The Journal of Prevention of Alzheimer's Disease 13 (2026) 100604

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Review

# Clinical and biological relevance of objectively-defined subtle cognitive decline in Alzheimer's disease: a narrative review of neuroimaging, biomarker, and clinical progression studies

Amanda I. Gonzalez [a], Jairo E. Martinez [a,b], Averi Giudicessi [a,b], Meredith Rowe [a], Vivian Ku [a], Catarina Tristão-Pereira [a,b], Bing He [a,b], Vincent Malotaux [a,b], Yakeel T. Quiroz [a,b,c,*]

[a] Department of Psychological & Brain Sciences, Boston University, Boston, Massachusetts, USA
[b] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
[c] Grupo de Neurociencias de Antioquia, Universidad de Antioquia, Medellín, Colombia

ARTICLE INFO

*Keywords:*
Dementia
Cognitive decline
Aging disorders
Biomarkers

ABSTRACT

Preclinical Alzheimer's Disease stages represent possible targets for disease-modifying intervention as well as opportunity for early identification of risk for future decline. Recent research has explored the use of objectively-defined subtle cognitive decline (Obj-SCD), an emerging classification that may identify individuals at risk for neurodegeneration before the onset of mild cognitive impairment (MCI). The Edmonds/Thomas actuarial Obj-SCD criteria (> 1 SD below expectations, single cognitive test impaired per domain) aims to capture those who exhibit minimal cognitive difficulties that do not meet a MCI or dementia diagnosis. Given the novelty of the Obj-SCD classification, this narrative review provides an overview of neuroimaging, biomarker, and clinical progression studies to evaluate its biological and clinical significance. Using fluid-based biomarkers, neuroimaging, and longitudinal designs, studies have indicated that the Obj-SCD classification has the potential to capture AD-related pathological changes detectable before the clinical onset of MCI. In particular, recent studies indicate a unique pathological profile of Obj-SCD, differentiating it from the cognitively unimpaired and MCI stages. Studies comparing Obj-SCD and subjective cognitive complaints show that the Obj-SCD criteria may be more closely associated to early AD pathology. While the existing literature is limited, findings uphold Obj-SCD as a sensitive classification able to identify individuals at risk for future cognitive impairment. Studies on Obj-SCD indicate utility in research settings, although it faces challenges regarding its clinical implementation and effectiveness.

## 1. Introduction

The Alzheimer's disease (AD) continuum describes the pathological changes in the brain that may manifest over time as cognitive and functional impairments. The continuum is typically divided into 3 phases: cognitively normal (CN), mild cognitive impairment (MCI), and dementia, each with their own distinct clinical and pathological markers [1]. Preclinical AD stages represent possible targets for disease-modifying intervention as well as opportunities for early identification of individuals at risk for future cognitive decline. Further, medications targeting AD pathology have been approved by the US Food and Drug Administration (FDA) and have shown efficacy in early AD stages, highlighting the urgent need for earlier identification of disease [2,3].

Recent research has explored the use of objectively-defined subtle cognitive decline (Obj-SCD), an emerging classification that may identify individuals at risk for neurodegeneration before the onset of MCI. Obj-SCD is the stage in which an individual exhibits minimal cognitive difficulties that do not meet a MCI or dementia diagnosis [4–6]. Participants are considered to have Obj-SCD if they perform over 1 standard deviation (SD) below the age, education, and sex adjusted mean on 1 impaired total test score in 2 cognitive domains, or 2 impaired neuropsychological process scores from the Rey Auditory Verbal Learning Test (AVLT), or 1 impaired total test score and one impaired process score [5,7,8]. The inclusion of neuropsychological process scores offers information regarding the individual's approach to a task, providing insight

* Corresponding author at: Psychological & Brain Sciences, Boston University, 610 Commonwealth Avenue, Suite #901, Boston, MA 02215, USA.
*E-mail address:* yquiroz@bu.edu (Y.T. Quiroz).

https://doi.org/10.1016/j.tjpad.2026.100604
Received 2 March 2026; Received in revised form 7 May 2026; Accepted 11 May 2026
Available online 19 May 2026

on cognitive processes beyond just total scores, such as error types. These criteria were designed based on Jak/Bondi MCI criteria, in which impairment is operationalized as over 1 SD below normative expectations on 2 tests per cognitive domain [9,10]. See Fig. 1 for Edmonds/-Thomas Obj-SCD and Jak/Bondi MCI criteria.

Given the novelty of the Obj-SCD classification, investigating the neuroimaging and other biomarker correlates of this classification is necessary to assess its biological and clinical significance. Additionally, assessing current literature will aid in answering whether Obj-SCD truly reflects early pathophysiological changes in AD.

## 2. Methods

We searched the PubMed database using the search terms "objectively-defined subtle cognitive decline" and "process scores AND subtle cognitive decline" to identify peer-reviewed studies that investigated the neuroimaging, biomarker, or clinical outcome correlates of Edmonds/Thomas actuarial neuropsychological Obj-SCD criteria in the context of AD. The final review included 13 studies published between 2018 and 2025.

## 3. Conversion to Dementia

Given that Obj-SCD is a proposed stage before MCI on the AD continuum, it is important to examine its ability to predict conversion to MCI and dementia. Longitudinal studies provide opportunities to assess the risk of future cognitive and functional impairment. Thomas et al. investigated the utility of Obj-SCD criteria in predicting progression to MCI within the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Individuals were classified as early subtle cognitive decline (E-SCD), if they either 1) performed >1 SD below the demographically-adjusted mean on 1 total score and also had 1 impaired process score, or 2) had 2 impaired process scores or late subtle cognitive decline (L-SCD) if they had 1 impaired total test score in 2 different cognitive domains. Results showed that those classified as E-SCD or L-SCD progressed to MCI 2.5-3.4 times faster than NC participants. Among NC participants, 31.4% progressed to MCI within 5 years and 36.0% within 10 years; 4.2% progressed to dementia within 5 years and 6.5% within 10 years. Comparatively, among E-SCD participants, 60.8% progressed to MCI within 5 years and 63.6% within 10 years; 11.9% progressed to dementia within 5 years and 15.4% within 10 years. Among L-SCD participants, 72.6% progressed to MCI within 5 years and 74.5% within 10 years; 14.2% progressed to dementia within 5 years and 15.1% within 10 years [7]. Another study by Thomas et al. explored the interaction between type 2 diabetes and Obj-SCD on future functional impairment. Findings showed that those with type 2 diabetes and Obj-SCD had a faster rate of functional decline over 5 years compared to those who had neither risk factor [11]. It should be noted that both studies indicated differences in some baseline demographics across the diagnostic groups, which may influence results [7,11].

| Stage | Domain Score Criteria | Process Score Criteria | Combination of Domain and Process Criteria |
|---|---|---|---|
| Early Obj-SCD | | 2 impaired process scores | 1 impaired process score AND 1 impaired total score |
| Late Obj-SCD | 1 impaired total score in 2 different cognitive domains | | |
| MCI | Impaired total score on 2 measures within a domain OR 1 impaired score in all three sampled cognitive domains | | |

**Fig. 1.** Proposed Edmonds/Thomas Obj-SCD and Jak/Bondi MCI Criteria. Impaired neuropsychological scores are defined as >1 SD below age/education/sex-adjusted mean. Fig. adapted from Thomas et al. [7,9].

The investigation of disease progression in individuals classified as Obj-SCD is an important consideration for the clinical relevance of such criteria. Overall, individuals classified as Obj-SCD were more likely to convert to MCI and dementia within 5 and 10 years, compared to NC individuals and among those with type 2 diabetes, Obj-SCD predicted faster functional decline over 5 years. However, a limitation of the current literature is that clinical progression associated with the classification has only been investigated within ADNI, which administers a relatively limited set of neuropsychological tests. More work is needed to determine whether process scores from other neuropsychological tests would yield similar results. Beyond the restricted neuropsychological battery used in ADNI, it is unclear if process scores derived from the AVLT could generalize to other widely used clinical assessments. While some evidence does exist that Obj-SCD criteria may identify those at risk for MCI and dementia, more research is needed to further investigate clinical outcomes.

## 4. Neuroimaging correlates (MRI & PET)

Neuroimaging studies offer a means of validating the biological and clinical relevance of the Obj-SCD criteria. Utilizing magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques allows for the exploration of associations between Obj-SCD and AD biomarkers. Among such biomarkers are core pathological indicators of AD within the ATN framework, a system that conceptualizes how amyloid-beta (Aβ), tau, and neurodegeneration levels define the AD continuum [12]. Previous literature has explored neuroimaging correlates of Obj-SCD including Aβ accumulation, tau burden, neurodegeneration, neurovascular alterations, and functional connectivity [5,6,13–17].

Accumulation of the Aβ protein is widely considered a primary driver of AD pathogenesis, occurring prior to clinical symptoms and influencing subsequent disease process [18]. As such, establishing Aβ associations is crucial to the validation of preclinical AD stages. A study by Thomas et al. found that individuals classified as Obj-SCD had faster Aβ accumulation compared to CN individuals, over 48 months, demonstrating the ability of Obj-SCD to capture cognitive changes before or during Aβ deposition. However, the Obj-SCD group in this study had a lower proportion of *Apolipoprotein* E ε4 (APOE ε4) carriers relative to the MCI group, which may influence results [5]. A later study by Thomas et al. again found higher prevalence of Aβ positivity in Obj-SCD compared to cognitively unimpaired (CU) individuals as well as lower prevalence of Aβ positivity compared to MCI individuals [6]. Given its intermediate levels of Aβ positivity compared to other diagnostic groups, Obj-SCD may represent a transitional stage from CN to MCI in which disease processes, such as amyloid accumulation, have already begun.

Some neuroimaging studies have compared whether Obj-SCD may be more closely tied to AD pathology than subjective cognitive complaints, which further evaluates the potential advantages of actuarial criteria at this stage. A study by Ren et al. examined Aβ pathology and its correlates in those with self-reported subjective cognitive decline (SCD) and Obj-SCD [15]. The SCD diagnosis was based on criteria described in a previous study: 1. subjective decline in memory; 2. occurrence within the last 5 years; 3. 50 years or older at onset; 4. concerns associated with SCD; and 5. feeling of lower performance than peers [19]. Results indicated that the Obj-SCD group had greater Aβ burden in the frontal and temporal lobes compared to the SCD and normal cognitive control (NCC) groups while the SCD and NCC individuals did not differ in amyloid deposition. When assessing the Aβ's relationship with cognitive function, the study found that increased Aβ deposition was associated with memory, language, and executive domains in Obj-SCD. Within the SCD group, Aβ burden was only associated with executive function [15]. Similarly, comparisons between subjective complaints and Obj-SCD have been investigated in the context of tau accumulation. A study by

Thomas et al. classified participants as positive or negative for subjective memory complaints (SMC) based on 12 items from the Cognitive Change Index. Results showed that increased tau accumulation was more closely tied to Obj-SCD status than was SMC and the Obj-SCD classification was associated with higher tau PET levels and a faster rate of cognitive decline. Contrastingly, SMC+ and SMC− participants did not differ in tau levels. When examining overlapping groups, the SMC−/Obj-SCD+ individuals had the highest tau burden and differed significantly from the SMC+/Obj-SCD− group [16].

Findings from neuroimaging studies report that Obj-SCD may be tied to early imaging biomarker changes associated with AD and cognitive dysfunction across different domains. While results extend Obj-SCD criteria to countries and cultures beyond the United States, the samples are still relatively culturally homogenous and Obj-SCD criteria should be examined across more races and ethnicities to enhance generalizability and validity. Future work should also include less rigorous self-reported SCD criteria for improved generalizability to clinical patients expressing subjective complaints. Overall, results provide important support that Obj-SCD criteria may be more closely tied to AD neuroimaging markers than subjective memory complaints and findings add to the growing body of literature examining Obj-SCD and AD biomarkers.

To determine whether Obj-SCD criteria may capture early neurodegeneration, previous work has also examined associations between medial temporal lobe neurodegeneration and these criteria. A study by Thomas et al. found that participants with Obj-SCD showed slower rates of entorhinal cortex thinning relative to MCI participants, but faster than the CN group. However, the rate of hippocampal atrophy over 48 months for Obj-SCD participants did not differ from that of CN or MCI participants [5]. This may be because neurodegeneration typically occurs later in disease progression, following Aβ and tau accumulation, meaning hippocampal atrophy may not be widely present until the MCI stage. Results explore the temporal sequence of Obj-SCD and associated cortical changes, highlighting the ability of these criteria to capture early changes in the entorhinal cortex. However, further studies are needed to examine if Obj-SCD is associated with neurodegeneration in other brain regions.

Neurovascular alterations, as indicated by neuroimaging markers like white matter hyperintensities (WMHs) and cerebral blood flow (CBF), are increasingly recognized biological mechanisms of AD which may manifest prior to clinical symptoms [20,21]. WMHs describe lesions in the white matter of the brain which are associated with underlying vascular damage and increased risk of future cognitive impairment [20,22–24]. A study by Calcetas et al. analyzed WMHs across CU, Obj-SCD, and MCI participants from ADNI. Compared to the CU group, the Obj-SCD group had greater temporal, occipital, and frontal WMH volume, while the MCI group had higher WMHs volume across all regions. The Obj-SCD and MCI groups had no differences in WMHs volume. However, it should be noted that Obj-SCD and MCI groups differed in number of participants and frequency of *APOE* ε4 carrier status, which may be a driver of observed differences [13]. In similar work, studies have also investigated associations between Obj-SCD and CBF using arterial spin labeling MRI. A study by Thomas et al. found that an Obj-SCD group had increased hippocampal and inferior parietal CBF compared to CU and MCI groups and greater inferior temporal CBF compared to the MCI group. Additionally, findings indicated an inverted-U-shaped pattern of CBF across stages in brain regions susceptible to early AD pathology, reflecting possible neurovascular compensation due to disease-related metabolic changes [6].

Previous research has also identified functional activity differences among Obj-SCD, MCI, and control individuals using resting-state functional MRI (fMRI). Investigating the underlying pathophysiology of Obj-SCD has the potential to elucidate network and connectivity disruptions present in this preclinical stage. A study by Cui et al. showed similar functional activity enhancements within Obj-SCD and amnestic MCI (aMCI) groups compared to healthy controls (HC), particularly in the inferior frontal gyrus, left median cingulate, and paracingulate gyri. However, those with Obj-SCD showed greater functional activity in the right middle occipital gyrus and less functional activity in the left precuneus and the left inferior temporal gyrus compared with the HC group, while the aMCI group did not [14]. The findings indicate a unique functional pattern with Obj-SCD individuals, differentiating them from aMCI while also suggesting a pathological relevance to the criteria. The greater functional activity observed in some brain regions of Obj-SCD individuals may reflect neurovascular compensation in response to metabolic stress when compared to NC. Further, differential regional activity, especially in brain areas vulnerable to early AD-related alterations, may contribute to progression of clinical symptoms. This study provides evidence for Obj-SCD utility outside of the ADNI cohort and within the Chinese-speaking community. However, future studies on functional patterns of Obj-SCD should integrate information on Aβ burden, which may mediate outcomes, as well as comparisons to other forms of MCI. The study only included individuals with memory and language impairments for the Obj-SCD group and a subgroup of MCI in which individuals only have memory impairments, which does not allow for generalizability to Obj-SCD or MCI based on impairment in other domains. A similar study by Qiu et al. investigated Obj-SCD functional connectivity within the ADNI cohort. Results showed that the Obj-SCD group had lower functional connectivity between left hippocampal subfields and the right thalamus, compared to the CN and MCI groups [17].

Overall, studies demonstrate associations between the Obj-SCD classification and MRI and PET biomarkers of AD, providing evidence for pathological changes even prior to an MCI diagnosis. When examining AD biomarkers, Obj-SCD has shown to be associated with AD-specific pathologies, such as Aβ and tau accumulation, as well as neurodegeneration and neurovascular changes. Findings seem to differentiate between Obj-SCD and MCI, indicating that they are separate stages on the AD continuum and frame the Obj-SCD stage in the context of the ATN framework.

## 5. Fluid Biomarkers

Plasma and CSF-based biomarkers are important for the detection of AD development and progression [25]. Examining associations between such biomarkers and Obj-SCD has the potential to elucidate plasma and CSF changes prior to cognitive impairment associated with MCI. Specifically, Obj-SCD has been explored in relation to plasma phosphorylated-tau181 (p-tau181), growth-associated protein 43 (GAP-43), and neurofilament light (NfL), as well as urine formaldehyde [4,26–29].

P-tau181 is an AD-specific marker of disease progression predicting cognitive and functional decline [30,31]. Consequently, whether p-tau181 is associated with preclinical stages of AD is an important and timely empirical question. A study by Thomas et al. examined relationships between Obj-SCD and plasma p-tau181 both cross-sectionally and longitudinally. At baseline, the Obj-SCD group had similar levels of plasma p-tau181 to CU participants, which were significantly lower than in the MCI group. However, the Obj-SCD group had the steepest p-tau181 increase over 4 years. Congruently, the Obj-SCD+/p-tau181-positive group had the fastest rates of cognitive and functional decline [4]. Similarly, a study by Huang et al. showed that plasma p-tau181 was significantly higher in the Aβ+ Obj-SCD group than in the NC groups [27]. Together, findings provide evidence that early subtle cognitive changes detectable by Obj-SCD criteria may occur before or with plasma p-tau181 changes. Combining Obj-SCD and p-tau181 levels may allow for the detection of those at risk for faster cognitive and functional decline. By assessing cross-sectional and longitudinal associations, previous studies provide a picture of Obj-SCD and plasma p-tau181 interactions over time. However, the process scores used in the Obj-SCD criteria of the study by Thomas et al. were derived from a verbal memory measure, meaning they may not be representative of all presentations of AD and earlier stages [4].

Another emerging AD biomarker of interest is GAP-43, a CSF marker of synaptic dysfunction. It has been proposed that synaptic loss and dysfunction are early central features of AD, contributing to memory loss [32–34]. Previous research has demonstrated associations between GAP-43 and cognitive decline, AD diagnosis, and AD neuropathology [35–37]. A study by Gonzalez et al. extended such findings to include the Obj-SCD stage, investigating its associations with functional decline. In longitudinal analyses, higher GAP-43 at baseline predicted faster functional decline over 4 years for the Obj-SCD Aβ+ and MCI Aβ+ groups in comparison to the CU Aβ- group [26]. Results suggest that synaptic dysfunction, as measured by CSF GAP-43, may manifest prior to MCI diagnosis and could be detectable among individuals with Obj-SCD. Additionally, findings demonstrate the utility of Obj-SCD criteria in identifying individuals at risk for future functional decline. It is important to note that longitudinal findings showed significant interaction effects between GAP-43 and elevated Aβ, specifically in Obj-SCD and MCI individuals, showing that GAP-43 levels alone did not predict future decline. Therefore, it is essential to assess individuals with Obj-SCD in combination with their full biomarker profile prior to making such predictions.

Some studies on CSF and plasma markers of preclinical AD have focused on the applicability of NfL, a cytoskeletal protein and marker of neuronal damage [38,39]. Previous research has recognized NfL as a core blood biomarker of neurodegeneration related to AD and a possible tool for monitoring disease progression [40–42]. A study by Huang et al. found that plasma NfL was significantly higher in Aβ+ Obj-SCD individuals compared to Aβ- NC individuals, after adjusting for covariates. In a diagnostic model, combined p-tau181 and NfL provided the most accurate discrimination between Aβ+ Obj-SCD and Aβ- NC [27]. Similarly, a study by Bangen et al. found that Obj-SCD and MCI participants had higher baseline plasma NfL relative to CN participants. In longitudinal analyses, results showed that elevated baseline NfL predicted faster rates of cognitive decline over 5 years in the Obj-SCD and MCI groups, compared to NC [28]. Findings across studies support the ability of NfL to differentiate Obj-SCD from NC and predict decline in Obj-SCD individuals. Importantly, results showcase Obj-SCD as a sensitive predictor for AD-related biomarker changes. Future studies should address the potential interactions of NfL and other biomarkers over time within the Obj-SCD stage.

Beyond CSF and plasma, urine has also been investigated as a potential biomarker for AD, which is especially appealing considering its non-invasive nature. Previous literature has indicated that urine formaldehyde levels increase with age and may be used to predict ensuing cognitive impairment [43–45]. A study by Wang et al. found that urine formaldehyde was found to be significantly upregulated in SCD compared to NC, Obj-SCD, and MCI groups. No differences in formaldehyde were observed between NC, Obj-SCD and MCI groups, although the AD group showed higher levels than the NC and MCI groups [29]. Findings contradict other studies which demonstrate closer associations between AD pathology with objectively-defined rather than subjectively-defined SCD. However, it is possible that the non-linear levels of urine formaldehyde across the AD continuum represent early disease compensation which then decreases as the individual enters the AD stage.

Altogether, studies indicate that changes at the plasma and CSF level are present in the Obj-SCD stage, although Obj-SCD did not seem to be associated with urine formaldehyde. Findings highlight the utility of Obj-SCD in predicting future amyloidosis and in combination with p-tau181, predicting future cognitive and functional decline. Synaptic dysfunction and neuronal damage, as measured by CSF GAP-43 and NfL, respectively, may manifest prior to MCI and could be detectable in individuals classified as Obj-SCD. When considering plasma for early AD screening, findings show that p-tau181 and NfL levels were relatively accurate at differentiating AD pathology Obj-SCD from NC. However, some findings from GAP-43 and NfL studies show associations specifically in Obj-SCD individuals with elevated Aβ, suggesting Aβ be considered when assessing the relevance of other biomarkers and cognitive data [26,27].

## 6. Discussion

Studying biomarkers of Obj-SCD is fundamental to informing intervention and to our understanding of dementia progression. Previous studies show convincing support for the ability of Obj-SCD criteria to detect subtle AD pathogenesis, neurovascular changes, and associated neurodegeneration, especially in regions vulnerable to early AD alterations. Obj-SCD is also associated with differing pathology compared to CU and MCI stages, highlighting its ability to capture transitional changes. Furthermore, studies comparing Obj-SCD and subjective cognitive complaints show that the Obj-SCD criteria may be more closely associated to early AD pathology. While the existing literature is limited, these converging findings uphold Obj-SCD as a sensitive classification able to identify individuals at risk for future cognitive and functional impairment.

Building upon these findings, future studies could further focus on different biomarkers, notably plasma p-tau217, which has been shown to be strongly associated with cognitive decline in AD. Plasma p-tau217 increases progressively along the disease continuum and demonstrates ability to detect Aβ pathology in a clinical setting [46]. The US FDA has approved the use of p-tau217/$A\beta_{1\text{-}42}$ ratio as diagnostic tool for AD, further highlighting the clinical relevance of such biomarkers [47]. Additionally, models combining plasma p-tau217, age, and neuropsychological tests exhibited excellent ability to predict incident dementia among community older adults suggesting it may be useful for preliminary screening of older adults at risk of dementia [48]. Further, some Obj-SCD findings indicate elevated GAP-43 and NfL specifically in Aβ positive individuals, which brings into question whether Aβ positivity serves as a driving factor of these results [26,27]. Given the complex biological mechanisms underlying preclinical AD, an integrative approach to disease assessment is necessary.

With the ever-emerging methods for capturing early AD-related changes, the need to compare Obj-SCD with other objective criteria for subtle cognitive decline is a timely and foremost endeavor. Though no universal criteria exist, one such approach is the Pre-MCI stage. Some studies have combined physician and neuropsychological diagnosis while others have integrated subjective cognitive criteria or informant reports [49–51]. One previous study indicated pre-MCI subjects showed intermediate cognitive, behavioral, and imaging features between CN and MCI subjects [49]. Hence, the biological and clinical relevance of Obj-SCD should be further compared with alternative neuropsychological methods for capturing early cognitive decline.

Future studies on Obj-SCD should focus on key areas that remain underexplored. Many of the existing studies utilized the ADNI database, which, although large and well-characterized, may hold limitations specifically in its lack of racial, ethnic, education-level, health diversity, and neuropsychological assessments administered. More work is still needed to investigate Obj-SCD in diverse datasets. Given that Obj-SCD was first developed within the ADNI cohort, it is also unclear if the process scores derived from the neuropsychological measures used in this study could generalize to other widely used clinical assessments. Further, the classification may also benefit from the integration of longitudinal neuroimaging and AD biomarkers to decipher intersecting biological relationships.

While the use of Obj-SCD in research appears well-validated, its utility in clinical settings requires more investigation. To our knowledge, there are only four studies exploring the use of Obj-SCD criteria in clinical samples [29,52–55]. Hence, empirical questions remain regarding the efficacy of these criteria within clinical populations. Longitudinal studies within clinical samples may further determine the efficacy of intervention at the Obj-SCD stage.

Another important consideration is the potential challenges regarding clinical implementation. One barrier regarding the clinical

use of this classification is the accessibility of neuropsychological evaluations to those very early in the AD continuum. Individuals who are younger than the average age of onset for MCI may not express concern for their cognitive status and therefore, may not seek an evaluation. Additionally, the high cost of neuropsychological evaluation, especially for adults in mid-life, may discourage individuals from seeking evaluation and possibly being diagnosed with Obj-SCD. Another barrier regarding clinical implementation of Obj-SCD is the heterogeneity within the classification. Neurodegenerative diseases outside of AD may manifest similar symptoms and mixed pathologies, making it difficult to determine diagnosis. Obj-SCD may represent subtle impairment within or across different cognitive domains, leading to a variety of clinical presentations. In essence, disease course and treatment may vary widely within the classification, relying on individual characteristics to determine clinical decisions.

## 7. Conclusions

Identifying those at risk for future cognitive decline and neurodegeneration is a high priority for dementia prevention and treatment. Earlier detection of AD risk can offer patients early treatment options and other preventative resources, possibly extending or improving the quality of their lives. This review highlights the evidence supporting Obj-SCD as sensitive classification and early detection method for AD-related pathology. Notably, early Aβ and tau accumulation, greater WMH burden, altered CBF patterns, greater plasma NfL, greater CSF GAP-43, altered functional activity patterns, and entorhinal cortex thinning were observed to be detectable in the Obj-SCD stage compared to cognitively unimpaired groups. While the utility of Obj-SCD in research is well-supported, less is known regarding its utility in clinical settings, and it faces challenges regarding its clinical implementation and effectiveness. As such, future research should continue exploring preclinical AD stages and methods for early identification.

## Funding

Supported by grants from the National Institute on Aging (NIA) (R01AG066823, R01AG077627) and the National Institute of Neurological Disorders and Stroke (NINDS) (RM1NS132996). The sponsors had no role in the design and conduct of the review; or in the preparation or approval of the manuscript;.

## Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in Fig.s, images and artwork

The authors declare that no generative AI or AI-assisted technologies were used in the writing of this manuscript or in the preparation of Figs., images, or artwork.

## Ethical statement

Not applicable.

## Data statement

Not applicable.

## CRediT authorship contribution statement

**Amanda I. Gonzalez:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization, Visualization. **Jairo E. Martinez:** Writing – review & editing. **Averi Giudicessi:** Writing – review & editing. **Meredith Rowe:** Writing – review & editing. **Vivian Ku:** Writing – review & editing, Visualization. **Catarina Tristão-Pereira:** Writing – review & editing. **Bing He:** Writing – review & editing. **Vincent Malotaux:** Writing – review & editing. **Yakeel T. Quiroz:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing interest

Dr. Quiroz has served as consultant for Biogen. The other co-authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors acknowledge the support of the Department of Psychological & Brain Sciences at Boston University. We thank Dr. Alice Cronin-Golomb for valuable discussions.

## References

[1] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):280–92. https://doi.org/10.1016/j.jalz.2011.03.003.

[2] Alkhalifa AE, Al Mokhlf A, Ali H, Al-Ghraiybah NF, Syropoulou V. Anti-amyloid monoclonal antibodies for alzheimer's disease: evidence, aria risk, and precision patient selection. J Pers Med 2025;15(9):437. https://doi.org/10.3390/jpm15090437.

[3] Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther 2021;13(1):80. https://doi.org/10.1186/s13195-021-00813-8.

[4] Thomas, K.R., Bangen, K.J., Edmonds, E.C., Weigand, A.J., Walker, K.S., Bondi, M. W., et al. Objective subtle cognitive decline and plasma phosphorylated tau181: Early markers of Alzheimer's disease-related declines. Alzheimers Dement Diagn Assess Dis Monit. 2021;13(1):e12238. doi:10.1002/dad2.12238.

[5] Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Wong CG, Cooper S, et al. Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration. Neurology 2020;94(4). https://doi.org/10.1212/WNL.0000000000008838.

[6] Thomas KR, Osuna JR, Weigand AJ, Edmonds EC, Clark AL, Holmqvist S, et al. Regional hyperperfusion in older adults with objectively-defined subtle cognitive decline. J Cereb Blood Flow Metab 2021;41(5):1001–12. https://doi.org/10.1177/0271678X20935171.

[7] Thomas KR, Edmonds EC, Eppig J, Salmon DP, Bondi MW. Alzheimer's disease neuroimaging initiative. Using neuropsychological process scores to identify subtle cognitive decline and predict progression to mild cognitive impairment. editorBrandt J, editor. Alzheimer's disease neuroimaging initiative. Using neuropsychological process scores to identify subtle cognitive decline and predict progression to mild cognitive impairment. J Alzheimer 19s Dis 2018;64(1):195–204. https://doi.org/10.3233/JAD-180229.

[8] Thomas KR, Eppig J, Edmonds EC, Jacobs DM, Libon DJ, Au R, et al. Word-list intrusion errors predict progression to mild cognitive impairment. Neuropsychology 2018;32(2):235–45. https://doi.org/10.1037/neu0000413.

[9] Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry 2009;17(5):368–75. https://doi.org/10.1097/JGP.0b013e31819431d5.

[10] for the Alzheimer's Disease Neuroimaging Initiative 1 Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Subtle cognitive decline and biomarker staging in preclinical Alzheimer's disease. editorBrandt J, editor. Subtle cognitive decline and biomarker staging in preclinical Alzheimer's disease. J Alzheimers Dis 2015;47(1):231–42. https://doi.org/10.3233/JAD-150128.

[11] Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Sundermann E, Wong CG, et al. Type 2 diabetes interacts with alzheimer disease risk factors to predict functional decline. Alzheimer Dis Assoc Disord 2020;34(1):10–7. https://doi.org/10.1097/WAD.0000000000000332. PubMed PMID: 31305320; PubMed Central PMCID: PMC6952586.

[12] Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;87(5):539–47. https://doi.org/10.1212/WNL.0000000000002923.

[13] Calcetas AT, Thomas KR, Edmonds EC, Holmqvist SL, Edwards L, Bordyug M, et al. Increased regional white matter hyperintensity volume in objectively-defined subtle cognitive decline and mild cognitive impairment. Neurobiol Aging 2022;118:1–8. https://doi.org/10.1016/j.neurobiolaging.2022.06.002.

[14] Cui L, Zhang Z, Zac Lo CY, Guo Q. Local functional MR change pattern and its association with cognitive function in objectively-defined subtle cognitive decline. Front Aging Neurosci 2021;13:684918. https://doi.org/10.3389/fnagi.2021.684918.

[15] Ren S, Li J, Huang L, Huang Q, Chen K, Hu J, et al. Brain functional alterations and association with cognition in people with preclinical subjective cognitive decline

and objective subtle cognitive difficulties. Neuroscience 2023;513:137–44. https://doi.org/10.1016/j.neuroscience.2023.01.004.
[16] Thomas KR, Weigand AJ, Edwards LC, Edmonds EC, Bangen KJ, Ortiz G, et al. Tau levels are higher in objective subtle cognitive decline but not subjective memory complaint. Alzheimers Res Ther 2022;14(1):114. https://doi.org/10.1186/s13195-022-01060-1.
[17] Qiu T, Zeng Q, Zhang Y, Luo X, Xu X, Li X, et al. Altered functional connectivity pattern of hippocampal subfields in individuals with objectively-defined subtle cognitive decline and its association with cognition and cerebrospinal fluid biomarkers. Eur J Neurosci 2022;56(12):6227–38. https://doi.org/10.1111/ejn.15860. Dec.
[18] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297(5580):353–6. https://doi.org/10.1126/science.1072994.
[19] Jessen F, Amariglio RE, Van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 2014;10(6):844–52. https://doi.org/10.1016/j.jalz.2014.01.001.
[20] Brickman AM, Provenzano FA, Muraskin J, Manly JJ, Blum S, Apa Z, et al. Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. Arch Neurol 2012;69(12):1621. https://doi.org/10.1001/archneurol.2012.1527.
[21] Wierenga CE, Hays CC, Zlatar ZZ. Cerebral blood flow measured by arterial spin labeling mri as a preclinical marker of Alzheimer's disease. De La Torre JC, editor. J Alzheimers Dis 2014;42(s4):S411–9. https://doi.org/10.3233/JAD-141467.
[22] Bangen KJ, Thomas KR, Weigand AJ, Sanchez DL, Delano-Wood L, Edmonds EC, et al. Pattern of regional white matter hyperintensity volume in mild cognitive impairment subtypes and associations with decline in daily functioning. Neurobiol Aging 2020;86:134–42. https://doi.org/10.1016/j.neurobiolaging.2019.10.016.
[23] Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TLS, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Ann Neurol 2016;79(6):929–39. https://doi.org/10.1002/ana.24647.
[24] Sui C, Liang C, Gao Y, Wang N, Zhang X, Wang Y, et al. The mediation effects of white matter microstructural abnormalities on the associations between cerebral small vessel disease burden and cognitive impairment. Neurobiol Dis 2025;214:107025. https://doi.org/10.1016/j.nbd.2025.107025.
[25] De Rino F, Rispoli F, Zuffi M, Matteucci E, Gavazzi A, Salvatici M, et al. Assessment of plasma and cerebrospinal fluid biomarkers in patients with alzheimer's disease and other dementias: a center-based study. Int J Mol Sci 2025;26(9):4308. https://doi.org/10.3390/ijms26094308.
[26] Gonzalez AI, Edwards LC, Thomas KR, Weigand AJ, Bordyug M, Brenner EK, et al. Growth-associated protein 43 is associated with faster functional decline among amyloid-positive individuals with objectively defined subtle cognitive decline and mild cognitive impairment. Neuropsychology 2025;39(3):248–58. https://doi.org/10.1037/neu0000981.
[27] Huang Y, Li Y, Xie F, Guo Q. Associations of plasma phosphorylated tau181 and neurofilament light chain with brain amyloid burden and cognition in objectively defined subtle cognitive decline patients. CNS Neurosci Ther 2022;28(12):2195–205. https://doi.org/10.1111/cns.13962.
[28] Bangen KJ, Thomas KR, Weigand AJ, Edmonds EC, Clark AL, Solders S, et al. Elevated plasma neurofilament light predicts a faster rate of cognitive decline over 5 years in participants with objectively-defined subtle cognitive decline and MCI. Alzheimers Dement 2021;17(10):1756–62. https://doi.org/10.1002/alz.12324.
[29] Wang Y, Pan F, Xie F, He R, Guo Q. Correlation between urine formaldehyde and cognitive abilities in the clinical spectrum of Alzheimer's disease. Front Aging Neurosci 2022;14:820385. https://doi.org/10.3389/fnagi.2022.820385. PubMed PMID: 35221998; PubMed Central PMCID: PMC8873387.
[30] Tropea TF, Waligorska T, Xie SX, Nasrallah IM, Cousins KAQ, Trojanowski JQ, et al. Plasma phosphorylated tau181 predicts cognitive and functional decline. Ann Clin Transl Neurol 2023;10(1):18–31. https://doi.org/10.1002/acn3.51695.
[31] De Meyer S, Vanbrabant J, Schaeverbeke JM, Reinartz M, Luckett ES, Dupont P, et al. Phospho-specific plasma p-tau181 assay detects clinical as well as asymptomatic Alzheimer's disease. Ann Clin Transl Neurol 2022;9(5):734–46. https://doi.org/10.1002/acn3.51553.
[32] Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30(4):572–80. https://doi.org/10.1002/ana.410300410.
[33] Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology 2007;68(18):1501–8. https://doi.org/10.1212/01.wnl.0000260698.46517.8f.
[34] Masliah E, Mallory M, Alford M, DeTeresa R, Hansen LA, McKeel DW, et al. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. Neurology 2001;56(1):127–9. https://doi.org/10.1212/WNL.56.1.127.
[35] Sandelius Å, Portelius E, Källén Å, Zetterberg H, Rot U, Olsson B, et al. Elevated CSF GAP-43 is Alzheimer's disease specific and associated with tau and amyloid pathology. Alzheimers Dement 2019;15(1):55–64. https://doi.org/10.1016/j.jalz.2018.08.006.
[36] Bogdanovic N, Davidsson P, Volkmann I, Winblad B, Blennow K. Growth-associated protein GAP-43 in the frontal cortex and in the hippocampus in Alzheimer's disease: an immunohistochemical and quantitative study. J Neural Transm 2000;107(4):463–78. https://doi.org/10.1007/s007020070088.
[37] Rekart JL, Quinn B, Mesulam MM, Routtenberg A. Subfield-specific increase in brain growth protein in postmortem hippocampus of Alzheimer's patients. Neuroscience 2004;126(3):579–84. https://doi.org/10.1016/j.neuroscience.2004.03.060.
[38] Kahn OI, Dominguez SL, Glock C, Hayne M, Vito S, Sengupta Ghosh A, et al. Secreted neurofilament light chain after neuronal damage induces myeloid cell activation and neuroinflammation. Cell Rep 2025;44(3):115382. https://doi.org/10.1016/j.celrep.2025.115382.
[39] Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry 2019;90(8):870–81. https://doi.org/10.1136/jnnp-2018-320106. Aug.
[40] Giacomucci G, Mazzeo S, Bagnoli S, Ingannato A, Leccese D, Berti V, et al. Plasma neurofilament light chain as a biomarker of Alzheimer's disease in subjective cognitive decline and mild cognitive impairment. J Neurol 2022;269(8):4270–80. https://doi.org/10.1007/s00415-022-11055-5.
[41] Bacioglu M, Maia LF, Preische O, Schelle J, Apel A, Kaeser SA, et al. Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and in Neurodegenerative diseases. Neuron 2016;91(1):56–66. https://doi.org/10.1016/j.neuron.2016.05.018.
[42] Zetterberg H, Skillbäck T, Mattsson N, Trojanowski JQ, Portelius E, Shaw LM, et al. Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. JAMA Neurol 2016;73(1):60. https://doi.org/10.1001/jamaneurol.2015.3037.
[43] Wang C, Cui Y, Yang J, Zhang J, Yuan D, Wei Y, et al. Combining serum and urine biomarkers in the early diagnosis of mild cognitive impairment that evolves into Alzheimer's disease in patients with the apolipoprotein E ε4 genotype. Biomarkers 2015;20(1):84–8. https://doi.org/10.3109/1354750X.2014.994036.
[44] Tong Z, Wang W, Luo W, Lv J, Li H, Luo H, et al. Urine formaldehyde predicts cognitive impairment in post-stroke dementia and Alzheimer's disease. editorZhang J, editor. Urine formaldehyde predicts cognitive impairment in post-stroke dementia and Alzheimer's disease. J Alzheimers Dis 2016;55(3):1031–8. https://doi.org/10.3233/JAD-160357.
[45] Zengi O, Karakas A, Ergun U, Senes M, Inan L, Yucel D. Urinary 8-hydroxy-2′-deoxyguanosine level and plasma paraoxonase 1 activity with Alzheimer's disease. Clin Chem Lab Med 2012;50(3). https://doi.org/10.1515/cclm.2011.792.
[46] Martínez-Dubarbie F, Guerra-Ruiz A, López-García S, Lage C, Fernández-Matarrubia M, Nevado-Cáceres Á, et al. Diagnostic performance of plasma p-tau217 in a memory clinic cohort using the Lumipulse automated platform. Alzheimers Res Ther 2025;17(1):68. https://doi.org/10.1186/s13195-025-01719-5.
[47] Hu S, Yu H, Gao J. The pTau217/A$\beta_{1-42}$ plasma ratio: The first FDA-cleared blood biomarker test for diagnosis of Alzheimer's disease. Drug Discov Ther 2025;19(3):208–9. https://doi.org/10.5582/ddt.2025.01055.
[48] Xiao Z, Zhou X, Zhao Q, Cao Y, Ding D. Significance of plasma p-tau217 in predicting long-term dementia risk in older community residents: Insights from machine learning approaches. Alzheimers Dement 2024;20(10):7037–47. https://doi.org/10.1002/alz.14178.
[49] Duara R, Loewenstein DA, Potter E, Barker W, Raj A, Schoenberg M, et al. Pre-MCI and MCI: neuropsychological, clinical, and imaging features and progression rates. Am J Geriatr Psychiatry 2011;19(11):951–60. https://doi.org/10.1097/JGP.0b013e3182107c69.
[50] Ruan Q, Zhang W, Ruan J, Chen J, Yu Z. Clinical and objective cognitive measures for the diagnosis of cognitive frailty subtypes: a comparative study. Front Psychol 2021;12:603974. https://doi.org/10.3389/fpsyg.2021.603974.
[51] Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology 2006;67(3):467–73. https://doi.org/10.1212/01.wnl.0000228231.26111.6e.
[52] Thomas KR, Edmonds EC. Objective criteria for subtle cognitive decline in aging and preclinical alzheimer disease: a systematic review. Neurology 2025;104(9):e213536. https://doi.org/10.1212/WNL.0000000000213536.
[53] Guo H, Wu Y, Fu G, Li J, Zhu J. Correlation between ankle-brachial index and subtle cognitive decline. Brain Behav 2023;13(6):e3019. https://doi.org/10.1002/brb3.3019.
[54] Huang L, Chen K, Liu Z, Guo Q. A conceptual framework for research on cognitive impairment with no dementia in memory clinic. Curr Alzheimer Res 2020;17(6):517–25. https://doi.org/10.2174/1567205017666200807193253. Oct 7.
[55] Pan FF, Huang L, liang CK, hua ZQ, hao GQ. A comparative study on the validations of three cognitive screening tests in identifying subtle cognitive decline. BMC Neurol 2020;20(1):78. https://doi.org/10.1186/s12883-020-01657-9.