Objectifying subjective cognitive decline: the prognostic role of Alzheimer biomarkers

Henrik Zetterberg[1,2,3,4,5*], Jonathan M Schott[3,4,6]

Word count: 937

References: 10

[1]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*

[2]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*

[3]*Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK*

[4]*UK Dementia Research Institute at UCL, London, UK*

[5]*Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China*

[6]*Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK*

*Correspondence: henrik.zetterberg@clinchem.gu.se; h.zetterberg@ucl.ac.uk

Conflicts of interest: HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). JMS has received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); has consulted for Roche, Eli Lilly, Biogen, Merck and GE; received royalties from Oxford University Press and Henry Stewart Talks; given education lectures sponsored by Eli Lilly, Biogen and GE; and served on a Data Safety Monitoring Committee for Axon Neuroscience SE. He is Chief Medical Officer for Alzheimer's Research UK, and Medical Advisor to UK Dementia Research Institute (outside submitted work).

Funding: HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712 and #101053962), Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C and #ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2019-0228), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). JMS acknowledges the support of the National Institute for Health Research University College London Hospitals Biomedical Research Centre, Wolfson Foundation, Alzheimer's Research UK, Medical Research Council, British Heart Foundation, UK Dementia Research Institute and Alzheimer's Association.

Subjective cognitive decline (SCD) refers to the self-reported experience of reduced cognitive function in individuals who perform within normal limits on objective cognitive testing.[1] A growing public awareness about dementia and the prospect of disease-modifying drugs and multi-domain intervention programs to improve brain health, both of which may be most effective in early or even pre-symptomatic disease, is leading an increasing number of individuals to seek medical advice due to concerns about cognitive functioning. SCD, most often reflecting concerns about memory and/or reduced processing speed, is common – between 50% and 80% of cognitively normal older individuals report some decline in cognitive function when specifically questioned.[2] Although most individuals with SCD will not develop progressive cognitive decline, in some the perceived dysfunction may be the first sign of a neurodegenerative dementia. It is a difficult clinical challenge to determine those individuals who have underlying brain disease, and those who will have alternative explanation, e.g. a functional cognitive disorder.[3] This distinction is already important, allowing for different treatments and predicting different outcomes, and will become even more pressing when disease-modifying treatments for neurodegeneration become available.

The most common neurodegenerative dementia, and thus a major concern for many individuals with SCD, is Alzheimer's disease (AD). The key pathological features of AD – extracellular amyloid β (Aβ) plaques, intra-neuronal tangles of phosphorylated tau, and neurodegeneration – can all now be detected *in vivo* using biomarkers which are incorporated into contemporary diagnostic criteria in patients with varying degrees of cognitive impairment.[4] The most established methods for detecting Aβ pathology are in CSF (Aβ42 concentration or Aβ42/Aβ40 ratio) or using amyloid positron emission tomography (PET).[5] CSF phosphorylated- and total tau concentrations were considered markers of tangle pathology and neurodegeneration respectively, but recent studies suggest that they may reflect Aβ pathology-driven phosphorylation and secretion of tau.[6] Candidate markers of neurodegeneration include volume loss on magnetic resonance imaging, fluorodeoxyglucose PET measures of hypometabolism, and CSF or plasma neurofilament[7,8]. Importantly all these biomarkers are thought to become abnormal well before symptoms emerge; it follows therefore that they may well have utility in distinguishing which individuals with SCD may be on the pathway to developing AD.

In the current issue of *Neurology*, Rostamzadeh *et al*. set out to address this question, using a meta-analytical approach to determine how well biomarkers of β-amyloid pathology (CSF

Aβ42, CSF Aβ42/Aβ40 or amyloid PET) and tau (CSF phosphorylated and total tau) can predict progression to mild cognitive impairment (MCI) or dementia in individuals with SCD.[9] More than 4000 articles were screened with eight studies fulfilling inclusion criteria. One or more biomarkers was abnormal in around one third of the individuals, with the highest odds ratio (11.36) for future cognitive decline over a mean follow-up period of 3.3 years being when both Aβ and tau biomarkers were abnormal ("full AD pathology"). This compares with odds ratio of 5.89 for Aβ and 3.99 when using phosphorylated tau only. While showing strong (89.4%) negative predictive power this full AD pathology profile was, however, only 58.7% predictive of conversion to MCI or AD.

This study highlights that AD biomarkers may have value – at least at the group level – in determining those who are, and importantly those individuals with SCD who may not be, at increased risk of progressive cognitive decline. There are however a number of important caveats. While there are various criteria for diagnosing SCD and MCI, how these are operationalized varies between studies and so comparing results across studies is not always easy. It is also unclear whether the clinicians involved in the reported studies were appropriately blinded to the results of the AD biomarkers; and if not, whether this influenced their subsequent diagnoses. This study relied on center-specific cut-points for biomarker positivity. Determining such cut-points is a complex issue with substantial variation between laboratories and across assays: standardization work addressing this issue is ongoing but far from complete. The biomarkers chosen for inclusion were necessarily specific for Alzheimer's disease, precluding investigations of other potential risks for SCD progression e.g. vascular pathologies. The average follow-up time of the included studies was relatively short and so the longer-term outcomes of these individuals – and critically whether they develop dementia or not – are not yet known. This is particularly important given that one of the outcomes of this study was a diagnosis of MCI, yet previous studies suggest that perhaps only half of unselected individuals diagnosed with MCI will progress to a diagnosis of dementia over the subsequent five years.[10] It is therefore not clear how these findings may best be used on an individual patient basis: while a negative biomarker profile may be reassuring, there are very considerably uncertainties of what a positive profile may portend, and how best to communicate this to an already worried patient is unlikely to be straightforward. Given the numbers of patients with SCD presenting to clinics the widespread use of current molecular diagnostics would be a considerable challenge: the emergence of blood-based biomarkers may allow for much wider and cheaper deployment,[8] but many of

these issues remain and will need to be considered when developing appropriate use criteria and guidelines for investigating SCD.

The results from the current meta-analysis are a useful early step in exploring how AD biomarkers may best be deployed in patients with SCD. Important take home messages, which are equally relevant to studies of MCI and to other dementias, are that negative biomarkers may have equal, or indeed more, prognostic utility than positive ones; and that longer-term follow-up to determine clinical and ultimately pathological outcomes is crucial as we develop a rational evidence base for the use of biomarkers in predicting progression to specific forms of dementia.

References

1. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. Lancet Neurol 2020;19:271-278.

2. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry 2010;67:414-422.

3. Ball HA, McWhirter L, Ballard C, Bhome R, Blackburn DJ, Edwards MJ, Fleming SM, Fox NC, Howard R, Huntley J, Isaacs JD, Larner AJ, Nicholson TR, Pennington CM, Poole N, Price G, Price JP, Reuber M, Ritchie C, Rossor MN, Schott JM, Teodoro T, Venneri A, Stone J, Carson AJ. Functional cognitive disorder: dementia's blind spot. Brain. 2020 Oct 1;143(10):2895-2903.

4. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535-562.

5. Cohen AD, Landau SM, Snitz BE, Klunk WE, Blennow K, Zetterberg H. Fluid and PET biomarkers for amyloid pathology in Alzheimer's disease. Mol Cell Neurosci 2019;97:3-17.

6. Sato C, Barthelemy NR, Mawuenyega KG, et al. Tau Kinetics in Neurons and the Human Central Nervous System. Neuron 2018;98:861-864.

7. Young PNE, Estarellas M, Coomans E, et al. Imaging biomarkers in neurodegeneration: current and future practices. Alzheimers Res Ther 2020;12:49

8. Zetterberg H, Schott JM. Blood biomarkers for Alzheimer's disease and related disorders. Acta Neurol Scand 2022;146:51-55

9. Rostamzadeh A, Bohr L, Wagner M, Baethge C, Jessen F. Progression of subjective cognitive decline to mild cognitive impairment or dementia in relation to biomarkers for Alzheimer's disease - A Meta-Analysis. Neurology 2022;In press.

10. van Maurik IS, Vos SJ, Bos I, Bouwman FH, Teunissen CE, Scheltens P, Barkhof F, Frolich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Rüther E, Nobili F, Frisoni GB, Spiru L, Freund-Levi Y, Wallin AK, Hampel H, Soininen H, Tsolaki M, Verhey F, Kłoszewska I, Mecocci P, Vellas B, Lovestone S, Galluzzi S, Herukka SK, Santana I, Baldeiras I, de Mendonça A, Silva D, Chetelat G, Egret S, Palmqvist S, Hansson O, Visser PJ, Berkhof J, van der Flier WM; Alzheimer's Disease Neuroimaging Initiative. Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study. Lancet Neurol. 2019 Nov;18(11):1034-1044.