Mild Cognitive Dysfunction: An Epidemiological Perspective With an Emphasis on African Americans

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ABSTRACT

This review begins with a historical accounting of the evolution of the concept of mild cognitive dysfunction, including nomenclature and criteria from Kral to Petersen. A critical analysis of the main elements relating to assessment and diagnosis of mild cognitive dysfunction is provided. Methodological limitations in design, measurement, and characterization, especially as they relate to older African Americans, are identified. Data from a 15-year longitudinal study of community-dwelling African Americans in Indianapolis, Indiana, indicate a 23% prevalence of all-cause mild cognitive dysfunction, with approximately 25% progressing to dementia in 2 years and another 25% reverting to normal cognition in the same interval. Factors contributing to this longitudinal variability in outcomes are reviewed, including the role of medical health factors. The review closes with suggestions for next steps in the epidemiological research of mild cognitive impairment. (*J Geriatr Psychiatry Neurol* 2007;20:215–226)

Keywords: cognition; memory; mild cognitive impairment; dementia; aging; epidemiology

Improved understanding of the pathogenesis of dementia brings renewed hope that scientists might soon discover disease-modifying treatments for this disorder. Initial evidence suggests that such treatments would be most effectively used in the preclinical phase of dementia[1] because the pathologic processes underlying dementia may predate clinical symptoms by many years.[2] Early identification of mild cognitive dysfunction will be critical to any programs directed toward prevention and treatment of dementing illnesses; however, there is substantial inaccuracy in the diagnosis of dementia, and these mistakes in diagnosis are associated with important mistakes in treatment.[3] Calls for even earlier diagnosis and treatment further complicate this situation because the natural history of mild cognitive dysfunction is unclear.

This article attempts to provide a historical accounting of the evolution of the concept of mild cognitive dysfunction, including nomenclature and criteria and a discussion of the areas of overlap and divergence between the different concepts. Following that, we describe the main elements relating to measurement and diagnosis, including the place of subjective complaint and psychometric assessment. Next, the epidemiology (prevalence, incidence, and risk factors) of mild cognitive dysfunction is reviewed, with an emphasis on population studies and presentation of data from a 15-year longitudinal study[4-6] of community-dwelling African Americans in Indianapolis, Indiana. We anticipate that this information will help to summarize current understanding of mild cognitive dysfunction and provide direction for future research.

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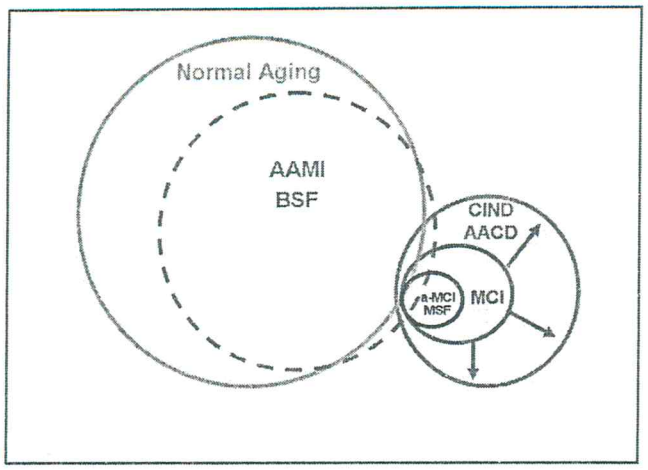

Figure 1. Relationships among cognitive impairment entities. Age-associated memory impairment (AAMI) and benign senescent forgetfulness (BSF) have indistinct borders with normal aging, and this is reflected in the porous outline of the circle separating AAMI and BSF from normal aging. The large size of the circles containing these nonclinical entities reflects the large proportion of the general population contained within. The circles representing cognitive impairment no dementia (CIND) and aging-associated cognitive decline (AACD) vs mild cognitive impairment (MCI) and malignant senescent forgetfulness (MSF) are smaller, reflecting the relative rarity of these clinical disorders compared with the general population of basically cognitively healthy older adults. The enclosure of MCI and amnestic MCI (a-MCI) and MSF within CIND and AACD indicates that these are subsets within CIND and AACD. The expansion of the MCI concept to include nonamnestic and multidomain forms is represented by the outward pointing arrows extending the disorder to be equivalent in scope to CIND.

APPROACHES TO CLASSIFICATION AND NOMENCLATURE

A variety of labels have been applied to the intermediate state between normal cognition and dementia. The first approaches were interview-based and did not rely on psychometric testing. Most current approaches include information from cognitive testing in the diagnostic process, although there are differences in the tests included and the thresholds for impairment.

Interview-Based Approaches

Malignant senescent forgetfulness (MSF) was first described by Kral[7] in 1962 to characterize a subgroup of older patients who had difficulty recalling recent events and who ultimately became globally demented in the span of a few years. Kral distinguished MSF from benign senescent forgetfulness (BSF), which was characterized by occasional and incomplete forgetfulness that did not have a progressive quality and was not qualitatively different from normal aging. The diagnosis was based on clinical bedside examination of the severity and depth of the memory dysfunction. No standardized procedures or explicit diagnostic criteria were enumerated. Malignant senescent forgetfulness is the forerunner of all clinic-based approaches to mild cognitive dysfunction that attempt to refer to a clinically pathologic entity.

In 1982, Hughes and colleagues,[8] and subsequently Morris and colleagues[9-11] and Rubin et al,[12] described a scale for establishing cognitive and functional status of older adults called the Clinical Dementia Rating (CDR). Based on detailed interviews with the patient and with an informant, a clinician rates impairment in each of 6 cognitive categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). The individual category ratings are combined into an overall or a global CDR. In this schema, a CDR of 0 indicates no dementia (normal-range function); a CDR of 0.5, questionable dementia; and CDR scores of 1 through 3, dementia. The CDR stage of 0.5 includes patients with isolated clinically important memory loss comparable to MSF as described by Kral.[7]

Age-Associated Memory Impairment

In 1986, a National Institute of Mental Health work group[13] laid out specific research criteria to operationally define memory loss that occurs in the elderly, called age-associated memory impairment (AAMI). The criteria call for a subjective complaint of memory loss that is gradual and is confirmed by a score on a memory test that is at least 1 SD below the mean for young adults and that occurs in the context of normal intellect and no dementia or neurologic disease. Given the well-documented age-related changes in memory and cognition,[14-20] the use of young adults as a comparison group substantially limits the clinical relevance of AAMI. The distinction between normal aging and AAMI is absent or at least unclear.

Aging-Associated Cognitive Decline

The designation of aging-associated cognitive decline (AACD) was first described in 1994 by the International Psychogeriatric Association in collaboration with the World Health Organization as a means of identifying memory or other cognitive losses that may include the prodrome of dementia, as well as other stable conditions associated with aging.[21] A key distinguishing feature is that cognitive loss is judged relative to age- and education-matched peers, not young adults (as in AAMI). The losses in any cognitive domain (eg, language, abstraction, and visuospatial skill) are also assessed. The criteria for AACD require a subjective report of cognitive decline (from the subject or from an informant) of at least 6 months' duration that is confirmed by a score that is at least 1 SD below age- and education-matched peers and occurs in the absence of known neurologic or psychiatric disease. There is no requirement for a clinical

examination. The psychometric threshold defining impairment is liberal. By definition, performances that are 1 SD below the mean will include 16% of any sample. This lack of specificity has served to limit the clinical relevance of AACD.

Mild Cognitive Impairment

In the mid 1990s, Petersen and colleagues[22,23] and Smith et al[24] at the Mayo Clinic described older adults with isolated memory loss that is normatively rare among matched peers as having mild cognitive impairment (MCI). The criteria for MCI require a subjective memory complaint (by the patient or by an informant), impaired memory function for age (>1.5 SD below the mean), preserved general cognition (Mini-Mental State Examination score, >24/30), intact activities of daily living, and no dementia on examination. Most studies on MCI have used the criteria as part of a clinical diagnosis process, although it has been adapted to an algorithm format in some large-scale studies.[25,26]

The concept of MCI has been expanded recently and allows for the classification of patients with deficits outside the memory domain and patients who have multiple cognitive deficits.[27,28] This phenotypic subtyping approach is based on the number and nature of the cognitive domains affected. The original designation is now called single-domain amnestic MCI to indicate the isolated and memory-dominant nature of the deficit. In addition, there are several single-domain nonamnestic MCI forms in which the deficit might involve linguistic, visuospatial, or executive ability. The possibility of a single patient having multiple deficits is also considered. When memory is 1 of the 2 or more domains involved, it is called multidomain amnestic MCI. When memory is not involved, it is called multidomain nonamnestic MCI. The revised MCI approach allows for the possibility that there may be more than 1 cause of MCI but does not require a cause to be identified.

Cognitive Impairment No Dementia

In 1997, researchers in the Canadian Study of Health and Aging (CSHA) were the first to describe cognitive impairment no dementia (CIND).[29,30] In their large population-based study of predominantly white older adults, the intent was to capture persons with clinically significant impairment on cognitive tests who did not meet criteria for dementia and who were also not cognitively normal. The CSHA used a large battery of neuropsychological tests and age-adjusted norms for interpretation and made clinical diagnoses using a consensus conference format (as opposed to an algorithm).

Epidemiological work has focused on community-dwelling, elderly African Americans living in Indianapolis in the Indianapolis Study of Health and Aging (ISHA); the ISHA is a 2-stage study with more than 2000 subjects and several years of longitudinal follow-up.[4,5] The methods closely parallel those of the CSHA; however, the ISHA has been explicit in presenting the following diagnostic criteria for CIND: (1) informant-reported or clinician-detected clinically significant decline in cognition or (2) cognitive test scores below approximately the seventh percentile of age- and education-adjusted norms and (3) normal-range function in daily living tasks.[6,31]

For the CSHA[29] and the ISHA,[6] CIND subtypes are identified according to presumed cause based on medical history and examination findings. In this approach, prodromal Alzheimer disease (AD) is defined by progressive, prominent, and medically unexplained memory impairment. Similarly, poststroke etiology, alcoholism and substance abuse, medical illnesses, depression, and other causes (eg, neoplasms) can be distinguished.

Summary

The CDR, MCI, and CIND approaches dominate the clinical and epidemiological research on mild cognitive dysfunction (Table 1). Of the 3, only the CDR approach does not use psychometric testing to inform the classification process, and it tends to be closely oriented to memory loss (or at least has less explicit assessment of nonmemory cognitive domains). These limitations diminish the usefulness of the CDR to an extent.

On the other hand, there has been a convergence in concept and methods between MCI and CIND during the past several years. Mild cognitive impairment and CIND allow fully for the possibility that nonmemory cognitive dysfunction may be the sole or primary presenting feature and that memory loss is frequently associated with deficits in other cognitive domains in subjects with mild cognitive dysfunction.[32] Both systems use formal psychometric tests of cognitive ability, have shared thresholds for impairment, and incorporate informant, clinician, and psychometric data in a clinical diagnostic process as opposed to an algorithm. At this point, the MCI and CIND classification schemes will identify substantially the same range of older adults with cognitive dysfunction. These systems differ in their approaches to subtyping (phenotypic for MCI and causative for CIND), and this variation may facilitate research on outcomes such as time to dementia, response to treatment, and correlation with neuropathologic findings. This type of research would help to establish the clinical relevance of mild cognitive dysfunction as a condition and any advantage of one approach over the other.

MEASUREMENT AND DIAGNOSIS

Just as the different research contexts (clinic based vs population based) shape the approach to diagnostic nosology already reviewed, so do the methods related to

Table 1. Methodological Characteristics of Several Approaches to Mild Cognitive Dysfunction

Variable	*Source*	*Cognitive Domain of Interest*	*Information Sources*	*Diagnostic Process*	*Psychometric Threshold-Defining Impairment and Type of Normative Group*
Malignant senescent forgetfulness	Kral[7]	Memory	MD	Clinical	Not applicable, no testing
Benign senescent forgetfulness	Kral[7]	Memory	MD	Clinical	Not applicable, no testing
Age-associated memory impairment	National Institute of Mental Health[13]	Memory	S, T	Psychometric	1 SD below young adult norms
Questionable dementia or clinical dementia rating of 0.5	Memory Aging Project[8,9]	Memory	MD, I	Clinical	Not applicable, no testing
Aging-associated cognitive decline	World Health Organization[21]	All	S/I, T	Psychometric	1 SD below age- and education-adjusted norms
Mild cognitive impairment	Mayo Clinic[22,23]	Memory	MD, S/I, T	Both	1.5 SD below age- and education-adjusted norms
Mild cognitive impairment (expanded)	Mayo Clinic[2728]	All	MD, S/I, T	Both	1.5 SD below age- and education-adjusted norms
Cognitive impairment no dementia	Canadian Study of Health and Aging[29,30]	All	MD, I, T	Both	Age-adjusted norms used. Unclear if education-adjusted norms used. Psychometric threshold defining impairment not specified.
Cognitive impairment no dementia	Indianapolis Study of Health and Aging[6]	All	MD, I, T	Both	1.5 SD below age- and education-adjusted norms

Abbreviations. I, informant interview; MD, physician examination; S, self-report; T, testing.

assessment and diagnosis flow from the different demands and practical needs of each situation, creating variability in approaches and outcomes. Continued cross-disciplinary exchange is crucial to progress in definition and assessment in this area.

Subjective Cognitive Complaint

There is diversity of opinion on the usefulness of subjective complaint in the criteria for cognitive dysfunction. The criteria for AAMI require complaint from the subject, while those for AACD are satisfied by a complaint from the subject or from an informant. A subjective sense of memory loss is not required but can satisfy the complaint criteria for MCI (along with informant-reported memory loss or physician-detected memory loss). Diagnosis of CIND does not require a self-report of memory loss from the subject, which is an adaptation borne of the fact that knowledgeable informants are frequently unavailable in population-based studies. Some investigations indicate clear limitations in the validity of self-report, including the fact that it tends not to be well correlated with psychometric memory performance but is highly correlated with depression.[33] Findings from other studies suggest that self-report of memory loss may represent the leading edge of MCI even before cognitive tests capture impairment[34] and that self-report may have more predictive validity among well-educated subjects and among subjects with incipient memory loss.[35,36] Self-report of memory loss has complex determinants. Studies relying on self-report in the diagnostic criteria require careful interpretation.

Informant Interview

The informant perspective is a fundamental aspect of the CDR,[9] MCI,[22] and CIND[6] approaches. Although informant report of ability loss is not immune to bias,[37] it corresponds to psychometric performance,[37] is superior to subject self-report,[38] and has been shown to have value in predicting incident dementia.[38,39] Documentation of cognitive and functional status via a knowledgeable informant is a critical aspect of the differential diagnosis of age-related cognitive disorders.

Neuropsychological Examination

Objective psychometric assessment of cognition is integral to most approaches to mild cognitive dysfunction. Although a standard battery has not been endorsed, most studies[6,23,29,40,41] attempt to assess major cognitive domains, including attention, memory, language, visuospatial skill, and executive function. Standardized assessments of mood are usually included as well. When subjects are few (eg, in the settings of registries and research centers), the assessment tends to be detailed with multiple tests of a given domain, resulting in administration times of many hours. When the number of subjects to be seen is high, as in epidemiological studies, the total assessment time needs to be shorter, and single tests of a domain may be used. There is no standard neuropsychological battery for MCI or CIND. There is no agreement on the number of tests per domain that should be included in an assessment or on the number of tests within a domain that must be failed to be considered impaired. There is agreement that only relatively

low scores define impairment (ie, 1.5 SD below the mean or below the seventh percentile of age- and education-adjusted norms) and that interpretation of raw scores requires the use of reference samples representative of the target population in terms of age, education, and race/ethnicity.[42,43]

Functional Competence

Self-report of functional competence (activities of daily living) is generally accurate in healthy subjects but is questionable in patients with incipient dementia.[38] Performance-based assessments have the advantage of objective measurement. However, they comprise limited assessment of behaviors and require nonnaturalistic props and context. Dementia research and clinical practice have historically relied on informant-based reporting or ratings in characterizing the daily functioning of patients, but this may be a weakness in the setting of mild cognitive dysfunction, in which the earliest changes in daily function may be represented by subjective difficulty in completing a task rather than by frank inability to perform a task. In addition, there is a clear need for fieldwide consensus on a specified set of tasks, response options, scoring convention, and a cut score that constitutes impairment in daily function. To our knowledge, there is no such standard at this time, which hinders further advances in the field.

Clinician Examination

A clinical examination with a history of the present illness, a mental status examination, and physical and neurological examinations are integral parts of the differential diagnosis and subtyping of mild cognitive dysfunction. A comprehensive assessment is time-consuming and, when performed by a physician, expensive. In the context of research studies, nonphysician clinical staff, after appropriate training and implementation of structured interview methods, can gather the key elements of the clinical examination reliably, validly, and cost-effectively, with the interpretation of the clinical data, diagnoses, and subtyping reserved for the physician and the multidisciplinary care team.

Special Issues in the Assessment of African Americans

A critical requirement is that appropriate norms be used when interpreting test scores of any patient or subject. Inattention to this procedure can result in overestimated rates of cognitive impairment[43,44] and poor diagnostic specificity.[45] Norms should be derived from a pool of community-dwelling persons who function independently and who live in the same community as the target sample under study. Several normative resources for elderly African Americans exist, including studies based on the global screening tests,[46,47] Consortium to Establish a Registry for Alzheimer Disease test battery,[43,48] and traditional clinical neuropsychological tests.[42,44,49-55] Age and education are known to affect cognitive test performance. Racial/ethnic disparities in education are an issue, particularly for older African Americans. Awareness of this has led to innovative studies[42,56-60] probing quality of education, reading ability, and degree of acculturation as factors that affect performance. The practical means of addressing these factors has not been settled, but regression-based approaches could allow for automated and granular accounting of the independent influences of sex, age, education, quality of education, reading ability, and acculturation on test performance.

In older subjects who have no or low literacy, changes to the form of the assessment need to be considered, particularly consideration toward replacing tests of constructional ability involving drawing geometric figures with tests of spatial processing and construction that do not rely on drawing.[61] More work needs to be done to determine the magnitude of the effect of race/ethnicity matched and mismatched examiner-examinee dyads during test administration on performance in subjects older than 65 years. In addition, systematic studies of racial/ethnic differences in informant reporting of functional status are needed.

Summary

Approaches to measurement are driven by the context (eg, clinic-based research vs epidemiological survey). Subjective complaint as a criterion has historical roots in clinical medicine but may have limited usefulness, at least in regard to self-report of cognitive status. For that reason, the informant perspective and cognitive testing are mainstays for the assessment of mild cognitive dysfunction. A thoughtful approach to interpretation of cognitive test scores is required because these are generated from within a cultural context; factors beyond age and years of education completed need to be carefully considered. The use of well-designed local norms will generally address these concerns. The most important remaining gap in methods of assessment is the lack of a gold standard measure for quantifying functional competence (instrumental activities of daily living). To advance, the field needs a single metric and a common cut score identifying impairment. Ideally, the measure of functional competence would be a self-administered questionnaire completed by an informant, with a parallel self-report version. To be most useful, the measure would need to assess all aspects of daily function, recognize sex roles and cultural influences, and not be overly memory-centric in its thrust (recognizing that there are multiple pathways to cognitive dysfunction beyond Alzheimer Disease).

EPIDEMIOLOGY OF MILD COGNITIVE DYSFUNCTION

Epidemiological studies of mild cognitive dysfunction are critical to establishing the dimensions of the condition and its natural history. As will be seen, many factors, including evolving definitions, variable methods, and diverse samples, combine to produce a range of results.

Prevalence and Incidence

The prevalence of cognitive impairment short of dementia is a function of the criteria used, the assessment and diagnostic methods, and the sample. In 5 large-scale epidemiological studies,[6,29,62-64] the prevalence of CIND ranged from 11% to 23%. The study[62] with the lowest prevalence used a 2-stage design but did not sample for false-negative, which creates an underestimate of actual cases. The prevalence of amnestic MCI and questionable dementia ranges from 3% to 27%.[6,25,29,40,41,63-70] Investigations with the highest rates tended to involve very old subjects,[67] a broad definition in which 1 or more of the MCI diagnostic criteria were expanded or dropped,[6,40,67] or the CDR may have included a substantial number of mild dementia cases.[70]

Using weighted logistic regression controlling for age and the probability of selection into the clinical assessment to determine overall and age-standardized CIND prevalence rates, the ISHA[6] found that approximately 23% of elderly community-dwelling African Americans met criteria for CIND; the most common subtype was prodromal AD, which had a community prevalence of 12%. The ISHA prodromal AD subtype corresponds roughly to a combination of single-domain amnestic and multidomain amnestic MCI. The community prevalences of the other CIND subtypes in the ISHA were 4% for medical illness, 3% for stroke, 1% for alcohol abuse, and 2% for other or indeterminate subtype. Increasing age was associated with higher prevalence of CIND (as is the case with dementia). Most important, CIND is much more common than dementia, especially in the younger age groups (up to 7 times more common among those aged 65-74 years) (Table 2).

The ISHA[6] estimate of the prevalence of CIND (23%) is greater than the 17% rate reported in the CSHA.[29] A general diagnostic bias seems an unlikely explanation for the difference because the rates for stroke- and alcohol-related CIND are comparable between the studies, and the prevalence rates for dementia and AD are almost identical.[4,71] Most of the difference in overall rates probably relates to the CIND subtype of prodromal AD (12% in the ISHA vs 5% in the CSHA). The CSHA investigators did not describe the cutoff point that they used to interpret psychometric test scores. If they used a more conservative cutoff point, it would produce a lower prevalence rate for circumscribed memory impairment. Alternatively, the higher rates of medical comorbidity and poor cardiovascular health among African American subjects in the ISHA could have contributed to the excess of CIND cases seen there.

Table 2. Overall and Age-Specific Prevalence Rates for Cognitive Impairment No Dementia (CIND), Dementia, and Alzheimer Disease in the Indianapolis Study of Health and Aging[a]

Age Group, y	*CIND*	*Dementia*	*Alzheimer Disease*
65-74	19.4	2.6	1.6
75-84	27.2	11.4	8.0
85+	30.2	32.4	28.9
Overall	22.9	8.2	6.2

[a] Data are given as percentages and are from Hendrie et al[4] and from Unverzagt et al.[6]

The ISHA[6] prevalence rates are comparable to those reported in a retrospective study[72] of MCI in a mixed racial/ethnic group consisting of non-Hispanic whites, non-Hispanic African Americans, and Hispanics in northern Manhattan, New York; among all subjects, MCI had a prevalence of 28%, and memory-related MCI had a prevalence of 11% (5% for amnestic MCI and 6% for multidomain amnestic MCI).[72] Race/ethnicity did not affect rates in that study.

The cognitive and functional characteristics of community-dwelling older African Americans with diagnosed normal cognition, CIND, and dementia in the ISHA[6] are shown in Figure 2. The cognitive tests have been standardized to z scores by indexing individual scores to the mean ± SD of a normative reference sample.[43] As can be seen, the CIND group's mean cognitive performances are intermediate between those of the healthy and demented groups on each test. In contrast, the right panel of Figure 2 shows the CIND group to be well functioning on instrumental and basic activities of daily living (higher scores on the Blessed scale indicate more dependence in daily function).[6]

Longitudinal Stability

Community- and population-based studies[6,39,40,73-75] indicate that patients with CIND develop dementia at rates ranging from 13% to 48% during 12 to 60 months of follow-up; however, a study[25] with a short follow-up and an algorithm-based approach to diagnosis reported no conversion to dementia after 12 months. Many of these studies have found some degree of reversion to normal cognition in patients initially classified as having CIND. Studies[6,39] with consensus-based clinical diagnosis report reversion rates in the range of 13% to 25%, while studies with algorithm-based diagnosis and shorter follow-up intervals had higher rates of reversion

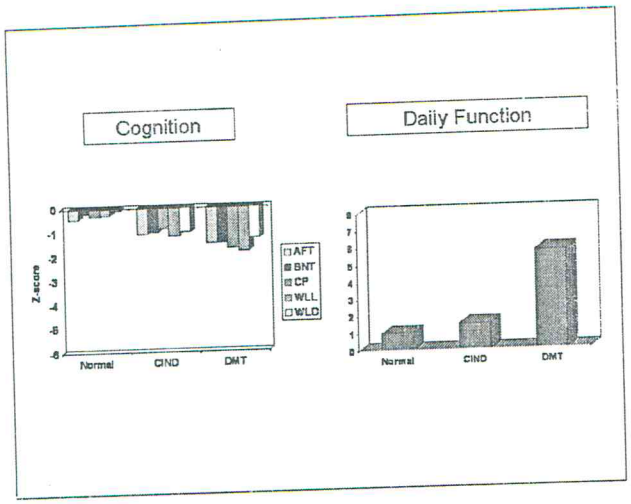

Figure 2. Cognitive test *z* scores and daily function characteristics of community-dwelling clinically assessed subjects in the Indianapolis Study of Health and Aging.[6] AFT indicates Animal Fluency Test; BNT, Boston Naming Test; CIND, cognitive impairment no dementia; CP, Constructional Praxis, DMT, dementia; WLD, Word List Delay; and WLL, Word List Learning.

to normal cognition, up to 93% for MCI[25] and 47% to 52% for CIND and AACD.[74,75] In the ISHA,[6] the rates of conversion to dementia and reversion to normal cognition were steady regardless of whether the subject was identified at the prevalence wave or at subsequent incidence waves. After about 2 ½ years of follow-up, just under one-third convert to dementia; just over one-fourth revert to normal cognition in the same interval (Table 3).

In the ISHA,[6] higher rates of conversion to dementia were seen in CIND subtypes of stroke (43%) and prodromal AD (34%) (Table 4). Rates of reversion to normal cognition were higher in the other or indeterminate (40%) and alcohol abuse (33%) subtypes.

The effect of the CIND criteria on rates of reversion and conversion were evaluated in the ISHA.[6] Among subjects having CIND at baseline, those who met the informant report of decline criterion (a yes response to queries about any evidence of mental, memory, or language decline) had a slightly lower rate of reversion to normal cognition (Table 5). Subjects who met the CIND criterion of cognitive test scores below the seventh percentile of age- and education-adjusted norms reverted to normal cognition at a rate of 24%, while subjects who met the adapted criteria by Petersen and colleagues[22,23] for MCI reverted to normal cognition at a rate of 35%.

Because psychometric test performance loads into the diagnostic criteria of CIND and MCI, a factor to consider in the phenomenon of reversion to normal cognition is statistical regression to the mean. The ISHA[6] examined this possibility by plotting scores from the Word List Learning test (sum of the 3 learning trials) among the subjects having CIND as a function of outcome

Table 3. Longitudinal Outcomes of Cognitive Impairment No Dementia (CIND) Cases at Follow-up in the Indianapolis Study of Health and Aging[a]

		Follow-up Diagnosis, %		
Variable	*No. Seen at Follow-up*	*Normal Cognition*	*CIND*	*Dementia*
Prevalence (n = 106)	67	25	49	25
2-y incidence (n = 26)	13	46	23	31
5-y incidence (n = 61)	21	24	29	48
Total	101	28	42	31

[a] Data are from Unverzagt et al.[6]

Table 4. Longitudinal Outcomes of Cognitive Impairment No Dementia (CIND) in the Indianapolis Study of Health and Aging as a Function of Causal Subtype at Baseline[a]

	Diagnosis at 2-y Follow-up, %	
Baseline CIND Subtype	*Reversion to Normal Cognition*	*Conversion to Dementia*
Prodromal Alzheimer disease	25	34
Poststroke	14	43
Medical or neurologic illness	14	29
Alcohol abuse	33	...
Other or indeterminate	40	10

[a] Data are from Unverzagt et al.[6]

Table 5. Effect of Cognitive Impairment No Dementia (CIND) Criteria on Longitudinal Outcomes in the Indianapolis Study of Health and Aging[a]

	Follow-up Diagnosis, % (n = 92)		
Criterion	*Normal Cognition*	*CIND*	*Dementia*
Informant report	19	51	30
Cognitive test	24	44	33
Amnestic mild cognitive impairment as described by Petersen and colleagues[22,23]	35	29	35

[a] Data are from Unverzagt et al.[6] Cases are collapsed across 3 waves (prevalence, 2-year incidence, and 5-year incidence).

status at baseline (reversion to normal cognition, stable CIND, or progression to dementia). Prevalent and incident cases were plotted separately to see if this factor had any independent effect. As shown in Figure 3, the Word List Learning test scores of the group reverting to normal cognition were stable to slightly improved at follow-up. This group may be a reservoir for some subjects with low-functioning normal cognition and persons who are potentially temporarily medically compromised. On the other hand, the group that ultimately went on to develop dementia clearly declined. Although this does not rule out statistical regression to the mean as a factor in reversion to normal cognition, it suggests that

cognition). There is also concern that rigid application of sometimes arbitrary cutoff scores may produce spurious findings. A consensus conference approach grounded in criteria but allowing for the exercise of clinical judgment seems to produce more solid and reproducible findings.

Finally, there is a need for prospective assessment of cardiovascular health factors in progression from mild cognitive dysfunction to dementia and for better understanding of factors associated with reversion to normal cognition. There is also a critical need to integrate reliable detailed medical information into risk factor analyses. Many older adults have acute and chronic conditions for which clinical manifestations, exacerbations, and treatments may affect performance on cognitive testing. The ability to map years of premorbid and current medical conditions and treatments onto trajectories of cognitive impairment would provide valuable insights into the factors affecting conversion to dementia and reversion to normal cognition.

We seem to be at a critical juncture where disease-modifying treatments for dementia may be at hand. Interventions that could achieve even modest reductions in the rate at which mild cognitive dysfunction converts to dementia would have major public health benefits by avoiding the use of unnecessary and expensive drugs in persons without underlying AD. Accurate information on the risk of conversion to dementia will improve management of the underlying illness, control of comorbid conditions, and planning for long-term concerns. Heterogeneity in the presentation and outcomes of mild cognitive dysfunction reflect, to some degree, variability in the condition and the forces that trigger and maintain it. Recognition of the possibility of non-AD contributions to cognitive impairment and dementia increases the range of factors manifesting as targets for early intervention.

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