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Original Research

Subjective Cognitive Decline in a Registry Sample: Relation to Psychiatric History, Loneliness, and Personality

G.O. Reynolds, L. Manning, D. Kirn, H. Klein, O. Hampton, O. Burke Jr., R. Buckley, D. Rentz, R. Sperling, G.A. Marshall, R.E. Amariglio

Department of Neurology, Brigham and Women's and Massachusetts General Hospital, Boston MA, USA

Corresponding Author: Gretchen Reynolds PhD, 60 Fenwood Road, Boston MA 02115, USA, Email: goreynolds@bwh.harvard.edu

Abstract

BACKGROUND: With the increasing focus on prevention of Alzheimer's disease, there is need for characterization of preclinical populations. Local participant registries offer an opportunity to facilitate research engagement via remote data collection, inform recruitment, and characterize preclinical samples, including individuals with subjective cognitive decline.

OBJECTIVES: We sought to characterize subjective cognitive decline in a registry sample, as related to psychiatric history and related variables, including personality and loneliness, quality of life, and factors related to dementia risk (e.g., family history of dementia).

DESIGN, SETTING, PARTICIPANTS: Participants were 366 individuals (mean age=67.2 (range 50-88), 65% female, 94% white, 97% non-Hispanic or Latino, 82% with at least a bachelor's degree) with no reported history of mild cognitive impairment or dementia. All participants had expressed interest in research, primarily via community outreach events and prior research involvement. Data was collected via electronic surveys, distributed using REDCap. Electronic questionnaires included questions on demographic variables, subjective cognitive decline, quality of life, loneliness, and personality.

RESULTS: There was a high prevalence of risk factors for dementia in the registry sample (68% with family history of dementia, 31% with subjective cognitive decline). Subjective cognitive decline was more common in women and associated with history of depression, but not with family history of dementia. Subjective cognitive decline was also associated with lower conscientiousness and lower emotional stability, as well as higher loneliness and lower quality of life. Among participants who endorsed a psychiatric history, most reported onset more than 10 years prior, rather than within the last 10 years.

CONCLUSIONS: Subjective cognitive decline in a registry sample may be more strongly associated with longstanding psychiatric and personality variables, rather than family history of dementia, adding to the literature on characterization of subjective cognitive decline across different settings. These findings highlight the acceptability of remote data collection and the potential of registries to inform recruitment by characterizing registrants, which may help to stratify dementia risk and match participants to eligible trials.

Key words: Registry, subjective cognitive decline (SCD), depression, anxiety, loneliness.

Introduction

In 2020, Alzheimer's disease (AD) affected more than 5 million individuals in the United States alone (1), resulting in considerable psychosocial and economic burden for patients, families, and healthcare providers, with these costs only expected to grow in the years ahead. As researchers in the field of AD and related dementias continue to search for disease-modifying treatments, there is increasing focus on prevention of AD and characterization of preclinical populations. Enrollment in AD trials is more critical now than ever, yet there remain significant challenges to recruitment (2–4), including lack of awareness about research opportunities, location/distance, study partner requirements, concern about study risks, and cultural barriers (4–7).

As one possible approach to facilitate enrollment, participant registries enhance recruitment via the creation and maintenance of an active pool of individuals who have expressed interest in research (8, 9). At the local and international level, participant registries have fostered engagement among adults interested in AD-related research (9, 10). Registries also allow for remote data collection to assist in the characterization of preclinical populations, as well as create opportunities for dissemination related to ongoing research and dementia psychoeducation more broadly (11).

Individuals with subjective concerns about cognitive decline or dementia risk may be interested in enrolling in registries to acquire further information about dementia and potential prevention or treatment strategies, and indeed, subjective cognitive decline (SCD) has been an important area of research in understanding AD risk. SCD is defined as self-reported concern of persistent cognitive changes within the past 1-3 years, in the absence of objective impairment on standardized cognitive testing (12–14). SCD is predictive of further cognitive decline among cognitively normal older adults (13, 15, 16), with SCD in combination with amyloid pathology conferring the greatest risk (17, 18). That said, SCD is nonspecific and is associated with affective symptoms in older adults, including depression and anxiety (19, 20), and select

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personality traits, such as neuroticism, that may moderate observed associations between SCD and underlying amyloid pathology (21). Affective symptoms and SCD are both associated with increased risk of cognitive decline (22), with comorbid SCD and anxiety being associated with greater risk of progression to mild cognitive impairment (MCI) or dementia, in comparison to those endorsing only SCD or only anxiety, respectively (23). Relatedly, it is important to consider the settings in which SCD is assessed; for example, SCD within a memory clinic setting has been associated with higher dementia risk relative to community samples (24).

In this study, we sought to characterize SCD within a registry sample, including the relation of SCD to psychiatric history and related variables, including personality and loneliness, quality of life, and also to factors related to dementia risk (e.g., family history of dementia). We hypothesized that SCD would be associated with psychiatric and personality variables, as well as family history of dementia. We also sought to demonstrate the acceptability of remote data collection using a local participant registry to broaden our understanding of SCD across different settings.

Methods

Procedures

All participants in this study were recruited from a local registry that initially started as a repository of contact information for individuals who had attended community outreach events or participated in research previously and expressed interest in being contacted about future research opportunities. Patients from memory clinics may also have been added to the registry if they expressed interest in research. Individuals in the registry were then contacted several years later and asked if they would like to remain in the registry and receive information about future studies. This resulted in a convenience sample of individuals who had expressed interest in research participation; there were no specific inclusion/exclusion criteria for this registry sample. The study was approved by the Partners IRB, and all participants provided electronic consent to participate via REDCap. All study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Mass General Brigham; REDCap is a secure, web-based software platform designed for research studies (25, 26).

Electronic delivery of the surveys was divided into 3 sessions, spaced out every two weeks to reduce participant burden. Each session was designed to be completed within ~15 minutes. Participants who consented to participate in the study received all surveys at each wave regardless of prior completion and could opt out of participation at any time. Several months after completion of the questionnaires, a second round of surveys was sent to all respondents, also via REDCap, with specific follow-up questions regarding family history of dementia and onset of depression and anxiety (e.g., onset within the past 10 years or not). Participants could choose to receive study emails via encrypted or unencrypted methods.

Measures

We collected demographic information (specific relevant questions below), as well as the following survey measures:

- Family history of dementia: "Has anyone in your family ever been diagnosed with dementia?": YES; NO
- Psychiatric history: "Have you ever been diagnosed with depression? // Have you ever been diagnosed with an anxiety disorder?": YES; NO
  - * Follow-up questions regarding onset of anxiety and depression (sent to all prior respondents, completed by subset of participants): "Do you have a history of depression?// Do you have a history of anxiety?": NO; YES with onset in the last 10 years; YES with onset more than 10 years ago
- Living situation: "What is your current living situation?": living alone; living with others
- Subjective cognitive decline (SCD): 3 questions based on the NIA-AA definition of stage 2 or "transitional cognitive decline" along the AD continuum (12)
  - o Q1: Have you experienced a change in your memory in the last 1-3 years? YES; NO
    - * Q2: Has this been a persistent change over the last 6 months? YES; NO
    - * Q3: Are you concerned about this change? YES; NO
  - o We defined SCD in our sample as those who endorsed at least Qs 1 and 3.
- Quality of life: World Health Organization (WHOQOL-BREF) Quality of Life Assessment (27); yields scores for overall quality of life and general health (range 2-10) and 4 domain scores [physical health (range: 7-35); psychological (range: 6-30); social relationships (range: 3-15); environment (range: 8-40)]; higher scores indicate higher quality of life.
- Loneliness: Three-Item Loneliness Scale (28); higher scores indicate higher levels of loneliness (range: 3-9; see also (29, 30)).
- Personality: Ten-Item Personality Inventory (TIPI) (31); yields 5 scores for extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience (range: 2-14); higher scores indicate higher levels of that personality trait.

Participants and Data Analysis

We excluded any individuals younger than age 50, as well as any individuals who self-reported prior diagnoses of MCI or dementia. We conducted descriptive

Table 1. Sample demographics

	SCD		Non-SCD		p-value
		N		N	
Age (mean in yrs)	67.4 (range: 50-87)	113	67.2 (range: 50-88)	253	.744
Sex (% women; F/M)	74%; (82/29)	111	61% (155/98)	253	.020*
Race (% white)	94%	113	94%	253	.921
Ethnicity (% not Hispanic or Latino)	98%	113	96%	253	.376
Education (% with bachelor's or higher)	78%	113	84%	253	.174
Family history of dementia	74%	113	66%	252	.151
History of depression	44%	113	33%	253	.046*
History of anxiety	21%	113	14%	253	.075
Living alone	26%	61	25%	155	.871
Quality of life (QoL)		82		196	
Overall QoL & general health	7.7 (1.5)		8.2 (1.3)		.003**
Physical health	26.4 (4.7)		29.0 (4.3)		<.001**
Psychological	20.6 (4.1)		23.2 (3.5)		<.001**
Social relationships	10.1 (2.4)		11.1 (2.3)		.002**
Environment	32.8 (4.7)		34.9 (4.0)		<.001**
Loneliness (mean (SD))	4.9 (2.0)	89	4.2 (1.6)	204	.001**
Personality (mean (SD))		80		194	
Extraversion	8.0 (3.4)		8.6 (3.2)		.205
Agreeableness	10.9 (2.4)		11.1 (2.2)		.369
Conscientiousness	10.4 (2.7)		11.5 (2.3)		.002**
Emotional stability	9.6 (3.1)		10.9 (2.7)		.001**
Openness to experience	10.5 (2.6)		10.9 (2.2)		.195

*significant at p<.05; **significant at p<.01; Loneliness mean=4.06±1.47 – 4.29±1.53 in large cohort studies (29,30)

and between-group analyses, using a combination of parametric and non-parametric tests depending on data distribution, including chi-square, t-tests, ANOVA, and Mann-Whitney U, setting the threshold for statistical significance at .05, and controlling for any demographic factors that were significantly associated with SCD status (sex) in parametric analyses (one-way ANOVA with sex as a covariate).

Results

Eight-hundred forty-eight individuals were initially contacted about the survey study; of those, 426 provided consent and agreed to participate (50% response rate), with 353 responding in 2019 and another 73 responding in 2020 after re-contacting individuals who had originally agreed to participate, but who had not completed the surveys in 2019. The response rate was higher for those who chose to receive unencrypted emails (66%) vs. encrypted emails (34%). We excluded any individuals younger than age 50 (n=13), as well as any individuals who reported prior diagnoses of MCI or dementia (n=47), resulting in a sample of 366 individuals (65% female; 94% white; 97% non-Hispanic or Latino; mean age=67.2 (range 50-88); 82% with a bachelor's degree or higher).

Among 366 participants, approximately one third of the sample (31%) endorsed SCD (n=113), and the majority of the sample (68%) endorsed a family history of dementia. SCD was more common among women ($X^2(1)=5.4$, p=.02). Regarding psychiatric history in the whole sample, 37% reported a history of depression and 16% reported a history of an anxiety disorder. SCD was associated with history of depression ($X^2(1)=4.00$, p=.046), but not with family history of dementia ($X^2(1)=2.07$, p=.151).

Controlling for sex, SCD was associated with select personality variables, including lower conscientiousness (F(1, 271)=10.84, p=.001) and lower emotional stability (F(1, 271)=10.64, p=.001), but not with other aspects of personality (agreeableness, extraversion, openness to experience). SCD was also associated with higher levels of loneliness (U=7045, p=.001) and lower quality of life (QoL) across all domains (all ps≤.004): physical health (F(1, 275)=18.67, p<.001), psychological health (F(1, 275)=26.47, p<.001), social relationships (F(1, 275)=10.54, p=.001), environment (F(1, 275)=13.15, p<.001), and

overall QoL and general health ($F(1, 275)=8.52$, $p=.004$), controlling for sex in the QoL analyses.

A subset of participants (n=216) responded to follow-up questions regarding onset of depression or anxiety and living situation. Among participants who reported a history of anxiety or depression, most reported onset more than 10 years prior, rather than within the last 10 years (anxiety: 48/62; depression: 63/82). The majority of participants (75%; 161/216) were living with others rather than living alone. Living situation was not associated with SCD or family history of dementia (ps >.20).

Discussion

In a registry sample, there was a high prevalence of risk factors for dementia, including family history of dementia (68%) and SCD (31%), as well as self-reported history of depression (37%) and anxiety (16%). SCD was more common in women and associated with history of depression, higher loneliness, and lower quality of life. Of those who reported a psychiatric history, most reported onset of depressive or anxiety symptoms more than 10 years prior. Further, lower conscientiousness and lower emotional stability on personality measures were associated with greater SCD. Together, these results may suggest that SCD within a registry sample, recruited primarily from community outreach events and prior research settings, may be more strongly related to longstanding psychiatric and personality variables, rather than family history of dementia. This finding was observed among highly-educated registrants at risk of developing dementia and interested in research, who may be well-versed and sensitive to cognitive changes but may not yet have presented to a memory clinic. It is also worth noting that mood and personality factors could certainly bias one's perception of cognitive abilities (and vice-versa). These findings add to the existing literature on SCD across different samples and highlight the importance of study setting. Prior work found that older adults with SCD from a memory clinic were at a higher risk of developing MCI compared to adults with SCD in the general population (32).

These findings may inform recruitment efforts by characterizing registry participants, stratifying risk for cognitive decline, and matching them to appropriate studies (e.g., studies focused on psychiatric variables, family history, SCD, etc.). For example, the subset of registrants endorsing SCD and a more recent onset of anxiety or depression (e.g., within the last ten years) may be particularly well-suited for screening into preclinical AD trials and/or biomarker studies, as new-onset affective symptoms in older adults may represent early signs of an underlying neurodegenerative process (33), rather than longstanding psychiatric conditions or personality traits. Another recruitment strategy for preclinical and/or biomarker studies may be to screen registrants at the highest risk for future cognitive decline, such as 1) individuals with SCD and family history of AD dementia or 2) females endorsing SCD, and possibly also by obtaining informant report among those with SCD to further characterize risk (34, 35).

Beyond directly informing recruitment, registries allow for engagement with potential participants with relatively minimal participant burden. We demonstrated the acceptability of remote data collection, with an overall response rate of 50%, which may allow researchers to better characterize registry samples. This is now particularly relevant in the context of the COVID-19 pandemic when other outreach events are not possible.

That said, this study had several limitations including selection and information bias and limited generalizability. First, our data consisted of only self-report measures, including self-reported psychiatric and neurologic history, which may be susceptible to information bias. That said, self-report of psychiatric symptoms is likely reliable among adults without MCI or dementia; participants may also have felt more comfortable disclosing psychiatric history via remote, self-report questionnaires rather than direct questioning by study staff in the clinic. Even so, the cross-sectional design precludes any discussion of directional or causal relationships between SCD and psychiatric history, loneliness, and personality. Next, our sample lacked objective cognitive data, which is relevant to the definition of SCD. Any participants with a self-reported history of MCI or dementia were excluded, but without current cognitive data, there is the possibility that some participants may have objective cognitive impairment despite never having received an MCI or dementia diagnosis. In addition, our registry sample lacked AD biomarker or genetic data on participants. Future research cohorts could consider including these variables to further characterize dementia risk among those with SCD. Longitudinal studies with objective and clinician-administered assessments are also warranted to better elucidate the nature and direction of associations between SCD and psychiatric history, loneliness, and personality.

Next, generalizability is largely limited to highly-educated, at-risk individuals with a family history of dementia, who may be particularly motivated to engage in research. The findings may also be biased towards those who had access to technology and prior experience completing remote assessments via smartphone, tablet, or computer. Future registry studies focused on remote data collection may need to consider modifications to optimize response rate (e.g., training in use of technology at outreach events, individualized assistance in technology set-up, psychoeducation regarding encrypted vs. unencrypted email formats, etc.). There was also minimal diversity in our registry, most notably in terms of race, ethnicity, and educational history. It will be crucial for future work to develop targeted strategies to engage more diverse samples in registries, particularly given that minority populations may be at an elevated

risk for developing AD and related dementias (36). The prevalence of SCD has also been shown to vary across racial and ethnic groups (37), a finding which could be explored further in more diverse registry samples. To do so, it will be critical to explore any barriers to either registry enrollment and/or research participation among minority populations, perhaps via active community outreach (38).

Moving forward, questions remain with regard to optimal design of registries to enhance retention of registrants over time and increase research engagement and trial enrollment (9), for remote studies as well as observational and clinical trials. Future work should also consider exploring participants' expectations of a registry to further optimize registry design and practices (8), possibly to include providing feedback to registrants about study results. In addition, local, and predominantly online/remote, registries have the potential to streamline recruitment and allow for objective examination of recruitment success, or alternatively, lack of success and exploration of barriers to research engagement. In addition, registries may allow for remote data collection to pilot new studies and/or better characterize registry samples, with regard to demographic and psychiatric variables, as well as AD risk factors. In summary, local registries can inform recruitment by characterizing registrants, stratifying their risk for future cognitive decline, and then matching them to studies for which they may be eligible. Furthermore, registries provide an opportunity to enhance research engagement, ranging from remote data collection, as demonstrated here, to participation in observational studies and ultimately, clinical trial enrollment.

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Conflicts of interest: G. Reynolds has nothing to disclose.

Ethical standards: Study protocols were approved by the Partners Institutional Review Board, and all participants provided electronic informed consent before completing any study procedures.

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