to these problems that are intrinsic to the pathobiological changes of neurodegeneration.

In conclusion, we do not think that the knowledge available today is sufficient to define AD as proposed by Dubois and colleagues, but believe that there is a strong need to further validate the currently existing biomarkers in large unsampled selected samples. We would be happy to contribute to concerted efforts to reach the common goal—to select the right patients for the right treatment.

CM has received costs for travel and accommodation from Eisai and has given conferences on the pathology of Alzheimer’s disease for Eisai. All other authors have no conflicts of interest.

Giorgio Giaccone*, Thomas Arzberger, Irina Alafuzoff, Saif Al-Sarraj, Herbert Budka, Charles Dyckjaerts, Peter Falkai, Isidro Ferrer, James W Ironside, Gábor Kovács, David Meyronet, Piero Parchi, James W Ironside, Gábor G Kovács, Peter Falkai, Isidro Ferrer, Herbert Budka, Charles Duyckaerts, Andrea Schmitt, Bengt Winblad, Hans Kretzschmar, on behalf of the BrainNet Europe consortium giaccone@istituto-besta.it

Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy (GG); Centre for Neuropathology and Prion Research, Ludwig-Maximilians-University Munich, Germany (TA, HK); Uppsala University, Uppsala, Sweden (IA); London Institute of Psychiatry, London, UK (SA-S); Institute of Neurology, Medical University of Vienna, Vienna, Austria (HB, GGK); Université Pierre et Marie Curie, Assistance Publique des Hôpitaux de Paris, France (CD); Department of Psychiatry, University of Gothenburg, Gothenburg, Germany (PF, AS); Universitat de Barcelona, Barcelona, Spain (FP); University of Edinburgh, Western General Hospital, Edinburgh, UK (JWI); Université de Lyon, Lyon, France (DM); Università di Bologna, Bologna, Italy (PP); National and Capodistrian University of Athens, Athens, Greece (EP); Institute of Neurology, London, UK (TR); University Wuerzburg, Wuerzburg, Germany (PF); Netherlands Brain Bank, Amsterdam, Netherlands (AR); Karolinska Institutet, I3-Alzheimer Disease Research Center, Huddinge, Sweden (BW)


We have been following the proposed diagnostic criteria for Alzheimer’s disease (AD) closely over the past few years. Recent revisions of the AD criteria proposed by Dubois and colleagues represent a clear improvement on their previously published Position Paper. In the new revision, Dubois and colleagues propose an important distinction between the clinical disorder (AD) and the neuropathological condition (“Alzheimer’s pathology”). They also describe several distinctions within the clinical disorder, including two preclinical conditions (“asymptomatic at-risk for AD” and “presymptomatic AD”), a prodromal condition (“prodromal AD”), and AD dementia with varying presentations (“typical AD,” “atypical AD,” and “mixed AD”).

The authors provide an evidence-based structure to improve the clarity of predementia conditions, particularly for individuals previously diagnosed with mild cognitive impairment but with biomarker evidence of AD pathology, who are now classified as having prodromal AD. However, the definitions provided for atypical and mixed AD could result in some confusion and need further diagnostic clarity. For example, atypical AD refers to the less common clinical features of the disease accompanying other clinical syndromes such as primary progressive non-fluent aphasia and logopenic aphasia. It should be recognised that, in these conditions, AD is not a prominent feature of the disease and applying atypical AD as the diagnosis might increase the possibility of a misleading or incorrect diagnosis. Furthermore, in the recently suggested frontal variant of AD, mentioned as an example of atypical AD by Dubois and colleagues, the antemortem diagnosis is uncertain and might not be reliable.

Similarly, in the revised criteria, mixed AD refers to a condition for which patients must present with full diagnostic criteria of typical AD plus the clinical and pathophysiological evidence of other diseases or disorders. The diagnostic, treatment, or research benefit achieved with this classification approach is unclear compared with simply applying a diagnosis of typical AD together with the associated comorbid diagnosis (eg, vascular disease). We believe that specifying the co-occurring pathology on the basis of comorbidity with AD would be more useful for the patients’ management.

Crucially, however, Dubois and colleagues have not acknowledged the importance of including age at onset as a factor in diagnostic classification. Specifically, there is a need for differential diagnoses of early-onset AD versus late-onset AD. Neurochemical and neuropathological differences between early-onset and late-onset AD have been previously reported. Additionally, age at onset can affect clinical presentation of AD. Therefore, using the diagnostic distinction of early-onset versus late-onset disease might promote differentially effective management approaches for each group of patients. Although current knowledge about the clinical course of early-onset AD versus late-onset AD remains incomplete, there are at least three reasons that this dichotomy should be included in the diagnostic criteria. First, the neuropsychological profile for pre-diagnostic and post-diagnostic phases could be different for these two groups, with subsequent implications for functional status. Second, the covariant factors affecting
treatment (e.g., other diseases and clinical conditions, the drugs used by each group of patients, psychosocial support, and responsibilities) are likely to vary across the diagnostic groups. Third, because age at onset might determine the prototype of the disease, incorporating this factor could change the clinical management of the patient and the disease prognosis.

In summary, the revised criteria proposed by Dubois and colleagues are an important step forward in the development of a new lexicon for AD for researchers and clinicians. However, further refinement of some diagnostic categories and consideration of age at onset as an important clinical feature are important next steps in this endeavour.

SEG is a member of the data safety monitoring board for the Alzheimer Immunotherapy Alliance and holds a grant from Amicus Pharmaceuticals. Other authors have no conflicts of interest.

Hamid R Sohrabi, Michael Weinborn, Johanna Badcock, Kristyn A Bates, Roger Clarnette, Darshan Trivedi, Giuseppe Verdile, Tom Sutton, Nat P Lenzo, Samuel E Gandy, Ralph N Martins*

r.martins@ecu.edu.au

School of Exercise, Biomedical and Health Science, Edith Cowan University, WA, Australia (HRS, RC, DT, GV, NPL, RNH); The Sir James McCusker Alzheimer’s Disease Research Unit, Hollywood Private Hospital, WA, Australia (HRS, RC, GV, TS, RNH); Department of Nuclear Medicine, Fremantle Hospital, WA, Australia (NPL); School of Psychology (MW), School of Animal Biology (KAB), School of Psychiatry and Clinical Neurosciences (TS, RNH), and Centre for Clinical Research in Neuropsychiatry, Graylands Hospital (JB), University of Western Australia, WA, Australia; and Department of Neurology, One Gustave L. Levy Place, New York, NY, USA (SEG)


Authors’ reply

We thank Giaccone and colleagues for commenting on our proposed new definition of Alzheimer’s disease (AD). In proposing the new research criteria and its lexicon, we wished to stimulate this type of active discourse. Giaccone and colleagues correctly characterise our intention with the lexicon to cover the range of both clinical symptoms and in-vivo Alzheimer’s pathology and to provide a framework for classification and research to supplement our previous Position Paper.

In reply to their first point, we agree with WHO’s definition of disease and have framed our definition of AD in this way. According to our lexicon, AD is now restricted to the clinical disorder and is only diagnosable when there is clinical expression of specific symptoms of the disease. We used the term “asymptomatic at risk” to cover cognitively normal individuals with in-vivo biological evidence of Alzheimer’s pathology. We designate these individuals as such because they do not have the disease but are at risk of developing it. The current uncertainty of the prognostic importance of being asymptomatic but at risk with in-vivo evidence of Alzheimer’s pathology led us to this nosological designation.

Giaccone and colleagues expressed concern that eliminating “probable” AD will impede the use of a diagnosis of “definite AD” according to the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer’s Disease and Related Disorders Association (NINCDS–ADRDA) criteria. Although this point of diagnostic assignment is technically correct, we believe that there are positive trade-offs that mitigate this concern. The addition of biomarkers of Alzheimer’s pathology to a purely clinical diagnostic algorithm should improve diagnostic accuracy. For example, a negative amyloid β PET scan will point away from a diagnosis of AD as the cause of the symptoms. Although “definite AD” has been a useful diagnostic construct for research purposes, the field has also taken up the Reagan neuropathological diagnostic criteria, which do not make specific reference to the “clinically probable” AD category in the NINCDS–ADRDA criteria.

In response to Giaccone and colleagues’ second point on “atypical AD”, we deliberately restricted this designation to well characterised and specific clinical phenotypes of syndromes that are most often associated with Alzheimer’s pathology. The disorders listed by Giaccone and colleagues are a more heterogeneous group of diseases that are either most often tauopathies that would not have Alzheimer’s pathology or that have substantial comorbidities with Alzheimer’s pathology. None of these has been included in our definition of “atypical AD”.

Finally, with regards to their third point, we do see a clearly specified role within the new research criteria and lexicon for neuropathological diagnosis. The new clinicobiological definition of AD that we have proposed needs to be validated with the conventional dual neuropathological criteria. We agree that it is also essential to verify or identify comorbid conditions, alternative diagnoses, and atypical cases. We have summarised this in the proposed shift to “neuropathologically verified AD” as an appropriate designation to follow the clinicobiological diagnosis.

Rather than symbolising a tower of Babel, this lexicon strives to provide a consistent and clear framework that takes into account the growth of knowledge around the specific clinical features of AD and biomarkers of Alzheimer’s pathology that have evolved since 1984. This framework should promote a uniform point of reference for the advances being made in the field. We hope that our