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Featured Article

Risk of progression from subjective cognitive decline to mild cognitive impairment: The role of study setting

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Abstract

Introduction: We compared risk of progression from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) in an academic memory clinic versus a population-based study.
Methods: Older adults presenting at a memory clinic were classified as SCD (n = 113) or as non-complainers (n = 82). Participants from a population study were classified as SCD (n = 592) and noncomplainers (n = 589) based on a memory complaint score. Annual follow-up performed for 3 years.
Results: The adjusted hazard ratio for SCD was 15.97 (95% confidence interval: 6.08–42.02, $P < .001$) in the memory clinic versus 1.18 (95% confidence interval: 1.00–1.40, $P = .047$) in the population study, where reported "worry" about memory further increased SCD-associated risk for MCI.
Discussion: SCD is more likely to progress to MCI in a memory clinic than the general population; participants' characteristics vary across settings. Study setting should be considered when evaluating SCD as a risk state for MCI and dementia.

Keywords: Memory complaints; Cognitive decline; Longitudinal design; Selection factors

1. Introduction

There has been increased interest in recent years in older adults' self-appraisal of memory and other cognitive abilities. "Subjective cognitive decline" (SCD) refers to self-perceived worsening over time of cognitive functions. In 2014, an international working group, the Subjective Cognitive Decline Initiative, put forth a conceptual framework for research efforts [1]. In addition to establishing common terminology, definitions, and proposed criteria, a goal was to identify potential features most strongly associated with presence of preclinical Alzheimer's disease (AD). Two proposed inclusion criteria for SCD are (1) self-experienced persistent decline in cognitive capacity in comparison with a previously normal status, unrelated to an acute event and (2) normal performance on standardized cognitive tests. Additional features potentially increasing the likelihood of preclinical AD include age of onset ≥60 years, reported worry or concern, and genetic or biomarkers for AD. Use of SCD as an enrichment strategy for preclinical AD in secondary prevention trials has been discussed [2].

A challenge to the SCD field is the fact that self-experienced decline in memory, even persistent, is a common or normative experience as we age [3,4]. Etiologies of this subjective experience are highly heterogeneous [1,5]. In populations at lower *a priori* risk for underlying

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AD pathology, SCD is less likely to represent a pre–mild cognitive impairment (MCI) and predementia AD stage than in other populations. Selection factors operating in different research settings are an important reflection of the degree of underlying AD pathology. In epidemiologic terms, predictive value is a function of underlying prevalence. This has been demonstrated in studies of MCI: progression to dementia is lower in population settings (3% per year) compared to MCI ascertained in specialized memory clinic settings (13 % per year) [6]. Furthermore, MCI that reverts to normal cognitive status is higher in population versus clinic samples [7]. Clinical and sociodemographic factors, such as age of memory symptom onset, family history of dementia, apolipoprotein E (*APOE*)*4* status, education, and income level, differ significantly among study settings and populations and are likely strongly associated with differences in outcomes [6,8–10].

Because SCD theoretically resides closer to the normal/early pathologic boundary in cognitive aging than does MCI, the influence of study setting on SCD outcomes may be even more important than in studies of MCI outcomes. Rodriguez-Gomez et al. [11] described a conceptual model of study settings in SCD, arranged as a continuum of sampling methods from random-based population studies to nonrandomly selected convenience samples. Clinical (i.e., help-seeking) samples constitute the most highly selected settings, with specialty clinics being more selected than general medical settings. Gomez-Rodriguez et al. called for SCD investigators to evaluate the impact of study setting and recruitment strategies via direct comparisons. We are unaware of studies to date directly comparing study settings on SCD outcomes. Thus, our present aim was to compare progression from SCD to MCI in a help-seeking, specialty clinic sample to the same outcome in a randomly recruited population-based cohort. We conducted a post hoc comparison of two different studies in different settings in the same geographic community, with similar aims and similar methods. We predicted a higher progression risk associated with SCD (relative to no SCD) in the specialty clinic setting, compared to the same risk in a population-based study setting. Secondary aims were to investigate whether additional AD-like features of SCD [1]—(1) reported worry or concern and (2) presence of the *APOE*4* allele—increased the predictive value of SCD for progression in the population study setting.

2. Methods

2.1. Participants

2.1.1. Memory disorders clinic

A total of 195 consecutive participants enrolled in the University of Pittsburgh Alzheimer Disease Research Center (ADRC) were included. Inclusion criteria were (1) English language fluency; (2) >7 years education; and (3) adequate vision and hearing to complete neuropsychological (NP) testing. Exclusion criteria were (1) lifetime history of schizophrenia, manic-depressive disorder, or schizoaffective disorder; (2) recent history of electroconvulsive therapy; (3) current alcohol or drug abuse/dependence; (4) history of cancer (other than skin and in situ prostate cancer) within previous 5 years; and (5) significant disease or unstable medical condition (i.e., chronic renal failure, chronic hepatic disease, or severe pulmonary disease).

2.1.1.1. Subjective cognitive decline

Participants in the ADRC further fulfilled these criteria: (1) concern regarding memory or other cognitive abilities was a reason for seeking evaluation; (2) performance was normal on a comprehensive NP test battery (see below); and (3) at least one annual follow-up visit was completed. SCD status corresponded to an ADRC consensus diagnosis of "subjective complaints with normal NP test performance." A total of 113 SCD-ADRC participants were selected for this analysis.

2.1.1.2. Noncomplainers

Participants in the ADRC setting fulfilled all the above criteria except for an absence of significant memory concerns at initial visit (i.e., contact was initiated for other reasons, such as volunteerism). Noncomplainer (NC) status corresponded to an ADRC consensus diagnosis of "normal control." A total of 82 NC-ADRC participants were included.

2.1.2. Population study

A total of 1982 participants were randomly selected for the Monongahela-Youghiogheny Health Aging Team (MYHAT) study [12] from the voter registration lists for several small towns in Allegheny County, the same Southwestern Pennsylvania county as the University of Pittsburgh ADRC. Inclusion criteria were age 65+ years, currently living in the community in one of the targeted towns, and not already residing in a long-term care facility. Exclusion criteria were being too ill to participate, severe hearing and vision impairment, and decisional incapacity. We further excluded individuals who had prevalent substantial cognitive impairment, defined as scores below 21 on the Mini–Mental State Examination corrected for age and education [13,14].

2.1.2.1. Subjective cognitive decline

Participants from the MYHAT study were classified as SCD based on (1) scores above the median from a subjective memory complaint scale [15,16] (see 2.2) at study baseline; (2) normal performance at baseline on a comprehensive NP test battery (see below); and (3) at least one annual follow-up visit completed. A total of 592 SCD-MYHAT participants were included.

2.1.2.2. Noncomplainers

Participants from the MYHAT study fulfilled all the above criteria, except that their scores on the subjective