

NEUROPSYCHIATRY AND BEHAVIORAL NEUROLOGY

Investigating the additive effects of Alzheimer's disease biomarker staging and subjective cognitive decline in the prediction of clinical progression

Melina Stark^{1,2} | Michael Wagner^{1,2} | Elizabeth Kuhn² | Katharina Bürger^{3,4} |
Emrah Düzel^{5,6} | Julian Hellmann-Regen^{7,8,9} | Michael T. Heneka¹⁰ |
Christoph Laske^{11,12} | Robert Perneczky^{4,13,14,15} | Oliver Peters^{7,16} |
Josef Priller^{7,17,18,19} | Matthias Schmid^{2,20} | Anja Schneider^{1,2} | Annika Spottke^{2,21} |
Stefan Teipel^{22,23} | Jens Wiltfang^{24,25,26} | Frank Jessen^{2,27,28} | Luca Kleineidam^{1,2}

¹Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn Medical Center, Bonn, Germany

²German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

³Institute for Stroke and Dementia Research (ISD), University Hospital, LMU, Munich, Germany

⁴German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

⁵German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

⁶Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany

⁷German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

⁸Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin – Institute of Psychiatry and Psychotherapy, Berlin, Berlin, Germany

⁹German Center for Mental Health (DZPG), Berlin, Germany

¹⁰Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Luxembourg, Luxembourg

¹¹German Center for Neurodegenerative Diseases (DZNE), Tuebingen, Germany

¹²Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tuebingen, Tuebingen, Germany

¹³LMU University Hospital, Munich, Germany

¹⁴Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

¹⁵Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

¹⁶Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin – Institute of Psychiatry and Psychotherapy, Berlin, Germany

¹⁷School of Medicine, Technical University of Munich; Department of Psychiatry and Psychotherapy, Munich, Germany

¹⁸University of Edinburgh and UK DRI, Edinburgh, United Kingdom

¹⁹Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany

²⁰Institute of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany

²¹Department of Neurology, University of Bonn, Bonn, Germany

²²German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany

²³Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Alzheimer's Association. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

²⁴German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany

²⁵Department of Psychiatry and Psychotherapy, University Medical Center, University of Goettingen, Goettingen, Germany

²⁶Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

²⁷Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

²⁸Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany

Correspondence

Melina Stark, Department of
Neurodegenerative Diseases and Geriatric
Psychiatry, University of Bonn Medical Center,
Bonn, Germany.

Email: Melina.Stark@dzne.de

Abstract

Background: The identification of cognitively unimpaired individuals at risk of short-term cognitive decline is a critical task for Alzheimer's disease (AD) research. Cognitively normal individuals with amyloid and/or tau pathology have a high risk for short-term cognitive decline. However, not all of these individuals show clinical progression. Individuals in clinical stage 2 of AD, characterized e.g. by subjective cognitive decline (SCD), are thought to be temporally closer to clinical progression to mild cognitive impairment (MCI), but this hypothesis has not been rigorously investigated yet.

Method: We included 195 memory clinic SCD patients and 83 cognitively normal participants without SCD (CN) with baseline CSF and longitudinal cognitive data from the observational DELCODE study. Participants were categorized into three AD biomarker stages (A-T-, A+T-, A+T+) based on their baseline CSF A β 42/40 and p-tau₁₈₁ status. The groups were compared in their longitudinal preclinical Alzheimer's cognitive composite (PACC5) trajectories and average time until progression to MCI. Group differences in the time until progression to MCI, over eight years of follow-up, were estimated with restricted mean survival time models. All analyses were adjusted for demographic covariates.

Result: Compared to the A-T- group (62 CN, 123 SCD), A+T- (16 CN, 49 SCD) and A+T+ (5 CN, 23 SCD) participants showed significantly accelerated PACC5 decline and a faster progression to MCI (A+T-: 2.7 [-5.7-11.2] and A+T+: 22.4 [8.1-36.8] months earlier than A-T-;). SCD patients had a significantly faster PACC5 decline and progression to MCI (15.5 [9.8-21.1] months) than CN participants. The effects of SCD and the biomarker stages on both outcome measures remained significant when the predictors were entered in the same models. In exploratory analyses, SCD patients tended to show a faster progression to MCI than CN participants within the same biomarker group (A+T-: 19.0 [6.3-31.7] and A+T+: 14.0 [-20.8-48.8] months earlier than CN in same biomarker group).

Conclusion: SCD provides incremental information for the identification of individuals at high risk of imminent cognitive decline beyond a biomarker-based classification of AD pathology. In cognitively unimpaired individuals, the clinical stage should be taken into account additionally to AD biomarkers for an improved prediction of the time until clinical progression.