Cognitive decline in Alzheimer's: faster in early onset than late onset disease.

Commentary on "Clinical characteristics of early-onset versus late-onset Alzheimer's disease - A systematic review and meta-analysis" by Seath *et al.*

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Conflict of interest

The authors have no conflicts to declare.

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The authors, Zuzana Walker and Tim Whitfield, equally contributed to the manuscript, revised, read, and approved the submitted version.

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The review by Seath *et al.* (2023) is important and timely, and very relevant to the present climate, where disease-modifying treatments (DMTs) for Alzheimer's disease (AD) are becoming a possibility but unlikely to be available soon for the majority of patients. It will thus be increasingly important to identify patients with the most aggressive disease. The general consensus in the field has been that, compared to late onset AD (LO-AD), early onset AD (EO-AD) takes longer to diagnose, has a different cognitive profile, and a more aggressive course of illness (Mendez, 2019). Surprisingly, no meta-analysis has ever been performed to evaluate these conclusions from individual studies systematically.

The meta-analysis by Seath *et al.* (2023) was an ambitious undertaking, addressing six different outcome domains. While it has some limitations, mainly due to constraints with the available studies, it still provides us with some more definitive and less biased results.

The most robust result was that, compared to LO-AD, EO-AD had poorer baseline cognitive performance and faster cognitive decline. The authors also showed that EO-AD, as would be

predicted, had better survival, most likely due to better physical health. In contrast, the authors did not find evidence that EO-AD patients differed from LO-AD in time from symptom onset to diagnosis, measures of activities of daily living (ADLs) or neuropsychiatric symptoms (NPS).

Beginning with the meta-analysis comparing baseline cognitive performance, which included the greatest number of studies (k = 35), there was strong evidence that patients with EO-AD present with poorer cognition (as measured using the Mini-mental state examination; MMSE), although the difference was small in magnitude. However, the MMSE is a very brief screening test; future research using more in-depth cognitive testing and/or age-adjusted scores may find the 'true' difference to be larger.

Because the meta-analysis (k = 6) showed that the time from symptom onset to diagnosis did not significantly differ between EO- and LO-AD, the poorer cognition at presentation in EO-AD cannot be explained by a longer period between onset of symptoms and diagnosis. Nevertheless, the direction of the pooled effect suggested that the diagnosis of EO-AD is relatively delayed, and thus the possibility that diagnostic delay contributed to the difference in initial cognition cannot be ruled out.

An important result was the confirmation that patients with EO-AD have a more rapid rate of cognitive decline on the MMSE (k = 6). This may partially account for the finding of poorer cognition at presentation in EO-AD.

The meta-analysis did not show a significant difference in NPS (as measured using total scores on the Neuropsychiatric Inventory) between EO- and LO-AD (k = 6), although there was a trend towards LO-AD having worse NPS. Whilst the behavioural/dysexecutive variant of AD – a subtype with elevated NPS versus typical AD – typically has a young age of onset, this subtype only accounts for a minority of EO-AD cases overall (Ossenkoppele et al., 2015).

A very small number of studies (k = 3) comparing ADLs between EO- and LO-AD using the Functional Activities Questionnaire (FAQ) were meta-analysed, finding no significant difference. The authors reported that the measures used to assess ADLs varied widely across studies, thus limiting the data that could be pooled and the statistical power of this element of the quantitative synthesis.

In contrast, whilst studies evaluating survival time were similarly few in number (k = 3), the meta-analysis indicated that survival was significantly longer in EO-AD (in-keeping with the findings reported within original studies); Seath *et al.* suggested that this may be accounted for by individuals with LO-AD having a higher burden of age-related health problems. It is

instructive to consider this finding with reference to the results obtained for rate of cognitive decline – patients with EO-AD have a more rapid cognitive decline but longer survival compared to LO-AD. Whilst not addressed in the review, this suggests that individuals with EO-AD may live with severe dementia for longer than people with LO-AD, which has personal, societal and financial implications (e.g., relating to care home costs); this may be a fruitful direction for future research (see Bakker et al. (2022)).

Interestingly, a recent meta-analysis by Sabates *et al.* (2023) pooled data from studies (k = 90) which investigated the relationship between NPS and cognition in clinical dementia. The results from Seath *et al.* are not entirely in keeping with the findings from Sabates *et al.* (2023). Sabates et al concluded that increased NPS were associated with worse cognition. However, Seath *et al.* suggest that EO-AD have poorer cognition but (non-significantly) *fewer* NPS at presentation versus LO-AD. One explanation for this could be that the review by Sabates *et al.* pertained to all types of dementia, rather than AD specifically, yet most of the included studies did feature AD patients (indeed, over 60% of included studies focused on AD exclusively). Whilst unlikely, it remains possible that the association between poorer cognition and greater NPS is unique to older individuals with dementia. Given the NPS meta-analysis in Seath *et al.* only included six studies, and that the effect suggesting greater NPS in LO-AD was only at a trend level, it is clear that further studies need to investigate this.

The work of Seath *et al.* is without doubt very timely. The field of AD research has been greatly energised by the encouraging results from the recent phase III trials of the anti-amyloid monoclonal antibodies lecanemab (van Dyck et al., 2023) and donanemab (Sims et al., 2023). These trials raise the possibility of DMTs for AD being available in the near future. Whilst exciting, the anticipated cost of treatment – including biomarker testing for candidate patients – suggests that, if they are licensed, not all patients will be offered DMTs. It is possible, therefore, that in some healthcare systems, DMTs will be offered to individuals who may benefit the most. The finding of Seath *et al.* that EO-AD has a more rapid progression may be one factor that influences clinical decision making regarding the targeting of DMTs. From a health economic perspective, one of the reasons that EO-AD incurs greater costs is that affected individuals are of working age but typically discontinue employment on health grounds; delaying this may have a wide range of benefits. However, it is important to note that most of the patients in recent DMT trials were aged >65 (the inclusion criteria were 50-90 years for the lecanemab trial and 60-85 for the donanemab trial). Furthermore, those aged <65 treated with lecanemab only showed a 6% slowing of decline on the Clinical Dementia Rating, compared to 40% in those aged >75. One commentator speculated that this may be due to more severe neuropathology in the younger group (Iwatsubo, 2023). We are not aware of the equivalent, age-stratified data for donanemab.

A further strength of the work by Seath *et al.* is that the vast majority of included studies were conducted in clinical services rather than academic settings. This suggests that the findings should generalise to real-world clinical settings.

Whilst the paper has a number of strengths, it is also instructive to note its limitations. Unfortunately, the only cognitive results that could be pooled were total scores from the MMSE; this is a crude measure and does not enable cognitive deficits to be compared between domains. It is regretable that the forest plots presenting the results of the meta-analyses did not include labels on the x-axes to enable the reader to quickly interpret the effects. That is, whilst differences 'in favour' of the LO-AD studies (i.e., for which LO-AD > EO-AD) were graphed to the right – and those in favour of the EO-AD studies to the left – of zero, for some outcomes positive differences would be viewed as salutatory (e.g., cognition), whilst for others they would be viewed as deleterious (e.g., NPS).

The authors acknowledged that comparing genetics (i.e., *APOE* ε4), neuropathology, or biomarkers was beyond the scope of the review. The review also did not consider whether findings were influenced by the prevalence of autosomal-dominant (as opposed to sporadic) EO-AD within original studies. More work including the genetics of EO-AD will be needed to establish the influence of genetics on the clinical differences between EA0AD and LO-AD (Sirkis et al., 2022). Namely, whilst autosomal-dominant inheritance is thought to account for only around 10% of EO-AD, there is a positive family history in a substantial proportion of cases, and the heritability of AD in those aged <65 is estimated to be 90-100%. This highlights that ongoing work is likely to identify additional causal and susceptibility genes (beyond *APOE*) for EO-AD, which may facilitate future comparisons of the kind recommended here.

Some additional material which is of interest in regard to the meta-analysis appeared in papers published in recent theme-based issues of *International Psychogeriatrics*. For example, Loi *et al.* (2022) found that the opening of a specialist early onset dementia service in Melbourne, Australia reduced the time taken to diagnose patients by 12 months versus the preceding period. Giebel *et al.* (2023) utilised National Alzheimer's Coordinating Center (NACC) data to compare medication use between early and late onset dementia, as well as across different ethnic groups. The authors found that, compared to late onset dementia, individuals with early onset dementia were more likely to use memantine and less likely to use cholinesterase inhibitors. Importantly, across the whole sample, White individuals were more likely to be prescribed any form of antidementia medication compared to other ethnic groups. Whilst the social mechanisms giving rise to these data are likely multifactorial (and certainly extend beyond healthcare services), these findings highlight that dedicated early

onset services need to be designed and delivered in ways that successfully engage and serve individuals across ethnic groups.

In conclusion, Seath *et al.* are to be congratulated for writing this timely, comprehensive and needed review, which addresses a clinically relevant topic. We hope that the work inspires further investigations into the characteristics of EO-AD, to support advances in the diagnosis and management of this extremely challenging form of dementia.

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