


# BMJ Open Effect of antiamyloid- $\beta$ drugs on Alzheimer's disease: study protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Alzheimer's disease (AD) is a neurodegenerative disease with a complex aetiology involving multiple targets and pathways. With the continuous growth of the ageing population, the burden of AD is increasing year by year. However, there has not been new drug approved for over a decade. In addition, the efficacy of memantine and cholinesterase inhibitors is not satisfactory. As amyloid- $\beta$  (A $\beta$ ) is regarded as the core pathological change and the trigger mechanism of AD, anti-A $\beta$  therapy may be an effective therapy. In recent years, a lot of clinical trials have been carried out in this field, but the results have not been well summarised and analysed.

**Methods and analysis** In this study, we will study the effect of anti-A $\beta$  antibodies versus placebo on the clinical efficacy, biomarkers, neuroimaging and safety in different stages of AD, as well as the factors that may affect the efficacy. Drugs that only target the existing A $\beta$  are regarded as anti-A $\beta$  antibodies. Following electronic databases will be searched from inception to April 2021: Medline-Ovid, EMBase-Ovid, Cochrane Central and clinical trial registration platform ClinicalTrials.gov. After identifying eligible studies through screening title, abstract and read full text of each retrieved literature, we will contact the correspondence authors for additional information and grey literatures. To get more reliable results, random effect model will be conducted for meta-analysis and analysis of subgroups or subsets. Funnel plot, Egger's test and sensitivity analysis will be conducted to explore potential heterogeneity. Meta-regression will be conducted to identify the factors that may affect clinical efficacy. Evidence quality assessment and trial sequential analysis will be conducted to assess the quality of evidence and confirm the reliability of the results in this study.

**Ethics and discussion** This study does not require formal ethical approval. The findings will be submitted to a peer-review journal.

**PROSPERO registration number** CRD42020202370.

## INTRODUCTION

With the continuous growth of the ageing population, the burden of Alzheimer's disease (AD) is increasing year by year.<sup>1</sup> It was estimated that there were over 50 million people living with dementia globally in 2019, and this population will increase to 152 million by 2050.<sup>2</sup> AD is estimated to cause a

## Strengths and limitations of this study

- This systematic review and meta-analysis will determine the effect of antiamyloid- $\beta$  drugs on Alzheimer's disease by evaluating clinical efficacy, biomarkers, neuroimaging and safety.
- The Grades of Recommendation, Assessment, Development and Evaluation, meta-regression and trial sequential analysis will be performed in this study.
- One limitation of this study is that language bias may exist as we will only search electronic databases of literatures and clinical trials published in English which may lead to some missing studies published in other languages.

huge economic burden of US\$2.54 trillion in 2030, and US\$9.12 trillion in 2050.<sup>3</sup> This heavy burden raises a serious challenge to the treatment of AD.

As a neurodegenerative disorder, AD is characterised by progressive cognitive impairment, especially in memory, and functional dysfunction. It has been more than 100 years since Alois Alzheimer reported the first patient with AD in 1906.<sup>4</sup> However, the key factors that can prevent or even reverse disease progression through targeted intervention have not yet been confirmed.<sup>5</sup> Scientists have proposed a variety of hypotheses for the pathogenesis and progression of AD, including hypotheses of two core pathological features: the formation of amyloid- $\beta$  (A $\beta$ ) plaques<sup>6</sup> and neurofibrillary tangles.<sup>7</sup> Other neuropathological changes, such as neurotransmitter imbalance,<sup>8</sup> blood-brain barrier disruption,<sup>9</sup> neuroinflammation<sup>10</sup> have also been proposed as possible pathogenesis hypotheses. Many risk factors which may lead to a higher risk of AD, like smoking, physical and mental exercise, have been identified through cohort studies.<sup>11</sup> However, neither the drugs associated with the pathogenesis hypotheses nor the prevention of the risk factors can inhibit the progression of AD. So far, five drugs have been approved by the Food and Drug



Administration for the treatment of AD: one N-methyl-D-aspartic acid receptor antagonist (memantine) and four cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine). Though they have been approved for AD treatment for decades, their benefit is unsatisfactory.<sup>12</sup> Since 2003, no new drugs have ever been approved with exact benefit for AD. Hundreds of pharmacological agents have been put into basic and clinical studies, but none of them achieved success until now.<sup>5</sup>

A $\beta$  is considered as the core pathological feature of AD since it was identified in 1984.<sup>6</sup> The diagnostic criteria of AD have been constantly changing, but A $\beta$  is always one of the core criteria.<sup>13 14</sup> Though some cases have suggested that neurofibrillary tangles of hyperphosphorylated tau may play a more important role in the progression of AD,<sup>15</sup> A $\beta$  is still recognised as the trigger mechanism.<sup>16</sup> Thus, the number of anti-A $\beta$  drugs and related studies is still the largest.<sup>5</sup> Scientists have designed drugs targeting the different stages of A $\beta$  metabolism and put them into basic research and clinical trials, including immunotherapies, antiaggregation agents, agents increasing clearance and anti-secretase agents.<sup>5</sup> However, most of the previous clinical trials reported that anti-A $\beta$  drugs could not improve cognitive function of AD patients significantly, while A $\beta$  deposition was reduced.<sup>17–19</sup> This result may indicate that anti-A $\beta$  therapy is ineffective, but it may also be related to the insufficient sample size, the stage of AD, the treatment duration, the administration of the drug, the insufficient dosage.

Among all kinds of anti-A $\beta$  drugs, antibodies targeting the existed A $\beta$  is mostly studied. In this systematic review, drugs targeting the existed A $\beta$ , which include A $\beta$  monoclonal antibodies, metal protein-attenuating compounds, etc will be regarded as ‘A $\beta$  antibodies’. Previous systematic review has also summarised this field in this way.<sup>20</sup> Since 2003, antibodies against A $\beta$  have shown the potential to slow cognitive decline among patients with AD.<sup>21</sup> Although the results of clinical trials in the following years mostly indicated that this direction might be hopeless, the report from Biogen and Eisai on the efficacy of aducanumab’s positive results in 2019 aroused people’s confidence again. Therefore, it is necessary to conduct a systematic review and meta-analysis to summarise the clinical effect of this kind of therapy, reveal the key factors that may affect the efficacy, and provide possible directions for further clinical trials and clinical practice. Previous systematic reviews were either out of date and insufficient in included literature<sup>22</sup> or biased from including clinical trials with different drug types.<sup>23</sup> What’s more, none of them has conducted a meta-regression to analyse the possible key factors that may affect the results.<sup>23</sup> A new, comprehensive and in-depth systematic review is necessary.

## Objectives

We are conducting this systematic review and meta-analysis to determine the clinical efficacy on cognitive function, changes of biomarkers and neuroimaging, and

safety of anti-A $\beta$  antibodies versus placebo. Furthermore, we will also identify the potential key factors that may affect the efficacy by using meta-regression, and confirm the reliability of the results by using trial sequential analysis (TSA).

## METHODS AND ANALYSIS

### Study guidelines and registration

This protocol for the systematic review and meta-analysis follows the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol (PRISMA-P)<sup>24</sup> statement. The systematic review and meta-analysis will be conducted following the Cochrane Handbook<sup>25</sup> and reported following the PRISMA statement.<sup>26</sup> We plan to conduct this study from April 2021 to December 2021. Amendments to PROSPERO registration information are listed as online supplemental table 1.

### Search strategy

We will search the following electronic databases from inception to April 2021 for published literatures: Medline-Ovid, EMBase-Ovid and Cochrane Central. Additional studies will be searched through ClinicalTrials registration platform for missing studies and unpublished or ongoing clinical trials. We will also check the reference lists of each literature that enters the full text screening and each review article in this field. After data extraction, we will ask the corresponding authors of the included literatures for more grey literature to avoid potential missing. The search strategy for EMBase-Ovid is presented as [table 1](#).

### Eligibility criteria

Studies will be included in the systematic review and meta-analysis following the below criteria: (1) Patients: The patients enrolled in the original clinical trials should be diagnosed with AD according to a clearly reported diagnostic criteria. All stages of AD will be accepted as long as there are clear descriptions in the literatures. Demographic indicators, including gender, age, education level, combined medication and so on, are not restricted in this systematic review.

1. Intervention: The intervention in the experimental group should be A $\beta$  antibodies, including A $\beta$  monoclonal antibodies, that target A $\beta$  but not any other pathological products of AD. Thus, drugs such as immunoglobulin will be excluded. There are no restrictions on the drug administration, treatment period and dosage.
2. Control: In each original study, the control group and the experimental group should have comparable baseline demographic characteristics. Subjects should receive placebo only, with the same administration way and frequency as experimental group. The placebo can be normal saline or other compounds, but must be described clearly.

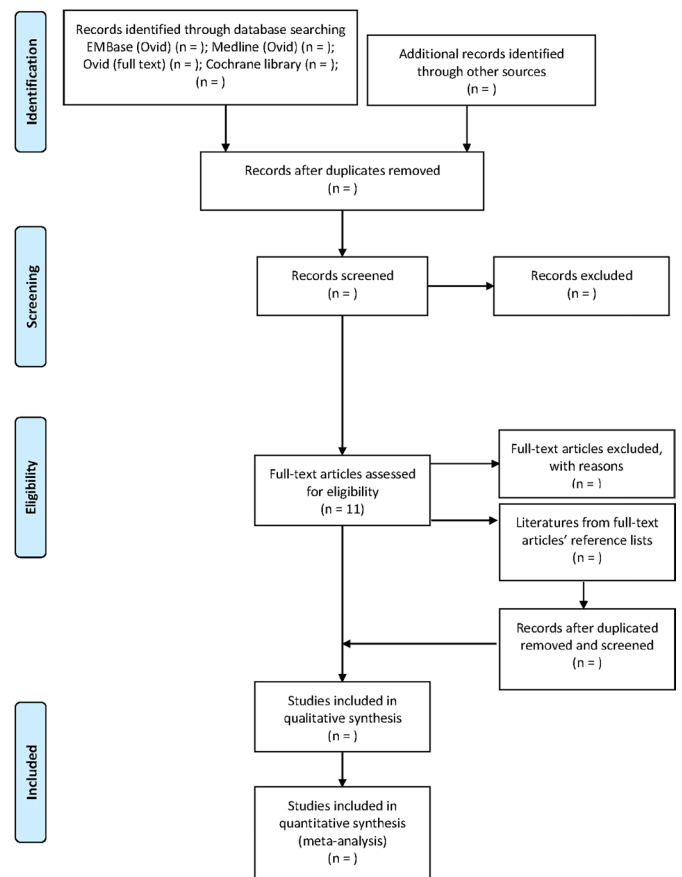
**Table 1** Search strategy for EMBase-Ovid

Search	Query
#1	exp dementia/
#2	exp alzheimer disease/
#3	(alzheimer* or dement* or AD). ti,ab,kw.
#4	((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorate* or degenerate* or complain* or disturb* or disorder*)). ti,ab,kw.
#5	(forgetful* or confused or confusion). ti,ab,kw.
#6	#1 or #2 or #3 or #4 or #5
#7	(abeta* or ab42 or ab40 or 'amyloid- beta*' or 'beta-amyloid*' or 'a?42' or 'a?40' or 'a beta').ti,ab,kw.
#8	(anti-ab* or anti-amyloid*).ti,ab,kw.
#9	#7 or #8
#10	exp randomized controlled trial/
#11	(clinical and trial*).ti,ab,kw
#12	exp clinical trial/
#13	random*.ti,ab,kw.
#14	('drug therapy' or 'therapeutic use' or placebo).ti,ab,kw.
#15	#10 or #11 or #12 or #13 or #14
#16	#6 and #9 and #15
#17	(animals not (humans and animals)). sh
#18	#16 not #17

- Outcomes: The primary outcomes will be Alzheimer's Disease Assessment Scale-Cognitive section<sup>27</sup> and Clinical Dementia Rating-Sum of boxes<sup>28</sup> to evaluate the clinical effect on cognitive function. Other scales on cognitive function including Mini-Mental State Examination (MMSE)<sup>29</sup> will be regarded as secondary outcomes. Biomarkers changes (A $\beta$  and tau in plasma or cerebrospinal fluid, etc), neuroimaging changes (standard uptake value ratio measured by positron emission tomography and brain volume measured by MRI, etc), safety indexes (adverse events, death and amyloid-related imaging abnormalities, etc) will also be included as secondary outcomes.
- Study design: Only randomised controlled trials (RCTs) will be included. Non-RCTs, quasi-RCTs and any other types of studies will be excluded. Studies with 'RCT' in the title but not in practice will also be excluded after verification.

### Study selection

Two independent reviewers (DL and YS) will screen the titles and abstracts of hit literatures from each electronic database after removing duplications with EndNote X9



**Figure 1** The PRISMA flow diagram of this systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

software. They will exclude literatures that are obviously inconsistent with the established criteria individually. After that, they will read the full text of the existing literatures and further exclude those that do not meet the criteria and record the reasons for each exclusion individually. An independent reviewer (XL) will solve the disagreement between the two reviewers when screening and selecting literatures according to the criteria. Any disagreement will be recorded with detailed reason as well. Details of the entire selection procedure will be presented as a PRISMA flow diagram (figure 1).

### Data extraction

Two independent reviewers (DL and YS) will extract the required information and data individually with Microsoft Excel software. Required information includes demographic data, disease stage and treatment at baseline, diagnostic criteria and inclusion/exclusion criteria, primary and secondary outcome indicators, drugs used, usage and dosage, etc. Information about study design will also be recorded for the next step quality assessment. Result data will be recorded as mean $\pm$ SD and group number for continuous variable, and group number with percentage for discrete variable. The above data will be verified by comparing the records of the two reviewers. All missing information and missing data will be obtained

**Table 2** Data and information extraction schedule

Subject	Content
Publication information	Name of the first author and correspondence author, contact email, publish year, country, corporate sponsorship, percentage of authors from sponsoring company.
Participant	Source, sample size, age, sex, height and weight or body mass index, education, human race, diagnose criteria, stage of disease, time since first symptom and since first diagnose, family history, inclusion and exclusion criteria.
Intervention	Drug name, administration, dosage and usage, frequency of the treatment and the total course.
Control	Choice of placebo, administration, dosage and usage, frequency of the treatment and the total course.
Outcome	Primary and secondary outcome measurements and each assessment time points, cognitive or biomarker endpoints, adverse events and the detailed information (eg, means with SD or counts with percentages).
Study design	Clinical trial phase, study duration, treatment and follow-up course, study sites, the application of randomisation and blinding, Description about statistical analysis, sample size calculation.
Other information	Attendance rate, reasons for withdrawing, combined treatment of AD, no of antibody responders.

AD, Alzheimer's disease.

by email from the corresponding authors of the literatures when necessary. Detailed list of information and data to be extracted is presented as [table 2](#).

### Quality assessment

We will assess the methodological quality of eligible studies with risk of bias tool V.2 (RoB2), which is the revised Cochrane RoB tool for randomised trials.<sup>30</sup> For this tool is still not available in the latest RevMan V.5.4.1 software, we will use the version based on Excel which is officially released by Cochrane Collaboration. What's more, RoB2 tool presents only five domains of RoB<sup>30</sup> while RoB tool presents seven domains.<sup>31</sup> Thus, we will also provide the assessment conducted with RoB tool as supplementary material. We will assess the following aspects with the guidance of Cochrane Handbook<sup>25</sup>: randomisation, allocation, blinding, data collection and statistical analysis, outcome reporting. For missing information, we will send email to the correspondence authors. In order to further verify the reliability of the information from original literatures, we will obtain their registration information from the clinical trial registration platform if available, and compare it with the information reported in the literature, and significant inconsistency will be considered to be 'high RoB'. For those launched after September 2005 and not registered,<sup>32</sup> any missing information will be considered to be 'high RoB'.

### Qualitative and quantitative synthesis

#### Qualitative synthesis

First of all, we will make a summary table to present the characteristics of all the included studies, including the year of publication, demographic characteristics of their included subjects, clinical trial phase, study design, outcome indicators, etc. Then, we will describe and summarise the results and study designs of studies included in each outcome to make a general summary.

#### Quantitative synthesis

After that, we will conduct a quantitative analysis for each outcome. Outcomes with complete data will be quantitatively synthesised with RevMan V.5.4.1. For continuous variables, mean difference or standard mean difference will be calculated with 95% CI; for dichotomous variables, such as adverse event or death, we will calculate risk ratio or OR with 95% CI. We will calculate  $I^2$  to test heterogeneity for each pooled result. Considering that  $I^2$  can only reflect bias from pooled data, and methodological bias may be difficult to detect, we will apply random effect model for all comparisons to obtain more conservative and reliable results regardless of the value of  $I^2$ . Certainly, we will apply analysis of subgroups or subsets and meta-regression to identify potential factors that may lead to a huge heterogeneity, or a high value of  $I^2$ . For those pooled estimations with a  $I^2$  value more than 90%, and the heterogeneity is unable to be explained with the results of analysis of subgroups or subsets or meta-regression, we will present forest plots without pooled estimation.

#### Analysis of subgroups or subsets

We will further analyse and explain the results with analysis of subgroups or subsets. Data from different phase of clinical trials (eg, phase I or phase II/III), different administration (eg, intravenous infusion or oral administration), different AD stages (mild, moderate or severe AD), etc, will be analysed separately.

#### Sensitivity analysis

After analysis of subgroups or subsets, we will conduct a sensitivity analysis by excluding studies one by one to observe whether the pooled estimations are stable or not. Significant changes may indicate significant heterogeneity among studies. Sometimes, such heterogeneity may exist among studies with different sample sizes.



### Assessment of publication bias

We will apply funnel plot to detect potential reporting bias while no less than 10 original studies are pooled in a meta-analysis.<sup>33</sup> For continuous variables, we will also apply Egger's test for funnel plot asymmetry. We will analyse the possible reason and give interpretation for possible publication bias.

### Meta-regression

To identify potential factors that may affect the efficacy, we will perform a meta-regression. In this step, following factors will be selected: age, AD stage, APOE genotype, baseline MMSE score, the application of other therapeutic drugs, dosage and administration, etc. We will perform meta-regression using the 'metafor' and 'meta' package in R V.4.0.3.<sup>34</sup> For missing values, we will contact the correspondence authors by email. If missing values are unavailable, we will remove regression factors or original studies with too many missing values. For those regression factors or original studies with less than 10% missing values, we will apply multiple imputation to deal with them with 'mice' package in R V.4.0.3.

### Trial sequential analysis

TSA is a method to reduce the risk of false-positive by taking into account multiple statistical test correction.<sup>35 36</sup> With this method, we will calculate the required sample size and information size for each outcome with TSA 0.9.5.10 Beta software. For continuous variables, we will use the observed SD, a mean difference of the observed SD/2, an alpha of 0.025 for primary outcomes, an alpha of 0.05 for secondary outcomes, and a beta of 0.10. For dichotomous variables, we will estimate the required information size based on the observed proportion of subjects with an event in the control group, a relative risk reduction of 0.25, an alpha of 0.05 for secondary outcomes and a beta of 0.10.

### Evidence grade evaluation

We will apply GRADEpro V.3.6.0 software to evaluate the quality of each outcome's evidence grade. Following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendation,<sup>37</sup> as this systematic review only includes RCTs, we will conduct the GRADE assessment with below items: reasons to decrease quality of evidence including limitations in study design, inconsistency, indirectness, imprecision, publication bias and reasons to increase quality of evidence including large effect, plausible confounding would change the effect, dose-response relationship. In the end, we will present a 'Summary of Findings' table to report the quality of each outcome's evidence grade.

### Ethics and dissemination

This study does not require formal ethical approval. The findings will be submitted for publication in a peer-review journal.

### Patient and public involvement

As this is a protocol for our systematic review and meta-analysis, we will obtain public data from published literatures or from authors. Thus, patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### DISCUSSION

This systematic review will comprehensively summarise and analyse the results of previous clinical trials on A $\beta$  antibodies. The specific contents are as follows: Clinical efficacy, changes in biomarkers and neuroimaging, safety, factors that may affect the results of clinical trials and verify the reliability of the above results.

Previous systematic reviews have paid attention to this field. However, their studies are insufficient. Two network meta-analyses have compared different anti-A $\beta$  immunotherapies, with 11<sup>22</sup> and 13<sup>38</sup> original articles included respectively. To our knowledge, they have both missed some original studies, such as some phase I clinical trials. This may lead to a biased result. Another meta-analysis included both phase I and phase II/III clinical trials. However, the authors merged data to perform meta-analysis regardless of the huge heterogeneity, and there was no necessary analysis or detailed discussion for the heterogeneity.<sup>39</sup> A recent systematic review and meta-analysis focused on all kinds of Anti-A $\beta$  agents. They included studies on mild-to-moderate AD and excluded phase I clinical trials as well. What's more, they included studies on anti-secretase agents and immunoglobulin.<sup>23</sup> Some included drugs, like immunoglobulin and tarenflurbil, may have therapeutic effects beyond regulating A $\beta$ , which may lead to a biased result as well. Some important studies in this field<sup>15 40</sup> were not included in their study, which may affect the reliability of their results. Hence, it is necessary to conduct a systematic review and meta-analysis focusing on A $\beta$  antibodies for AD treatment.

There are some limitations about this study. We will search databases and clinical trial registration platform in English only. Although the vast majority of previous clinical trials were registered on our retrieval platform, and we will contact the correspondence authors for more information, we may still miss some valuable studies.

From this systematic review and meta-analysis, it is anticipated that our findings will help scientists and drug developers conduct more A $\beta$ -targeted clinical trials and identify the direction of drug development for AD in the future. In a word, we will provide evidence for further clinical practice and scientific studies.

**Contributors** DL and XL designed this study. DL and YS developed the search strategy and the data extraction list. DL drafted the manuscript. YS and XL revised the manuscript and provided methodological perspectives. DL and YS will search and screen literatures and perform data extraction. DL will assess the quality of included studies and conduct data analyses. All authors read and approved the final manuscript.

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**Competing interests** None declared.

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## REFERENCES

- GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2019;18:88–106.
- Bhatt J, Comas Herrera A, Amico F. The world Alzheimer report 2019: attitudes to dementia2 019.
- Jia J, Wei C, Chen S, et al. The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimer's & Dementia* 2018;14:483–91.
- Alzheimer A, Stelzmann RA, Schnitzlein HN, et al. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". *Clin Anat* 1995;8:429–31.
- Cummings J, Lee G, Ritter A. Alzheimer's disease drug development pipeline: 2020. *Alzheimer's dementia* 2020;6:e12050.
- Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* 1984;120:885–90.
- Seubert P, Mawal-Dewan M, Barbour R, et al. Detection of phosphorylated Ser262 in fetal tau, adult tau, and paired helical filament tau. *J Biol Chem* 1995;270:18917–22.
- Zott B, Simon MM, Hong W. A vicious cycle of  $\beta$  amyloid-dependent neuronal hyperactivation. *Science* 2019;365:559–65.
- Sweeney MD, Kisler K, Montagne A, et al. The role of brain vasculature in neurodegenerative disorders. *Nat Neurosci* 2018;21:1318–31.
- Kinney JW, Bemiller SM, Murtishaw AS. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's dementia* 2018;4:575–90.
- Yu J-T, Xu W, Tan C-C, et al. Evidence-Based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry* 2020;91:1201.
- Joe E, Ringman JM. Cognitive symptoms of Alzheimer's disease: clinical management and prevention. *BMJ* 2019;367:l6217.
- Mckhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 2011;7:263–9.
- Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535–62.
- Arboleda-Velasquez JF, Lopera F, O'Hare M. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nature medicine* 2019;25:1680–3.
- Bloom GS. Amyloid- $\beta$  and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol* 2014;71:505–8.
- Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:311–21.
- Sevigny J, Chiao P, Bussière T. The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature* 2016;537:50–6.
- Egan MF, Kost J, Tariot PN, et al. Randomized trial of Verubecestat for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2018;378:1691–703.
- Young SC. A Systematic Review of Anti-amyloidogenic and Metal-Chelating Peptoids: Two Structural Motifs for the Treatment of Alzheimer's Disease. *Molecules (Basel, Switzerland)* 2018;23.
- Hock C, Konietzko U, Streffer JR. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* 2003;38:547–54.
- Mo J-J, Li J-Y, Yang Z, et al. Efficacy and safety of anti-amyloid- $\beta$  immunotherapy for Alzheimer's disease: a systematic review and network meta-analysis. *Ann Clin Transl Neurol* 2017;4:931–42.
- Lu L, Zheng X, Wang S, et al. Anti-A $\beta$  agents for mild to moderate Alzheimer's disease: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2020;91:1316–24.
- Shamseer L, Moher D, Clarke M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
- Higgins JPT TJ, Chandler J, Cumpston M. Cochrane Handbook for systematic reviews of interventions version 6.1 (updated September 2020). The Cochrane collaboration, 2020. Available: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook)
- Liberati A, Altman DG, Tetzlaff J. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- Mohs RC, Rosen WG, Davis KL. The Alzheimer's disease assessment scale: an instrument for assessing treatment efficacy. *Psychopharmacology bulletin* 1983;19:448–50.
- Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–4.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:129–98.
- Sterne JAC, Savović J, Page MJ, Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:14898.
- Higgins JP, Altman DG, Gotzsche PC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- De Angelis C, Drazen JM, Frizelle FA. Clinical trial registration: a statement from the International Committee of medical Journal editors. *The New England journal of medicine* 2004;351:1250–1.
- Sterne JA, Sutton AJ, Ioannidis JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- Team RDC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, R Foundation for Statistical Computing, 2010: 14. 12–21.
- Thorlund KEJ, Wetterslev J, Brok J, et al. *User manual for trial sequential analysis (TSA)*. Copenhagen, Denmark: Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2011.
- Wetterslev J, Thorlund K, Brok J. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75.
- Guyatt GH, Oxman AD, Schünemann HJ, et al. Grade guidelines: a new series of articles in the Journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.
- Foroutan N, Hopkins RB, Tarride J-E, et al. Safety and efficacy of active and passive immunotherapy in mild-to-moderate Alzheimer's disease: a systematic review and network meta-analysis. *Clin Invest Med* 2019;42:E53–65.
- Penninkilampi R, Brothers HM, Eslick GD. Safety and efficacy of Anti-Amyloid- $\beta$  immunotherapy in Alzheimer's disease: a systematic review and meta-analysis. *J Neuroimmune Pharmacol* 2017;12:194–203.
- Landen JW, Andreasen N, Cronenberg CL. Ponezumab in mild-to-moderate Alzheimer's disease: Randomized phase II PET-PIB study. *Alzheimer's dementia* 2017;3:393–401.