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Sommario

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A systematic review of standard diagnostic criteria for Cognitive Impairment No Dementia (CIND), risk factors and conversion rates

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Abstract: Ageing research has focused on pathological processes that lead to cognitive decline, such as Alzheimer's disease, while Cognitive Impairment No Dementia (CIND) has received less attention. The study's goal was to identify the diagnostic standards used in the development of CIND as well as the major risk factors for its conversion and progression to dementia. Scopus was searched for literature published up to October 2023 using keywords, MeSH, and Emtree entries, in accordance with PRISMA guidelines for search structure, eligibility requirements, and selection processes. CIND is significantly more heterogeneous than other cognitive classifications, with dementia being only a clear exclusion criterion. Neuropsychiatric, vascular, social, and comorbidity factors are all risk factors for progression from CIND to dementia. This review highlights the critical importance of standardised methodologies in CIND research. Future research should focus on longitudinal studies using consistent diagnostic criteria to further our understanding of CIND and its progression to dementia.

Keywords: Cognitive Impairment No Dementia, Standard Diagnostic Criteria, Risk factors, Conversion.

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The work here detailed is the result of a collaborative effort, however Pepe I. edited paragraphs 1, 3, and 4, while Toma E. wrote paragraph 2.1. Both authors are responsible for paragraph 2.2.

1. Introduction

The bulk of research on aging and cognitive function has typically focused on two ends of the spectrum: pathological processes leading to significant cognitive decline, such as Alzheimer's dementia (AD), and the physiological developmental trajectories during growth (Tucker, 2019). Less attention has been paid to the more prevalent cognitive impairments associated with normal age-related cognitive changes that don't escalate to the clinical stages of dementia. This intermediate stage is often referred to as Mild Cognitive Impairment (MCI) or Cognitive Impairment No Dementia (CIND).

The term "Cognitive Impairment, No Dementia" was initially introduced in the Canadian Study of Health and Aging, targeting individuals aged 65 and older who experienced cognitive challenges, particularly memory-related, which did not align with the criteria for dementia as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (Chertkow et al., 2007). These individuals were considered a distinct group from those of similar age with normal cognitive functioning. On the other hand, "Mild Cognitive Impairment", as defined by Petersen and colleagues, encompasses features like memory-related symptoms, objectively assessed memory issues relative to one's age and education, intact overall cognitive function, and the ability to manage daily activities, all without meeting the diagnostic criteria for dementia (Bradfield, 2023). Recent definitions of MCI have expanded to include impairment in single or multiple cognitive domains (Yu et al., 2023).

CIND is remarkably heterogeneous compared to other cognitive classifications like age-associated cognitive impairment (Levy, 1994) and mild cognitive impairment (MCI; Winblad et al., 2004). The only clear-cut exclusion criterion for CIND is a dementia diagnosis. According to Peters et al. (2004), CIND is therefore thought to represent a larger subset of people who are potentially at risk of developing dementia in the future.

Standard diagnostic criteria for this clinical condition are noticeably lacking, and there is little information on how well this definition works to identify people who are more likely to develop dementia or more severe cognitive impairment (Ritchie & Tuokko, 2011).

The variations in reported statistics can be attributed to discrepancies in the demographics of the studied populations, the duration of follow-up, the choice of diagnostic criteria, the diversity, and quantity of neuropsychological assessments employed, and the selected cutoff values. This wide array of differences compli-

cates endeavors to gain a comprehensive understanding of the actual impact of these conditions. In Italy, only a limited number of population-based studies have explored the prevalence and conversion rate of CIND to dementia (Fei et al., 2009). Whereas there is evidence relating several risk factors to the disease's progression, most research has focused solely at cognitive and functional abilities and emphasised on variations in prevalence and conversion rates for different definitions of MCI (Robertson et al., 2019). Additionally, comparing these studies is challenging due to disparities in diagnostic criteria, the battery of neuropsychological tests employed, and the chosen cutoff values. Participants with CIND have a variety of risk factors for dementia progression (Wu et al., 2022, Dove et al., 2023, McDowell, 2022,) Neuropsychiatric factors (psychosis, anxiety, depression) (Martin et al., 2020, Peters et al., 2015, Peters et al., 2008), vascular factors (hypertension, diabetes, stroke) (Li et al., 2011, Rentería et al., 2022, Dove et al., 2023) , social factors (limited physical and social activities, dysregulated lifestyle) (Amano, 2019. Hsiung et al., 2004: Chen et al., 2018) and finally comorbidity with chronic diseases is all associated with an increased risk of conversion (Narasimhalu et al., 2005, Dove et al., 2023).

This review is primarily centered on research involving individuals with CIND. We will begin by examining studies where individuals with CIND were initially identified based on their performance on neuropsychological assessments. Subsequently, we will delve into studies that involved following these individuals over time. We will provide a concise overview of recurring themes in these studies, focusing on the criteria for identifying CIND and factors that predict decline among those with CIND.

2. Methods

2.1 Search strategy and Inclusion and Exclusion Criteria

The Scopus database was used to carry out this comprehensive review of the literature. According to the PRISMA guidelines, the search question's structure, eligibility requirements, and selection and evaluation processes were predefined (Page et al., 2021). The PICO scheme (Patient, Intervention, Comparison or Control, Outcome) (Huang et al., 2006; Schardt et al., 2007) was utilised to formulate the following question to incorporate various experimental study types: Which are the primary diagnostic standards used in the development of CIND? What are the primary risk factors for conversion and how does CIND dementia progress?

In the search fields, "title, abstract, and keywords," the following query string was used on October 11, 2023:

TITLE-ABS-KEY (Progression) OR TITLE-ABS-KEY (Criteria*) AND TITLE-ABS-KEY (Diagnostic*) AND (Title-ABS-KEY (risk)) Option TITLE-ABS-KEY (variables*) Furthermore, DOCTYPE (ar) AND (LIMIT-TO (SUBJAREA, "PSYC")) AND (LIMIT-TO (LANGUAGE, 'English')).*

The studies that emerged from the string had to meet the following requirements to be included in the review.

Table 1. *Inclusion and exclusion criteria.*

Inclusion Criteria	*Exclusion Criteria*
Observational studies using objective neuropsychological measures.	Observational studies not using subjective neuropsychological measures for diagnosis
Longitudinal studies conducted in population-based samples with at least 1 year of follow-up.	Participants who were not followed for at least one year during the study period for dementia risk
Participants were those with a diagnosis of CIND/MCI according to internationally accepted and validated classifications (e-g. the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, the DSM-IV).	Studies that included participants with "memory problems" or "self-reported memory disorders" and without a clear diagnosis of CIND/MCI and Included people affected by dementia at baseline
CIND/MCI subjects at baseline who progressed to dementia	CIND/MCI subjects at baseline who remained CIND or progressed to normal cognition

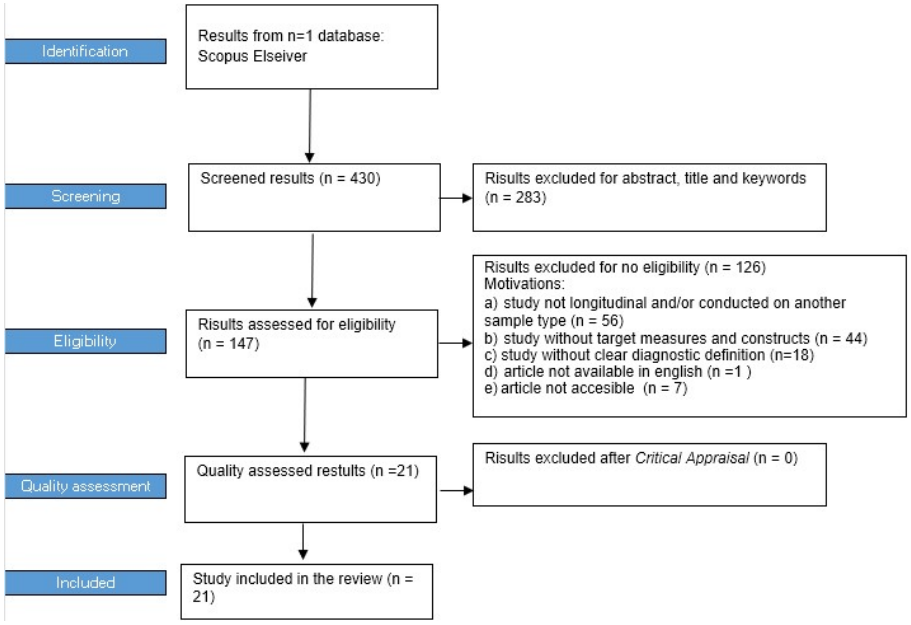
2.2 Screening process and data extraction

IP and ET, two independent reviewers, evaluated potentially pertinent articles for eligibility. To weed out studies that were blatantly irrelevant, the decision to include or exclude studies was made hierarchically, first based on the study title and abstract (see Figure 1). In cases where the title or abstract of a study could not be definitively disregarded, the complete article was acquired for assessment.

Data from the included studies were extracted using a 7 form to assess study quality and synthesise evidence. Information on the following was extracted from

the data: (1) author and year of publication; (2) sample size; and (3) CIND and diagnostic criteria. (4) objective neuropsychological tests; (5) the results of the transition from CIND to dementia; and (6) the risk factors (comprising information on all risk factors evaluated, both significant and non-significant) for the conversion to dementia. Data extraction was done by one author (IP), and extraction control was done by another (ET).

Figure 1. *Review procedure flowchart (PRISMA format)*



3. Results

3.1 Study selection

From the electronic search, the titles, and abstracts of 430 publications were selected and the full texts of 80n articles were examined. two independent judges (IP and ET) went through the following process (Fig. 1): (1) preliminary screening by title, abstract, and keywords; (2) inclusion of all eligible articles (% agreement=97.54%; Cohen's k = 0.93); and (3) evaluation to confirm the quality and clarity of the evidence reported in the studies included based on the study designs (CASP - Critical Appraisal Skills Programme: http://www.casp-uk.net/casp-tools-checklists). Every article that was included and assessed based on quality using the CASP criteria received a score of at least 7/11, which was deemed acceptable by earlier research

(Al-Dirini et al., 2012). The study screening and selection process is illustrated in the PRISMA flowchart (Figure 1). Twenty-one articles met the eligibility criteria. The most common reasons for exclusion were that the study did not use standardized neuropsychological measures, the sample did not have a clear diagnosis of CIND/MCI, and the study did not report any type of risk factors.

Table 1 summaries 14 studies along a range of criteria and dimensions that classify CIND, it is arranged according to the operationalization of the criteria used to diagnose Mild Cognitive Impairment No dementia. Table 2 contains a compilation of most studies on the conversion of CIND to dementia at different times, including (1) prevalence of conversion; (2) statistical analysis (3) Risk factors.

3.2 Study characteristics

In the first eleven studies examined, the sample size of CIND ranged from n=1850 to n = 48, with a mean of n = 591 (standard deviation [SD] = 582). Most studies (n=9) included participants over 70 years of age, while others included participants over 80 years of age (n = 1) and over 60 years of age (n = 1). The follow-up period in the subsequent ten studies ranged from 2 to 12 years, with a mean of 5.3 years (SD = 3.49 years).

3.3 Operationalization of Diagnostic criteria for CIND

The Mini- Mental- State Examination (MMSE) (n=6) was used as the main screening test in most studies to diagnose CIND; others included the Montreal Cognitive Assessment (MoCA) (n=1), an abbreviated version of the modified Telephone Interview for Cognitive Status (n=1), and the Clinical Dementia Scale (n=1).

The domain-specific neuropsychological measures for the diagnosis and operationalization of the CIND criteria used investigated Executive Functions n=6 (Digit Cancellation test; Trail Making Test part B; ETS Letter Sets, CANTAB Stockings of Cambridge, Ravens Progressive Matrices), Episodic Memory n=6 (Babcock Story Recall Test; Free recall; the Enhanced cued recall test; Delayed Recall; CANTAB Delayed Verbal Memory, New York Paragraph - Delayed; the Enhanced cued recall test), Semantic Memory n=1 (2 questions on common objects and 2 questions on political knowledge) Working Memory n = 4 (erasure of digits; CANTAB Spatial Span Length - Reverse, CANTAB Spatial Working Memory, Size Judgment Span); Language n = 6 (Category and letter fluency; Categorical fluency task; Animal fluency, CANTAB Graded Naming Test, Shipley Institute of Living - Vocabulary; category and letter fluency; the number of animals; Letter Fluency; the

number of animal names produced within 1 minute) Visuospatial Functions n = 4 (Mental rotation; the clock drawing test; Constructive praxis).

All articles (n=11) used Cognitive Impairment Without Dementia as a classification system. The operationalization of the presence of objective cognitive impairment based on the neuropsychological measures used is shown in Table 1. According to the Petersen and DSM-V criteria, CIND is diagnosed when there is: (1) normal daily and instrumental activity; and (2) objective cognitive impairment in at least one of the following domains: memory, executive function, language, visuospatial or perceptual speed function.

Most studies (n=6) operationalized CIND as performance on neuropsychological measures >1.5 SD below published norms on any test. N=3 studies used a neuropsychological measure score that was at least >0.5 SD below published norms. Lastly, studies (n=2) employed a score >1 SD below the mean of the normative reference sample (Table 2).

3.4 Conversion from CIND to Dementia

For all-cause dementia (n = 11 studies), rates of conversion from CIND to dementia ranged from 8.2% to 40%3 over an average follow-up of 5.3 years (SD= 3.4 years). (Table 3). Conversion rates to all-cause dementia were generally higher for definitions that captured broader impairment; for example, conversion range for all CINDs (n = 5 studies) and MCI (n = 5 studies),44 with conversion range for CIND 8.2% to 40% on 2.0-10.0 years of follow-up, and for MCI 16.8 to 37 on 2.0-5.0 years of follow-up (Table 3).

3.4 Risk factors for Dementia

In all studies (n = 10), risk factors for the conversion of CIND/MCI to dementia were examined. Sociodemographic factors such as age (n = 4/10 studies), low education level (n = 2/10), low social status (n = 1/10), psychological factors (n = 2/10 studies; anxiety, depression, personality traits), comorbid pathologies (n = 3/10; history of stroke, hypertension), impairment in activities of daily living and instrumental activities (n = 2/10), and apolipoprotein E (APOE) ε4 status tests (n = 1/4 studies) were among the significant risks. Table 3 provides a comprehensive overview of all conversion rates and risk factors evaluated in each study.

Table 2. *Study characteristics (grouped by operationalisation of the criteria for the diagnosis of CIND and neuropsychological tests used)*

Source	Study sample	Criteria for CIND	Clinical and Neuropsychological evaluation
Di Carlo et al. (2007)	N=264 (mean age=73.3)	**1 SD** below the age- and education-specific mean of the MMSE and 1+ domains	the Mini-Mental State Examination (MMSE), The Babcock Story Recall Test (BSRT), The Digit Cancellation Test (DCT).
Grande et al. (2020)	N=441 (mean age=72) =	**1.5 SD** or more below age group-specific means in at least one domain. **Moderate to severe CIND** was defined as scoring **2.0 SD** or more below the age group specific mean	Episodic memory (Free recall), Executive function (Trail Making Test, part B), Language (Category and Letter fluency), Visuospatial abilities (Mental rotation) and Perceptual Speed (Digit cancellation and Pattern comparison)
Rodríguez-Sánchez et al. (2011)	N= 48 (mean age=76.35)	**0.5 SD** below published norms on any test in 1+ domains	Mini-Mental State Examination (MMSE); the Benton temporal orientation test (temporal orientation); the Enhanced cued recall test (episodic memory); the Clock drawing test (constructive praxias; the Categorical fluency task (language)
Hanzevacki et al. (2011)	N=67 (mean age= 76.11)	**1 SD** below the mean adjusted for age and education in MMSE and 1+ domains.	The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA)
Unverzagt et al. (2011)	N=1727 (mean age=73.5)	**1.5SD** below the mean of the normative reference sample in 1+ domains	Mini-Mental State Examination, Animal Fluency, 15-item Boston Naming Test, Constructional Praxis and Recall, and Word List Learning and Delayed Recall
Zhang et al (2014)	N=1295 (mean age=73.32)	**0.5 SD** below published norms on any test in 1+ domains	Mini-Mental State Examination, the Activities of Daily Living and Clinical Dementia Rating questionnaires
Plassman et al. (2011)	N=110 (mean age=81.80)	**1.5 SD** below published norms on at least 1 test	HRS interview (an abbreviated version of the modified Telephone Interview for Cognitive Status); Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
Lovett et al. (2020)	N=863 (mean age=63.1)	**Mild** (-1 to -1.49 SD), **moderate (-1.5 to -1.99 SD)**, or **severe (<-2 SD)** on one or more tests.	Processing speed (Digit Comparison, Pattern Comparison, Symbol Digit Modalities), working memory (CANTAB Spatial Span Length – Reverse, CANTAB Spatial Working Memory, Size Judgment Span), delayed memory (CANTAB Delayed Verbal Memory, New York Paragraph – Delayed), executive function (ETS Letter Sets, CANTAB Stockings of Cambridge, Ravens Progressive Matrices), language (CANTAB Graded Naming Test, Shipley Institute of Living – Vocabulary).
Wu et al. (2022)	N=301 (mean age=74.1)	**1.5** SD below age-specific means in 1+ domains	Free recall (episodic memory), Trail Making Test Part B (executive function), Category and Letter Fluency (language), mental rotation (visuospatial ability), and digit cancellation and pattern comparison (perceptual speed).
Bertola et al. (2023)	N=422 (mean age=70.1)	**1.5 SD** or more below means in 1+ domains	Questions about temporal orientation (day, month, year, and day of the week), semantic verbal fluency (the number of animal names produced within 1 minute), 10-word list test for immediate recall and late recall, prospective memory (remember to write own name when finishing another test), and 4 semantic memory questions (2 questions about common items, and 2 questions about political knowledge)
Zhang et al. (2018)	N=1295 (mean age=73.30)	**0.5 SD** below published norms on any test in 1+ domains	The Activities of Daily Living and Clinical Dementia Rating questionnaires; Mini-Mental State Examination and/or a Clinical Dementia Rating.

Table 3. *Study characteristics (grouped by conversion rates from CIND/MCI to dementia, statistical tests used and type of risk factor).*

Source	Conversion to Dementia	Statistical analysis	Risk factors
Di Carlo et al. (2007)	CIND (8.2%) increased by almost three times the risk of dementia at follow-up (3years)	Logistic regression and Cox regression analysis	Previous stroke and impairment in instrumental activities of daily living
Hsiung et al. (2008)	N=70 CIND baseline progression after 2 years to AD n=28 (40%)	MANCOVA	Impairment in instrumental activities of daily living
Wu et al. (2022)	118 out of 607 participants with CIND at baseline that developed dementia during the 12 years follow-up (19 %)	Cox proportional hazards models	Lower education levels, earlier retirement, lower SES status, fewer smokers, more physically inactive, long-term exposure to ambient air pollutants and air pollution
Ehrlich et al. (2021)	N=92 CIND baseline progression to AD=24 in 10 years follow up (26%)	Multivariable Cox proportional hazards models and logistic regression	Vision impairment and Age
Terracciano et al. (2017)	N= 1850 individuals with CIND at baseline, of whom 615 developed dementia after 8 years (33%)	Cox regression models	Lower conscientiousness
Chen et al. (2018)	37.2% of patients progressed to dementia after 2 years.	multiple logistic regression model	Age
Li et al. (2011)	N= 837 at baseline; n=298 converted to AD dementia after 5 years follow up (35%)	Cox proportional hazard models	Vascular risk factors (VRF)
Ding et al. (2016)	The conversion rate to dementia was 6.0 per 100 person-years (4 years)	Kaplan–Meier survival analysis; Cox proportional hazards regression model	Age, apolipoprotein E (APOE ε4)
Yang et al. (2020)	16, 8% (78/465) after 3 years follow up	Logistic regression model	Depression
Paddick et al. (2015)	15 patients (32.6%) progressed to dementia after 4 years follow up	Cox regression models	Age, sex, education levels, body mass index, hypertension

4. Discussion

We found in this systematic review that very few studies have been conducted on individuals diagnosed with CIND and their risk of dementia conversion. This stands in a severe contrast to the significant investment in research into the possibility of acting in terms of primary prevention to detect the disease's prodromal stage as early as possible (Caicedo et al., 2020; McKeown et al., 2021). The findings of this systematic review allowed us to highlight the standard diagnostic criteria for cognitive impairment in the absence of dementia, as well as clarify the correlates and rates of conversion to dementia by examining the relevant risk outcomes.

Although somewhat heterogeneous, the criteria in terms of cut-offs using the mean observed in a normative population or published normative scores for each reference test are compacted around the use of 1.5 SD below the mean on one or

more cognitive domains (n=6 studies) (Grande et al., 2020; Unverzagt et al., 2011; Plassman et al., 2011; Lovett et al., 2020; Wu et al., 2020; Bertola et al., 2023) along with the presence of preserved daily living and instrumental activities in the first 11 selected studies that aimed to collect agreeable gold standard parameters for a commonly usable nomenclature of CIND. Only n = 2 (Di Carlo et al., 2007; Hanzevacki et al., 2011) and n = 3 studies (Rodríguez-Sánchez et al., 2011; Zhang et al., 2014; Zhang et al., 2018) respectively, used a cut-off of 1 SD below the mean and 0.5 SD below the mean; however, in two of these, a cut-off of 1.5 SD below the mean was used to define a moderate CIND. On the basis of this evidence, although the definition of CIND is very diverse, with different tests, domains, and cut-offs for each study, it is possible to consider a diagnosis of objective impairment or objective evidence of decline in the absence of dementia as a gold standard 1.5 SD below the mean on a cognitive domain between memory, executive functions, language, and visuospatial functions in the presence of non-impaired daily living and instrumental activities (Cerbone et al., 2022).

In all the studies that assessed the risk of dementia from a CIND condition (n=10), the conversion rate was high and varied, ranging from 8.2% to 40% over a 5-year follow-up period.

Age and the presence of the APOE ε4 allele are non-modifiable risk factors for the progression from CIND and/or MCI to dementia (Chen et al., 2018; Ehrlich et al., 2021; Ding et al., 2016; Paddick et al., 2015). Only two out of ten studies that looked at the relationship between social status and educational level found that having a lower social status and education level was a risk factor for the conversion from CIND/MCI to dementia (Wu et al., 2022; Paddick et al., 2015). This is even though lower social status and education levels have been linked to an increased risk of prevalent CIND and/or MCI as well as a higher risk of dementia progression, especially in CIND. There is evidence from research, mostly in MCI, that education level and cognition are related (Fei et al., 2009; Marengoni et al., 2011). However, these studies' interpretations are limited by methodological flaws and the possibility of reverse causality, necessitating longer-term follow-up studies.

Poor cardiometabolic health, smoking, the presence of vascular risk factors, and poor neuropsychiatric health, such as the presence of depression, are among the most powerful predictors of conversion (Di Carlo et al., 2007; Wu et al., 2022; Terraciano et al., 2017; Li et al., 2011; Yang et al., 2020; Paddick et al., 2015).Targeting these factors could be a proactive strategy for not only preventing CIND but also reducing the burden of dementia. According to two of the ten studies reviewed, acting on 12 modifiable risk factors, many of which can be influ-

enced by diet and lifestyle (Scarmeas et al., 2018), can prevent up to 40% of dementia cases (Livingston et al., 2020).

According to other research, impairments in instrumental activities of daily living (ADLs) that require cognitive load, like using a phone or managing finances or medications, are an early indicator of conversion (n = 2/10) (Di Carlo et al., 2007; Hsiung et al., 2008). Because their cognitive deficits are not severe enough to substantially interfere with daily activities, people with CIND do not meet the criteria for dementia. But because the condition worsens over time, patients may find it harder to carry out activities of daily living (ADLs), especially instrumental ADLs (IADLs) like cooking, using a phone, or managing finances, which call for more sophisticated skills (Rodakowski et al., 2014) Previous research has primarily looked at cross-sectional studies to examine the relationship between MCI and impairment of IADLs (Cornelis et al., 2017; Bruderer-Hofstetter et al., 2022). There aren't many longitudinal studies examining the course of changes in IADLs in the years before an AD diagnosis, so it's unclear how IADL impairment evolves over time. Recognizing when IADLs become impaired is critical because these impairments occur early in the disease process and may be a sign of future decline (Villeneuve et al., 2019; Jutten et al., 2020). Furthermore, it is imperative to delineate their trajectory and temporal evolution, given that the shift in function is frequently regarded as a more precise and sensitive indicator of impending decline than the performance level at any given moment.

This is the first study to synthesize research on the operationalization of diagnostic standards for CIND recognition, as well as the risk of dementia in CIND patients. We conducted an extensive literature search that, despite capturing many of the different definitions of CIND due to extremely variable nomenclatures, resulted in the inclusion of only a few studies on its diagnostic standards. Some limitations must be highlighted. As the electronic search was conducted in English, studies published in other languages may have been overlooked. Despite this, a thorough search strategy was employed to guarantee the acquisition of all relevant studies. There was variation in the robustness of the study, for example, concerning the diagnosis of CIND (including the cognitive tests used) and participant selection criteria, even though many studies were linked to a low risk of bias. The methodology of the studies varied widely, even though they were all population- or community-based. This included differences in the definition of CIND, how the CIND criterion was operationalized, how long the follow-up period was, how conversion rates were reported (either annually or after several years of follow-up), and how dementia was diagnosed. All these factors could have an impact on the findings. The find-

ings highlight the critical need to standardise methodology in CIND research, both in terms of the cognitive assessment protocol and the diagnostic criteria used for each test, to improve study comparability and arrive at a common nomenclature and clinical correlates (Stephan et al., 2020). Until there is a globally agreed-upon methodology for CIND research, the results of evidence synthesis, such as those reported here, should be interpreted with caution.

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