International Psychogeriatrics (2024), 36:12, 1093–1109
doi:10.1017/S1041610223000509

REVIEW

Clinical characteristics of early-onset versus late-onset Alzheimer's disease: a systematic review and meta-analysis

Paige Seath,[1] Luis Enrique Macedo-Orrego,[2,3] and Latha Velayudhan[1,4]

[1]*Academic Psychiatry Division, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK*
[2]*Departamento de Psiquiatría, Universidad Nacional Mayor de San Marcos, Lima, Peru*
[3]*Departamento de atencion especializada de adultos mayores, Instituto Nacional de Salud Mental, Lima, Peru*
[4]*South London and Maudsley NHS Foundation Trust, London, UK*

ABSTRACT

Objectives: A number of studies have compared Alzheimer's disease (AD), the commonest form of dementia, based on their age of onset, i.e. before the age of 65 years (early-onset AD, EO-AD) to those developing after 65 years of age (late-onset AD, LO-AD), but the differences are not clear. We performed a systematic review and meta-analysis to compare clinical characteristics between EO-AD and LO-AD.

Design, measurements, and participants: Medline, Embase, PsycINFO, and CINAHL databases were systematically searched for studies comparing time to diagnosis, cognitive scores, annual cognitive decline, activities of daily living (ADLs), neuropsychiatric symptoms (NPS), quality of life (QoL), and survival time for EO-AD and LO-AD patients.

Results: Forty-two studies were included (EO-AD participants $n = 5{,}544$; LO-AD participants $n = 16{,}042$). An inverse variance method with random effects models was used to calculate overall effect estimates for each outcome. People with EO-AD had significantly poorer baseline cognitive performance and faster cognitive decline but longer survival times than people with LO-AD. There was no evidence that EO-AD patients differ from people with LO-AD in terms of symptom onset to diagnosis time, ADLs, and NPS. There were insufficient data to estimate overall effects of differences in QoL in EO-AD compared to LO-AD.

Conclusions: Our findings suggest that EO-AD differs from LO-AD in baseline cognition, cognitive decline, and survival time but otherwise has similar clinical characteristics to LO-AD. Larger studies using standardized questionnaires focusing on the clinical presentations are needed to better understand the impact of age of onset in AD.

Key words: Alzheimer's disease (AD), early-onset dementia, young onset dementia, cognitive assessment, meta-analysis

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 60–70% of the current 55 million dementia cases worldwide (WHO, 2021). Most often, symptoms develop after 65 years of age and known as late-onset AD (LO-AD) (WHO, 1992). However, it can also develop before 65 years of age, called early-onset AD (EO-AD), which accounts for approximately 5.5% of all AD cases (Zhu *et al.*, 2015).

Correspondence should be addressed to: Latha Velayudhan, Academic Psychiatry Division, Institute of Psychiatry, Psychology, and Neuroscience, 16 De Crespigny Park, London SE5 8AF, UK. Phone: 020 7848 0508. Email: latha.velayudhan@kcl.ac.uk. Received 11 Jul 2022; revision requested 18 Jan 2023; revised version received 02 Mar 2023; accepted 29 May 2023. First published online 11 July 2023.

There is evidence that EO-AD and LO-AD differ in clinical presentation. For instance, many researchers have observed that a significantly larger proportion of EO-AD patients exhibit non-amnestic presentations in which their main symptoms involve language deficits, apraxia, and visuospatial deficits, more so than memory complaints, which are typical in LO-AD patients (Gumus *et al.*, 2021). However, non-memory symptoms are not exclusive to EO-AD. Licht *et al.* (2007) observed poorer verbal fluency and motor-executive scores in LO-AD compared to EO-AD. Differences in the clinical characteristics and disease course have been compared between EO-AD and LO-AD; however, there are no reviews that compared EO-AD and LO-AD. Better understanding of the characteristics of EO-AD relative to LO-AD could facilitate early

recognition of EO-AD in clinical settings and, therefore, enable appropriate management. It could also provide patients and their caregivers or families with more information regarding the symptoms and prognostic course for planning care. We undertook a systematic review and meta-analysis to examine if there were any differences in clinical characteristics such as time to diagnosis, cognition, neuropsychiatric symptoms (NPS), activities of daily living (ADLs), quality of life (QoL), and survival time between patients with EO-AD and LO-AD.

Method

Study selection

The review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (Moher *et al.*, 2009). A systematic search was conducted in the databases Medline, EMBASE, PsycINFO, and CINAHL for papers published until October 26, 2021. More relevant references were identified by the snowballing method, with manual search of reference lists of identified papers. The search terms were "Alzheimer's disease" (as a sub-heading) AND ("early-onset Alzheimer* disease" OR "young*-onset Alzheimer* disease") AND "late-onset Alzheimer* disease" AND "age of onset" (sub-heading) OR "Mini-Mental State Examination" OR "cognitive decline" OR "Neuropsychiatric Inventory" OR "Activities of Daily Living" (sub-heading) OR "survival" (sub-heading) OR "patient outcome assessment" (sub-heading).

Studies were included if (1) they included original research comparing diagnosed EO-AD and LO-AD patients in terms of time to diagnosis, cognitive status, cognitive decline, NPS, functional status, quality of time, or survival; (2) they defined EO-AD as any age below 65-years-old at onset and LO-AD as any age from over 65-years-old at onset; and (3) they were published as peer-reviewed journal articles in English language. Studies were excluded if they (1) had EO dementias without sub-typing into EO-AD; (2) were non-English; or (3) published as any publication type other than peer-reviewed journal article such as conference abstracts.

The process of selecting the final studies is demonstrated in the PRISMA chart (Figure 1) (Page *et al.*, 2021). Studies were independently assessed by two researchers and disagreements resolved through consensus or discussions with a senior researcher.

Data extraction

A modified version of the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies, Adapted for Prognostic Factor Studies (CHARMS-PF) was used to guide information extraction (Moons *et al.*, 2014; Riley *et al.*, 2019) (Table 1). Information relating to statistical techniques and model development, study dates, and missing data is addressed in the assessment of risk of bias (Moons *et al.*, 2014). Extracted data were then inputted into the software program Review Manager (RevMan) 5.4 (The Cochrane Collaboration, 2020).

Quality assessment

The risk of bias assessment of individual studies was done according to the PROGRESS framework by the application of the quality in prognostic factor studies (QUIPS) tool (Hayden *et al.*, 2013; Riley *et al.*, 2019). The prognostic factor in this review is considered the age (at onset) variable that is used to separate the groups into EO-AD and LO-AD, where EO-AD is before 65 years and LO-AD is after 65 years. The authors made a priori decisions as to which QUIPS domains are most important to this review (described in the supplementary material).

Instruments

Time to diagnosis was defined as the time from symptom onset to diagnosis (Brück *et al.*, 2021). Any studies that reported time to diagnosis in months were converted into years. Cognitive scores as obtained using the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) assessed baseline cognition and cognitive decline. In AD populations specifically, there is an abundance of evidence suggesting that the MMSE is appropriate (Kørner *et al.*, 1996). This, as well as the measure's wide use in the literature (Stanley and Walker, 2014; Stanley *et al.*, 2019), is the rationale for selecting this measure for the current review. NPS are psychological and behavioral disturbances that are core features of AD and measured commonly using Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994). Another variable of interest in the current review was functionality, defined as the ability to independently engage in and complete ADLs (Lawton and Brody, 1969). We also looked at QoL, which, in elderly populations, concerns physical condition, mood, relationships, ability to participate in meaningful activities, financial well-being, and the individual's perceptions of their QoL,

https://doi.org/10.1017/S1041610223000509

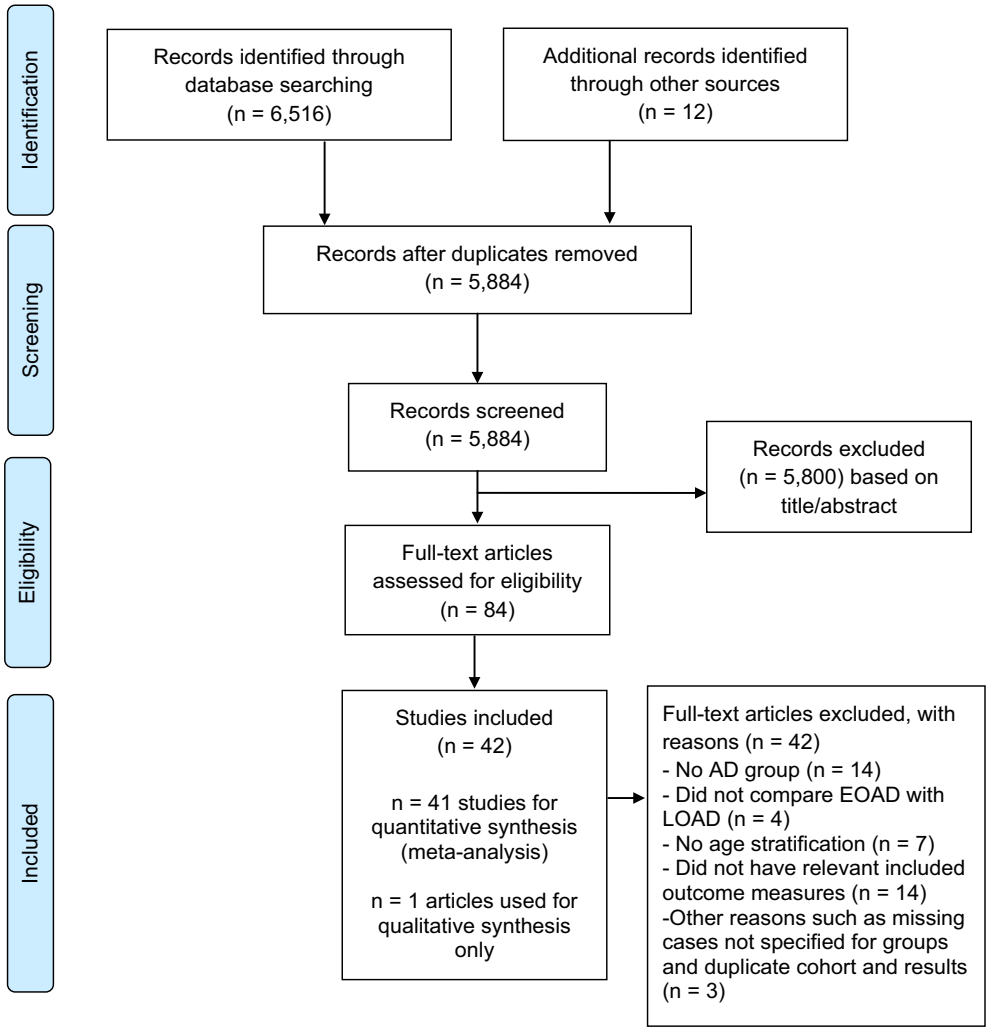

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

and, in this review, is operationalized as scores on the Quality of Life in Alzheimer's disease (QoL-AD) scale (Logsdon *et al.*, 1999). We extracted both self- and informant-reported QoL-AD scores. Finally, the survival time was defined as time from symptom onset or diagnosis to death (Brodaty *et al.*, 2012).

Data synthesis and analysis

For continuous variables (time to diagnosis, MMSE scores, mean annual change in MMSE scores, total NPI scores, ADL scores, QoL-AD scores, and survival times), an inverse variance statistical method with a random effects model was used. Random effects models allow for variation in studies' true effect sizes due to differences in sample characteristics. Standardized mean difference (SMD) was the effect measure to account for differences in scales between studies (Higgins *et al.*, 2022), for example modified or translated versions. RevMan 5.4 automatically calculated the SMD when means, standard deviations (SDs), and sample sizes for each group for each relevant study were inputted. Heterogeneity is assessed in each analysis using the Chi square test and the I^2 statistic. Interpretations of I^2 are based on the cutoff values suggested in the Cochrane Handbook (Higgins *et al.*, 2022). The results of these analyses are illustrated in forest plots (Figures 2 and 3).

The Cochrane Group suggests that two studies are adequate to perform a meta-analysis given that those studies are compatible and found similar results (Ryan, 2016). As some of the studies included in the current review were compatible but not with similar results, we performed a meta-analysis where there were three or more studies that reported a mean and SD. When a meta-analysis could not be conducted, the studies were reviewed and reported narratively. When a study had multiple results from the same sample, for example before and after propensity score matching (PSM), analysis was conducted with the original cohort only, but, when a study investigated an outcome after PSM

https://doi.org/10.1017/S1041610223000509

Table 1. Table of the included studies' characteristics

AUTHOR	LOCATION	DESIGN	EO-AD N	EO-AD MEAN AGE (SD)	LO-AD N	LO-AD MEAN AGE (SD)	RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
Baillon *et al.* (2019)	UK	Cross-sectional prospective cohort	24	59.3 (6.0)	56	82.3 (4.9)	Hospital memory services	At onset: EO-AD < 65, LO-AD > 65	MMSE, NPI, ADL	NINCDS-ADRDA for probable AD	Low
Carotenuto *et al.* (2012)	Italy	Retrospective longitudinal cohort	13	–	82	–	Memory clinic	Age: EO-AD < 65, LO-AD ≥ 65	MMSE, ADL, I-ADL	NINCDS-ADRDA for AD	Moderate
Chagué *et al.* (2021)	France	Retrospective cohort	34	59.29 (4.58)	49	73.04 (5.92)	Memory clinic	At clinical onset: EO-AD < 65, LO-AD > 65	MMSE	Diagnosis of each participant according to IWG-2 AD criteria assessed by three neurologists based on clinical, biological, and neuroimaging data	Moderate
Chang *et al.* (2017)	Korea	Retrospective longitudinal cohort	331	–	3,280	–	CREDOS memory disorder clinics	At clinical onset: EO-AD < 65, LO-AD > 65	Survival time, MMSE, ADL, NPI	NINCDS-ADRDA and DSM-IV for AD	Low
Chishiki *et al.* (2020)	Japan	Retrospective cohort	12	62.4 (6.3)	65	77.7 (5.3)	University hospital medical records	At symptom onset: EO-AD < 65, LO-AD ≥ 65	MMSE	NINCDS-ADRDA	Low
Cho *et al.* (2013)	Korea	Prospective longitudinal cohort	14	62.6 (7)	22	75.1 (3.6)	Clinic	At clinical onset: EO-AD < 65, LO-AD ≥ 65	MMSE	DSM-4 and NINCDS-ADRDA for probable AD	Moderate
Contador *et al.* (2021)	Barcelona	Prospective longitudinal cohort	14	60.7 (3.38)	55	79.41 (3.45)	ADNI GO/2 database from clinic	EO-AD < 65, LO-AD ≥ 75	MMSE	Unspecified	Moderate
Dourado *et al.* (2016)	Brazil	Cross-sectional cohort	52	65.6 (3.4)	155	74.2 (5.4)	Outpatient unit	According to age of onset, but unspecified cutoff value	MMSE, QoL-AD	DSM-IV-TR and NINCDS-ADRDA for possible or probable AD	Low
Eckerström *et al.* (2018)	Sweden	Prospective cross-sectional case-control cohort	24	61.2 (3.1)	39	72.3 (4.9)	Hospital memory clinic	Age: EO-AD ≤ 65, LO-AD > 65	MMSE	NINCDS-ADRDA	Moderate

Table 1. Continued

AUTHOR	LOCATION	DESIGN	EO-AD		LO-AD		RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
			N	MEAN AGE (SD)	*N*	MEAN AGE (SD)					
Elahi *et al.* (2020)	USA	Cross-sectional sampling from existing longitudinal cohort	33	61 (6.2)	30	79 (4.7)	University clinic	At onset of cognitive symptoms: EO-AD < 65, LO-AD unspecified	MMSE	NIA-AA for MCI or dementia due to probable AD, with positive amyloid PET scan and blood tests for patients with possible AD	Low
Falgàs *et al.* (2019)	Barcelona	Retrospective cross-sectional case-control cohort	58	61 (5.47)	30	75 (3.74)	Clinic	All patients ≤ 65 at clinical onset	MMSE	NIA-AA for MCI due to AD or AD dementia	Moderate
Ferreira *et al.* (2018)	Portugal	Retrospective cohort	35	64.5 (6.5)	35	76 (3.5)	Outpatient clinic	At disease onset: EO-AD < 65, LO-AD > 65	Disease duration, MMSE, NPI	NIA-AA for probable AD	Low
Frisoni *et al.* (2005)	Unclear	Cross-sectional case–control cohort	9	62 (7)	9	78 (4)	Hospital AD unit	At disease onset: EO-AD ≤ 65, LO-AD > 65	Disease duration, MMSE	NINCDS-ADRDA for probable AD	High
Gerritsen *et al.* (2016)	Netherlands	Prospective cross-sectional comparative cohort	177	61.1 (5)	155	79.4 (6.7)	EO-AD: memory clinics of AD centers, memory clinics of general hospitals, and mental health services, and LO-AD: community-dwelling patients from AD centers	EO-AD < 65, LO-AD < 65	MMSE	NINCDS-ADRDA for possible or probable AD	Moderate
Gour *et al.* (2014)	France	Prospective cross-sectional case–control cohort	14	60.3 (5.6)	14	75.1 (2.9)	Hospital clinic	At symptom onset: EO-AD < 65, LO-AD > 65	MMSE, disease duration	NINCDS-ADRDA and NIA-AA for probable AD	Moderate

Table 1. Continued

AUTHOR	LOCATION	DESIGN	EO-AD		LO-AD		RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
			N	MEAN AGE (SD)	*N*	MEAN AGE (SD)					
Grønning *et al.* (2012)	Denmark	Longitudinal case–control cohort	21	–	21	–	Memory clinic	At time of diagnosis: EO-AD ≤ 65, LO-AD > 70	MMSE, annual change in MMSE, ADL	NINCDS-ADRDA for probable AD	Low
Guven *et al.* (2020)	Istanbul	Cross-sectional case–control cohort	30	55.3 (6.4)	38	76.5 (5.8)	Neurology unit of hospital	At clinical onset: EO-AD < 65, LO-AD > 65	MMSE	NINCDS-ADRDA for probable AD	Low
Jacobs *et al.* (1994)	USA	Prospective multi-center longitudinal cohort	44	63.55 (4.95)	83	78.17 (6.5)	Outpatient hospital clinics	At symptom onset: EO-AD < 65, LO-AD ≥ 65	MMSE, change in MMSE	NINCDS-ADRDA for probable AD	Low
Kaiser *et al.* (2012)	USA	Prospective cross-sectional cohort	21	57.78 (4.35)	24	80.32 (5.89)	Healthcare center and university school of medicine	At disease onset: EO-AD < 65, LO-AD > 65	MMSE	NINCDS-ADRDA for probable AD	High
Kimura *et al.* (2018)	Brazil	Cross-sectional prospective cohort	53	65.5 (4.4)	57	73.4 (3)	Outpatient memory clinic	At onset: EO-AD < 65, LO-AD unclear	QoL-AD, MMSE, ADL	DSM-IV-TR	Low
Koedam *et al.* (2010)	Netherlands	Retrospective cross-sectional cohort	270	–	90	–	Medical center	At clinical onset: EO-AD < 65, LO-AD ≥ 65	MMSE, disease duration	NINCDS-ADRDA for possible or probable AD	Moderate
Licht *et al.* (2007)	USA	Retrospective cohort	44	61.66 (6.09)	44	87.00 (2.30)	Memory clinic	Age of onset: EO-AD < 65, LO-AD ≥ 84	Disease duration, MMSE	NINCDS-ADRDA for clinically probable AD	Moderate
Mendez *et al.* (2012)	Unclear	Retrospective longitudinal cohort	125	–	56	–	EO-AD: university clinic, LO-AD: existing cohorts	At clinical onset: EO-AD < 65, LO-AD > 65	MMSE, disease duration	NIA-AA for probable AD dementia with intermediate evidence of AD pathophysiological process	Low
Migliaccio *et al.* (2015)	USA	Retrospective longitudinal case–control cohort	15	56 (5)	10	76 (4)	University memory center's database	At disease onset: EO-AD < 65, LO-AD > 65	MMSE	Not specified	Low

Table 1. Continued

AUTHOR	LOCATION	DESIGN	EO-AD N	EO-AD MEAN AGE (SD)	LO-AD N	LO-AD MEAN AGE (SD)	RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
Mushtaq *et al.* (2016)	India	Cross-sectional prospective cohort	40	63.1 (1.12)	40	84.28 (2.17)	University memory clinic	At onset: EO-AD < 65, LO-AD > 65	MMSE, NPI	NINCDS-ADRDA for probable AD	Low
Palasí *et al.* (2015)	Spain	Cross-sectional cohort	38	59.4 (4.8)	143	77.2 (5.4)	Hospital referred	At disease onset: EO-AD ≤ 65, LO-AD > 65	MMSE	NINCDS-ADRDA for probable AD	Low
Panegyres and Chen (2013)	Unclear	Retrospective longitudinal cohort	614	–	3,133	–	CAMD's C-Path Online Data Repository database	At disease onset: EO-AD < 65, LO-AD not specified	MMSE	Not specified	Moderate
Park *et al.* (2015)	South Korea	Multi-center prospective cross-sectional cohort	616	62.6 (5.6)	2,351	76.8 (5.2)	Clinics at universities and hospitals	At clinical onset: EO-AD < 65, LO-AD not specified	Disease duration, MMSE, NPI	NINCDS-ADRDA and DSM-IV for probable AD	Low
Picard *et al.* (2011)	France	Multi-center prospective cross-sectional cohort	181	–	1,277	–	Memory clinic	At symptom onset: EO-AD < 65, LO-AD not specified	MMSE	Not specified but included possible and probable AD patients	Moderate
Rhodius-Meester *et al.* (2019)	Netherlands	Longitudinal cohort	608	–	1,082	–	Data from Dutch Municipal Register obtained about patients recruited from a medical center	Age: EO-AD ≤ 65, LO-AD > 65	Survival time	NINCDS-ADRDA and NIA-AA for dementia due to AD	High
Robbins *et al.* (2021)	USA	Prospective cross-sectional cohort	15	62.4 (5.2)	50	76.9 (5.2)	Neurological disorders clinic	At clinical onset: EO-AD < 65, LO-AD > 65	MMSE	NIA-AA	Low
Sá *et al.* (2012)	Portugal	Cross-sectional cohort	109	58.98 (6.45)	171	75.4 (4.95)	Hospital and private clinics	At clinical onset: EO-AD < 65, LO-AD > 65	MMSE	NINCDS-ADRDA and DSM-IV-TR for probable AD	Low
Shinotoh *et al.* (2000)	Japan	Prospective case–control longitudinal cohort	14	61 (6)	14	72 (4)	Five AD patients from outpatient university clinic, recruitment of the remaining is not provided	At disease onset: EO-AD < 65, LO-AD ≥ 65	Disease duration, MMSE	NINCDS-ADRDA for probable AD	Moderate

Table 1. Continued

AUTHOR	LOCATION	DESIGN	EO-AD		LO-AD		RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
			N	MEAN AGE (SD)	*N*	MEAN AGE (SD)					
Smirnov *et al.* (2021)	USA	Retrospective cohort	485	64 (5.6)	1,265	80.1 (6.3)	National Alzheimer's Coordinating Center database of USA AD centers	Age: EO-AD ≤ 63, LO-AD > 63	Disease duration, MMSE, NPI, I-ADL	NIA-Reagan criteria for high likelihood AD	Low
Spina *et al.* (2021)	USA	Retrospective longitudinal cohort	96	–	48	–	University Neurodegenerative Diseases Brain Bank database	At symptom onset: EO-AD ≤ 65, LO-AD > 65	MMSE, disease duration	Not specified, but AD confirmed post-mortem by expert neuropathologists	Moderate
Stage Jr *et al.* (2020)	USA	Cross-sectional cohort	50	64.7 (6.3)	148	78.3 (5.9)	ADNI study database	At symptom onset: EO-AD ≤ 65, LO-AD > 65	MMSE	NINCDS-ADRDA for probable AD	Moderate
Stanley *et al.* (2019)	UK	Retrospective longitudinal cohort	56	–	249	–	Memory clinic	At time of diagnosis: EO-AD < 65, MO-AD = 65 to 74, LO-AD ≥ 75	MMSE, rate of change in MMSE, disease duration	NINCDS-ADRDA for possible or probable AD	Low
Toyota *et al.* (2007)	Japan	Prospective cross-sectional cohort	46	58.8 (5)	261	78.5 (5.1)	Clinic for hospital outpatient	At first interfering symptom's onset: EO-AD < 65, LO-AD > 70	MMSE, NPI	NINCDS-ADRDA for probable AD	Low
van der Vlies *et al.* (2009)	Netherlands	Retrospective longitudinal cohort	99	–	192	–	Outpatient memory clinic	At disease onset: EO-AD ≤ 65, LO-AD > 65	Disease duration, MMSE, rate of change in MMSE	NINCDS-ADRDA for probable AD	Low

Table 1. Continued

AUTHOR	LOCATION	DESIGN	EO-AD N	EO-AD MEAN AGE (SD)	LO-AD N	LO-AD MEAN AGE (SD)	RECRUITMENT	CUTOFF AGE	OUTCOME MEASURES	DIAGNOSTIC CRITERIA	OVERALL RISK OF BIAS RATING
van Vliet *et al.* (2012)	Netherlands	Prospective longitudinal cohort	98	61.2 (4.9)	123	78.8 (5.9)	EO-AD: AD center and hospital clinics, other mental health services, and specialized day care facilities, and LO-AD: university or mental health-care clinic	At clinical onset: EO-AD < 65, LO-AD not specified	MMSE, NPI	DSM-IV-TR	Low
van Vliet *et al.* (2013)	Netherlands	Prospective longitudinal cohort	139	–	122	–	EO-AD: See above	At clinical onset: EO-AD < 65, LO-AD not specified	Disease duration	DSM-IV-TR and NINCDS-ADRDA	Moderate
Wattmo and Wallin (2017)	Sweden	Prospective longitudinal open-label non-randomized multi-center cohort	143	62.7 (5.4)	874	77.3 (4.7)	Memory clinics	At clinical onset: EO-AD < 65, LO-AD ≥ 65	MMSE, I-ADL	DSM-IV and NINCDS-ADRDA for possible or probable AD	Low

Values are presented as *n* or mean (standard deviation) unless otherwise specified.
AD = Alzheimer's disease, EO-AD = Early-onset Alzheimer's disease, LO-AD = Late-onset Alzheimer's disease, MMSE = Mini-Mental State Examination, ADL = Activities of Daily Living, NPI = Neuropsychiatric Inventory, I-ADL = Instrumental Activities of Daily Living, QoL-AD = Quality of Life-Alzheimer's Disease, NINCDS-ARDRA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, IWG = International Working Group, DSM-IV (or DSM-4) = Diagnostic and Statistical Manual of Mental Disorders fourth edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision, NIA-AA = National Institute of Aging-Alzheimer's Association, CREDOS = Clinical Research Center for Dementia of South Korea, ADNI GO/2 = Alzheimer's Disease Neuroimaging Initiative Grand Opportunity/2, CAMD = Coalition Against Major Diseases, MCI = Mild cognitive impairment, PET = Positron emission tomography, UK = United Kingdom, USA = United States of America.

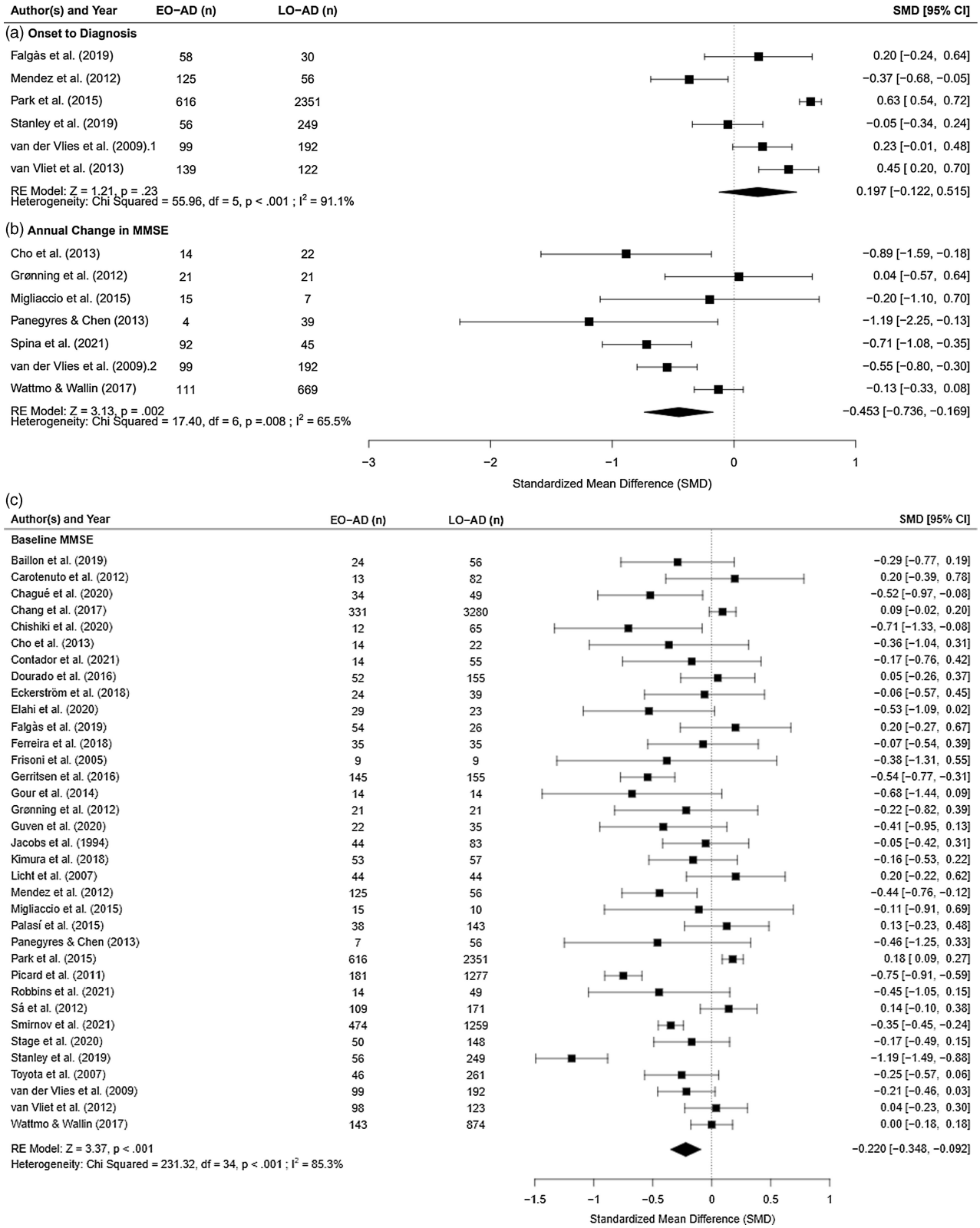

Figure 2. (a) and (b) Forest plots comparing symptom onset to diagnosis and cognitive decline of early-onset Alzheimer's disease (EO-AD) and late-onset Alzheimer's disease (LO-AD). (c) Forest plot comparing cognitive performance of early-onset Alzheimer's disease (EO-AD) and late-onset Alzheimer's disease (LO-AD).

https://doi.org/10.1017/S1041610223000509

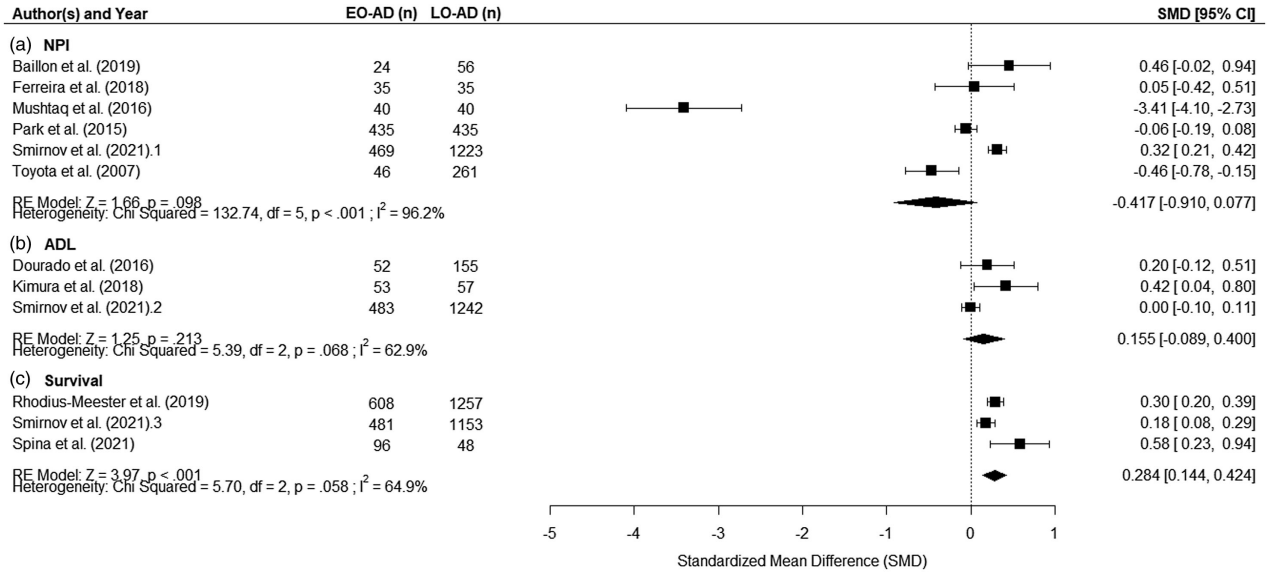

Figure 3. (a–c) Forest plots comparing neuropsychiatric symptoms, functionality, and survival times of early-onset Alzheimer's disease (EO-AD) and late-onset Alzheimer's disease (LO-AD).

only, the post-PSM result was included in the analysis. Sensitivity analyses were conducted only when the original meta-analysis result is significant (Tawfik *et al.*, 2019). The factors considered in sensitivity analyses were decided a priori and included study setting, country, and samples' disease severities when they were reported (Brück *et al.*, 2021).

Where variables or measures relevant to the current review were mentioned but no data were reported in a paper, authors were contacted to request for the data, and if we received no response and unable to access the information, the study was not included in the relevant analysis. Where studies used samples stratified by variables in conjunction with age at onset, the data re-stratified by only age at onset with a cutoff value of 65-years-old were requested for from the authors. If provided with raw datasets without summary statistics, we calculated the means and SDs as appropriate. Relevant data from newly stratified versions were only extracted if the equivalent data were published in the original paper. When no inferential test results were provided and the full dataset was available, we used the relevant tests in SPSS version 25 to compare EO- and LO-AD group means. In the case of missing summary statistics data in published papers, they were computed where possible according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al.*, 2022). Mean and SDs were obtained upon request from authors for the survival time variable (Rhodius-Meester *et al.*, 2019). If sample size data were missing and unable to be provided, the study was excluded from the analysis (Koedam *et al.*, 2010). All meta-analyzed means and SDs are presented in Supplementary Table 1.

Results

Data selection

Figure 1 (PRISMA flow chart) summarizes the study selection procedure. A total of 42 studies (EO-AD participants, $n = 5{,}544$, age $= 61.32 \pm 2.47$; LO-AD participants, $n = 16{,}042$, age $= 77.45 \pm 3.27$) were included. Main characteristics and outcome measures of each study are included in Table 1. Overall quality assessment of the 42 studies showed 23 (54.8%) had overall low risk of bias, 16 (38.1%) had overall moderate risk of bias, and 3 (7.1%) had overall high risk of bias (Table 1, Supplementary Figures 1 and 2).

Time to diagnosis

Six studies (EO-AD, $n = 1{,}093$; LO-AD, $n = 3{,}000$) compared the time to diagnosis of AD from symptom onset to diagnosis in EO and LO participants (Falgàs *et al.*, 2019; Mendez *et al.*, 2012; Park *et al.*, 2015; Stanley *et al.*, 2019; van Vliet *et al.*, 2013; van der Vlies *et al.*, 2009). The overall effect estimate was not statistically significant (SMD = 0.20, 95% confidence interval (CI) [−0.12, 0.52], $Z = 1.21$, $p = 0.23$) (Figure 2a). These data therefore do not provide evidence of a difference in the time period between onset of symptoms and diagnosis for EO-AD and LO-AD patients.

https://doi.org/10.1017/S1041610223000509

Cognition at presentation

Of the 36 studies that compared EO-AD and LO-AD cognitive performance using the MMSE, Koedam *et al.* (2010) did not provide exact sample size data for the two groups so was excluded. The remaining 35 studies (EO-AD, $n = 3{,}059$; LO-AD, $n = 11{,}524$) (Figure 2c) showed a statistically significant overall effect estimate (SMD = −0.22, 95% CI [−0.35, −0.09], $Z = 3.37$, $p < 0.001$), implying that EO-AD patients had lower MMSE scores than LO-AD patients at initial presentation. However, there was high heterogeneity ($I^2 = 85\%$, $\chi^2(34) = 231.32$, $p < 0.001$).

Cognitive decline

Ten of the included studies compared the rate of annual cognitive decline in EO-AD versus LO-AD patients using MMSE. Although Jacobs *et al.* (1994) compared six-monthly rate of change over 2 years, the exact change in MMSE scores for the annual period was not available; hence, we could not include them. However, they did report that EO-AD patients showed a more rapid decline than LO-AD ($F = 12.50$, $p < 0.001$). We also could not include Stanley *et al.* (2019) as they did not report or provide information on means and SDs. The mean difference of MMSE from the analysis of the remaining seven studies (EO-AD, $n = 356$; LO-AD, $n = 995$) was statistically significant (SMD = −0.45, 95% CI [−0.74, −0.17], $Z = 3.13$, $p = 0.002$), suggesting that EO-AD patients had a greater decrease in their MMSE score per year than LO-AD patients (Figure 2b). There was however significant heterogeneity ($I^2 = 66\%$, $\chi^2(7) = 17.40$, $p = 0.008$).

Neuropsychiatric symptoms

Six studies (EO-AD, $n = 1{,}049$; LO-AD, $n = 2{,}050$) compared mean NPI scores of EO-AD and LO-AD participants. LO-AD participants had a greater total NPI score than the EO-AD group; however, this difference was not statistically significant (SMD = −0.42, 95% CI [−0.91, 0.08], $Z = 1.66$, $p = 0.10$) (Figure 3a). There was considerable heterogeneity in the effect estimates ($I^2 = 96\%$; $\chi^2(5) = 132.74$, $p < 0.001$).

There were three studies that compared EO-AD and LO-AD's mean scores for the NPI subdomains (Baillon *et al.*, 2019; Mushtaq *et al.*, 2016; Toyota *et al.*, 2007). Toyota *et al.* (2007) compared only 10 of the subdomains, so we conducted meta-analysis for the original 10 subdomains (EO-AD, $n = 110$; LO-AD, $n = 357$). Overall effect estimates for agitation, disinhibition, and irritability could not be calculated in RevMan because SDs were reported as zero by Mushtaq *et al.* (2016), leaving too few studies to conduct a meta-analysis for these domains. Of the remaining seven subdomains, there were no significant effect estimates, suggesting that EO-AD and LO-AD do not differ in these subdomains (Supplementary Figure 3) or for the total NPS.

Functional status

A number of studies compared ADL scores in EO-AD and LO-AD patients. However, they used different questionnaires such as Lawton ADL (Lawton and Brody, 1969), FAQ (Pfeffer *et al.*, 1982), Bristol Activities of Daily Living (BADL) (Bucks *et al.*, 1996), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) (Galasko *et al.*, 1997), and Barthel Index (Mahoney and Barthel, 1965).

Analysis conducted on the three studies that used FAQ (EO-AD, $n = 588$; LO-AD, $n = 1{,}454$) showed the effect estimate was not statistically significant (SMD = 0.16, 95% CI [−0.09, 0.40], $Z = 1.25$, $p = 0.21$), suggesting that EO-AD and LO-AD patients have similar independence in instrumental ADLs (Figure 3b). The heterogeneity was not significant ($I^2 = 63\%$, $\chi^2(2) = 5.39$, $p = 0.07$) (Figure 3b). LO-AD patients had greater functional independence using Lawton I-ADL scores (Wattmo and Wallin, 2017), whereas EO-AD were shown to have less severe functional impairment on the ADCS-ADL scores (Grønning *et al.*, 2012). On the other hand, some studies showed no difference between the groups using Lawton I-ADL (Carotenuto *et al.*, 2012), BADL (Baillon *et al.*, 2019), and ADCS-ADL (Kaiser *et al.*, 2012). Two studies compared Barthel Index scores (basic ADLs) between EO-AD and LO-AD patients. Park *et al.* (2015) reported that EO-AD patients ($n = 616$) scored higher on the Barthel ADL scale than the LO-AD patients ($n = 2{,}351$), without any reference to values. Chang, 2017) suggested EO-AD had significantly higher ADL scores ($n = 331$, mean (± SD) = 18.7 (± 3.2)) compared to LO-AD ($n = 3{,}280$, mean (± SD) = 17.9 (± 4.1) ($p < 0.001$)).

Quality of life

Two studies compared EO-AD and LO-AD and reported both the patient-reported and informant-reported QoL-AD scores separately. For the patient-reported data, EO-AD patients' ($n = 52$) mean score was 33.2 (± 6.5), similar to LO-AD ($n = 155$, 34.3 ± 6.2) (Dourado *et al.*, 2016). For the informant-reported data, EO-AD patients' ($n = 52$) mean score of 29.6 (± 6.2) was similar to LO-AD patients ($n = 155$, 30.4 ± 7.6). A similarly non-significant finding was reported by Kimura *et al.*

https://doi.org/10.1017/S1041610223000509

(2018), wherein EO-AD patients had a self-reported QoL-AD score ($n = 53$, 33.6 ± 6.5) versus LO-AD ($n = 57$, 32.9 ± 5.8, $p = 0.540$). The difference between EO-AD and LO-AD's caregiver-reported QOL-AD scores was also non-significant ($p = 0.895$).

Survival time

Three studies examined survival in EO-AD and LO-AD patients. Rhodius-Meester *et al.* (2019) defined survival as time in years from diagnosis to death, whereas Smirnov *et al.* (2021) and Spina *et al.* (2021) defined it as time in years from symptom onset to death. A meta-analysis could be conducted with these studies after Smirnov *et al.* (2021) provided summary statistics stratified by the cutoff of 65-years-old upon request (D. Smirnov, personal communication, December 5, 2021). The overall effect estimate was significant (SMD = 0.28, 95% CI [0.14, 0.42], $Z = 3.97$, $p < 0.001$) with moderate but non-significant heterogeneity ($I^2 = 65\%$, $\chi^2(2) = 5.70$, $p = 0.06$), suggesting that EO-AD patients survive for longer than LO-AD patients (Figure 3c).

Discussion

To our knowledge, this is the first systematic review and meta-analysis comparing clinical characteristics of EO-AD to LO-AD. We found people with EO-AD had poorer baseline cognitive scores and faster cognitive decline but longer survival times. They did not differ from people with LO-AD in terms of time to diagnosis, ADLs, and NPS. There were insufficient data to estimate overall effects in QoL.

EO-AD participants showed significantly poorer cognitive performance than LO-AD participants. LO-AD patients typically present mainly with episodic memory complaints, whereas a higher proportion of EO-AD patients exhibit non-amnestic cognitive syndromes that affect domains such as language and visuospatial abilities (Mendez *et al.*, 2012), which could explain their lower MMSE scores. EO-AD presents with more non-cognitive symptoms such as depression and anxiety (Gumus *et al.*, 2021), and they may use association areas to compensate for their cognitive difficulties (Solé-Padullés *et al.*, 2009) and it is not until later when the cognitive symptoms are more obvious and impacting their day-to-day life that they approach for assessment, which may also be a reason for lower scores at presentation. Although the effect size was small, this is of potential theoretical interest and an area to study further.

People with EO-AD showed a more rapid rate of annual decline in global cognitive function compared to LO-AD, with a medium effect size, which is potentially clinically meaningful and needs to be established in future studies. This may be due to the faster, more severe neuropathological changes that have been observed in EO-AD patients (Sakai *et al.*, 2013). The faster EO-AD decline has been observed with multiple measures of cognition (Schneider *et al.*, 2015), so it would not have been affected by our choice of limiting the cognitive measure to the MMSE. The faster cognitive decline has also been noted beyond the period of 24 months from baseline. Sakai *et al.* (2013) found that EO-AD patients' MMSE decreased at an average rate of 1.9 (SD = 1.0) points per year, up to 90 months from baseline, which was significantly greater than LO-AD patients whose MMSE decreased by 1.1 (SD = 0.8) points on average per year ($p < 0.001$).

We did not see a difference in time to diagnosis from symptom onset to getting diagnosed between the two groups. Previous evidence that EO dementia has longer time to diagnosis may be influenced by the other subtypes of EO-dementias such as frontotemporal dementia which are more prevalent in younger age, more non-amnestic presentations, total number of specialist services consulted which increased the time to diagnosis, and maybe also lack of competence even in specialist services (Kvello-Alme *et al.*, 2021; Loi *et al.*, 2022). However, when we focussed on EO-AD versus LO-AD there seems to be no difference, as also seen when time to diagnosis was compared for different types of young onset dementia, with shorter time to diagnosis in people with AD compared to the "other" dementia group (Loi *et al.*, 2022). This needs to be further investigated and compared between different dementia subtypes for the age groups. A recent study found delay in time to diagnosis of people with EO-AD who were mostly diagnosed using biomarkers (Kvello-Alme *et al.*, 2021). This study however did not compare with LO-AD group. It would be useful and important for future studies to have accurate diagnosis using biomarkers which are now more available to compare EO-AD versus LO-AD.

Our meta-analysis of studies investigating EO-AD and LO-AD's ADL using FAQ suggested that there was no difference in functional dependence, indicating the illness affects both younger and older adults similarly. In the literature, there is high variability in use of measures to assess functional status in AD. Future studies should aim to use consistent measures.

There was no significant difference in NPS between EO-AD and LO-AD. This is consistent with recent studies that also found no significant difference between LO-AD and EO-AD for overall NPI scores (Altomari *et al.*, 2022; Falgàs *et al.*, 2022). We also found no significant group differences in any

https://doi.org/10.1017/S1041610223000509

of the NPI sub-domain scores. Most NPI sub-domain difference effect sizes were negligible to small; however, the effect size for the group difference in aberrant motor behavior was large, but because of the small sample of studies limited the analysis' power to detect statistical significance.

Two identified studies suggested that QoL for EO-AD and LO-AD patients was not significantly different regardless of who was reporting it, patient or the caregiver. More research in QoL comparing EO-AD versus LO-AD is needed (Ducharme *et al.*, 2016).

The lack of difference in NPS, functional dependence, and QoL possibly demonstrates that AD impacts people in similar ways irrespective of age at onset.

There were three studies comparing survival times (Rhodius-Meester *et al.*, 2019; Smirnov *et al.*, 2021; Spina *et al.*, 2021). Contrary to the assumption that EO-AD progresses quickly with a short survival period, the effect estimate suggested that EO-AD patients survive longer than LO-AD patients. The explanation could be that younger people are in better physical health and medical conditions compared to elderly with LO-AD (Spina *et al.*, 2021). EO-AD patients may also have protective factors, such as more commonly experiencing atypical presentations such as language symptoms or executive dysfunction, which are associated with longer survival (Pavisic *et al.*, 2020). It could also be because the studies included in the review were sporadic EO-AD cases which are unlike familial EO-AD which is known to have rapid progression (Loeffler, 2021). Future research could investigate survival in different types of EO-AD cases compared to LO-AD.

It is interesting that our meta-analysis showed that EO-AD had lower cognitive performance at presentation and greater cognitive decline but longer survival rate. Higher age at diagnosis, higher number of medical comorbidities, and greater disability have been shown to predict shortened survival better than cognitive impairment (Lichtenstein *et al.*, 2018). Later age at diagnosis and greater disease severity at presentation have been associated with shorter survival time (Brodaty *et al.*, 2012; Schaffert *et al.*, 2022). Future studies should examine the role of cognitive impairment in predicting life expectancy in those with milder dementia using more sensitive neuropsychological measures (Schaffert *et al.*, 2022).

Our review and meta-analysis are limited by methodological weaknesses in the included studies as identified during quality assessment, specifically pertaining to sample size, selective outcome reporting, and variability of questionnaires used in the studies. Of the included studies, 18 were investigating neuroimaging and/or biomarkers and, although we excluded studies that matched groups by MMSE scores, there may have been potential confounders in some studies that may have clinically homogenous groups.

Our review was limited to studies that directly compared EO-AD and LO-AD. Some studies identified in the literature search divided their samples into EO-AD, middle-onset AD (MO-AD), and LO-AD (Stanley *et al.*, 2019). Their findings suggest that MO-AD may be another separate sub-type of AD, as found that MO-AD patients have a significantly different monthly rate of MMSE decline compared to EO-AD and LO-AD patients (Stanley *et al.*, 2019). Future meta-analyses could also compile research comparing EO-AD, MO-AD, and LO-AD in order to provide a further elucidated and more specific understanding of the effects of age of onset on AD characteristics if there are enough studies. We conducted a meta-analysis for the survival time including studies which defined them either as diagnosis to death or symptom onset to death similar to the criteria previously used (Brodaty *et al.*, 2012). However, future studies should have uniform and similar definitions for better comparisons. More research comparing EO-AD and LO-AD patients, particularly in the domains of basic ADLs and QoL, is needed to improve clinical knowledge of how these conditions differ based on age of onset. We did not test the influences of prevalence of APOE $\epsilon 4$ allele, presence of co-pathologies, or compare biomarkers such as blood and CSF markers, or neuroimaging (brain volumes). Future reviews should examine influences of these too.

Conclusion

Our meta-analysis suggests that people with EO-AD have poorer cognitive performance at presentation, faster cognitive decline, and longer survival times compared to people with LO-AD but did not differ in time to diagnosis, functional dependence, and total NPS. This implies that the AD condition is similar and affects people in similar way irrespective of age of onset. However, further research is warranted for clarification about differences in EO-AD and LO-AD's QoL. It is important to understand EO-AD's characteristics to facilitate early identification, diagnosis, and management and to alleviate the burdensome social, emotional, and financial, as well as medical consequences. A greater understanding of EO-AD symptoms, course, and prognosis will also aid patients and their caregivers and families for future care needs and planning. Better understanding of clinical features along with their underlying neuropathologies would also support precision

https://doi.org/10.1017/S1041610223000509

medicine with appropriate pharmacological and non-pharmacological interventions.

Conflict of interest

None.

Description of author(s)' roles

LM and PS did the literature review. PS did data extraction, assessed risk of bias, carried out the analysis, and drafted the manuscript. LV conceived the project, was involved in study selection, assessed risk of bias, supervised data extraction and analysis, interpretation of the results, and finalized the manuscript.

Acknowledgements

The authors would like to thank Sara Pisani for help with R codes.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610223000509.

References

Altomari, N. *et al.* (2022). A comparison of behavioral and psychological symptoms of dementia (BPSD) and BPSD sub-syndromes in early-onset and late-onset Alzheimer's disease. *Journal of Alzheimer's Disease*, 85, 691–699.

Baillon, S., Gasper, A., Wilson-Morkeh, F., Pritchard, M., Jesu, A. and Velayudhan, L. (2019). Prevalence and severity of neuropsychiatric symptoms in early- versus late-onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 34, 433–438.

Brodaty, H., Seeher, K. and Gibson, L. (2012). Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. *International Psychogeriatrics*, 24, 1034–1045.

Brück, C. C., Wolters, F. J., Ikram, M. A. and de Kok, I. M. C. M. (2021). Heterogeneity in reports of dementia disease duration and severity: a review of the literature. *Journal of Alzheimer's Disease*, 84, 1515–1522.

Bucks, R., Ashworth, D., Wilcock, G. and Siegfried, K. (1996). Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. *Age and Ageing*, 25, 113–120.

Carotenuto, A. *et al.* (2012). Late and early onset dementia: what is the role of vascular factors? A retrospective study. *Journal of Neurological Sciences*, 322, 170–175.

Chagué, P. *et al.* (2021). Radiological classification of dementia from anatomical MRI assisted by machine learning-derived maps. *Journal of Neuroradiology*, 48, 412–418. https://doi.org/10.1016/j.neurad.2020.04.004

Chang, K. J. *et al.* (2017). 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*, 56, 1341–1348.

Chishiki, Y. *et al.* (2020). Different patterns of gray matter volume reduction in early-onset and late-onset Alzheimer disease. *Cognitive and Behavioral Neurology*, 33, 253–258. https://doi.org/10.1097/WNN.0000000000000245

Cho, H. *et al.* (2013). Longitudinal changes of cortical thickness in early- versus late-onset Alzheimer's disease. *Neurobiology of Aging*, 34, 1921.e9–e1921.e15. https://doi.org/10.1016/j.neurobiolaging.2013.01.004

Contador, J. *et al.* (2021). Longitudinal brain atrophy and CSF biomarkers in early-onset Alzheimer's disease. *NeuroImage: Clinical*, 32, 102804. https://doi.org/10.1016/j.nicl.2021.102804

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A. and Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44, 2308–2314.

Dourado, M. C. N., Laks, J. and Mograbi, D. (2016). Functional status predicts awareness in late-onset but not in early-onset Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, 29, 313–319.

Ducharme, F., Lachance, L., Kergoat, M.-J., Coulombe, R., Antoine, P. and Pasquier, F. (2016). A comparative descriptive study of characteristics of early- and late-onset dementia family caregivers. *American Journal of Alzheimer's Disease & Other Dementias*, 31, 48–56.

Eckerström, C., Klasson, N., Olsson, E., Selnes, P., Rolstad, S. and Wallin, A. (2018). Similar pattern of atrophy in early- and late-onset Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 10, 253–259. https://doi.org/10.1016/j.dadm.2018.02.001

Elahi, F. M. *et al.* (2020). Plasma biomarkers of astrocytic and neuronal dysfunction in early- and late-onset Alzheimer's disease. *Alzheimer's and Dementia*, 16, 681–695. https://doi.org/10.1016/j.jalz.2019.09.004

Falgàs, N. *et al.* (2019). Hippocampal atrophy has limited usefulness as a diagnostic biomarker on the early onset Alzheimer's diseases patients: a comparison between visual and quantitative assessment. *NeuroImage: Clinical*, 23, 101927.

Falgàs, N. *et al.* (2022). The severity of neuropsychiatric symptoms is higher in early-onset than late-onset Alzheimer's disease. *European Journal of Neurology*, 29, 957–967.

Ferreira, M. C., Abreu, M. J., Machado, C., Santos, B., Machado, Á. and Costa, A. S. (2018). Neuropsychiatric profile in early versus late onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 33, 93–99. https://doi.org/10.1177/1533317517744061

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.

Frisoni, G. B., Testa, C., Sabattoli, F., Beltramello, A., Soininen, H. and Laakso, M. P. (2005). Structural correlates of early and late onset Alzheimer's disease: Voxel-Based morphometric study. *Journal of Neurology, Neurosurgery & Psychiatry*, 76, 112–114. https://doi.org/10.1136/jnnp.2003.029876

Galasko, D. *et al.* (1997). An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Disease and Associated Disorders*, 11, S33–S39.

Gerritsen, A. A. J. *et al.* (2016). Prevalence of comorbidity in patients with young-onset Alzheimer disease compared with late-onset: a comparative cohort study. *Journal of the American Medical Directors Association*, 17, 318–323. https://doi.org/10.1016/j.jamda.2015.11.011

Gour, N. *et al.* (2014). Functional connectivity changes differ in early and late-onset Alzheimer's disease. *Human Brain Mapping*, 35, 2978–2994. https://doi.org/10.1002/hbm.22379

Grønning, H., Rahmani, A., Gyllenbuorg, J., Dessau, R. B. and Høgh, P. (2012). Does Alzheimer's disease with early onset progress faster than with late onset? A case-control study of clinical progression and cerebrospinal fluid biomarkers. *Dementia and Geriatric Cognitive Disorders*, 33, 111–117.

Gumus, M., Multani, N., Mack, M. L. and Tartaglia, M. C. (2021). Progression of neuropsychiatric symptoms in young-onset versus late-onset Alzheimer's disease. *GeroScience*, 43, 213–223.

Guven, G. *et al.* (2020). Peripheral TREM2 mRNA levels in early and late-onset Alzheimer's disease patients. *Molecular Biology Reports*, 47, 5903–5909. https://doi.org/10.1007/s11033-020-05661-7

Hayden, J., van der Windt, D., Cartwright, J., Côté, P. and Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Annals of Internal Medicine*, 158, 280–286.

Higgins, J. P. T. *et al.* (2022). *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane. Available at: www.training.cochrane.org/handbook

Jacobs, D. *et al.* (1994). Age at onset of Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. *Neurology*, 44, 1215–1220.

Kaiser, N. C. *et al.* (2012). Neuropsychological and neuroimaging markers in early versus late-onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 27, 520–529.

Kimura, N. R. S. *et al.* (2018). Caregivers' perspectives of quality of life of people with young- and late-onset Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, 31, 76–83.

Koedam, E. L. G. E., Lauffer, V., van der Vlies, A. E., van der Flier, W. M., Scheltens, P. and Pijnenburg, Y. A. L. (2010). Early- versus late-onset Alzheimer's disease: more than age alone. *Journal of Alzheimer's Disease*, 19, 1401–1408.

Kørner, A., Lauritzen, L. and Bech, P. (1996). A psychometric evaluation of dementia rating scales. *European Psychiatry*, 11, 185–191.

Kvello-Alme, M., Bråthen, G., White, L. R. and Sando, S. B. (2021). Time to diagnosis in young onset alzheimer's disease: a population-based study from central Norway. *Journal of Alzheimer's Disease*, 82, 965–974.

Lawton, M. P. and Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activity of daily living. *The Gerontologist*, 9, 179–186.

Licht, E. A., McMurtray, A. M., Saul, R. E. and Mendez, M. F. (2007). Cognitive differences between early- and late-onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 22, 218–222.

Lichtenstein, M. L. *et al.* (2018). 16-year survival of the Canadian collaborative cohort of related dementias. *Canadian Journal of Neurological Sciences*, 45, 367–374.

Loeffler, D. A. (2021). Modifiable, non-modifiable, and clinical factors associated with progression of Alzheimer's disease. *Journal of Alzheimer's Disease*, 80, 1–27.

Logsdon, R. G., Gibbons, L. E., McCurry, S. M. and Teri, L. (1999). Quality of life in Alzheimer's disease: patient and caregiver reports. *Journal of Mental Health and Aging*, 5, 21–32.

Loi, S. M. *et al.* (2022). Time to diagnosis in younger-onset dementia and the impact of a specialist diagnostic service. *International Psychogeriatrics*, 34, 367–375.

Mahoney, F. I. and Barthel, D. W. (1965). Functional evaluation: the Barthel index. *Maryland State Medical Journal*, 14, 61–65.

Mendez, M. F., Lee, A. S., Joshi, A. and Shapira, J. S. (2012). Nonamnestic presentations of early-onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 27, 413–420.

Migliaccio, R. *et al.* (2015). Mapping the progression of atrophy in early and late-onset Alzheimer's disease. *Journal of Alzheimer's Disease*, 46, 351–364. https://doi.org/10.3233/JAD-142292

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. and The, P. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, 6, e1000097.

Moons, K. G. M. *et al.* (2014). Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Medicine*, 11, e1001744.

Mushtaq, R. *et al.* (2016). A comparison of the behavioral and psychological symptoms of dementia (BPSD) in early-onset and late-onset Alzheimer's – a study from South East Asia (Kashmir, India). *Cureus*, 8, e625.

Page, M. J. *et al.* (2021). The PRISMA. 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Medicine*, 18, e1003583.

Palasí, A. *et al.* (2015). Differentiated clinical presentation of early and late-onset Alzheimer's disease: is 65 years of age providing a reliable threshold? *Journal of Neurology*, 262, 1238–1246. https://doi.org/10.1007/s00415-015-7698-3

Panegyres, P. K. and Chen, H. Y. (2013). Differences between early and late onset Alzheimer's disease. *American Journal of Neurodegenerative Disease*, 2, 300–306.

Park, H. K. *et al.* (2015). Cognitive profiles and neuropsychiatric symptoms in Korean early-onset Alzheimer's disease patients: a CREDOS study. *Journal of Alzheimer's Disease*, 44, 661–673.

Pavisic, I. M. *et al.* (2020). Disease duration in autosomal dominant familial Alzheimer disease: a survival analysis. *Neurology Genetics*, 6, e507.

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., Filos, S. (1982). Measurement of functional activities

in older adults in the community. *Journal of Gerontology*, 37, 323–329.

Picard, C., Pasquier, F., Martinaud, O., Hannequin, D. and Godefroy, O. (2011). Early onset dementia: characteristics in a large cohort from academic memory clinics. *Alzheimer's Disease and Associated Disorders*, 25, 203–205. https://doi.org/10.1097/WAD.0b013e3182056be7

Rhodius-Meester, H. F. M. *et al.* (2019). Survival in memory clinic cohort is short, even in young-onset dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, 90, 726–728.

Riley, R. D. *et al.* (2019). A guide to systematic review and meta-analysis of prognostic factor studies. *The British Medical Journal*, 364, k4597.

Robbins, C. B. *et al.* (2021). Assessing the retinal microvasculature in individuals with early and late-onset Alzheimer's disease. *Opthalmic Surgery, Lasers, & Imaging Retina*, 52, 336–344. https://doi.org/10.3928/23258160-20210528-06

Ryan, R. (2016). *Cochrane consumers and communication review group: Meta-analysis*. Available at: http://cccrg.cochrane.org/

Sá, F. *et al.* (2012). Differences between early and late-onset Alzheimer's disease in neuropsychological tests. *Frontiers in Neurology*, 3, 81. https://doi.org/10.3389/fneur.2012.00081

Sakai, M. *et al.* (2013). Rate of progression of Alzheimer's disease in younger versus older patients: a longitudinal single photon emission computed tomography study. *Geriatrics & Gerontology International*, 13, 555–562.

Schaffert, J. *et al.* (2022). Predictors of life expectancy in autopsy-confirmed Alzheimer's disease. *Journal of Alzheimer's Disease*, 86, 271–281.

Schneider, L. S., Kennedy, R. E., Wang, G. and Cutter, G. R. (2015). Differences in Alzheimer disease clinical trial outcomes based on age of the participants. *Neurology*, 84, 1121–1127.

Shinotoh, H. *et al.* (2000). Progressive loss of cortical acetylcholinesterase activity in association with cognitive decline in Alzheimer's disease: a positron emission tomography study. *Annals of Neurology*, 48, 194–200. https://doi.org/10.1002/1531-8249(200008)48:2<194::AID-ANA9>3.0.CO;2-X

Smirnov, D. S., Galasko, D., Hiniker, A., Edland, S. D. and Salmon, D. P. (2021). Age-at-onset and APOE-related heterogeneity in pathologically confirmed sporadic Alzheimer disease. *Neurology*, 96, e2272–e2283.

Solé-Padullés, C. *et al.* (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, 30, 1114–1124.

Spina, S. *et al.* (2021). Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. *Brain*, 144, 2186–2198.

Stage Jr, E. C. *et al.* (2020). Neurodegenerative changes in early- and late-onset cognitive impairment with and without brain amyloidosis. *Alzheimer's Research & Therapy*, 12, 93. https://doi.org/10.1186/s13195-020-00647-w

Stanley, K. and Walker, Z. (2014). Do patients with young onset Alzheimer's disease deteriorate faster than those with late onset Alzheimer's disease? A review of the literature. *International Psychogeriatrics*, 26, 1945–1953.

Stanley, K., Whitfield, T., Kuchenbaecker, K., Sanders, O., Stevens, T. and Walker, Z. (2019). Rate of cognitive decline in Alzheimer's disease stratified by age. *Journal of Alzheimer's Disease*, 69, 1153–1160.

Tawfik, G. M., Dila, K. A. S., Mohamed, M. Y. F., Tam, D. N. H., Ahmed, A. M., and Huy, N. T. (2019). A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Tropical Medicine and Health*, 47, 46. https://doi.org/10.1186/s41182-019-0165-6

The Cochrane Collaboration (2020). Review manager.

Toyota, Y. *et al.* (2007). Comparison of behavioral and psychological symptoms in early-onset and late-onset Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 22, 896–901.

van der Vlies, A. E., Koedam, E. L. G. E., Pijnenburg, Y. A. L., Twisk, J. W. R., Scheltens, P. and van der Flier, W. M. (2009). Most rapid cognitive decline in APOE ϵ4 negative Alzheimer's disease with early onset. *Psychological Medicine*, 39, 1907–1911.

van Vliet, D. *et al.* (2012). Prevalence of neuropsychiatric symptoms in young-onset compared to late-onset Alzheimer's disease - part 1: findings of the two-year longitudinal NeedYD-study. *Dementia and Geriatric Cognitive Disorders*, 34, 319–327. https://doi.org/10.1159/000342824

van Vliet, D. *et al.* (2013). Time to diagnosis in young-onset dementia as compared with late-onset dementia. *Psychological Medicine*, 43, 423–432.

Wattmo, C. and Wallin, Å.K. (2017). Early-versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. *Alzheimer's Research & Therapy*, 9, 70.

World Health Organization (1992). *The ICD-10 Classification of Mental and Behavioural Disorders*. Switzerland: WHO Library Cataloguing.

World Health Organization. (2021). Dementia.

Zhu, X.-C. *et al.* (2015). Rate of early onset Alzheimer's disease: a systematic review and meta-analysis. *Annals of Translational Medicine*, 3, 38.