# Systematic Review

**Prognostic and Predictive Factors in Early Alzheimer's Disease: A Systematic Review**

**Supplementary Table 1.** PRISMA checklist for abstract

| Section and Topic | Item # | Checklist item | Reported (Yes/No) |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Y |
| **BACKGROUND** | | | |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Y |
| **METHODS** | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | Y |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Y |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | Y |
| Synthesis of results | 6 | Specify the methods used to present and synthesise results. | Y |
| **RESULTS** | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Y |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Y |
| **DISCUSSION** | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Y |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Y |
| **OTHER** | | | |
| Funding | 11 | Specify the primary source of funding for the review. | |
| Registration | 12 | Provide the register name and registration number. | |

**Supplementary Table 2.** PRISMA checklist for manuscript

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Supplementary table 1 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 5 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 6 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Table 1, Page 7 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Supplementary Table 3, Page 6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Supplementary Table 3 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 6-7 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 7-8 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Table 1, Page 6-8 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Table 1, Page 6-8 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Table 1 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 8-9, 11 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Page 8-9 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 8-9, 11 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 8-9 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | NA |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | NA |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | NA |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | NA |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure 1, Page 10 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Supplementary table 5 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 2, Supplementary table 4 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplementary table 7 & 8 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Tables 3-5, pges 11-19 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Tables 3-5, pges 11-19 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Tables 3-5, pges 11-19 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | NA |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | NA |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | NA |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Tables 3-5, pges 11-19 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 20-21 |
| | 23b | Discuss any limitations of the evidence included in the review. | Page 22 |
| | 23c | Discuss any limitations of the review processes used. | Page 22 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Page 21-22 |
| **OTHER INFORMATION** | | | |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 7 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 7 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 25 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 25-27 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 27 |

**Supplementary Table 3.** Search Strategy
Embase (Ovid): 1974 to 2022 August 02, searched 3.8.22

| # | Searches | Results |
|---|---|---|
| 1 | mild cognitive impairment/ | 33048 |
| 2 | (MCI or aMCI or mild cognit$ impair$ or CIND or cognitive impair$ no dementia).ti,ab,hw. | 58186 |
| 3 | ((early$ or mild$ or prodromal) adj6 (alzheimer$ or alzeimer$ or alzhiemer$ or alziemer$ or AD)).mp. | 39844 |
| 4 | Alzheimer disease/ | 228367 |
| 5 | (alzheimer$ or alzeimer$ or alzhiemer$ or alziemer$ or AD).ti,ab. | 347567 |
| 6 | (early$ or mild$ or prodromal).ti,ab. | 2948283 |
| 7 | (dementia adj2 stage adj2 ('2' or '3' or II or III or two or three)).ti,ab. | 54 |
| 8 | 4 and 6 | 54812 |
| 9 | 5 and 6 | 75234 |
| 10 | 1 or 2 or 3 or 7 or 8 or 9 | 113071 |
| 11 | random*.ti,ab. | 1816998 |
| 12 | factorial*.ti,ab. | 44342 |
| 13 | (crossover* or cross over*).ti,ab. | 119139 |
| 14 | ((doubl* or singl*) adj blind*).ti,ab. | 259545 |
| 15 | (assign* or allocat* or volunteer* or placebo*).ti,ab. | 1183821 |
| 16 | crossover procedure/ | 71057 |
| 17 | double blind procedure/ | 197270 |
| 18 | single blind procedure/ | 47071 |
| 19 | randomized controlled trial/ | 720768 |
| 20 | or/11-19 | 2705585 |
| 21 | aducanumab/ | 736 |
| 22 | (aducanumab or aduhelm or biib037 or "biib 037" or biib37 or biib 37).mp. | 796 |
| 23 | gantenerumab/ | 388 |
| 24 | (gantenerumab or r 1450 ir r1450 or rg1450 or rg 1450 or RO4909832 or RO 490?9832).mp. | 399 |
| 25 | lecanemab/ | 114 |
| 26 | (lecanemab or ban 2401 or ban2401).mp. | 204 |
| 27 | donanemab/ | 81 |
| 28 | (donanemab or ly 3002813 or ly3002813 or N3pG).mp. | 95 |
| 29 | donepezil plus memantine/ or memantine/ | 11999 |
| 30 | ('1 amino 3, 5 dimethyladamantane' or '1, 3 dimethyl 5 adamantanamine' or '1, 3 dimethyl 5 aminoadamantane' or '3, 5 dimethyl 1 adamantamine' or '3, 5 dimethyl 1 adamantanamine' or '3, 5 dimethylaminoadamantane' or '5 amino 1, 3 dimethyladamantane' or 'adamantane, 5 amino 1, 3 dimethyl' or akatinol or alzantin or axura or d 145 or d145 or ebix or ebixa or ebixza or marixino or maruxa or memantine or memantine hcl or memantine hydrochloride or memantine nitrate or memary or "mn 08" or mn08 or namenda or namenda xr or nemdatine or nsc 102290 or nsc102290 or sun y7017 or suny701).mp. | 12721 |
| 31 | donepezil/ | 14616 |
| 32 | (aricept or asenta or doneliquid geriasan or donepezil or donepezil hydrochloride or e 2020 or e2020 or eranz or memac or memorit).mp. | 15143 |
| 33 | rivastigmine/ | 8174 |

| | | |
|---|---|---|
| 34 | (alzest or ena 713 or ena713 or exelon or nimvastid or prometax or rivastigmin or rivastigmine or sdz 212 713 or sdz 212-713 or sdz 212713 or sdz ena 713 or sdz ena713 or sdz212 713 or sdz212-713 or sdz212713).ti,ab,tn. | 3845 |
| 35 | galantamine/ | 8201 |
| 36 | (acumor or alenzo or aneprosil or bergal or consion or elmino or galantex or galanthamine or galanthen or galanyl or galatamin$ or galema or galnora or galsya or gamyl or gatalin or gazylan or girlamen or jilkon or lotprosin or loxifren or luventa or lycoremin$ or margal or masparen or memoton life or natagal or nivalin$ or razadyne or reminyl or spegal or vertusal or zentan or zoroflog).mp. | 1738 |
| 37 | exp cholinesterase inhibitor/ | 89506 |
| 38 | (((acetylcholinesterase or cholinesterase or phosphoorganic choline esterase or ache) adj3 (inhibit$ or block$)) or anticholesterinase or anticholinesterase or anticholinesterase or achei$ or chei$).mp. | 46762 |
| 39 | or/21-38 | 114162 |
| 40 | 10 and 20 and 39 | 1734 |
| 41 | Clinical study/ | 159876 |
| 42 | Case control study/ | 190992 |
| 43 | Family study/ | 25668 |
| 44 | Longitudinal study/ | 176037 |
| 45 | Retrospective study/ | 1283450 |
| 46 | Prospective study/ | 783517 |
| 47 | Randomized controlled trials/ | 231273 |
| 48 | 46 not 47 | 774341 |
| 49 | Cohort analysis/ | 874967 |
| 50 | (Cohort adj (study or studies)).mp. | 413549 |
| 51 | (Case control adj (study or studies)).tw. | 156367 |
| 52 | (follow up adj (study or studies)).tw. | 69923 |
| 53 | (observational adj (study or studies)).tw. | 222699 |
| 54 | (epidemiologic$ adj (study or studies)).tw. | 116756 |
| 55 | (cross sectional adj (study or studies)).tw. | 296955 |
| 56 | or/41-45,48-55 | 3502022 |
| 57 | (register or registr$).ti,ab. | 507609 |
| 58 | 56 or 57 | 3850140 |
| 59 | 10 and 58 | 21383 |
| 60 | 40 or 59 | 22703 |
| 61 | prognosis/ or prediction/ | 1066527 |
| 62 | (course or prognos$ or predict$).ti,ab. | 4021315 |
| 63 | 61 or 62 | 4217291 |
| 64 | 60 and 63 | 6436 |
| 65 | limit 64 to yr="2005 -Current" | 6111 |
| 66 | limit 65 to conference abstract | 2330 |
| 67 | 65 not 66 | 3781 |

**Supplementary Table 4.** Prognostic factors in eAD studies with high risk of bias (deprioritized)

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| Chen 2018 [1] | Taiwan Single (n=1) | Retrospective cohort (Dementia care database) | Patients attending the neurological department at the MacKay Memorial Hospital *Dates: January 2014 to June 2017* | MCI: n=279 | NIA-AA (Albert 2011) | NINCDS-ADRDA (McKhann 2011) | NR | NR | NR | NR | Mean 27.09 months (SD 15.09)* |
| Chung 2021 [2] | Canada, USA (n=NR) | Retrospective cohort (ADNI) | Patients with prodromal AD who underwent a baseline MRI scan *Dates: Up to June 2020* | MCI: n=189 | Presence of objective memory impairment without meeting the criteria for dementia | Presence of memory complaints, a global CDR score of ≥ 0.5, and significant impairments in objective cognition and ADL | NR | Y | 86 (45.5%) | 72.6 (6.7) | 3 years |
| Cova 2016 [3] | Italy Single (n=1) | Prospective cohort (Clinical information was collected by a senior neurologist) | Consecutive subjects with MCI were recruited at the Center for Research and Treatment on Cognitive Dysfunctions, Sacco Hospital, Milan *Dates: Jan 2001 to Sep 2009* | MCI: n=228 | Subjective cognitive impairment, objective cognitive impairment, preserved daily functioning and absence of dementia (Winblad 2004) | NINCDS-ADRDA criteria (McKhann 1984) | NR | NR | 129 (56.6%) | 74.0 (6.94) | 2.40 years (SD:1.58) |
| Degerman Gunnarsson 2016 [4] | Sweden Single (n=1) | Retrospective cohort (Memory Clinic at the Uppsala University Hospital) | Patients who underwent a lumbar puncture (LP) as part of the diagnostic procedure and were diagnosed with AD (prodromal/MCI, mild or moderate AD) *Dates: 2003-2011* | MCI: n=134 Mild AD dementia: n=85 | NINCDS/ADRDA criteria (McKhann 1984)<br><br>DSM-4 criteria (APA 1994) | NINCDS/ADRDA criteria (McKhann 1984)<br><br>DSM-4 criteria (APA 1994) | NR | NR | 145 (62%) | 70 (46–86) | Median 4.9 years* |
| Divers 2022 [5] | USA Multicenter (n~31) | Retrospective cohort (NACC UDS) | Data on participants with a diagnosis of MCI at initial UDS appointment, English speaker, at least 50 years old, and presence of a reliable informant were acquired from the publicly available | MCI: n=2614 | Diagnosis of MCI was made by a clinician or consensus conference at each ADCC | Diagnosis of AD was made by a clinician or consensus conference at each ADCC | NR | NR | 1371 (52.4%) | 72.71 (SD: 8.99) | 3 years |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | | | NACC database<br>*Dates: Up to December 2018* | | | | | | | | |
| Galasko 2019 [6] | UCSD<br>USA<br>Single (n=1)<br><br>ADNI<br>Canada and USA<br>Multiple (n=NR) | UCSD<br>Prospective cohort (UCSD)<br><br>ADNI<br>Retrospective cohort (ADNI) | UCSD<br>Patients with NC, MCI and mild AD followed at the UCSD Shirley-Marcos ADRC<br>*Dates: NR*<br><br>ADNI<br>Patients with NC, MCI or AD from the ADNI<br>Dates: NR | UCSD<br>MCI: n=57<br>Mild AD dementia: n=46<br><br>ADNI<br>MCI: n=140 | UCSD<br>NIA-AA but did not require a amyloid biomarker (Albert 2011)<br><br>ADNI<br>As reported in ADNI | ADNI<br>As reported in ADNI | NR | NR | UCSD<br>MCI: 20 (35%)<br>eAD: 19 (41%)<br><br>ADNI<br>MCI: 44 (31%) | UCSD<br>MCI: 74.3 (6.5)<br>eAD: 70.7 (9.4)<br><br>ADNI<br>MCI: 74.7 (7.2) | UCSD<br>Up to 3 years*<br><br>ADNI<br>Up to 5 years |
| Goukasian 2019 [7] | Canada, USA<br>Multiple (NR) | Retrospective cohort (ADNI) | Patients from ADNI with diagnosis of MCI and available clinical, behavioral and amyloid data<br>*Dates: 2003 to 2015* | MCI: n=599 | As described in the ADNI | NINCDS-ADRDA criteria (McKhann 1984) | NR | Y | 240 (42.9%) | NR | NR |
| Han 2021 [8] | China<br>Multicenter (n=6) | Prospective cohort | Normal older adults, patients diagnosed with MCI and patients with probable AD<br>*Dates: Oct 2010 to May 2016* | MCI: n=142<br>MSCI: n=47 | MCI: Modified Petersen 2004<br>MSCI: MoCA score reduced by more than 2 points from the baseline of patients with MCI | National Institute of Related Disorders Association (Reiman 2011) | NR | NR | NR | NR | NR |
| Hanon 2022 [9] | France<br>Multicenter (n=23) | Prospective cohort BALTAZAR study (NCT01315639) | Patients with MCI from the BALTAZAR study<br>*Dates NR* | MCI: n=485 | Petersens' criteria (Petersen 1999) | NIA–AA (McKhann 2011) | Y | NR | 293 (60.4%) | 77.7 (5.5) | 3 years |
| Ito 2015 [10] | Japan<br>Multicenter (n=9) | Prospective cohort Memory clinics specializing in AD | Patients with amnestic MCI from memory clinics across Japan<br>*Dates: January 2006 to March 2007* | MCI: n=114 | 50 and 80 years, with an MMSE score ≥24, a GDS score ≤10, a WMS-R LM I score ≤13, a LM II part A and part B score (maximum = 50) ≤8, and a CDR memory box score equal to 0.5 | NINCDS-ADRDA (no reference) | NR | Y | 64 (56.1%) | 70.8 (7.5) | 3 years |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| Julayanont 2014 [11] | Canada Single (n=1) | Retrospective cohort (CEDRA/Neuro Rive-Sud memory clinic) | Individuals with MCI who met MCI Peterson's criteria were selected from the review charts *Dates: November 2004 and May 2011* | MCI: n=165 | Petersen criteria (Petersen 1999) | DSM-IV and NINCDS/ADRDA criteria (McKhann 1984) | NR | NR | 17 (64.8%) | NR | 18.2 (SD 1.0) month |
| Karikari 2020 [12] | Canada, USA Multicenter (n=NR) | Retrospective cohort (ADNI) | Patients from ADNI diagnosed with cognitively unimpaired (CU), mild cognitive impairment (MCI) and AD dementia patients with available plasma p-tau181 data *Dates: 7th September 2005 to 16th June 2016* | MCI: n=558 | ADNI (Petersen 2010) | NINCDS/ADRDA criteria (McKhann 1984) | Y | Y | 212 (43.6%) | NR | 48 months * |
| Kim 2015 [13] | Korea Multicenter (n=NR) | Prospective cohort (CREDOS) | Patients aged 60 years or older, met the MCI criteria at baseline, and they had at least one longitudinal clinical review at least 6 months post-baseline. *Dates: 2005-2009* | MCI: n=294 | Presence of memory complaints; intact function in ADL; objective cognitive impairment; CDR of 0.5; and not demented according to DSM-IV criteria | NINCDS/ADRDA criteria (McKhann 1984) | NR | NR | 193 (65.6%) | 72 (IQR 67-76) | 13.8 (6.0–36.0) months |
| Lan 2021 [14] | USA Multicenter (n=37) | Retrospective cohort (NACC's Uniform data set) | Patients who were over 50 years old at baseline, with body weight measurements from at least 3 visits, and free of clinically diagnosed dementia and stroke at the initial visit were included from 37 past and current ADRC's *Dates: September 2005 and September 2020* | MCI: n=2897 | Modified Petersen's criteria (Winblad 2004) | NINCDS/ADRDA criteria (McKhann 2011) | NR | NR | 60.9%* | 72 (9) | 5.5 years * |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| Lee 2014 [15] | Canada, USA Multiple (n=NR) | Retrospective cohort (ADNI) | Participants aged 55–90 diagnosed with aMCI enrolled in the ADNI, had at least one follow-up visit and did not have any critical missing data. *Dates: 2003 to July 2012* | MCI: n=382 | Amnestic MCI: memory complaint, abnormal memory function, MMSE score of 24–30, CDR score of 0.5, and cognitive and functional impairment not severe enough to meet criteria for AD or dementia (ADNI) | NINCDS/ADRDA (McKhann 1984) | NR | NR | 137 (36%) | 75 (7) | Mean 2.9 years (SD: 1.1; Range: 0.5–4.0) |
| Lehman 2013 [16] | Canada, USA Multiple (n>50) | Retrospective cohort (ADNI) | MCI subjects from the ADNI with one 1.5 T MRI scan available (time to AD conversion analysis) and one 1.5 T MRI scan (CSF analysis) *Dates 2003 to June 2011* | MCI: n=192 | As described in the ADNI | As described in the ADNI | NR | NR | 63 (33%) | 74.7 (7.4) | 3 years |
| Liew 2021 [17] | USA Multicenter (n=39) | Retrospective cohort (NACC database) | Participants who fulfilled the following criteria at baseline: age ≥ 65 years; diagnosed with dementia; no concurrent diagnosis of delirium at baseline; had global CDR of 1 (indicating early dementia) and provided information on NPI-Q *Dates: September 2005 and August 2019* | eAD: n=6221 | NA | McKhann 1984 criteria, DSM-IV criteria or McKhann 2011 criteria | NR | NR | 3368 (54.1%) | 79 (IQR 73–83) | 3.5 years |
| Mai 2022 [18] | Canada, USA Multiple (n=NR) | Retrospective cohort (ADNI (ADNI-1, ADNIII-GO/2, ADNI-3)) | Patients from ADNI with diagnosis of MCI made at first admission Dates: NR | MCI: n=733 | As described in ADNI | NIA–AA (McKhann 2011) | NR | NR | 300 (40.1%) | NR | Up to 15 years |
| Matsuoka 2020 [19] | Canada, USA | Retrospective cohort (ADNI) | Patients with MCI were recruited from ADNI | MCI: 237 | MMSE score of 24–30, having a memory | NINCDS/ADRDA criteria (McKhann 1984), and MSME | NR | NR | 100 (42.25) | NR | Converted to AD: 41.4 months (21.1) Didn't convert to |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | Multicenter (n=NR) | | *Dates: Data was downloaded in July 2018* | | complaint, objective memory loss, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, largely preserved ADL, and an absence of dementia | score of 20–26 and clinical dementia rating of 0.5 to 1.0 | | | | | AD: 41.8 months (20.4) |
| Mecca 2018 [20] | USA Multicenter (n=NR) | Retrospective cohort (ADNI) | Patients in the ADNI database who have MCI or AD or are cognitively normal *Dates: 2003 -28th September 2014* | MCI: n=869 | As in ADNI** | NINCDS/ADRDA (McKhann 1984) | NR | NR | 355 (40.9%) | NR | Early MCI (PSD): 21.3 months Early MCI (NSD): 19.6 months Late MCI (PSD): 20.9 months Late MCI (NSD): 20.1 months |
| Mielke 2017 [21] | USA Single (n=1) | Retrospective cohort (MCSA) | Participants aged 56 to 95 years from the MSCA population-based study with plasma total tau measures, Aβ PET imaging, and cognitive testing at the same study visit and at least 1 follow-up visit with cognitive testing. *Dates: 2008 to 2013* | MCI: n=123 | Peterson 2004 | McKhann 2011 | Y | NR | 45 (36.6%) | 79.9 (7.4) | Median 3 years (Range: 1.1–4.9)* |
| Moon 2017 [22] | Canada, USA Multiple (n>50) | Retrospective cohort (ADNI) | Patients with amnestic MCI who had completed baseline [18F]AV45 PET as well as T1-weighted MRI at baseline and 2-year follow-up from ADNI database *Dates: 2003 to September 2016* | MCI: n=337 | Petersen criteria (Petersen 1999) | As described in ADNI | NR | NR | 156 (46.2%) | 71.8 (1.3) | Average: 1.94 years (SD 1.3) |
| Morgan 2019 [23] | Cross-European Multicenter (n=NR) | Retrospective cohort (AddNeuroMed) | Plasma samples were used from the patients, selected based solely on | MCI: n=285 | Peterson 2004 | NINCDS/ADRDA criteria | NR | NR | NR | NR | NR |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | | | availability of plasma samples *Dates: NR* | | | | | | | | |
| Muscari 2021 [24] | Italy Single (n=1) | Retrospective cohort (Medical records) | Consecutive outpatients at the CDCD of the Geriatric Unit of the S. Orsola-Malpighi Hospital in Bologna *April 2015 to January 2019* | MCI: n=143 | Petersen's criteria (Petersen 2009) | NIA–AA (McKhann 2011) | N | Y | 67 (46.9%) | NR | 1 year |
| Myung 2016 [25] | South Korea Multicenter (n=56) | Prospective cohort (CREDOS) | Patients from CREDOS with presence of memory complaints that raise concern about a change in cognition; intact function in ADL except performing complex functional tasks; objective cognitive impairment in more than one cognitive domain on standardized neuropsychological testing; CDR of 0.5; and not demented according to DSM-IV-TR criteria *Dates: November 2005 to May 2012* | MCI: n=961 | MCI – criteria for the clinical and cognitive syndrome | NIA–AA (Albert 2011) | NR | NR | 631 (65.7%) | 71 (IQR 66-76) | 17.64 months |
| Palmqvist 2012 [26] | Sweden Single (n=1) | Prospective cohort Study conducted at Memory Clinic of Skane University Hospital in Malmo, Sweden | Patients referred to the Memory Clinic of Skane University Hospital in Malmo, Sweden who were diagnosed with MCI *Dates: October 200 to January 2006* | MCI: n=133 | Peterson 2004 | McKhann 1984 | NR | NR | 82 (61.7%) | NR | 5.9 Years (Range: 3.2–8.8 years) |
| Pelkmans 2022 [27] | Amsterdam Dementia Cohort Netherlands Unclear (n=NR) | Retrospective cohort (Amsterdam Dementia Cohort and ADNI) | Patients who fulfilled the consensus criteria for MCI, had abnormal levels of CSFAβ(1–42), an available baseline | MCI: n=491 | Albert 2011 Petersen 1999 | Pre-2011: NINCDS/ADRDA criteria (McKhann 1984)<br><br>2011 onwards: | NR | NR | 217 (44.2%) | NR | 2 years |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | ADNI<br>USA and Canada<br>Multiple (n=NR) | | structural MRI scan, and at least one follow-up neuropsychological assessment<br>*Dates: December 2005 and April 2016* | | | NIA-AA (McKhann 2011)<br>Van der Flier 2014 | | | | | |
| Pyun 2021 [28] | Canada, USA<br>Multicenter (n=NR) | Retrospective cohort (ADNI) | Data from ADNI on patients with a diagnosis of MCI who had available GWAS data, older than 60 years at baseline assessment, and had at least one or more follow-up visits<br>*Dates: 2003 to NR* | MCI: n=732 | Objective memory impairment but without meeting the criteria for dementia. (Aisen 2015) | As described in the ADNI | NR | NR | 284 (38.8%) | NR | Up to 5 years |
| Qin 2019 [29] | Canada, USA<br>Multiple (n=NR) | Retrospective cohort (ADNI) | MCI individuals from the ADNI who developed AD during the follow up period of ADNI1, ANDI2 or ADNI GO<br>*Dates: 2005 to 2014,* | MCI: n=245 | Gerstenecker and Mast 2014 and Petersen 2009 | NINCDS/ADRDA (As described in ADNI) | NR | NR | 100 (40.8%) | 74.0 (5.5) | Unclear |
| Reija 2017 [30] | Unclear<br>Multiple (n=NR) | Retrospective cohort<br>DESCRIPA, KUOPIO L-MCI | DESCRIPA: MCI patients aged >55 years referred to the memory clinic for an evaluation of complaints, cognitive impairment on neuropsychological tests and absence of dementia<br>*Dates: 2003 to 2005*<br><br>KUOPIO L-MCI: memory complaint by patient, family, or physician; normal activities of daily living; normal global cognitive function; objective impairment below –1.5 SD in any cognitive domain; | MCI: n=353 | Petersen 2004<br>Hall 2015 | NINCDS-ADRDA criteria (McKhann 1984) | Y | Y | 208 (59%) | 70.6 (6.9) | Average: 2.4 years (SD: 1.3)* |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | | | CDR score of 0.5; and absence of dementia<br>*Dates: 1996 to 2001* | | | | | | | | |
| Ruthirakuhan 2019 [31] | USA<br>Multiple (n=NR) | Prospective cohort (NACC UDS) | Patients with diagnosis of MCI at baseline and had one or more follow up visits at ADCs in the USA and provided imaging and laboratory specimens at specific ADCs<br>*September 2005 to February 2018* | MCI: n=4932 | No details reported | Prior 2015: NINCDS-ADRDA criteria (McKhann 1984)<br>After 2015: NINCDS-ADRDA criteria (McKhann 2011) | NR | NR | 2450 (50%) | 3659 | Median 23 months |
| Steenland 2012 [32] | USA<br>Multiple (n=30) | Retrospective cohort (NACC UDS) | Subjects from the NACC UDS with at least two visits who were considered to have either normal cognition or MCI at baseline<br>*Dates: September 2005 to January 2011* | MCI: n=3010 | Presence of cognitive complaint not normal for age, cognitive decline (without dementia), and essentially normal functional activities as reported in NACC | Dementia established by clinical examination and documented by the Mini-Mental Test or some similar examination and confirmed by neuropsychological tests; deficits in two or more areas of cognition; progressive worsening of memory and other cognitive functions; no disturbance of consciousness; onset between ages 40 and 90, most often after age 65; and absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficit in memory and cognition (NINCDS/ADRDA) | NR | NR | 1552 (52%) | 74 (9) | Mean 2.5 years (SD: 1) |
| Sugarman 2020 [33] | USA<br>Multicenter (n~30) | Retrospective cohort (BU ADC Clinical Core Registry) | Community-dwelling, English-speaking older adults with and without cognitive impairment who have adequate | MCI: n=185 | Winblad 2004 | McKhann 1984 | NR | NR | 108 (58.4%) | 74.99 (7.24) | 5.10 (SD: 2.64) |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | | | hearing and visual acuity from the BU ADC Clinical Core Registry *Dates 2008 to 2018* | | | | | | | | |
| Suh 2019 [34] | South Korea Single (n=1) | Retrospective cohort (Medical records) | Retrospectively reviewed the medical records of a consecutive series of patients who visited the Neurocognitive Behavioral Center of Seoul National University Bundang Hospital and were diagnosed with probable AD by the NIA–AA *August 2012 to July 2016* | Mild AD dementia: n=159 | NA | NIA–AA (McKhann 2011) | NR | Y | 91 (57.2%) | 76.4 (7.70) | 1 year |
| Tifratene 2015 [35] | France Multicenter (n=28) | Retrospective cohort BNA | Patients diagnosed with MCI by medical doctors in the BNA *Dates: January 2009 to January 2014.* | MCI: n=11451 | Diagnoses in the BNA are collected according to the ICD-10 (table e-1 on the Neurology® Web site at Neurology.org). The definition of MCI was based on code F06.7. | Diagnoses in the BNA are collected according to the ICD-10 (table e-1 on the Neurology® Web site at Neurology.org). The definition of AD dementia was based on the corresponding ICD-10 code F00.9 a. | NR | NR | 6,568 (57.4%) | 76.5 (7.8) | Mean 1.1 years (Range 1 day to 5 years) |
| Van Der Mussele 2014 [36] | Belgium Single (n=1) | Prospective cohort (Ongoing prospective longitudinal study (BPSD)) | Recruited from database for cognitive impairment (not demented) BPSD research purposes *Dates: Since 2003* | MCI: n=183 | Petersen's diagnostic criteria | NINCDS/ADRDA criteria | Y | NR | 106 (57.9%) | 74.9 (7.5) | 4 years (SD: 3.8 ± 2.3) |
| Vos 2013 [37] | Finland Multicenter (n=16) | Retrospective cohort (DESCRIPA) | Recruited from the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease (DESCRIPA) cohort and Alzheimer Center of the VU | MCI: n=625 | Baseline diagnosis of MCI (Petersen 2004) | DSM-IV (APA 1994) and NINCDS-ADRDA criteria (McKhann 1984) | NR | NR | 335 (53.6%) | NR | Up to 5 years (Average 2.5 years, SD 1.0)* |

| Study | Country (centers) | Study design (source) | Recruitment (Dates) | Population n | Diagnostic criteria | | Diagnostic use | | Female: N (%) | Mean age (SD) | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MCI due to AD | AD dementia | CSF | PET | | | |
| | | | University Medical Center (VUmc) *Dates: 2003 to 2006* | | | | | | | | |
| Xue 2017 [38] | China Multiple (n=NR) | Prospective cohort (Face-to-face interviews and self-administered questionnaires) | Patients ≥65 years with MCI at baseline in eight communities in Taiyuan, China who were visited biannually over 5 years Face-to-face interviews and self-administered questionnaires were carried out. *Dates 2010 to 2014* | MCI: n=437 | MoCA (Lu 2011) | NINCDS-ADRDA criteria (McKhann 1984) | NR | NR | 302 (69.1%) | NR | 5 years |
| Yi 2016 [39] | Netherlands Single (n=1) | Retrospective cohort (Review of clinical records of Amsterdam Dementia Cohort) | All patients from the Amsterdam Dementia Cohort, who visited the memory clinic for evaluation of their cognitive symptoms *Dates: January 2008 and December 2011* | MCI: n=201 | Petersen criteria (Petersen 2004) | NINCDS-ADRDA (McKhann 1984) | NR | NR | 82/201 (40.8%) | 70 (9) | Mean 2.11 years (SD 0.96) |
| Zhou 2012 [40] | Canada, USA Multiple (n=NR) | Retrospective cohort ADNI | Patients with MCI from the ADNI database *Dates: 2003 to Nov 2010* | MCI: n=397 | As described in the ADNI | As described in the ADNI | NR | NR | 141 (35.5%) | 78.4 (Range: 55–90) | Up to 53 months |

*Reported for broader population, ** Subjective memory concern, mildly abnormal memory performance, and preserved functional performance such that a diagnosis of AD-dementia could not be made (early MCI), or subjective memory concern, memory performance that was abnormal and below that of EMCI subjects, and preserved functional performance such that a diagnosis of AD-dementia could not be made (late MCI)

AChEI, Acetylcholinesterase inhibitor; AD, Alzheimer's Disease; ADC, Alzheimer's Disease Centers; ADCC, Alzheimer's Disease Core Centers; ADL, Activities of daily living; ADRC; Alzheimer's Disease Research Centers; ADNI, Alzheimer's Disease Neuroimaging Initiative; APA, American Psychiatric Association; AVLT: Auditory Verbal Learning Test; BNA, Banque Nationale Alzheimer (French Alzheimer Databank); BSPD, Behavioral and psychological signs and symptoms of dementia; BU ADC, Boston University Alzheimer's Disease Center; CDCD, Centre for Cognitive Disorders and Dementias; CDR, The Clinical Dementia Rating; CEDRA, Center for Diagnosis and Research on Alzheimer's disease; CREDOS Clinical Research Center for Dementia of South Korea; CSF, Cerebrospinal Fluid; CU, cognitively unimpaired; DCN, German Dementia Competence Network; DSM, Diagnostic and Statistical Manual of Mental Disorders; EMCI, early MCI; KBASE-V Korean Brain Aging Study for the Early Diagnosis and Prediction of AD; ICD, International Classification of Diseases; LOC, loss of consciousness; LMCI, late MCI; MCI, mild cognitive impairment; MCSA, Mayo Clinic Study on Aging; MoCA, The Montreal Cognitive Assessment; MMSE, Mini Mental State Examination; MSCI, Moderate/Severe Cognitive Impairment; MRI, Magnetic resonance imaging; NACC, National Alzheimer's Coordinating Center; NIA-AA, National Institute on Aging and the Alzheimer's Association criteria; NINCDS/ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NPI-Q Neuropsychiatric Inventory– Questionnaire; NR, not reported; NSD, negative for sleep disturbances; PET, positron emission tomography; PSD, positive for sleep disturbances; SD, standard deviation; TBI, traumatic brain injuries; UCSD, University of California, San Diego; UDS, uniform data set

**Supplementary Table 5.** Excluded Studies

| Author | Title | Journal | Year | Citation |
|---|---|---|---|---|
| **Population n=97** | | | | |
| Aguilar-Navarro | Clinical and demographic predictors of conversion to dementia in Mexican elderly with Mild cognitive impairment | Revista de Investigacion Clinica | 2017 | 69(1):33-39. |
| Ahman | Dual-task tests predict conversion to dementia-a prospective memory-clinic-based cohort study | International Journal of Environmental Research and Public Health | 2020 | 17(21):1-14. |
| Angevaare | Predictors of Incident Mild Cognitive Impairment and Its Course in a Diverse Community-Based Population | Neurology | 2022 | 98(1):E15-E26. |
| Barca | Trajectories of depressive symptoms and their relationship to the progression of dementia | Journal of Affective Disorders | 2017 | 222:146-152. |
| Bernick | Age and rate of cognitive decline in Alzheimer disease: Implications for clinical trials | Archives of Neurology | 2012 | 69(7):901-905. |
| Bertens | Unbiased estimates of cerebrospinal fluid beta-amyloid 1-42 cutoffs in a large memory clinic population | Alzheimer's Research and Therapy | 2017 | 9(1) (no pagination)(8). |
| Bleckwenn | Impact of coronary heart disease on cognitive decline in Alzheimer's disease: A prospective longitudinal cohort study in primary care | British Journal of General Practice | 2017 | 67(655):e111-e117. |
| Borda | Association of Malnutrition with Functional and Cognitive Trajectories in People Living with Dementia: A Five-Year Follow-Up Study | Journal of Alzheimer's Disease | 2021 | 79(4):1713-1722. |
| Borda | Neuropsychiatric Symptoms and Functional Decline in Alzheimer's Disease and Lewy Body Dementia | Journal of the American Geriatrics Society | 2020 | 68(10):2257-2263. |
| Cai | Associations of Anxiety with Amyloid, Tau, and Neurodegeneration in Older Adults without Dementia: A Longitudinal Study | Journal of Alzheimer's Disease | 2021 | 82(1):273-283. |
| Campos-Magdaleno | Changes in visual memory in mild cognitive impairment: a longitudinal study with CANTAB | Psychological Medicine | 2021 | 51(14):2465-2475. |
| Cao | High blood caffeine levels in mci linked to lack of progression to dementia | Journal of Alzheimer's Disease | 2012 | 30(3):559-572. |
| Cardoso | The Outcome of Patients with Amyloid-Negative Amnestic Mild Cognitive Impairment | Journal of Alzheimer's Disease | 2022 | 86(2):629-640. |
| Chang | Mortality Risk after Diagnosis of Early-Onset Alzheimer's Disease versus Late-Onset Alzheimer's Disease: A Propensity Score Matching Analysis | Journal of Alzheimer's Disease | 2017 | 56(4):1341-1348. |
| Charisis | Plasma GSH levels and Alzheimer's disease. A prospective approach.: Results from the HELIAD study | Free Radical Biology and Medicine | 2021 | 162:274-282. |
| Chau | Visual Selective Attention Toward Novel Stimuli Predicts Cognitive Decline in Alzheimer's Disease Patients | Journal of Alzheimer's Disease | 2017 | 55(4):1339-1349. |

| Author | Title | Journal | Year | Citation |
|---|---|---|---|---|
| Cogswell | CSF dynamics as a predictor of cognitive progression | NeuroImage | 2021 | 232 (no pagination)(117899). |
| Connors | Mortality in mild cognitive impairment: A longitudinal study in memory clinics | Journal of Alzheimer's Disease | 2016 | 54(1):149-155. |
| Conti | Odor identification deficit predicts clinical conversion from mild cognitive impairment to dementia due to alzheimer's disease | Archives of Clinical Neuropsychology | 2013 | 28(5):391-399. |
| Dapic | No effect of thyroid hormones on 5-year mortality in patients with subjective cognitive decline, mild cognitive disorder, and Alzheimer's disease | Journal of Neuroendocrinology | 2022 | 34(4) (no pagination)(e13107). |
| Davis | Estimating alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia | Current Alzheimer Research | 2018 | 15(8):777-788. |
| Defrancesco | Specific Neuropsychiatric Symptoms Are Associated with Faster Progression in Alzheimer's Disease: Results of the Prospective Dementia Registry (PRODEM-Austria) | Journal of Alzheimer's Disease | 2020 | 73(1):125-133. |
| Degerman Gunnarsson | High tau levels in cerebrospinal fluid predict rapid decline and increased dementia mortality in alzheimer's disease | Dementia and Geriatric Cognitive Disorders | 2014 | 37(3-4):196-206. |
| Devine | Do cerebral white matter lesions influence the rate of progression from mild cognitive impairment to dementia? | International Psychogeriatrics | 2013 | 25(1):120-127. |
| Dhiman | Cerebrospinal Fluid Neurofilament Light Predicts Risk of Dementia Onset in Cognitively Healthy Individuals and Rate of Cognitive Decline in Mild Cognitive Impairment: A Prospective Longitudinal Study | Biomedicines | 2022 | 10(5):30. |
| Dicks | Gray matter network measures are associated with cognitive decline in mild cognitive impairment | Neurobiology of Aging | 2018 | 61:198-206. |
| Dong | Neutrophil hyperactivation correlates with Alzheimer's disease progression | Annals of Neurology | 2018 | 83(2):387-405. |
| Donovan | Subjective cognitive concerns and neuropsychiatric predictors of progression to the early clinical stages of Alzheimer disease | American Journal of Geriatric Psychiatry | 2014 | 22(12):1642-1651. |
| Duits | Four subgroups based on tau levels in Alzheimer's disease observed in two independent cohorts | Alzheimer's Research and Therapy | 2021 | 13(1) (no pagination)(2). |
| Dutt | Brainstem Volumetric Integrity in Preclinical and Prodromal Alzheimer's Disease | Journal of Alzheimer's Disease | 2020 | 77(4):1579-1594. |
| Dyer | Gait speed, cognition and falls in people living with mild-to-moderate Alzheimer disease: data from NILVAD | BMC geriatrics | 2020 | 20(1):117. |
| Gao | Mild Cognitive Impairment Reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort | Dementia and Geriatric Cognitive Disorders Extra | 2018 | 8(2):226-237. |
| Glynn | Clinical utility of mild cognitive impairment subtypes and number of impaired cognitive domains at predicting progression to dementia: A 20-year retrospective study | International Journal of Geriatric Psychiatry | 2021 | 36(1):31-37. |

| Author | Title | Journal | Year | Citation |
|---|---|---|---|---|
| Gottesman | Association between Early Psychotic Symptoms and Alzheimer's Disease Prognosis in a Community-Based Cohort | Journal of Alzheimer's Disease | 2021 | 81(3):1131-1139. |
| Gross | Alzheimer's disease severity, objectively determined and measured | Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring | 2016 | 4:159-168. |
| Halminen | Early Start of Anti-Dementia Medication Delays Transition to 24-Hour Care in Alzheimer's Disease Patients: A Finnish Nationwide Cohort Study | Journal of Alzheimer's Disease | 2021 | 81(3):1103-1115. |
| Hamelin | Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease | Brain | 2018 | 141(6):1855-1870. |
| Hayakawa | Orthostatic blood pressure behavior in people with mild cognitive impairment predicts conversion to dementia | Journal of the American Geriatrics Society | 2015 | 63(9):1868-1873. |
| Herrmann | Risk factors for progression of Alzheimer disease in a Canadian population: The Canadian Outcomes Study in Dementia (COSID) | Canadian Journal of Psychiatry | 2015 | 60(4):189-199. |
| Hohman | The role of vascular endothelial growth factor in neurodegeneration and cognitive decline: Exploring interactions with biomarkers of Alzheimer disease | JAMA Neurology | 2015 | 72(5):520-529. |
| Huang | Sleep Quality Improvement Enhances Neuropsychological Recovery and Reduces Blood Abeta42/40 Ratio in Patients with Mild-Moderate Cognitive Impairment | Medicina | 2021 | 57(12). |
| Hughes | Engagement in social activities and progression from mild to severe cognitive impairment: the MYHAT study | International Psychogeriatrics | 2013 | 25(4):587-595. |
| Jiang | Metabolomics in the Development and Progression of Dementia: A Systematic Review | Frontiers in Neuroscience | 2019 | 13:343. |
| Kahle-Wrobleski | Dependence Levels as Interim Clinical Milestones Along the Continuum of Alzheimer's Disease: 18-Month Results from the GERAS Observational Study | The journal of prevention of Alzheimer's disease | 2017 | 4(2):72-80. |
| Katz | Subjective cognitive decline prediction of mortality: Results from the Einstein aging study | Journal of Alzheimer's Disease | 2018 | 66(1):239-248. |
| Kim | The cerebellum could serve as a potential imaging biomarker of dementia conversion in patients with amyloid-negative amnestic mild cognitive impairment | European Journal of Neurology | 2021 | 28(5):1520-1527. |
| Kinsella | Who benefits from cognitive intervention in older age? The role of executive function | The Clinical neuropsychologist | 2020 | 34(4):826-844. |
| Lauriola | Late-life depression versus amnestic mild cognitive impairment: Alzheimer's disease incidence in 4 years of follow-up | Dementia and Geriatric Cognitive Disorders | 2018 | 46(3-4):140-153. |

| Author | Title | Journal | Year | Citation |
|---|---|---|---|---|
| LeBlanc | Weight Trajectory over 20 Years and Likelihood of Mild Cognitive Impairment or Dementia Among Older Women | Journal of the American Geriatrics Society | 2017 | 65(3):511-519. |
| Lee | Amnestic multiple cognitive domains impairment and periventricular white matter hyperintensities are independently predictive factors progression to dementia in mild cognitive impairment | International Journal of Geriatric Psychiatry | 2014 | 29(5):526-532. |
| Lee | Association of plasma oligomerized beta amyloid with neurocognitive battery using Korean version of consortium to establish a registry for Alzheimer's disease in health screening population | Diagnostics | 2020 | 10(4) (no pagination)(237). |
| Liew | Subjective cognitive decline, APOE e4 allele, and the risk of neurocognitive disorders: Age- and sex-stratified cohort study | Australian and New Zealand Journal of Psychiatry. | 2022 | |
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| Morar | A study of the longitudinal changes in multiple cerebrospinal fluid and volumetric magnetic resonance imaging biomarkers on converter and non-converter Alzheimer's disease subjects with consideration for their amyloid beta status | Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring | 2022 | 14(1):e12258. |
| Mueller | Proper names from story recall are associated with beta-amyloid in cognitively unimpaired adults at risk for Alzheimer's disease | Cortex | 2020 | 131:137-150. |
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|---|---|---|---|---|
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| Regal | Apolipoprotein E epsilon4 is superior to apolipoprotein E epsilon2 in predicting cognitive scores over 30 months | Clinical Interventions in Aging | 2013 | 8:1461-1465. |
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| Author | Title | Journal | Year | Citation |
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| Author | Title | Journal | Year | Citation |
|---|---|---|---|---|
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**Supplementary Table 6.** Deprioritized studies

| **Citation** |
|---|
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**Supplementary Table 7.** Risk of bias assessment (QUIPS)

| Study | 1. Study Participants | 2. Study Attrition | 3. PF Measurement | 4. Outcome Measurement | 5. Study Confounding | 6. Statistical Analysis and Presentation | Overall |
|---|---|---|---|---|---|---|---|
| **Chen 2018 [1]** | High | Low | Moderate | Moderate | Moderate | Low | High |
| **Chung 2021 [2]** | Low | Low | Moderate | Low | Moderate | Low | High |
| **Cova 2016 [3]** | High | Low | Low | Moderate | Low | Low | High |
| **Cullen 2021 [41]** | Low | Moderate | Low | Low | Low | Low | Moderate |
| **Degerman Gunnarsson 2016 [4]** | High | High | Low | Moderate | Moderate | Low | High |
| **Divers 2022 [5]** | Low | Low | Low | Moderate | High | Low | High |
| **Goukasian 2019 [7]** | Low | Moderate | Low | Low | Low | Low | High |
| **Galasko 2019 [6]** | **Low** | Moderate | **Low** | Moderate | **Moderate** | Low | High |
| **Han 2021 [8]** | Low | High | Moderate | Low | Low | Low | High |
| **Hanon 2022 [9]** | Moderate | High | Moderate | Low | Moderate | Low | High |
| **Ito 2015 [10]** | Low | Moderate | High | Low | Moderate | Low | High |
| **Janelidze 2020 [42]** | Low | Moderate | Moderate | Moderate | Low | Low | High |
| **Julayanont 2014 [11]** | High | Low | High | Low | Moderate | High | High |
| **Karikari 2020 [12]** | Low | High | Moderate | Low | Moderate | Low | High |
| **Kim 2015 [13]** | Low | Low | Moderate | Moderate | Moderate | Low | High |
| **Lan 2021 [14]** | Low | Low | Low | Moderate | Moderate | Low | High |
| **Lee 2012 [43]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Lee 2014 [15]** | Low | Low | Moderate | Moderate | Moderate | Low | High |
| **Lehman 2013 [16]** | Low | Low | Low | Moderate | High | High | High |
| **Liew 2021 [17]** | Low | Low | Moderate | Moderate | Moderate | Low | High |
| **LoBue 2018 [44]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Mai 2022 [18]** | Moderate | Low | Low | Moderate | Low | Low | High |
| **Matsuoka 2020 [19]** | Low | Low | Moderate | Moderate | Moderate | High | High |
| **Mecca 2018 [20]** | Low | High | Low | Moderate | Moderate | Low | High |
| **Mielke 2017 [21]** | High | Low | Low | Low | Low | Low | High |
| **Moon 2017 [22]** | Low | Low | Low | Moderate | Moderate | Low | High |
| **Morgan 2019 [23]** | High | High | Low | Moderate | Moderate | Low | High |
| **Mouchet 2021 [45]** | Low | Low | Low | Low | Moderate | Low | Moderate |
| **Muscari 2021 [24]** | High | Low | Low | Low | Low | Low | High |
| **Myung 2016 [25]** | Low | Low | Moderate | Moderate | Moderate | Low | High |
| **Palmqvist 2012 [26]** | High | Low | Low | Moderate | Moderate | Low | High |
| **Palmqvist 2021 [46]** | Low | Low | Low | Low | Low | Low | Low |
| **Pelkmans 2022 [27]** | Low | Low | Moderate | Moderate | Low | Low | High |
| **Pichet Binette 2022 [47]** | Low | Low | Low | Low | Low | Low | Low |
| **Pyun 2017 [48]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Pyun 2021 [28]** | Moderate | Low | High | Moderate | Low | Low | High |
| **Qin 2019 [29]** | Low | Low | Low | Moderate | Moderate | Low | High |
| **Reija 2017 [30]** | Low | Low | High | Low | Low | Low | High |

| Study | 1. Study Participants | 2. Study Attrition | 3. PF Measurement | 4. Outcome Measurement | 5. Study Confounding | 6. Statistical Analysis and Presentation | Overall |
|---|---|---|---|---|---|---|---|
| **Richard 2012 [49]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Ruthirakuhan 2019 [31]** | Low | Moderate | Low | Moderate | Moderate | Low | High |
| **Salloway 2022 [50]** | Low | Low | Low | Low | Moderate | Low | Moderate |
| **Spalletta 212 [51]** | Low | Low | Low | Low | Low | Low | Low |
| **Spencer 2019 [52]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Steenland 2012 [32]** | Low | Moderate | Low | Moderate | Low | Low | High |
| **Sugarman 2020 [33]** | Low | Low | Low | Moderate | Moderate | Low | High |
| **Suh 2019 [34]** | High | Low | Low | Low | Low | Low | High |
| **Therriault 2021 [53]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Tifratene 2015 [35]** | Low | Low | Low | Moderate | Moderate | Low | High |
| **Tosto 2014 [54]** | Moderate | Low | Low | Low | Low | Low | Moderate |
| **Van Der Mussele 2014 [36]** | High | Low | Low | Low | Low | Low | High |
| **Van Loenhoud 2022 [55]** | High | Low | Low | Low | Low | Low | High |
| **Vos 2013 [37]** | Low | High | High | Low | Low | Low | High |
| **Wolfsgruber 2017 [56]** | Moderate | Low | Low | Low | Low | Low | Moderate |
| **Xue 2017 [38]** | Low | Low | High | Moderate | Moderate | Low | High |
| **Xue 2020 [57]** | Low | Low | Low | Moderate | Low | Low | Moderate |
| **Yi 2016 [39]** | High | Low | Low | Moderate | Low | Low | High |
| **Zhou 2012 [40]** | Low | Moderate | Low | Moderate | Low | Low | High |

**Supplementary Table 8.** Risk of bias assessment (ROB2)

| Study | Outcome | Randomization | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|---|---|---|---|---|---|---|---|
| **Swanson 2021 BAN2401-G000-201 [58]** | Primary: Change from baseline in ADCOMS at 12 months | Some concerns | Low | High | High | Low | High risk |
| **Budd Haeberlein 2022 EMERGE [59]** | Primary: Change from baseline in CDR-SB at week 78 | Some concerns | Low | Low | Low | Low | Some concerns |
| **Budd Haeberlein 2022 ENGAGE [59]** | Primary: Change from baseline in CDR-SB at week 78 | Some concerns | Low | Low | Low | Low | Some concerns |
| **Ostrowitzki 2017 Scarlet Road [60]** | Safety | Low | Low | Low | High | Low | High risk |
| **Mintun 2021 TRAILBLAZER-ALZ [61]** | Safety | Low | Low | Low | High | Low | High risk |
| **Sevigny 2016 [62]** | Safety | Some concerns | Some concerns | Low | Some concerns | Low | Some concerns |

ADCOMS, the Alzheimer's disease composite score; CDR-SB, clinical dementia rating score – sum of boxes

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