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SYSTEMATIC REVIEW

Anticholinergic drugs and incident dementia, mild cognitive impairment and cognitive decline: a meta-analysis

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Abstract

Background: the long-term effect of the use of drugs with anticholinergic activity on cognitive function remains unclear.
Methods: we conducted a systematic review and meta-analysis of the relationship between anticholinergic drugs and risk of dementia, mild cognitive impairment (MCI) and cognitive decline in the older population. We identified studies published between January 2002 and April 2018 with ≥12 weeks follow-up between strongly anticholinergic drug exposure and the study outcome measurement. We pooled adjusted odds ratios (OR) for studies reporting any, and at least short-term (90+ days) or long-term (365+ days) anticholinergic use for dementia and MCI outcomes, and standardised mean differences (SMD) in global cognition test scores for cognitive decline outcomes. Statistical heterogeneity was measured using the I^2 statistic and risk of bias using ROBINS-I.
Results: twenty-six studies (including 621,548 participants) met our inclusion criteria. 'Any' anticholinergic use was associated with incident dementia (OR 1.20, 95% confidence interval [CI] 1.09–1.32, $I^2 = 86\%$). Short-term and long-term use were also associated with incident dementia (OR 1.23, 95% CI 1.17–1.29, $I^2 = 2\%$; and OR 1.50, 95% CI 1.22–1.85, $I^2 = 90\%$). 'Any' anticholinergic use was associated with cognitive decline (SMD 0.15; 95% CI 0.09–0.21, $I^2 = 3\%$) but showed no statistically significant difference for MCI (OR 1.24, 95% CI 0.97–1.59, $I^2 = 0\%$).
Conclusions: anticholinergic drug use is associated with increased dementia incidence and cognitive decline in observational studies. However, a causal link cannot yet be inferred, as studies were observational with considerable risk of bias. Stronger evidence from high-quality studies is needed to guide the management of long-term use.

Keywords: *systematic review*, *meta-analysis*, *anticholinergics*, *dementia*, *cognition*, *older people*

Key Points

- We synthesised evidence from 26 observational studies.

- Anticholinergic drug use, particularly long-term use, is associated with greater incidence of dementia and cognitive decline.
- However, all but one study was at serious or critical risk of bias, and the findings were heterogeneous.
- The potential benefits and harms should be carefully considered when initiating and continuing anticholinergic drugs.
- Higher-quality studies are needed, targeting specific medication classes, and designed to reduce biases in previous studies.

Introduction

Dementia affects more than 40 million people with direct healthcare costs of $818 billion in 2015 [1]. Dementia is characterised by irreversible and progressive cognitive impairment, with consequent disability and dependence. 'Cognitive impairment' itself refers to problems with cognitive abilities such as memory, problem solving, learning, perception and language. Cognitive impairments are common in the older population, with different aspects of cognition independently affected with age and by different neurological diseases [2]. While cognitive impairment does not always progress to dementia, it nevertheless presents a social and economic cost. A classification of 'mild cognitive impairment (MCI)' identifies those with cognitive impairments that are not severe enough to meet the definition of dementia [3]. Many different operational definitions of dementia, cognitive impairment and MCI are used in clinical and research contexts.

Identification of possible modifiable risk factors for dementia is paramount [4]. Some studies have suggested that anticholinergic medication use might be a modifiable risk factor for cognitive impairment or dementia [5, 6]. Drugs with anticholinergic properties inhibit the action of acetylcholine at its receptor [7]. Such drugs have many indications [7], including urinary incontinence and depression [8]. Short-term cognitive impairments are well-known side effects of anticholinergic drugs, but several recent observational studies suggest links to longer-term cognitive impairment and dementia incidence [9–11]. Around 10% of people aged 65 years and older regularly use strongly anticholinergic drugs [12, 13].

Several observational studies report an association between anticholinergic drug use and cognitive function [9,10,14,15]; however, the magnitude of effects and strengths of their study designs vary considerably [16]. A review conducted by the members of our study team identified 33 observational studies of cognitive effects of anticholinergics, with 23 studies reporting lower cognitive function among users [16]. However, this review did not include a meta-analysis, nor specifically consider long-term effects or risks of bias. A separate meta-analysis reported an association between anticholinergic use and dementia incidence but included only three cohort studies [17]. Larger and more carefully controlled observational studies have since been published addressing limitations of earlier work; hence a new quantitative systematic review is warranted [9,10]. The evidence regarding these relationships arises from non-randomised observational studies, which are subject to uncontrolled confounding, misclassification and selection bias. Hence a careful assessment of risk of bias is needed when interpreting individual or pooled study findings.

Here we report a systematic review and meta-analysis of the association between strongly anticholinergic drug use and subsequent cognitive decline, incident dementia and incident MCI, in older adults. We carefully assess risk of bias and the reasons for any heterogeneity in study findings.

Methods

Registration

The study protocol was registered with PROSPERO (Registration:CRD42016039289). This systematic review and meta-analysis was reported according to the Meta-analyses of Observational Studies in Epidemiology guidelines [18].

Search strategy

An updated search from our 2014 review [16] was undertaken by one researcher (YKL) using Ovid SP MEDLINE and EMBASE between January 2013 and March 2016 (search terms given in Appendix 1), using recommended methods for updating searches [19]. Further studies identified using this search were automatically forwarded between March 2016 and April 2018. There were no language restrictions. The previous review search began in 2002 to capture studies using anticholinergic scales, with studies published before 2002 generally using serum anticholinergic activity (SAA) [20]. We also re-evaluated all studies included in the previous review for inclusion in the current review [16] and re-screened abstracts from non-English and retrospective studies excluded from that review. References in published systematic reviews were hand searched, and we contacted experts within the field for further eligible studies.

Selection criteria

Abstracts were independently assessed for inclusion by two researchers (NP and WYC or CH). Inclusion criteria were randomised controlled trials (RCTs) or observational studies investigating anticholinergic effects on human adults (using an anticholinergic scale [8, 21, 22] or specific anticholinergic drugs), on the following outcomes: (i) dementia, (ii) MCI or (iii) cognitive decline.

Exclusion criteria were <12 weeks follow-up between measurement of drug exposure and outcome; cross-sectional studies, case reports, literature reviews, clinical audits, editorials and conference abstracts; mean participant age less than 50 years; anticholinergic exposure based on SSA alone (due to inconsistent relationships with cognitive outcomes [23]); and studies including mostly participants with existing dementia.

Data extraction

The following were independently extracted by two researchers (NP and WYC or CH): study design, data source, country, proportion of male participants, mean participant age, number of participants, definition of anticholinergic drug, primary exposure measure, length of follow-up time, effects on cognitive outcomes (as odds ratios [OR], hazard ratios or raw data that could be converted into an OR) and covariates included in multivariable analysis. Authors were contacted for additional data when studies provided insufficient data for calculating an OR. The extracted information was reviewed by two statisticians (KR and CG) and discrepancies resolved by consensus.

Risk of bias assessment

Risk of bias with respect to estimating causal effects was independently assessed for each study effect by two researchers (WYC and NP) using the Cochrane Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool [24]. Discrepancies were resolved through consensus.

Data synthesis

Results were pooled using random-effects meta-analysis and the inverse variance method where studies used similar definitions of both drug exposure and outcome. Findings for dementia or MCI outcomes were pooled separately. The relative risk was assumed to approximate the OR as dementia and MCI were sufficiently rare events. ORs were pooled separately for studies reporting any (≥1 day), at least short-term (≥90 days) and long-term (≥365 days, or at baseline and 1- or 2-year follow-up for studies using patient interviews) anticholinergic use. Only the effects of drugs with definite/strong anticholinergic activity (scores 2 or 3 on the ACB scale or an equivalent definition) were included. Many drugs are considered to have mild anticholinergic activity (scored 1 on anticholinergic scales), i.e. serum anticholinergic activity or in vitro affinity to muscarinic receptors, but no known clinically relevant cognitive effects, and are excluded from this review. Some studies estimate the 'anticholinergic load' by summing the individual anticholinergic scale scores for each drug participants are taking; however, there were too few studies reporting these associations to include in the meta-analysis.

For each study that reported decline in global cognition measured as a continuous outcome, we derived the standardised mean difference (SMD). This was estimated as the mean difference in decline between exposed and non-exposed groups, divided by the standard deviation of the change scores. For studies that only reported an OR for decline following dichotomisation of change scores, we assumed that cognitive decline was normally distributed and converted this to the SMD by dividing the log-odds ratio by 1.81 [25]. Estimated SMDs were then pooled using the random-effects inverse variance method.

We measured statistical heterogeneity using the I^2 statistic. The following sources of heterogeneity were assessed using random-effects meta-regression: mean participant age, proportion female, mean baseline Mini-Mental State Examination (MMSE) score (where recorded), study follow-up time, population type (community versus care home) and patient disease group (general, specific condition). We report subgroup results for characteristics associated with the effect estimate at $P < 0.10$. We also performed three post hoc sensitivity analyses: first excluding studies with a critical risk of bias, second excluding studies only examining a single drug class and third including only studies using the ACB scale [8], as the most common scale used aimed at central anticholinergic effects. Data was analysed using Stata version 14.0 (StataCorp, College Station, TX).

Results

Study selection

We screened 521 study abstracts: 347 identified through the new literature search, 46 from the previous review, 42 retrospective studies, 74 non-English studies excluded from the previous review and 12 via other sources (Appendix Figure 1). Full text was extracted for 79 studies, with 26 studies meeting our inclusion criteria; 23 cohort studies [10,11,14,15,26–44]; and three case-control studies [9,45,46]. Nineteen studies are included in the meta-analyses.

Demographics

The 26 identified studies included 621,548 participants with mean study duration of 73 months (range 3–241 months, Table 1, Appendix Tables 1 and 2). Studies were conducted in Europe, North America or Taiwan and were mainly community based, except for three studies of outpatients and two studies of care home residents. The mean proportion of female participants was 60%, and mean participant age was 74 years (range 52–86 years).

Drug use was assessed by patient interview, self-reported written survey and review of prescriptions and drug containers or directly from insurance claims, pharmacy or primary care records. Studies varied according to how they classified anticholinergic drug exposure: 14 studies used a published anticholinergic rating scale (ACB or ADS), four used a literature review and/or expert panel analysis, one used their own validated clinician-rated scale and two studies used national drug/therapeutic formulary classifications. The scales generally aimed to examine central anticholinergic effects, but some were more likely to also capture peripheral effects (Appendix Table 1). One study specifically tested selective serotonin reuptake inhibitors (SSRIs) only and three examined bladder anticholinergics only.

Risk of bias

Findings from six studies were rated as having a critical risk of bias, 19 as serious, one as moderate and none as low (Appendix Tables 3 and 4). Of the risk of bias subsections: 14

Table 1. Design and characteristics of included studies

Study	Study design, data source, country	Setting and population	Number of participants	Mean age (years), % male	Study duration (months)
Ancelin 2006	Cohort, Eugeria longitudinal study of cognitive decline, France	Community	327	66, NS	12 and 96
Bali 2015	Cohort, Medicare health insurance data, USA	Nursing home, residents with depression	23,748	NS, 28	24
Boustani 2007	Cohort, surveyed African Americans identified by residential addresses, USA	Community	1,558	78, 34	60
Cai 2013	Cohort, Indianapolis Dementia Screening and Diagnosis study, USA	Community	3,413	72, 29	12
Campbell 2010	Cohort, Indianapolis Ibadan Dementia Project, USA	Community	1,652	82, 31	72
Campbell 2018	Cohort, Indiana Network for Patient Care, USA	Community	350	71, 21	48
Carriere 2009	Cohort, The 3 City Study, France	Community	6,463	74, 40	48
Chatterjee 2016	Case-control, Medicare health insurance data, USA	Community	141,940	80, 19	36
Chuang 2017	Cohort, Baltimore Longitudinal Study of Aging, USA	Community	723	52, 69	241[a]
Esin 2015	Cohort study, Geriatric medicine outpatient clinic, Turkey	Outpatients, overactive bladder patients	168	74, 8	3
Fox 2011	Cohort, MRC-CFAS, UK	Community and institutions	8,334	75, 40	24
Gomm 2016	Cohort, AgeCoDe study, Germany	Community	73,679	83, 24	84
Gray 2015	Cohort, Adult Changes in Thought Study, USA	Community, patients with health insurance	797	74[b], 40	120
Grossi 2019	Cohort, MRC-CFAS, UK	Community and institutions	3,045	75, 40	96
Han 2008	Cohort, Connecticut Veterans Longitudinal Cohort, USA	Community	544	74, 100	24
Kashyap 2014	Cohort, Outpatient clinics in Quebec, Canada	Outpatient, urinary incontinence patients	102	72, 16	12
Koyama 2013	Cohort, Study of Osteoporotic Fractures, USA	Community	1,429	83, 0	60
Moga 2017	Case-control, National Alzheimer's Co-ordinating Center cohort, USA	Community	7,735	77, 42	15[a]
Papenberg 2017	Cohort, SNAC-K, Sweden	Community	1,473	70, 39	72
Richardson 2018	Case-control, Clinical Practice Research Datalink, UK	Community	324,703	71, 37	240
Saczynski 2015	Cohort, Health and Retirement Study and Prescription Data Study, USA	Community	3,714	72, 37	72
Shah 2013	Cohort, Religious Orders Study, USA	Community, Catholic clergy	896	75, 31	216
Whalley 2012	Cohort, 1932 Scottish Mental Survey, Scotland	Community	210	77, 58	120
Wu 2017	Cohort, The Longitudinal Older Veterans Study, Taiwan	Veterans care homes	274	86, 100	6
Yang 2017	Cohort, Taiwan National Health Insurance Research Data set, Taiwan	Community	10,160	62, 64	132
Yarnall 2015	Cohort, ICICLE-PD, UK	Community and outpatients	195	69, 58	18

[a]Mean number of months. [b]Median age. Abbreviations: AgeCoDe = German Study on Aging, Cognition and Dementia in Primary Care Patients, ICICLE-PD = Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation—Parkinson's Disease, MRC-CFAS = Medical Research Council Cognitive Function and Ageing Studies, NS = not stated, SNAC-K = Swedish National Study on Aging and Care in Kungsholmen.

(54%) had a serious or critical risk of bias for confounding; 23 (88%) had a serious risk of bias for participant selection; and 10 (40%) had a serious risk of bias for missing data. Although many studies controlled for age, sex and education, few accounted for anticholinergic drug indications such as depression (Appendix Table 2). However, 24 (92%) had a low risk of bias for outcome measurement, and 23 (88%) had a low or moderate risk of bias for selection of the reported result.

Anticholinergics and dementia

Eleven of the 12 studies reporting dementia as an outcome were included in the quantitative analyses. The pooled OR for any use of drugs with definite anticholinergic activity and incident dementia was 1.20 (95% confidence interval [CI] 1.09–1.32) from seven studies (Figure 1). There was substantial heterogeneity (I^2 = 86%); however, this is likely influenced by the inclusion of three large studies with small variances [47]. No study-level characteristics examined using meta-regression were significantly associated with the OR for dementia. Three large studies dominated the analysis and were similarly derived from US and UK population-based electronic health records [9,10,45]. All had good confounding control: two studies adjusted for a wide range of confounders [9,10], and the other restricted to the main indication of depression [45]. The pooled OR for anticholinergic use for ≥90 days and ≥365 days and dementia were 1.23 (95% CI 1.17–1.29) and 1.50 (95% CI 1.22–1.85) from three and six studies, respectively (Figure 1). There was little heterogeneity (I^2 = 2%) for ≥90 days use, but substantial heterogeneity for ≥365 days use (I^2 = 90%). One further cohort study reported no association between anticholinergic use and dementia, reporting an OR of 0.67 (95% CI 0.40–1.15) [39]. However, the definition of anticholinergics was broad, being dominated by drugs with 'mild' anticholinergic activity, and so findings were not comparable with the other studies.

Anticholinergics and MCI

Six cohort studies estimated the effect of drugs with definite anticholinergic activity and incident MCI. Three studies estimated the effect of any definite anticholinergic use (pooled OR 1.24; 95% CI 0.97–1.59; I^2 = 0%) (Figure 2). One study reported an OR of 1.70 (95% CI 0.52–5.57) for ≥60 days use [26], and we estimated a pooled OR of 2.52 (95% CI 0.71–8.95) from two studies examining long-term use, albeit with substantial heterogeneity (I^2 = 80%). A further study reported an OR of 1.15 (95% CI 1.01–1.31) per year of standardised daily doses and incident MCI and hence could not be numerically combined with the other exposure classifications [43]. For a further cohort study of Parkinson's disease patients, we estimated an unadjusted OR of 1.17 (95% CI 0.66–2.06) between anticholinergic use including mild anticholinergics and MCI [42].

Anticholinergics and cognitive decline

Cognitive decline was reported on by 14 studies. We calculated the SMD of global cognitive decline for six studies [11,14,31,36,38,46]: five studies reported MMSE, while one calculated a composite score from 19 cognitive tests [38]. All but one study adjusted for some potential confounders [31]. Greater cognitive decline was consistently observed among patients taking anticholinergic drugs (SMD 0.15; 95% CI 0.09–0.21, I^2 = 3%) (Figure 3). There was some evidence that studies with longer follow-up reported greater cognitive decline (P = 0.08 from meta-regression) (Appendix Figure 2).

A further seven cohort studies were excluded from the meta-analysis. Two studies reported cognition at follow-up and not decline since baseline [27,35]. The Scottish Mental Survey of 1932 provided insufficient detail for pooling, but reported lower mean MMSE scores with anticholinergic use [39]. Finally, four studies used incompatible definitions of anticholinergic use. We were able to calculate SMDs in MMSE scores with anticholinergic use of 0.26 (95% CI −0.02, 0.55) over 18-month follow-up and 0.55 (95% CI 0.17, 0.92) over 6-month follow-up within a Parkinson's disease study and Taiwan Veterans care home study, respectively [40,42]. However, both studies included drugs with mild anticholinergic activity. The SMD in the decline in the Health and Retirement Study (HRS) 27-point Cognition Measure was 0.02 (95% CI −0.08, 0.12) over a 6-year follow-up for a total anticholinergic load of ≥3 in US HRS study [37]. A Canadian cohort study of urinary incontinence clinic outpatients reported no significant decline in MMSE with increased total anticholinergic load, but provided insufficient data for pooling [26].

Sensitivity analyses

None of the sensitivity analyses had a substantial effect on the pooled estimates (Appendix Figures 3–11).

Updated search

Further automated study searches between April 2018 and November 2019 identified eight additional studies meeting our inclusion criteria [48–55]. Two studies focussed on depression [48, 49], and one on Parkinson's disease [50], with the others having no specific disease focus. Five studies would be excluded from meta-analysis due to incompatible definitions of anticholinergic exposure, cognition or by patient duplication [48–52]. Using ROBINS-I, all study estimates were at serious/critical risk of bias and consistent with our review [24]. One large study replicated findings from the UK primary care population [9], in another UK primary care cohort [55], confirming that associations with dementia are limited to certain classes of anticholinergic medications. Similarly, a cohort study from the Netherlands reported greater dementia incidence with a higher anticholinergic burden score, but not once excluding antipsychotics and antidepressants [51].

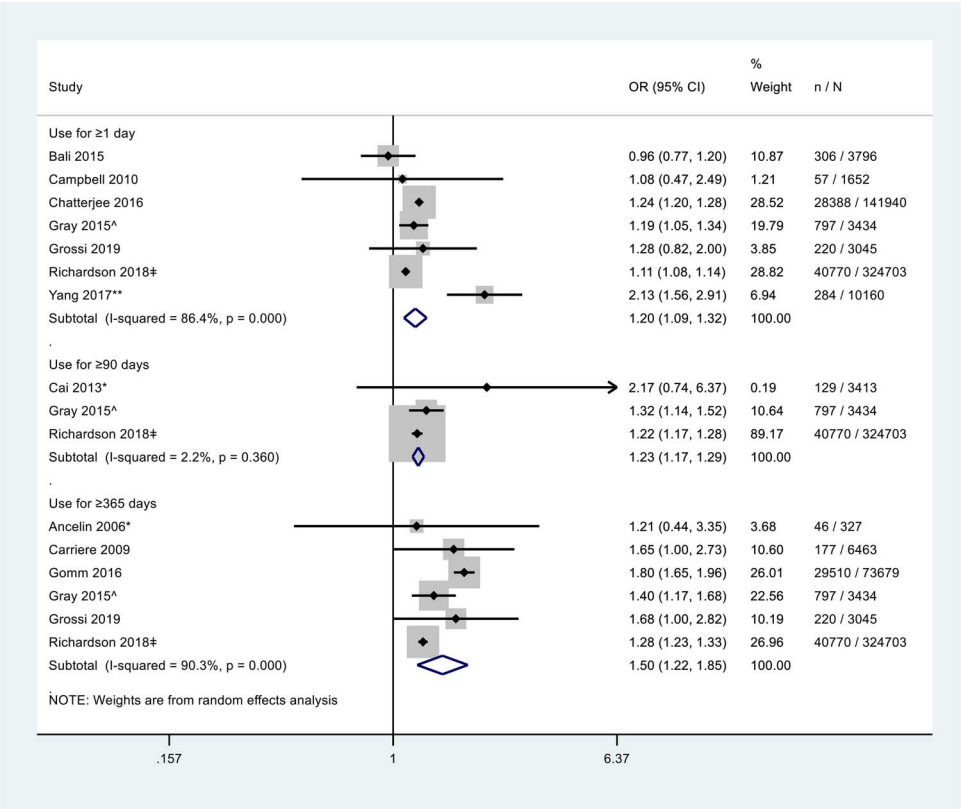

Figure 1. Meta-analysis of odds ratios for dementia by any, at least short-term and long-term definite anticholinergic use versus no use. ^OR (95% CI) estimated as the inverse variance weighted average of the published adjusted ORs for exposures of 1–90, 91–365, 366–1095 and >1095 daily doses for any use, of 91–365, 366–1095 and >1095 daily doses for short-term use (90+ days) and of 366–1095 and >1095 daily doses for long-term use (365+ days). ‡OR (95% CI) estimated as the inverse variance weighted average of the published adjusted ORs for exposures of 90–364, 365–1459 and >1460 daily doses for short-term use (90+ days) and of 365–1459 and >1460 daily doses for long-term use (365+ days). *The Cai 2013 estimate is for 60+ days use versus <60 days, Ancelin 2006 estimated long-term use (365+ days) as use at baseline and at 1-year follow-up and Gomm 2016 estimated long-term use (365+ days) as a prescription every quarter for 6 consecutive quarters. **OR (95% CI) estimated as the inverse variance weighted average of the published adjusted ORs for exposures of oxybutynin, solifenacin and tolterodine. Abbreviations: *n*, number of dementia cases; *N*, number of participants.

Discussion

Observational studies report, on average, a 20% greater incidence of dementia associated with the use of drugs with definite anticholinergic activity. Greater associations with dementia are also reported with longer durations of exposure. Observational studies also report anticholinergic drug use is associated with long-term global cognitive decline. However, there was no randomised evidence, study findings are heterogeneous and all but one study had a serious or critical risk of bias. No reported factor could explain the heterogeneous study findings.

To our knowledge, this is the most comprehensive systematic review and meta-analysis on the long-term cognitive effects associated with anticholinergic drug use. We excluded cross-sectional studies and studies with insufficient follow-up. We used recognised methods for performing an updated search [19] and minimised the risk of missing studies. We provided a thorough assessment of risk of bias by utilising the latest rating scales. The included studies used different scales to measure anticholinergic burden, and although they differ in how they classify anticholinergic burden, they are typically consistent in which drugs they classify as strongly or definitely anticholinergic [56].

A major limitation in drawing substantive conclusions from this review is that all studies were observational and most were rated at serious/critical risk of bias [24]. In particular, 88% included participants who began taking anticholinergic drugs before the study period. As such, the ROBINS-I tool rates these study estimates at serious risk of selection bias [24] and therefore a serious overall risk of bias at best. For short-term effects, examining only new users of therapy reduces biases by capturing early events and confounders for prescribing therapy [57]. However the impact of excluding prevalent users on selection bias when examining long-term effects is unclear [58]. The largest threat to study validity is likely residual confounding, given that anticholinergics

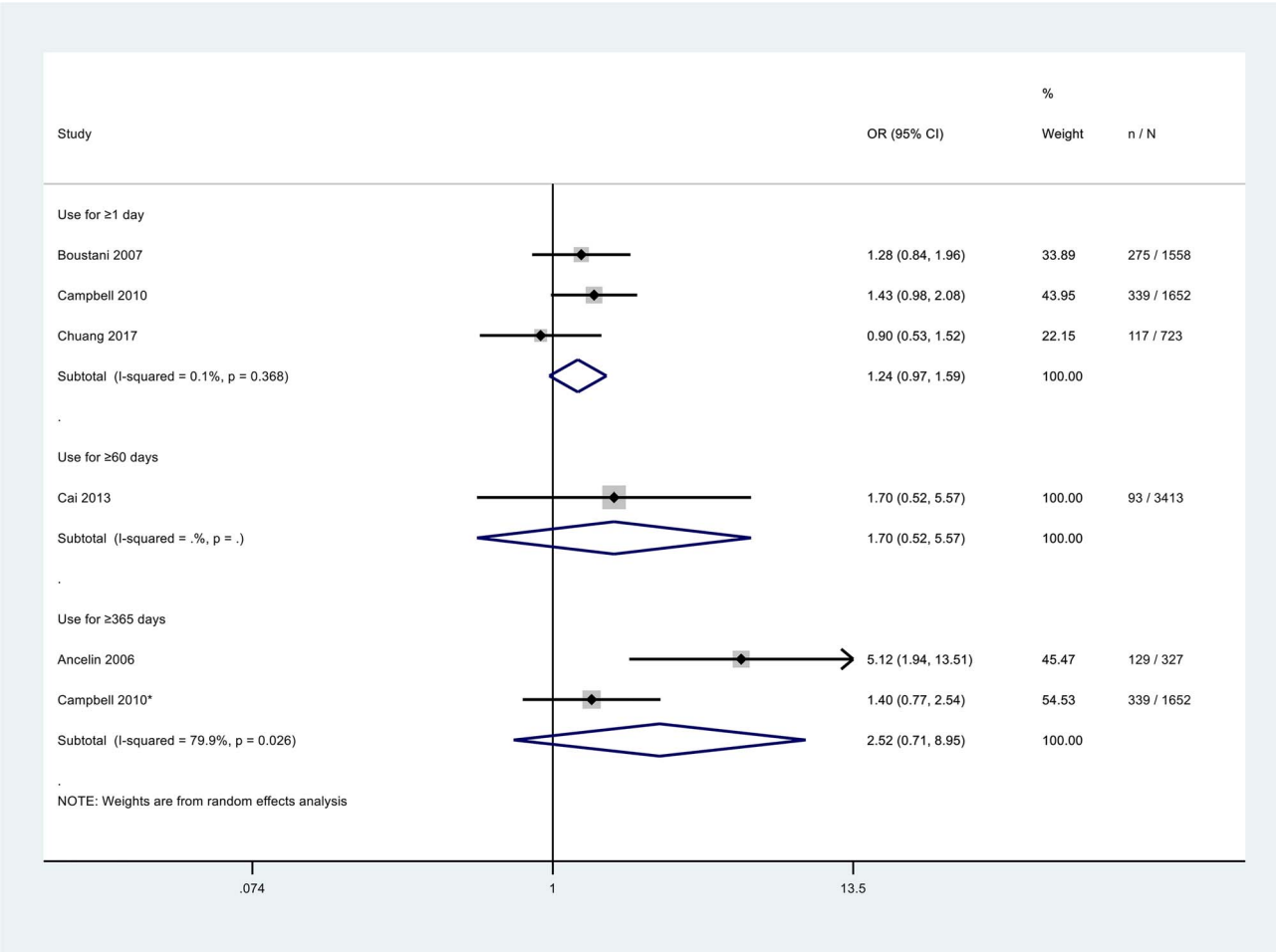

Figure 2. Meta-analysis of odds ratios for mild cognitive impairment by any, at least short-term and long-term definite anticholinergic use versus no use. *Campbell 2010 estimated long-term use (365+ days) as use at all participating waves (baseline, 3-year and 6-year follow-up).

are indicated for conditions also associated with cognitive decline such as depression and Parkinson's disease [59–61]. There may also be residual confounding by frailty, as only one study explicitly adjusted for frailty [40]. Definitions of incident dementia and MCI were generally consistent. Studies varied, however, on how they assessed and reported cognitive function; therefore we could only pool results from six studies. There was moderate risk of exposure misclassification, particularly for studies relying on self-reported use or prescription records. Self-reported use of anticholinergic drug classes has only moderate agreement with pharmacy dispensing records [62]. Publication bias is possible, but difficult to assess owing to the lack of registration requirements for observational studies. Unfortunately, we were unable to pool absolute risks, as only one study provided these [9].

Our findings concur with previous reviews. A previous meta-analysis reported a stronger association between anticholinergic use and incident dementia (OR 1.43; 95% CI 1.16–1.73) but only pooled results from three cohort studies [17]. Whether the observed associations between anticholinergic drug use and dementia is a causal relationship or reflects risk factors or early symptoms of dementia (such as depression or bladder instability) remains unclear from the available evidence. Some studies reported an increasing dementia risk with greater exposure to anticholinergic drugs, consistent with a causal link [9,10,26]. However, few studies excluded drug exposure in the period just prior to dementia [9,10,41], and so drugs may have been prescribed for early symptoms of dementia. Two large UK studies report differences in dementia risk according to anticholinergic drug class, inconsistent with a causal link [9,55].

Mechanistic evidence is limited, although some neuropathological studies in humans and mice support a role of anticholinergics in affecting neurodegenerative pathology [63], and anticholinergic use has been associated with increased brain atrophy and reduced glucose metabolism [64]. Evidence from RCTs on anticholinergic cessation has failed to show improvements in cognition, but has generally been underpowered and has focussed on short-term outcomes [65].

This study adds to the weight of evidence supporting current recommendations that prescribers should be cautious about using medications with anticholinergic activity

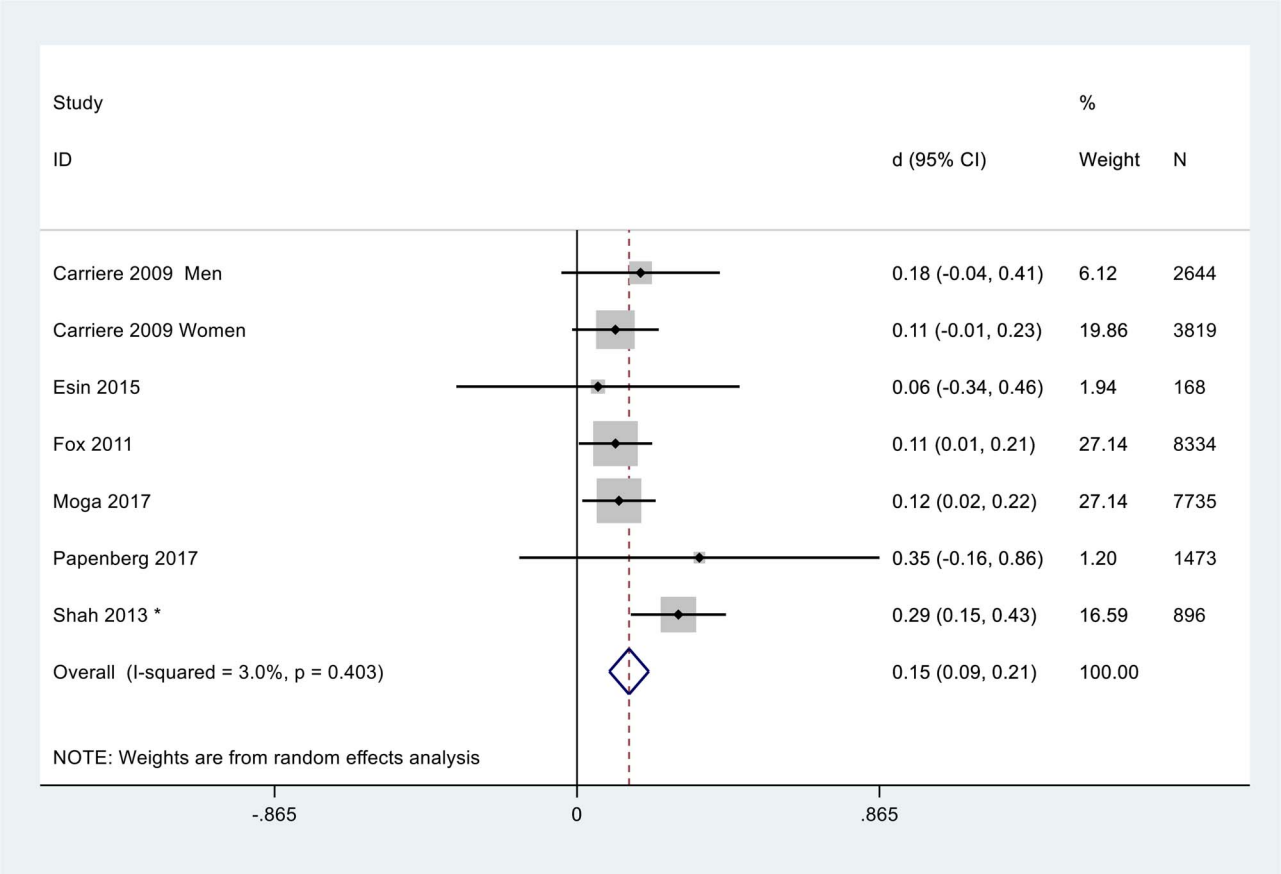

Figure 3. Meta-analysis of standardised mean differences in global cognitive decline by any definite anticholinergic use versus no use. *Standardised mean difference (95% CI) estimated as the inverse variance weighted average of the estimated standardised mean difference for prevalent and incident users. Decline in global cognition was defined as the change in mean z-score across 19 cognitive tests. Abbreviations: *d*, standardised mean difference.

in older people. Prescribers should discuss the risks and benefits of anticholinergic drugs with patients and their carers and consider either avoiding medication or using alternatives where appropriate [66]. However, the current evidence is insufficient to warrant aggressive deprescribing of these drugs due to long-term cognitive effects. Nevertheless, other known effects such as dry mouth and eyes, confusion, constipation and urinary retention remain a concern [58, 59]. Due to our findings of stronger associations with long-term use, clinicians should regularly review and consider stopping anticholinergic drugs if there is no clear evidence of benefit. There is a need for consensus on the management of the long-term use of anticholinergic drugs, particularly on developing clear timeframes regarding proposed durations of use.

The decision to prescribe anticholinergic drugs needs careful weighing up of the risks and benefits, and this review highlights the lack of reliable research evidence on cognitive risks.

Although such evidence will be difficult to obtain, we offer suggestions in Appendix 3. There is also a need to regularly update anticholinergic assessment tools and agree consensus on their ratings. Due to the growing number of assessment tools, we recommend a systematic harmonisation of current tools specifically aimed at examining central anticholinergic effects, taking into consideration blood–brain barrier permeability, to facilitate care and research [67].

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: The authors report no conflicts of interest, except that IDM reports personal fees for guest lectures from Astellas Pharmaceuticals, Y.K.L. reports personal fees from Thame Pharmaceuticals and C.F. reports grants and personal fees from Astellas Pharmaceuticals, and I.D.M., Y.K.L., C.F., C.M.G., G.M.S., N.S., A.J.A., P.K.M., L.R., F.E.M., C.B. and K.R. are co-authors of some studies included in the review.

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