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PERSPECTIVE

The role of dyadic cognitive report and subjective cognitive decline in early ADRD clinical research and trials: Current knowledge, gaps, and recommendations

Rachel L. Nosheny[1,2] | Rebecca Amariglio[3] | Sietske A.M. Sikkes[4] | Carol Van Hulle[5] | Maria Aparecida Camargos Bicalho[6] | N. Maritza Dowling[7] | Sonia Maria Dozzi Brucki[8] | Zahinoor Ismail[9] | Kensaku Kasuga[10] | Elizabeth Kuhn[11] | Katya Numbers[12] | Anna Aaronson[2] | Davide Vito Moretti[13] | Arturo X. Pereiro[14] | Gonzalo Sánchez-Benavides[15] | Allis F. Sellek Rodríguez[16] | Prabitha Urwyler[17] | Kristina Zawaly[18] | for the Dyadic Patterns of Subjective Report working group within the Subjective Cognitive Decline Professional Interest Area, Alzheimer's Association ISTAART

[1]University of California San Francisco, Department of Psychiatry, San Francisco, California, USA

[2]Veteran's Administration Advanced Research Center, San Francisco, California, USA

[3]Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Department of Neurology Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4]Amsterdam University Medical Centers, Department of Neurology, Alzheimer Center Amsterdam, North Holland, the Netherlands/VU University, Department of Clinical, Neuro & Development Psychology, North Holland, the Netherlands

[5]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison, Madison, Wisconsin, USA

[6]UFMG: Federal University of Minas Gerais, Department of Clinical Medicine, Jenny de Andrade Faria – Center for Geriatrics and Gerontology of UFMG, Belo Horizonte, Brazil

[7]George Washington University, Department of Acute & Chronic Care, School of Nursing, Department of Epidemiology & Biostatistics, Milken Institute School of Public Health, Washington, District of Columbia, USA

[8]Group of Cognitive and Behavioral Neurology – University of São Paulo, São Paulo, Brazil

[9]Hotchkiss Brain Institute and O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[10]Department of Molecular Genetics, Brain Research Institute, Niigata University, Niigata, Japan

[11]UNICAEN, INSERM, PhIND "Physiopathology and Imaging of Neurological Disorders,", Institut Blood and Brain @ Caen-Normandie, Normandie University, Caen, France

[12]Centre for Healthy Brain Ageing (CHeBA), Department of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia

[13]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Alzheimer Rehabilitation Operative Unit, Brescia, Italy

[14]Faculty of Psychology, Department of Developmental Psychology, University of Santiago de Compostela, Galicia, Spain

[15]Barcelona Beta Brain Research Center, Barcelona, Spain

[16]Costa Rican Foundation for the Care of Older Adults with Alzheimer's and Other Dementias (FundAlzheimer Costa Rica), Cartago, Costa Rica

[17]ARTORG Center for Biomedical Engineering, University of Bern, University Neurorehabilitation Unit, Department of Neurology, Inselspital, Bern, Switzerland

[18]University of Auckland, Department of General Practice and Primary Health Care, School of Population Health, Faculty of Medical and Health Sciences, Auckland, New Zealand

Correspondence
Rachel L. Nosheny, 4150 Clement Street, 114 M, San Francisco, CA 94121, USA.
E-mail: Rachel.Nosheny@ucsf.edu

Abstract

Efficient identification of cognitive decline and Alzheimer's disease (AD) risk in early stages of the AD disease continuum is a critical unmet need. Subjective cognitive decline is increasingly recognized as an early symptomatic stage of AD. Dyadic cognitive report, including subjective cognitive complaints (SCC) from a participant and an informant/study partner who knows the participant well, represents an accurate, reliable, and efficient source of data for assessing risk. However, the separate and combined contributions of self- and study partner report, and the dynamic relationship between the two, remains unclear. The Subjective Cognitive Decline Professional Interest Area within the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment convened a working group focused on dyadic patterns of subjective report. Group members identified aspects of dyadic-report information important to the AD research field, gaps in knowledge, and recommendations. By reviewing existing data on this topic, we found evidence that dyadic measures are associated with objective measures of cognition and provide unique information in preclinical and prodromal AD about disease stage and progression and AD biomarker status. External factors including dyad (participant–study partner pair) relationship and sociocultural factors contribute to these associations. We recommend greater dyad report use in research settings to identify AD risk. Priority areas for future research include (1) elucidation of the contributions of demographic and sociocultural factors, dyad type, and dyad relationship to dyad report; (2) exploration of agreement and discordance between self- and study partner report across the AD syndromic and disease continuum; (3) identification of domains (e.g., memory, executive function, neuropsychiatric) that predict AD risk outcomes and differentiate cognitive impairment due to AD from other impairment; (4) development of best practices for study partner engagement; (5) exploration of study partner report as AD clinical trial endpoints; (6) continued development, validation, and optimization, of study partner report instruments tailored to the goals of the research and population.

KEYWORDS
activities of daily living, Alzheimer's disease, informant-reported outcomes, mild cognitive impairment, study partner–reported outcomes, subjective cognitive decline

1 | INTRODUCTION

Subjective reports from dyads (participant and study partner pairs) have great potential for applications in research and care of older adults. Subjective report of decline in cognition, activities of daily living, and behavioral changes can be efficiently collected from individuals themselves or a study partner. Study partners are a vital source of information about the cognitive and functional status of participants in dementia research, due to individuals' declining awareness about their diagnosis, or anosognosia.[1,2] Study partners are often required for enrollment into Alzheimer's disease (AD) clinical trials and observational studies.[3] A study partner (e.g., a spouse, adult child, other family member, or friend) is someone who knows the participant well enough to report on their current cognitive and functional abilities, as well as recent changes. As the field focuses on the asymptomatic, biomarker positive (preclinical), and early symptomatic (prodromal) AD disease stages as key timepoints for therapeutic intervention, it is crucial to understand the role of dyadic report at these earlier disease stages. Yet, crucial challenges remain in understanding how and in what contexts dyadic report should be used to facilitate AD clinical research. More research is needed to understand the role of different subjective constructs, the dynamic relationship between self- and study partner report, and the many factors influencing subjective dyadic report.

Why should AD researchers use dyad report of subjective cognitive changes (SCC), when objective and validated cognitive and functional measures are available? There are multiple advantages. Dyad report of SCC can efficiently capture measures of cognitive and functional

RESEARCH IN CONTEXT

1. **Systematic Review**: The Subjective Cognitive Decline Professional Interest Area within the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment convened a working group, which conducted a narrative review of existing literature on the use of dyadic (participant–study partner) subjective cognitive complaints (SCC) in dementia research. The goal was to obtain a broad perspective on the topic for a broad target audience.
2. **Interpretation**: Dyadic SCC is associated with objective measures of cognition. In preclinical and prodromal Alzheimer's disease (AD), SCC measures provide information about clinical progression and AD biomarker status. Factors such as clinical stage, dyad relationship, and sociocultural factors contribute to these associations.
3. **Future Directions**: Future research should: (1) elucidate contributions of external factors to the validity of SCC measures; (2) define agreement and discordance between self- and study partner report across the AD disease continuum; (3) identify domains of dyad report that best predict AD risk outcomes; (4) develop best practices for study partner engagement; (5) consider dyad SCC measures as AD clinical trial endpoints; and (6) continue to develop, validate, and optimize dyadic SCC instruments.

decline within a single, cross-sectional assessment by asking about recent changes. They provide unique insight into decline in complex and high-level activities of daily living and cognitive function that may begin to decline early in the AD continuum, are associated with AD biomarkers,[4–6] are difficult to assess using traditional testing, and are important outcomes for participants and families. Dyad report SCC offer good portability across cultures, languages, and educational levels and high specificity compared to many traditional neuropsychological tests; and easy adaptation into remote, unsupervised assessments.[7–9] This may be especially important for research in low-resource countries and settings. A number of validated instruments exist to capture changes in cognition, function, and behavior (see Table S1 in supporting information). There are also challenges to relying on dyadic SCC, such as the lack of an available and reliable study partner for many older adults, and the fact that SCC measures are influenced by factors such as sociocultural factors and dyad relationship. Herein we discuss evidence supporting the use of dyadic SCC measures in AD research and care, challenges, and recommended next steps.

An important area of recent research focuses on elucidating the relationship between self- and study partner–reported SCC across the cognitively unimpaired (CU) to mild cognitive impairment (MCI) continuum. For example, in some cases, agreement between self- and study partner report indicates a robust, reliable corroboration of cognitive impairment. In other cases, discrepancy between the two may provide unique information. Two main types of discrepancy are: (1) overreport of SCC by study partners compared to participants themselves, which is often thought to indicate individuals' declining awareness, or anosognosia; or (2) overreport of SCC by participants themselves compared to their study partners, which may indicate more awareness than study partners about actual cognitive impairment, or an overestimation of one's cognitive deficits and available cognitive capacity due to factors such as mood and personality traits.[10] Compared to self-reported SCC, study partner–reported SCC are not influenced by lack of insight associated with dementia,[11–13] and may be less influenced by factors such as participant mood,[14–16] although study partner mood may also play a role.[17]"

In this perspectives article, we review evidence regarding the use of dyad-reported measures, identify key gaps in knowledge and challenges, and make recommendations regarding research priorities for using dyad-reported information in preclinical and prodromal AD research. We review past work in the field in two main areas: (1) evidence for the validity of dyad report, and (2) use of dyad-reported SCC as early indicators or predictors of cognitive decline and cognitive impairment due to AD. For each of these research areas, we consider the relationship between self- and study partner–reported SCC. Findings are summarized in Table 1.

2 | EVIDENCE FOR VALIDITY OF DYAD-REPORTED MEASURES: ASSOCIATIONS BETWEEN STUDY PARTNER–REPORTED SCC AND OBJECTIVE MEASURES OF COGNITION

Self- or study partner–reported SCC are a core criterion in the diagnosis of MCI and subjective cognitive decline. Subjective cognitive decline is defined by self-report of cognitive symptoms in the absence of objective cognitive impairment and is increasingly recognized as the earliest symptomatic stage of AD.[18–20] Study partner–reported SCC are associated with objective cognitive performance and predict future cognitive decline,[21–23] whereas evidence for associations between self-reported SCC and objective cognitive measures is inconclusive (e.g., Lubitz et al.,[24] Jonker et al.,[25] Glodzik-Sobanska et al.,[26] Slavin et al.,[27] Purser et al.,[28] and Lenehan et al.[29]).

In CU individuals, both corroborating self- and study partner–report SCC (agreement between the two), and discrepancy between the two (with participants overreporting SCC compared to study partners) have been found to predict objective cognitive performance and cognitive decline.[30,31] Conflicting results in this space are likely due to differences in cohorts and subjective assessments used. This contrasts the findings at the MCI stage, in which discrepancy between self- and study partner–reported SCC (overreport by study partners compared to participants) are more strongly associated with objective cognitive performance, and provide better risk estimates of cognitive decline.[12,31,32]

TABLE 1 Summary of findings: Associations between subjective cognitive complaints and various outcomes of interest

	Disease stage		
	CU	MCI	Dementia
SCC vs. objective cognition			
Self-report	+	+/−	−
Study partner report	++	++	++
Dyad agreement	+/−	?	−
Dyad discrepancy	+/−	++	−
SCC vs. diagnosis[a]			
Self-report	N/A	+/−	−
Study partner report	N/A	++	++
Dyad agreement	N/A	+/−	−
Dyad discrepancy	N/A	+/−	++
SCC vs. disease progression[a]			
Self-report	N/A	+	−
Study partner report	N/A	++	++
Dyad agreement	N/A	+	−
Dyad discrepancy	N/A	++	++
SCC vs. AD biomarkers			
Self-report	+/−	+/−	−
Study partner report	+	+	+
Dyad agreement	?	+	−
Dyad discrepancy	+	?	+

Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; SCC, subjective cognitive complaints.
[a]Results are shown with CU individuals as the reference value.
+: Positive relationship
++: Robust evidence for positive relationship based on multiple studies
−: Negative relationship
+/−: Conflicting results (showing both positive and negative relationships)
?: Lack of evidence

An important issue when considering the association between study partner–reported SCCs and objective cognition is domain specificity. Memory-specific study partner -report, compared to non-memory report, have been found to best predict global cognitive decline, decline in domains of executive function and memory, and incident dementia.[21,27] Conversely, CU and MCI individuals are better able to report executive function decline compared to their study partners.[33] These results suggest that participants and study partners may have unique insight into different types of cognitive changes and/or decline, and that measures from both sources should be considered, when possible, for the best approximation of underlying cognitive impairment.

3 | DYAD-REPORTED SCC AS A PREDICTOR OF COGNITIVE IMPAIRMENT DUE TO AD AND DISEASE PROGRESSION

3.1 | Associations with clinical diagnosis

Study partner report adds value in identifying individuals with AD dementia.[12,13,34–44] Discrepancy between self- and study partner–report SCC, in which study partners overreport SCC compared to participants, has also been found to predict AD dementia diagnosis,[10,12,13,32,34,36–47] although there is variability in the degree of anosognosia in dementia.[44,45,48–51]

The association between dyad-reported SCC and clinical diagnosis along the CU to MCI stages of AD is less well defined. Study partner–report SCC discriminates CU from MCI with moderate to high accuracy.[13,52–59] In many cases, study partner–report SCC shows better diagnostic discrimination compared to self-reported SCC along the early disease continuum (CU to MCI), whereas both self- and study partner–report SCC discriminate CU from AD dementia with high accuracy.[13,34,53,55] Additionally, study partner–rated neuropsychiatric symptoms in older adults are associated with MCI, with a predictive value for incident cognitive decline in those with normal cognition, subjective cognitive decline, and MCI.[60–63]

Past work demonstrates variability in the relationship between dyad-reported SCC along the CU to MCI disease continuum. In individuals with MCI, a significant discordance is reported in some,[34,38,40,44,64] but not all studies,[12,13,39,41,43] with one study reporting higher self-reported SCC compared to study partner–reported SCC in "high functioning" MCI patients.[39] Furthermore, evidence about this discordance is still scarce in individuals with subjective cognitive decline, and conflicting results are likely confounded by the fact that many studies do not distinguish CU from subjective cognitive decline. Self-report of more SCC, combined with lower levels of study partner–report SCC, were found to best distinguish subjective cognitive decline from MCI.[34] Most studies have found that self-reported SCC are higher than study partner–reported SCC in subjective cognitive decline compared to CU.[13,34,65] However, a few other studies have found the opposite pattern (higher study partner–reported SCC), possibly due to loss of cognitive awareness in some individuals with subjective cognitive decline.[66,67] More research is needed to elucidate the utility of self, study partner, and combined SCC report, including research that carefully defines subjective cognitive decline.

3.2 | Associations with cognitive decline and disease progression

In CU individuals, study partner–reported SCC predict progression to MCI[23,32,68–70] and dementia.[8,21,22] Study partner–reported SCC were associated with a nearly 5-fold higher risk of progression from CU to MCI from CU to MCI compared to a 3-fold higher risk associated with self-report,[23] although only self-reported SCC was found to be associated with CU to MCI progression in amyloid-positive participants in the Alzheimer's Disease Neuroimaging Initiative study.[32] Another study found stable self-reported SCC in CU and MCI, but with increased study partner–reported SCC in MCI over 2 years of follow-up.[71] There is some evidence that combined reports of SCC are most predictive of diagnostic outcome,[36,70] including in CU individuals who are apolipoprotein E ε4 allele carriers.[59] Interestingly, Nuño et al. found that in a cohort of CU older adults, participants themselves were better at predicting future cognitive performance, whereas spousal study

partners were better than participants at predicting current cognitive performance.[72]

Past work is mixed regarding the relationship between self- and study partner–reported SCC along the MCI to dementia continuum. Most work supports greater accuracy of study partner–reported SCC compared to self-report in predicting MCI to dementia disease progression, and more recently, discrepancy has been demonstrated as a useful predictor of incident dementia, specifically study partner overreport of SCC compared to self-report.[64,71,73,74] However, there is some evidence that agreement between self- and study partner–reported SCC could also be useful at this stage as well.[70] Moreover, studies show that individuals with anosognosia have a 3-fold increased risk of conversion to dementia within 2 years of follow-up,[75] with anosognosia occurring 3.2 years before the onset of dementia,[76] and that discrepancy between self- and study partner–reported SCC increased over time in MCI patients who progressed to AD dementia. Most studies, therefore, suggest that a greater risk of progression to dementia is linked to self-reported underestimation of difficulties or overestimation of cognitive and functional abilities compared to study partner–reported SCC.

4 | ASSOCIATIONS BETWEEN DYAD-REPORTED SCC AND AD BIOMARKERS

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed the AT(N) classification system for research, in which AD is defined by its underlying pathological processes: the combined presence of amyloid (A) plaques and neurofibrillary tangles of tau (T),[77] and biomarkers of neurodegeneration (N) not specific to AD.[78] Study partner–report measures that are associated with AD biomarkers have the potential to facilitate efficient identification of, or enrichment for, AD biomarker–positive older adults for preclinical and prodromal clinical trials

The role of self- and study partner–reported SCC at the preclinical stage, as defined by amyloid and tau (AT) burden, has not yet been thoroughly examined. However, SCC at this stage is more commonly associated with greater amyloid[79–81] and tau[82,83] in individuals who are otherwise CU, although not across all studies.[13,84] Recently, two cohorts of participants with SCC classified according to the AT(N) framework confirmed that the majority of participants with SCC were biologically normal, but around one fifth had elevated brain amyloid. These individuals exhibited steeper subsequent decline compared to participants with SCC but no AD-related pathologic changes.[85,86] In another study, participants with SCC had lower cerebrospinal fluid (CSF) levels of amyloid beta (Aβ)42, consistent with amyloid plaque burden, and elevated sTREM2, a marker of neuroinflammation linked to AD risk, compared to CU individuals.[87]

Increasing evidence suggests that among individuals who are CU and functioning normally in their everyday activities, a study partner can detect subtle cognitive changes that are associated with elevated amyloid.[88,89] For example, in a large sample of individuals screened for a secondary prevention trial, both self- and study partner–reported SCC were associated with elevated amyloid positron emission tomography (PET).[88] When looking at specific items reported by participants and their study partners,[90] there was considerable overlap in the types of complaints associated with amyloid PET, including a change in memory over the last year, misplacing belongings, and trouble with names and words. However, repeating questions was only associated with amyloid for study partner–reported SCC. Study partner report also correlates with lower CSF Aβ42 and higher phosphorylated tau (p-tau) levels in AD dementia, MCI, and CU individuals.[13] Valech et al.[55] found that across CU, subjective cognitive decline, and MCI participants, study partner–report SCC correlated significantly with markers of AD pathology (Aβ42, p-tau, and total tau [t-tau] levels). Moreover, study partner–reported SCC, but not self-report, differed significantly between CU participants who were amyloid positive and those who were amyloid negative.[55] Wolfsgruber et al.[83] reported that performance on multiple cognitive domains (especially memory and executive function) were correlated with biomarkers CSF Aβ42/40, p-tau, and t-tau, as well as study partner report, but not self-report, in participants with SCC.

Self- and study partner–reported SCC are most divergent at the AD dementia clinical stage.[45] Several studies focused on the association between anosognosia and imaging biomarkers.[75,91,92] At the dementia stage, greater amyloid burden seems to be characterized by partner overreport of SCC compared to self-report-SCC, while lower amyloid burden seemed to be characterized by consistent estimation of difficulties between self- and study partner.[76,93] The relationship between self-report, study partner report, and amyloid in participants with MCI and mild AD is less clear. One likely explanation is the wide range of metacognitive abilities at the MCI and mild AD dementia stages. These disease stages are known to include individuals with both preserved and impaired awareness of their own memory loss.[94–97] Another possible contributor to the lack of clarity is the wide range of cognitive impairment levels within this disease stage. Study partner–rated report of decline in instrumental activities of daily living were shown to be positively associated with multiple biomarkers for AD, including amyloid PET (in late MCI), hippocampal volume (in late and early MCI), and CSF p-tau (in late MCI).[13] This lends relative validity to study partner report on functional status across MCI groups. Recent studies comparing study partner–rated SCC between amyloid PET-positive and -negative patients (MCI and mild to moderate AD) also confirm that study partner–report SCC converges with AD pathology.[93] Recently, James et al.[98] examined the level of concordance of SCC between dyads of persons with MCI or dementia and their study/care partners as predictors of amyloid positivity. Accuracy in classifying amyloid positivity was above 80% for self- and study partner dyads, similar to blood-based biomarkers;[99] a separate cohort, evaluating self-reported SCC alone, did not predict amyloid positivity.[100]

Beyond amyloid and tau, some studies have investigated associations between SCC and alterations in fluorodeoxyglucose PET. Subjective memory impairments are known to be associated with decreased volume and hypometabolism in the medial temporal lobe.[101–103] One study found divergent cross-sectional association with glucose

metabolism in individuals with AD dementia, where lower metabolism was related to lower self-reported SCC and to higher study partner–reported SCC.[92] Roy et al.[104] reported that study partner–reported SCC was related to lower metabolism in the parahippocampus and posterior cingulate cortex in AD dementia relative to MCI, itself relative to CU. This study also highlighted an association between an increase in study partner–reported SCC over 2 years of follow-up and a low baseline metabolism. Therefore, at the MCI and dementia stage, anosognosia seems to be associated with higher amyloid burden and functional alterations, although it should be noted that not all studies find an association between mutual report of SCC and either functional imaging measures or amyloid burden in individuals with AD dementia patients.[13]

Regarding hippocampal volume, which can also be considered a measure of neurodegeneration, a study[105] in CU individuals found that study partner report SCC was related to lower volumes in the left posterior hippocampus and cerebellum irrespective of the presence or absence of self-report SCC. However, hippocampal volume was positively correlated with memory performance only in individuals classified as "unaware decliners," with study partner–reported SCC in the absence of self-report SCC.

Taken together, growing evidence suggests that both self- and study partner–reported SCCs are important measures to assist in determining AD risk at the preclinical disease stage, due to associations with AD biomarkers. Because amyloid and tau can accumulate in the brain decades before clinical symptom onset, but require invasive or expensive methods to measure, development and validation of assessments that comport with early disease stages are critical.

5 | DYAD CHARACTERISTICS THAT INFLUENCE SCC

Factors such as age, education level, living arrangement, caregiver burden, neuropsychiatric symptoms, and a study partner's cognitive status can impact study partner–reported SCC.[106–109] Study partners enrolled in clinical trials are often participants' spouses.[109] In a cross-sectional study, Lin et al. found that spouse study partners reported higher participant quality of life for amnestic MCI and AD participants than did non-spouse study partners.[106] Spouses who willingly participate as study partners in clinical trials may have greater investment and capability in caring for a cognitively impaired spouse.[106] Spousal study partners have a higher willingness to participate, a more positive attitude toward research, and a lower dropout rate than non-spousal study partners.[109–111] According to Ready et al., study partners who are spouses and who live with participants provide the most accurate ratings of elderly participants' memories.[107]

Neuropsychiatric symptoms and mood of study partners can also influence their report of participant SCC.[112] Caregiver burden and depression are associated with negative assessments of participants' psychological and behavioral symptoms, and quality of life.[113,114] Therefore, discrepancy in SCC reports might be due not only to the participant's anosognosia but also to an overestimation of difficulties by the study partner because of burden, depression, or other negative outcomes associated with caring.[36,41,106,115] Furthermore, neuropsychiatric symptoms of participants influence their own self-report SCCs. Jiménez et al. found that subjective information collected from participants is correlated with mood, whereas study partner reports are correlated with both the function and mood of participants.[16] Depression and anxiety,[116,117] and certain personality traits like neuroticism and conscientiousness,[117,118] may affect self-reported SCCs.

Study partner retention can also impact outcomes. Whether a study partner is replaced, and the frequency of replacement during longitudinal studies, may cause inconsistency in data reporting and increased outcome measure variance. Within one study of AD patients, Grill et al. found that replacement was less frequent for participants with spouse study partner versus those with other study partners.[119] Among spouse study partners, Latino ethnicity, male study partner sex, and older study partner age were associated with study partner replacement. In turn, study partner replacement was associated with increased variability in participant Functional Activities Questionnaire, Clinical Dementia Rating Sum of Boxes, and Neuropsychiatric Inventory Questionnaire scores across study visits.[119]

Based on these findings, information such as dyad relationship type, neuropsychiatric symptoms of both participant and study partner, and caregiver burden and cognitive status of study partners, should be included in analyses of dyadic report of SCC. Further, although some work has been done to define subjective cognitive decline in underrepresented ethnocultural groups and elucidate contributions of race and ethnicity to SCC measures,[120,121] very little is known about the contributions of race, ethnicity, and other sociocultural and demographic factors to study partner report subjective measures.[122] Increased inclusion of historically underrepresented populations in clinical trials and studies, including participants and study partners from underrepresented ethnocultural and socioeconomic status groups, is essential.[123]

6 | LIMITATIONS AND CHALLENGES OF USING DYAD REPORT SCC

AD and related disorders clinical research often requires enrollment of participant and study partner dyads. Requirement of a study partner is one of the most important barriers to enroll participants to clinical research. Being a study partner requires adequate free time, effort, and insight into the research participant's cognition and function to provide additional information. Some participants do not have a study partner willing and able to follow them to all study visits.[124,125] Depending on the clinical study, being a study partner can be quite burdensome. As the participant experiences cognitive decline, the role of the study partner changes and may become more time consuming and labor intensive. Due to logistical constraints or the death of a study partner, the person serving as a study partner may change during the study, which can affect reliability of study partner report. Study partners have been shown to experience emotional distress related to traveling to

study visits and travel expenses as well as to length, schedules, delay, and frequency of study visits. Studies conducted in multiple places and including many different procedures are also associated with study partner burden. Study partners have reported difficulties in following study protocols and management of medications.[111,126] Because study partners provide essential information in dementia research, future efforts should focus on facilitating study partner recruitment and engagement, and mitigating study partner burden. One promising area is remote assessment,[9,127] which may help to reduce burden and therefore improve study partner participation. Furthermore, because many older adults do not have an available study partner, more research is needed to understand whether and how self-report subjective measures or other assessments could be used as alternative measures to allow those without study partners to be included in more AD research and trials.[128] Another limitation is that dyadic SCC can be influenced by many factors, as described above. Some are unique to dyadic SCC, such as the influence of dyadic relationship. Others, such as sociocultural factors, can influence both objective and subjective measures, although the influence may be more pronounced for dyadic subjective measures.

7 | CURRENT GAPS IN KNOWLEDGE

As the AD field moves toward an emphasis on detection of early stages of disease and prevention of symptoms, the development of accurate and efficient methods to identify preclinical and prodromal AD, and to predict and track cognitive and functional decline is critical. Dyad-report measures of SCC have great potential to play a crucial role in addressing this need. It is well established that study partners can assess the cognitive and functional status of those with moderate to severe dementia more accurately than participants themselves, due to factors such as anosognosia. However, more recently, study partner–reported SCC have shown promise as an important indicator of preclinical and prodromal AD, especially when considered in combination with self-reported SCC. The prodromal/MCI stage is heterogeneous and dynamic in terms of cognitive and functional status, and thus the importance of study partner report at this stage is also variable and inconsistent. Intriguing new evidence suggests that individuals and their study partners may each contribute domain-specific insight. The use of study partner data in dementia research is complicated by many factors that are likely to influence the accuracy of study partner report and its ability to identify preclinical and prodromal AD such as dyad relationship, cognitive status of the study partner, the specific constructs (e.g., decline, current level of functioning, concerns) and domains (e.g., memory, language, executive function) being interrogated, and demographic and sociocultural profiles of both members of the dyad. Despite multiple studies controlling for the effects of age, education, sex, ethnicity, depressive symptoms, and cognitive status or impairment severity, evidence regarding the underlying cause of discrepant results between participants and study partners is still not conclusive.[10,12,34,36,39,64,66]

8 | RECOMMENDATIONS

Based on the past work reviewed here, we make the following recommendations (see Table 2) regarding the use of dyad-report data in AD research.

1. Further investigation of the agreement and discordance between self- and study partner report, and whether levels of discordance are meaningful predictors of relevant outcomes such as biomarker status and disease progression.

The relationship between self- and study partner report is influenced by multiple factors. Most notable is the dynamic relationship over the CU to MCI stages. Corroborating dyadic report is most useful in CU individuals, where loss of insight is not likely. We believe this line of investigation should work toward identification of the stage along the AD disease continuum (defined by objective cognitive status and clinical diagnosis) at which it is most appropriate to use dyad report, to consider discordance between self- and study partner report, or to rely solely on study partner report. Methodological heterogeneity across studies makes it difficult to determine the origin of the discrepancy, and therefore, standardized measures and covariates should be confirmed for the assessment of anosognosia to better understand how this impacts self- and study partner–reported SCCs.[129]

2. Elucidation of additional factors that influence the relationship between self- and study partner report, and the relationship of each to outcomes of interest.

These factors include demographic and sociocultural factors (e.g., ethnocultural status, socioeconomic status) and dyad relationship (e.g., type of relationship, amount of time spent together cognitive status of the study partner). Establishment of diverse cohorts and more concerted efforts to collect the relevant demographic, sociocultural, and relationship information in trials and observational studies and account for these variables in analyses is crucial. This line of work will enable researchers to better use dyadic SCC measures that are influenced by these factors. Regarding the contributions of dyad relationship, this line of research may lead to recommendations of a required minimum level of "dyad familiarity" with the participant for inclusion in the study. Researchers should evaluate study partner cognition, especially of older adult study partners, such as spouse, siblings, and friends of the participant,[125,126,130] and consider limitations, accuracy, and reliability of study partner report in cases in which study partners show signs of cognitive impairment.

3. Further investigation of the domain specificity of dyad reports as they relate to objective measures; and further analysis of how participants and study partners understand the domains of SCC, including multiple cognitive domains, instrumental activities of daily living, neuropsychiatric symptoms, and memory concerns.

TABLE 2 Recommendations for areas of focus

Recommendation	Areas of focus
1. Investigation of self- vs. study partner SCC agreement and discordance.	• Whether levels of discordance are meaningful predictors of relevant outcomes such as biomarker status and disease progression. • Dynamic relationship between self- and study partner report over various disease stages • Identification of the disease stage (defined by objective cognitive status and clinical diagnosis) at which it is most appropriate to use dyad report, to consider discordance between self- and study partner report, or to rely solely on study partner report. • Investigation of sources of discordance. • Use of standardized measures and covariates for the assessment of anosognosia to better understand how this impacts self- and study partner–reported SCCs.
2. Elucidation of additional factors that influence the relationship between self- and study partner report, and the relationship of each to outcomes of interest.	• Establishment of diverse cohorts and more concerted efforts to collect the relevant demographic, sociocultural, and relationship information in trials and observational studies. • Inclusion of important variables in analyses (e.g., demographic and sociocultural factors, dyad relationship). • Evidence-based best practices for a required minimum level of "dyad familiarity" with the participant for inclusion in the study. • Evaluation of study partner cognition, especially of older adult study partners.[125,126,130] • Consideration of limitations, accuracy, and reliability of study partner report in cases in which study partners show signs of cognitive impairment.
3. Investigation of the domain specificity of dyad reports as they relate to objective measures.	• Further analysis of how participants and study partners understand the domains of SCC, including multiple cognitive domains, Instrumental Activities of Daily Living, neuropsychiatric symptoms, and memory concerns.
4. Definition of best practices to use dyadic-report data in AD clinical trials.	• Utility of study dyadic report SCC to enrich for biomarker positivity at the screening stage. • Exploration of whether dyadic-report SCC and other subjective report constructs are suitable endpoints in AD clinical trials.
5. Strategies to facilitate study partner participation	• Removing logistical barriers. • Increasing engagement and incentives in studies and trials. • Increasing opportunities for remote participation and assessment. • Greater compensation. • More engagement throughout the study. • Better recognition of the valuable role that study partners play in dementia research. • Recruitment and consent materials that provide relevant information explaining study partner roles, responsibilities, logistical requirements, and potential emotional burdens. • Emotional support, education programs, and good relationships with study team members to reduce study partner burden.[111,126]
6. Instrument development	• Development, validation, optimization, and use of instruments tailored to the goals of the research and to the research population in terms of demographics and disease stage.

Abbreviations: AD, dementia due to Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; SCC, subjective cognitive complaint.

4. Definition of best practices to use dyadic-report data in AD clinical trials.

Future studies should explore the utility of study dyadic report SCC to enrich biomarker positivity in the screening stage, and explore whether dyadic report SCC and other subjective report constructs are suitable endpoints in AD clinical trials. More research is needed to determine whether SCC measures are reliable and sensitive enough to be used as endpoints in trials, either alone or together with objective measures of cognition and function.

5. Identification of strategies to facilitate study partner participation, such as removing logistical barriers, reducing study partner burden, and increasing engagement and incentives in studies and trials.

This may include opportunities for remote participation and assessment, greater compensation, more engagement throughout the study, and better recognition of the valuable role that study partners play in dementia research. Recruitment and consent materials should provide relevant information explaining study partner roles, responsibilities, logistical requirements, and potential emotional burdens. Because at some point along the disease continuum it is likely that investigators will need to rely heavily on the study partner to provide accurate information, they should be engaged throughout longitudinal studies. Emotional support advice, education programs, and good relationships with study team members are essential to addressing study partner burden.[111,126] Remotely collected data for research settings are a promising tool for longitudinal monitoring in clinical trials, lessening the in-clinic burden of participation, which is a known barrier to study partner participation.[9]

6. Development, validation, optimization, and use of instruments tailored to the goals of the research and to the research population in terms of demographics and disease stage.

9 | CONCLUSIONS

Existing research findings support greater use and further investigation of dyadic report to identify those at risk for or with preclinical and prodromal AD, and better characterize the earliest stages of disease. This approach has great potential to facilitate dementia research and clinical trials.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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