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[Prognosis Review]

Anticholinergic burden for prediction of cognitive decline or neuropsychiatric symptoms in older adults with mild cognitive impairment or dementia

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ABSTRACT

Background

Medications with anticholinergic properties are commonly prescribed to older adults with a pre-existing diagnosis of dementia or cognitive impairment. 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 a high anticholinergic burden may be a risk factor for further cognitive decline or neuropsychiatric disturbances in people with dementia. Neuropsychiatric disturbances are the most frequent complication of dementia that require hospitalisation, accounting for almost half of admissions; hence, identification of modifiable prognostic factors for these outcomes is crucial. There are various scales available to measure anticholinergic burden but agreement between them is often poor.

Objectives

Our primary objective was to assess whether anticholinergic burden, as defined at the level of each individual scale, was a prognostic factor for further cognitive decline or neuropsychiatric disturbances in older adults with pre-existing diagnoses of dementia or cognitive impairment. Our secondary objective was to investigate whether anticholinergic burden was a prognostic factor for other adverse clinical outcomes, including mortality, impaired physical function, and institutionalisation.

Search methods

We searched these databases from inception to 29 November 2021: MEDLINE OvidSP, Embase OvidSP, PsycINFO OvidSP, CINAHL EBSCOhost, and ISI Web of Science Core Collection on ISI Web of Science.

Selection criteria

We included prospective and retrospective longitudinal cohort and case-control observational studies, with a minimum of one-month follow-up, which examined the association between an anticholinergic burden measurement scale and the above stated adverse clinical outcomes, in older adults with pre-existing diagnoses of dementia or cognitive impairment.

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Data collection and analysis

Two review authors independently assessed studies for inclusion, and undertook data extraction, risk of bias assessment, and GRADE assessment. We summarised risk associations between anticholinergic burden and all clinical outcomes in a narrative fashion. We also evaluated the risk association between anticholinergic burden and mortality using a random-effects meta-analysis. We established adjusted pooled rates for the anticholinergic cognitive burden (ACB) scale; then, as an exploratory analysis, established pooled rates on the prespecified association across scales.

Main results

We identified 18 studies that met our inclusion criteria (102,684 older adults). Anticholinergic burden was measured using five distinct measurement scales: 12 studies used the ACB scale; 3 studies used the Anticholinergic Risk Scale (ARS); 1 study used the Anticholinergic Drug Scale (ADS); 1 study used the Anticholinergic Effect on Cognition (AEC) Scale; and 2 studies used a list developed by Tune and Egeli.

Risk associations between anticholinergic burden and adverse clinical outcomes were highly heterogenous. Four out of 10 (40%) studies reported a significantly increased risk of greater long-term cognitive decline for participants with an anticholinergic burden compared to participants with no or minimal anticholinergic burden. No studies investigated neuropsychiatric disturbance outcomes. One out of four studies (25%) reported a significant association with reduced physical function for participants with an anticholinergic burden versus participants with no or minimal anticholinergic burden. No study (out of one investigating study) reported a significant association between anticholinergic burden and risk of institutionalisation. Six out of 10 studies (60%) found a significantly increased risk of mortality for those with an anticholinergic burden compared to those with no or minimal anticholinergic burden. Pooled analysis of adjusted mortality hazard ratios (HR) measured anticholinergic burden with the ACB scale, and suggested a significantly increased risk of death for those with a high ACB score relative to those with no or minimal ACB scores (HR 1.153, 95% confidence interval (CI) 1.030 to 1.292; 4 studies, 48,663 participants). An exploratory pooled analysis of adjusted mortality HRs across anticholinergic burden scales also suggested a significantly increased risk of death for those with a high anticholinergic burden (HR 1.102, 95% CI 1.044 to 1.163; 6 studies, 68,381 participants).

Overall GRADE evaluation of results found low- or very low-certainty evidence for all outcomes.

Authors' conclusions

There is low-certainty evidence that older adults with dementia or cognitive impairment who have a significant anticholinergic burden may be at increased risk of death. No firm conclusions can be drawn for risk of accelerated cognitive decline, neuropsychiatric disturbances, decline in physical function, or institutionalisation.

PLAIN LANGUAGE SUMMARY

The impact of cumulative medications with anticholinergic effects on future adverse clinical outcomes in people with dementia

Key messages

Anticholinergic medicines may increase the risk of death in older adults who have dementia. However, the evidence is low certainty, and we cannot say for certain if the anticholinergic medicines cause death, or if they are simply more likely to be used by people who are already at an increased risk of dying due to ongoing health problems.

We cannot draw firm conclusions for the risk that anticholinergic medicines pose to the development of other undesirable clinical outcomes, such as further deterioration of memory and thinking, or behavioural and psychological issues. More research is needed to establish whether anticholinergic medicines cause unintended problems for older adults who have dementia.

What are anticholinergic medicines?

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, and therefore, are referred to as anticholinergic medicines.

What did we want to find out?

Anticholinergic medicines are commonly used to treat a number of medical conditions that people with dementia frequently experience. Typical examples are medicines used to treat urinary tract infections or episodes of agitation. However, because the cholinergic system in the brain plays an important role in learning, memory, and emotional regulation, there are theoretical reasons to believe that the use of anticholinergic medicines may unintentionally exacerbate psychological problems in this population. In this review, we investigated the link between anticholinergic medicines and future occurrence of undesirable clinical outcomes in people with dementia.

What did we do?

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We searched for studies that looked at the link between anticholinergic medicines and a range of clinical outcomes in people with dementia. We compared and summarised the results of identified studies and rated our confidence in the evidence, based on factors, such as study methods and sizes.

What did we find?

We found a total of 18 studies, involving 102,684 adults aged 50 years or more, who had issues with memory and thinking. We found that the evidence was highly inconsistent regarding the link between anticholinergic medicines and increased issues with memory and thinking in people with dementia. There were no studies that investigated the link between anticholinergic medicines and frequency of behavioural disturbances. Therefore, we could not draw any conclusions about whether anticholinergic medicines cause issues with memory and thinking, or behavioural disturbances in this population. However, we did find there was a more consistent link between anticholinergic medicines and the risk of death. Those who were taking anticholinergic medicines had a 15% higher risk of dying than those who were not taking anticholinergic medicines.

What are the limitations of the evidence?

The available evidence is very low certainty because of the inconsistency of study results, and the lack of control for health conditions that could be linked with both the clinical outcomes and the prescribing of anticholinergic medicines themselves. It is possible that anticholinergic medicines may not actually cause death, but are simply more likely to be given to people who are already at an increased risk of dying due to ongoing health problems.

How up to date is this evidence?

We searched for studies published up to 29 November 2021.

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SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

-Risk of cognitive decline or neuropsychiatric outcomes in people with dementia for those with an anticholinergic burden compared to those with no or minimal anticholinergic burden

Patient or population: older adults with cognitive impairment at baseline

Intervention: anticholinergic burden

Comparison: no or minimal anticholinergic burden

Outcomes: cognitive decline (multi-domain) or neuropsychiatric disturbances

Timing: prognostic factors measured at baseline; outcomes obtained at a minimum of 1-month follow-up via longitudinal, observational cohort or case-control study design

Setting: mixed (care homes, community, hospitals)

Outcomes	Relative effect (95%CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cognitive decline	NA	18213 (10)[a]	⊕⊖⊖⊖ Very low[b,c,d,e]	Studies were too heterogeneous to pool. The majority of studies did not identify a significantly increased risk for those with an anticholinergic burden compared to those with no or minimal burden. However, the inconsistency and high risk of bias of the available evidence means no firm conclusions can be drawn.
Neuropsychiatric outcomes	NA	0	NA	None of the included studies assessed this outcome.

AChEI: acetylcholinesterase inhibitor; **CI:** confidence interval; **NA:** not applicable
GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: 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 certainty: we are very uncertain about the estimate
[a]Bishara 2020; Bottiggi 2007; Dyer 2020; Fox 2011; Haaksma 2019; Landi 2014; Lu 2003; Trevisan 2021; Jenraumjit 2020; Lopez-Matons 2018
[b]Most studies were at high risk of bias; downgraded 2 levels
[c]Results and measurement methods across studies werehighly heterogeneous; downgraded 2 levels
[d]Most studies conducted in Alzheimer disease population only, or dementia population who were also on AChEIs; downgraded 2 levels
[e]We were unable to formally investigate publication bias via a funnel plot; however, publication bias is assumed within this literature; downgraded 1 level

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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, 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 is a major public health issue. 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).

As cognitive functioning declines, people's ability to live independently also decreases. In turn, this increases caregiver burden, healthcare support requirements, and institutionalisation. In addition, neuropsychiatric disturbances are a common consequence of declining cognition. Up to 90% of people with Alzheimer's disease experience neuropsychiatric symptoms, such as mood disturbance, depression, agitation, anxiety, sleep disorder, psychosis, hallucinations, and delusions (Steinberg 2008). Occurrence of neuropsychiatric disturbances are the most frequent complication of dementia that require hospitalisation, accounting for 49.4% of admissions (Soto 2012).

Some prognostic factors, such as type of dementia and number of comorbidities, can predict more rapid cognitive decline or increased neuropsychiatric disturbances in people with dementia (Haaksma 2019). Identification of prognostic factors can assist healthcare professionals to predict outcomes for people with MCI or dementia, provide prognostic information to people with dementia and their families, and help policymakers to plan for future population healthcare needs. If these prognostic factors are modifiable, they serve as potential targets to reduce the rate of decline, and frequency or severity (or both) of neuropsychiatric disturbances in people with these cognitive syndromes.

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.

People with dementia are commonly prescribed medications that have antagonist activity at acetylcholine receptors, known as anticholinergic medications. Prevalence varies internationally and by setting; however, example estimates suggest around 23.3% of community-based people with dementia in the USA, 11.7% of memory clinic attendees in Australia, and 37.9% of 'Psychiatry of Later Life' service attendees in Ireland are reported to be taking clinically significant anticholinergic medications (Cross 2016; Sura 2013; Vaughan 2019). 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. The accumulation of medications with anticholinergic properties is referred to as the anticholinergic burden.

Anticholinergics block the binding of acetylcholine to cholinergic receptors in the brain and elsewhere in the body. In the brain, acetylcholine is a neurotransmitter that plays a major role in numerous functions, including cognition, behaviour, and emotion. As such, anticholinergics are hypothesised to cause disruption to cognitive functioning and increase neuropsychiatric disturbance, with greater anticholinergic burden causing greater disruption.

Measures of anticholinergic burden

Anticholinergic burden can be measured using a variety of approaches. Serum radioreceptor anticholinergic activity assay (SAA) is often considered to be a gold standard for measuring peripheral anticholinergic burden; however, it has limited clinical utility and is a poor predictor of effects on the central nervous system (Salahudeen 2016). Alternative (non-SAA) anticholinergic burden measures generally use a person's medication list and assign a score to certain medications. A cumulative total, based on all prescribed medications, is then calculated. There is no consensus on which non-SAA anticholinergic burden measure provides the most accurate and clinically useful prognostic information. Although these measures should be similar, overlap is limited; they include different medications and assign differing scores to these medications. Scales measuring anticholinergic burden have been developed using a variety of methodologies. For instance, the Drug Burden Index (DBI) measures anticholinergic

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burden according to pharmacological first-principles of dose-response (i.e. through an understanding of the pharmacokinetics and pharmacodynamics of the drug class (Hilmer 2018)); some scales use a literature review, or incorporate expert clinical opinion (or both) in their development, and are designed to measure both central and peripheral anticholinergic effects; while others focus on serum radioreceptor anticholinergic activity assays or muscarinic receptor affinity measurements, and may only capture peripheral anticholinergic effects (Mayer 2015). Therefore, when reviewing the literature about the prognostic impact of anticholinergic medications, it is important to estimate effects at the level of the individual scale, as well as across different scales.

In order to determine if anticholinergic burden measures can be used to predict increased cognitive decline or neuropsychiatric disturbance in people with MCI or dementia, a comprehensive assessment of the available literature is needed. The relationship between anticholinergic burden and outcome may vary with multiple factors, including the clinical and demographic make-up of the population being investigated (e.g. care-home populations versus non-care-home populations), or the duration of drug exposure. The severity and subtype of dementia may also be important; for instance, the cholinergic hypothesis proposes that disruption of cholinergic neurotransmission may play an important role in the cognitive deterioration seen in Alzheimer's disease (Francis 1999); hence, prolonged use of anticholinergic medications may affect the rate of cognitive deterioration more substantially in people with Alzheimer's dementia than in other dementia subtypes. If anticholinergic burden is a prognostic factor, then 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 for anticholinergic burden assessment in clinical practice.

Why is it important to do this review?

This review is intended to serve as a companion to the recently published Cochrane Review on anticholinergic burden as a prognostic factor for development of cognitive decline or dementia in cognitively healthy older adults, as associations between anticholinergic burden and cognitive decline in cognitively healthy older adults have been consistently reported (Taylor-Rowan 2021). Drugs with anticholinergic properties are hypothesised to cause further disruption to cognition and increased occurrence of neuropsychiatric disturbance in those with MCI and dementia. However, to date, the evidence to support this hypothesis has been mixed (Wang 2021). Consequently, there is uncertainty regarding the clinical value of measuring anticholinergic burden within an already cognitively impaired population. In this review, we aimed to estimate the prognostic utility (adjusted and unadjusted) of different anticholinergic burden measures for predicting cognitive decline or neuropsychiatric disturbances in people with MCI or dementia, and to assess the certainty of the supporting evidence.

OBJECTIVES

Primary objective

To assess whether anticholinergic burden, at the level of individual measurement scales, is a prognostic factor for further cognitive decline or neuropsychiatric disturbances in people with mild cognitive impairment (MCI) or dementia.

Secondary objective

- To compare the prognostic validity of different anticholinergic burden scales
- To examine the effect of type of dementia and severity of dementia on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances
- To examine the effect of setting (care home versus non-care home) on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances
- To examine whether anticholinergic burden is a prognostic factor for other clinical outcomes in people with MCI or dementia

METHODS

We followed best practice in design, conduct, and reporting for 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 stringent peer review. Languages deemed viable for translation were Greek, French, Spanish, and Dutch.

Types of participants

We included any studies that recruited middle-aged and older adults (defined as mean age 50 years or older) who, at the time of recruitment and the time of application of the anticholinergic burden measure, had either a known diagnosis of mild cognitive impairment (MCI) or dementia established by a medical practitioner, cognitive impairment established via a cut-off on a formal cognitive assessment, or were taking cholinesterase inhibitor drugs. For studies in which a mixed population was recruited, we only included the study if the prevalence of dementia or MCI was more than 70%.

We made no restrictions based on comorbidity or polypharmacy, but recorded these factors in our data extraction. We assessed whether acetylcholinesterase (AChE) inhibitor use was measured, and considered any potential impact of this in our risk of bias assessment. We included studies conducted in specific population subgroups, such as Parkinson's disease, schizophrenia, or stroke, provided they met our other inclusion criteria.

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We included studies conducted in all settings. People recruited in various settings (e.g. care home versus community care) may differ in important demographics (e.g. mean age, dementia severity, clinical or lifestyle factors) that could alter the strength of the association between anticholinergic burden and cognitive decline or neuropsychiatric disturbance. If a study was conducted in a care-home setting, but did not report numbers with previous MCI or dementia, we included the study in the review but removed it via a sensitivity analysis, as required.

Index prognostic factor

The prognostic factor of interest was anticholinergic burden from medications. We included any study describing use of a scale that purports 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.

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, when the Drug Burden Index (DBI) scale was used, we only included data if anticholinergic burden data were reported separately.

Due to our expectation of a relatively sparse literature, we did not exclude studies that simply used a dichotomised present/absent method to investigate the association between anticholinergic medication use and risk of cognitive decline or neuropsychiatric disturbance. However, as severity of anticholinergic burden may play an important role in identifying any association, we considered the potential impact of this approach in our risk of bias assessment.

We did not include studies that only measured anticholinergic burden via serum radioreceptor assay (SAA) levels, as this has limited clinical applicability.

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 after adjustment for core variables, identified as fundamental to the putative link between anticholinergic burden and further cognitive decline or neuropsychiatric disturbance in people with MCI or dementia. We selected these variables 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, comorbidities, and use of AChE inhibitors (N.B. the use of AChE inhibitors was only considered to be a core variable for cognitive outcomes).

We assessed use of additional adjustments in our risk of bias assessment.

Outcome measures

Primary outcomes

We included any study that assessed cognitive decline (i.e. change on a measure of cognitive function) or neuropsychiatric disturbance (defined as stressed and distressed behaviours, such as those measured via the Neuropsychiatric Inventory) as an outcome. In the case of people with MCI, we also included studies that assessed incident dementia as an outcome. For the outcome of cognitive decline, we accepted any multi-domain cognitive assessment tool that was validated for the direct assessment of cognition. We did not include papers that only measured a single cognitive domain. We only included primary outcomes in our summary of findings table.

Secondary outcomes

We also included studies that assessed risk of mortality, decline in physical functioning, and institutionalisation, defined as admission to a care home, in people with pre-existing cognitive impairment.

Timing

On the basis that anticholinergic effects on cognition or neuropsychiatric disturbance may be more rapid in a dementia population than in a cognitively unimpaired population, we accepted assessment for cognitive decline or neuropsychiatric disturbance at one month or longer following baseline anticholinergic burden assessment. We evaluated the risk of reverse causality, based on the duration of follow-up in our risk of bias assessment.

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 combined our prognostic factor (anticholinergic burden) with the population of interest (people with MCI or dementia).

We searched the following databases: MEDLINE OvidSP (1946 to 29 Nov 2021), Embase OvidSP (1974 to 29 Nov 2021), PsycINFO OvidSP (1806 to 29 Nov 2021), CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1950 to 29 Nov 2021), and ISI Web of Science Core Collection ISI Web of Science (1928 to 29 Nov 2021; Appendix 3). We did not apply any language restrictions in our primary search, although at title selection, studies that could not be translated into English by the review authors were excluded.

Searching other resources

We supplemented this with handsearches of references 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 Dementia and Cognitive Improvement Group's Information Specialist performed a 'first pass' screen to remove clearly irrelevant titles.

Three review authors (AA, OK, and CK) independently screened studies identified via our search methods. They screened the titles and abstracts first, then accessed the full text of potentially relevant studies to determine if the study met our inclusion criteria. In cases

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of disagreement, a fourth review author (MT) acted as arbiter, and made the final decision on study inclusion or exclusion.

Data extraction and management

Two review authors (OK and CK) independently extracted the data to a piloted pro forma, 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 when required. We selected two studies to trial our data extraction pro forma (Bishara 2020; Fox 2011). We extracted all data onto a standard form (Appendix 4).

Assessment of methodological quality

Two review authors (OK and CK) independently used the QUIPS (Quality in Prognosis Studies) checklist to assess 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 (Hayden 2012). A third review author (MT) evaluated all risk of bias estimates and assigned a final rating. We used the QUIPS anchoring statements, but modified the content to suit our review topic, based on consensus within the review team.

We judged each domain as low risk of bias, unclear risk of bias, or high risk of bias (Appendix 5). In cases of uncertainty, we contacted original study authors for clarification, when 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) can 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 population (people with MCI or dementia) and the prognostic factor (anticholinergic burden), without any specific filter for prognostic research to increase retrieval.

Data synthesis

We evaluated risk of future adverse clinical outcomes narratively, summarising the number and details of studies reporting significant and non-significant associations for all outcomes of interest. A significant effect was defined as confidence intervals (CI) that did not cross 1.0, or a P value < 0.05, or both. We used a random-effects model for the meta-analysis to investigate risk of future mortality. Specifically, we pooled fully adjusted hazard ratio (HR) data, provided that at least age, sex, and comorbidities were controlled for. We initially pooled hazard ratio data for the Anticholinergic Cognitive Burden (ACB) tool individually; then, as an exploratory analysis, we pooled across all scales. Our meta-analysis compared participants with moderate or high anticholinergic burden against those with no or low burden, depending on the type of comparison that was reported within a given study. 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 used Comprehensive Meta-Analysis software to conduct all meta-analyses (CMA 2013).

Investigation and description of heterogeneity

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

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 sought to explain the mechanisms behind an underlying association between anticholinergic burden and cognitive decline or neuropsychiatric disturbances in people with MCI or dementia were considered to be a high level of evidence. Phase 2 explanatory studies that sought to confirm an independent association between anticholinergic burden and cognitive decline or neuropsychiatric disturbances were treated as moderate evidence; and hypothesis-generating, phase 1 explanatory studies were treated as weak evidence for any association between anticholinergic burden and cognitive decline or neuropsychiatric disturbances.

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 we considered most (more than 50%) included studies to be at high risk of bias, we downgraded the evidence accordingly.

Inconsistency: we downgraded the evidence if associations between anticholinergic burden and cognitive decline or neuropsychiatric disturbances were heterogeneous (i.e. estimates of effect were variable across studies with regard to showing beneficial or detrimental effects, and their confidence intervals showed minimal or no overlap; the measure of the prognostic factor was highly variable; outcome measurement was highly variable; and there was methodological heterogeneity due to study design); and if the P value was low (< 0.05) for the test of the null hypothesis that all studies in a meta-analysis had the same underlying magnitude of effect.

Indirectness: we downgraded studies in which their investigation did not fully match with our broader review question. Specifically, if the population in the included studies only represented a subset of the population of interest (e.g. a specific subtype of dementia only), then we downgraded the evidence for the association between anticholinergic burden and cognitive decline or neuropsychiatric disturbances for indirectness.

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Imprecision: we downgraded if the evidence was generated by few studies and a small number of participants, and most of the studies provided imprecise results; if there were insufficient numbers to meet the optimal information size in the meta-analysis (i.e. if the total number of participants included was less than the number of participants generated by a conventional sample size calculation for a single, adequately powered study); or if the confidence intervals failed to exclude important benefit or important harm.

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 had 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 the evidence if there was an incremental increase in effect size with increasing anticholinergic burden.

RESULTS

Results of the search

Description of the studies

Our search identified a total of 18,358 records. We did not identify any additional studies by handsearching references. After de-duplication and assessment of titles and abstracts, we evaluated 55 full-text reports for relevance, 18 studies of which met our inclusion criteria. Reasons for exclusion can be seen in the Characteristics of excluded studies table. Figure 1 shows the PRISMA flow chart.

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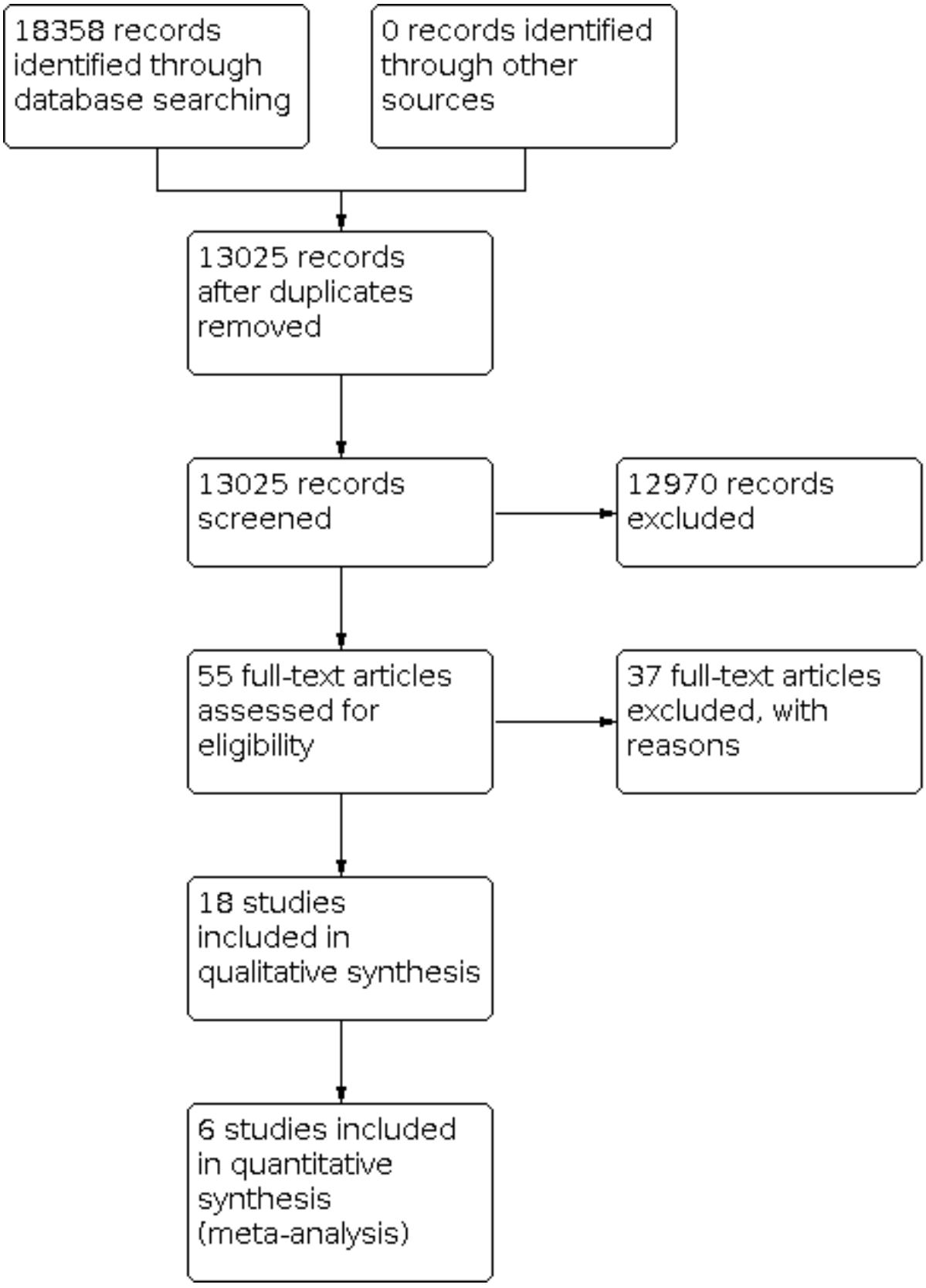
Figure 1.



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Included studies

Seventeen studies were longitudinal cohort designs, and one used data from participants in a randomised controlled trial (Dyer 2020). All studies were conducted in a retrospective manner, therefore, we were using data that were originally obtained for a purpose other than investigating the association between anticholinergic burden and adverse outcomes in a cognitively impaired older adult population. Study sample sizes ranged from 69 to 39,107. The studies were conducted in Asia, North America, Europe, and Oceania (1 study in Korea, 1 in Thailand, 3 in the USA, 4 in UK, 1 in Ireland, 3 in Italy, 1 in Spain, 2 in Sweden, 1 in Finland, and 1 in Australia). Follow-up times ranged from one to eight years.

See our Characteristics of included studies section for details.

Participant characteristics

The total number of participants in all included studies was 102,684, the overwhelming majority of whom (97%) had pre-existing cognitive impairment. Around 63% of the sample were female, and the mean or median age across studies ranged from 72 to 88 years. Ten studies recruited 87,846 participants from a population-level database, or a mixed setting (Ah 2019; Bishara 2020; Dyer 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Lu 2003; McMichael 2021; Tan 2018; Trevisan 2021); 5625 participants were from an integrative care setting (1 study, Boudreau 2011); 1390 were from secondary care (3 studies: Bottiggi 2007; Cross 2017; Lopez-Matons 2018); 1154 were from primary care lists (1 study, Porter 2019); and 6669 participants were from a care- or nursing-home setting (3 studies, Kumpula 2011; Landi 2014; Vetrano 2016).

Eleven studies recruited only participants with dementia (Ah 2019; Bishara 2020; Bottiggi 2007; Boudreau 2011; Dyer 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Lu 2003; McMichael 2021; Tan 2018). Of these, 6/11 studies were restricted to people with dementia on cholinesterase inhibitor drugs (Ah 2019; Bottiggi 2007; Boudreau 2011; Jenraumjit 2020; Lu 2003; McMichael 2021); 5/11 studies were conducted in an Alzheimer's disease-specific population (Bottiggi 2007; Dyer 2020; Fox 2011; Jenraumjit 2020; Lu 2003); and 6/11 studies were conducted in a population with non-specific dementia (Ah 2019; Bishara 2020; Boudreau 2011; Haaksma 2019; McMichael 2021; Tan 2018). Three studies were conducted in a mixed mild cognitive impairment (MCI) and dementia population (Cross 2017; Lopez-Matons 2018; Porter 2019), and one study was conducted in an MCI-only population (Trevisan 2021). Three studies were not restricted to a cognitively impaired population exclusively, but had a high proportion of cognitively impaired participants within their study sample (Kumpula 2011; Landi 2014; Vetrano 2016). Severity of cognitive impairment at baseline was variable across included studies: seven studies were conducted in a predominantly mild dementia or MCI population, or both (Cross 2017; Dyer 2020; Lu 2003; Porter 2019; Tan 2018; Trevisan 2021), while six involved a moderately or severely impaired dementia population (Bishara 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Landi 2014; Vetrano 2016). Severity of cognitive impairment was not reported in five studies (Ah 2019; Bottiggi 2007; Boudreau 2011; Kumpula 2011; McMichael 2021).

Prognostic factor

Anticholinergic burden was measured with five measurement tools: 12 studies used the Anticholinergic Cognitive Burden (ACB) scale (Ah 2019; Cross 2017; Dyer 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Lopez-Matons 2018; McMichael 2021; Porter 2019; Tan 2018; Trevisan 2021; Vetrano 2016); three studies used the Anticholinergic Risk Scale (ARS (Kumpula 2011; Landi 2014; Trevisan 2021)); one study used the Anticholinergic Drug Scale (ADS (Boudreau 2011)); one study used the Anticholinergic Effect on Cognition (AEC) Scale (Bishara 2020); and two studies used a list developed by Tune 1999 (Bottiggi 2007; Lu 2003).

The specific anticholinergic drugs used varied between studies. Antipsychotics, such as haloperidol, quetiapine, or risperidone, were the most commonly used drugs contributing to anticholinergic burden in six studies (Cross 2017; Dyer 2020; Jenraumjit 2020; Kumpula 2011; Landi 2014; Lopez-Matons 2018); two studies reported antidepressant or anxiolytic drugs as the most commonly used anticholinergic drugs (McMichael 2021; Porter 2019); one study reported beta blockers (Metoprolol (Tan 2018)), and one study reported histamine blockers as the most commonly used anticholinergic drugs (Boudreau 2011). Eight studies did not report the types of anticholinergic drugs used in their study sample in detail (Ah 2019; Bishara 2020; Bottiggi 2007; Fox 2011; Haaksma 2019; Lu 2003; Trevisan 2021; Vetrano 2016).

Long-term historic or lifetime anticholinergic drug use before diagnosis of a cognitive syndrome was not recorded in any studies. The longest duration of measurement of pre-diagnosis anticholinergic drug use was 12 months (Boudreau 2011; Tan 2018).

Outcome measures

Nine studies assessed cognitive decline via change in score on a cognitive assessment or dementia severity, or disability rating measure (Bishara 2020; Bottiggi 2007; Dyer 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Landi 2014; Lopez-Matons 2018; Lu 2003). Multiple studies used more than one cognitive assessment scale: seven studies used the Mini Mental State Exam (MMSE (Bishara 2020; Bottiggi 2007; Fox 2011; Haaksma 2019; Jenraumjit 2020; Lopez-Matons 2018; Lu 2003)), two used the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog (Dyer 2020; Fox 2011)), one used the Severe Impairment Battery (SIB (Fox 2011)), one used the Clinical Dementia Rating (CDR) scale (Dyer 2020), one used the Disability Assessment for Dementia (DAD (Dyer 2020)), and one study used the Cognitive Performance Scale (CPS (Landi 2014)). One study assessed progression to dementia (from MCI) as an outcome, evaluated via a multi-component assessment using standardised cut points for impairment (Trevisan 2021).

No studies assessed neuropsychiatric disturbances.

Ten studies assessed mortality as an outcome; all studies used database codes or death registry records to establish mortality (Ah 2019; Bishara 2020; Boudreau 2011; Cross 2017; Kumpula 2011; Landi 2014; McMichael 2021; Porter 2019; Tan 2018; Vetrano 2016).

Four studies assessed physical function or performance of activities of daily living (Bottiggi 2007; Haaksma 2019; Landi 2014; Lopez-Matons 2018): one study used the Instrumental Activities of Daily Living (IADL) scale, and Physical Activities of Daily Living (PADL) scale (Bottiggi 2007); one used the Katz Activities of Daily Living (ADL) scale (Haaksma 2019); one used a summary ADL score imbedded within the Resident Assessment Instrument Minimum Data Set (version 2.0) for Nursing Homes (MDS-NH (Landi 2014));

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and one study used the Barthel Index (BI), and Lawton and Brody Index (LBI (Lopez-Matons 2018)).

Institutionalisation was assessed in one study; database claims for care in nursing homes were used as a proxy for residing in a nursing home (Boudreau 2011).

Risk of bias in included studies

Risk of bias was substantial across studies: 16/18 (89%) studies were at high risk of bias in at least one domain (Figure 2). The most prominent issue of concern was adjustment for covariates bias (Figure 3). Nine of 18 (50%) studies did not control for severity of dementia or cognitive impairment at baseline (Ah 2019; Bottiggi 2007; Boudreau 2011; Haaksma 2019; Jenraumjit 2020; Kumpula 2011; Lu 2003; McMichael 2021; Trevisan 2021). Of the two studies investigating a cognitive outcome in a non-specific dementia-only population (Bishara 2020; Haaksma 2019), only one study controlled for type of dementia (50% (Haaksma 2019)).

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Figure 2. Authors' assessment of risk of bias for each domain, for each trial

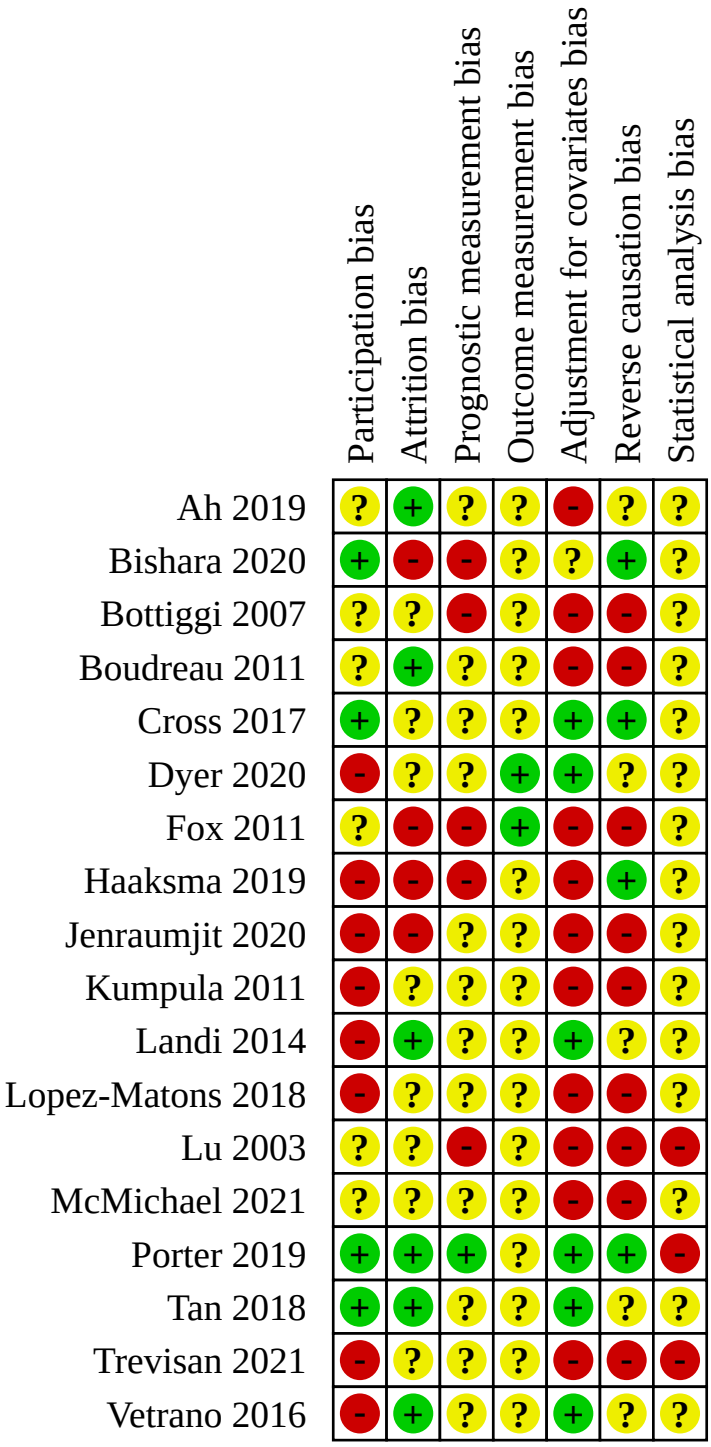

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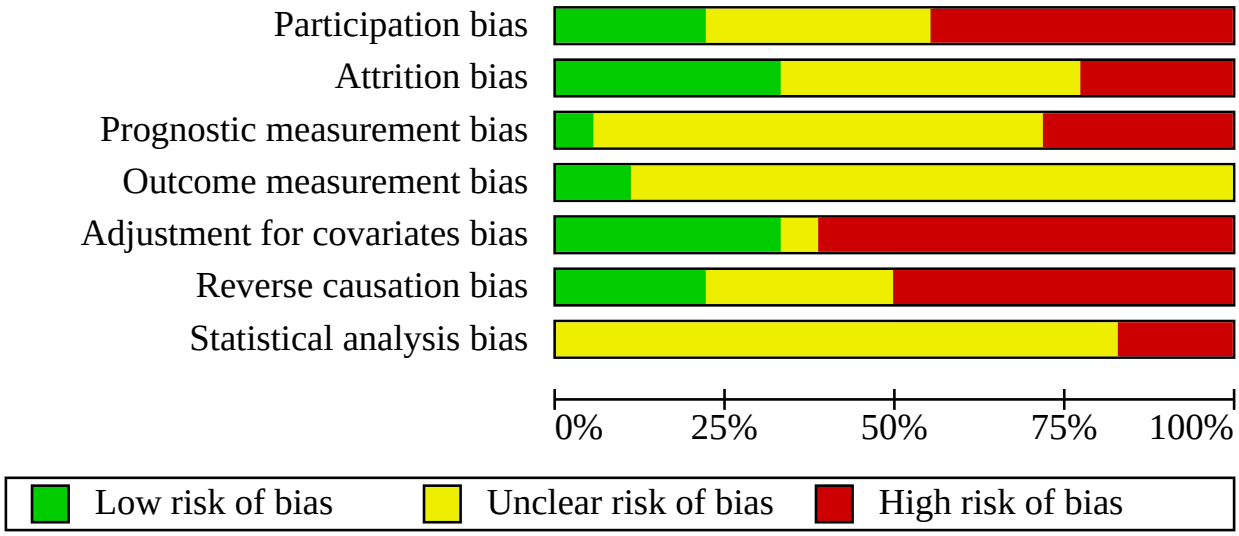
Figure 3. Risk of bias for each domain, across studies



Additional issues of note were:

- **Outcome measurement bias**: no studies reported blinding of investigators to outcome when scoring anticholinergic burden; only 2/18 (11%) studies reported scoring outcomes or anticholinergic burden in duplicate to minimise potential for outcome measurement bias (Dyer 2020; Fox 2011). In studies that assessed change in a cognitive outcome, 6/9 (66%) used the MMSE alone when assessing cognitive decline (Bishara 2020; Bottiggi 2007; Haaksma 2019; Jenraumjit 2020; Lopez-Matons 2018; Lu 2003). Four out of 6 (66%) of these were conducted in moderate to severe dementia populations, for whom floor effects are possible.
- **Reverse causation bias**: we judged 9/18 (50%) studies to be at high risk of bias for reverse causation (Bottiggi 2007; Boudreau 2011; Fox 2011; Jenraumjit 2020; Kumpula 2011; Lopez-Matons 2018; Lu 2003; McMichael 2021; Trevisan 2021), and just 4/18 (17%) to be at low risk of bias (Bishara 2020; Cross 2017; Haaksma 2019; Porter 2019). Only 10/18 (56%) studies controlled for a covariate that could cause confounding by indication, such as urinary tract infections, mood, anxiety, or behavioural or psychological disorders (Ah 2019; Bishara 2020; Boudreau 2011; Cross 2017; Dyer 2020; Haaksma 2019; Landi 2014; Porter 2019; Tan 2018; Vetrano 2016).
- **Statistical analysis bias:** no studies registered a protocol outlining planned statistical analyses, and only 3/18 (17%) studies reported assessing statistical assumptions (Fox 2011; Boudreau 2011; McMichael 2021).

Associations between anticholinergic burden and clinical outcomes reported in individual studies

Three out of nine (33%) studies involving people with dementia reported a significantly increased risk of greater long-term cognitive decline for participants with an anticholinergic burden, compared to participants with no or minimal anticholinergic burden: one of these studies reported the association to be independent of core variables (age, sex, comorbidities, and use of anticholinesterase inhibitors (Dyer 2020)); one study reported the association was independent of age, sex, and time (Jenraumjit 2020); and one study reported univariable association only (Lu 2003). Five out of nine (56%) studies reported no significant difference in risk of long-term cognitive decline between those with an anticholinergic burden and those with no or minimal burden (Bottiggi 2007; Fox 2011; Haaksma 2019; Landi 2014; Lopez-Matons 2018), while one study reported that cognition significantly improved for those with the highest anticholinergic burden in the initial six months post-dementia diagnosis, before demonstrating similar slopes of decline to those with no or lower burden for the remaining 6 to 36 months (Bishara 2020). Of three studies conducted in a population with mild dementia (Dyer 2020, Lu 2003, Lopez-Matons 2018), 2/3 (67%) reported a significant association between anticholinergic burden and reduced long-term cognition (Dyer 2020; Lu 2003), compared to one out of five (20% (Jenraumjit 2020)), which investigated this association in a moderately or severely impaired population (Bishara 2020; Fox 2011; Haaksma 2019; Jenraumjit 2020; Landi 2014).

One study evaluated the progression from MCI to dementia, and reported a significantly increased risk for those with an anticholinergic burden compared to those with no burden, based on anticholinergic burden defined by the ARS (Trevisan 2021). This association was independent of age, sex, education level, baseline instrumental activities of daily living (IADL), diabetes, and cardiovascular diseases.

Six out of 10 studies (60%) reported a significantly increased risk of mortality. One study reported a significantly increased risk for those with a high anticholinergic burden relative to those with mild or no burden (Ah 2019); one reported an increased risk for those with at least moderate anticholinergic burden compared to those with no anticholinergic burden (Tan 2018); three reported significant differences for any anticholinergic burden versus no burden (Bishara 2020; Cross 2017; McMichael 2021); and one study reported significant differences for users of antipsychotic anticholinergic drugs versus non-users of antipsychotic anticholinergic drugs,

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specifically (Porter 2019). All significant associations were adjusted for covariates; however only 4/6 studies controlled for all core covariates (Bishara 2020; Cross 2017; Porter 2019; Tan 2018). Three out of four studies (75%) that failed to find an association with mortality were conducted in a nursing home setting that included non-cognitively impaired individuals (Kumpula 2011; Landi 2014; Vetrano 2016).

One out of four studies (25%) reported a significantly increased risk of reduced physical function for people with an anticholinergic burden compared to people with no burden (Landi 2014). This association was independent of core covariates, but was conducted in a nursing home population that included non-cognitively impaired individuals.

One study investigated the risk of institutionalisation for moderate to severe anticholinergic drug users versus no or low anticholinergic drug users. Boudreau 2011 did not observe a significant difference between groups after adjusting for age, sex, and comorbidities; however, they did not control for baseline severity of dementia.

Variables that moderated the observed association with the outcome

There was observable alteration of results based upon within-study variables.

One study reported different results based on method for assessing outcome (Dyer 2020). Specifically, they observed a significant association between anticholinergic burden and cognitive decline when they used the CDR and DAD scales to assess cognition, but observed no association between anticholinergic burden and ADAS-cog scores.

One study observed variability based on type of dementia (Tan 2018). Specifically, they observed a significantly increased risk association between anticholinergic burden and the composite outcome of mortality and stroke, for participants with Alzheimer's disease and unspecified dementia; they observed no association for those with mixed dementia, vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, or 'other dementia'.

One study reported APOe4 allele status moderated the association between anticholinergic burden and cognition (Dyer 2020). The association between ACB and CDR-defined dementia severity was only significant when the ACB interaction with APOe4 allele status was included in the analysis.

The scale used to measure anticholinergic burden altered results in one study. Trevisan 2021 found that progression to dementia was only predicted by the ARS scale, not by the ACB scale.

Four studies investigated the effect of drug type and class on association; results were highly heterogeneous. McMichael 2021 found that respiratory, urological, and 'other' anticholinergic drugs were associated with an increased risk of mortality, but antipsychotics, antidepressants, antiparkinsonian, gastrointestinal, and antihistamine drugs were not. Porter 2019 found that only antipsychotic anticholinergic drugs were associated with increased risk of mortality, but they observed no association for tricyclic antidepressants or 'other' anticholinergic drugs. Boudreau 2011 found no association between anticholinergics and mortality risk in general, but the use of anticholinergic drugs targeting the bladder was associated with a reduced mortality risk. By contrast, Dyer 2020 found no significant class-based effect on cognition for any individually investigated anticholinergic drug type (specifically, antidepressants, neuroleptics, and bladder antimuscarinics).

Six studies examined the effects of severity of anticholinergic burden on outcome significance (Bishara 2020; Dyer 2020; Kumpula 2011; McMichael 2021; Tan 2018; Vetrano 2016). Tan 2018 reported that a baseline ACB ≥ 2 was significantly associated with death, whereas a baseline ACB of 1 was not. No other studies reported variation in the significance of association when stratifying by severity of anticholinergic burden.

One study reported that the association between anticholinergic burden and mortality or hospitalisation (analysed as a composite outcome) was only present in those with coronary artery disease (Vetrano 2016).

Meta-analysis

We considered that the studies were too heterogeneous to pool data for all cognitive outcomes—particularly in relation to the control for minimum core covariates, and the method for assessing outcome. There were no studies from which we could pool data for neuropsychiatric disturbance outcomes, and insufficient data to pool for physical function and institutionalisation outcomes.

We extracted mortality-based hazard ratio data directly from seven studies (Ah 2019; Bishara 2020; Boudreau 2011; Kumpula 2011; McMichael 2021; Porter 2019; Tan 2018); we were able to obtain data for one additional study after contacting the authors (Cross 2017). Sufficient data for this outcome were only available for fully adjusted multivariable analysis. Two studies did not adjust for the minimum variables (age, sex, and comorbidities), and hence, we excluded them from the analysis (Kumpula 2011; McMichael 2021).

The primary analysis was restricted to four studies that measured anticholinergic burden using the ACB scale (Ah 2019; Cross 2017; Porter 2019; Tan 2018). Results suggest that cognitively impaired people with a high ACB score (≥ 3), may have an increased risk of mortality compared to those with no or low ACB scores (hazard ratio (HR) 1.153, 95% confidence interval (CI) 1.030 to 1.292; 4 studies, 48,663 participants; Figure 4).

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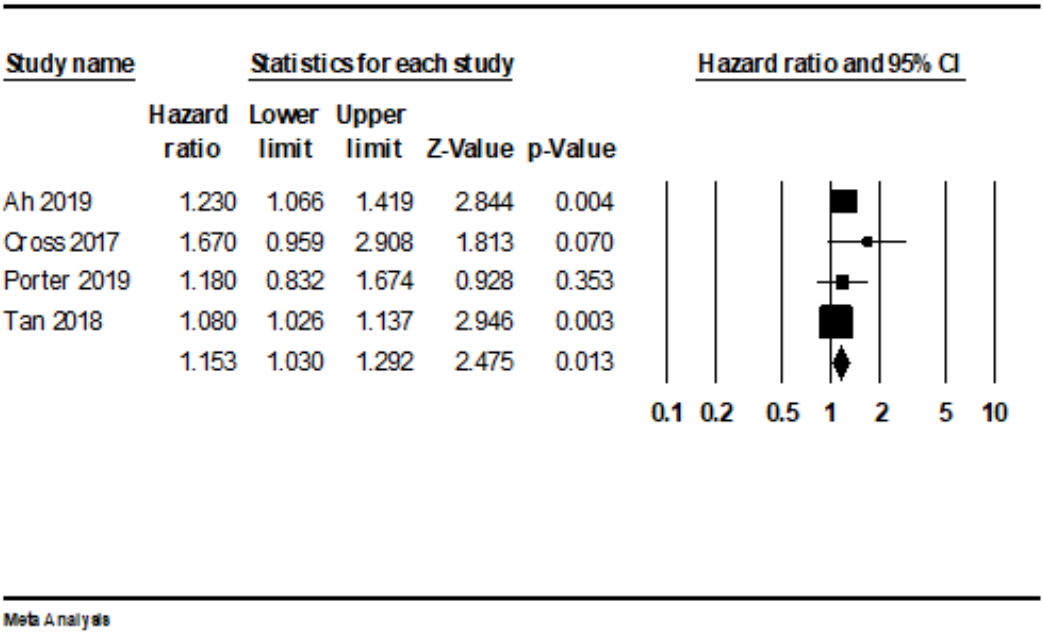
Figure 4. Relative mortality risk of those with a high anticholinergic burden vs those with minimal/no anticholinergic burden, measured by the Anticholinergic Cognitive Burden scale.



As an exploratory analysis, we also examined the association with mortality regardless of anticholinergic measurement scale used. We included data from six studies (Ah 2019; Bishara 2020; Boudreau 2011; Cross 2017; Porter 2019; Tan 2018). Results were consistent with our primary analysis, suggesting that regardless of the scale used to measure anticholinergic burden, those with a high anticholinergic burden may be at increased risk of mortality compared to those with no or minimal burden (HR 1.102, 95% CI 1.044 to 1.163; 6 studies, 68,381 participants; Figure 5).

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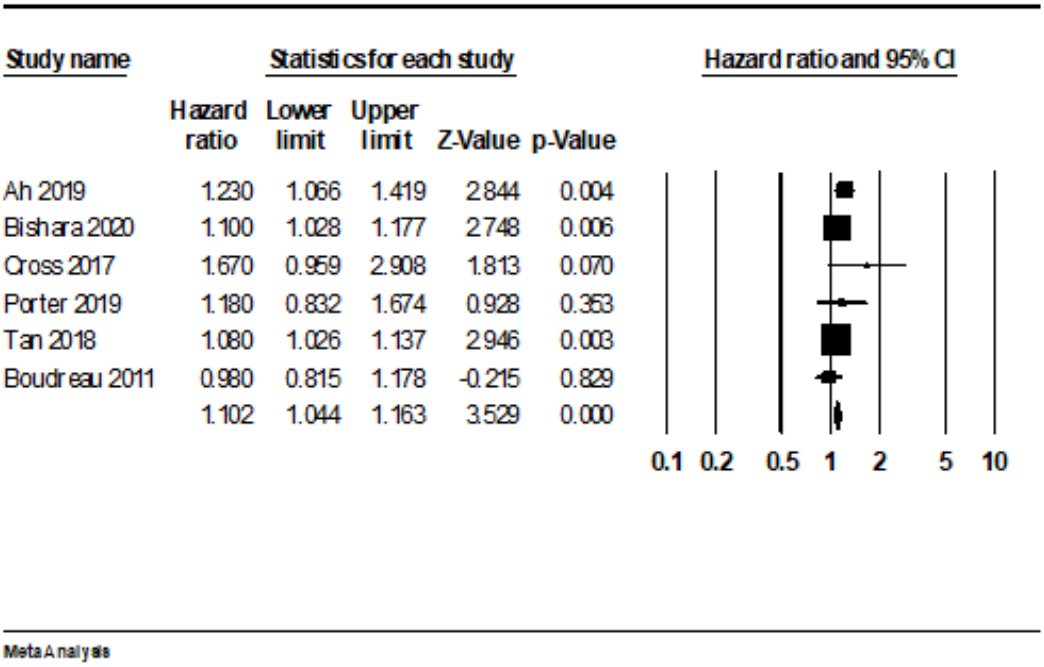
Figure 5. Relative mortality risk of those with a high anticholinergic burden vs those with minimal/no anticholinergic burden, regardless of scale used to measure anticholinergic burden.



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

There were insufficient data to explore the relationship between anticholinergic burden and mortality at different levels of anticholinergic severity. Similarly, there were insufficient data to conduct any planned subgroup analyses, or meta-regression. There were also insufficient data to pool from any other secondary outcomes (see Differences between protocol and review).

Certainty of the evidence (GRADE)

The overall certainty of the evidence for the primary outcome of cognitive decline was very low. Evidence was downgraded for risk of bias, inconsistency, indirectness, and publication bias.

We had low or very low confidence in the evidence for all secondary outcomes. For mortality, we considered the evidence to be of low certainty, downgraded due to risk of bias and presumed publication bias. For physical function, we considered the evidence to be of very low certainty, downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias. For institutionalisation, we also considered the evidence to be of very low certainty, downgraded for risk of bias, indirectness, imprecision, and publication bias (see Appendix 6).

Comparison of scales

There were too few studies to conduct a network meta-analysis to examine comparative prognostic validity of different anticholinergic burden measurement scales. Only one study directly compared scales within a single sample (Trevisan 2021). Results of this study suggested that the ARS may have greater prognostic ability than the ACB scale for predicting progression from MCI to dementia; however, statistical power was severely limited due to a short (1 year) follow-up, and only 14 participants with dementia.

Of the individual anticholinergic scales used in the literature, 2/6 (33%) studies that used the ACB scale found a significant association with cognitive decline (Dyer 2020; Jenraumjit 2020). A single study that used the AEC scale reported mixed results for the association with cognitive decline (Bishara 2020). Of the two studies that used the ARS (Landi 2014; Trevisan 2021), 1/2 (50%) found a significant association with cognitive decline (Trevisan 2021). No studies investigated cognitive decline or neuropsychiatric outcomes using the ADS; and 1/2 (50%) of the studies that

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investigated the association with cognitive decline using the Tune 1999 list found a significant association (Lu 2003).

DISCUSSION

waSummary of main results

The evidence pertaining to the association between anticholinergic burden and long-term cognitive decline in older adults with pre-existing cognitive impairment is inconclusive. Results are highly inconsistent. Most studies do not support an association. Examination of the relationship between the anticholinergic burden and secondary outcomes that we would expect to co-occur with declining cognition, do not generally support an important effect either. There was no evidence that anticholinergic burden increases the risk of institutionalisation, and most studies failed to find any association with decline in physical function. There is also an absence of any evidence to determine whether anticholinergic burden is a prognostic factor for long-term neuropsychiatric outcomes.

Increased risk of death is the adverse outcome most consistently associated with anticholinergic burden in a cognitively impaired population. The majority of studies (6/10) included in our review found a significant association with an increased risk of mortality. This is further supported by our meta-analysis, which suggests an increase in risk of around 15% for those with a high anticholinergic burden.

The relative ability of different anticholinergic burden scales to predict adverse clinical outcomes in a cognitively impaired population cannot yet be established. Although there is evidence from one study that the Anticholinergic Risk Scale (ARS) may be more capable than the Anticholinergic Cognitive Burden (ACB) scale of predicting future dementia onset in a mild cognitive impairment (MCI) population, the limitations of the study make this result highly uncertain (Trevisan 2021). The ACB scale was the most widely used of the anticholinergic burden tools; however, the lack of consistent associations with cognitive outcomes observed for this tool make its prognostic value for predicting cognitive decline in a dementia population questionable. Moreover, some of the most commonly used drugs (e.g. beta blockers (e.g. Metoprolol) and histamine blockers) have a dubious ability to contribute to overall anticholinergic burden according to first-principle pharmacology. Hence, the predictive ability of anticholinergic burden scales at the level of the individual may vary considerably, depending on the relative contribution of specific drug types to the assigned anticholinergic burden score.

Overall completeness and applicability of evidence

Most studies were conducted at a population level or in mixed settings, therefore, our results are most applicable at a population level, rather than any individual setting. Currently, there is a lack of evidence to determine whether different anticholinergic burden scales perform differently across settings.

While this topic was investigated in a range of geographic locations, no studies have been conducted in the Middle East, South America, or Africa. The ability of anticholinergic scales to predict adverse clinical outcomes may vary by country, due to differences in routine prescribing practice. Drugs with anticholinergic properties that are prescribed in some countries may not be prescribed in the country where a scale was developed and validated. On this basis, we cannot be sure that our results will generalise globally, and it is important that evaluations of anticholinergic burden scales are conducted in other regions.

Certainty of evidence

There were major issues with study quality that weakened the certainty of our evidence. Using GRADE, we evaluated the certainty of the evidence as low or very low for all outcomes. Study risk of bias was a particularly significant concern. Most studies had a relatively short follow-up that may have limited their ability to observe associations. The Mini Mental State Examination (MMSE) was the most commonly used tool for assessing cognitive outcomes, yet, it may lack the sensitivity to measure change in some cognitive domains, and has the potential for floor effects in more severely impaired populations (Herrmann 2007). Many studies did not control for key variables, and despite regular reports that antipsychotics were the most widely used anticholinergic medication, control for confounding by indication was frequently lacking. As some anticholinergic drugs may be prescribed in response to increasing severity of dementia, many observed associations between anticholinergic burden and clinical outcomes could be driven by between-group differences in severity of dementia, wherever this was not controlled for.

Limitations of the review process

We attempted to minimise bias in the review process by conducting study selection, data extraction, and risk of bias assessment in duplicate. We followed the recommended guidance for design, reporting, and statistical analysis, and adapted previously used assessment forms to improve compatibility with this topic. Despite this, there were several limitations of note.

The major limitation of our review was the lack and heterogeneity of data for several outcomes, including variation in the measurement of cognitive decline and physical function. This prevented us from drawing firm conclusions for our main objectives, and conducting our planned subgroup analyses.

Although we were able to minimise issues of heterogeneity in our meta-analysis, there was still variability in numerous study characteristics, including the point of dichotomisation used on the anticholinergic burden scale, and the type of comparison used in different studies (e.g. comparing any burden to no burden versus comparing high burden to minimal burden). This affected the degree of nuance we were able to provide for the associations. In addition, there was one study that reported no significant association between anticholinergic burden and mortality, which we were unable to include in our meta-analysis due to lack of hazard ratio data (Vetrano 2016). This may have biased our meta-analysis towards a significant effect.

Lastly, publication bias is a general concern within this literature, and we did not include grey literature in our review, which may have exacerbated this problem.

Agreements and disagreements with other studies or reviews

The lack of a consistent association between anticholinergic burden and cognitive outcomes conflicts with the findings of our companion review that examined the association in cognitively healthy older adults (Taylor-Rowan 2021). It is possible that a

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significant deterioration of the cholinergic system in dementia limits the adverse impact of anticholinergic drugs on cognition. By extension, this may suggest that the severity of pre-existing impairment is crucial to the prognostic relationship in the dementia population (Dyer 2020). In support of this, the majority (2/3) of studies that investigated the association in people with mild dementia or cognitive impairment found a significant deleterious effect associated with anticholinergic burden; this contrasts with just one in five of the studies that investigated the association in people with moderate to severe dementia. However, various study limitations and differences in methodology may also contribute to these different results. Therefore, a possible association with severity of baseline cognitive impairment requires further investigation.

Our results are broadly consistent with a recently published review that reported inconclusive findings for the association between anticholinergic burden and cognitive decline in a dementia population (Wang 2021). That review found highly consistent reports of increased mortality risk for anticholinergic users. Our review builds upon these prior findings by presenting a more comprehensive depiction of the available prognostic literature. We also found the association between anticholinergic burden and mortality to be less homogenous than was previously suggested, and we provided an adjusted hazard ratio summary figure of the possible increased risk of mortality.

AUTHORS' CONCLUSIONS

Implications for practice

The inconclusive evidence warrants the need for caution when prescribing anticholinergic medications in a cognitively impaired population. While we cannot be certain of any causal relationship, most studies found an association with a higher risk of mortality for people with a high anticholinergic burden, and adverse associations were observed for all clinical outcomes, bar institutionalisation, by at least one study.

Implications for research

The lack of studies investigating neuropsychiatric outcomes is a major gap in the literature. Psychological and behavioural disturbances are main causes of hospitalisation in the dementia population (Soto 2012); hence, identification of modifiable variables that influence their occurrence is extremely important. It is biologically plausible that anticholinergic drugs could induce behavioural disturbances in people with dementia (Cancelli 2009), and there is evidence from interventional studies that a reduction of anticholinergic burden diminishes the occurrence of neuropsychiatric disturbance (Jaïdi 2018; Jaïdi 2019). Thus, it would be reasonable to expect a prognostic association to exist between anticholinergic burden and neuropsychiatric outcomes. Therefore, high quality studies to investigate whether such an association exists, and in what circumstances, would be valuable.

Our review highlighted the considerable number of variables that could potentially influence the relationship between anticholinergic burden and clinical outcomes in a cognitively impaired population. At present, most studies do a poor job of controlling for and reporting details of these variables. This may reflect an over-reliance upon pre-existing datasets that were not designed to investigate the association between anticholinergic burden and clinical outcomes. We would encourage more prospectively designed research studies in this area, as this would enable researchers to tailor important design features to the specific requirements of the area. Our Characteristics of included studies section presents a list of potentially important variables, and we would recommend that future investigators consider these when designing studies, and record them in detail, whenever possible.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ah 2019

Study characteristics	
Demographics	Sample size: 7438
	Gender (% female): 65.6%
	Mean age: not reported

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Ah 2019 *(Continued)*

	Country: Korea
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) Scale
Outcome measurement method	Mortality: medical/database records
Covariates controlled for	Age, sex, comorbid disease, Ginko extract use, sedative load
Additional key study characteristics	Dementia type: non-specific dementia Dementia severity: not stated Duration of follow-up: 2 years Setting: population-based APOE status measured (Y/N): N AChEi only population (Y/N): Y Types of anticholinergics included (ratio reported): not stated Breakdown of anticholinergic severity: 0 < average ACB ≤ 1 category = 51%; 1 < average ACB ≤ 2 categories = 17.4%, 2 < average ACB ≤ 3 categories = 7.7%, average ACB > 3 categories = 6.0% Type of comparison analysed: high vs minimal (average ACB > 3 vs ACB ≤ 1) Historic anticholinergic use (duration reported): not reported; measured average ACB use up to 3 months before index
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Unclear	Age, sex, and comorbidities described. Type and severity of dementia not stated. Exclusion criteria mean it's likely mild to moderate dementia population, and cholinesterase inhibitor use likely means predominantly Alzheimer's/Lewy body dementia population
Attrition bias	Yes	No attrition mentioned, but used databases, so possibly there was none
Prognostic measurement bias	Unclear	Only single method of assessing anticholinergic drug use and reliant on database records. No measure of adherence
Outcome measurement bias	Unclear	No blinding or assessing in duplicate
Adjustment for covariates bias	No	Age, sex, and comorbidities all controlled for. All included participants were using AChE. No control for severity of dementia at baseline; took steps to try and minimise possible differences between these groups, but not clear how well this was achieved.
Reverse causation bias	Unclear	Limited to 2-year follow-up
Statistical analysis bias	Unclear	No protocol and no assumptions checked

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Bishara 2020

Study characteristics	
Demographics	Sample size: 14,093 Gender (% female): 60.7% Mean age: 79.8 Country: UK
Anticholinergic measurement method	Anticholinergic Effect on Cognition (AEC) Scale
Outcome measurement method	Cognitive decline: MMSE Mortality: database codes
Covariates controlled for	Model 1 adjusted for age, gender, ethnicity, marital status, MMSE score, deprivation score. Model 2 additionally adjusted for HoNOS65+ symptoms and functioning scores, and AChE inhibitors use
Additional key study characteristics	Dementia type: non-specific dementia Dementia severity: moderate to severe (Mean MMSE score at diagnosis: 18.6 (6.4)) Duration of follow-up: 3 years Setting: population-based APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): not recorded Breakdown of anticholinergic severity: anticholinergic burden (caution required) = 19.8%; anticholinergic burden (review needed) = 16.7% Type of comparison analysed: dichotomized based on severity of burden (compared to no central anticholinergic activity) Historic anticholinergic use (duration reported): 6 month window before and after dementia diagnosis recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Yes	Age, sex, comorbidities, and baseline MMSE scores all reported
Attrition bias	No	Cognitive decline analysis was restricted to those with at least 3 MMSE scores, which was only 6067/14,093 participants. Some differences in characteristics of people with 3 MMSE scores vs people without. No mention of attrition for mortality (possible there was none, so low bias for that outcome). 27% had missing covariate data, though appropriate method was applied to deal with this

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Bishara 2020 *(Continued)*

Prognostic measurement bias	No	Anticholinergic use only established via medical records, and at single time point, despite 36-month follow-up
Outcome measurement bias	Unclear	MMSE used to assess cognitive functioning
Adjustment for covariates bias	Unclear	Controlled for age, sex, comorbidities, and AChE prescription, and baseline MMSE score. However, no control for dementia type and those in the 'review needed' and 'caution required' groups were less likely to have AChEs administered, which may suggest different balance of dementia types in respective groups. Also, no control for delirium, which may drive the steeper rate of cognitive decline in the high ACh group, who saw an initial increase in cognitive scores despite a lower baseline.
Reverse causation bias	Yes	Restricted measurement to baseline and first 6 months, and observed follow-up at 36 months
Statistical analysis bias	Unclear	No protocol or assumptions checked

Bottiggi 2007

Study characteristics	
Demographics	Sample size: 300 Gender (% female): not stated Mean age: not stated Country: USA
Anticholinergic measurement method	Tune and Egeli list
Outcome measurement method	Cognitive assessment: MMSE Physical and functional assessment: PADL, IADL
Covariates controlled for	Age and education
Additional key study characteristics	Dementia type: Alzheimer's disease Dementia severity: not stated Duration of follow-up: 2 years Setting: Alzheimer's Disease Center at the University of Kentucky APOE status measured (Y/N): N AChEi only population (Y/N): Y Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised: users vs non-users Historic anticholinergic use (duration reported): not recorded

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Bottiggi 2007 *(Continued)*

Notes

Item	Authors' judgement	Support for judgement
Participation bias	Unclear	Inadequate reporting of comorbidities and demographics
Attrition bias	Unclear	Lack of details given on missing data or any loss to follow-up
Prognostic measurement bias	No	No mention of repeated measurements of AC use, despite 2-year follow-up
Outcome measurement bias	Unclear	No mention of missing data. MMSE used for all assessments. No mention of blinding, but as is a retrospective study, reasonable to assume that MMSE conducted before anticholinergic measurements were made.
Adjustment for covariates bias	No	Analyses used repeated measures analyses of covariance, adjusting for age and education—insufficient control for comorbidities in analysis
Reverse causation bias	No	Not clear how often, and at which time points MMSE was measured. Maximum follow-up was only 2 years. No control for comorbidities that may increase prescriptions of anticholinergic medications due to indication.
Statistical analysis bias	Unclear	No protocol registered or assumptions checked

Boudreau 2011

Study characteristics	
Demographics	Sample size: 5625 Gender (% female): 60.3% Mean age: 79 Country: USA
Anticholinergic measurement method	Anticholinergic Drug scale (ADS)
Outcome measurement method	Mortality: obtained from state death records Nursing home placement: claims for care received in nursing homes were used as a proxy for residing in a nursing home
Covariates controlled for	Age, sex, and Charlson Comorbidity Index
Additional key study characteristics	Dementia type: not stated Dementia severity: not stated Duration of follow-up: 1 year Setting: acquired data from integrative delivery system APOE status measured (Y/N): N

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Boudreau 2011 *(Continued)*

	AChEi only population (Y/N): Y Types of anticholinergics included (ratio reported): of concomitant users of the ADS who were categorised moderate to potent ACh medications, the most commonly used medication class was histamine blockers (46%) Breakdown of anticholinergic severity: ADS mild = not measured; ADS moderate to potent = 47% Type of comparison analysed: dichotomised: ADS moderate to severe vs not moderate to severe (note ADS mild scores not measured) Historic anticholinergic use (duration reported): measured up to 1 year prior to index date
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Unclear	Age, sex, and comorbidities described. Type and severity of dementia not stated. Cholinesterase inhibitor use likely means predominantly Alzheimer's/Lewy body dementia population.
Attrition bias	Yes	No attrition mentioned, but used databases, so possibly there was none.
Prognostic measurement bias	Unclear	Only single method of assessing anticholinergic drug use, and reliant on database records. No measure of adherence.
Outcome measurement bias	Unclear	No mention of blinding or scoring in duplicate
Adjustment for covariates bias	No	Age, sex, and comorbidities all controlled for. All included participants were using AChE. No control for severity of dementia at baseline.
Reverse causation bias	No	ACh use measured right up to event or study completion at 1 year.
Statistical analysis bias	Unclear	No protocol but did check assumptions

Cross 2017

Study characteristics	
Demographics	iSample size: 964 Gender (% female): 47.3% Mean age: 77.6 Country: Australia
Anticholinergic measurement method	Anticholinergic Cognitive Burden scale (ACB scale)
Outcome measurement method	Mortality: ICD 10 codes

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Cross 2017 *(Continued)*

Covariates controlled for	Age, gender, education, dementia/MCI diagnosis, total number of medications, MDBI score, MMSE, SMAF, and NPI score
Additional key study characteristics	Dementia type: non-specific dementia and MCI Dementia severity: mild (median baseline MMSE score: 24 (20 to 27)) Duration of follow-up: 3 years Setting: memory clinic APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): antipsychotics: 27/104 (26%); tricyclic antidepressants: 27/104 (26%); antimuscarinics: 20/104 (19%); antispasmodics: 13/104 (12.5%); first generation antihistamines: 7/104 (6.7%); other antidepressants (with anticholinergic properties): 7/104 (6.7%); antiparkinson agents: 3/104 (3%); other antihistamines: 0/104; skeletal muscle relaxants: 0/104. Breakdown of anticholinergic severity: median (IQR) baseline ACB score = 0 (0 to 1) Type of comparison analysed: each 1-point increase (0 vs any) Historic anticholinergic use (duration reported): not reported
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Yes	Age, sex, and comorbidities and dementia severity and type all reported
Attrition bias	Unclear	Substantial degree of attrition (310/964 lost to follow-up). Older participants and those with more severe dementia (etc) were more likely to withdraw. However, used medical records to establish mortality outcome, and appropriate use of censoring in analysis reduces potential impact of bias.
Prognostic measurement bias	Unclear	Recorded via 2 measures, and assessed over the counter as well as prescribed medications. Assessed use over multiple time points. Details on duration of exposure and dosage not recorded. No measure of establishing adherence reported.
Outcome measurement bias	Unclear	No mention of blinding
Adjustment for covariates bias	Yes	Control for age, sex, comorbidities (via drug count), and baseline cognitive severity and neuropsychiatric disturbance (both proxy for dementia severity). No control for ACHE inhibitor use, but less relevant for a mortality outcome.
Reverse causation bias	Yes	Restricted to 3 years before mortality for baseline analysis. Time-based analysis was similar, and so ACB use unlikely to have changed much over time.
Statistical analysis bias	Unclear	No mention of assumptions or protocol registered

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Dyer 2020

Study characteristics	
Demographics	ample size: 510 Gender (% female): 61.7% Mean age: 72 to 74 Country: Ireland
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Cognitive decline: ADAS-Cog, CDR, DAD
Covariates controlled for	Age, gender, BMI, years of education, baseline CDR-sb/DAD score, diagnosis duration, study group and cholinesterase inhibitor, total number of medications/comorbidities, known history of mood/anxiety disorder or behavioral and psychological symptoms of dementia (BPSD), benzodiazepine use, urinary incontinence.
Additional key study characteristics	Dementia type: Alzheimer's disease Dementia severity: Mild (Median MMSE=21) Duration of follow-up: 1.5 years Setting: Mixed APOE status measured (Y/N): Y AChEi only population (Y/N): N (although overwhelming majority were; ~ 90%) Types of anticholinergics included (ratio reported): the most frequent definite anticholinergics prescribed included quetiapine, oxybutynin, paroxetine, and amitriptyline; the most common potential anticholinergics included trazodone, venlafaxine, alprazolam, furosemide, and risperidone (specific numbers not given) Breakdown of anticholinergic severity: ACB1 = 12%; ACB2 = 2%%; ACB3 = 8%; ACB4+ = 6% Type of comparison analysed: ACB score (0 vs any)*visit*Apoe3 interaction Historic anticholinergic use (duration reported): not measured
Notes	

Item	**Authors' judgement**	**Support for judgement**
Participation bias	No	Uses RCT population with non-generalisable exclusion criteria; restricted to mild to moderate Alzheimer's population
Attrition bias	Unclear	Degree of attrition at 18 months is not clear
Prognostic measurement bias	Unclear	Only examined prescribed medications. Evaluated change in ACB over time via repeated measurements.
Outcome measurement bias	Yes	No blinding, but ACB scored retrospectively and by 2 investigators independently, so minimal risk of bias.

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Dyer 2020 *(Continued)*

Adjustment for covariates bias	Yes	Controlled for age, sex, comorbidities, ACHE inhibitor use, and dementia severity at baseline.
Reverse causation bias	Unclear	Only 18-month follow-up. Controlled for confounding by indication, by assessing medical histories for presence of urinary incontinence, mood and anxiety, and BPSDs, and only included medications used for whole 18-month duration of study in baseline ACB rating. However, was established manually, so possible some diagnoses may have been missed.
Statistical analysis bias	Unclear	No protocol registered or assumptions checked. Limited sample size and lack of info on 18 month follow-up data available, so study may have lacked power.

Fox 2011

Study characteristics	
Demographics	Sample size: 224 Gender (% female): 71.4% Mean age: 81 Country: UK
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Cognitive decline: ADAS-cog, MMSE, SIB
Covariates controlled for	Baseline measures of cognition, age, gender, and whether participants were receiving a cholinesterase inhibitor
Additional key study characteristics	Dementia type: Alzheimer's disease Dementia severity: moderate to severe (baseline MMSE mean: 13.5 to 16) Duration of follow-up: 18 months Setting: mixed APOE status measured (Y/N): N AChEi-only population (Y/N): N (just over half were taking) Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: mean anticholinergic load was 1.1 (SD 1.4), with a range of 0 to 7 (individual ACB proportions not given) Type of comparison analysed: any ACB vs none (dichotomised) Historic anticholinergic use (duration reported): not recorded
Notes	

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Fox 2011 *(Continued)*

Item	Authors' judgement	Support for judgement
Participation bias	Unclear	No reporting of comorbidities (though does report mean number of drugs). Quite a severe dementia population. Alzheimer's only. Participants required to be in regular contact with carer, and recruited from a very mixed source of settings.
Attrition bias	No	< 75% completed follow-up; those who did not were older, more cognitively impaired than those who did
Prognostic measurement bias	No	Only 1 method used, but interviewers recorded both prescribed and non-prescribed drugs. Not possible to establish ACB at multiple time points. No recording of dosage, or methods to check adherence. General lack of detail on how interviews were conducted (i.e. with dementia participants themselves or with carer).
Outcome measurement bias	Yes	No blinding, but ACB measured after cognitive assessment and established independently by 3 researchers, which significantly reduced the risk of bias.
Adjustment for covariates bias	No	Controlled for age, sex, baseline cognition, and AChE use. No control for any comorbidities.
Reverse causation bias	No	18-month follow-up and no control for covariates that may reduce impact of confounding by indication.
Statistical analysis bias	Unclear	Checked assumptions, but no protocol. Compared ACB 0 with ACB > 0. Numbers with high (ACB 3+) anticholinergic burden not reported. Inclusion of possible (ACB 1) drugs may have limited ability to find association.

Haaksma 2019

Study characteristics	
Demographics	Sample size: 512 Gender (% female): 78.3% Mean age: 88.3 Country: Sweden
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Cognitive decline: MMSE Physical function: ADL
Covariates controlled for	Age, sex, comorbidity burden, education, social network, and dementia type
Additional key study characteristics	Dementia type: late-onset, non-specific dementia Dementia severity: moderate-severe (baseline mean MMSE = 17.4) Duration of follow-up: 6 years

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Haaksma 2019 *(Continued)*

	Setting: population-based APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: ACB Scale, mean (SD) 1.0 (1.4); individual ACB ratings not reported Type of comparison analysed: unclear Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	No	Age, sex, dementia type and severity, and comorbidities all reported. Very high mean age population—late onset-dementia only.
Attrition bias	No	56% death or dropout at 3-year follow-up from point of dementia diagnosis. Only 35% had MMSE available at 3-year follow-up.
Prognostic measurement bias	No	Participants asked to bring in current medications, with no external corroboration of use. ACB only calculated at baseline, with no measure of change over time.
Outcome measurement bias	Unclear	No blinding reported, but ACB use likely assessed in retrospect. No mention of multiple people establishing ACB score independently.
Adjustment for covariates bias	No	Controlled for age, sex, comorbidity burden, and dementia type, but no AChE use. Unclear if controlled for dementia severity at baseline.
Reverse causation bias	Yes	3- to 6-year follow-up. Controlled for comorbidities that increase risk of prescription by indication.
Statistical analysis bias	Unclear	Appropriate analysis, but no protocol registered

Jenraumjit 2020

Study characteristics	
Demographics	Sample size: 133 Gender (% female): 60.2% Mean age: 78.4 Country: Thailand
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale

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Jenraumjit 2020 *(Continued)*

Outcome measurement method	Cognitive decline: Thai MMSE
Covariates controlled for	Age, sex, time
Additional key study characteristics	Dementia type: Alzheimer's disease Dementia severity: moderate dementia (mean baseline MMSE: 18.56) Duration of follow-up: 1 year Setting: mixed APOE status measured (Y/N): N AChEi only population (Y/N): Y Types of anticholinergics included (ratio reported): quetiapine: 54.8%; aripiprazole: 16.7%; trazodone: 7.1%; hydroxyzine: 4.8%; others: 4.8% Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised (any vs none) Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	No	AD population only; had to be taking AChEIs; must have Thai mental status available (Thai version of MMSE), examination regularly during each visit. 80% were women.
Attrition bias	No	No mention of attrition; however, availability of MMSE scores at follow-up was an inclusion requirement for the study, and scores appear to increase over time, suggesting that more severe cases dropped out.
Prognostic measurement bias	Unclear	Repeated measurements over duration of study, but only measured prescribed meds. Very minimal detail of process of assessing meds.
Outcome measurement bias	Unclear	ACB measured after MMSE scores obtained. No mention of blinding or scoring in duplicate.
Adjustment for covariates bias	No	Controlled for age and sex. AChEI was taken by all participants. No control for comorbidities or dementia severity. ACh group had significantly lower MMSE at baseline than no-ACh group, so likely had more severe dementia, and this alone could explain resultant association with lower cognition at 1-year follow-up.
Reverse causation bias	No	1-year follow-up with no control for prescription by indication.
Statistical analysis bias	Unclear	Relatively small sample size. No assumptions checked. No protocol.

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Kumpula 2011

Study characteristics	
Demographics	Sample size: 1004 Gender (% female): 75% Mean age: 81.3 Country: Finland
Anticholinergic measurement method	Anticholinergic Risk Scale (ARS)
Outcome measurement method	Mortality: database records
Covariates controlled for	Age, sex, malnutrition score
Additional key study characteristics	Dementia type: mixed cognitively impaired and unimpaired cohort Dementia severity: not reported Duration of follow-up: 1 year Setting: long-term care ward residents (people who require more intensive care than those in a nursing home, but do not require acute hospitalisation) APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): the most commonly used anticholinergic drugs were risperidone (n = 184 residents), mirtazapine (n = 89 residents), olanzapine (n = 84 residents), and hydroxyzine (n = 73 residents) Breakdown of anticholinergic severity: 363 (36%) had a mild anticholinergic load (ARS score 1 to 2), and 186 (19%) had a high anticholinergic load (ARS score ≥ 3) Type of comparison analysed: dichotomised; ARS 1 to 2 vs 0 & ARS 3+ vs 0 Historic anticholinergic use (duration reported): N
Notes	

Item	**Authors' judgement**	**Support for judgement**
Participation bias	No	Non-cognitive impairment specific population
Attrition bias	Unclear	5% removed from analysis due to missing data. No comparative analysis performed.
Prognostic measurement bias	Unclear	Medication data restricted to 2-week period. Collated via patient medication charts, but in this case, may be more reliable as most of the population have severe dementia, so unlikely to be buying meds themselves, and adherence will have been ensured, as administered by nursing staff. No follow-up medication use measured, but just 1-year follow-up. No measure of dosage.
Outcome measurement bias	Unclear	No mention of blinding or duplicate scoring

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Kumpula 2011 *(Continued)*

Adjustment for covariates bias	No	Controlled for age, sex, and malnutrition score only
Reverse causation bias	No	1-year follow-up. No control for severity of dementia or BPSD, despite drugs like risperidone being the most commonly used anticholinergic drug at baseline.
Statistical analysis bias	Unclear	Appropriate power. No protocol or assumptions checked. 1-year follow-up may have been too short to find association (although 28% of population did die by 1 year).

Landi 2014

Study characteristics	
Demographics	Sample size: 19,004 Gender (% female): 71.5% Mean age: 83.6 Country: Italy
Anticholinergic measurement method	Anticholinergic Risk Scale (ARS)
Outcome measurement method	Functional decline: ADL score Mortality: Medical records Cognitive decline: Cognitive Performance Scale (CPS)
Covariates controlled for	age, gender, comorbidity, baseline functional impairment, and cognitive impairment
Additional key study characteristics	Dementia type: mixed impaired and unimpaired sample Dementia severity: CPS suggests predominantly a moderate to severely impaired population Duration of follow-up: 12 months Setting: nursing home APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): among anticholinergic drugs considered in the ARS, the most used were haloperidol (14.5%, n = 216), levodopa (7.4%, n = 110), quetiapine (6.8%, n = 102), risperidone (4.8%, n = 72), and paroxetine (4.7%, n = 70) Breakdown of anticholinergic severity: the median ARS score was 0, with an interquartile range of 0 to 1; the highest score was 8 (individual proportion of ACB scores not reported) Type of comparison analysed: ARS treated as continuous variable Historic anticholinergic use (duration reported): not recorded
Notes	

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Landi 2014 *(Continued)*

Item	Authors' judgement	Support for judgement
Participation bias	No	Not exclusively a cognitively impaired population
Attrition bias	Yes	No attrition mentioned. 90% complete data. Appropriate methods used for dealing with missing data.
Prognostic measurement bias	Unclear	Only single method of assessing anticholinergic drug use. No measure of adherence.
Outcome measurement bias	Unclear	No mention of blinding or scoring in duplicate.
Adjustment for covariates bias	Yes	Age, sex, and comorbidities, cognitive performance or dementia diagnosis all controlled for. No control for type of dementia.
Reverse causation bias	Unclear	Just 12-month follow-up. ACh use restricted to baseline measurement.
Statistical analysis bias	Unclear	No protocol no assumptions checked

Lopez-Matons 2018

Study characteristics	
Demographics	Sample size: 126 Gender (% female): 72.2% Mean age: 81.1 Country: Spain
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Cognitive decline: MMSE Physical function: Barthel index and Lawton and Brody index
Covariates controlled for	Age, sex, BMI, smoking, HBP, diabetes mellitus, dyslipidaemia, heart disease, stroke, and diagnosis of dementia
Additional key study characteristics	Dementia type: mixed MCI and non-specific dementia cohort Dementia severity: mild (baseline MMSE: 22.5) Duration of follow-up: 1 year Setting: comprehensive geriatric assessment unit—a Public Health Network in Barcelona that treats elderly people referred from primary care APOE status measured (Y/N): N AChEi only population (Y/N): N

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Lopez-Matons 2018 *(Continued)*

	Types of anticholinergics included (ratio reported): antipsychotics (39.7%), antidepressants (33.5%), antimuscarinics used in urologic disorders (12.3%), analgesics (9%), and antihistamines (1.3%) Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised: exposed vs not exposed Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	No	Sample restricted to those assessed in 2015, then reassessed in 2016, which is a highly restricted approach, and prone to excluding those with more severe dementia or health problems.
Attrition bias	Unclear	No attrition reported, but analyses appear to have been limited to those with available follow-up data. No analysis on properties of those reassessed vs not.
Prognostic measurement bias	Unclear	Measured using ACB. Limited details available on method of establishing medication use, reliant on prescription records. No measure of duration exposed to anticholinergics.
Outcome measurement bias	Unclear	Measured cognition using MMSE
Adjustment for covariates bias	No	Controlled for age, sex, and physical comorbidities, but no psychiatric or BPSD. No control for AChE. Controlled for dementia diagnosis (as not everyone had dementia level cognitive impairment), but not severity/type of dementia.
Reverse causation bias	No	ACB measurement based on exposure to ACB in 2015, or 2016, or both (so no restriction to prior year only). No control for prescription due to indication, as no control for BPSDs, despite most commonly prescribed anticholinergics being antipsychotics
Statistical analysis bias	Unclear	Dichotomised ACB use into users vs non-users (so did not differentiate possible and definite anticholinergics). No protocol or assumptions checked.

Lu 2003

Study characteristics	
Demographics	Sample size: 69 Gender (% female): 52% Mean age: 77 Country: USA
Anticholinergic measurement method	Tune and Engeli list

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Lu 2003 *(Continued)*

Outcome measurement method	Cognitive decline: MMSE
Covariates controlled for	None
Additional key study characteristics	Dementia type: Alzheimer's disease Dementia severity: mild (mean baseline MMSE per group: 22 and 20) Duration of follow-up: 2 years Setting: Emory University Alzheimer's Disease Centre database APOE status measured (Y/N): N AChEi only population (Y/N): Y Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised; any vs none Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Unclear	Alzheimer's disease only population. All using cholinesterase inhibitors. No description of comorbidities.
Attrition bias	Unclear	No mention of attrition
Prognostic measurement bias	No	Lack of detail on how anticholinergic medications were identified. No mention of measuring changes in anticholinergic use over duration of 2-year study time-frame.
Outcome measurement bias	Unclear	MMSE used to measure outcome. No blinding, but retrospective design.
Adjustment for covariates bias	No	No control for comorbidities
Reverse causation bias	No	2-year follow-up, but unclear if membership of anticholinergic group was based on use at any point throughout the duration of study. No control for confounding by indication between groups, as did not assess for any BPSDs or comorbidities.
Statistical analysis bias	No	Very small sample size (69 participants). Used basic t-tests to examine association between ACh use and MMSE scores. No control for covariates. No assumptions checked or protocol.

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McMichael 2021

Study characteristics	
Demographics	Sample size: 25,418 Gender (% female): 65% Mean age: 77.2 Country: Northern Ireland
Anticholinergic measurement method	Anticholinergic Burden Scale (ACB scale)
Outcome measurement method	Mortality: ICD 10 codes
Covariates controlled for	Age, gender, marital status, urban/rural, area deprivation
Additional key study characteristics	Dementia type: non-specific dementia Dementia severity: not stated Duration of follow-up: 6 years Setting: population-based APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): diazepam (42.4%), risperidone (18.05%), quetiapine (16.6%), isosorbide preparations (10.6%), and warfarin (10%) Breakdown of anticholinergic severity: ACB0 = 15%, ACB1-4 = 57%, ACB5-9 = 24%, ACB10-14 = 4%, ACB15+ = 0.35% Type of comparison analysed: dichotomised based on total severity of burden but in unconventional way (e.g. ACB 1 to 4 vs 0; ACB 15 vs 0) Historic anticholinergic use (duration reported): not recorded
Notes	

Item	**Authors' judgement**	**Support for judgement**
Participation bias	Unclear	Age and sex reported; no reporting of comorbidities, dementia type or severity. All participants on AChE inhibitors (which was method for identifying dementia population)
Attrition bias	Unclear	No mention of attrition. Possible there was none. No mention of how missing data was dealt with.
Prognostic measurement bias	Unclear	Relied on prescribing records to establish ACh burden. Unclear if baseline ACh use was established, or if ACh use until date of death or end of study measured. No measure of adherence, dosage, or over the counter meds.
Outcome measurement bias	Unclear	No blinding, but mortality database diagnosis, so limited risk of bias.

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McMichael 2021 *(Continued)*

Adjustment for covariates bias	No	No comorbidities or dementia severity controlled for.
Reverse causation bias	No	6-year follow-up, but ACh burden appears to have been based on total ACh use to end of study period or date of death (so risk of increasing prescriptions due to deteriorating health)
Statistical analysis bias	Unclear	Appropriate model applied and checked assumptions. No protocol registered.

Porter 2019

Study characteristics	
Demographics	Sample size: 1154 Gender (% female): 62% Mean age: 79 Country: England
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Mortality: database records
Covariates controlled for	Age, sex, living situation, cognitive impairment (MMSE score), and number of self-reported comorbidities
Additional key study characteristics	Dementia type: mixed MCI and non-specific dementia population Dementia severity: mild (baseline MMSE: 93% in 19 to 24 range) Duration of follow-up: 8 years (median 5.6 years of follow-up) Setting: primary care APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): antipsychotics: 1.8%; tricyclic antidepressants:6.6%; other anticholinergics: 6.8% Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised; analysed based on anticholinergic drug type (though did not exclude other anticholinergic drug types from the comparator group for each analysis) Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement

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Porter 2019 *(Continued)*

Participation bias	Yes	Population-based primary care sample. All demographics reported.
Attrition bias	Yes	Mortality outcome data available for all participants, so no attrition.
Prognostic measurement bias	Yes	Measured both prescribed and non-prescribed medications during interview, and cross-checked with medication packs or medication lists. Medication use also established at 2-year follow-up for ~ 50% of sample who were re-interviewed.
Outcome measurement bias	Unclear	No mention of blinding or scoring in duplicate
Adjustment for covariates bias	Yes	Controlled for age, sex, severity of cognitive impairment, and comorbidities. No AChE use, but not needed for this outcome. Limited dementia population, so reduced need to control for dementia type.
Reverse causation bias	Yes	6-year follow-up
Statistical analysis bias	No	Only 71 people in the anticholinergic category (30% of surviving participants had stopped using by 2 years), and people on antipsychotics and antidepressants were not classified as part of this group. According to the authors, people on antipsychotics and antidepressants were included in the non-anticholinergic group for this comparison, so there is a high risk of cross-group anticholinergic use confounding, which diminishes power to find effect.

Tan 2018

Study characteristics	
Demographics	Sample size: 39,107 Gender (% female): 60.7% Mean age: 79.9 Country: Sweden
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Mortality: ICD-10 codes
Covariates controlled for	Age, sex, Charlson Comorbidity Index, living situation, home care, dementia disorder, MMSE, and use of anti-dementia drugs at baseline
Additional key study characteristics	Dementia type: non-specific dementia Dementia severity: mild (mean baseline MMSE: 20.43 (6.03)) Duration of follow-up: 2.3 years Setting: mixed APOE status measured (Y/N): N AChEi only population (Y/N): N

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Tan 2018 *(Continued)*

	Types of anticholinergics included (ratio reported): the most commonly used drugs contributing to ACB score ≥ 1 were metoprolol (C07AB02; 39.6%), furosemide (C03AC01; 25.0%), and warfarin (B01AA03; 13.4%) Breakdown of anticholinergic severity: ACB 0 = 63%; ACB1 = 21%; ACB2+ = 16% Type of comparison analysed: dichotomised time-varying ACB 1 vs 0 and ACB 2+ vs 0 Historic anticholinergic use (duration reported): ACB use up to 1 year prior to dementia diagnosis recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	Yes	All demographics appropriately recorded
Attrition bias	Yes	No mention of attrition, but is a database study and excluded those with missing data (which was just 7%), so is reasonable to assume there was none
Prognostic measurement bias	Unclear	Relied on prescription records. Measured ACB annually for each participant, but no mention of blinding or duplicate scoring to minimise measurement bias.
Outcome measurement bias	Unclear	Mortality death records well captured by patient records. No mention of blinding for measurement or assessing in duplicate.
Adjustment for covariates bias	Yes	Controlled for age, sex, dementia severity (via MMSE score at baseline) and dementia type, and anti-dementia drug use. Controlled for comorbidities via Charlson.
Reverse causation bias	Unclear	ACB baseline score calculated for year before dementia diagnosis. Mean of 2.3-year follow-up.
Statistical analysis bias	Unclear	No mention of checking assumptions; no protocol registered.

Trevisan 2021

Study characteristics	
Demographics	Sample size: 342 Gender (% female): 61.1% Mean age: 76 Country: Italy
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale and Anticholinergic Risk Scale (ARS)
Outcome measurement method	Progression to dementia: multi-domain cognitive and physical function assessment

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Trevisan 2021 *(Continued)*

Covariates controlled for	age, sex, and educational level, baseline IADL (as continuous variable), diabetes, and cardiovascular diseases (as yes vs no)
Additional key study characteristics	Dementia type: MCI participants only Dementia severity: very mild Duration of follow-up: 1 year Setting: population-based APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised: any ACB (1+) vs none Historic anticholinergic use (duration reported): not recorded
Notes	

Item	Authors' judgement	Support for judgement
Participation bias	No	Restricted to MCI participants who were followed up 1 year later. MMSE scores at baseline quite high (mean 26)
Attrition bias	Unclear	No mention of attrition, but inclusion criteria may have been restricted to those with available follow-up data. No comparison of those with or without data described.
Prognostic measurement bias	Unclear	Restricted to prescription records only
Outcome measurement bias	Unclear	No mention of blinding, but ACB likely measured in retrospect. No mention of scoring in duplicate.
Adjustment for covariates bias	No	Controlled for age, sex, educational level, IADL, diabetes, and cardiovascular diseases. No control for baseline cognition or type of MCI.
Reverse causation bias	No	Limited to 1-year follow-up, and no control for prescribing, due to prodromal symptoms of dementia (such as depression or insomnia). Those on ACB drugs had significantly lower MMSE scores at baseline than non-users, but this was not controlled for in the analysis.
Statistical analysis bias	No	Only 14 dementia events and 41 CIND events. 7 variables included in logistic regression model, so severely underpowered to detect effect. No protocol or assumptions checked. Follow-up only 1 year, which was likely too short. Analysis categorised into ACh groups of 0 vs 1+ rather than separating out definite from possible.

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Vetrano 2016

Study characteristics	
Demographics	Sample size: 3761 Gender (% female): 72% Mean age: 83 Country: Italy
Anticholinergic measurement method	Anticholinergic Cognitive Burden (ACB) scale
Outcome measurement method	Mortality: death records
Covariates controlled for	Age, sex, activities of daily living, Depression Rating Scale, Cognitive Performance Scale, dementia, heart failure, stroke, chronic obstructive pulmonary disease, cancer, diabetes, IHD, and hip fracture
Additional key study characteristics	Dementia type: mixed impaired and unimpaired population Dementia severity: moderate to severe (Cog performance scale average of ~3) Duration of follow-up: 5 years (mean 1.4 years) Setting: nursing home APOE status measured (Y/N): N AChEi only population (Y/N): N Types of anticholinergics included (ratio reported): not reported Breakdown of anticholinergic severity: not reported Type of comparison analysed: dichotomised; ACB1 vs ACB 0, ACB2+ vs ACB 0 Historic anticholinergic use (duration reported): not recorded
Notes	

Item	**Authors' judgement**	**Support for judgement**
Participation bias	No	Not exclusively a cognitively impaired population
Attrition bias	Yes	No attrition mentioned, but used databases so possible there was none
Prognostic measurement bias	Unclear	Only single method of assessing anticholinergic drug use. No measure of adherence. No repeat measurement despite 5-year follow-up—although as nursing home setting, there was probably minimal variation in use.
Outcome measurement bias	Unclear	No mention of blinding or scoring in duplicate
Adjustment for covariates bias	Yes	Age, sex, and comorbidities, cognitive performance and dementia diagnosis all controlled for

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Vetrano 2016 *(Continued)*

Reverse causation bias	Unclear	ACh use restricted to baseline. Follow-up was for 5 years, but mean follow-up was only 1.4 years.
Statistical analysis bias	Unclear	No protocol no assumptions checked

ACh: anticholinergic
AChE: acetylcholinesterase
AD: Alzheimer's Disease
ADAS-Cog: the Alzheimer's disease assessment scale – cognitive subscale
BMI: body mass index
BPSD: behavioral and psychological symptoms of dementia
CDR: Clinical Dementia Rating scale
CIND: cognitive impairment no dementia
DAD: Disability Assessment for Dementia
HBP: high blood pressure
HoNOS 65+: the Health of the Nation Outcome Scales 65+
IADL: instrumental activities of daily living
IHD: ischaemic heart disease
info: information
MCI: mild cognitive impairment
meds: medication
MMSE: Mini Mental State Examination
NPI: Neuropsychiatric Inventory
PADL: physical activities of daily living
SIB: Severe Impairment Battery
SMAF: Functional Autonomy Measurement System
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agnoli 1983	Wrong study design
Ang 2015	Wrong population
Boccardi 2017	Wrong study design
Cancelli 2009	Wrong study design
Cejudo 2018	Wrong study design
Desmarais 2012	Wrong population
Dharia 2011	Grey literature
Fortin 2009	Wrong study design
Gnjidic 2013	Wrong method of assessment
Green 2016	Wrong outcome
Green 2018	Wrong outcome
Green 2019	Wrong outcome

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Study	Reason for exclusion
Green 2020	Wrong outcome
Hilson 2016	Wrong study design
Jewart 2005	Wrong population
Kachru 2021	Wrong outcomes
Kidd 2014	Wrong population
Kumar 2019	Wrong population
Lakey 2009	Wrong outcomes
Landi 2007	Wrong population
Lattanzio 2018	Wrong population
MartinezArrechea 2021	Wrong study design
Mate 2015	Wrong outcomes
Minzenberg 2004	Wrong population
Naharci 2017	Wrong population
Oken 1994	Wrong study design
Palmer 2015	Wrong outcomes
Rehse 2016	Wrong population
Reinold 2019	Wrong outcomes
Roe 2002	Wrong outcomes
Rumpel 2014	Foreign language (German) and does not restrict to DBI (ACh)
Supina 2010	Grey literature
Sura 2013	Wrong study design
Sura 2014	Wrong outcome
Swami 2016	Wrong study design
Veselinovic 2015	Wrong population
Williams 2019	Wrong outcome

ACh: anticholinergic
DBI: Drug Burden Index

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ADDITIONAL TABLES

Table 1. Patient/Problem; Intervention; Comparison; Outcome; Timing (PICOTS)

Population	Older adults (mean age ≥ 50 years) with prior cognitive impairment, MCI, dementia, or AChE use at baseline
Index prognostic factor	Anticholinergic burden, measured by any validated ordinal anticholinergic burden scale
Comparator prognostic factors (covariates of interest)	Age, sex, comorbidity, and AChE use
Outcomes	Cognitive decline (multidomain) or neuropsychiatric disturbances
Timing	Prognostic factors should be measured at baseline. Outcomes should be obtained at a minimum of 1-month follow-up via longitudinal, observational cohort/case-control study design
Setting	Recruitment from primary, secondary, or community, or care-home settings

AChE: anticholinesterase inhibitor
MCI: mild cognitive impairment

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 EFect 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

DBI(ACh): Drug Burden Index (anticholinergic subscale)

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Appendix 2. Contributors 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 Martin Taylor-Rowan, Professor Phyo Myint, Dr Terry Quinn, and Dr Amanda Cross.

Appendix 3. Sources searched and search strategies

Source	Search strategy	Hits
MEDLINE In-process and other non-indexed citations and MEDLINE OvidSP from 1946 [Date of most recent search: 29 November 2021]	1. cholinergic antag*.ti,ab. 2. anticholinergic*.ti,ab. 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. 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.	Mar 2020: 2907 Mar 2021: 252 Nov 2021:266

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(Continued)

	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.	
	44. Neurocognitive Disorders/	
	45. or/16-44	
	46. 15 and 45	
Embase OvidSP from 1974 [Date of most recent search: 29 November 2021]	1. cholinergic antag*.ti,ab.	Mar 2020: 4544 Mar 2021: 552 Nov 2021: 474
	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/	

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(Continued)

	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.	
	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 most recent search: 29 November 2021]	1. cholinergic antag*.ti,ab. 2. anticholinergic*.ti,ab. 3. anti-cholinergic*.ti,ab. 4. exp Cholinergic Receptors/ 5. AAS.ti,ab.	Mar 2020: 3489 Mar 2021: 164 Nov 2021: 124

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(Continued)

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.

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.

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(Continued)

	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*	Mar 2021: 260
[Date of most recent search: 29 November 2021]	S3 TX anti-cholinergic*	Nov 2021: 196
	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+")	
	S16 (MH "Cognition Disorders+")	
	S17 (MH "Dementia+")	
	S18 TX cognit*	
	S19 TX dement*	
	S20 TX alzheimer*	
	S21 TX "lewy bod*"	
	S22 TX FTLD	
	S23 TX PDD	
	S24 TX "executive function*"	
	S25 (MH "Attention")	
	S26 TX speed AND processing	
	S27 TX memory	

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(Continued)

	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 [Date of most recent search: 29 November 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 FTLD 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 Nov 2021: 907
TOTAL		Mar 2020: 14517 Mar 2021: 1874 Nov 2021: 1967 **TOTAL: 18358**
TOTAL after de-duplication		Mar 2020: 9767 Mar 2021: 1493 Nov 2021: 1765 **TOTAL: 13025**
TOTAL after first assessment by CDCIG information specialist		Mar 2020: 1034 Mar 2021: 168

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(Continued)

	Nov 2021: 251
	TOTAL: 1453

Appendix 4. Contents of pro forma

Extracted information	Includeddetails
General information	author, title, source, publication date, language, related or duplicate publications
Source of data	cohort (retrospective or prospective data collection), case-control, 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, severity/type of dementia); details of ongoing treatments/medications; study dates; country of recruitment; setting (using our definitions of primary, secondary, community and care-home 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); when 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 cognitive decline or neuropsychiatric disturbance. Where possible, we extracted estimates and corresponding confidence intervals from each included paper. We also recorded additional clinical outcome variables assessed.

Appendix 5. QUIPS (Quality in PrognosisStudies) 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, sex, severity/type of dementia). If either a convenience sample was used, or there was inadequate reporting of comorbidities/demographics, we assigned an unclear risk of bias.

Attrition: we assessed extent of loss to follow-up. Specifically, if attrition was greater than 20%, we assigned a high risk of bias rating. In addition, we assessed reporting of, and methods for dealing with, missing data. We assigned an unclear 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 capable of establishing non-prescription medications taken, along with duration of exposure and adherence, we assigned an

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unclear 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 was a 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 comprehensive neuropsychological assessment or via a brief cognitive assessment tool only (such as the MMSE). If outcome was reliant upon brief screening tools alone, we assigned an unclear risk of bias rating, as these may be subject to practice effects or floor effects (particularly for more severe forms of dementia). 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.

Covariates: we assessed whether studies adjusted for age, sex, comorbidities, and for cognitive outcomes (AChE inhibitor use 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 unclear risk of bias.

Reverse causation: we evaluated studies on perceived risk that anticholinergic drugs were prescribed for treatment of symptoms of worsening of dementia. If studies did not explicitly report restricting anticholinergic burden measurement to at least 12 months before outcome measurement, a rating of high risk of bias was applied. Studies that restricted anticholinergic burden measurement to 1 to 2 years before outcome assessment were rated as unclear risk of bias. In addition, if studies did not control for a range of comorbidities that could lead to prescription of anticholinergic drugs, we considered the study to be high risk of bias.

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 a sample size calculation or the '10 events per covariate' rule for logistic regression; if the method for selecting covariates for inclusion in a multivariate model was based on P values in a univariate analysis without incorporating prior knowledge of relevant associations into selection; if the method of analysis was inconsistent with the stated protocol (where protocols were not available, we assigned an unclear risk of bias); and if the reported results were inconsistent with the stated method of analysis. We assigned an unclear risk of bias if relevant assumptions were not checked.

Key: MMSE: Mini Mental State Examination; **AChE:** acetylcholinesterase

Appendix 6. GRADE outcome tables

Outcome: mortality		
Criteria	**Rating**	**Reason**
Number of studies	6*	*study numbers restricted to those included in meta-analysis
Study limitations	Serious (-1)	Most studies at high RoB, however, 2 studies at lower RoB both found significant association of similar size
Inconsistency	No issues	
Indirectness	No issues	Vast majority of studies conducted in non-specific dementia population
Imprecision	No issues	
Publication bias	Serious (-1)	Publication bias assumed
Effect size	No	Effect size is small
Exposure-response gradient	NA	Unable to investigate
Overall rating	**Low**	

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Outcome: physical function		
Criteria	**Rating**	**Reason**
Number of studies	4	
Study limitations	Very serious (-2)	Most studies at high RoB for confounding bias
Inconsistency	Serious (-1)	Variable results
Indirectness	Very serious (-2)	1 study conducted in an AD-AChEI population, and 1 conducted in mixed impaired/unimpaired population
Imprecision	Serious (-1)	Limited study numbers available
Publication bias	Serious (-1)	Publication bias assumed
Effect size	No	Small effect sizes; most non-significant
Exposure-response gradient	No	No evidence of dose response
Overall rating	**Very Low**	

Outcome: institutionalisation		
Criteria	**Rating**	**Reason**
Number of studies	1	
Study limitations	Very serious (-2)	Study at high RoB for confounding and reverse causation bias
Inconsistency	No issues	Only 1 study
Indirectness	Very serious (-2)	AChEI users only
Imprecision	Very serious (-2)	Only 1 study available
Publication bias	Serious (-1)	Publication bias assumed
Effect size	No	Effect is non-significant
Exposure-response gradient	No	No evidence of dose response effect
Overall rating	**Very Low**	

AChEI: acetylcholinesterase inhibitors; **AD**: Alzheimer's disease; **RoB**: risk of bias

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HISTORY

Protocol first published: Issue 11, 2021

CONTRIBUTIONS OF AUTHORS

Martin Taylor-Rowan drafted the initial manuscript. Christina Kolliopoulou and Olga Kraria were primary reviewers of all studies. Dr Terry Quinn was the supervising author. Ahmed Abdulrahman S Alharthi, Jenny Mcleery, Amanda Cross, Carrie Stewart, Phyo Myint, and Terry Quinn revised the manuscript and contributed to intellectual content. All authors contributed to writing.

DECLARATIONS OF INTEREST

MT: none

TQ: none

JM: none

CS: none

PM: none

AJC: none

OK: none

CK: none

AA: none

SOURCES OF SUPPORT

Internal sources

- none, Other

  nothing to declare

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We originally planned to evaluate risk of future cognitive decline or neuropsychiatric disturbance for anticholinergic drug users against non-users via meta-analysis. We had planned to pool summary estimates for each anticholinergic burden tool individually; then, as an exploratory analysis, pool summary estimates across all scales. In the first instance, we had planned to pool data obtained from unadjusted analyses, then, in the second instance, pool data from fully adjusted analyses, provided age, sex, and comorbidities were controlled for, as a minimum. Limitations in available data required a number of deviations from our planned synthesis, and as an alternative, we synthesised data narratively for all outcomes apart from mortality.

We were also unable to conduct planned sensitivity analyses, excluding studies that were at high risk of bias in one or more domains, due to the lack of studies at uniform low risk of bias.

Similarly, we were unable to conduct a number of planned secondary (subgroup) analyses due to lack of suitable data. Specifically, we planned to assess risk by type of dementia, severity of dementia, APOe4 status, and by setting. We also planned to conduct analyses based on duration of follow-up. We also planned to assess exposure to anticholinergic drugs, including exposure before enrolment into the study and exposure during the study, but this was not well recorded in identified studies.

Finally, we had planned to conduct a comparative analysis of the prognostic performance of the differing anticholinergic burden measures, using a network meta-analysis, but there were insufficient studies to investigate this.

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INDEX TERMS

Medical Subject Headings (MeSH)

Cholinergic Antagonists [adverse effects]; *Cognitive Dysfunction [chemically induced]; *Dementia [chemically induced]; Prospective Studies; Retrospective Studies

MeSH check words

Aged; Humans

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