admissions) sample.

We included studies where initial recruitment was in primary care, secondary care, and community settings. Participants in these respective settings may differ in important demographics (e.g. mean age, clinical or lifestyle factors) that could alter the strength of the association between anticholinergic burden and cognitive decline or dementia. We defined primary care as settings in which the patient self-presented to a non-specialist service, such as general practice. We defined secondary care as any settings where patients were referred for expert care, including general hospitals and more specialist settings. We defined community settings as

settings in which the cohort was completely unselected, that is 'population screening.'

As this review focused on prognosis in people who were cognitively well, we did not include studies conducted in care-home settings where the prevalence of cognitive syndromes is substantial.

We made no other restriction based on comorbidity or polypharmacy but recorded these factors in our data extraction. We assessed whether comorbid conditions that are associated with dementia (depression, stroke, other neurological diseases) were measured and considered any potential impact of this in our 'Risk of bias' assessment. We included studies conducted in specific patient subgroups, such as Parkinson's disease or stroke, provided they met our other inclusion criteria.

Index prognostic factor

The prognostic factor of interest was anticholinergic burden from medications. We included any study that used an ordinal scale that purported to measure cumulative exposure to medications with anticholinergic properties. Scales did not need to be described as validated for prediction of cognitive outcomes. Previously identified scales are listed in [Appendix 1](#).

Different approaches to quantifying anticholinergic burden have been used. Some scales sum ordinal scores for each relevant drug to give a continuous measure; others create a summary ordinal hierarchical measure that scores, for example, 0 to 3 or 0 to 4 based on the cumulative anticholinergic exposure. Most scales define thresholds of 'low' and 'high' burden. As our focus in this review was on the extent of anticholinergic burden, we did not include studies that established anticholinergic exposure via a simple dichotomised present/absent method.

Some anticholinergic burden measures were developed specifically to predict dementia, while others were developed to predict other adverse events, including death. Anticholinergic activity should be an objective drug effect, and so we included any anticholinergic burden measure, not just those developed for cognitive outcomes.

We did not choose a particular measure of primary interest as there is no consensus on the preferred measure, and there is substantial heterogeneity in clinical practice. However, if the Drug Burden Index (DBI) scale was utilised, we only included data if anticholinergic burden data were reported separately.

Comparator prognostic factors

We were interested in the value of anticholinergic burden as a prognostic factor over and above other prognostic factors that may be common in this population. Hence, while we included studies that only assessed the unadjusted anticholinergic burden prognosis, we also evaluated the prognostic effect of anticholinergic burden adjustment for core variables identified as fundamental to the putative link between anticholinergic burden and dementia. These variables were selected on the basis of a Delphi discussion between the review authors and a wider multicentre collaborative, working in the field of anticholinergic burden research ([Appendix 2](#)). The chosen core variables were age, sex, and comorbidity. We recognise that comorbidity may be described in various ways. We accepted any classification that the original study authors defined as a measure of comorbidity,

including measures that offered quantitative data, for example, number of medications, number of medical conditions listed, or formal measures such as the Charlson Comorbidity Index.

We assessed use of additional adjustments in our 'Risk of bias' assessment.

Outcome measures

Primary outcome: we included any study that assessed incident dementia, MCI, or cognitive decline (i.e. change on a measure of cognitive function) as an outcome. We accepted any validated diagnostic criteria for dementia or MCI. For the outcome of cognitive decline, we accepted any multidomain cognitive assessment tool that is validated for the direct assessment of cognition. We did not include papers that only measured a single cognitive domain.

Timing: we accepted assessment for cognitive decline or dementia at one year or longer following baseline anticholinergic burden assessment to mitigate the risk of reverse causality between any observed risk associations.

Search methods for identification of studies

Electronic searches

As reporting of prognostic factor studies is variable, it can be challenging to identify all relevant studies. We adopted the procedure proposed by [Geersing 2012](#) to maximise our ability to identify relevant prognostic studies. Specifically, as we searched for one prognostic factor, we did not adopt any specific search filter, but instead adopted a search that combines our prognostic factor (anticholinergic burden) with the disease outcome (dementia/cognitive impairment).

We searched the following databases: MEDLINE (1946 to 24 March 2021; OvidSP), Embase (1974 to 24 March 2021; OvidSP), PsycINFO (1806 to 24 March 2021; OvidSP), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1950 to 24 March 2021; EBSCOhost), and ISI Web of Science Core Collection (1928 to 24 March 2021; ISI Web of Science) ([Appendix 3](#)). We applied no language restrictions.

Searching other resources

We supplemented this with handsearches of all included studies and identified systematic reviews.

Data collection and analysis

Selection of studies

We used Covidence systematic review software to identify relevant studies ([Covidence](#)). The review group Information Scientist performed a 'first pass' screen to remove clearly irrelevant titles. Two review authors (MT and SE) independently screened studies identified via our search method. Titles and abstracts were screened in the first instance, with the full text of potentially relevant studies then accessed to determine if the study met our inclusion criteria. In case of disagreement, a third review author (TQ) acted as arbiter and made the final decision on study inclusion/exclusion.

Data extraction and management

Two review authors (MT and SE) extracted the data to a piloted proforma based on the CHARMS-PF (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies, adapted for prognostic factors) template (Riley 2019). We contacted authors for missing data where required. We selected two studies to trial our data extraction proforma (Gray 2015; Richardson 2018a). We extracted all data onto a standard form (Appendix 4).

Assessment of methodological quality

Two review authors (MT and SE) independently used the QUIPS (Quality in Prognosis Studies) checklist (Hayden 2012), assessing the included studies across the domains of: study participation; study attrition; prognostic factor measurement; outcome measurement; adjustment for covariates; reverse causation; statistical analyses; and reporting. We used the QUIPS anchoring statements but modified the content to suit our review topic based on consensus within the review author team. We judged each domain as low risk of bias, moderate risk of bias, or high risk of bias (Appendix 5). In cases of uncertainty we contacted original study authors for clarification, where possible.

Discussing reporting deficiencies: prognosis research is frequently confounded by poor reporting and possible publication bias. We supplemented our 'Risk of bias' assessment with a narrative discussion of reporting issues, highlighting when missing information may have affected results. Prognostic factor studies often do not register protocols, increasing the risk that not all studies (published and unpublished) will be identified, and there is a risk of small-study effects (in which smaller studies with higher odds ratios (ORs) are more likely to be published than smaller studies with non-significant ORs), which can bias meta-analyses (Peat 2014; Riley 2019). We used sensitive search filters for the disease (dementia) and the prognostic factor (anticholinergic burden) without any specific filter for prognostic research to increase retrieval, and attempted to examine the likelihood of small-study effects in our review by generating a funnel plot.

Data synthesis

We evaluated risk of future cognitive decline or dementia for anticholinergic drug users against non-users. Where possible, we pooled summary estimates for each anticholinergic burden tool individually; then, as an exploratory analysis, pooled summary estimates across all scales. We conducted each meta-analysis in two ways. First, as an all-encompassing 'any anticholinergic drug use' variable; second, as an ordinal, hierarchical variable in which low, moderate, and high users were pooled separately, to investigate possible differential relationships based on anticholinergic burden severity. Low users were defined as those with a cumulative score of 1 on an anticholinergic scale; moderate users were defined as those with a cumulative score of 2 on an anticholinergic scale; high users were defined as those with a cumulative anticholinergic scale score of 3 or above.

We pooled data in two separate ways. In the first instance, we pooled data obtained from unadjusted analyses. In the second instance, we pooled data from fully adjusted analyses, provided age, sex, and comorbidity were controlled for as a minimum. We pooled ORs and hazard ratios separately. We planned to calculate standardised mean difference (SMD) for linear data and

pool this separately from dichotomous outcome data. Where data were not available, we attempted to estimate data based on methods suggested by Tierney 2007. Where data were sufficiently similar to permit pooling, we used a random-effects approach given our expectation of high heterogeneity between studies. We used Comprehensive Meta-Analysis software to conduct all meta-analyses (Comprehensive Meta-Analysis Version 3).

We conducted a sensitivity analysis, restricting to studies that had no high risk of bias domains.

For secondary (subgroup) analysis, we assessed risk by setting. We also conducted analysis based on duration of follow-up. We created categories of one to five years, and longer than five years and considered pooled rates for each timeframe individually. These additional outcomes were decided upon through discussion among the review authors.

We planned to assess exposure, including exposure before enrolment into the study and exposure during the study.

Finally, we planned to conduct a comparative analysis of the prognostic performance of the differing anticholinergic burden measures using a network meta-analysis.

Investigation/description of heterogeneity

We described heterogeneity narratively based on consistency of association and effect size between anticholinergic burden and future cognitive decline or dementia, measurement of prognostic factor, outcome measurement and definition, and study design. We did not employ the I^2 statistic in our evaluation of heterogeneity. In prognosis research, individual studies often have large sample sizes resulting in narrow confidence intervals (CIs); this can cause high I^2 values even if inconsistency between studies is moderate (Iorio 2015).

It is possible that observed associations between anticholinergic drugs and future cognitive decline or dementia are driven by uncontrolled variables. Number of medical conditions or overall polypharmacy are two possible moderators of observed effects and could differ by setting. To investigate this, we planned to conduct a meta-regression based on study recruitment setting (primary versus secondary care versus community care), comorbidity ('number of comorbidities' controlled for as a covariate, yes/no), and polypharmacy (controlled for as a covariate, yes/no).

Grading the evidence

We used the GRADE approach to evaluate our overall confidence in the results. We adapted the GRADE approach to suit prognosis research using methods consistent with Huguet 2013. Specifically, we evaluated reported evidence in the following eight areas.

- Phase of investigation: phase 3 explanatory studies derived from bespoke cohort study designs that seek to explain the mechanisms behind an underlying association between anticholinergic burden and dementia/cognition were considered a high level of evidence. Phase 2 explanatory studies that seek to confirm an independent association between anticholinergic burden and dementia/cognition were treated as moderate evidence, and hypothesis-generating phase 1 explanatory studies were treated as weak evidence for any

association between anticholinergic burden and dementia/cognition.

- Study limitations: we used the previously described QUIPS tool to evaluate the overall risk of bias of included studies. Our GRADE judgement was based upon the overall certainty of the evidence, that is, if most (more than 50%) included studies were considered at high risk of bias in their reported association between anticholinergic burden and dementia/cognition, we downgraded the evidence accordingly.
- Inconsistency: we downgraded the evidence if associations between ACB and dementia/cognition were heterogeneous (i.e. the reported ORs/hazard ratios fell either side of 1.0 on a forest plot, the measure of the prognostic factor was highly variable, outcome measurement was highly variable, and methodological heterogeneity due to study design/potential biases study design); and if the P value was low for the test of the null hypothesis that all studies in a meta-analysis have the same underlying magnitude effect.
- Indirectness: we downgraded the studies where their investigation did not fully match with our broader review question. We considered two areas of indirectness when judging if evidence should be downgraded on this basis: 1. if the population in the included studies only represented a subset of the population of interest (e.g. if only very old, i.e. older than 80 years, were assessed); 2. if the outcome investigated in the included studies was overly restricted (e.g. if the included studies explored only the association between anticholinergic burden and Alzheimer's dementia), then the evidence for the association between anticholinergic burden and all-cause dementia was downgraded for indirectness.
- Imprecision: we downgraded the evidence if there were insufficient numbers in the meta-analysis or if the CIs were wide.

We did not set an absolute value, but assessed this in the context of effect size and minimally important clinical difference.

- Publication bias: due to inherent issues regarding publication bias in prognostic research, we adopted the default position that publication bias was likely and downgraded the evidence unless our assessment of publication bias provided significant evidence to the contrary (i.e. a symmetrically distributed funnel plot, and evidence that the prognostic factor has been investigated in numerous cohort studies).
- Effect size: we upgraded our confidence in the effect estimate when the effect size was moderate to large (e.g. a hazard ratio of 2.5 or above).
- Exposure-response gradient: we upgraded our confidence in the effect estimate if there was evidence (via subgroup analysis) that a longer duration of anticholinergic burden was associated with an increased risk of dementia/cognitive decline. Similarly, we upgraded the evidence if there was an incremental increase in effect size with increasing anticholinergic burden.

RESULTS

Description of studies

Results of the search

Our search identified 16,391 results. We identified a further four eligible studies via handsearching references. After deduplication and assessment of abstracts, we assessed 93 studies via full-text screening, of which 25 met our inclusion criteria. See [Characteristics of excluded studies](#) table for reasons for exclusion. [Figure 1](#) shows the PRISMA flow chart ([Moher 2009](#)).

Figure 1. Study flow diagram.

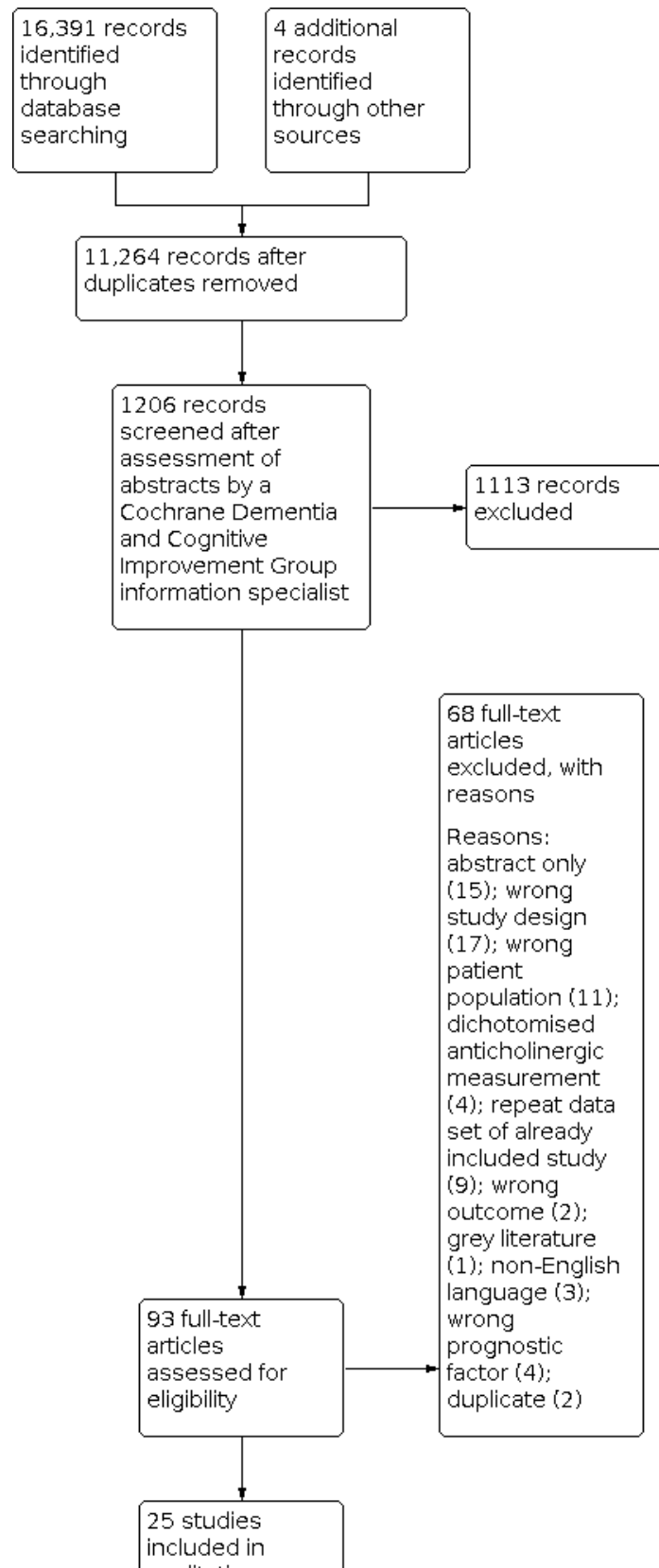
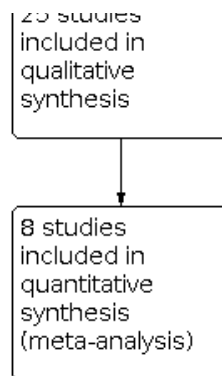


Figure 1. (Continued)



Included studies

Twenty-two studies were longitudinal 'cohort' designs and three were 'case control' studies (Coupland 2019; Richardson 2018; Yarnall 2015). All but one study (Iyer 2020) were conducted in a retrospective fashion, utilising databases in which participant information was obtained for a purpose other than investigating the association between anticholinergic burden and risk of future cognitive decline or dementia. Study sample sizes ranged from 102 to 324,703 participants and were conducted in Europe, North America, Asia, and Oceania: specifically, eight in the US; six in the UK; two in Taiwan; and one each in Sweden, Canada, France, Italy, Australia, Germany, Netherlands, Ireland, and South Korea. Follow-up times for development of cognitive decline or dementia ranged from one to 11 years. See [Characteristics of included studies](#) table for details.

Participant characteristics

The review included 968,428 older adults; about 60% were women, mean/median age range across studies was 52 to 83 years. Participants were recruited overwhelmingly from community settings (963,081; 99.4%); 3716 (0.4%) were recruited via attendance at primary care clinics and 1525 (0.1%) were recruited in a secondary care setting. Most included studies were inclusive of the general 'older adult' population. However, two studies were conducted in people with Parkinson's disease (Sheu 2019; Yarnall 2015); one study was conducted in people with an overactive bladder (Iyer 2020); and one study was restricted to a 'young old' population (Low 2009).

Prognostic factor

Anticholinergic burden was assessed via 10 distinct methods. Eight studies used more than one method (Ancelin 2006; Brombo 2018; Coupland 2019; Gray 2015; Hsu 2017; Joung 2019; Kashyap 2014; Richardson 2018). Nineteen studies used an anticholinergic measurement scale: 17 used the Anticholinergic Cognitive Burden scale (ACB scale) (Brombo 2018; Campbell 2016; Chuang 2017; Coupland 2019; Fox 2011a; Grossi 2019; Hafdi 2020; Hsu 2017; Iyer 2020; Joung 2019; Kashyap 2014; Koyama 2014; Moriarty 2020; Richardson 2018; Risacher 2016; Shah 2013; Sheu 2019), four used the Anticholinergic Drug Scale (ADS) (Kashyap 2014; Low 2009; Richardson 2018; Yarnall 2015), three used the Anticholinergic Risk Scale (ARS) (Brombo 2018; Hsu 2017; Kashyap 2014), and two used the anticholinergic component of the Drug Burden Index (DBI-ach) (Hsu 2017; Kashyap 2014). One study evaluated anticholinergic burden via a list defined by Chew 2008 (Jessen 2010); one study

used a clinician-rated anticholinergic score (Han 2008); one study used the Anatomical Therapeutic Chemical classification system (Papenberg 2017); two studies used the ACB scale in combination with Beers criteria (Coupland 2019; Joung 2019); one study used a literature review of drugs' anticholinergic activity (Whalley 2012); one study used Beers criteria combined with a literature review (Gray 2015); and one study used serum radioreceptor assay combined with a summation of mean estimated clinical effects of specific drugs, established via a pharmacologist, physician, and biologist (Ancelin 2006).

Outcome measures

Eleven studies reported assessing for dementia as an outcome (Ancelin 2006; Coupland 2019; Gray 2015; Grossi 2019; Hafdi 2020; Hsu 2017; Jessen 2010; Joung 2019; Richardson 2018; Sheu 2019; Whalley 2012); three reported MCI and dementia combined (Campbell 2016; Chuang 2017; Risacher 2016); four reported MCI alone (Ancelin 2006; Kashyap 2014; Low 2009; Yarnall 2015); and 13 reported multidomain cognitive impairment based on standardised cognitive test scores (Ancelin 2006; Brombo 2018; Fox 2011a; Han 2008; Iyer 2020; Kashyap 2014; Koyama 2014; Low 2009; Moriarty 2020; Papenberg 2017; Risacher 2016; Shah 2013; Whalley 2012; Yarnall 2015). Six studies established dementia or MCI via a consensus diagnosis based on a multidisciplinary evaluation (Campbell 2016; Chuang 2017; Gray 2015; Hafdi 2020; Jessen 2010; Whalley 2012). Three studies established dementia or MCI via a clinical examination from a single expert (e.g. neurologist, psychiatrist) (Ancelin 2006; Kashyap 2014; Low 2009). Five studies relied upon clinical codes recorded in medical records for diagnoses (Coupland 2019; Hsu 2017; Joung 2019; Richardson 2018; Sheu 2019), and one study employed a computer algorithm (Grossi 2019). Method for diagnosing dementia or MCI was unclear in two studies (Risacher 2016; Yarnall 2015). Dementia was diagnosed according to the DSM (APA 2000) criteria in seven studies (Ancelin 2006; Campbell 2016; Chuang 2017; Gray 2015; Grossi 2019; Hafdi 2020; Jessen 2010), and ICD-10 (WHO 1992) criteria in three studies (Jessen 2010; Sheu 2019; Whalley 2012). Three studies did not explicitly state dementia diagnostic criteria (Coupland 2019; Hsu 2017; Richardson 2018). MCI was diagnosed according to DSM-5 criteria in one study (Kashyap 2014), Peterson criteria (Petersen 2001) in one study (Chuang 2017), Jack criteria (Jack 1999) in one study (Low 2009), DSM III criteria in one study (Campbell 2016), Stockholm consensus group criteria (Winbald 2004) in one study (Ancelin 2006), and Movement Disorder Society criteria (Litvan 2012) in one study (Yarnall 2015). One study did not state criteria by which MCI was defined (Risacher 2016).

Risk of bias in included studies

Nineteen studies were at high risk of bias in at least one domain. No studies were at low risk of bias in every domain.

Most common issues were around lack of control for reverse causation (14 studies at high risk of bias), study attrition/missing data (nine studies at high risk of bias), and population generalisability (nine studies at high risk of bias).

Only two studies employed a dual approach to establishing medication use that would enhance identification of both prescription and non-prescription drugs, along with recording dosage, duration of exposure, and adherence (Fox 2011a; Kashyap 2014). Two studies did not record anticholinergic drug usage at

multiple time points, despite a follow-up duration of more than one year (Koyama 2014; Risacher 2016).

Most studies controlled for age, sex, and comorbidities as covariates; however, only 13 studies controlled for psychiatric conditions, such as depression, that may heighten risk, or even be prodromal signs of dementia as well as increase anticholinergic burden (Ancelin 2006; Coupland 2019; Gray 2015; Grossi 2019; Hafdi 2020; Han 2008; Iyer 2020; Joung 2019; Moriarty 2020; Papenberg 2017; Richardson 2018; Sheu 2019; Yarnall 2015).

There were also general issues around good methodological practice: no protocols were registered; only three studies reported tests of statistical assumptions in analysis (Joung 2019; Moriarty 2020; Risacher 2016), and no studies reported blinding to outcome when assessing anticholinergic burden scores (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Reverse causation	Statistical analysis and reporting
Ancelin 2006	?	?	?	?	?	-	?
Brombo 2018	-	-	?	?	?	-	?
Campbell 2016	-	-	?	?	?	-	?
Chuang 2017	?	-	?	?	?	-	?
Coupland 2019	+	?	?	?	+	+	?
Fox 2011a	?	-	+	?	?	?	?
Gray 2015	+	?	?	?	+	?	?
Grossi 2019	+	-	?	?	+	+	?
Hafdi 2020	+	?	?	?	+	?	?
Han 2008	-	?	?	?	+	-	?
Hsu 2017	+	?	?	?	?	-	?
Iyer 2020	-	-	?	-	+	-	?
Jessen 2010	?	?	?	?	-	-	?
Joung 2019	+	?	?	?	+	+	?
Kashyap 2014	?	?	+	?	-	-	-
Koyama 2014	-	-	-	?	?	?	?
Low 2009	?	?	?	-	?	-	-
Moriarty 2020	?	+	?	?	+	?	?
Papenberg 2017	+	-	?	?	+	-	?
Richardson 2018	+	?	?	?	+	+	?
Risacher 2016	-	?	-	?	?	-	-
Shah 2013	-	?	?	?	?	-	?
Sheu 2019	-	?	?	?	+	?	?
Whalley 2012	?	-	?	?	?	?	-
Yarnall 2015	-	?	?	?	+	-	-

Association between anticholinergic burden and dementia/cognitive decline

Twenty-three of 25 studies reported a significant association between anticholinergic use and increased risk of cognitive impairment (of any type). However, specific associations between anticholinergic use and risk of dementia, MCI, and cognitive decline were more heterogeneous.

- **Dementia:** 9/11 studies reported a significantly increased risk for dementia (Coupland 2019; Gray 2015; Grossi 2019; Hafdi 2020; Hsu 2017; Jessen 2010; Joung 2019; Richardson 2018; Sheu 2019); two studies reported no association (Ancelin 2006; Whalley 2012).
- **MCI and dementia:** 3/3 studies reported significant increased risk for MCI and dementia combined (Campbell 2016; Chuang 2017; Risacher 2016).
- **MCI alone:** 1/4 studies reported significantly increased risk for MCI (Ancelin 2006); 3/4 studies reported no association (Kashyap 2014; Low 2009; Yarnall 2015).
- **Cognitive decline:** 12/14 studies reported significantly increased risk for reduced performance on cognitive tests (Ancelin 2006; Brombo 2018; Fox 2011a; Han 2008; Kashyap 2014; Koyama 2014; Low 2009; Moriarty 2020; Papenberg 2017; Risacher 2016; Shah 2013; Whalley 2012); two studies reported no association (Iyer 2020; Yarnall 2015). Investigated domains were extremely diverse and affected domains inconsistently reported. There were statistically significant declines for memory (seven studies; Ancelin 2006; Han 2008; Kashyap 2014; Koyama 2014; Moriarty 2020; Papenberg 2017; Risacher 2016), executive functioning (four studies; Han 2008; Kashyap 2014; Risacher 2016; Whalley 2012), visuospatial construction (one study; Ancelin 2006), language (two studies; Ancelin 2006; Koyama 2014), processing speed (two studies; Ancelin 2006; Low 2009), and attention (one study; Ancelin 2006). Three studies reported a global cognitive decline on cognitive testing (Brombo 2018; Fox 2011a; Shah 2013).

One study investigated the association between anticholinergic use and cognitive decline via a univariate regression only (Kashyap 2014). Choice of comorbidities varied across all studies that assessed the association via multiple regression (see [Characteristics of included studies](#) table).

A variety of factors influenced the observed association between anticholinergic burden and cognitive impairment.

Associations differed by anticholinergic burden score and dosage. Most studies suggested that a higher anticholinergic burden score/dosage is more strongly associated with cognitive impairment than lower scores/dosages. Two studies found the association was only apparent in those with a low anticholinergic burden (anticholinergic burden = 1), though both studies had low numbers of moderate/high anticholinergic burden (Ancelin 2006; Chuang 2017), and one study reported that those with an anticholinergic burden of 2 or 3 had a shorter duration of exposure and frequency of use than those with an anticholinergic burden of 1 (Chuang 2017).

Duration of use was a modifying factor in five studies. Three studies found an association between anticholinergic burden and cognitive impairment for recurrent/persistent drug users only (Grossi 2019; Hafdi 2020; Papenberg 2017), while one study found

that continuous use of anticholinergic drugs was more strongly associated with cognitive impairment than intermittent use (Joung 2019). By contrast, one study found that the gradient of global cognitive decline was greater for incident users, but not for prevalent users (Shah 2013); while one study reported a larger decline in cognitive scores for new users compared to persistent users, and no significant difference in decline on cognitive scores between discontinued users and non-users (Moriarty 2020).

Drug type was a factor explored in five studies. Three studies found drug type altered the relationship between anticholinergic burden and risk of cognitive impairment (Coupland 2019; Hafdi 2020; Richardson 2018). Specifically, antidepressants, analgesics, anti-Parkinson's, antipsychotics, antiemetics, urological, and respiratory drugs were significantly associated with increased risk of cognitive impairment; while antihistamines, cardiovascular, and gastrointestinal drugs were not. Two studies found risk for dementia in the highest exposure category was independent of anticholinergic drug type (Gray 2015; Joung 2019).

The population investigated also appears to be an important moderator of the association. The two studies that reported no association between anticholinergic use and future cognitive impairment (of any type) were conducted in a people with Parkinson's disease (Yarnall 2015) and overactive bladder (Iyer 2020). All studies that investigated the association in a more 'general' older adult population reported a significant association of some type.

Meta-analysis

Twelve studies provided OR or hazard ratio (or both) data for meta-analysis. Thirteen studies provided linear data (Ancelin 2006; Brombo 2018; Fox 2011a; Han 2008; Iyer 2020; Koyama 2014; Low 2009; Moriarty 2020; Papenberg 2017; Risacher 2016; Shah 2013; Whalley 2012; Yarnall 2015). However, hazard ratio and linear data were too heterogeneous to pool; therefore, we report only on the results of pooled ORs. See [Characteristics of included studies](#) table for the specific covariates controlled for in each study included in our meta-analyses.

Some of the included papers described associations for various cognitive outcomes. For our primary cognitive analysis, we had to prioritise a single outcome. We prespecified that we would favour data that described the association with incident clinical dementia. We chose this outcome as we anticipated it would be most commonly reported and arguably it is the most clinically relevant. Similarly, some papers included multiple scales that purport to measure anticholinergic burden. In these instances, we favoured the ACB scale as we anticipated that this would be the most commonly used.

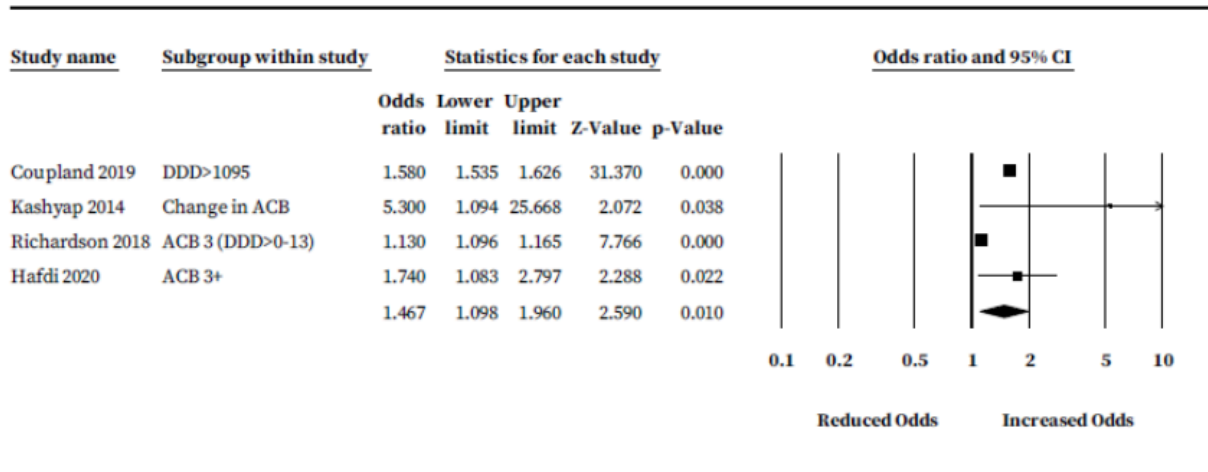
Univariate association

Four studies (287,546 participants) provided unadjusted ORs (Coupland 2019; Hafdi 2020; Kashyap 2014; Richardson 2018). Three of four studies reported ORs for risk of dementia only; one study reported ORs for cognitive decline (Kashyap 2014). There were insufficient numbers to pool ORs subgrouped by anticholinergic measurement scale; hence, we pooled rates across all scales. Where studies provided ORs subgrouped by anticholinergic burden score only, we selected anticholinergic burden values of 3 or closest to evaluate 'definite' anticholinergic drugs while maximising statistical power

and minimising heterogeneity. Richardson 2018 subgrouped cumulative anticholinergic burden score by defined daily dosage (DDD); therefore, we selected the largest group (DDD greater than 0 to 13) in the ACB scale 3 category. One study reported dosage-based subgroups only; for this study, the ORs from the largest 'dosage subgroup' (1 to 90) had asymmetrical CIs, hence we selected the

ORs from the dosage with the second highest participant numbers ('greater than 1900') (Coupland 2019). Pooled rates suggested a significant increase in risk of cognitive impairment or dementia for anticholinergic drug users compared to non-users (OR 1.47, 95% CI 1.09 to 1.96) (Figure 3).

Figure 3. Unadjusted analysis: anticholinergic burden and odds of future cognitive decline or dementia.

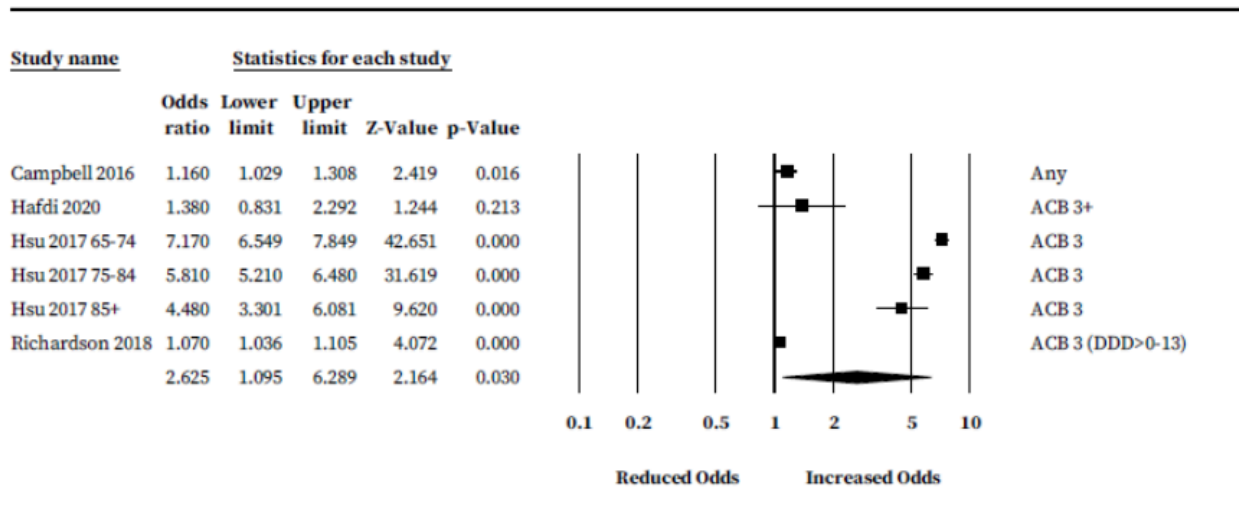


Fully adjusted multivariate model

For our primary analysis on the association between anticholinergic drug use and risk of cognitive decline or dementia, three studies (121,833 participants) provided ORs based on use of the ACB scale *exclusively* to establish anticholinergic burden (Campbell 2016; Hsu 2017; Richardson 2018). One additional study provided ORs after contacting the author (Hafdi 2020). One other study reported ORs in a form that could be included in our ACB scale meta-analysis (Sheu 2019). However, this study compared those with a moderate and severe anticholinergic burden against

those with a low burden (instead of against non-users) and was conducted in people with Parkinson's disease; therefore, we excluded it from analysis. As in our univariate analysis, we selected ORs with an ACB score of 3 or closest where multiple ORs were reported. Total number of ORs pooled for this analysis was six, as one study provided three suitable ORs due to subgrouping based on age (Hsu 2017). Results suggest drugs classified as having 'definite' anticholinergic properties by the ACB scale may have an increased risk of future cognitive decline or dementia (OR 2.63, 95% CI 1.09 to 6.29) (Figure 4). There were insufficient studies to establish specific associations for other anticholinergic measurement scales.

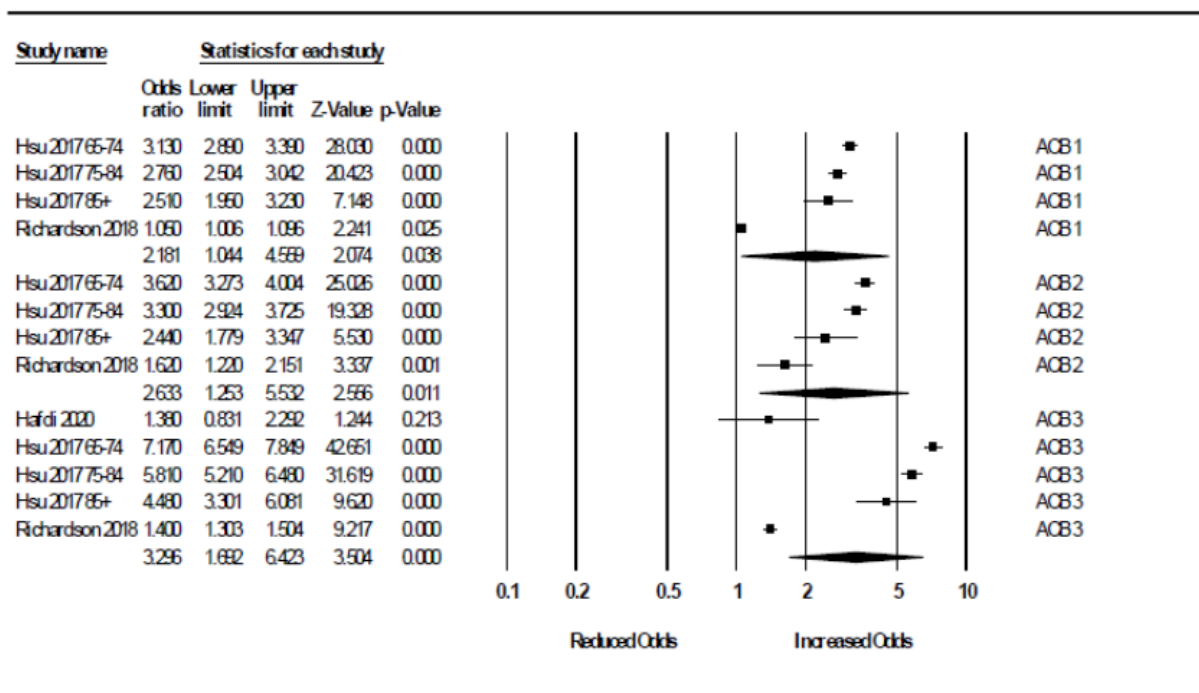
Figure 4. Primary analysis: adjusted association between ACB scale and odds of future cognitive decline or dementia.



We ran further analyses to quantify ORs for each 'low', 'moderate', and 'high' ACB scale subgroup. From Richardson 2018, we selected the DDD greater than 1460 from each 'low', 'moderate', and 'high' ACB scale group based on utilising the highest available participant numbers while maintaining consistency of DDD across subgroups. A relationship between severity of cumulative anticholinergic burden and risk of dementia was apparent. Four ORs from two studies

(145,663 participants with low ACB) were pooled for 'low' ACB (OR 2.18, 95% CI 1.11 to 4.29) (Hsu 2017; Richardson 2018). Four ORs from two studies (1719 participants with moderate ACB) were pooled for 'moderate' ACB (OR 2.71, 95% CI 2.01 to 3.56) (Hsu 2017; Richardson 2018). Five ORs from three studies (8451 participants with high ACB) were pooled for 'high' ACB (OR 3.27, 95% CI 1.41 to 7.61) (Hafdi 2020; Hsu 2017; Richardson 2018) (Figure 5).

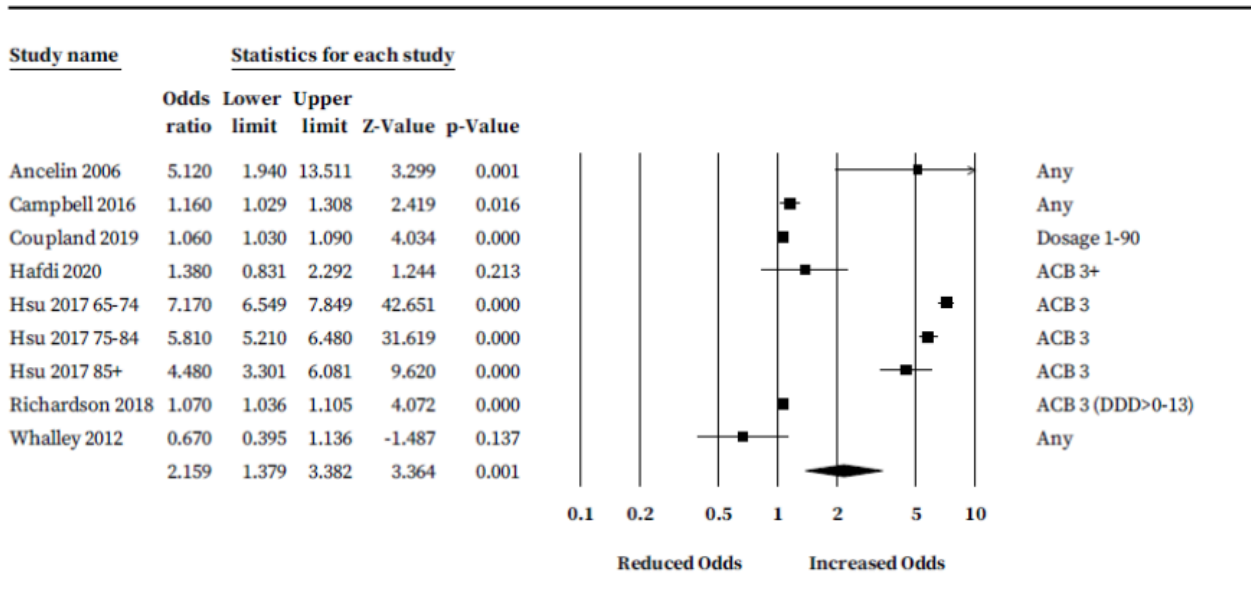
Figure 5. Primary analysis: relationship between severity of anticholinergic burden (defined according to ACB scale) and odds of future cognitive decline or dementia.



As an exploratory analysis, we pooled ORs across scales. Seven studies (317,216 participants) reported ORs suitable for analysis (Ancelin 2006; Campbell 2016; Coupland 2019; Hafdi 2020; Hsu 2017; Richardson 2018; Whalley 2012). Five of the seven studies reported the odds for risk of dementia only; one assessed the odds of developing MCI or dementia (combined) (Campbell 2016), and one assessed odds of developing MCI only (Ancelin 2006). We

pooled ORs with an anticholinergic burden score of 3 or closest; or in the case of one study (Coupland 2019), a dosage of 'strong' anticholinergic drugs of 1 to 90. Pooled rates suggest people taking anticholinergic drugs may have a significantly increased risk of future cognitive decline or dementia (OR 2.16, 95% CI 1.38 to 3.38) (Figure 6).

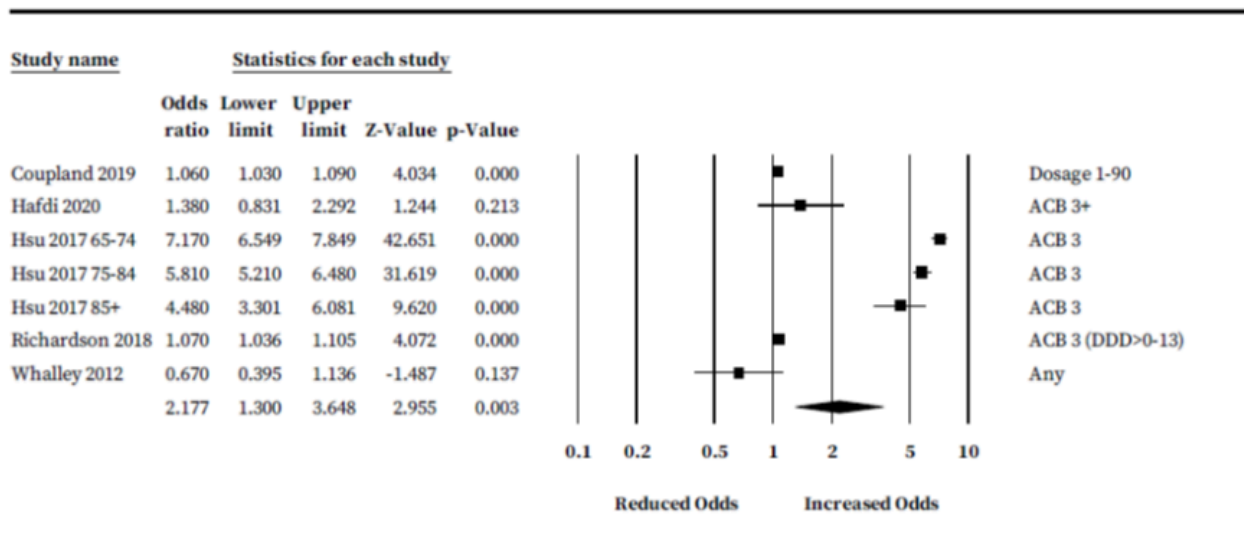
Figure 6. Exploratory 'cross scale' analysis: adjusted association between anticholinergic burden and odds of future cognitive decline or dementia.



We ran a post-hoc analysis to investigate the association with dementia specifically (296,523 participants). We removed two studies that did not assess 'dementia only' as an outcome (Ancelin

2006; Campbell 2016). Results show risk of dementia may be higher for anticholinergic drug users compared to non-users (OR 2.18, (95% CI 1.33 to 3.57) (Figure 7).

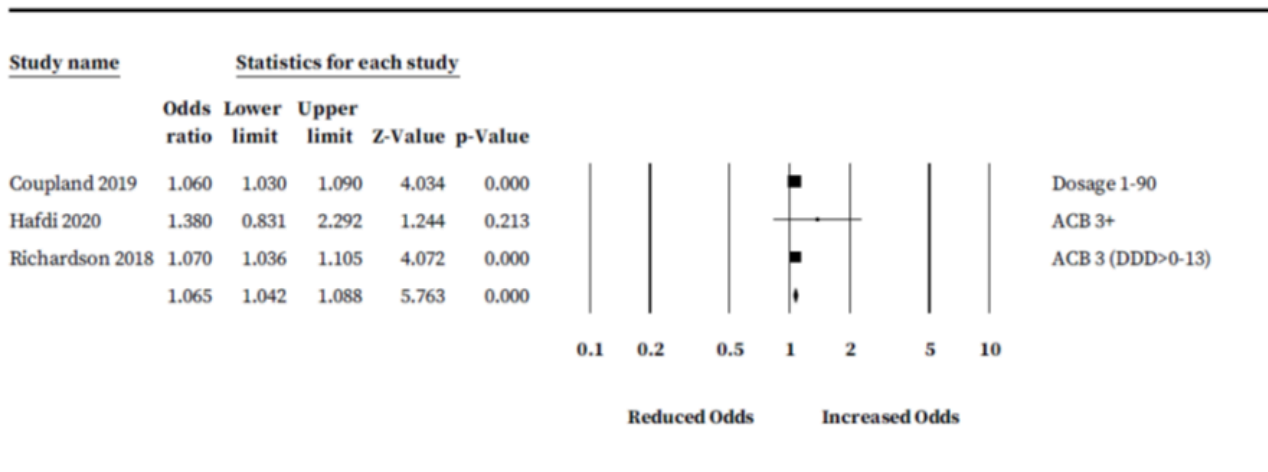
Figure 7. Post hoc analysis: adjusted association between anticholinergic burden and odds of future dementia specifically.



We conducted a sensitivity analysis to investigate the effect of risk of bias on our pooled rates. We restricted analysis to three studies (468,830 participants) that reported ORs but had no high risk of bias categories (Coupland 2019; Hafdi 2020; Richardson 2018).

Results were consistent with our exploratory analysis: people taking anticholinergic drugs may be at increased risk of developing future dementia; however, the size of the risk was lower (OR 1.07, 95% CI 1.04 to 1.09) (Figure 8).

Figure 8. Risk of bias analysis: adjusted association between anticholinergic burden and odds of future cognitive decline or dementia restricted to low risk of bias studies only.



We were unable to formally investigate the possibility of publication/small-study bias by generating a funnel plot due to limited study numbers. However, risk of publication bias is assumed within this field.

Certainty of evidence (GRADE)

The overall quality of evidence from our primary analysis was low. Evidence was downgraded based on extent of risk of bias within studies, imprecision, and possible publication bias. Evidence was upgraded based on the apparent incremental increase in risk

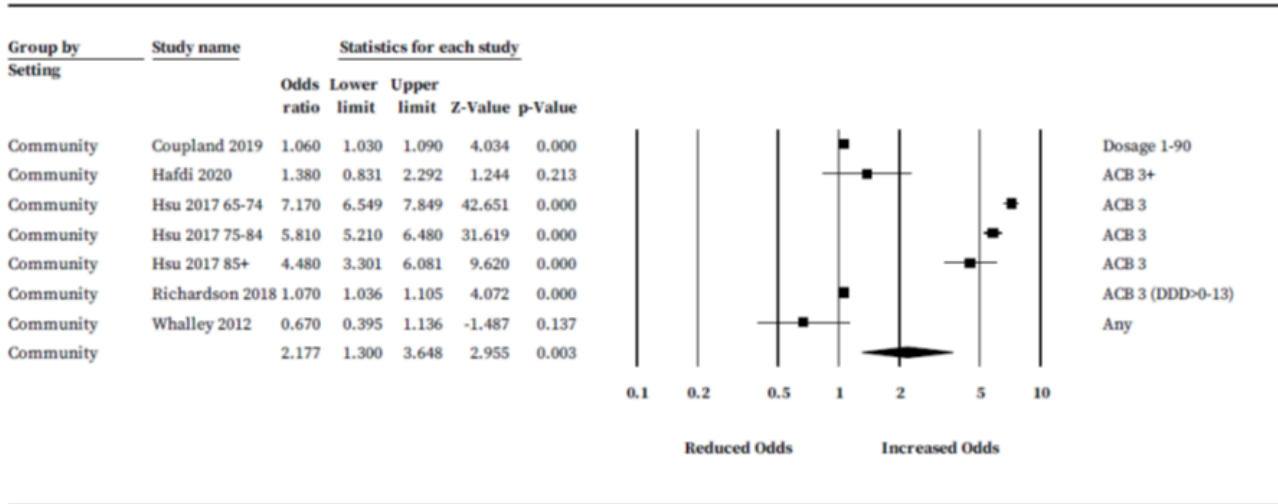
based on severity (low, moderate, and high) of ACB scores. Specific judgements in each respective domain are shown in Table 2.

Secondary analyses

We conducted a subgroup analysis based on 'setting.' Five studies (295,666 participants) were conducted in a community setting and suggested anticholinergic drug users in the community may have an increased risk of cognitive decline or dementia (OR 2.18, 95% CI 1.30 to 3.65) (Figure 9) (Coupland 2019; Hafdi 2020; Hsu 2017;

Richardson 2018; Whalley 2012). There were insufficient studies conducted in primary or secondary care to establish pooled rates.

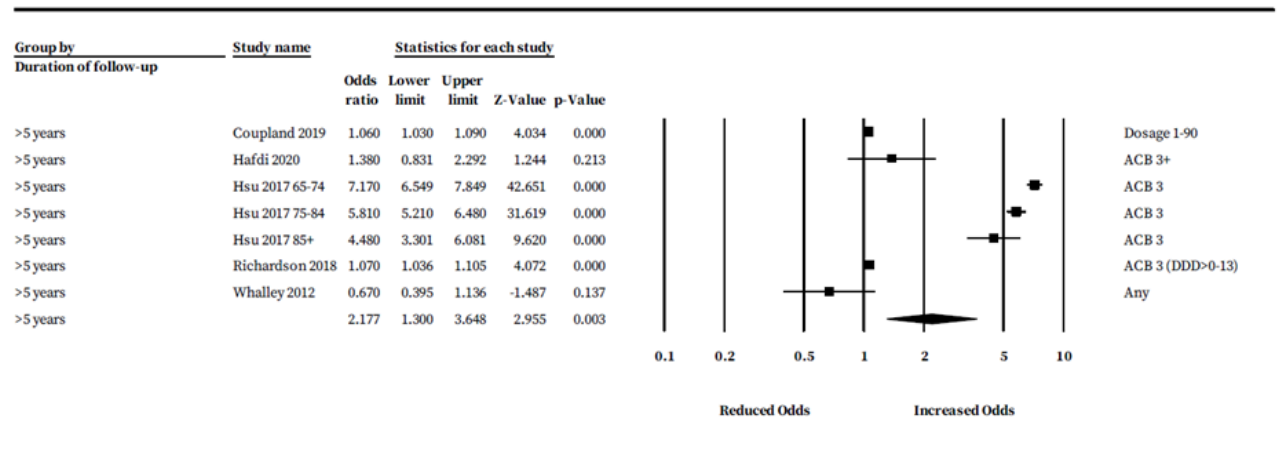
Figure 9. Subgroup analysis: adjusted association between anticholinergic burden and odds of future cognitive decline or dementia subgrouped by setting.



We examined the pooled ORs based on duration of follow-up. Five studies (295,666 participants) provided suitable ORs for duration greater than five years (OR 2.18, 95% CI 1.30 to 3.65) (Figure 10)

(Coupland 2019; Hafdi 2020; Hsu 2017; Richardson 2018; Whalley 2012). There were insufficient studies to investigate OR for one to five years' follow-up.

Figure 10. Subgroup analysis: adjusted association between anticholinergic burden and odds of future cognitive decline or dementia subgrouped by duration of follow-up.



Duration of exposure to anticholinergic medications was too poorly reported to be investigated as a source of potential variability regarding the association between anticholinergic burden and cognitive decline or dementia.

We were unable to run a meta-regression to investigate the influence of number of comorbidities controlled for on the relationship between anticholinergic burden and cognitive decline or dementia due to lack of study numbers. This was similarly the case for polypharmacy and setting.

Association based on scale

Low study numbers meant presenting pooled rates for all but the ACB scale was not possible; hence, we could not conduct a comparative statistical analysis, as planned. However, four studies compared scales within the same participant pools, enabling narrative comparisons to be drawn (Brombo 2018; Hsu 2017; Kashyap 2014; Richardson 2018).

Respective performance of scales was relatively heterogeneous across studies. Nevertheless, some patterns were apparent.

First, while all anticholinergic measurement scales showed an association with cognitive decline or dementia, the DBI-ach was consistently the least strongly associated scale, demonstrating lower odds for future cognitive decline or dementia than all scales it was compared against in two separate studies (Hsu 2017; Kashyap 2014). The ARS scale showed some of the strongest reported associations with cognitive decline or dementia when compared to other scales. Importantly, however, there was evidence that associations are strongest at lower and higher ARS scores, suggesting a U-shaped relationship with cognitive decline or dementia (Hsu 2017). The ADS and ACB scales were on the whole comparable, demonstrating a similar strength of association in the two studies that compared them (Kashyap 2014; Richardson 2018). All other available scales described in this review were not evaluated in tandem with a secondary scale in the same study population and as such cannot be reliably compared.

DISCUSSION

Summary of main results

Anticholinergic drug use is consistently associated with future cognitive decline or dementia. Our results suggest that cognitively unimpaired older adults who use drugs defined as 'definitely' anticholinergic by the ACB scale may have more than two-times greater odds of developing future cognitive decline or dementia than non-users, independent of age, sex, and comorbidities. Moreover, a relationship between severity of anticholinergic burden and future dementia appears to be apparent: odds of developing future cognitive decline or dementia may rise as extent of anticholinergic burden increases. People with a severe anticholinergic burden might see their odds of cognitive decline or dementia increase by as much as 227%.

While our findings are largely based on anticholinergic drugs as measured by the ACB scale, the association appears to exist regardless of which anticholinergic scale is used. All anticholinergic measurement scales evaluated in this review showed an association with cognitive decline or dementia. Interestingly, the DBI-ach was consistently less strongly associated with future cognitive decline or dementia than other scales when making within-study comparisons. This is contrary to previous assertions that scales incorporating dosage are more likely to be reliable risk predictors (Mayer 2015). Of all the available scales, the evidence suggests the ARS is less well suited to the role of predicting future cognitive decline or dementia; this is due to an apparent U-shaped relationship that violates the assumption that severity of anticholinergic drug scores are additive to the overall risk (at least until a plateau is reached). This curious trend may be a by-product of increased prescribing of drugs rated 'less severe' by the ARS scale as treatments for prodromal symptoms of dementia (Hsu 2017).

At present, the ACB scale is the most popular available anticholinergic burden measurement tool. Although no anticholinergic burden scale can be considered the 'gold standard', there is some justification for the popularity of the ACB scale in this area. Specifically, it was explicitly designed to evaluate the association between anticholinergic burden and cognition (Boustani 2009), and as such considers factors such as the anticholinergic potency of a drug when assigning an anticholinergic burden rating. Furthermore, it demonstrates a trend suggesting a steady increase in risk as severity of anticholinergic burden increases, as seen both in our meta-analysis and in previous

studies (Pasina 2013); it incorporates the second highest number of drugs (99) of all available scales (Mayer 2015), and was ranked the highest quality of 19 available scales in a comprehensive systematic review (Lisibach 2021), achieving the best score for 'rigour of development.' It is also one of only three available scales to offer guidance on use in clinical practice along with clear scoring rules that allow reproducibility. Limitations of the ACB scale relate to it not considering dosage, drug interactions, or clearance of respective drugs – all of which are likely relevant to the evident risk of future cognitive decline or dementia. Supplementation of the ACB scale with other existing anticholinergic measurement systems, such as 'Beers criteria', was an approach adopted by several studies included in this review. Augmenting the ACB scale with additional measures may seem like an attractive approach to enhance ACB scale-based anticholinergic burden measurement; but, currently there is insufficient evidence to determine the extent to which this improves prognostic accuracy compared to when the ACB scale is used alone.

Overall completeness and applicability of evidence

Most included studies were conducted in older adult populations in various regions throughout the world. However, there was little to no representation from Middle Eastern, South American, or African populations; therefore, we cannot say our results generalise 'globally.' Similarly, included participants were overwhelmingly from community-based settings and we could not delineate specific pooled rates for older adults in secondary care settings, or reliable pooled rates for those attending primary care. People recruited in primary or secondary care settings likely differ in important demographics, including mean age and number of health conditions, which may increase or reduce the influence of anticholinergic burden on future risk of cognitive decline or dementia. As such, our reported rates of increased risk for older adults are particularly relevant to those in the community.

Our evidence is also restricted to older adults who are 'cognitively healthy.' Anticholinergic burden may be equally important for those with an established cognitive syndrome but this was not a focus of this review.

Certainty of the evidence

Our results are tempered by lack of control for reverse causation, imprecision in reported effect size, risk of publication bias, and the general risk of bias observed throughout included studies. Consequently, our overall confidence in the evidence for our primary pooled analysis was low.

If anticholinergic drugs are prescribed as a treatment for prodromal signs of dementia, such as mood symptoms or sleep disorders, any risk association will be inflated as a consequence. Similarly, if symptoms and subsequent prescriptions increase right up to the point of the dementia diagnosis, the observed trend of increasing risk based on severity of anticholinergic burden could simply reflect this. While it is not known what lag time is sufficient to reduce protopathic bias (i.e. risk of reverse causation), when we restricted pooled rates to those studies that had at least a two-year lag-time and not thought to be at high risk of bias overall, the association between anticholinergic drug use and dementia remained. This runs contrary to the reverse causation hypothesis and provides some reassurance that the observed effects are related to the

anticholinergic properties of the drugs themselves. Regardless, our pooled rates are likely an overestimation.

Limitations of the review process

To minimise bias in the review process, two review authors independently screened all titles, extracted data, and conducted risk of bias assessment. Despite this, we encountered several issues.

Tools that were used throughout our review were not explicitly designed for use with prognostic research. To mitigate this problem, we followed best available guidelines to adapt GRADE for evaluation of prognostic study evidence and enhanced QUIPS by incorporating specific guidance when rating each category.

We evaluated cognition and dementia as a composite variable since both are important to older adults and combining these outcomes increases power to detect smaller, but still clinically meaningful prognostic associations. Despite this, our meta-analyses were limited by power constraints. One recurring issue was the tendency of authors to report ORs subgrouped into low, moderate, and high user categories and compare against a common reference standard (non-users). As a consequence, we were required to select single ORs from a specific subgroup for each analysis. Although we were able to extract relevant data from many of the included studies, we received a poor response from authors who we contacted about providing additional data, further reducing the strength of our analyses. In combination, these issues challenge the veracity of our results – particularly our subgroup analyses. For instance, our quantification of the association between low, moderate, and high anticholinergic burden and future cognitive decline or dementia are derived from just three studies, thus are of questionable validity.

We were also unable to conduct a number of analyses that we prespecified in our protocol due to issues with the types of data that were presented in available studies (Quinn 2020). Specifically, we could not pool linear or hazard ratio outcome data, investigate the association between anticholinergic burden and duration of exposure, or determine if number of comorbidities or polypharmacy were sources of the high heterogeneity in observed effect sizes between studies.

Lastly, we did not include grey literature in our review. Although we were unable to formally assess for publication bias, we identified few small studies that reported an absence of association between the ACB scale and dementia. Existent studies that did report a lack of association typically reported a significant association with another form of cognitive impairment (e.g. MCI) (Whalley 2012); hence, there is a real risk of publication bias in this field.

Agreements and disagreements with other studies or reviews

Our results are broadly consistent with three previous meta-analyses (Dmochowski 2021; Pieper 2020; Ruxton 2015). These prior reviews report a 20% to 46% increased risk for dementia (Dmochowski 2021; Pieper 2020), and a 45% increased risk for cognitive impairment (Ruxton 2015). This is lower than our primary pooled rates but in line with our analysis restricted to studies at lower risk of bias, which may be more accurate. Our findings also build upon these previous meta-analyses by quantifying risk of ACB

scale measured drugs specifically, along with risks for each ACB scale subgroup (low, moderate, high).

The increasing risk based on extent of anticholinergic burden is consistent with prior evidence: Jung 2019 found people on moderate-to-high dosages of anticholinergic drugs were at significantly greater risk of Alzheimer's disease than people on very low dosages, while Coupland 2019 similarly found a dose-response effect. Low anticholinergic burden represents the most common category that those with any form of anticholinergic burden reside, and although we observed a significant association with dementia at this level, it remains a point of contention due to frequent negative findings within the literature (Hafdi 2020).

Lastly, previous studies have suggested that the cholinergic system may play a particular role in episodic memory (Bentley 2011). It has been theorised that any impact of anticholinergic drugs may be largely confined to this domain (Papenberg 2017). We found considerable variability throughout the literature regarding reported cognitive domains affected by anticholinergic drug use. As such, our results do not support this theory and the available evidence suggests that disruption of the cholinergic system leads to widespread cognitive impairment.

AUTHORS' CONCLUSIONS

Implications for practice

Clinicians should think carefully about the need to prescribe anticholinergic drugs to older adults. Estimates suggest as many as 20% to 50% of older people are prescribed at least one anticholinergic medication (Fox 2014). If the observed link between anticholinergic drug use and future dementia is causal, these exposure rates imply anticholinergics meaningfully contribute to the global dementia burden; albeit the extent of this contribution is difficult to determine due to the risk of bias present within studies. Moreover, there are associations with increased risk of mortality (Grave-Morris 2020), impaired physical function, and reduced quality of life (Stewart 2020), emphasising the potential dangers anticholinergic drugs pose to older adults.

While we would advise caution in prescribing anticholinergic drugs, we cannot comment on the potential benefits of deprescribing for people already receiving anticholinergic drugs. It is uncertain to what extent any adverse effects of anticholinergic medicines are reversible upon cessation. One randomised controlled trial (RCT) provided no evidence that deprescribing can benefit cognition (Kersten 2013), albeit this RCT was underpowered and focused only on short-term cognitive changes (Pieper 2020). We can also hypothesise from observational studies that circumstances may exist in which the increased risk of dementia associated with use of anticholinergic drugs is irreversible. For example, risk of future dementia for older adults with high anticholinergic burden has been found to be unaltered by recency of use: those who are historic heavy users of anticholinergic drugs might be at similar risk to recent or even long-term continuous heavy users (Gray 2015).

Implications for research

Several outstanding issues remain to be resolved. Most prominently, clarification is needed regarding the importance of medication type on the association between anticholinergic burden and risk of future cognitive decline or dementia. Although plausible mechanisms exist by which anticholinergic drugs

may impact the cognition of older adults (Shah 2013), some studies only observed significant associations for certain types of anticholinergic drugs, many of which are prescribed for prodromal symptoms of dementia. While this variability based on drug-type was not consistent across studies, there remains a possibility that anticholinergic effects may not be driving the observed association. It is likely that the only way a causal role for anticholinergic drugs and risk of future cognitive decline or dementia can be conclusively established (or disregarded) is via an RCT in which some people have their anticholinergic medications stopped to determine if the risk of future cognitive decline or dementia is reduced.

We likewise do not know precise details regarding the interaction between severity of anticholinergic burden, duration of exposure, and the frequency of use required to cause long-term harm. If anticholinergic drugs play a causal role, establishing the relationship between these variables could be key to our ability to alter future dementia risk. As such, this is a crucial avenue for future research.

Methodological standards also require improvement. Authors should be sure to register protocols before conducting their study. This is necessary to determine the extent of publication bias within the field as well as adequately evaluate statistical approaches. Drug use measurement is currently extremely limited. Reported study methods are typically not sufficient to reliably establish dosage

or adherence, and total exposure period is often inadequately reported. Use of anticholinergic drugs can vary over the course of a study (Shah 2013), which is likely to have a bearing on results, yet not all studies take measurements at multiple time points. Researchers should also ensure that those who ascribe anticholinergic ratings are blinded to cognitive outcomes (and vice versa) to minimise bias, and ensure inclusion of psychiatric conditions when controlling for comorbidities. Addressing these limitations would go some way to improving our understanding of the relationship between anticholinergic burden and risk of cognitive decline or dementia.

ACKNOWLEDGEMENTS

We would like to thank our funders for supporting this work. We would like to thank the CDCIG Information Specialist for helping develop the MEDLINE search strategy.

We would also like to thank Dr Melanie Hafdi for providing OR data for our meta-analysis.

We would like to thank peer reviewers Amanda J Cross and Christopher Etherton Beer, consumer reviewer Delia Bishara and Prognosis Methods Group reviewer Angela Aldin for their comments and feedback.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Ancelin 2006
Study characteristics

Methods	Design: retrospective cohort Setting: primary care Country: France Duration of follow-up: 1 year Covariates controlled for: age, sex, education, untreated depression, and treated hypertension
Participants	Participants numbers: 372 Population type: older adults Sex: not clear Age (mean): not stated
Prognostic factors	Anticholinergic burden measurement method: combined rating of drugs' serum radioreceptor assay and mean estimated clinical effects, established via literature review
Outcomes	Outcomes assessed: MCI; dementia; cognitive decline Outcome ascertainment dementia/MCI: independent clinical assessment via expert Outcome ascertainment cognitive decline: computerised neuropsychometric examination Diagnostic criteria dementia: DSM-III criteria for neurogeriatric disorder Diagnostic criteria MCI: revised criteria proposed by the Stockholm consensus group Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	French Social Security (CNAM-TS), the Fondation de France, the Direction Générale de la Santé, and the Region Languedoc Roussillon
Notes	
Item	Authors' judgement Support for judgement

Ancelin 2006 (Continued)

Study participation	Unclear	Poor reporting of comorbidities.
Study attrition	Unclear	Only 80% followed up. No analysis carried out to evaluate if participants with missing data differed in baseline anticholinergic burden score compared to participants with full data.
Prognostic factor measurement	Unclear	Repeated measurements of drug use at 1 year. Used self-report to establish prescribed and non-prescribed medication use. Had second method of establishing drugs (checking with GP). No mention of recording dosage, frequency, or adherence.
Outcome measurement	Unclear	No blinding but anticholinergic burden scores assigned after cognitive diagnosis.
Study confounding	Unclear	Controlled for age, sex, and comorbidities that covered both physical and psychiatric conditions, but only controlled for 2 comorbidities.
Reverse causation	No	No mention of restricting anticholinergic drug use to 1 year before MCI onset.
Statistical analysis and reporting	Unclear	No protocol or assumptions checked.

Brombo 2018
Study characteristics

Methods	Design: retrospective cohort Setting: secondary care Country: Italy Duration of follow-up: 1 year Covariates controlled for: age, sex, education, smoking, hypertension, coronary heart disease, renal failure, anaemia, infectious diseases, and ARS score at first follow-up
Participants	Participants numbers: 1123 Population type: older adults Sex: 56% women (629) Age (mean): 81 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale; ARS scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment: MMSE Diagnostic criteria: cognitive decline: scores on cognitive testing
Source of funding	Italian Ministry of Labour, Health and Social Policy
Notes	

Brombo 2018 (Continued)

Item	Authors' judgement	Support for judgement
Study participation	No	Baseline dementia prevalence was 20%.
Study attrition	No	Cognition of follow-up data only available for 53.6% of baseline sample.
Prognostic factor measurement	Unclear	Medication use established via questionnaire only.
Outcome measurement	Unclear	No blinding but anticholinergic burden likely assessed after cognitive score established.
Study confounding	Unclear	Age, sex, and comorbidities (including physical and depression) all measured; however, did not control for depression in regression analysis.
Reverse causation	No	No restriction to anticholinergic burden measurement (assessed at 12 months before and 9 months before).
Statistical analysis and reporting	Unclear	Relevant assumptions not checked.

Campbell 2016
Study characteristics

Methods	Design: retrospective cohort Setting: primary care Country: USA Duration of follow-up: 1 year Covariates controlled for: age, sex, race, arthritis, cancer, CAD, CHF, COPD, diabetes, liver disease, renal disease, stroke, number of non-anticholinergic drugs, prior inpatient admissions, prior ED visits, prior outpatient visits
Participants	Participants numbers: 3344 Population type: older adults Sex: 71% women (2374) Age (mean): 71 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: dementia + MCI Outcome ascertainment dementia/MCI: consensus diagnosis based on multidisciplinary evaluation Diagnostic criteria dementia/MCI: DSM-III criteria
Source of funding	Not stated

Campbell 2016 (Continued)

Notes

Item	Authors' judgement	Support for judgement
Study participation	No	Describes age, sex, and comorbidities of population. However, almost all had hypertension (99%, which was not reported in this study but in Cai 2013 , which uses the same data source) and high prevalence of stroke and other cardiovascular conditions so population may not be very generalisable.
Study attrition	No	No tests of missing data.
Prognostic factor measurement	Unclear	Only 1 method used to determine medications.
Outcome measurement	Unclear	No blinding but anticholinergic burden likely assessed after cognitive assessment.
Study confounding	Unclear	Controls for age, sex, and comorbidities, but comorbidities did not cover psychiatric domain.
Reverse causation	No	Anticholinergic burden measurement was collected over the 12 months before cognitive evaluation. Does not mention restricting to anticholinergic drugs that were prescribed only 12 months before cognitive assessment.
Statistical analysis and reporting	Unclear	No protocol or assumptions checked.

Chuang 2017
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: USA Duration of follow-up: 11 years Covariates controlled for: sex, race, birth year (age), years of education, follow-up time, smoking status (current, former, never), drinker (never, ever), number of cardiovascular comorbidities
Participants	Participants numbers: 723 Population type: older adults Sex: 31% women (226) Age (mean): 52 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: Alzheimer's disease + MCI Outcome ascertainment dementia/MCI: consensus diagnosis based on multidisciplinary evaluation

Chuang 2017 (Continued)

Diagnostic criteria for dementia and Alzheimer's disease: DSM-III
 and NINCDS-ADRDA criteria

Diagnostic criteria for MCI: Petersen's criteria

Source of funding Intramural Research Program, National Institute on Aging, and National Institutes of Health

Notes

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Demographics and comorbidities all reported; however, population was majority male (69%) with low mean age (52 years).
Study attrition	No	Less than a third of baseline sample remaining for inclusion in analysis.
Prognostic factor measurement	Unclear	Patients brought unused medications to visit. Cross-checked by study nurses but no measurement of dosage or frequency of use. Repeated measurements made at each visit.
Outcome measurement	Unclear	No blinding but using data obtained from previously conducted longitudinal cohort study so anticholinergic burden likely measured after cognitive assessment already complete.
Study confounding	Unclear	Comorbidities controlled for did not include psychiatric conditions.
Reverse causation	No	No restriction mentioned on anticholinergic drug use time frame before cognitive assessment and information on duration of use only available for 49% of participants.
Statistical analysis and reporting	Unclear	No assumptions checked or protocol registered.

Coupland 2019
Study characteristics

Methods	Design: retrospective case-control Setting: community Country: UK Duration of follow-up: 11 years Covariates controlled for: BMI, smoking status, alcohol consumption, Townsend deprivation score, ethnic group, coronary heart disease, atrial fibrillation, heart failure, hypertension, hyperlipidaemia, diabetes (type 1 and type 2), stroke, transient ischaemic attack, subarachnoid haemorrhage, renal disease, asthma, COPD, anxiety, depression, bipolar disorder, schizophrenia, severe head injury, cognitive decline/memory loss, antihypertensive drugs, aspirin, hypnotics, anxiolytic drugs, non-steroidal anti-inflammatory drugs. Cases and controls were matched for age (within 1 year), sex, general practice, and calendar time.
Participants	Participants numbers: 284,343

Coupland 2019 (Continued)

Population type: older adults

Sex: 63% women (179,420)

Age (mean): 82 years

Prognostic factors	Anticholinergic burden measurement method: ACB scale and Beers criteria
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: clinical codes recorded in official records Diagnostic criteria for dementia: not stated
Source of funding	National Institute for Health Research School for Primary Care Research
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Age, sex, and comorbidities all described.
Study attrition	Unclear	No comparison of missing values with anticholinergic burden.
Prognostic factor measurement	Unclear	Relied on prescriptions for establishing medications.
Outcome measurement	Unclear	Relied on database diagnosis.
Study confounding	Yes	Cases and controls were matched for age and sex; comorbidities controlled for in regression analysis and covered physical and psychiatric domains.
Reverse causation	Yes	Restricted medications to 12 months, 3 and 5 years before diagnosis.
Statistical analysis and reporting	Unclear	Did not check assumptions or register a protocol.

Fox 2011a
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: UK Duration of follow-up: 2 years Covariates controlled for: age, sex, baseline MMSE, education, social class, number of non-anticholinergic medications, and number of comorbidities
Participants	Participants numbers: 12,423 Population type: older adults

Fox 2011a (Continued)

Sex: 60% women (7417)

Age (mean): not stated

Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: MMSE Diagnostic criteria for cognitive decline: scores on cognitive testing
Source of funding	Medical Research Council, UK
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Lack of detail in reporting exclusion criteria. Did not state numbers with baseline dementia.
Study attrition	No	No analysis of missing data. High % of attrition (only 64% remaining at 2-year follow-up).
Prognostic factor measurement	Yes	Used self-report cross-checked by counting remaining medications. Recorded dosage, frequency, and quantity.
Outcome measurement	Unclear	No blinding to outcome but anticholinergic burden likely established after cognitive assessment.
Study confounding	Unclear	Age, sex, and comorbidities all measured (comorbidities included both physical and psychiatric). However, controls for 'number of health conditions' rather than each condition individually.
Reverse causation	Unclear	Restricted analysis to anticholinergic burden baseline association with change in MMSE score at 2 years.
Statistical analysis and reporting	Unclear	No assumptions checked or protocol registered.

Gray 2015

Study characteristics

Methods	Design: retrospective cohort Setting: community Country: USA Duration of follow-up (mean): 7.3 years
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Gray 2015 (Continued)

Covariates controlled for: ACT cohort, age, age at ACT study entry, sex, education, BMI, current smoking, regular exercise, self-rated health, hypertension, diabetes, stroke, coronary heart disease, Parkinson's disease, history of depressive symptoms, and current benzodiazepine use

Participants	Participants numbers: 3434 Population type: older adults Sex: 60% women (20,470) Age (mean): 74 years
Prognostic factors	Anticholinergic burden measurement method: Beers criteria combined with a literature review
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: consensus diagnosis based on multidisciplinary evaluation Diagnostic criteria dementia: DMS-IV and NINCDS-ADRDA criteria
Source of funding	National Institute on Aging, NIH Grants, and the Branta Foundation
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Random community sampling and reports age, sex, and comorbidities.
Study attrition	Unclear	Conducted series of sensitivity analyses but did not assess for differences in missing and anticholinergic burden score.
Prognostic factor measurement	Unclear	Relied on pharmacy dispensing data. Updated exposure as participants were followed forward in time.
Outcome measurement	Unclear	No blinding to outcome but anticholinergic burden likely measured after cognitive assessment.
Study confounding	Yes	Controlled for age, sex, and comorbidities.
Reverse causation	Unclear	Excluded prescriptions in the most recent 1-year period.
Statistical analysis and reporting	Unclear	Analysis was appropriately conducted (including tests of assumptions) but no protocol.

Grossi 2019
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: UK Duration of follow-up: 10 years
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Grossi 2019 (Continued)

Covariates controlled for: sex, age, education, social class, residential accommodation, centre of recruitment, study arm, health conditions at year 0 or year 2 (stroke, Parkinson's disease, epilepsy, sleep problems, anxiety, depression), self-reported health at year 2, disability at year 2, MMSE at year 2, MMSE orientation subscore at year 2, decrease in MMSE score between year 0 and year 2, and self-perceived change in memory function between year 0 and year 2.

Participants	Participants numbers: 8216 Population type: older adults Sex: about 69% women (5669) Age (mean): 74 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: computer-assisted algorithm Diagnostic criteria dementia: AGE-CAT scores ≥ 3 (which is equivalent to dementia as diagnosed by DSM-III-R)
Source of funding	UK Alzheimer's Society
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Reported age, sex, and comorbidities.
Study attrition	No	Major loss to follow-up.
Prognostic factor measurement	Unclear	Self-report only. No measurement of dosage, frequency of use, or adherence. Anticholinergic burden measurement repeated at each interview (year 0 and year 2).
Outcome measurement	Unclear	No blinding but seemed like anticholinergic burden likely assigned after dementia diagnosis ascertained.
Study confounding	Yes	Age, sex, and relevant comorbidities all controlled for.
Reverse causation	Yes	Anticholinergic burden measurement taken 8 years before dementia diagnosis and those who developed dementia at year 2 (2 years after anticholinergic burden use was first measured) were excluded.
Statistical analysis and reporting	Unclear	No protocol or assumptions checked.

Hafdi 2020
Study characteristics

Methods	Design: retrospective cohort Setting: community
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Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome (Review)

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Hafdi 2020 (Continued)

Country: Netherlands

Duration of follow-up (mean): 6.7 years

Covariates controlled for: age, sex, history of cardiovascular disease or stroke (or both), education, MMSE at baseline, and Geriatric Depression Scale at baseline

Participants	Participants numbers: 3526 Population type: older adults Sex: 54% women (1919) Age (mean): 74 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: consensus diagnosis based on multidisciplinary evaluation Diagnostic criteria dementia: DSM-IV
Source of funding	Dutch Ministry of Health, Welfare and Sport; the Dutch Innovation Fund of Collaborative Health Insurances; and the Netherlands Organisation for Health Research and Development
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Reported age, sex, and comorbidities. Minor issue with slightly restricted age population.
Study attrition	Unclear	No comparison between completers vs non-completers/missing data.
Prognostic factor measurement	Unclear	2 methods (self-report cross-checked with electronic records). Repeated measurement at 2 years – though only once and this study ran for 8 years; no mention of whether anticholinergic scores changed and lack of detail on the question so could not be certain if asked about non-prescribed drugs. No measure of adherence or dosage. On basis of these issues assigned unclear risk of bias.
Outcome measurement	Unclear	No blinding but anticholinergic burden assignment conducted after cognitive diagnosis established.
Study confounding	Yes	Age, sex, and comorbidities all measured.
Reverse causation	Unclear	Anticholinergic burden measurement taken 2 years before dementia assessment and excluded those who developed dementia in first 2 years after taking anticholinergics.
Statistical analysis and reporting	Unclear	No protocol or assumptions.

Han 2008

Study characteristics

Methods	Design: retrospective cohort Setting: community Country: USA Duration of follow-up: 1 year Covariates controlled for: age, education, race, living arrangement, before enrolment. history of alcohol use and smoking, and depressive symptoms, ADL function, Charlson Comorbidity Index
Participants	Participants numbers: 544 Population type: older adults Sex: 100% men Age (mean): 74 years
Prognostic factors	Anticholinergic burden measurement method: clinician-rated
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: HVRT, IADL Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine
Notes	

Item	Authors' judgement	Support for judgement
Study participation	No	Men only with hypertension.
Study attrition	Unclear	Attrition was high but just below the 20% high risk mark. Conducted analysis to investigate potential impact of missing values on final model and did not alter conclusions but did not explain what these missing data analyses entailed.
Prognostic factor measurement	Unclear	No measurement of dosage or frequency of use. No measurement of non-VA sources of drugs. Conducted repeated measurements over the follow-up period for the 12 months preceding each assessment at 1 and 2 years.
Outcome measurement	Unclear	No mention of blinding. Unclear if anticholinergic burden was applied before or after cognitive assessment score was determined.
Study confounding	Yes	Only men in sample so no sex. Controlled for comorbidities via Charlson Comorbidity Index along with depression.
Reverse causation	No	Anticholinergic burden exposure time frame defined as the 12 months preceding each follow-up at 1 year and 2 years. (so seems to have covered medication use right up to the point of each follow-up assessment).
Statistical analysis and reporting	Unclear	No assessment of assumptions. Referred to a protocol but was not a protocol specifically for this study so no mention of an analysis plan.

Hsu 2017
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Taiwan Duration of follow-up: 10 years Covariates controlled for: sex and time-varying comorbidities. ARS and ACB scales were further adjusted for defined daily dose of drugs with anticholinergic properties (age controlled for by subgrouping)
Participants	Participants numbers: 116,043 Population type: older adults Sex: 50% women (57,552) Age (mean): not stated
Prognostic factors	Anticholinergic burden measurement method: ARS scale; ACB scale; DBI-ach scale
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: clinical codes recorded in health records Diagnostic criteria dementia: not stated
Source of funding	Ministry of Science and Technology
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Reported age, sex, and covariates. Random sampling of population contained in a national insurance database registry.
Study attrition	Unclear	No mention of missing data. No mention of mortality over 10-year follow-up or how dealt with this.
Prognostic factor measurement	Unclear	Only 1 method (prescription records) employed for determining medications. Anticholinergic burden assessed monthly for 120 months.
Outcome measurement	Unclear	Relied on medical record diagnoses.
Study confounding	Unclear	Controlled for most relevant variables including comorbidities (used Charlson Comorbidity Index). Age not controlled for in the model but categorised people into distinct age groups and conducted 3 analyses on that basis. No psychiatric domains assessed.
Reverse causation	No	No mention of restricting anticholinergic burden measurement other than removing people with dementia at baseline (1 year after enrolment). Anticholinergic burden was measured monthly over the 10-year time frame so appeared

Hsu 2017 (Continued)

that beyond the initial 1 year following study enrolment, anticholinergic drug use could be at risk of being prescribed for prodromal dementia symptom.

Statistical analysis and reporting	Unclear	No protocol described and no measure of assumptions.
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Iyer 2020
Study characteristics

Methods	Design: prospective cohort Setting: secondary care Country: USA Duration of follow-up: 1 year Covariates controlled for: age, BMI, time, group, GDS, total number of medications, neurological diagnosis
Participants	Participants numbers: 106 Population type: overactive bladder population Sex: 100% women Age (mean): 77 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: MoCA Diagnostic criteria cognitive decline: change in scores on cognitive testing
Source of funding	None.

Notes

Item	Authors' judgement	Support for judgement
Study participation	No	Women only. Overactive bladder population.
Study attrition	No	Considerable attrition.
Prognostic factor measurement	Unclear	Only 1 method employed (ACB scale). No mention of assessing non-prescription anticholinergic medications.
Outcome measurement	No	No mention of blinding and not a retrospective design so knowledge of anticholinergic use may have biased MoCA scoring. Repeated MoCA-based testing could also induce practice effects, masking any cognitive decline.
Study confounding	Yes	Age and comorbidities controlled for.

Iyer 2020 (Continued)

Reverse causation	No	No restrictions placed on ACB use before follow-up assessments up to 12 months.
Statistical analysis and reporting	Unclear	No protocol or assumptions checked.

Jessen 2010
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Germany Duration of follow-up (mean): 4.5 years Covariates controlled for: sex, age, level of education, depression, ApoE genotype
Participants	Participants numbers: 2605 Population type: older adults Sex: 65% women (1701) Age (mean): 79 years
Prognostic factors	Anticholinergic burden measurement method: Chew list
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: consensus diagnosis based on multidisciplinary evaluation Diagnostic criteria dementia: DSM-IV and ICD-10 criteria
Source of funding	German Federal Ministry for Education and Research, and the Federal Institute for Drugs and Medical Devices
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Random sampling of GP registries. > 50% participation rate. No reporting of comorbidities (other than depression and ApoE) so scored as moderate.
Study attrition	Unclear	No mention of missing data or attrition (despite extensive follow-up period). In original study that they used data from, the baseline cohort was 3327; however, may be more exclusion criteria for this study so assigned unclear risk of bias.
Prognostic factor measurement	Unclear	Lack of detail regarding how medication use was established. Repeated measurements of anticholinergic use at each 8-month follow-ups.

Jessen 2010 (Continued)

Outcome measurement	Unclear	No blinding but seemed likely that anticholinergic burden score was assigned retrospectively after cognitive diagnosis was established in earlier study.
Study confounding	No	Did not control for comorbidities other than depression and ApoE genotype.
Reverse causation	No	No restriction on anticholinergic burden time frame measurement reported.
Statistical analysis and reporting	Unclear	No protocol and no assessment of assumptions.

Joung 2019
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: South Korea Duration of follow-up: 10 years Covariates controlled for: age, sex, level of income, diabetes mellitus, hypertension, myocardial infarction, cardiovascular diseases, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, neuralgia, skin disease, sleep disorder, prescribed doses of weak anticholinergics, and cumulative prescribed days of other non-anticholinergic agents that could impair cognitive function (all psychotic diseases including depression, psychosis, and anxiety were excluded in the step of participant selection in advance).	
Participants	Participants numbers: 191,805 Population type: older adults Sex: 55% women (105,493) Age (mean): 67 years	
Prognostic factors	Anticholinergic burden measurement method: ACB scale plus Beers criteria	
Outcomes	Outcomes assessed: Alzheimer's disease Outcome ascertainment dementia: clinical codes recorded in medical records Diagnostic criteria dementia: ICD-10: F00 or G30) and a prescription for anti-Alzheimer's disease agents (i.e. donepezil, rivastigmine, galantamine, or memantine)	
Source of funding	Not stated	
Notes		
Item	Authors' judgement	Support for judgement
Study participation	Yes	Population-based study with adequate reporting of demographics and comorbidities.

Joung 2019 (Continued)

Study attrition	Unclear	No mention of missing data.
Prognostic factor measurement	Unclear	Relied on prescription records. Exposure measurement taken throughout follow-up.
Outcome measurement	Unclear	Relied on medical record diagnoses.
Study confounding	Yes	All appropriate variables controlled for. Depression controlled for via exclusion of antidepressant use in sensitivity analysis only.
Reverse causation	Yes	Restricted to dementia onset 2 years after baseline anticholinergic use. Also various statistical analysis to control for protopathic bias (reverse causation) did not change results so scored as low risk of bias on this basis.
Statistical analysis and reporting	Unclear	Checked assumptions. No protocol registered, however.

Kashyap 2014
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Canada Duration of follow-up: 1 year Covariates controlled for: None.
Participants	Participants numbers: 102 Population type: older adults Sex: 84% women (86) Age (mean): 72 years
Prognostic factors	Anticholinergic burden measurement method: DBI-ach scale; ACB scale; ADS scale; ARS scale
Outcomes	Outcomes assessed: MCI; cognitive decline Outcome ascertainment MCI: independent clinical assessment via expert Outcome ascertainment cognitive decline: neuropsychological tests and an MoCA Diagnostic criteria MCI: DSM-5 criteria for a mild neurocognitive disorder. Diagnostic criteria cognitive decline: 3 different ways: worsening in the raw neuropsychological test scores for each test; a change in scores on each test that exceeded an expected cut-off based on the test-retest reliable change index; and a change in scores on each test that persisted when regression to the mean, practice effects, and age were accounted for using the standardised regression-based measure method
Source of funding	Canadian Institutes of Health Research
Notes	

Kashyap 2014 (Continued)

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Report on age and sex but did not report which comorbidities they measured.
Study attrition	Unclear	No comparison with missing data. Did not describe the proportion or potential impact of loss to follow-up.
Prognostic factor measurement	Yes	Established by patient self-report. Validated by nurse checking medication box. Recorded frequency, adherence, and dosage.
Outcome measurement	Unclear	There was blinding to the mild neurocognitive disorder diagnosis but not to the change in cognition evaluation; retrospective anticholinergic burden determination.
Study confounding	No	Only conducted univariate analysis. No confounders adjusted for.
Reverse causation	No	No time restriction on anticholinergic burden measurement (anticholinergic burden measured at baseline then again at 12 months – combined measures and used 'increase in anticholinergic burden' as the independent variable.
Statistical analysis and reporting	No	No multivariate analysis conducted.

Koyama 2014
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: USA Duration of follow-up: 4.9 years Covariates controlled for: age, race, education, smoking, physical activity, modified Charlson Comorbidity Index, and baseline MMSE score
Participants	Participants numbers: 1429 Population type: older adults Sex: 100% women (1429) Age (mean): 83 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: battery of 7 cognitive tests Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	National Institute of Aging at the National Institutes of Health and the Alzheimer's Association

Koyama 2014 (Continued)

Notes

Item	Authors' judgement	Support for judgement
Study participation	No	Women only.
Study attrition	No	Final sample was 1429/4606 at baseline.
Prognostic factor measurement	No	Participants asked to bring in all medication used in 30 days prior to baseline visit. No measurement of dosage or frequency of use. No subsequent measurement of medication use despite 5-year follow-up.
Outcome measurement	Unclear	No blinding but cognitive assessment results likely defined before anticholinergic burden calculated.
Study confounding	Unclear	Controlled for comorbidities via a modified Charlson Comorbidity Index; however, no depression controlled for.
Reverse causation	Unclear	Anticholinergic drug use at baseline only and follow-up was at 2 years. However, no exclusion around dementia at baseline or 1 year reported.
Statistical analysis and reporting	Unclear	No assumption checked.

Low 2009

Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Australia Duration of follow-up: 4 years Covariates controlled for: age, gender, education, depression, and self-rated health
Participants	Participants numbers: 2058 Population type: 'young old' Sex: 48% women (992) Age (mean): 62 years
Prognostic factors	Anticholinergic burden measurement method: ADS scale
Outcomes	Outcomes assessed: cognitive decline; MCI Outcome ascertainment MCI: independent clinical assessment via expert Outcome ascertainment cognitive decline: a neuropsychological assessment Diagnostic criteria MCI: Jack 1999 criteria

Low 2009 (Continued)

Diagnostic criteria cognitive decline: scores on cognitive testing

Source of funding National Health and Medical Research Council grants

Notes

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Sample was restricted to 'young old' (aged 60–64 years) and had high mean education (14 years).
Study attrition	Unclear	87% of participants followed up. Comparison of lost to follow-up vs followed up participants conducted but showed people lost to follow-up were more likely to be on anticholinergic medicine.
Prognostic factor measurement	Unclear	Anticholinergic drug use reported at baseline and 4-year follow-up. Used self-reported medication use but only 1 method employed. No measurement of frequency, duration, or dose.
Outcome measurement	No	No blinding to anticholinergic burden during clinical diagnosis, but anticholinergic burden likely measured retrospectively. MCI was defined according to dated criteria (Jack 1999 rather than Peterson). MMSE used to assess cognition but study had high education mean and displays a ceiling effect.
Study confounding	Unclear	Controlled for age, sex, and comorbidities that cover both physical and psychiatric domains. However, minimal comorbidities.
Reverse causation	No	Excluded people with dementia at baseline but did not seem to be any formal restriction in anticholinergic drug use and time of outcome assessment at 4 years.
Statistical analysis and reporting	No	No protocol and no assumptions checked. Also analysis for MCI outcome was underpowered as only 38 MCI cases at follow-up.

Moriarty 2020
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Ireland Duration of follow-up: 2 years Covariates controlled for: baseline wave (i.e. whether the period was wave 1–2 or 2–3), age at baseline wave, sex, education, marital status, employment, incontinence, quintiles of CES-D score, pain, trouble falling asleep, disabilities, smoker, vision, hearing, self-reported doctor-diagnosed conditions, eye conditions, cardiovascular conditions (listed in paper supplementary materials), other health conditions (listed in paper supplementary materials)
Participants	Participants numbers: 7027 Population type: older adults

Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome (Review)

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Moriarty 2020 (Continued)

Sex: 55.6% women (3906)

Age (median): 61 years

Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: 3 cognitive tests (MMSE, animal naming, assessment of recall) Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	Alzheimer's Society, Grant/Award Number: AS-PG-2013-017; Atlantic Philanthropies; Irish Government; Irish Life
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Relatively young participant pool.
Study attrition	Yes	Minimal attrition (7027 included out of 8504 total study sample)
Prognostic factor measurement	Unclear	Assessed via 2 methods but duration and dosage only recorded for a subset of participants and adherence not recorded.
Outcome measurement	Unclear	No blinding to cognitive assessment mentioned but ACB scores likely applied after cognition scores derived.
Study confounding	Yes	All essential covariates adjusted for including psychiatric conditions.
Reverse causation	Unclear	Most people had ≥ 2 years between medication assessment and outcome assessment; however, time frame for new users not restricted so some risk of protopathic bias.
Statistical analysis and reporting	Unclear	Appropriate analysis. Checked assumptions but no protocol registered.

Papenberg 2017
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Sweden Duration of follow-up: 6 years Covariates controlled for: age, sex, education, CRFs, cardiovascular disease, physical inactivity, total number of drugs, and depression
Participants	Participants numbers: 1473

Papenberg 2017 (Continued)

Population type: older adults

Sex: 61% women (902)

Age (mean): 70 years

Prognostic factors	Anticholinergic burden measurement method: Anatomical Therapeutic Chemical classification system
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: cognitive test battery Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	Ministry of Health and Social Affairs
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Age, sex, and comorbidities all reported adequately. Random selection of community.
Study attrition	No	High degree of attrition (only 1724/3363 underwent cognitive testing at baseline and follow-up).
Prognostic factor measurement	Unclear	Patients asked to bring in medications they were taking (including non-prescription medications); medical records checked if participant could not provide information. No mention of recording dosage, frequency, or adherence.
Outcome measurement	Unclear	No blinding but cognition recorded after cognitive assessment.
Study confounding	Yes	All relevant comorbidities controlled for.
Reverse causation	No	No restriction to time frame of anticholinergic drug use mentioned.
Statistical analysis and reporting	Unclear	No protocol or assumptions checked.

Richardson 2018
Study characteristics

Methods	Design: retrospective case-control Setting: community Country: UK Duration of follow-up: 4 years Covariates controlled for: age, region, any falls, any fractures, number of doctor consultations in the 12 months before the drug exposure period, number of prescriptions during the drug exposure period, BMI, smoking status, harmful alcohol use, depression duration, cardiovascular or cerebrovascular and related diagnoses, mental health diagnoses, other comorbidities. Cases and controls matched on
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Richardson 2018 (Continued)

sex, year of birth (within 3 years), years of 'up to standard' data history, and area level deprivation measured by the index of multiple deprivation quintile of each practice based on its postcode.

Participants	Participants numbers: 324,703 Population type: older adults Sex: 63% women (204,563) Age (mean): 83 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale; ADS scale
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: clinical codes recorded in medical records or prescription for a cognitive enhancer Diagnostic criteria dementia: not stated
Source of funding	Alzheimer's Society
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Yes	Reported age, sex, and comorbidities. All seemed generalisable.
Study attrition	Unclear	Conducted several sensitivity analyses based on missing data and outcomes, but did not compare missing data with anticholinergic burden scores.
Prognostic factor measurement	Unclear	Only used prescribing records to establish current drug use.
Outcome measurement	Unclear	Relied on database diagnosis.
Study confounding	Yes	Controlled for a vast number of covariates including psychiatric and physical conditions.
Reverse causation	Yes	Restricted measurement of anticholinergic drug use to ≥ 4 years before index date for dementia diagnosis.
Statistical analysis and reporting	Unclear	No assessment of validity of assumptions for logistic regression analysis.

Risacher 2016
Study characteristics

Methods	Design: retrospective cohort Setting: secondary care Country: USA Duration of follow-up: 32 months
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Risacher 2016 (Continued)

Covariates controlled for: age, sex, total number of medications, cardiac surgery, total number of co-morbid conditions, other psychiatric conditions and amyloid- β positivity

Participants	Participants numbers: 402 Population type: older adults Sex: 53% women (213) Age (mean): 73 years
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: dementia and MCI; cognitive decline Outcome ascertainment dementia/MCI/cognitive decline: comprehensive cognitive and clinical battery Diagnostic criteria dementia/MCI: not stated Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	ADNI and Department of Defense ADNI
Notes	

Item	Authors' judgement	Support for judgement
Study participation	No	High numbers of participants with subjective cognitive decline.
Study attrition	Unclear	No analysis carried out to evaluate if participants with missing data differed in baseline anticholinergic burden score compared to those with full data.
Prognostic factor measurement	No	Relied on self-report data (according to discussion) for medication use. Not clear if there were multiple measurements but seems to only be based on baseline use and follow-up was for several years.
Outcome measurement	Unclear	No blinding. Is unclear how Alzheimer's disease and MCI were diagnosed in the study.
Study confounding	Unclear	Age, sex, and relevant comorbidities all controlled for.
Reverse causation	No	There were dementia/MCI converters in first 6 and 12 months (figure 4) and no mention of any exclusions of these participants from analysis.
Statistical analysis and reporting	No	Checks assumptions. No protocol. Only 58 odd cases of dementia so seemed underpowered based on number of covariates they claimed to have controlled for (which seemed to differ in the methods section vs in the results table). Did not control for depression in analysis despite this differing between anticholinergic users and non-users.

Shah 2013
Study characteristics

Methods	Design: retrospective cohort
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Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome (Review)

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Shah 2013 (Continued)

Setting: community
Country: USA
Duration of follow-up: 10 years
Covariates controlled for: age, gender, and education. For incident users only in a secondary analysis: ApoE e4 allele, MCI, number of chronic medical conditions, urinary incontinence, number of depressive symptoms, physical activity, and disability on the Katz Index

Participants	Participants numbers: 895 Population type: older adult priests and nuns Sex: 70% women (623) Age (mean): 74 years (never users); 75.9 years (incident users); 76.5 years (prevalent users)
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: cognitive decline Outcome ascertainment cognitive decline: battery of 19 cognitive function tests was administered in addition to the MMSE Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	American Philosophical Society, the National Institute on Aging grants, and by the Illinois Department of Public Health to DAB
Notes	

Item	Authors' judgement	Support for judgement
Study participation	No	Sample restricted to priests and nuns. Majority of population were women (> 70%) so not particularly generalisable.
Study attrition	Unclear	No evaluation of people excluded vs included. No comparison of missing values against anticholinergic burden score.
Prognostic factor measurement	Unclear	Repeated measurements conducted (at each follow-up assessment). Medication assessed using only 1 method (self-report). No measurement of dosage and frequency of use.
Outcome measurement	Unclear	Anticholinergic burden likely measured after cognitive assessment complete (medications recorded before each evaluation but was part of religious order study so anticholinergic burden not primary focus during assessments).
Study confounding	Unclear	Only controls for age, sex, and education in primary analysis. Did not control for any comorbidities, despite measuring these. In secondary analysis it then controls for covariates but is restricted to incident anticholinergic drug users only.
Reverse causation	No	No restrictions placed on time frame of anticholinergic drug use before cognitive assessment.

Shah 2013 (Continued)

Statistical analysis and reporting Unclear No protocol or assumptions checked.

Sheu 2019
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: Taiwan Duration of follow-up: 4 years Covariates controlled for: age, sex, duration of Parkinson's disease before index date, conditions (hypertension, stroke, hypercholesterolaemia, diabetes mellitus, depression, anxiety, psychotic-related disorder, alcohol-related disorder, sleep disorder, and head injury), and medications (antihypertensives, antidiabetics, anticoagulants, antihyperlipidaemics, antidepressants, benzodiazepines, and antipsychotics)
Participants	Participants numbers: 1232 Population type: people with Parkinson's disease Sex: 44% women (542) Age (mean): not stated
Prognostic factors	Anticholinergic burden measurement method: ACB scale
Outcomes	Outcomes assessed: dementia Outcome ascertainment dementia: clinical codes recorded in medical records Diagnostic criteria dementia: ICD-9-CM codes 290.0–290.4, 294.1, 331.0–331.2
Source of funding	Ministry of Science and Technology
Notes	

Item	Authors' judgement	Support for judgement
Study participation	No	Parkinson's disease population.
Study attrition	Unclear	No mention of attrition.
Prognostic factor measurement	Unclear	Relied on prescription records. Measured cumulative dose over 3-year exposure period.
Outcome measurement	Unclear	Relied on database diagnoses.
Study confounding	Yes	All relevant covariates controlled for.
Reverse causation	Unclear	Excluded participants taking anticholinergic drugs 1 year before diagnosis.

Sheu 2019 (Continued)

Statistical analysis and reporting Unclear No assumptions checked or protocol registered.

Whalley 2012
Study characteristics

Methods	Design: retrospective cohort Setting: community Country: UK Duration of follow-up: 6.25 years Covariates controlled for: age and childhood IQ for linear regression; age, sex, family history of dementia, education, heart history, blood pressure history, ApoE e4 for logistic regression
Participants	Participants numbers: 281 Population type: older adults Sex: 42% women (119) Age (mean): 77 years
Prognostic factors	Anticholinergic burden measurement method: literature review of drugs' mean anticholinergic activity
Outcomes	Outcomes assessed: dementia; cognitive decline Outcome ascertainment dementia: consensus diagnosis based on multidisciplinary evaluation Outcome ascertainment cognitive decline: MMSE and cognitive test battery of 5 cognitive tests Diagnostic criteria dementia: ICD-10 criteria Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	Wellcome Trust
Notes	

Item	Authors' judgement	Support for judgement
Study participation	Unclear	Adequate reporting of age, sex, and comorbidities. However, limited age range included (77–82 years).
Study attrition	No	281/324 participated. Only 136/281 (48%) participants had complete cognitive data sets available after follow-up.
Prognostic factor measurement	Unclear	Relied on patient self-report.
Outcome measurement	Unclear	No blinding but anticholinergic burden score likely applied in retrospect.
Study confounding	Unclear	No control for depression.

Whalley 2012 (Continued)

Reverse causation	Unclear	Excluded people with lower MMSE at baseline from analysis. Follow-up 15 months minimum after baseline anticholinergic measurement taken.
Statistical analysis and reporting	No	Model was underpowered to assess dementia association (only 45 cases of dementia included in model yet 9 covariates).

Yarnall 2015
Study characteristics

Methods	Design: retrospective case-control Setting: community and outpatient Country: UK Duration of follow-up: 1.5 years Covariates controlled for: age, gender, years of education, disease duration, MDS-UPDRS III, levodopa equivalent daily dose and GDS-15 (note: unclear what was controlled for in final model)
Participants	Participants numbers: 219 Population type: people with Parkinson's disease Sex: 40% women (88) Age (mean): 69 years
Prognostic factors	Anticholinergic burden measurement method: ADS scale
Outcomes	Outcomes assessed: MCI; cognitive decline Outcome ascertainment MCI: not clear Outcome ascertainment cognitive decline: MMSE, MoCA, in addition to tests of attention, visual memory, executive, language and visuospatial function Diagnostic criteria MCI: PD-MCI was determined using the MDS criteria Diagnostic criteria cognitive decline: scores on cognitive testing
Source of funding	Parkinson's UK grant
Notes	

Item	Authors' judgement	Support for judgement
Study participation	No	Parkinson's disease population.
Study attrition	Unclear	No comparison of completers vs non-completers.
Prognostic factor measurement	Unclear	Not particularly clear how prognostic factor was measured but seems to be self-report. Repeated measurements taken at baseline and 18 months.
Outcome measurement	Unclear	No blinding but ADS ratings likely assigned in retrospect.

Yarnall 2015 (Continued)

Study confounding	Yes	Appropriate variables controlled for.
Reverse causation	No	ADS at baseline and at 18 months pooled so no restriction on ADS use before cog assessment at 18 months.
Statistical analysis and reporting	No	Uses backward stepwise regression to determine model covariates for use in exploring ADS association with various measures of cognition. Not stated what variables were controlled for in the final model.

ACB: Anticholinergic Cognitive Burden; ACT: Adult Changes in Thought; ADS: Anticholinergic Drug Scale; AGE CAT: Automated Geriatric Examination for Computer Assisted Taxonomy; ANDI: Alzheimer's Disease Neuroimaging Initiative; ApoE: apolipoprotein E; ARS: Anticholinergic Risk Scale; BMI: body mass index; CAD: coronary artery disease; CES-D: Center for Epidemiologic Studies Depression Scale; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CNAM-TS: Caisse Nationale d'Assurance Maladie des Travailleurs Salariés; CRF: cardiovascular risk factor; DBI-ach: anticholinergic component of the Drug Burden Index; DSM-III: Diagnostic and Statistical Manual of Mental Disorders Third Edition; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; ED: emergency department; GDS: Geriatric Depression Screen; GP: general practitioner; HVRT: Hopkins Verbal Recall Test; IADL: instrumental activity of daily living; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10: International Classification of Diseases, Tenth Revision; MCI: mild cognitive impairment; MDS-UPDRS III: Motor Rating Scale – Unified Parkinson's Disease Rating Scale III; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; NIH: National Institutes of Health; NINCDS-ADRDA: Association Internationale pour la Recherche et l'Enseignement en Neurosciences; PD-MCI: Parkinson's disease mild cognitive impairment; VA: Veteran's Affairs.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aalto 2018	Wrong study design.
Andrade 2019	Wrong study design.
Andre 2019	Wrong patient population.
Ang 2015	Abstract only.
Ang 2017	Wrong patient population.
Aparasu 2014	Wrong patient population.
Asano 2019	Abstract only.
Ben Omar 2013	Abstract only.
Bostock 2013	Wrong study design.
Bottiggi 2006	Dichotomises anticholinergics.
Bouchard 2017	Grey literature (dissertation).
Broder 2020	Abstract only.
Cai 2013	Repeat data set of already included study.
Campbell 2010	Repeat data set of already included study.

Study	Reason for exclusion
Campbell 2018	Repeat data set of already included study.
Cancelli 2008	Wrong study design.
Cao 2008	Wrong study design.
Cardwell 2020	Wrong prognostic factor (DBI-ach not reported separately).
Carriere 2009	Dichotomised anticholinergic burden.
Cherniaeva 2019	Abstract only.
Cooley 2020	Duplicate.
Cooley 2021	Wrong population.
Dmochowski 2021	Wrong study design (systematic review).
Drag 2012	Abstract only.
Ehrt 2010	Wrong patient population (baseline dementia = 20% for community dwelling population).
Fox 2011b	Wrong patient population.
Gnjidic 2012	Wrong prognostic factor (DBI-ach not reported separately).
Hanlon 2020	Wrong population (middle aged).
Hong 2019	Dichotomised anticholinergic burden.
Huang 2012	Non-English language.
Jakeman 2020	Conference abstract.
Kada 2019	Non-English language.
Kamkwala 2020	Abstract only.
Kar 2004	Wrong study design (review).
Kashyap 2013	Abstract only.
Khan 2021	Wrong study design.
Lampela 2013	Wrong study design.
Lattanzio 2018	Wrong outcome.
Lavrador 2020	Duplicate.
Lavrador 2021	Wrong study design (duration of follow-up too short).
Lawson 2015	Abstract only.
Lechevallier-Michel 2005	Wrong study design.

Study	Reason for exclusion
Liu 2020	Repeat data set of already included study.
Lucas 2016	Abstract only.
Naharci 2017	Wrong patient population.
Neelamegam 2020	Repeat data set of already included study.
Nishtala Prasad 2020	Wrong patient population.
Park 2017	Repeat data set of already included study.
Pasina 2013	Wrong study design (follow-up only for Barthel index; none for cognition).
Pasina 2020	Wrong study design.
Perez 2019	Abstract only.
Pfistermeister 2017	Wrong study design.
Richardson 2018b	Abstract only.
Rudolph 2008	Wrong outcome.
Salyer 2019	Wrong study design.
Shetty 2020	Abstract only.
Shiota 2020	Wrong study design.
Suh 2020	Repeat data set of already included study.
Tanaka 2019	Non-English language.
Tristancho-Perez 2019	Abstract only.
Tsoutsoulas 2017	Wrong study design.
Verdoux 2020	Wrong population.
Wang 2019	Repeat data set of already included study.
Weigand 2020	Repeat data set of already included study.
Welk 2020	Dichotomises anticholinergic use.
Wouters 2017	Wrong prognostic factor (DBI-ach not reported separately).
Wouters 2020	Wrong prognostic factor (DBI scale; anticholinergic not reported separately).
Ziad 2021	Wrong patient population (middle-aged adults).

DBI: Drug Burden Index; DBI-ach: anticholinergic component of the Drug Burden Index.

ADDITIONAL TABLES

Table 1. PICOTS

Population	Older adults (mean age \geq 50 years) free of cognitive impairment at baseline
Interventions	Anticholinergic burden as measured by any validated ordinal anticholinergic burden scale
Comparators (covariates of interest)	Age, sex, and comorbidity
Outcomes	Incident dementia or cognitive function (multidomain)
Type of study	Longitudinal, observational cohort/case-control
Timing and setting	Recruitment from primary, secondary, or community settings Minimum of 1-year follow-up

Table 2. GRADE

Quality criteria	Rating (circle 1 for each criterion)	Footnotes (explain reasons for upgrading or downgrading)	Quality of the evidence (circle 1 per outcome)
Prognostic factor: anticholinergic burden (defined by ACB scale) and risk of future cognitive impairment/dementia in cognitively healthy older adults			
Phase of investigation	No issues	Most studies were phase 3 confirmatory investigations.	High Moderate
Study limitations	Serious (-1)	2 studies were at high risk of bias, with issues around reverse causation. The remaining 2 studies were at unclear risk of bias, 1 of which had uncertain risk of bias due to reverse causation.	Low Very Low
Imprecision	Serious (-1)	Relatively wide confidence intervals.	
Inconsistency	No issues	Included studies were predominantly assessed using similar prognostic outcome measures, definitions, in similar settings with similar follow-up durations. Direction of effect was also consistent.	
Indirectness	No issues	Included studies represented the review question adequately.	
Publication bias	Serious (-1)	Publication bias was assumed.	
Effect size	No	Moderate effect size in primary analysis but lower bound confidence intervals suggested a low effect size.	
Dose-response gradient	Yes (+1)	Clear relationship between severity of ACB scale score and risk of dementia was apparent.	

ACB: Anticholinergic Cognitive Burden.

APPENDICES

Appendix 1. Anticholinergic burden scales

AAS: Anticholinergic Activity Scale

AAS-r: Revised Anticholinergic Activity Scale

ABC: Anticholinergic Burden Classification

ABS: Anticholinergic Burden Scale

ACB: Anticholinergic Cognitive Burden

ADS: Anticholinergic Drug Scale

AEC: Anticholinergic Effect on Cognition

AIS: Anticholinergic Impregnation Scale

ALS: Anticholinergic Loading Scale

ARS: Anticholinergic Risk Scale

BAAS: Brazilian Anticholinergic Activity Scale

Chew's list

CrAS: Clinician-rated Anticholinergic Scale

Ellett's list

KABS: Korean Anticholinergic Burden Scale

MARANTE: Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale

mARS: Modified Anticholinergic Risk Scale

Appendix 2. Contributions to Delphi

Contributors to Delphi for selection of adjustment variables were researchers and clinicians from a range of specialities (medicine and psychology). Specific contributors were Dr Carrie Stewart, Dr Roy Soiza, Professor Phyo Myint, Dr Terry Quinn, and Dr Yoon Loke.

Appendix 3. Sources searched and search strategies

Source	Search strategy	Hits retrieved
MEDLINE In-process and other non-indexed citations and MEDLINE (OvidSP) from 1946 Date of search: 24 March 2021	1. cholinergic antag*.ti,ab.	Mar 2020: 2907
	2. anticholinergic*.ti,ab.	Mar 2021: 252
	3. anti-cholinergic*.ti,ab.	
	4. cholinergic Antagonists/tu	
	5. Cholinergic Antagonists/ae	
	6. AAS.ti,ab.	
	7. ACB.ti,ab.	
	8. ADS.ti,ab.	
	9. DAPs.ti,ab.	

(Continued)

10. ARS.ti,ab.
11. DBI-ACh.ti,ab.
12. SAMS.ti,ab.
13. ("chew* score" or "chew* list").ti,ab.
14. ("han's score" or "han score").ti,ab.
15. or/1-14
16. Cognition/
17. Cognition Disorders/
18. Dementia/
19. cognit*.ti,ab.
20. dement*.ti,ab.
21. alzheimer*.ti,ab.
22. "lewy bod*".ti,ab.
23. FTLD.ti,ab.
24. PDD.ti,ab.
25. "executive function*".ti,ab.
26. Attention/
27. (speed adj2 processing).ti,ab.
28. memory.ti,ab.
29. Memory Disorders/
30. "episodic memory".ti,ab.
31. Memory, Episodic/
32. MCI.ti,ab.
33. Mild Cognitive Impairment/
34. (nMCI or aMCI or mMCI or MCIa).ti,ab.
35. AAMI.ti,ab.
36. ACMI.ti,ab.
37. ARCD.ti,ab.
38. CIND.ti,ab.
39. VCI.ti,ab.
40. VAD.ti,ab.
41. major neurocognitive disorder*.ti,ab.
42. minor neurocognitive disorder*.ti,ab.
43. neurocognitive dysfunction.ti,ab.

(Continued)

44. Neurocognitive Disorders/
45. or/16-44
46. 15 and 45

EMBASE (OvidSP) from
1974

Date of search: 24
March 2021

1. cholinergic antag*.ti,ab.
2. anticholinergic*.ti,ab.
3. anti-cholinergic*.ti,ab.
4. *cholinergic receptor blocking agent/
5. AAS.ti,ab.
6. ACB.ti,ab.
7. ADS.ti,ab.
8. DAPs.ti,ab.
9. ARS.ti,ab.
10. DBI-ACh.ti,ab.
11. SAMS.ti,ab.
12. ("chew* score" or "chew* list").ti,ab.
13. ("han's score" or "han score").ti,ab.
14. or/1-13
15. Cognition/
16. Cognition Disorders/
17. Dementia/
18. cognit*.ti,ab.
19. dement*.ti,ab.
20. alzheimer*.ti,ab.
21. "lewy bod*".ti,ab.
22. FTLD.ti,ab.
23. PDD.ti,ab.
24. "executive function*".ti,ab.
25. Attention/
26. (speed adj2 processing).ti,ab.
27. memory.ti,ab.
28. Memory Disorders/
29. "episodic memory".ti,ab.
30. Memory, Episodic/
31. MCI.ti,ab.

Mar 2020: 4544

Mar 2021: 552

(Continued)

32. Mild Cognitive Impairment/
33. (nMCI or aMCI or mMCI or MCIa).ti,ab.
34. AAMI.ti,ab.
35. ACMI.ti,ab.
36. ARCD.ti,ab.
37. CIND.ti,ab.
38. VCI.ti,ab.
39. VAD.ti,ab.
40. major neurocognitive disorder*.ti,ab.
41. minor neurocognitive disorder*.ti,ab.
42. neurocognitive dysfunction.ti,ab.
43. Neurocognitive Disorders/
44. or/15-43
45. 14 and 44

PsycINFO (OvidSP) from 1806 Date of search: 24 March 2021	1. cholinergic antag*.ti,ab.	Mar 2020: 3489
	2. anticholinergic*.ti,ab.	Mar 2021: 164
	3. anti-cholinergic*.ti,ab.	
	4. exp Cholinergic Receptors/	
	5. AAS.ti,ab.	
	6. ACB.ti,ab.	
	7. ADS.ti,ab.	
	8. DAPs.ti,ab.	
	9. ARS.ti,ab.	
	10. DBI-ACh.ti,ab.	
	11. SAMS.ti,ab.	
	12. ("chew* score" or "chew* list").ti,ab.	
	13. ("han's score" or "han score").ti,ab.	
	14. or/1-13	
	15. exp Cognition/	
	16. exp Dementia/	
	17. cognit*.ti,ab.	
	18. dement*.ti,ab.	
	19. alzheimer*.ti,ab.	
	20. "lewy bod*".ti,ab.	

(Continued)

21. FTLD.ti,ab.
22. PDD.ti,ab.
23. "executive function*".ti,ab.
24. exp Attention/
25. (speed adj2 processing).ti,ab.
26. memory.ti,ab.
27. exp Memory Disorders/
28. "episodic memory".ti,ab.
29. exp Episodic Memory/
30. exp Cognitive Impairment/
31. MCI.ti,ab.
32. exp Cognitive Assessment/
33. (nMCI or aMCI or mMCI or MCIa).ti,ab.
34. AAMI.ti,ab.
35. ACMI.ti,ab.
36. ARCD.ti,ab.
37. CIND.ti,ab.
38. VCI.ti,ab.
39. VAD.ti,ab.
40. major neurocognitive disorder*.ti,ab.
41. minor neurocognitive disorder*.ti,ab.
42. neurocognitive dysfunction.ti,ab.
43. exp Neurocognitive Disorders/
44. or/15-43
45. 14 and 44

CINAHL (EBSCOhost)	S1 TX cholinergic antag*	Mar 2020: 2229
	S2 TX anticholinergic*	
Date of search: 24 March 2021	S3 TX anti-cholinergic*	Mar 2021: 260
	S4 (MH "Cholinergic Antagonists+")	
	S5 TX AAS	
	S6 TX ACB	
	S7 TX ADS	
	S8 TX DAPs	
	S9 TX ARS	
	S10 TX DBI-ACh	
	S11 TX SAMS	
	S12 TX "chew* score" or "chew* list"	
	S13 TX "han's score" or "han score"	
	S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	
	S15 (MH "Cognition+")	

(Continued)

S16 (MH "Cognition Disorders+")
 S17 (MH "Dementia+")
 S18 TX cognit*
 S19 TX dement*
 S20 TX alzheimer*
 S21 TX "lewy bod*" ¹
 S22 TX FTL D
 S23 TX PDD
 S24 TX "executive function*" ²
 S25 (MH "Attention")
 S26 TX speed AND processing
 S27 TX memory
 S28 (MH "Memory Disorders")
 S29 TX "episodic memory"
 S30 (MH "Memory Disorders") OR (MH "Memory")
 S31 TX MCI
 S32 "Mild Cognitive Impairment"
 S33 TX nMCI or aMCI or mMCI or MCIa
 S34 TX AAMI
 S35 TX ACMI
 S36 TX ARCD
 S37 TX CIND
 S38 TX VCI
 S39 TX VAD
 S40 TX major neurocognitive disorder*
 S41 TX minor neurocognitive disorder*
 S42 TX neurocognitive dysfunction
 S43 "Neurocognitive Disorders"
 S44 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43
 S45
 S14 AND S44

Web of Science core collection (ISI Web of Science) Date of search: 24 March 2021	TOPIC: ("cholinergic antag*" OR anticholinergic* OR "anti-cholinergic*" OR AAS OR ACB OR ADS OR DAPs OR ARS OR "DBI-ACh" OR SAMS OR "chew* score" OR "chew* list" OR "hands score" OR "hans score" OR "han score") AND TOPIC: (cognit* OR dement* OR alzheimer* OR "lewy bod*" OR FTL D OR PDD OR "executive function*" OR attention OR memory OR MCI OR "major neurocognitive disorder*" OR "minor neurocognitive disorder*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	Mar 2020: 1348 Mar 2021: 646
TOTAL before deduplication		Mar 2020: 14,517 Mar 2021: 1874
TOTAL after deduplication		Mar 2020: 9767 Mar 2021: 1493
TOTAL after first assessment of abstracts by CDCIG Information Specialist		Mar 2021: 1034 Mar 2020: 168

Appendix 4. Contents of proforma

Extracted information	Included details
General information	Author, title, source, publication date, language, related or duplicate publications.
Source of data	Cohort (retrospective or prospective data collection), case-control, randomised trial, or secondary analysis of registry data.
Participant information	Participant eligibility and recruitment method (e.g. consecutive or other recruitment, number of centres, inclusion and exclusion criteria); participant demographics (e.g. age, sex); details of ongoing treatments/medications; study dates; country of recruitment; setting (using our definitions of primary, secondary, and community settings).
Prognostic factor	Definition and method of measurement of prognostic factor. Duration of exposure (pre- or post-study commencement) was not regularly recorded; however, where possible, we recorded timing of prognostic factor measurement (number of weeks participants had been on the anticholinergic drugs prior to baseline assessment); where data were available, we also collected duration of exposure during the study.
Outcomes to be predicted	Definition and method of measurement of outcome; time of outcome ascertainment, or summary of duration of follow-up.
Adjustment for other prognostic factors (covariates)	List of all the covariates that were adjusted for in any regression model.
Sample size	Number of participants and number of outcomes/events; how missing data were handled (e.g. complete-case analysis, imputation, or other methods).
Reported results	We recorded incidence of dementia and cognitive decline. Where possible, we extracted estimates and corresponding confidence intervals from each included paper. We also recorded overall survival (including duration of follow-up) and dementia-free survival (including duration of follow-up).

Appendix 5. QUIPS (Quality in Prognosis Studies) anchoring statements

Specific considerations

- Study participation: we considered whether the method of recruitment was at risk of selection bias (e.g. consecutive recruitment versus convenience sample) and if there was adequate reporting of comorbidities and demographics (age and sex). If either a convenience sample was used or there was inadequate reporting of comorbidities/demographics, we assigned a moderate risk of bias.
- Attrition: we anticipated that most studies would utilise databases, hence attrition was less of an issue. Therefore, we focused on reporting of, and methods for dealing with, missing data. We assigned a moderate risk of bias if no analysis was carried out to evaluate if participants with missing data differed in baseline anticholinergic burden score compared to those with full data.
- Prognostic factor measurement: we considered how medication data were obtained. If medication was not established via at least two methods and capable of establishing non-prescription medications taken, along with duration of exposure and adherence, we assigned a moderate risk of bias. If repeated anticholinergic burden measurements were not made over time for studies with a follow-up duration of more than one year, we assigned a high risk of bias. We anticipated that some studies would utilise validated anticholinergic burden scales but adjust these scales, for instance to incorporate dosage into the anticholinergic calculation. We did not consider utilisation of anticholinergic burden scales as part of the 'Risk of Bias' assessment, as it is the purpose of the review to establish which anticholinergic burden scales have the greatest prognostic accuracy.
- Outcome measurement: we considered the method utilised for dealing with missing data in relation to the outcome. If 'last diagnosis carried forward' was used when final outcome data were not available, we assigned a high risk of bias. We assessed whether the outcome was established via a clinical follow-up or was reliant upon database diagnoses. If outcome was reliant upon database diagnoses alone, we assigned a moderate risk of bias. We also assessed if the outcome was determined without knowledge of the prognostic factor. If there was no blinding to outcome and the cognitive diagnosis was conducted after the anticholinergic burden measurement was taken, we assigned a high risk of bias; if the cognitive diagnosis preceded the anticholinergic burden measurement, we assigned a moderate risk of bias.

- **Covariates:** we assessed whether studies adjusted for age, sex, and comorbidities as a minimum. If these covariates were not adjusted for, we assigned a high risk of bias. Assessment for comorbidities required control for at least three comorbidities that covered both physical and psychiatric domains; failure to do so resulted in a rating of moderate risk of bias.
- **Reverse causation:** we evaluated studies regarding perceived risk that anticholinergic drug use was prescribed for treatment of early signs of dementia. If studies did not explicitly report restricting anticholinergic burden measurement to at least 12 months before dementia onset, a rating of high risk of bias was applied. If studies imposed restrictions of anticholinergic burden measurement for one to two years before the dementia index date, a moderate risk of bias rating was applied.
- **Statistical analysis:** we evaluated how the analysis was conducted. Specific issues of consideration in each area were decided upon via discussion among the review authors. We assigned a high risk of bias if: a multivariate analysis was not conducted; if the analysis was not appropriately powered based on the '10 events per covariate' rule; if the method for selecting covariates for inclusion in a multivariate model was based on P values in a univariate analysis without incorporation of prior knowledge of relevant associations into selection; if the method of analysis was inconsistent with the stated protocol; and if the reported results were inconsistent with the stated method of analysis. We assigned a moderate risk of bias if relevant assumptions were not checked.

HISTORY

Protocol first published: Issue 2, 2020

Review first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

TQ conceived the idea.

ANS conducted the search.

MT and SE screened the search results, selected studies for inclusion and exclusion, and performed data extraction and 'Risk of bias' assessment for each study.

MT conducted the analysis and wrote the manuscript.

PM, TQ, JM, RS, CS, and YL contributed to data interpretation and the writing of the manuscript.

DECLARATIONS OF INTEREST

MT: none

SE: none

ANS: none

JM: none

PM: none

RS: none

CS: none

YK: none

TQ: none

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK

This protocol was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health

- The Dunhill Medical Trust, UK

This work was supported by a Dunhill Medical Project Grant (RPGF1806/66)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made some minor changes to our review process to those specified in the protocol ([Quinn 2020](#)).

- Four review authors joined the review team (SE, ANS, RS, and YL).
- We did not employ the I^2 statistic to evaluate heterogeneity in included studies, choosing instead to evaluate heterogeneity narratively. This was due to evidence that the I^2 statistic can exaggerate levels of heterogeneity in prognostic research.
- We decided not to report mortality, overall survival or dementia-free survival as secondary outcomes on the basis that we found very few data on this in included reviews and since mortality has already been the focus of other recently published systematic reviews.
- We conducted a sensitivity analysis restricted to studies with no 'high risk of bias' categories, rather than restricted to studies at 'low risk of bias' overall, due to the lack of studies judged at low risk of bias.
- We added additional criteria to our outcome risk of bias and reverse causation evaluation. Specifically, if the cognitive diagnosis preceded the anticholinergic burden measurement, we assigned a moderate risk of bias to the outcome. If studies imposed a restriction on anticholinergic drug use to one to two years before the dementia index date, we applied a moderate risk of bias rating.
- We were unable to perform our planned meta-regressions due to lack of study numbers. Similarly, we could not pool linear or hazard ratio outcome data, investigate the association between anticholinergic burden, and duration of exposure due to insufficient data.