DOI:
10.1007/s00228-021-03089-x

Document Version
Peer reviewed version

European Journal of Clinical Pharmacology

Aspirin in people with dementia, long-term benefits and harms: A systematic review

--Manuscript Draft--

Manuscript Number:	EJCL-D-20-00824R1
Full Title:	Aspirin in people with dementia, long-term benefits and harms: A systematic review
Article Type:	Review
Funding Information:	National Institute of Health Research (Biomedical Research Centre at King's College London and South London and Maudsley NHS Foundation Trust) — Dr Katrina A. S. Davis
Abstract:	Purpose: People with dementia may have indications for aspirin prescription and clinicians are asked to balance the potential risks against benefits. This review examines the evidence for risk and benefit of long-term aspirin use in people with dementia aged over 65 years, including randomised controlled trials and observational studies. Methods: We searched three databases for research published between 2007 to 2019. Each eligible article was assessed for risk of bias, and confidence in findings was rated using Grading of Recommendations Assessment, Development and Evaluation (GRADE). Results: Four papers met inclusion criteria, one randomised controlled trial, two cohort study, and one with pooled data. All looked only at dementia of the Alzheimer's type, and none addressed myocardial or cerebral infarction as outcomes. Dementia progression was reported by two studies, with conflicting results. The trial found no significant effect of aspirin on mortality (odds ratio aspirin vs no aspirin 1.07, 95% confidence interval 0.58-1.97) but found more events of severe bleeding with aspirin (OR aspirin vs no aspirin 6.9, 1.5-31.2). An excess in intracranial haemorrhage in the aspirin group was judged plausible based on two non-randomised studies. Conclusions: The review findings are limited because studies include only people with Alzheimer's type dementia and lack confirmatory studies, although an increased risk of bleeding events is recognised. Further research that addresses the benefits and risks of aspirin in more representative groups of people with dementia is needed to guide prescribing decisions.
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	Aspirin in people with dementia, long-term benefits and harms: A systematic review Katrina AS Davis, Delia Bishara, Mariam Molokhia, Christoph Mueller, Gayan Perera & Robert J Stewart Thank you for considering our review. As per the instruction for authors of unsolicited reviews, we make the following remarks: (i) This is a systematic review carried out in accordance to the PRISMA guidelines; (ii) The objective of the review is to evaluate the evidence regarding the use of aspirin in people with dementia, providing evidence on benefits and harms that would be useful for clinicians and patients in deciding whether to start or stop aspirin in someone with dementia. Previous reviews have covered either the effects of aspirin on the progress of dementia alone, or considered benefits and harms in people without dementia. (iii) We set out our search in a protocol, involving searches for keywords in three key databases. We included both randomised trials and observational studies with robust design. As the characteristics of people with dementia has changed over time, we restricted our search to the last twelve years. Extraction was based around four major outcomes – prevention of cardiovascular events, general health, progress of dementia, and adverse events. Studies were evaluated for risk of bias and findings evaluated for confidence using established tools. (iv) The major limitation of the review for the original purpose is that we found limited evidence, particularly regarding prevention of cardiovascular events and for people with dementia other than Alzheimer's. However, we believe that this is a major finding in itself, considering how frequent this dilemma is in clinical practice, and serves to show how difficult evidence-based prescribing is for people with dementia or multimorbidity in general. Prescribing for people with dementia is more complex than standard single-condition guidelines allow for. We have performed this review, that reminds practitioners that there are different considerations in people with dementia. It shows that there is little evidence about routine use of aspirin in this population, meaning that clinical and patient judgement is key in decision-making, and that it is important to make sure that data on outcomes is utilised to help inform the judgements of the future. We look forwards to hearing from you. Yours sincerely, Katrina AS Davis, on behalf of the authors.
Response to Reviewers:	•The authors thank for the reviewers for their helpful comments. We have updated the the search, and made some other minor changes. Reviewer #1: Comments to the Author Thank you for the opportunity to review the manuscript entitled 'Aspirin in people with dementia, long-term benefits and harms: A systematic review'. I applaud the authors thorough review to specifically examine the evidence for the benefits and risks of aspirin in older adults with dementia. General comments: The abstract and introduction sections provide clear and succinct overviews of the background to this systematic review. However, there are some issues that should be addressed. Page 4, Line 46-59: on the intervention/exposure - why dual antiplatelet therapy was not considered, i.e. aspirin plus clopidogrel? •Response: Since any concomitant medication was allowed, a trial of dual antiplatelet therapy would have been eligible if it could also meet the requirement that the control group had no antiplatelet (see the protocol methods > eligibility > interventions & controls). The reason for this is that aspirin is first-line treatment for prevention of MACE, often prescribed by primary care or generalists, and it was this routine use that we wished to review. The new study that is included in this updated review (Lee et al 2020), for example, finds that in a national database, of the people prescribed any antiplatelet in any combination, 80% are prescribed aspirin alone. Other medications are usually prescribed for specific indications or by specialists, and comparing aspirin to these alternative medications was not within our scope. Page 4, Line 1-15: Major adverse cardiovascular events (MACE) - there exist several definitions re MACE components - including heart failure, unstable angina, etc. - is

there any specific reason for the selection of myocardial infarction, cerebrovascular accident, transient ischemic attack in this review. Also, it is not clearly specified whether the goal is for primary or secondary MACE prevention.
•Response: The definition of MACE in the study was left deliberately loose to allow for inclusion of studies who had defined it in any particular combination. However, in defining individual disorders to extract, it was felt that limiting to three was sensible given the need to balance information with resources.
•Response: In the aims we use the phrase “reduction of MACE”, by which we include both prevention of first and subsequent events. This is stated explicitly in the protocol: “Aim of aspirin must be for primary or secondary prevention” (methods > eligibility > intervention) We would ideally have liked to be able to distinguish efficacy between primary and secondary prevention as part of the clinical factors mentioned in the next line. For clarity I have added this example, so that the text now reads:
•<<We planned to investigate any demographic or clinical featuresthat predict benefit and/or harm, including whether aspirin was for primary or secondary prevention, if suitable evidence was available>>.

On the published Prospero protocol - there was a deviation on the inclusion criteria - "Participants of studies must include a majority of people with a diagnosis of dementia (or any dementia subtype) or a majority of people with a diagnosis of MCI and at least 10% of people with dementia". Actually, there were several changes in this manuscript compared to the published Prospero protocol (particularly re outcome parameters (e.g. drug interaction, falls, fracture etc.) - that would be good if you give a bit of explanation.
•Response: We have provided the protocol, which was lodged with PROSPERO and used by our researchers when selecting and extracting from papers. In order to meet word count requirements for journals and make the paper easier to read, we have reduced detail where it turned out to have little influence on the resultant review. We have also referenced the protocol and included a copy of it for people wanting more detail. We have now made this more explicit with the phrases: “screened abstracts… using the criteria in the protocol.”
•Response: We do however notice that the addition of bleeding as a category of interest was made after the protocol was saved in response to the literature of aspirin use. Therefore we have inserted the sentence:
•<<Given concerns about bleeding events, including intracranial haemorrhage, demonstrated in the literature, bleeding events was added post-protocol as a subject of particular interest>>

Authors could consider updating searches given that the search was conducted until 22/05/2019.
•Response: We have updated the search to 09/11/2020, which has added one paper to the review (Lee et al 2020), and the introduction and discussion were updated where necessary. We have called this a “top-up” search, and it covered papers published between 01/01/2019-09/11/2020 and indexed before 09/11/2020. The PRISMA flowchart in the main text shows both searches combined, but separated numbers are available in the supplementary material. Note that due to constraints of time and clinical commitments during the coronavirus pandemic, only one person was able to screen abstracts for the top-up searches, although there were still discussions between three authors (KD, DB and RS) regarding inclusions.

Lines 6, page 7: please delete 'not'
•Response: Many thanks. We have corrected this typo.

Discussion (paragraph 2, line 28): it would have been good as well if you had an expanded discussion on the prevalent use of aspirin and bias associated with it in the included cohort study, including the different measures used for dementia progression
•Response: We have rewritten this paragraph as follows:
•The difference between the trial findings [28] and the cohort study [29] on dementia progression could be an artefact due to different measures or chance. However an important difference is that the trial excluded anyone with an indication for aspirin, stating that “almost 50% of patients were ineligible, most commonly because of a potential indication for aspirin [secondary prophylaxis after myocardial infarction, unstable angina, or a cerebral transient ischaemic attack]”, which means that although the control group of the trial and cohort studies might be equivalent, the group taking aspirin were different, as the people from the cohort study who happen to be on aspirin

at time of dementia diagnosis can be assumed to have an indication for aspirin, most likely vascular disease. Although the cohort study corrects for vascular disease and cerebrovascular pathology in the analysis, this may not have been sufficient to correct confounding by indication. Second, those who are on aspirin at diagnosis can be assumed to have been taking it beforehand, whereas those in the trial were newly started on aspirin. Aspirin at a pre-clinical stage of dementia and a greater vascular component to the overall clinical condition could plausibly contribute to greater efficacy of aspirin. A possible inference may be that aspirin is unlikely to help when used as primary prevention (as per the trial) but may affect the rate of decline in dementia where it is otherwise indicated (as per the cohort study). This interpretation concurs with recent studies suggesting that aspirin did not appear to reduce the incidence of dementia in people who did not have any other indication for aspirin (Aspirin in Reducing Events in the Elderly Trial, ASPREE)[13]. >>

Discussion (para 2): Also, please include a bit about the effects of aspirin on the incidence of dementia and cognitive decline in older adults (although not your outcome of interest, would give additional perspective to the topic -e.g. findings from the recently published "Aspirin in Reducing Events in the Elderly (ASPREE)" trial)
•Response: We agree that this finding is very pertinent to the interpretation of our results. We mention this in the introduction as the evidence on the lack of efficacy for dementia prevention (even before the cognitive results on ASPREE were published) shaped the aims of our review. We now also mention it in the discussion (i) as above, and (ii) in a later paragraph include reference to the the Beers criteria guidance, which the Beers authors state is as a result of the overall ASPREE findings.
Discussion - given inadequate evidence-based data on the topic, one element that could be added to the discussion is some clinical interpretation of the results - including the use of aspirin for prevention of vascular events, deprescribing and use of aspirin in people with dementia (Limited life expectancy due to comorbidities). For instance, the 2019 updated Beers Criteria recommends extra caution when using aspirin for prevention of Atherosclerotic Cardiovascular Disease (ASCVD) among adults >70 years.
•Response: Thank you for this prompt to say more about the clinical ramifications. Our findings do not fall into the realm where it is possible to make general guidance that would apply to all, but emphasise the importance of making a good individual decision on holistic considerations. We have added a brief word on this:
•<<This review finds that there is no evidence that initiating aspirin in someone with dementia with no vascular risk factors will have benefit, but may cause harm. This accords with the 2019 Beers Criteria of potentially inappropriate medication in older people, which advises “extra caution” in prescribing aspirin to people aged 70 or above for primary prevention.[41] However, there are a number of uncertainties, for instance what to do if someone already has aspirin prescribed or if their dementia has cerebrovascular pathology. Clinical uncertainty also arises because people with dementia present often with complex multimorbidity and polypharmacy.[2] Adopting medication reviews in people with recently-diagnosed dementia would allow for the indications for aspirin to be recorded, letting clinicians evaluate individual risk/benefit profiles and utilise available evidence-based guidance, taking into account patient preferences.[37-39] ”.
Table 1: please include outcome parameters and their definition (e.g. adverse events) for included studies.
•This has been added. Please note that we could not fit this into the existing table, therefore we have inverted the table to better accommodate extra text.

Reviewer #2: This systematic review provides overview of benefits and risks for using aspirin in patients with dementia. It is known from previous publications that there is no evidence to support aspirin use to reduce the risk of onset of dementia in people who are given this treatment prior to diagnosis and in fact that this intervention may be associated with harm. What this systematic review adds is specific consideration of benefit of aspirin in patients with diagnosis of Alzheimer's disease as well as provision of data on adverse events.

It notes that no evidence is available for incidence of major cardiovascular events in the selected studies; there was no significant difference in positive outcomes

	(death/entry into care home and MMSE decline - although cohort study suggested some effect in this area, this evidence was graded as very low in confidence) however there was moderate risk of adverse events including severe bleeding from the RCT data. No data was available on use of gastroprotection in the cohort study nor the dose of aspirin (European doses usually higher than those used in the UK). In terms of clinical application, the systematic review included trials which contained long-term follow up (>2years) which transfers to real life clinical scenarios. The use of data from cohort study adds real life observational information to the conclusion with noted caution about confounding issues (in particular slowing down of progression of dementia). Other confounding factors which may have influenced outcomes - use of donepezil may increase the GI bleed risk as could presence of anticoagulants/SSRIs/steroids and/or absence of gastroprotection. It is hoped that observational studies can be utilised in the future to provide more definitive evidence on the benefits and risk of aspirin in dementia patients. For a practicing clinician performing polypharmacy review, this paper is a reminder that each individual's risk of bleed should be considered alongside decision to continue treatment rather than deprescribe aspirin in dementia patients. •Thank you for this summary. We agree with the clinical implications, and hope these are now incorporated where appropriate minor feedback on language used page 3 line 13 instead of "high" frailty - consider rephrasing to increased levels of •Thank you for the suggestion. Change made. page 3 line 24 instead of "prevention" - consider rephrasing to preventing events in •Thank you for the suggestion. Change made. page 7 line 6 - "not" duplicated - consider rephrasing •Thank you, correction made. page 7 lines 18-24 - consider rephrasing, unclear sentence •Thank you. We have rephrased as follows: “In the risk of bias assessment the study lost three points for lack of clarity over: how the use of aspirin was ascertained; whether assessors were blinded to aspirin usage; and how the analysed sample differed from those who were not followed for two years (Supplementary Table 4, Online Resource).”

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Aspirin in people with dementia, long-term benefits and harms: A systematic review

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Abstract

Purpose: People with dementia may have indications for aspirin prescription and clinicians are asked to balance the potential risks against benefits. This review examines the evidence for risk and benefit of long-term aspirin use in people with dementia aged over 65 years, including randomised controlled trials and observational studies.

Methods: We searched three databases for research published between 2007 to 2019. Each eligible article was assessed for risk of bias, and confidence in findings was rated using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: Four papers met inclusion criteria, one randomised controlled trial, two cohort study, and one with pooled data. All looked only at dementia of the Alzheimer's type, and none addressed myocardial or cerebral infarction as outcomes. Dementia progression was reported by two studies, with conflicting results. The trial found no significant effect of aspirin on mortality (odds ratio aspirin vs no aspirin 1.07, 95% confidence interval 0.58-1.97) but found more events of severe bleeding with aspirin (OR aspirin vs no aspirin 6.9, 1.5-31.2). An excess in intracranial haemorrhage in the aspirin group was judged plausible based on two non-randomised studies.

Conclusions: The review findings are limited because studies include only people with Alzheimer's type dementia and lack confirmatory studies, although an increased risk of bleeding events is recognised. Further research that addresses the benefits and risks of aspirin in more representative groups of people with dementia is needed to guide prescribing decisions.

Keywords

Aspirin; Dementia; Multimorbidity; Systematic Review; Evidence-Based Medicine

Declarations

Funding: National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London

Conflicts of interest/Competing interests: RS declares research funding/support from Janssen, GSK and Takeda in the last 3 years. All other authors declare that they have no conflicts of interests.

Ethics approval: Not applicable

Consent to participation: Not applicable

Consent to publication: Not applicable

Availability of data and material: All data generated or analysed during this study are included in this published article [and its Online Resource supplementary tables]

Code availability: Not applicable

Authors' contributions: Study concept and design - Katrina Davis, Delia Bishara, Mariam Molokhia and Robert Stewart; Literature search – Katrina Davis and Delia Bishara; Analysis and interpretation of data – Katrina Davis and Robert Stewart; Drafting of the manuscript – Katrina Davis; Critical revision of the manuscript for important intellectual content – Katrina Davis, Delia Bishara, Mariam Molokhia, Christoph Mueller, Gayan Perera and Robert Stewart. All authors approved the version to be submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements: This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Title: Aspirin in people with dementia, long-term benefits and harms: A systematic review

1.1

Introduction

More people than ever are living with dementia, and an increasingly recognised challenge is the management of comorbid disorders and risk states [1]. Risks and benefits of any medication may be different in people with dementia due to issues such as altered permeability at the blood-brain barrier, increased levels of frailty and polypharmacy [2, 3] so recommendations for treatment or cessation of treatment (deprescribing) would ideally be made using evidence from people with dementia. The risk of major cardiovascular events (MACE), such as cerebrovascular accidents and myocardial infarctions, is related to many factors that are also risk factors for dementia, including age and cardiovascular disease [4]. The use of aspirin to prevent MACE is well-established, with a reduction of about 25% in MACE regardless of baseline risk, making it a valuable tool in preventing such events in people at high risk of MACE [5, 6] but for people at lower risk the incidence of adverse events may negate any potential benefits [5, 7], with risks such as gastric irritation [8] and intracerebral haemorrhage (ICH) [9]. Studies specifically looking at older people at low or medium risk of MACE have failed to show consistent benefit of aspirin and have shown harm [10, 11] but these studies excluded participants with dementia.

Post-mortem examination of people who have died of dementia in old age typically finds both vascular and inflammatory lesions, regardless of clinical sub-type allocated in life [12]. As aspirin is anti-inflammatory and anti-thrombotic,[6] it has been suggested that it may be useful in preventing or treating such lesions, but large trials and reviews of observational studies suggest aspirin does not prevent dementia [13, 14] nor slow dementia labelled as Alzheimer’s disease type (AD) [15], while there is insufficient evidence on aspirin's effect on progression of vascular dementia.[16, 6] There is no available evidence for other non-steroidal anti-inflammatory drugs or other anti-platelet drugs preventing or treating dementia.[17, 18, 15] Therefore, the main indication for people with dementia to take aspirin is to reduce MACE.

1.2

Aims & Objectives

This systematic review evaluates the evidence for the long-term effectiveness and harm of aspirin, compared to no antiplatelet, for people with dementia aged over 65 years. The primary outcome was reduction of MACE, but we also considered other possible benefits on general health and dementia progression, and possible harms. We considered evidence from observational studies as well as trials since recruitment and follow up can be difficult in people with dementia due to frailty, high mortality, and difficulties maintaining consent [19]. We planned to investigate any demographic or clinical featuresthat predict benefit and/or harm, including whether aspirin was for primary or secondary prevention, if suitable evidence was available.

2.1 Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) main statement and 'harms' checklist [20, 21]. The checklist is available in Supplementary Table S1 (Online Resource). The review protocol is registered at **PROPSERO:** CRD42019144773, a copy of which is available as Supplemental Text (Online Resource) [22].

2.1 Search strategy and selection criteria

Full details of search are in the protocol (Supplemental Text, Online Resource), and summarised here. We searched PubMed (Medline), Web of Science (Embase) and Cochrane trial database using terms 'dementia' and 'aspirin or antiplatelet', as described in the protocol with a time window of 01/01/2007 to 09/11/2020 (main search performed 22/05/2019 and ‘top-up’ search performed 09/11/2020). The results were imported into Endnote and de-duplicated. Forward and back citation searches of included papers and relevant systematic reviews were used. The search start date was chosen to maximise applicability to modern clinical practice, as the nature of dementia cohorts over time and between countries has changed, with a current emphasis on early diagnosis and use of anticholinesterase inhibiting medication [1].

Two investigators (KD, DB) independently screened abstracts (KD only for the ‘top-up’ search) and discussed possible papers for inclusion with another author (RS) using the criteria in the protocol. We included longitudinal controlled studies (trials and observational), but due to the danger of confounding by indication in observational studies, we pre-specified that non-randomised studies must account for vascular risk in the design

or analysis. The target population was people with dementia (all subtypes) where the mean age of the sample was over 65 years. Comorbid disease and other medication use were allowed. The exposure of interest was daily aspirin, whether prevalent or newly initiated (minimum six months). The comparator was no aspirin and no other anti-platelet pharmacological treatment, and allowed for studies of discontinuation (minimum six months). The outcomes had to be reported at a minimum of two years after the start of aspirin or the period of observation. Primary outcomes were:

i) Major cardiovascular events (MACE) or individual myocardial infarction, cerebrovascular accident, transient ischaemic attack

ii) General health outcomes (mortality, hospital admission)

Secondary outcomes were:

iii) Dementia progression (clinical dementia rating or score on cognitive function scale)

iv) Secondary health outcomes (admission to care home, quality of life, falls, fractures, change in frailty, patient-reported outcomes)

Adverse events were counted at any time, and included adverse drug events and drug interactions as counted by the study. Given concerns about bleeding events, including ICH, demonstrated in the literature, bleeding events was added post-protocol as a subject of particular interest.

2.3

Data Extraction and Study Quality

Data from included papers were extracted and risk of bias assessments carried out by KD in discussion with RS. For adverse events, it was pre-specified that all events reported would be extracted, as the designation of 'treatment-related' events may not be consistent across studies. It was pre-specified that randomised controlled trials (RCTs) were assessed for risk of bias using the Cochrane Collaboration tool and all other studies by the Newcastle-Ottowa Quality Assessment Scale. The Cochrane Collaboration tool v2.0[23] has five domains for risk of bias: i) randomisation; ii) deviation from intended interventions; iii) missing outcome data; iv) measurement of outcome; v) selection of reported result. Each of the domains is rated "high risk", "some concerns" and "low risk", with an overall rating of the same. The Newcastle-Ottowa Quality Assessment Scale for cohort studies [24] gives scores in the domains of (i) selection; (ii) comparability; (iii) exposure/outcome, and requires that we pre-define confounders that it would be preferable for studies to control for: we designated vascular risk as the primary, and age and other vascular medications as secondary confounders.

2.4

Data Synthesis

Results were tabulated and plotted, and effect sizes calculated (odds ratio for relative and events per 1,000 for absolute) using Review Manager [25] and GRADE Pro [26], using the default Review Manager handling of zero event cells. We used 95% confidence intervals throughout. Clinical significance was set at an absolute increase or decrease of 10 or more per 1,000.

The strength of the overall evidence for each finding was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [27] giving 'High', 'Moderate', 'Low' and 'Very Low' confidence in findings. Evidence from RCTs starts at "High" and is then downgraded if found to have one of five indicators: i) risk of bias (assessed described in section 2.3), ii) inconsistency (between studies), iii) indirectness (deviation from the population or intervention of the review), iv) imprecision (confidence intervals cross clinical significance line), v) other considerations (including publication bias). Non-randomised studies start "Low" quality, can be downgraded as above, or upgraded in the presence of indicators that increase confidence: (i) large effect size; (ii) remaining confounding could only plausibly reduce effect size / reduce the chance of finding a significant result; (iii) dose-sensitivity.

3.1

Results

From 1074 search results, 95 papers were selected for relevance, and four met eligibility criteria, as shown in Supplementary Table S2 (Online Resource) and Figure 1. Table 1 describes these studies. An RCT named AD2000 from the UK [28] and a cohort study from Italy by Ferrari et al [29] were designed to investigate dementia progression, and AD2000 also included general health outcomes and adverse events. The third and fourth studies only look at risk of ICH, using pooled data from two trials (including AD2000) [30] and a national health registry [31]. All studies included only people with AD subtype of dementia.

Figure 1 PRISMA flow diagram for inclusion in aspirin systematic review

Table 1 Included studies

AD2000 [28] was a multi-site study that recruited 310 people with mild-moderate dementia without a vascular component from memory services in the UK. It was a 2x2 randomised study of donepezil and aspirin. Individuals with an indication for aspirin (cardio- or cerebro-vascular disease) were excluded from the aspirin aspect of the trial. The trial was open-label, with the treatment group advised to take 75mg enteric-coated aspirin and the control group was advised to avoid aspirin. It was not stated whether gastric protection was routinely used. At two years, 44% (33/75) of those allocated to aspirin arm had stopped and 11% (8/72) of those allocated to avoiding aspirin were taking it. In the risk of bias assessment this 'switching' between groups led to concerns in the deviation from intended treatment group category (Supplementary Table S3, Online Resource) with the intention to treat analysis meaning that bias was likely to be in the direction of not finding a true effect; a high loss to follow-up was also noted. Thoonsen et al [30] conducted an individual patient data meta-analysis of 2 trials: AD2000 and Richard et al's trial of enhanced vascular care in 130 people with AD and vascular lesions, where aspirin was not randomised [32].

Ferrari et al [29] was a virtual cohort study from electronic records of a neurology service in Florence consisting of 160 people with AD who had routine mini-mental state assessments (MMSE) recorded two years apart. The study categorised people into fast or slow declining MMSE based on the median MMSE decline of the cohort. Aspirin use was one of a number of predictor variables. The dose of aspirin and use of gastric-protection were not mentioned. In the risk of bias assessment the study lost three points for lack of clarity over: (i) how the use of aspirin was ascertained; (ii) whether assessors were blinded to aspirin usage; and (iii) how the analysed sample differed from those who were not followed for two years (Supplementary Table 4, Online Resource). Ferrari et al examined prevalent aspirin use, whereas AD2000 examined incident aspirin use. Those already taking aspirin in Ferrari et al would likely have been excluded from AD2000, as they likely had indications for aspirin (an exclusion criterion in AD2000). Lee et al [31] reported an observational study using the Taiwanese national population database, examining whether antiplatelets in dementia increase the risk of ICH by comparing those taking aspirin after a dementia diagnosis to matched samples of people without dementia or not taking antiplatelets. On risk of bias assessment, the paper lost only one point, for not adjusting for other medications (Supplementary Table 4, Online Resource).

3.2

Findings

3.2.1

Major cardiovascular events

Not reported in the three papers except for ICH, discussed as an adverse event in section

3.2.2

General health outcomes and secondary health outcomes

The AD2000 trial investigated mortality (primary outcome in this review) and admission to care home (secondary outcome), as shown in Table 2 and Supplementary Figures S1 and S2 (Online Resource). During the first two years of the study, 17% of the cohort died, with deaths being approximately equal in the two arms (odds ratio 1.07 (95% CI 0.58-1.97) for aspirin vs. control). Over the course of the trial, 52% of the surviving participants entered a care home, with no significant difference between the two groups (*hazard* ratio 0.94 (95% CI 0.67-1.31) for aspirin vs. control). The findings of no effect on general health were rated 'Very Low' confidence in Table 2.

Table 2 GRADE table for health outcomes, Aspirin vs. Control

3.2.3

Dementia progression

Table 3 shows two results regarding dementia progression and aspirin, both of which used MMSE to monitor dementia progression over a period of 24 months. The control arm of AD2000 had a mean deterioration of 5.0pt, while the aspirin arm had a mean deterioration of 4.8pt. The mean difference was not significantly different (0.2pt, 95% CI from 2.4 pts worse to 2.6 pts better in aspirin vs. control) as shown in Supplementary Figure S3 (Online Resource). In Ferrari et al, the fully adjusted model found that the odds of someone with AD having a rapid decline of MMSE were lower in the group taking aspirin (OR 0.34, CI95% 0.11-0.88). In Table 3 the GRADE ratio for the finding of no effect from AD2000 was 'Very Low', and the finding of beneficial effect from the Ferrari cohort was also 'Very Low'.

Table 1 GRADE tables for dementia progression, Aspirin vs. Control

3.2.4

Adverse events

The AD2000 trial reported all adverse events in both arms as shown in Table 4 and Supplementary Figure 4 (Online Resource). Significantly more people in the aspirin arm experienced any adverse event (OR 1.89, 1.20-2.97), but not serious adverse events (OR 1.33, 0.84-2.11) or mortality (see 3.2.2). Severe bleeding events (requiring hospital admission or fatal) were significantly more common in the aspirin arm (OR 6.91, 1.53-31.15), including four gastric bleeds in the aspirin arm, and one in the control arm. Thoonsen's pooled analysis shows seven (7/221) ICH in people taking aspirin and none (0/212) in the control group, the equivalent of 30 extra cases per 1,000. This gives a large odds ratio with very wide 95% confidence intervals (OR 14.86, 0.83 to 250.43). The Lee registry study found that having dementia was significantly associated with ICH. Compared with matched controls who had no dementia diagnosis and were not prescribed antiplatelets, individuals with AD not prescribed antiplatelets have a hazard ratio for ICH of 2.02 (1.10-3.72) and individuals with AD who were prescribed aspirin have a hazard ratio for ICH of 2.22 (1.07-4.62). Comparing these two groups suggests an extra risk of ICH of around one case per thousand people with dementia taking aspirin (from 15 less to 20 more). The GRADE ratings for aspirin causing any adverse events and severe bleeding events was 'Moderate' (Table 4), but the GRADE ratings for aspirin not causing a clinically significant increase in serious adverse events and ICH compared to placebo were 'Very Low' since the risk of bias assessment had shown the risk was in the direction of preventing the detection of a real difference between the groups.

Table 2 GRADE table for adverse events, Aspirin vs. control

4.1

Discussion

This review of studies investigating the long-term efficacy and safety of aspirin in people with dementia found four reports, all concentrating on AD dementia. For the primary outcome of MACE, there was no evidence identified. Other efficacy outcomes had evidence, but the confidence in the findings was rated 'Very Low'. A protective effect on dementia progression was seen in a cohort study (Ferrari [29]) of prevalent aspirin use, but not in a trial of aspirin initiation. (AD2000 [28]). The trial also found no significant differences in mortality but an excess of serious bleeding events in the aspirin group.

No clear conclusion can be drawn on the efficacy of aspirin. The difference between the trial findings [28] and the cohort study [29] on dementia progression could be an artefact due to different measures or chance. However an important difference is that the trial excluded anyone with an indication for aspirin, stating that "almost 50% of patients were ineligible, most commonly because of a potential indication for aspirin [secondary prophylaxis after myocardial infarction, unstable angina, or a cerebral transient ischaemic attack]", which means that although the control group of the trial and cohort studies might be equivalent, the group taking aspirin were different, as the people from the cohort study who happen to be on aspirin at time of dementia diagnosis can be assumed to have an indication for aspirin, most likely vascular disease. Although the cohort study corrects for vascular disease and cerebrovascular pathology in the analysis, this may not have been sufficient to correct confounding by indication. Second, those who are on aspirin at diagnosis can be assumed to have been taking it beforehand, whereas those in the trial were newly started on aspirin. Aspirin at a pre-clinical stage of dementia and a greater vascular component to the overall clinical condition could plausibly contribute to greater efficacy of aspirin. A possible inference may be that aspirin is unlikely to help when used as primary prevention (as per the trial) but may affect the rate of decline in dementia where it is otherwise indicated (as per the cohort study). This interpretation concurs with recent studies suggesting that aspirin did not appear to reduce the incidence of dementia in people who did not have any other indication for aspirin (Aspirin in Reducing Events in the Elderly Trial, ASPREE)[13].

The studies in this review involved only people with AD. This may be because aspirin treatment is standard care for those with vascular dementia. However, two studies in vascular dementia from the literature that were not included as they fell outside our search window show conflicting results regarding the potential benefit: an RCT (Meyer et al 1989)[33] found aspirin to be beneficial on cognitive outcomes, but an observational study (Devine and Rands 2003)[34] found no benefit on time-to-death-or-institutionalisation.

For adverse events, mostly we relied on the report of the AD2000 trial[28]. There was evidence that people in the aspirin arm had more adverse events, but not significantly more serious events or deaths. The finding that they had significantly more severe bleeding events is credible because it agrees with other studies of aspirin in older people [11]. A weakness of these studies is the lack of information given about concomitant medication such as proton pump inhibitors, selective serotonin uptake inhibitors and steroids that may have increased or

decreased risk of bleeding [35, 36]. It seems likely that there is a higher risk of intracerebral haemorrhage despite the lack of statistical significance in both studies[9, 30].

This review finds that there is no evidence that initiating aspirin in someone with dementia with no vascular risk factors will have benefit, but may cause harm. This accords with the 2019 Beers Criteria of potentially inappropriate medication in older people, which advises "extra caution" in prescribing aspirin to people aged 70 or above for primary prevention.[37] However, there are a number of uncertainties, for instance what to do if someone already has aspirin prescribed or if their dementia has cerebrovascular pathology. Clinical uncertainty also arises because people with dementia present often with complex multimorbidity and polypharmacy.[2] Adopting medication reviews in people with recently-diagnosed dementia would allow for the indications for aspirin to be recorded, letting clinicians evaluate individual risk/benefit profiles and utilise available evidence-based guidance, taking into account patient preferences.[38-40] It may not be ethical or practical to randomise people with dementia with indications for aspirin to a placebo-controlled trial, but observational studies may be able to leverage variation in treatment as a "natural experiment" to obtain real-world data [20] and close this knowledge gap.

4.1.1

Strengths and Limitations

To our knowledge, this is the first review of the use of aspirin in dementia that has included observational data, potentially adding real-world evidence. We have tried to address possible weaknesses in observational studies by requiring longitudinal data with a control arm and correction for the main indicator/confounder, vascular risk.

A limitation is that there were few studies to review, partially due to search criteria that aimed to maximise the applicability of any findings to the current clinical dilemma and restricted to published data. The studies that we found varied in quality and all had at least one potential item of concern on risk of bias assessment. We were only able to study AD and were unable to find any data on MACE. We were unable to further examine data for characteristics that may predict benefit and harm. Lastly, we looked only at aspirin, whereas other antiplatelet medications may have clinically relevant differences.

4.2

Conclusions

There are inadequate data available to make an informed recommendation regarding the prescribing or deprescription of aspirin in dementia, except to say it is likely that there is an increased risk of clinically important bleeding events in individuals with AD receiving aspirin. Given the established efficacy for preventing MACE in people with high vascular risk, clinicians are likely to continue considering aspirin for those with dementia and comorbidities. The outcomes of these decisions, captured in electronic health records should be used for creating more applicable evidence through well-designed observational studies to help ensure that people with dementia get the most appropriate treatment.

Acknowledgements

This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. MM is supported by the National Institute for Health Research Biomedical Research Center at Guy's and St Thomas' National Health Service Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Authors' contributions: Study concept and design - Katrina Davis, Delia Bishara, Mariam Molokhia and Robert Stewart; Literature search – Katrina Davis and Delia Bishara; Analysis and interpretation of data – Katrina Davis and Robert Stewart; Drafting of the manuscript – Katrina Davis; Critical revision of the manuscript for important intellectual content – Katrina Davis, Delia Bishara, Mariam Molokhia, Christoph Mueller, Gayan Perera and Robert Stewart. All authors approved the version to be submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables for inclusion:

Table 1: Included studies

Table 2: GRADE table for general health outcome, aspirin vs. control

Table 3: GRADE tables for dementia progression, aspirin vs. control

Table 4: GRADE table for adverse events, aspirin vs. control

Figure for inclusion:

Figure 1: PRISMA flow diagram for inclusion in aspirin systematic review

Supplementary material for Online Resource:

Supplemental text, supplemental figures S1-S4, supplemental tables S1-S4

Table 1 Included studies

Main paper	A.D. Collaborative Group 2008	Thoonsen 2010	Ferrari 2018	Lee 2020
Study type	AD2000 trial Open label RCT 2x2 arms	Non-randomised data analysis from two trials (AD2000 and Richard)	Virtual cohort	Virtual cohort
Population	Multi-centre trial recruited from memory clinics in the UK for a trial of donepezil and aspirin. Likely AD, with or without vascular component. Community-dwelling with a proxy informant. No indications for aspirin nor contraindications.	331 people from AD2000 trial and 123 from Richard et al 2009[28], a trial of enhanced vascular care for people with mild AD with vascular lesions on MRI	Patients with probable AD, or with possible AD with positive AD biomarkers, seen between 2009 and 2012 in neurology clinic. Required at least 2y follow-up and genetic testing for ApoE	Taiwan National Health Insurance Research Database, people with AD identified through diagnosis code or prescription, based on a random extract from the full database.
Age	<60y, 5%; 60-69, 19%; 70-79, 51%; >80y, 25% median 74y	74y AD2000, 76y Richard	mean 76y 38% <66y	>65y, 93% in antiplatelet group, 85% in no antiplatelet group
Cardiovascular risk profile	Excluded those with indications for aspirin, which included hx of myocardial infarction, unstable angina, cerebrovascular accident or transient ischaemic attack.	AD2000: Excluded those with indications for aspirin. Richard: Not an exclusion. Required white matter lesion/s of vascular origin	All included. Vascular diseases were ascertained from medical documentation and testing done during assessment	Vascular risk factors extracted from claims history and used to create propensity score.
Dementia subtype Dementia severity	Alzheimer's Dementia Mild-moderate	Alzheimer's Dementia Mild-moderate	Alzheimer's Dementia Any (average MMSE 22)	Alzheimer's Dementia Any (first recorded dementia event)

Intervention (n, %) Control (n, %)	Aspirin (156, 50%) Avoid aspirin (154, 50%)	Aspirin (156 + 65, 51%) Control (154 + 58, 49%)	Aspirin (73, 46%) No aspirin (87, 54%)	Antiplatelet (including aspirin 100mg+) prescribed for >3 months: 824 (with subgroup aspirin = 656) No more than one-off antiplatelet prescription after first dementia event: 824 matched
Length of intervention Background treatment	3 years (but sample size reduces after 1 year) Approximately half were also randomised to take donepezil	Mean time of follow-up: 29 months (AD2000), 22 months (Richard) Donepezil by around 50% (AD2000), 20% (Richard)	Prevalent use of aspirin (length unspecified); Any allowed. Around 27% on statins, 44% on AChEI and 29% on Memantine	Prevalent or incident aspirin, for mean 22 months. Follow-up up to 12 years. Mean 4.8y. Any treatment except anti-coagulants allowed.
Outcomes extracted (i-iv from methods)	Mortality: ascertained through follow-up and national records (24 months) Cognition: change in MMSE ascertained during follow-up assessments (36 months) Care-home entry: ascertained through follow-up (36 months) Adverse events: multiple side-effects elicited by follow-up interviews and investigation of any hospitalisation or death (severe / severe bleeding)	Adverse: Intracranial haemorrhage – ascertainment in AD2000 as for that cohort, unspecified for Richard	Cognition: 'Fast decline' classified through routine administration of MMSE at least 2y apart. Fast decline if faster than median decline ≥4pts in 24 months (24 months)	Adverse: Intracranial haemorrhage – ascertained through routine reporting in national insurance database

2 Abbreviations: AD = dementia in Alzheimer disease; MMSE = mini-mental state exam out of 30; RCT = Randomised controlled trial

Table 2 GRADE table for health outcomes, Aspirin vs. Control

Certainty assessment							№ of patients		Effect of aspirin vs control			Confidence in efficacy statement
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Aspirin**	**Avoid aspirin**	**Relative (95% CI)**	**Absolute (95% CI)**	**Efficacy statement**	
Deaths (follow up: mean 24 months)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	26/150 (17.3% mortality)	24/147 (16.3% mortality)	**OR 1.07** (0.58 to 1.97)	**9 more deaths per 1,000** (from 62 fewer to 114 more)	Aspirin has no significant effect on deaths	⨁◯◯◯ VERY LOW
Entry into care home (follow up: mean 36 months)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	156	154 52.0% care home entry	**HR 0.94** (0.67 to 1.31)	**22 fewer entry per 1,000** (from 132 fewer to 98 more)	Aspirin has no significant effect on entry into care home	⨁◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

[a] Cochrane risk of bias tool highlighted risk from deviation from intended treatment (includes lack of blinding) and missingness

[b] Includes only those with Alzheimer's disease and without high vascular risk

[c] Confidence interval crosses lines of clinical importance on both benefit and harm

Table 3 GRADE tables for dementia progression, Aspirin vs. Control

Certainty assessment							№ of patients		Effect of aspirin vs control			Confidence in efficacy statement
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**aspirin**	**no aspirin**	**Relative (95% CI)**	**Absolute (95% CI)**	**Efficacy statement**	
MMSE decline (follow up: mean 24 months)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	inconsistency with below	83 4.8pt decline	86 5.0pt decline	-	**MD 0.2 pts less decline** (2.4 more to 2.6 less)	Aspirin has no significant effect on MMSE decline	⨁◯◯◯ VERY LOW
Rapid MMSE decline (follow up: mean 24 months; assessed with: Above median decline of 2pts in first year and 4pts in two years)												
1	observational studies	serious[d]	not serious	serious[e]	not serious	strong association; inconsistency with above	73 adjusted model	87 adjusted model	**OR 0.34** (0.11 to 0.88)	**262 fewer rapid decliners per 1,000** (from 31 fewer to 458 fewer)	Aspirin protects against rapid MMSE decline	⨁◯◯◯ VERY LOW

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

[a] Cochrane risk of bias tool highlighted risk from deviation from intended treatment (includes lack of blinding) and missingness

[b] Includes only those with Alzheimer's disease and without high vascular risk

[c] Although this measure of difference does not have pre-specified line of clinical effect, authors considered that >2.5pt difference on MMSE was significant, and therefore this was imprecise.

[d] Newcastle Ottowa assessment scale highlighted concern re ascertainment of exposure, no detail on those followed up vs. not followed up and no mention of assessor blinding

[e] Includes only those with Alzheimer's disease who were followed up

Table 4 GRADE table for adverse events, Aspirin vs. control

Certainty assessment							№ events / patients (% experienced)		Effect of aspirin vs control			Confidence in efficacy statement
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Aspirin**	**No aspirin**	**Relative (95% CI)**	**Absolute (95% CI)**	**Efficacy statement**	
Adverse events - Any												
1	RCT	not serious[a]	not serious	serious[b]	not serious	none	82/156 (52.6%)	57/154 (37.0%)	**OR 1.89** (1.20 to 2.97)	**156 more per 1,000** (from 43 more to 266 more)	Aspirin increases risk of adverse events	⊕⊕⊕◯ MODERATE
Adverse events - Serious												
1	RCT	serious[a]	not serious	serious[b]	very serious[c]	none	63/156 (40.4%)	52/154 (33.8%)	**OR 1.33** (0.84 to 2.11)	**66 more per 1,000** (from 38 fewer to 181 more)	Aspirin has no significant effect on the risk of serious adverse events	⊕◯◯◯ VERY LOW
Adverse events - Severe bleeding												
1	RCT	not serious[a]	not serious	serious[b]	not serious	none	13/156 (8.3%)	2/154 (1.3%)	**OR 6.91** (1.53 to 31.15)	**70 more per 1,000** (from 7 more to 278 more)	Aspirin increases risk for severe bleeding	⊕⊕⊕◯ MODERATE
Adverse events - Intracranial haemorrhage												
3[d]	Non-RCT	serious[d]	not serious	serious[e]	not applicable[f]	none	**Pooled data** from trials: Aspirin group 7/221 (3.2%), Control group 0/212 (0%). OR 14.86 (0.83 to 250.43) 30 more per 1,000 (0.2 less to 353 more)[g] **Registry data** (after adjustments and competing risk correction):				Aspirin has no statistically significant effect on risk of intra-cranial haemorrhage	⊕◯◯◯ VERY LOW

							Compared to no dementia/no aspirin -- Aspirin group HR 2.22 (1.07-4.62), Control group HR 2.02 (1.10-3.72) Est. numbers of ICH – Aspirin 9 (4-19) /3476 person-years, control group 11 (6-20) /4452 person-years Est. absolute difference – 1 more per 1,000 people (15 less to 20 more)		

CI: Confidence interval; **OR:** Odds ratio

Explanations

[a] Cochrane risk of bias tool highlighted high levels of deviation from intended treatment (decreases confidence in null findings but not positive findings as intention-to-treat analysis used)

[b] Includes only those with Alzheimer's disease and without high vascular risk

[c] Confidence interval crosses lines of clinical importance on both benefit and harm

[d] Includes: Pooled randomised and non-randomised data (Thoonsen et al), primarily randomised from AD2000 (risk of bias felt possible from deviation from intended treatment) and Registry study (Lee et al, observational but low formal risk of bias)

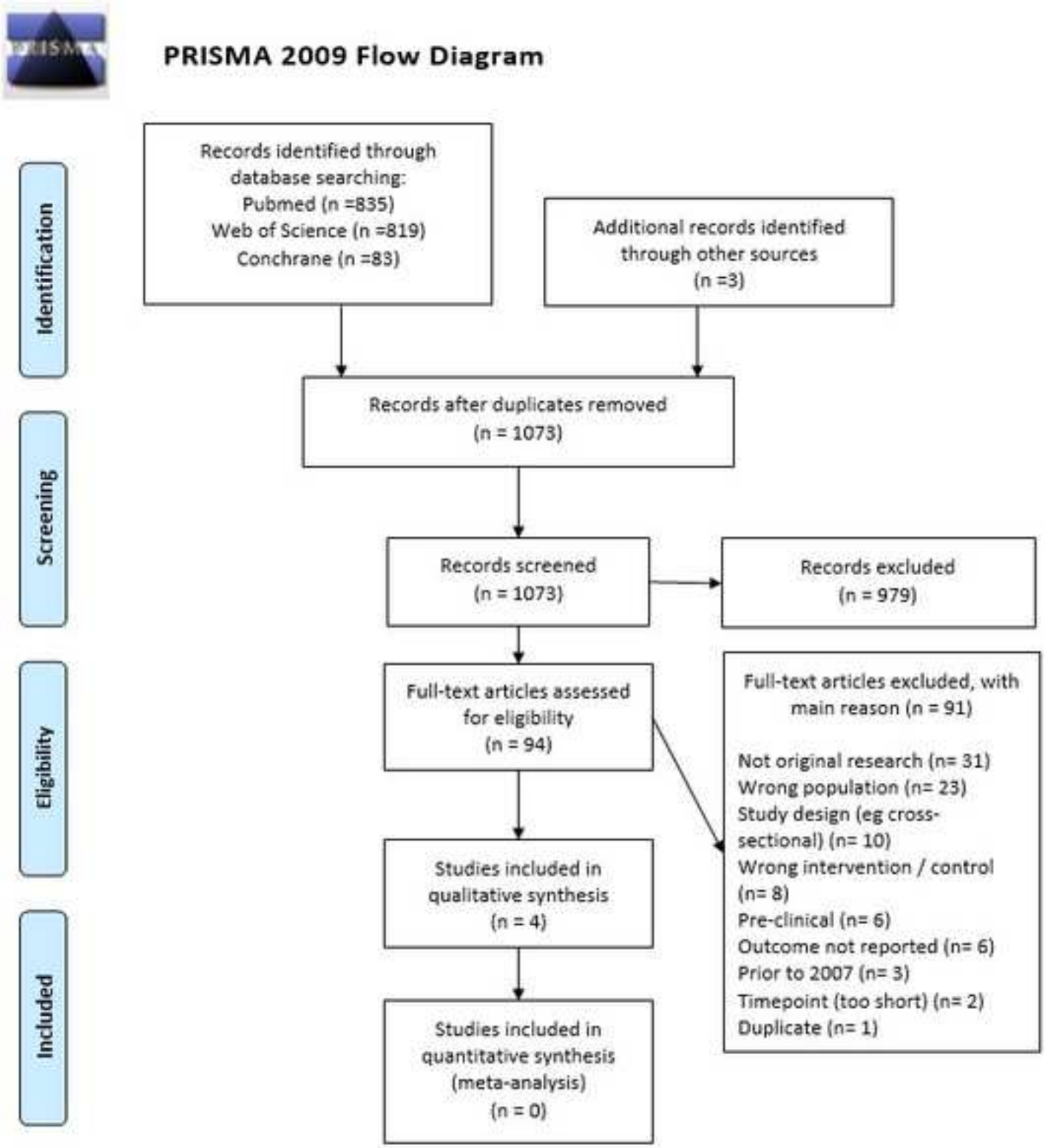
[e] Includes only those with Alzheimer's disease

[f] Studies are not combined, however it is noted that estimates from one study crosses the line of clinically significant harm, and the other study crosses the lines of both significant harm and significant benefit.

[g] Effect rare, and calculation of absolute effect confidence intervals are based on estimates of background rate based on 1:1000 over 2y.

[f] As calculated by Cochrane Review Manager

Figure



Figure