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Featured Article

# Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease

Rachel F. Buckley[a,*], Paul Maruff[b], David Ames[c], Pierrick Bourgeat[d], Ralph N. Martins[e,f,g], Colin L. Masters[h], Stephanie Rainey-Smith[e,g], Nicola Lautenschlager[c,f], Christopher C. Rowe[i,j], Greg Savage[k], Victor L. Villemagne[h,i,j], Kathryn A. Ellis[c], and on behalf of the AIBL study

[a]*Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia*
[b]*Cogstate Ltd, Melbourne, Australia*
[c]*The Academic Unit for Psychiatry of Old Age, St. Vincent's Health, Department of Psychiatry, University of Melbourne*
[d]*The Australian eHealth Research Centre, CSIRO Health & Biosecurity Flagship, QLD, Australia*
[e]*Centre of Excellence for Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, WA, Australia*
[f]*School of Psychiatry and Clinical Neurosciences and West Australian Centre for Health & Ageing, University of Western Australia*
[g]*Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital), Perth, WA, Australia*
[h]*The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia*
[i]*Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Australia*
[j]*Department of Medicine, Austin Health, University of Melbourne, Melbourne, Australia*
[k]*ARC Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, Australia*

**Abstract**

**Introduction:** The objective of this study was to determine the utility of subjective memory decline (SMD) to predict episodic memory change and rates of clinical progression in cognitively normal older adults with evidence of high β-amyloid burden (CN Aβ+).

**Methods:** Fifty-eight CN Aβ+ participants from the Australian Imaging, Biomarkers, and Lifestyle study responded to an SMD questionnaire and underwent comprehensive neuropsychological assessments. Participant data for three follow-up assessments were analyzed.

**Results:** In CN Aβ+, subjects with high SMD did not exhibit significantly greater episodic memory decline than those with low SMD. High SMD was related to greater rates of progression to mild cognitive impairment or Alzheimer's disease (AD) dementia (hazard ratio = 5.1; 95% confidence interval, 1.4–20.0, $P = .02$) compared with low SMD. High SMD was associated with greater depressive symptomatology and smaller left hippocampal volume.

**Discussion:** High SMD is a harbinger of greater rates of clinical progression in preclinical AD. Although SMD reflects broader diagnostic implications for CN Aβ+, more sensitive measures may be required to detect early subtle cognitive change.



*Keywords:* Preclinical AD; Prodromal AD; Subjective cognitive decline; Subjective memory decline cognitively normal older adults; Amyloid; PET imaging

## 1. Introduction

Expressions of subjective memory decline (SMD) are common in cognitively normal (CN) older adults, and mounting evidence supports the inclusion of SMD as a risk factor for future clinical progression [1–3]. In cross-sectional neuroimaging studies, greater SMD severity in

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*Corresponding author. Tel.: +61-3-8344-8860; Fax: +61-03-9347-6618.

E-mail address: rachel.buckley@unimelb.edu.au

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CN older adults has also been associated with greater β-amyloid (Aβ) burden [4–10] as indexed by lower cerebrospinal fluid (CSF) levels of $A\beta_{1–42}$ [11] and higher neuritic Aβ plaques at postmortem [12,13]. Although there has been inconsistency in the nature of relationships between SMD and objective memory performance in CN adults [14–16], high levels of SMD in some contexts do predict subsequent subtle memory decline [17,18]. Inconsistency in observed relationships between SMD and clinical outcomes may be the result of the variable methods used for the identification and staging of SMD in CN groups [19]. It is also possible that varying levels of Aβ burden exhibited by CN older adults may add to this level of heterogeneity. One approach to reducing heterogeneity is to examine SMD in CN older adults who have confirmed preclinical Alzheimer's disease (AD) that is individuals with evidence of neocortical Aβ burden [20]. There is now strong evidence from multiple studies showing that CN individuals with high Aβ burden demonstrate worse clinical prognosis [21], and faster rates of decline in episodic memory [22], compared with CN individuals without amyloid.

Older adults with preclinical AD, therefore, make an ideal group to examine the extent to which SMD can indicate the worsening prognostic outcomes or objectively defined memory decline. SMD has been argued to have the potential to indicate rapid cognitive decline in preclinical AD [17]; however, CN adults with both high amyloid and objectively defined memory decline over 18 months have not been found to exhibit increasing SMD severity over the same time frame [23]. These seemingly contradictory findings from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study of aging [24] used the memory assessment clinics questionnaire (MAC-Q) [25], a questionnaire that compares current cognitive abilities to when the individual was in high school, to measure SMD on a continuous scale. SMD is often treated as a continuum of severity; however, as a wide variety of SMD measures are used across studies [19], this makes comparability very difficult. To align levels of SMD from the AIBL study with those of other groups, the present study will treat the MAC-Q as a categorical outcome measure. Using an approach implemented by previous studies [26,27], which allows for the scaling of SMD severity to align with other large, longitudinal studies of SMD [2,18,28,29], it will be possible to analyze categorical levels of SMD in CN older adults with high Aβ burden.

The aim of the present study was to examine the influence of categorical levels of SMD on subsequent memory decline and rates of clinical progression in preclinical AD. Cognitive decline in CN older adults with high Aβ burden was hypothesized to be greater in the high SMD group, along with greater rate of clinical progression to mild cognitive impairment (MCI) or AD dementia in comparison in those with low SMD.

## 2. Methods

### 2.1. Participants

In the present study, only CN older adults who had undergone positron emission tomography (PET) Aβ neuroimaging and who had undergone SMD and cognitive testing at 18, 36, and 54 months were included. A total of 288 CN older adults from the AIBL study [24,30] were, thus, included in our study. At baseline, 58 CN participants exhibited high Aβ burden (CN Aβ+) and 230 CN had low Aβ burden (CN Aβ−).

The process of recruiting CN older adults for the AIBL study has been described in detail elsewhere [24]. Human research approval for the AIBL study was obtained in Victoria from St Vincent's Hospital and the Austin Health, and in Western Australia, Hollywood Private Hospital, and Edith Cowan University [24]. The SMD measure was included in the AIBL study at the 18-month follow-up; hence, this time point was treated as the "baseline" point for the present study [14]. General exclusion criteria for the AIBL study were psychiatric illness (such as significant current but not past depression, which was determined by a geriatric depression scale [31] score of >5), Parkinson's disease, cancers within the last few years, symptomatic stroke, uncontrolled diabetes, alcohol consumption greater than recommended levels, and sleep apnea requiring continuous positive airway pressure treatment.

### 2.2. Determining clinical classification

Clinical classifications were measured as maintaining CN status by the last time point, or attracting a diagnosis of MCI or AD over time. A diagnostic review panel of neurologists, geriatricians, psychiatrists, and neuropsychologists, blind to the neuroimaging data chaired by D.A., oversaw the classification into healthy control (HC), MCI, and dementia of the Alzheimer's type (DAT) groups according to well-established criteria [32,33]. MCI classification was based on Petersen et al. [32] and Winblad et al. [33] criteria of performance falling 1.5 standard deviation (SD) below age-adjusted levels on at least two neuropsychological tasks within any cognitive domain [24], the expression of memory difficulties arising from the self or an informant and current preservation of activities of daily living. Those participants who attracted a classification of MCI at follow-up but reverted back to a CN classification were considered as "unstable" and were excluded from analyses. The number of participants who changed classification status at each assessment time point is represented in Table 1.

### 2.3. SMD measurement

The MAC-Q is a six-item Likert-scale questionnaire and is self-administered [25]. The questionnaire was included in the mail-out questionnaires that were sent to participants before the neuropsychological assessment. The MAC-Q involves five items that focus on specific everyday memory