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Preclinical Alzheimer's disease criteria

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We agree with Prof Petersen in his Comment¹ that the findings in our Article,² which used CSF measures, and those of the Mayo Clinic Study of Aging (MCSA),³ which used imaging variables, together provide strong support for the construct of preclinical Alzheimer's disease (AD). As illustrated in Prof Petersen's figure, the frequencies of the stages as defined in the two studies are virtually identical. However, several inaccuracies in the Comment warrant correction to prevent misinterpretation of our data.

Prof Petersen writes that we "state that participants are either normal (clinical dementia rating [CDR] 0), or have dementia (CDR 0.5); there is no predementia symptomatic state". This is untrue. We state "the global CDR stages are 0, indicating cognitive normality, and 0.5, 1, 2 and 3, indicating very mild impairment or very mild dementia, and mild, moderate, and severe dementia, respectively" (second paragraph, second page). We further state that "in individuals with a CDR score of 0.5, AD was diagnosed if a score of at least 0.5 was given for memory and at least one other domain and the clinician deemed the cognitive impairments to be due to AD (probable AD; referred to as CDR 0.5, symptomatic AD)." Indeed, many participants in our cohort rated CDR 0.5 received a diagnosis of "uncertain" or reflecting a different (non-AD) cause.

Prof Petersen writes "the investigators contend that symptomatic AD, CDR at least 0.5, is different from MCI since MCI requires an absolute cutoff score on psychometric testing and also requires a CDR of 0.5." We describe MCI as requiring impairment in any cognitive domain and subjective complaints of cognitive decline (second paragraph, third page, and table 2 of appendix). Nowhere did we state that MCI requires a CDR of 0.5.

The statement that "all participants... who progressed to CDR 0.5 were categorised as having developed symptomatic AD, including those who were at stage 0 (normal) and those with [suspected non-Alzheimer's pathology] SNAP" also is incorrect. Some individuals characterised as normal or SNAP at baseline who received a CDR 0.5 at follow-up were

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diagnosed as “uncertain” or as having other (non-AD) underlying causes of their impairment. However, in view of the goal of the proposed preclinical stages (to predict clinical AD), the primary outcome of interest in this study was CDR at least 0.5, symptomatic AD, not CDR at least 0.5 owing to uncertain or other causes.

Prof Petersen writes “the investigators contend that the CDR is sufficient to verify symptomatic AD irrespective of cognitive test results.” This is inaccurate. The CDR determines the presence or absence of clinical cognitive impairment and, when present, stages its severity. It is not a diagnostic instrument. When there is impairment, we use all clinical information, including cognitive testing, to establish the cause or causes (second paragraph, third page). There is much in our clinical assessment protocol that is not used in the CDR determination, but is used to inform the diagnosis of the impairment, including examinations of behaviour and mood, language, motor abnormalities, and cerebral ischaemic insults. The statement that we asserted that “a CDR greater than 0 is sufficient for diagnosis of pathological AD” is untrue. Prof Petersen misrepresents our work by implying that we accept that a CDR greater than 0 alone is all that is necessary for a diagnosis of AD (symptomatic or pathological).

We trust that our responses have resolved the identified errors and misrepresentations, and we look forward to more studies of biomarkers (imaging and CSF) in defining and diagnosing the earliest (preclinical) stages of this devastating disease.

References

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