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Implementation of Subjective Cognitive Decline criteria in research studies

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Abstract

INTRODUCTION—Subjective Cognitive Decline (SCD) manifesting prior to clinical impairment could serve as a target population for early intervention trials in Alzheimer's disease (AD). A working group, the Subjective Cognitive Decline Initiative (SCD-I), published SCD research criteria in the context of preclinical AD. To successfully apply them, a number of issues regarding assessment and implementation of SCD needed to be addressed.

METHODS—Members of the SCD-I met to identify and agree upon topics relevant to SCD criteria operationalization in research settings. Initial ideas and recommendations were discussed with other SCD-I working group members and modified accordingly.

RESULTS—Topics included SCD inclusion and exclusion criteria, together with the informant's role in defining SCD presence and the impact of demographic factors.

DISCUSSION—Recommendations for the operationalization of SCD in differing research settings, with the aim of harmonization of SCD measurement across studies are proposed, to enhance comparability and generalizability across studies.

1. INTRODUCTION

Subjective cognitive decline (SCD) is receiving increasing attention as a risk factor for incident dementia due to Alzheimer's disease (AD) (1). SCD manifests prior to the onset of clinical impairment (2), and as such could serve as a potential target population for early intervention trials (3). Recently, an international working group, The Subjective Cognitive Decline Initiative (SCD-I), published research criteria for SCD in the context of preclinical AD (4). To successfully apply these criteria, several issues with regard to assessment and implementation of SCD need to be addressed.

The categorization of SCD is largely based on self-report by an individual, but also potentially by an informant and by the interpretation of this report by the investigator. Currently, there is neither a neuropsychological test score nor any accepted self- or observer/informant scale to classify an individual with SCD. SCD assessment also varies by research setting - *i.e.*, epidemiological (5–11) versus memory clinic (12–16). In memory clinics, the mere fact that an individual was referred may serve to define the existence of decline. Moreover, a detailed clinical history is often obtained in addition to neuropsychological

testing, similar to the clinical diagnosis of mild cognitive impairment (MCI) (17–19) and dementia (20). This is in contrast to epidemiologic studies, typically comprised of volunteer-based samples, where the meaning and significance of decline may differ. For multicenter research trials and for comparability across studies, however, it is crucial to define research criteria for SCD, that promote consistency across sites (4). This implies that subjective clinical judgment has to be reduced and objective scales and tests with defined cut-offs are needed to provide an operationalized diagnosis (21). This permits a transparent understanding and potential replication of the definition of SCD across studies. At the same time, it is evident that different studies have different objectives, participant populations, and available methods and measures (21–23). Therefore, flexibility of SCD operationalization is required to serve the aim of each respective study. The need for flexibility precludes one general SCD operationalization for identical application across studies. Furthermore, a single approach would limit research because, currently, variability of SCD operationalization continues to increase scientific understanding of SCD. Finally, a single approach would not be practical with regard to ongoing studies and may not be feasible when considering effects of culture and language on SCD reporting.

The aim of this opinion paper is to address core issues in SCD research in more depth and to provide recommendations on how to begin operationalizing and implementing SCD criteria with the long-term goal of fostering comparability and harmonization of criteria for future clinical trial enrollment.

2. METHODS

To achieve the study goals, a writing group was established, comprising 10 members of the SCD-I working group. The writing group met at the 2015 Alzheimer's Association International Conference (AAIC) in Washington, DC to identify and agree upon topics relevant to the operationalization of SCD criteria in research settings (4). Selected topics included those related to SCD inclusion and exclusion criteria, together with the role of the informant in defining the presence of SCD and the impact of key demographic factors.

Members of the writing group drafted individual sections of this paper. The manuscript was then discussed with other members of the SCD-I working group, and modified accordingly.

Recommendations on the operationalization of SCD in research settings were formulated based on theoretical considerations, the existing literature, and expert opinion.

3. RESULTS

In the following section, components of the SCD criteria are discussed in detail with regard to their use in research studies.

3.1. Operationalization of the SCD inclusion criteria

Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status, and not related to an acute event—SCD in the context of preclinical AD refers to the self-perception of a decline in cognitive performance in daily

life (4). The term “normal status” refers to the state of subjectively unimpaired (normal) cognition. This decline from “normality” to a state with experienced cognitive difficulities only refers to the subjective experience of the individual and not to objective neuropsychological measures, which are by definition within the normal range. Nonetheless, there may be subtle decline from a prior level on objective tests, as demonstrated in studies where SCD was preceded by a subtheshold decline in immediate and delayed verbal recall (24) and by decline in psychomotor processing speed (25). This supports the idea that SCD represents the self-experience of cognitive decline before impairment becomes detectable on standardized neuropsychological tests (2, 7, 8, 24, 26).

The criterion also states that SCD is not related to an acute event and is persistent (4). SCD is thought to arise from a variety of etiologies, both preclinical AD as well as non-neurodegenerative conditions. Thus, the course and progression of SCD potentially speaks to possible etiology. For individuals with preclinical AD, it is thought that SCD develops gradually, corresponding to the gradual disease progression in AD (2, 27). A recent study showed that individuals perceived a decline in cognition as early as five years before the onset of MCI (28) and in autosomal dominant AD, memory decline precedes MCI by twelve years. It has long been postulated that SCD has a duration of 15 years prior to MCI (29) and this estimate has been supported by a 9 year prospective study (30, 31). In the SCD position paper (4) it was therefore stated that complaints should last longer than six months. On the other hand, when complaints persist without progressing to objective cognitive impairment, it is possibly less likely that they reflect underlying preclinical AD or other neurodegenerative dementias.

Therefore, it is important to document the timeframe of the decline, allowing future studies to define the optimal timeframe to identify preclinical AD or other preclinical neurodegenerative conditions. This is suggested even though the validity of such retrospective estimation is limited.

Although the internal experience of cognitive decline is phenomenologically complex and difficult to capture quantitatively (32), most research studies employ quantitative measures such as questionnaires. Currently, the field lacks a single, commonly adopted and validated approach to the assessment of SCD with great variability in key features of questions posed (21, 22). The variability of assessment tools is problematic, because characteristics of questionnaire items (e.g., format, phrasing, scaling, and reference points) can influence the nature of responses and the reported rates of SCD. In addition, the majority of the instruments used to measure SCD focus on memory (21). However, it might be too restrictive to limit the SCD assessment to memory, in particular for atypical forms of AD, or in the context of non-AD dementias (33). Therefore it is sensible to include other cognitive domains (e.g. executive functions, attention, visuospatial functioning, language) in SCD assessments (34, 35). For example, recent work by Smart and collaborators demonstrated decrements in attention and decision-making, respectively, in persons with SCD as compared to healthy older controls (36, 37). Moreover, there has been almost no discussion of thresholds or cutoffs for subjective cognitive measures to determine when an individual has sufficient experience of decline to be described as having “significant” cognitive concerns, making it difficult to compare findings across studies (4). While comprehensive

review of the methods used to classify SCD is beyond the scope of the current paper [mainly covered by (21)], Table 1 presents a sample of approaches used by a select sample of SCD-I Working group members (along with the names and key study features). These data reveal considerable variability in every dimension examined such as number of items/ questionnaires, mode of administration, key structural and content features of questionnaire items, nature and scaling of response options, approaches to scoring of items, and classification criteria. Of note, no two studies used the same method to assess or classify SCD and this remains true if one turns to the wider literature. Moreover, while the studies reported in Table 1 provided detailed information about their approaches, many other published studies fail to report how objective and/or subjective cognition are assessed and how test data were used to assign participant groups. Further, while most studies appear to take a categorical approach to SCD, a possibility is to consider the potential value of continuous approaches that capture features such as frequency and severity of cognitive complaints. At present, the field lacks empirical data on the best way to classify SCD to maximize the identification of individuals at-risk for AD dementia and to minimize false-positive identification of individuals not at-risk for AD. Due to practical and conceptual barriers with regard to one universal SCD operationalization, with a standard set of SCD items, and in order to facilitate communication and comparison of study findings, we recommend including the information shown in Table 2 in research reports on SCD.

Recommendations for assessment of inclusion criterion 1: In terms of the items or measures that offer the “best” approach to assessment of SCD, there is at present no simple recommendation or gold standard questionnaire. In addition, and although there are currently no concrete guidelines for which tools are most appropriate for specific research contexts, we now offer the following recommendations. We hope that future research will clarify this important issue. However, we are in the process of analyzing data from 19 SCD-I working group studies, which may result in a short standardized scale (SCD-I basic scale), that could be routinely incorporated in future SCD studies. Using such a basic scale, in addition to other scales, would be beneficial for fostering future harmonization and cross-calibration across research studies. For now, we offer the following recommendations (for further discussion see (21)), as a first step for SCD harmonization:

- Consult the literature for validated measures developed for a target population similar to your own in terms of key demographics and clinical characteristics.
- Consider the research environment, which may impact measurement selection decisions. As an example, individuals recruited from a memory clinic (versus a volunteer/community sample) may have a higher probability of having preclinical AD because they have specific concerns sufficient to prompt a medical visit. One suggestion is to inquire about cognitive “concern” or “worry” as distinct from “complaints” in community samples to maximize the likelihood of identifying the subgroup of individuals with non-normative changes.
- Determine whether to collect self-report data only or, additionally, self- and informant-report data. Use of questionnaires that include a study informant is recommended (see section 3.3.1), particularly for volunteer/community samples where complaints may actually reflect normal age-related changes (i.e., there is a

greater probability for false positives in community versus clinical samples). Informant report of significant cognitive decline would thus provide convergent evidence for complaints reflecting more than normal aging in these settings.

- Select measures with appropriate content coverage for the target population. This requires attention to features of questionnaire items including: quality (evidence of reliability and validity), content coverage (should tap cognitive domains of relevance), face validity (items should be simple and easy to understand and should inquire about cognitive issues encountered frequently daily life), cultural appropriateness, and specificity (should contain more specific than broadly worded items to enhance accuracy of reporting).
- Select measures whose response options correspond to the research question (dichotomous scales might be sufficient if the goal is to classify groups, while Likert scales are better for quantifying frequency or severity of problems or degree of change over time).
- Ensure that reference periods are appropriate for the target population (timeframes >1 year could pose difficulties for older adults trying to recall specific recent events).
- Include validated measures of mood and anxiety, given their influence on cognitive complaints (see section 3.2.1), particularly in volunteer/community samples where participants may not receive such measures as part of a routine clinical workup. Validated, brief measures with specific clinical cut scores are preferable.
- Include information recommended on Table 2 in order to harmonize across SCD studies.

Normal performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI)—In most cases, cognitive impairment emerges gradually in the course of neurodegenerative disease (38), and at some point reaches a threshold where standardized neuropsychological testing can identify a cognitive deficit with a reasonable degree of certainty (17, 39). Conceptually, once this detection threshold is met, and major functional deficits are still absent, individuals can be classified as having objective cognitive impairment (40). Practically, however, this boundary between SCD (hypothetically indicating a pre-MCI stage) and MCI is not a clear line but rather a grey zone (41, 42), for several reasons.

First, the precision (reliability) of cognitive tests is inherently limited, and for psychometric reasons this is particularly true when short scales or single measures are used to define MCI, as is often the case. Second, in the late preclinical period individuals may be able to compensate for mild deficits, with variable success (43). Such deficits may be best unmasked with highly demanding, sensitive tests (44, 45), but currently such tests are largely experimental procedures lacking a normative database (46), limiting broad applicability. Third, depending on the research question, researchers have employed either more liberal (sensitive) or more restrictive (specific) definitions of impairment for adjudicating MCI.

Liberal criteria (e.g. (47)) typically require more than 1 SD deficit in any cognitive domain or test (which will necessarily yield false positives MCI "cases" but may also pick up earlier disease stages), while stricter criteria typically require a deficit of at least 1.5 SD on specific tests, usually memory tests (e.g. the AIBL study – (48)). Partly as a result of these measurement issues and operational differences, MCI samples differ widely regarding the prevalence of AD biomarkers and clinical progression rates (47).

Given these complexities, the SCD-I agreed not to propose a uniform and "optimal" definition of MCI, which would demarcate the upper boundary of SCD. Rather, the following levels of objective impairment are considered to exclude a research diagnosis of SCD:

- CDR = 0.5 or more (where the CDR score reflects an objective cognitive impairment e.g. as assessed with the CDR interview), or a Global Deterioration Scale stage 3 or more, or a neuropsychological profile indicating MCI;
- Deficit of more than 1.5 SD on a single test currently used in studies to define MCI (e.g. an episodic memory test); or
- Deficit of more than 1.0 SD on two tests within one cognitive domain or of three single tests in three different domains (actuarial MCI definition according to Jak and Bondi)

It is acknowledged that these different pragmatic "upper boundaries" for cognitive impairment will not yield identical results in all cases. Rating scales are valid and well established, but rely strongly on self- and informant report and do not assess cognitive performance against demographic norms. In specialist settings, the neuropsychological profile in an extensive test battery will be judged by experienced clinicians based on appropriate norms, and this will likely give a reliable identification of cognitive impairment. Reliance on just one single "deviant" test score will result in many false positives (i.e. cognitive impairment is assumed despite "true normality"). The actuarial method of Jak and Bondi balances reliability and sensitivity and has been shown to reduce the number of "misclassified" (i.e. AD-biomarker negative, non-progressing) cases with MCI as defined by the ADNI "late MCI" criterion of 1.5 SD deficit in the Wechsler Memory Scale, Logical Memory Story A Delayed Recall Story A (49, 50).

A practical advantage of accepting this degree of heterogeneity in defining the cognitive normality is that within studies subjects can be classified as either MCI or SCD depending on the respective cognitive impairment criterion of this study (avoiding unclassified clinical cases). An obvious disadvantage of this heterogeneity is the limited comparability of "cognitive normality" between studies, which could become a barrier to progress in SCD research.

Whether it will become possible, with psychometrically sound methods, to lower the threshold for objective impairment (e.g. to 1.0 SD deficit in a single well-normed, sensitive memory task) is an issue for further research. One study addressing this issue found that subjects with 1.0–1.5 SD deficit in a Delayed Recall test (termed "early MCI" in ADNI2) were indistinguishable from SCD without a cognitive deficit in terms of dementia

conversion risk (8). By contrast, using stricter criteria for the definition of MCI, the AIBL study has reported that high levels of SCD and evidence of Ab burden in cognitively normal older adults at baseline relates to approximately five-fold greater rates of progression to MCI or AD (51). Another recent study also found that SCD without cognitive deficit but carriers of the APOE ε4 allele showed abnormal changes in amyloid and tau biomarkers, but no hypometabolism or medial temporal lobe neurodegeneration, reflecting the at-risk nature of the SCD group (52). Taken together, these studies provide promising evidence reflecting the at-risk nature of the SCD group. The same cognitive exclusion criteria would also apply to define cognitively normal subjects (in the absence of subjective cognitive deficits).

Regarding the distinction with normal aging, cognitive complaints are quite frequent across all ages (53). Whether or not these complaints reflect pathological change (in contrast to "normal aging"), depends on a number of context features like age of the subject, or help-seeking. Features known to increase specificity (*i.e.* the likelihood that SCD indicates pathological change due to AD) have been summarized in the SCD-plus criteria (see see section 3.3.4 and (4)). In addition, recent qualitative research has begun to identify predominant complaint themes in subjects with preclinical AD or MCI, which differ somewhat from complaints related to ageing in general. For example, Buckley et al (32) found that amyloid-positive healthy subjects, more often than amyloid negative healthy subjects, noted a progressive memory, and amyloid-positive subjects with MCI expressed more burdensome coping strategies as compared to amyloid-negative MCI subjects. Further qualitative research, also involving depressed or anxious ("hypochondriac") subjects, will be needed to further delineate the features indicative SCD due to AD, and to develop questionnaires or structured interviews to capture this construct with increased specificity.

Operationalization of SCD also requires attention to basic Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), which should be unimpaired as corroborated by an informant. A change in IADL, e.g. in managing finances, may occur early in AD, even before significant impairment on cognitive tests (5, 54, 55). When asked for examples of SCD, patients, as well as informants, may report subtle difficulties in handling complex everyday activities, which earlier had been mastered. In SCD, similar to MCI, IADL changes are most likely to take the form of a perceived decrease in the ease and efficiency of completing specific tasks rather than a significant loss of functional capacity manifest by inability to perform previously accomplished tasks. Clear loss of capacity to perform IADLs would be consistent with a diagnosis of dementia. Individuals with MCI may show subtle decline in functional capacity without frank impairment. Thus, SCD to some degree reflects the aggregated experience of subtle decreases in the ease and efficiency of everyday cognitive activities, which may or may not be observable by others. However, marked functional ADL/IADL impairments must be excluded as they are indicative of MCI or dementia. An operational definition with an established scale (for an overview, see (56)) showing absence of significant functional impairment is therefore recommended. This approach is identical to the case definition of MCI (57).

Recommendations for assessment of inclusion criterion 2

- Use standardized validated clinical tests to properly assess cognitive performance.
- Define impairment boundaries between SCD and MCI, as a function of the study design and objective.
- Confirm preservation of ability to perform IADLs with an appropriately validated scale or through interview. Subtle self-perceived decreases in ease and efficiency of performing otherwise intact IADLs are consistent with SCD.

3.2. Operationalization of SCD exclusion criteria

Cannot be explained by a psychiatric or neurologic disease (apart from AD), medical disorder, medication, or substance use—SCD research criteria list the presence of a psychiatric diagnosis (e.g. major depression according to DSM-5, depressive episode according to ICD-10) as an exclusion criterion for SCD in the context of preclinical AD (4). Individual symptoms of depression or anxiety, or subsyndromal levels of these disorders that do not reach the threshold for diagnosis, are common in older adults and not considered exclusion criteria. Many psychiatric disorders are associated with significant cognitive complaints and even cognitive impairment (6, 55, 58, 59). Thus, including individuals with an active psychiatric disorder in studies of SCD in the context of preclinical AD would lower the specificity of the study design for AD and inflate the number of false positive cases. However, subjective and objective cognitive performance in the context of psychiatric disorders and the interaction of AD pathology and psychiatric disorders, such as depression, are topics of great interest (60). Some studies may specifically aim to include individuals with a psychiatric disorder and subjective and/or objective cognitive impairment to study the association with AD pathology. These studies, however, should make their aims clear and distinguish their approach from the study of SCD in preclinical AD. The majority of SCD studies will focus on early AD identification and prediction of cognitive decline and dementia or will aim to identify subjects in the preclinical stage of AD for intervention trials (2, 8, 16, 26, 61). These studies will treat a major psychiatric diagnosis as an exclusion criterion. Nevertheless, more subtle behavioral or psychological symptoms (not fulfilling criteria for a major psychiatric disorder) may be contributing factors in SCD, and therefore we recommend incorporation of appropriate scales for psychiatric symptoms in SCD studies.

Scales for depression or anxiety can be observer-based (e.g. Hamilton Rating Scale for Depression) or self-ratings (e.g. Beck Depression Inventory, BDI-II or Geriatric Depression Scale, GDS). Observer-based scales are recommended to measure subthreshold psychiatric symptoms. However, in general self-rating scales reflect more subjective well-being and less “objective” depressive symptoms. Individuals with SCD may be more introspective and more sensitive to perceived changes in their own mental status (62). Thus, they may score higher on some items on self-rating depression scales, which may not necessarily reflect depressive symptoms. The application of both types of scales (observer-based, self rating) in a single study could be of value for detecting potential differences in what those scales

measure in SCD and may allow the estimation of the magnitude of difference between both approaches.

Notably, depression scales often include items tapping subjective cognition. Individuals with SCD will endorse these items, which may not reflect a depressive symptom but rather a cognitive complaint related to SCD. This could be the reason for the frequent finding that SCD subjects score slightly higher on depression scales than non-SCD cognitively normal control subjects without being depressed (6, 63). Some studies remove cognitive items from depression scales and create an “adjusted” score (e.g., (64)). On the other hand, subthreshold symptoms of depression and anxiety may actually be more frequent in SCD individuals than in non-SCD controls (65). For example, Reisberg and colleagues (25) observed more such symptoms in SCD participants (Global Deterioration Scale stage 2) than in those without subjective cognitive decline (Global Deterioration Scale stage 1 subjects) including disturbed sleep, fatigue, weakness, disinterest, and others. In studies with group differences, in mood scores, these can be treated as covariates in statistical models, because, since covarying for mood and related factors could potentially attenuate or eliminate biomarker differences if they share variance with the underlying disorder.

By contrast, an argument against treating subthreshold depression and anxiety symptoms as covariates is the possible interaction of these symptoms with SCD, AD pathology, and cognitive decline. It has been shown in different samples that particular worries and concerns related to SCD are associated with an increased risk of cognitive decline and dementia (e.g. (66)). Recently, it has been reported that in amyloid positive healthy elderly, symptoms of anxiety predict cognitive decline (67). These and other studies suggest that subthreshold symptoms of depression and anxiety should be considered features of interest in research. Affective symptoms may be accelerating factors for cognitive decline at the late stage of preclinical AD or may even be considered part of the late preclinical AD syndrome together with subtle cognitive dysfunction and SCD (on some occasions being the explanation for SCD) (68, 69). In this regard, personality traits, which are related to increased levels of stress, anxiety and depression have frequently been found to be associated with SCD (61, 70). While factors such as openness, conscientiousness, and self-esteem, correlate with low SCD scores, in particular neuroticism has been associated with high SCD reporting (71–73). Neuroticism refers to the tendency of a person to experience distressing states such as anxiety, worry, frustration, and loneliness. It is a risk factor for mental disorders and a variety of poor health outcomes (74). Neuroticism has also been identified as a risk factor for dementia (75). In fact, it has been shown that both, subjects with MCI and SCD, who are worried about their memory decline are at higher risk for dementia than those just confirming worsening of memory without particular worries (8, 76). Recently, it was demonstrated that particular worries about memory decline in MCI predicts biomarker evidence for AD in CSF (77). In cognitively healthy individuals, an association of the SCD report with amyloid deposition has been observed in those individuals, who report high on neuroticism (61). Overall, the interaction of SCD, neuroticism, AD pathology and risk of dementia seems complex. High stress levels induced by neuroticism may accelerate AD pathology and cognitive decline and may also provide high sensitivity to intra-individual change such as the development of a neurodegenerative disease. Importantly, the data suggest that the notion that SCD is reported in those with high

neuroticism and therefore is not related to neurodegeneration or AD seems too simple. In particular, in memory clinics a large proportion of individuals report SCD due to non-neurodegenerative causes. Besides being related to depression or anxiety, these include, but are not limited to an attentional focus on normal age associated cognitive decline, with the interpretation of being pathologic and increased anxiety about dementia, often in spouses or relatives of dementia patients (78). Also normal aging is associated with SCD, however, there are a proportion of elderly individuals, who deny cognitive worsening, even on active inquiry. In a German sample of over 3327 individuals without dementia over the age of 75 (average age 80 years, AgeCoDe study), about 30% answered that they did not experience memory decline (79). Overall, the causes of SCD reporting in individuals are numerous, including age-related factors, personality traits and medical factors, one of which is early neurodegeneration. Importantly, in many cases, these causes are not exclusive, but interact. Understanding of these interactions may increase the knowledge on the development of dementia. In addition, post-mortem studies have shown that neuroticism is associated with greater risk of cognitive decline, independent of AD pathology (80). Thus, personality and related traits can be of interest in SCD studies as they are a risk factor for symptoms of depression and anxiety as well as for cognitive concerns, cognitive decline and dementia (75, 81). There is, at present, no reason to exclude any personality profiles from SCD studies.

With regard to neurological disorders, medical conditions, medications and substances that may impact cognition, it is important to screen for these issues and decide whether they are to be treated as exclusionary conditions, given individual study goals. Relevant effects of these conditions may be indicated by a temporal association of onset with the onset of SCD, although for some disorders past history may also be relevant to understanding cognitive functioning and perceived decline. Medications with evidence of impact on cognition and brain structure and function, especially in domains similar to AD, warrant particular consideration, with drugs having anticholinergic properties being a particularly important example (82). A full discussion of potential cognitive effects of medication and substance use in older adults at risk for AD is beyond the scope of this report.. Recommendations for assessment of exclusion criteria for psychiatric and other comorbidities:

- Exclude individuals with a current major psychiatric diagnosis according to ICD-10 or DSM-5 in studies that focus on SCD in preclinical AD, unless the studies specifically focus on the association of SCD with preclinical AD in the context of a psychiatric disorder.
- Carefully assess whether a history of major psychiatric disorders may impact cognition and especially self-perception of cognitive functioning, and hence may be related to SCD. If so, exclude these conditions.
- Include measures of depression and anxiety in SCD studies. Analyze any items in those scales that focus on cognition and consider creating adjusted scores. Potentially include the mood scale scores in statistical models. We also recommend the application of cut-offs on mood scales to help identify subjects who should potentially be excluded based on fulfilling diagnostic criteria for a psychiatric disorders.

- Carefully consider as exclusion criteria and report neurological or medical conditions, medication and substance use, which may be linked to SCD.

3.3. Additional factors of relevance in SCD research

The role of the study partner /informant—Although confirmation of decline by the informant is not necessary according to the SCD definition, the initial subjective cognitive decline initiative (SCD-I) consensus paper noted that confirmation by knowledgeable others was a feature that increased the risk of AD dementia (4). As consistently reported in the literature, the progression of AD and other dementias is associated with poorer insight into cognitive deficits (12), and informant report is of increasing value and relevance along the disease *continuum* (83, 84). The progression of these changes from both the subject perspective and the informant perspective in terms of memory, emotional changes and functional changes from no cognitive decline, to SCD, to MCI, to mild, moderate and moderately severe dementia was described in a study by Reisberg and colleagues (85). In another study using National Alzheimer's Coordinating Center data, Gifford and colleagues found that self and informant reports were independently and additively predictive of future risk of dementia (84). In this study, the odds for predicting a poor cognitive trajectory were approximately two-fold for self and informant reports separately, but increased to an odds ratio of 4 when considered together.

Informant report has been associated with the risk for developing AD in SCD in community elders (9, 86, 87). There is also evidence that the composite of both self and informant report accurately predicts hippocampal atrophy (64) and longitudinal decline at the earliest stages of disease, possibly better than self or partner report alone (5, 84). When examining the association between self- and informant-reported everyday function and brain volumes across the disease spectrum, the strength of the associations tended to be higher for the informant ratings than for self-report (10). Moreover, a recent study showed that informants' ratings of the subjective cognitive decline questionnaire (SCD-Q) were significantly higher in preclinical AD compared to elderly controls, presenting, by contrast, no significant differences in the self-rating scores were obtained with the SCD-Q (88). In the same study, the relation of the SCD-Q score with AD cerebrospinal fluid (CSF) biomarker levels was explored in a sample including SCD subjects and cognitively impaired subjects, showing that informant ratings of SCD-Q correlated significantly with Aβ42 and tau levels, while self-rating did not correlate with any AD biomarker (88). Although the number of studies reporting the relation between CSF AD biomarkers and informant ratings of SCD is low, they seem to point in the same direction. Rueda and colleagues (10) found that in a sample constituted by cognitively normal and impaired subjects, informant ratings of SCD significantly correlated with Aβ42 and ptau CSF levels and a smaller hippocampal volume. Similarly, Okonkwo and colleagues found that CSF Aβ42, tau and ptau levels correlated with informant report of functional decline in cognitively normal elders and in a MCI group (89). By contrast, very early on in the disease course, self report may better track disease progression, while later on informant report may supercededs self report (83, 90). Taken together, the literature strongly suggests that both the informant and self report can provide both synergistic and individually meaningful information along the AD trajectory, and as such, both should be measured in future studies. In that regard, informant report reflects

potentially a slightly more progressed state of decline, where cognitive dysfunction becomes evident for an observer, while earlier, full compensation is still possible and cognitive dysfunction is only noted by the individual him- or herself.

In summary, current evidence suggests that in cognitively normal SCD subjects, informant reports have prognostic value and may correlate better with cognitive performance and with AD biomarkers than self-report alone. Therefore, when possible assessment of SCD should be performed with questionnaires that also include an informant report.

Assessment of SCD longitudinally—As has been noted, tools to identify individuals with SCD vary considerably across studies and can range from a single question about memory decline to exhaustive questionnaires that tap multiple cognitive domains. While using a brief measure to classify SCD individuals *a priori* may be appropriate, this strategy is less likely to be useful in tracking the evolution of SCD longitudinally. Several studies have investigated longitudinal change in SCD and its correspondence to cognitive outcomes (5, 25, 91, 92). The relation between cognitive performance and subjective decline is further complicated when self and informant reported measures of SCD are introduced. Very early on the disease course, self-report may better track disease progression, while later on informant report may supersede self report (83, 90). In addition, self and informant reports although may initially align, they diverge when objective cognitive impairment is present. In fact, MCI subjects associated with greater informant concern, present poorer cognitive performance, exposing a changing insight with advancing memory impairment (83). These findings suggest a dynamic relationship between subjective and objective measures along the early disease trajectory, such that there are points where they are more and less associated, with the clearest divergence by the stage of clinical impairment.

In the future, change in SCD may be one way of assessing longitudinal functional benefit in secondary prevention trials (5) but there will need to a consensus on which particular measure(s) are most effective in capturing the full realm of subjective cognitive changes early in the disease. Most research to date has focused on sensitive measures of cognitive concerns for the purposes of early detection rather than as dynamic outcome markers optimized for measuring longitudinal change, though both applications are important.

Demographic issues that may be of relevance in SCD research—Factors such as demographics, knowledge of genetic risk, and medical issues may impact SCD. Concerns about memory typically increase as individuals grow older (93, 94), and the types of complaints may vary by age range, perhaps due to the fact that younger and older individuals assume different reasons to explain their memory lapses (95). Because SCD related to AD is thought to occur before the MCI stage at the late preclinical phase, the likelihood that SCD is associated with AD increases with age. Within older individuals, however, there is evidence to suggest that SCD becomes less predictive of dementia risk in 80 year olds compared to persons in their 70s, as memory complaints become more ubiquitous and less specific as individuals age (94). Thus, there may be in optimal age range in which SCD is useful for predicting risk for AD progression.

Several studies indicate that education attainment level may modify the relationship between SCD and risk for AD. While less education has been associated with greater overall memory concerns in some studies (93, 96), paradoxically the role of SCD in predicting longitudinal cognitive decline may be stronger in the high education group (97, 98). One possibility is that individuals with lower cognitive reserve report greater memory complaints that reflect longstanding difficulties, but SCD in more highly educated individuals may reflect more recent changes due to underlying pathology. Also, highly educated subjects can sustain a greater degree of pathology and still perform within normal limits on cognitive tests due to greater cognitive reserve (99). A recent FDG-PET study showed, that cognitively normal subjects with emerging amyloid pathology showed stronger temporal and parietal lobe FDG-PET hypometabolism at higher levels of education (100). Thus, SCD individuals with higher cognitive reserve may perceive cognitive changes at relatively later stages in the neuropathological disease process where cognitive decline is imminent. Further studies are needed, but SCD in individuals with higher education may be particularly sensitive as an early indicator of AD risk.

Findings on the relationship between SCD and sex differences are equivocal. Some studies have reported greater memory complaints in women compared to men (96, 101), but the reverse has also been shown (94), while others have found no impact (6, 102). Presently, it is unclear if sex modifies the relationship between risk for AD and SCD.

Few studies have investigated SCD across race and ethnicity. In one study of African Americans, SCD was found to be associated primarily with factors of psychological well-being, such as higher levels of perceived stress, rather than longitudinal cognitive decline (103). In another study that directly compared African Americans and Caucasians, African Americans were less likely to report memory complaints, despite greater evidence of objective cognitive decline longitudinally (104). Further work is needed to determine whether SCD may manifest differently in different racial or ethnic groups. A family history or knowledge about increased risk for developing AD may impact report of SCD. In one study, older adults with a positive family history of AD rated their memory functioning lower than those without a family history (105). Knowledge of *APOE* gene status has also been shown to impact subjective report of memory. Specifically, individuals who were known to have *APOE-ε4* judged their memory more harshly than those who were *APOE-ε4* without knowledge of their genotype (106). By contrast, individuals who knew that they were *APOE-ε4* negative judged their memory more positively than those who were blinded *APOE-ε4* negative. Increasingly, clinically normal individuals may now have the opportunity to know their amyloid status if enrolled in clinical trials in certain countries (107, 108), although human research ethics boards still restrict this information in most settings. Understanding how knowledge of amyloid status may impact self-perceived memory will be important as data become available.

Finally, it is not surprising that other non-AD medical issues could underlie SCD. For example, poor overall physical health (9), greater white matter hyperintensities (109), and Parkinson's disease (110) among others, have all been shown to be related to higher report of SCD. Thus, SCD in individuals with significant medical issues, particularly those that

impact cognition, should be interpreted carefully, as it may be hard to disentangle the etiology of memory complaints in these cases.

Specific assessment of SCD plus criteria—Other relevant factors in SCD research are those that may be associated to increased likelihood of preclinical AD. Indeed, in the consensus paper on SCD in preclinical AD (4), a list of SCD-features was presented, which, according to the current standard of the literature are associated with an increased likelihood for preclinical AD (SCD-plus). These features are: (1) subjective decline in memory, rather than other domains of cognition, (2) onset of SCD within the last 5 years, (3) age at onset of SCD > 60 years, (4) paricular concerns (worries) associated with SCD, (5) feeling of worse performance than others of the same age group, (6) confirmation of perceived cognitive decline by an informant, and (7) presence of the APOE ε4 genotype. Although, initial efforts to validate the SCD plus criteria have started (111), they may still be subject to change as research progresses.

Recommendations on additional relevant factors

- Assessment of SCD should include both self- and informant report questionnaires when possible.
- Special attention should be applied when measuring SCD in people with greater cognitive reserve. Interpreting SCD measures in the context of cognitive reserve, such as by recording education attainment levels, appears warranted.
- Exercise caution in interpreting SCD with individuals who are aware of their amyloid status, as this may impact their self perceived cognition.
- The presence of multiple medical issues in SCD study participants should be collected and interpretation of SCD due to AD should be made with caution.
- To integrate SCD-plus assessment in most or all SCD studies to extend the empirical database on SCD plus items to validate or reject them as being associated with preclinical AD in the future.

4. DISCUSSION

In this paper, we propose recommendations for the operationalization of SCD in differing research settings, with the aim of harmonization of SCD measurement across studies. This is challenging, however, and a gold standard for the investigation of SCD is not yet available. Nonetheless, we recommend a number of topics that need to be clearly described in any paper addressing SCD to enhance comparability and generalizability across studies. This may reduce inconsistencies that are currently evidenced in the literature.

Regarding the assessment of SCD, defined as self-experienced persistent decline in cognitive capacity, rather than an operational definition we recommend a set of guidelines to start harmonizing SCD detection and assessment. We also suggest the type of information to be reported in each SCD study, to ensure consistency and learning over time. Assessing the presence of SCD based on self-report data only or self- and informant-report data yields different results and outcomes. The evidence provided above suggests that both are of value

in SCD participants, self reports possibly being more critical at earlier stages and informant reports having a greater prognostic value and correlating better with cognitive performance and AD biomarkers. Therefore, we recommend collecting how SCD has been assessed and when feasible assessing SCD with questionnaires that also include informant report data. In order to assess and quantify SCD, validated measures should be employed. These measures should be suitable for the target population, in terms of demographics and clinical characteristics, and with appropriate content coverage, in terms of quality, face validity, cultural appropriateness and specificity. Currently, SCD questionnaire items present a limited overlap with 75% of the items used uniquely in a single study (21). Therefore, in order to advance the field, harmonization and pooling of international SCD data is necessary. Future studies should also strive to use a short set of identical questions, not only to define the presence of SCD but also to measure it. In this sense, dichotomous questionnaires might be sufficient if the goal is to classify groups, while Likert scales might be more benefitial for quantifying frequency or severity of problems, or degree to which changes occur over time. Using a single, standardized questionnaire across studies does not seem feasible in the near future, but we should now aim to implement questionnaires with comparable face validity going forward. For the vast majority of SCD instruments, there is little evidence for psychometric quality, and a majority are newly developed within the past decade. This highlights the need for cross-validation of these measures. Self-report measures will need to be psychometrically evaluated, showing adequate internal consistency, content and construct validity, test-retest reliability, and differences between subgroups of interest [see (112)]. Item response theory might offer a method to select qualitative items, as currently being tested by the SCD-I in the ‘item analysis project’.

Regarding the timeframe of the persistent decline in cognitive capacity relative to a prior baseline, it is important to collect information about how long the participant has been experiencing the decline. As stated in Jessen et al. (4) shorter periods, may have greater relations to preclinical AD. It is equally important to ensure that reference periods are appropriate for the target population because asking older adults to recall specific recent events from periods of time longer than one year can yield non-reliable results. Establishment of clear criteria for what constitutes “significant” or “meaningful” subjective concern is challenging. In particular, there is an unmet need to define “SCD-positivity” and to harmonize methods for its determination. Currently, it is uncertain whether within the continuum of subjective perception of decline there is a threshold that could be defined on the basis of predictive value for subsequent cognitive impairment. It also remains unknown whether this threshold should be adjusted for age, gender, or education. When sound approaches to SCD classification are met, significant improvements will be made in characterizing the specific cognitive phenotypes of SCD. A major issue regarding operationalization is determining what normal cognition means in the context of SCD. The suggested approach is defining the impairment threshold for normality, in other words defining what will constitute the beginning of MCI from a normative perspective hence the end of SCD stage (65). Unfortunately, there is no operational consensus in the field on how to measure objective cognitive impairment and what threshold of impairment is required for an MCI diagnosis. In part, this is due to the fact that, depending on the research question, a more liberal (sensitive) or a more restrictive (specific) definition can be chosen. Liberal

criteria for MCI typically set the impairment threshold at - 1 SD magnitude deficit in any cognitive domain or test (which will necessarily yield false positives, but may identify earlier disease stages), while stricter criteria typically require a deficit of at least 1.5 SD in specific tests, usually memory tests. Using strict criteria (47) to define MCI would necessarily suggest that some patients with minimal/subtle cognitive impairment may be considered SCD; on the other hand using liberal criteria will exclude people from the SCD group, who in some cases may have questionable MCI. We acknowledge that as a function of the research question, either approach may be appropriate, so rather than suggesting a definite operationalization approach we recommend using standardized validated tests, specifying the upper cognitive impairment boundaries used in the study, and confirming preservation of iADLs with a proper validated scale. Future work comparing different SCD studies with a harmonized methodology, although with different boundaries, will be of value to define the optimal boundaries between SCD and MCI to define SCD prognosis and the sensitivity and specificity of the different approaches to detect the presence of preclinical AD. It is not uncommon to observe anxiety and depresive symptoms among SCD particpants. In fact, self reported measures of SCD correlate more with personality traits than with AD biomarkers, being the opposite with proxy-related questionnaires (61, 90). Neverthelees, patients at early stages of AD also present emotional, psychological and mild behavioral disturances (113). Excluding individuals based on the presence of mild psychiatric symptoms is therefore not recommended.

Operationalization and harmonization of SCD is beginning. This paper represents a starting approach to begin harmonizing and operationalizing the SCD criteria in order to move the field forward. With more uniformity of ascertainment of SCD we will be better positioned to understand the generators of SCD, heterogeneity of outcomes, and the optimal measures for early detection and as dynamic outcome metrics.

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RESEARCH IN CONTEXT

1. *Systematic review:* The authors reviewed the literature using traditional sources. Studies investigating subjective cognitive decline (SCD) are appropriately cited throughout the manuscript.
2. *Interpretation:* This opinion paper addresses core issues in SCD research in more depth and provides recommendations on how to begin operationalizing and implementing SCD criteria with the long-term goal of fostering comparability and harmonization of research studies. Main topics include those related to SCD inclusion and exclusion criteria, the role of the informant in defining the presence of SCD and the impact of key demographic factors
3. *Future directions:* Operationalization and harmonization of SCD is beginning. This paper represents a consensus approach to harmonize and operationalize SCD criteria to move the field forward. With more uniformity of ascertainment of SCD we will be better positioned to understand the generators of SCD, heterogeneity of outcomes, and the optimal measures for early detection and as dynamic outcome metrics.

TABLE 1

Approaches to Classifying SCD among a Sample of Subjective Cognitive Decline Initiative (SCD-I) Working Group studies. For references of the tests mentioned in the table see (21).

Study name, Country, Institutional Affiliation(s)	Research Environment and Administration Mode of Subjective Report Items	SCD Classification Approach
AgeCoDe (German study on Aging, Cognition and Dementia in primary care patients); Germany; University of Bonn and 5 other German universities	General practice registry-based; Examiner-administered in person at participants' homes	Subjective cognition: Assessed by the question: Do you feel like your memory is becoming worse? Response options include no; yes, but this does not worry me; and yes, this worries me. Participants reporting a memory decline with worry are rated as having SCD. In an alternative classification approach, participants reporting a memory decline without associated concerns (worries) are rated as SCD-C and those reporting a memory decline with associated concerns are rated as SCD+C. Objective cognition: Performed less than 1.0 SD below the normative mean on the CERAD verbal memory delayed recall performance [Jessen-2014] or performed less than 1.0 SD below the normative domain scores on the cognitive assessment of the DSM-IV and ICD-10 [i.e. SIDAM score (SISCO)].
AIBL (Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing); Australia; University of Melbourne	Volunteer and physician referred; Examiner-administered by telephone	Subjective cognition: Assessed by the question: Do you have difficulties with your memory, yes or no?. Objective cognition: Scores of MMSE >27/30, normal performance on Logical Memory test, no evidence of significant difficulty on standardized neuropsychological tests of memory, language, attention, executive functioning, and psychomotor speed, and a CDR score of less than 0.5. Additional criteria: no medical illness likely to impair cognitive function, no informant or personal history suggestive of impaired cognitive function, and no medications or substances that could affect cognition.
Alzheimer's Disease Center Clinical Core and Center for Brain Health; United States; New York University School of Medicine	Volunteer; Clinician interview	Subjective cognition: Subjective complaints of cognitive deficit on two clinician interview measures: Global Deterioration Scale for age-associated cognitive decline and dementia which cites the SCD complaints, i.e, memory for names of people and placement of common objects, subsequently found to be represented in the greatest percentage of measures (56 % each) surveyed (n= 34 measures) and the Brief Cognitive Rating Scale, which assesses the presence of subjective impairments in concentration and calculation, memory, orientation, and functional abilities. Objective cognition: No objective evidence of memory deficit on clinical interview. Performed normally on the objective portion of the Brief Cognitive Rating Scale, which includes tests of concentration and calculation, memory, orientation, and functioning abilities, carried out during the clinical interview. Additional criteria: No objective deficit in employment or social situations. Appropriate concern with respect to symptomatology.
Dartmouth-Indiana Longitudinal Cohort; United States; Dartmouth Medical School, Indiana University School of Medicine	Volunteer and physician referred; Self-administered paper questionnaire	Subjective cognition: Assessed with a Cognitive Complaint Index (CCI) ranging from 0 to 100, based on items endorsed across measures including: Memory Self-Rating Questionnaire, Activities of Daily Living Rating Scale- self and informant , Informant Questionnaire on Cognitive Decline in the Elderly short form- self and informant, cognitive

Study name, Country, Institutional Affiliation(s)	Research Environment and Administration Mode of Subjective Report Items	SCD Classification Approach
		items from the Geriatric Depression Scale, and cognitive items from the Memory and Aging Telephone Screen. Presence of significant cognitive complaints required endorsement of approximately >20% of complaints on the CCI or complaints deemed significant by clinical consensus. Additional criteria: normal activities of daily living and no depression or psychiatric disorder that would account for the cognitive complaints. Diagnoses made by multidisciplinary consensus. Objective cognition: Scores within 1.5 standard deviations of the mean established for age- and education-matched controls on standardized neuropsychological testing of memory, attention, executive function, language, spatial ability, general intellectual functioning, psychomotor speed, and standard dementia screens.
IMAP Caen Group; France; Inserm, University and Hospital of Caen	Memory clinic; Self-administered paper questionnaire and clinician interview	Subjective cognition: Self-reported cognitive complaint + 10-item cognitive complaint questionnaire. Clinician established that SCD was not caused by medication, mood, or other medical conditions. Diagnoses made by multidisciplinary consensus. Objective cognition: Performed in the normal range for age and education on standardized neuropsychological tests of global cognition, verbal and visual episodic memory, visuospatial functioning, language, verbal fluency, working memory, and executive functions.
INSIGHT-AD; Inserm and the city of Paris public hospital system (AP-HP) at the Institute of Memory and Alzheimer's Disease and the Brain and Spinal Cord Institute, together in the Research Institute for Translational Neuroscience; France.	Volunteer; Clinician interview	Subjective cognition: Cognitive complaint assessment (Visual Analogic Scale), Questionnaires of Memory complaint. Questionnaire of Conversion (QOC). The QOC was developed as a new tool to detect the early signs that may be associated with the onset of a clinical AD at a prodromal stage. It was especially designed to follow-up for the "asymptomatic-at-risk" population of the INSIGHT cohort. The QOC informant-based questionnaire consists of 12 'Yes/No' questions and covers memory, behavioural, mood, motivation and attention items. The questions are given to the respondent on the paper for self–administration or can be read aloud to the respondent either in person or over the phone. The total score (positive answers) is recorded. Objective cognition: Performed in the normal range for age and education on standardized neuropsychological tests of global cognition and verbal episodic memory.
Amsterdam Dementia Cohort; Netherlands; VU University Medical Center	Memory clinic; (self) referred	Subjective cognition: By definition as patients were referred by their GP to the memory clinic based on cognitive complaints. Objective cognition: Performed in the normal range for age and education on standardized neuropsychological test battery.
Memory Clinic - Fundació ACE; Spain; Fundació ACE. Barcelona Alzheimer Treatment and Research Center	Community-based; Self-administered paper questionnaire	Subjective cognition: Assessed with the Memory Failures Everyday (MFE-30)[Lozoya-Delgado 2012]; Scores ≥8 considered significant. Additional criteria: no depression, anxiety, psychiatric disorder, or systemic conditions or medications to account for the complaints. Objective cognition: Performed in the normal range for age and education on the standardized Fundació ACE Neuropsychological Battery.

Study name, Country, Institutional Affiliation(s)	**Research Environment and Administration Mode of Subjective Report Items**	**SCD Classification Approach**
Barcelona Biomarker cohort – Hospital Clinic Barcelona - Spain	Memory clinic; community-based; Self-administered and Informants' ratings	Subjective cognition: SCD-Q, which include "MyCog" (self-reported cognitive complaint) and "TheirCog" (informant's ratings). Objective cognition: Performed in the normal range for age and education on standardized neuropsychological tests of global cognition, verbal and visual episodic memory, visuospatial functioning, language, verbal fluency, working memory, and executive functions.

TABLE 2

Information recommended to be included in research reports on SCD:

1	Measurement approach: • Research environment (e.g., memory clinic, volunteer sample, population-based cohort) • Names of measures (where relevant) and information about their psychometric properties • Respondent category (e.g., self, informant, clinician, self- and informant) • Administration mode (e.g., paper-and-pencil, spontaneous report, phone interview) • Timeframe and reference group (e.g., comparison to age-peers, comparison to oneself at an early time point, compared to previously normal state) • Domains tapped (e.g., memory only; memory, language, attention)
2	Defined cutoffs on subjective report measures, or other approach used, with explanation for how cutoffs were derived to quantify level of subjective cognitive impairment (including information about normative comparisons and any demographic adjustments)
3	Defined cutoffs on objective report measures, or other approach used, with explanation for how cutoffs were derived to quantify level of objective cognitive impairment (including information about normative comparisons and any demographic adjustments)