Outcomes of Cognitively Impaired Not Demented at 2 Years in the Canadian Cohort Study of Cognitive Impairment and Related Dementias

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Key Words

Dementia · Cognitively impaired not demented · Mild cognitive impairment · Alzheimer's disease · Longitudinal cohort · ApoE

Abstract

Background: People who are cognitively impaired not demented (CIND) can be at an increased risk for developing dementia, but little is known about the natural history of CIND in clinical settings. **Method:** We examined the 2-year outcome of CIND subjects in the Canadian Cohort Study of Cognitive Impairment and Related Dementias. CIND was diagnosed when at least one positive item was endorsed on the DSM-III-R dementia criteria, but not all criteria were met. CIND was further subclassified as: pre-Alzheimer's disease (pre-AD), vascular cognitive impairment (VCI-ND), non-AD degenerative, psychiatric, other neurologic, other medical conditions, mixed disorders and no etiology identified (not otherwise specified [NOS]). **Result:** Of 146 CIND patients with 2-year follow-up data available, 49 (34%) progressed to dementia, while 20 (14%) recovered to not cognitively im-

paired (NCI). Progressors were significantly older than stable CIND and reverts ($p < 0.0001$; mean age = 71.1, 64.3, and 59.1, respectively), and there were significantly ($p = 0.001$) more ApoE $\epsilon 4$ carriers among progressors (67%) than stable CIND (29%) and reverts (12%). Pre-AD CIND and VCI-ND had the highest rate of conversion to dementia (41.0 and 40.0%, respectively), while psychiatric CIND and CIND NOS had highest rate of recovery to NCI (20.0 and 30.0%, respectively). All conversions in pre-AD CIND were to 'probable AD'. **Conclusion:** CIND consists of a heterogeneous group of disorders that can be classified syndromically. Many subclassess – not just those with pre-AD CIND – are at high risk of progression to dementia, usually to Alzheimer's disease.

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Introduction

There is considerable interest in examining the characteristics of the earliest stages in dementia. Changes in cognitive function occur in a continuum from normal aging to dementia, but progression is neither inevitable

nor uniform. Various constructs have been used to define the intermediate stage between normal aging and dementia. Mild cognitive impairment (MCI) depicts subjects with demonstrable impairment in cognitive function who otherwise perform normally on instrumental activities of daily living. MCI criteria initially emphasized memory difficulties [1], and was conceptualized as a precursor to Alzheimer's disease (AD). This was soon revised to reflect that cognitive domains other than memory can be impaired, so that the definition of MCI now includes impairment in non-memory domains and in multiple domains [2]. Another term, age-associated memory impairment (AAMI), has been used to depict elderly subjects with memory complaints substantiated by impairment in tests of recent memory in comparison to norms [3]. However, this broad concept includes individuals who score 1 standard deviation below norms of 'young adults', but may still be considered within the norm for 'older adults' who are otherwise functioning normally in their daily lives [4, 5]. Another construct, age-associated cognitive decline, has been developed to identify individuals who experience cognitive decline but fall short of dementia, and includes people with impairment in memory and learning, attention and concentration, problem solving, abstraction, language, and visuospatial functioning, in relation to healthy individuals of the same age and level of education [6]. In population epidemiologic studies, the term 'cognitive impairment with no dementia' (CIND) [7] has been used to describe subjects who have some positive items on the DSM-III-R [8] checklist (Appendix 1) for diagnosis of dementia, but do not fulfill all the criteria for dementia. In the Canadian Study of Health and Aging, it was estimated that 16.8% of the population over 65 years old suffer from CIND, twice the prevalence of dementia [9]. The diagnosis of CIND has the advantage of being inclusive and comprehensive, spanning the spectrum between normal cognition and dementia, and includes all the categories from which other groupings (amnesic MCI, single-domain and multi-domain MCI, more severe forms of AAMI when memory impairment was clinically significant for age, age-associated cognitive decline) are derived. It is potentially applicable to both epidemiologic and clinical research [10, 11]. However, it is heterogeneous and includes a variety of disorders which may or may not progress to dementia. Little is known about the natural history of CIND in the clinical setting.

The Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD) is a prospective longitudinal cohort of subjects referred to eight dementia

clinics across Canada. The current study describes the 2-year outcome of subjects who were initially diagnosed as CIND at their entry to the study. Factors which may influence the progression of CIND, including demographics and ApoE carrier status, are also examined.

Methods

As detailed elsewhere [12], the ACCORD cohort consists of 1,136 patients newly referred to eight university-based dementia research clinics across Canada with annual follow-up. The patients may be referred from family physicians or other specialists. Consent was obtained at the initial visit. Demented subjects assented and co-consent was obtained from their next of kin, legal guardian, or substitute decision maker as per provincial guideline for consent to research in incompetent subjects. A separate consent was obtained for anonymous ApoE genotyping.

Site investigators diagnosed not cognitively impaired (NCI), CIND, or dementia according to criteria adapted from the DSM-III-R criteria (Appendix 1) [8]. Clinicians were asked to apply clinical judgement in determining the presence or absence of each checklist item of the DSM-III-R taking into account all available clinical, laboratory, neuroimaging and neuropsychological test data. Patients who fulfilled the full criteria of the DSM-III-R were diagnosed as demented ($n = 670$). Subjects were diagnosed NCI, if they did not fulfill any of the DSM-III-R criteria for cognitive impairment ($n = 124$). CIND was diagnosed ($n = 342$) in people with at least one positive item endorsed on the DSM III-R cognitive function checklist, but who did not otherwise meet all the DSM-III-R criteria for dementia. The CIND diagnosis was further subclassified by etiology with all available investigation data. The subclassification categories included pre-Alzheimer disease (pre-AD), vascular cognitive impairment (VCI-ND), non-AD degenerative disorders, psychiatric, other neurological, other medical conditions, mixed disorders, and no clear etiology identified (not otherwise specified [NOS]). CIND subjects who were classified as pre-AD, (referred to as amnesic CIND in the baseline/methods paper [12]) generally had a predominant memory complaint, with no other cognitive domains significantly affected. This may include MCI (MCI-amnesic type and MCI multi-domain type with predominant amnesic features) as defined by Petersen et al. [1, 13], more severe forms of AAMI when memory impairment was clinically significant for age, and CIND with strong family history of AD (two or more affect family members with at least one first degree relative diagnosed with clinical probable or pathologically confirmed AD). Subjects who were classified as VCI-ND had a history of cerebrovascular disease, associated focal neurological signs, or a history of multiple vascular risk factors with neuroimaging evidence of large or small vessels ischemic changes in the brain. VCI-ND data were collected following a protocol for the investigation of vascular cognitive impairment, as detailed previously [14]. The non-AD degenerative CIND group included suspected syndromes of early frontotemporal dementia, Parkinson disease with dementia, Lewy body dementia, corticobasal degeneration, multiple systems atrophy, and progressive supranuclear palsy, but not yet fulfilling their respective diagnostic criteria. Patients with 'psychiatric CIND' had a previ-

Table 1. Baseline characteristics of the CIND cohort

Groups	Attended 2-year follow-up	Lost to follow-up	Died
Subjects	146	190	6
Female (% within group)	73 ± 50.0	95 ± 50.0	3 ± 50.0
Age	65.8 ± 10.4	66.5 ± 11.0	81.3 ± 6.0*
Years of education	12.4 ± 3.8	12.5 ± 4.4	10.8 ± 4.3
MMSE	27.5 ± 2.1	26.3 ± 3.5*	25.5 ± 3.9*
CIRS	4.8 ± 3.5	4.7 ± 3.3	7.2 ± 4.4
FRS	13.8 ± 3.0	14.0 ± 4.1	13.8 ± 2.9
DAD	93.7 ± 10.0	89.0 ± 12.0*	92.0 ± 5.7
NPI	8.6 ± 15.6	11.4 ± 15.2	7.3 ± 7.6

* Denotes significant differences by ANOVA and post-hoc Dunnett test with $p < 0.05$ compared to those who attended follow-up.

ous or current diagnosis of a major psychiatric illness (i.e. depression, schizophrenia) that was felt to be responsible for their cognitive impairment. The 'other medical CIND' subcategory consisted of medical illnesses that were judged to be significantly affecting cognition such as B12 deficiency, hypothyroidism, and chronic alcohol use including Wernicke encephalopathy and Korsakoff syndrome. The category of 'other neurological CIND' included post-encephalitis, cerebral palsy, metabolic leukoencephalopathy, traumatic brain injury, multiple sclerosis, and normal pressure hydrocephalus. The 'mixed CIND' designation consisted of subjects with mixed or multiple causes of cognitive impairment. The remaining CIND patients who had no clear cause identified after extensive clinical evaluation were grouped as 'NOS'.

For those who converted to dementia, the primary cause of dementia (i.e. the cause that was clinically designated as the most significant) was further subclassified based on clinical criteria. AD was diagnosed by NINCDS-ADRDA criteria [15]. Vascular dementia (VaD) was diagnosed based on the presence of history of stroke, neurological signs consistent with previous cerebrovascular accidents, risk factors, or neuroimaging data consistent with stroke or chronic small vessels ischemic changes. Frontotemporal dementia was diagnosed based on criteria published by the Lund and Manchester group [16]. Dementia with Lewy body (DLB) was diagnosed by criteria by McKeith et al. [17].

All patients had detailed clinical evaluations at inception and subsequent visits, including: (1) the Mini-Mental Status Examination (MMSE) [18] – used as a general measure of cognitive impairment, (2) the Functional Rating Scale (FRS) [19, 20] – used as a measure of global severity of dementia, and (3) the Cumulative Illness Rating Scale (CIRS) [21, 22] – used to assess co-morbid medical conditions. Other assessments, where there were available informants, included the Disability Assessment for Dementia (DAD) [23], and the Neuropsychiatric Inventory (NPI) [24]. On both the MMSE (a 30-point scale) and the DAD (a 100 point scale), a higher total score represents better performance, while for the FRS (40 points total), CIRS (maximum 96 points), and NPI (maximum 144 points), the higher the score the worse the rating. Each CIND patient was eligible to have neuropsychological testing, the result of which was not available at the time of the CIND diagnosis by the investigator, but was available at the time of etio-

logical subclassification. The ACCORD data collection was comparable to the clinical assessments for the Canadian Study of Health and Aging [9], and for the Consortium to Investigate Vascular Impairment of Cognition [14].

Our study population consists of people who completed 2 years of follow-up, as well as those who were lost to follow-up. For those who completed the second year assessment, descriptive statistics were used to depict the progression and change in diagnostic category of the cohort. Chi-square test was used to compare proportions between categorical factors. Comparisons of numerical scales were made by analysis of co-variance adjusted for age, sex, and education, with the use of Student-Newman-Keuls test for post-hoc analysis. For comparison of NPI scores which increases geometrically, the natural log of the scores was used for comparison, while the actual mean of the raw scores are presented in the results tables. For the CIND subjects who were lost to follow-up or died, baseline characteristics were compared to those who completed the second assessment using ANOVA with post-hoc Dunnett test.

Results

At 2-year follow-up of the 342 CIND patients, 146 had completed their second annual assessment. Six had died and 190 were lost to follow-up (table 1). In comparing the baseline characteristics of these three groups, those who died were significantly older and had lower total MMSE and DAD scores. When the lost to follow-up group was compared to the group who completed their second assessment, the former had significantly lower total MMSE scores. Otherwise there were no significant differences between the three groups in baseline characteristics and distribution of etiologic subtypes. There were significant differences on loss to follow-up among sites ($p < 0.001$), with two sites accounting for over 50% (96/190) of the

Table 2. Age and baseline clinical rating scales of CIND etiologic subtypes

CIND subtypes (n = 342)	Age	MMSE	CIRS	DAD	FRS	NPI
Pre-AD (n = 88)	69.7 ± 8.4 ^{a, b}	26.6 ± 3.4	4.0 ± 3.1 ^b	93.7 ± 10.8 ^{a, b}	13.0 ± 3.3 ^b	3.9 ± 5.9 ^c
Vascular (VCI-ND) (n = 66)	72.1 ± 9.8 ^a	26.4 ± 3.3	6.5 ± 4.1 ^a	86.3 ± 17.1 ^b	13.8 ± 4.1 ^b	12.6 ± 16.4 ^{b, c}
Psychiatric (n = 59)	61.7 ± 11.5 ^b	26.9 ± 2.6	5.0 ± 2.9 ^{a, b}	85.2 ± 16.8 ^b	15.3 ± 4.2 ^a	18.9 ± 16.7 ^{a, b}
Non-AD degenerative (n = 7)	65.4 ± 9.1 ^{a, b}	27.6 ± 1.6	3.9 ± 4.1 ^b	85.4 ± 19.1 ^b	14.0 ± 3.2 ^b	27.6 ± 30.1 ^a
Neurological (n = 25)	61.5 ± 10.9 ^b	27.2 ± 3.0	4.1 ± 2.8 ^b	92.0 ± 12.1 ^{a, b}	12.8 ± 2.8 ^b	12.0 ± 14.3 ^{b, c}
Medical (n = 11)	71.5 ± 6.0 ^a	26.0 ± 3.3	3.8 ± 1.9 ^b	97.7 ± 3.9 ^a	13.8 ± 2.7 ^b	3.70 ± 5.6 ^c
Mixed (n = 24)	65.5 ± 11.6 ^{a, b}	26.9 ± 2.2	4.1 ± 2.2 ^b	85.9 ± 17.4 ^b	15.3 ± 4.2 ^a	10.9 ± 14.4 ^{b, c}
CIND NOS (n = 66)	62.5 ± 10.6 ^{a, b}	27.2 ± 3.1	4.5 ± 3.9 ^{a, b}	96.7 ± 6.8 ^a	13.4 ± 3.2 ^b	7.2 ± 14.7 ^{b, c}
p value	<0.001	0.95	0.004	0.001	0.004	<0.0001

The p values are obtained by ANCOVA with effect of age, sex, and education included in the model.

^{a-c} Denote groups that are significantly different from each other by post-hoc Student-Newman-Keuls test with p < 0.05.

Table 3. Outcome of CIND at 2 years follow-up by CIND etiologic subtypes

CIND subtypes	Reverters (NCI)	Stable CIND	Progressors (dementia)	Total
Pre-AD	2 (4.4)	25 (55.6)	18 (40.0)	45 (30.8)
Vascular (VCI-ND)	2 (8.0)	13 (52.0)	10 (40.0)	25 (17.1)
Psychiatric	4 (19.0)	12 (57.1)	5 (23.8)	21 (14.4)
Non-AD degenerative	1 (33.3)	1 (33.3)	1 (33.3)	3 (2.1)
Other neurologic	0 (0.0)	5 (71.4)	2 (28.6)	7 (4.8)
Other medical	0 (0.0)	2 (40.0)	3 (60.0)	5 (3.4)
Mixed	1 (14.3)	4 (57.1)	2 (28.6)	7 (4.8)
CIND NOS	10 (30.3)	15 (45.5)	8 (24.2)	33 (22.6)
Total	20 (13.7)	77 (52.7)	49 (33.6)	146 (100)

Figures in parentheses are percentage.

Percentages of reverters, stable CIND, and progressors represent proportions within each CIND subclass (within rows), while percentages in last column represent proportions of total (within column).

loss. However, even when these two sites were excluded in our subsequent analyses, the findings were the same.

We evaluated baseline demographics and test scores of the CIND etiologic subtypes (table 2). The mean MMSE scores were similar across all groups. The VCI-ND and medical CIND were significantly older than the neurological and psychiatric CIND, and those with VCI-ND had the most co-morbid problems. The medical CIND and the CIND NOS group were the least impaired at baseline based on the DAD. The non-AD degenerative CIND had the highest NPI scores, higher even than those of the psychiatric CIND subjects.

Of the 146 subjects who completed a second annual assessment, 49 (34%) progressed to dementia, while 20

(14%) reverted to NCI, and 77 (52%) remained stable. The outcome varied by etiologic subtype (table 3). The pre-AD group was the largest, and with VCI-ND, had the highest rate of conversion to dementia over 2 years at 40.0% each. By contrast, CIND NOS had the highest rate of reversion (30%) to NCI. The numbers in the etiologic subtypes of non-AD degenerative, other neurologic, other medical, and mixed CIND are too small to make meaningful inferences. Overall, patients who progressed to dementia were significantly older (mean age = 71.1, SD = 8.7) and had lower MMSE (mean MMSE = 26.2, SD = 1.72) at baseline compared to the stable CIND (mean age = 64.3, SD = 10.1; mean MMSE = 28.1, SD = 1.7) and reverters to NCI (mean age = 59.1, SD = 9.1; mean

Table 4. Outcome of CIND progressors based on CIND subclassification

CIND subclasses	Primary cause of dementia after conversion					Total
	AD	VaD	FTD	PDD/LBD	Other	
Pre-AD	18 (100)	–	–	–	–	18 (36.7)
Vascular (VCI-ND)	3 (30)	5 (50)	–	2 (20)	–	10 (20.4)
Psychiatric	3 (75)	–	1 (20)	–	1 (20)	5 (10.2)
Non-AD degenerative	–	–	1 (100)	–	–	1 (2.0)
Other neurologic	1 (50)	–	1 (50)	–	–	2 (4.1)
Mixed CIND	2 (100)	–	–	–	–	2 (4.1)
Other medical	3 (100)	–	–	–	–	3 (6.1)
NOS	5 (62.5)	1 (12.5)	2 (25.0)	0 (0.00)	0 (0.00)	8 (16.3)
Total (% of Total)	35 (71.4)	6 (12.2)	5 (10.2)	2 (4.1)	1 (2.0)	49 (100)

Figures in parentheses are percentage.

AD = Alzheimer disease; FTD = frontotemporal dementia; LBD = Lewy body dementia; PDD = Parkinson disease with dementia; VaD = vascular dementia.

MMSE = 28.8, SD = 1.2). However, the sex distribution, level of education, and the baseline total scores on the FRS, DAD, and NPI did not differ significantly among the three outcomes (progressors, stable CIND, and reverts to NCI).

Although the majority (71%) of CIND progressors across all subtypes developed probable AD as the primary cause of their dementing illness, patients who progressed to dementia followed different patterns, depending on their etiologic subtype (table 4). Within the pre-AD CIND, all progressors developed probable AD by NINCDS-ADRDA criteria. For the VCI-ND, 50% developed VaD, while 30% were subsequently diagnosed with AD. Subjects who progressed to dementia had the highest rates of decline on the standard assessments, and those who did not progress showed the least (data not shown). The CIRS indicated significantly more medical decline in subjects with VCI-ND (mean change in CIRS = -0.53 , SD = 1.0) and psychiatric CIND (mean change in CIRS = -0.58 , SD = 2.2), while those with CIND NOS showed an improvement (mean change in CIRS = $+1.0$, SD = 2.8). The changes in DAD, FRS and NPI across the CIND subtypes were not significantly different.

ApoE genotype was available for 74 out of 146 CIND subjects. ApoE $\epsilon 4$ carriers were much more likely to progress to dementia (21/31–67%) compared to the stable CIND (10/35–29%) and reverts (1/8–12.5%). All homozygous $\epsilon 4$ subjects (7/7) converted to dementia at 2-year follow-up. Among non- $\epsilon 4$ carriers, 76% (32/42) remain

stable or improved to NCI. The odds ratio of progression in $\epsilon 4$ carriers compared to non- $\epsilon 4$ carriers is 6.72 (95% CI = 2.93–11.9, $p = 0.001$).

Discussion

We analyzed the outcome of CIND patients referred to specialized dementia clinics across Canada. The data allow for a comparison of CIND as identified and followed in referral dementia clinics with its prevalence and outcome in Canadian population-based epidemiological studies [7, 10, 25, 26]. In the population-based studies of CSHA, CIND had a higher prevalence (16.8%) [7] than the more specified MCI (2.8–4%) [25, 27], reflecting the more restrictive definition of MCI [1, 2, 28] contrasting with the more inclusive nature of CIND. Data from this study show that CIND represents an important proportion (30%) of all subjects referred to specialized memory disorder clinics [12].

The CIND group was heterogeneous in both cause and prognosis, the two were only incompletely related. Although many progressed to dementia (34% over 2 years), most (52%) remained stable at 2 years, with an appreciable 14% improving to be classified as NCI. Our data also show that our CIND subjects have one of the highest rates of conversion to dementia (34%/2 year) that has been reported to date, as compared to other population-based studies (ranging from 11 to 16%/2–3 year [25] to 19.3%/5 year [10]). The ACCORD CIND also have a lower rever-

sion to normal rate (13.9%/2 year) compared to some of the population-based estimates with return to normal rates of 40–55% over 2–3 years [10, 25, 27]. These findings likely reflect on the referral process in the clinical setting. In Canada, patients are referred to specialized memory disorder clinics when their symptoms are sufficiently concerning to either themselves, their families, their family physicians, or their community specialists. This differs from the epidemiological studies where CIND is identified through testing of random population samples, where patient symptoms are not mandatory and where cognitive impairment may be incidentally picked up with cognitive tests. In the centers of the ACCORD, a screening test is often required as part of the referral process. Even though there is no specific 'cutoff' for referral, patients often exhibit some demonstrable objective impairment at the time a referral is made. It is also possible that CIND may be more advanced or more unstable when the referral is requested.

This broad-based approach of CIND allows for inclusion of all subjects who fall between the spectrum of normal cognition and dementia. This is also more applicable to the clinician in the usual care settings where amnesic MCI may account for only 25% of their CIND subjects. In this study, we have furthered the efforts to subclassify CIND into etiologic subtypes [7, 12]. The pre-AD CIND represented 30% of the total CIND population – a finding similar to the PAQUID cohort [27] and the CSHA [7], with MCI representing about 27–33% of all CIND subjects. However, it is not only the pre-AD subtype that converts to dementia. Rather our data demonstrates that despite the clinicians effort to classify the CIND patients into etiologic subtypes, all CIND subtypes can progress to dementia, with high conversion rates as well in the vascular and medical CIND, and lower but still sizable rates in the psychiatric CIND and CIND NOS.

Our data suggest that etiologic subclassification can have prognostic value in predicting the outcome of CIND. All of the pre-AD group who converted to dementia were classified as having clinically probable AD. This indicates that the pre-AD CIND construct, although not sensitive, is a specific predictor of AD. It also suggests that in the future, it may be possible to refine the clinical diagnostic criteria of early AD to allow inclusion of those with pre-AD that have identifiable AD symptoms but not yet sufficiently advanced for formal diagnosis by criteria, perhaps with the aid of forthcoming biomarkers. The pathway to earlier diagnosis for this pre-AD group may reside within the patterns of early higher order functional impairments particularly in the domain of executive dys-

function. Both the psychiatric and NOS groups stand out for their high rates of reversion to NCI and for their least predictable outcomes.

There are however, certain important limitations to our study. A sizable number of CIND subjects ($n = 190$) were lost to follow-up at 2 years from the 342 subjects with CIND at entry. The loss to follow-up within our CIND group was proportional to the loss to follow-up rates in our NCI and dementia groups. Two sites were responsible for over 50% of the loss to follow-up, suggesting variability between sites regarding recontact efforts and techniques. However, when subjects from these two sites were excluded from other analyses, our findings remain the same. In considering the potential bias introduced by those lost to follow-up within our CIND group, we compared the baseline characteristics of missing subjects with those who completed their 2 year assessments, finding that their mean MMSE at entry was significantly lower, and that they were on average more impaired on their global staging, their level of neuropsychiatric symptoms, and their functional assessments. On this basis, we speculate that if there is bias introduced with this lost to follow-up, it is likely to be conservative, underestimating the rate of progression to dementia of the CIND subjects. In comparing the lost to follow-up group with the other CIND groups by outcome, we have noted that their age and MMSE were most similar to the stable CIND, and intermediate between the progressors and reverts to NCI. This again would suggest that the lost to follow-up group likely consisted of a mix of reverts, stable CIND, and progressors. Unfortunately, the number of loss to follow-up also lead to relatively small numbers in some of the CIND subtypes (i.e. non-AD degenerative CIND, medical CIND, and other neurological CIND) limiting any inference from these categories. We are currently conducting a longer-term (6 year) follow-up with the intention of re-engaging the lost to follow-up subgroup to allow for a larger CIND subgroup analysis.

As in the CSHA cohort [29, 30], we found that older age and a lower MMSE score at baseline are strong predictors of progression to dementia, probably because these subjects are at a more advanced stage of their condition. We also showed that homozygous ApoE $\epsilon 4$ status, despite the clinically heterogeneous presentation of CIND, is a strong predictor of conversion to dementia, of which the majority were AD and VaD. Interestingly, there was no obvious distinction between progressors and reverts of CIND by other clinical rating scales at baseline, perhaps reflecting the large variability within each group. However, when we examined the change in these clinical

scales in the 2-year follow-up, there was significant decline in the progressors' functional abilities by DAD, FRS, and NPI, confirming the responsiveness and clinical utility of these scales in measuring progression of dementia.

The current study provides some insight into the natural history of CIND in the clinical setting. CIND is heterogeneous and dynamic. Subclassification of CIND by etiologic syndromes assists with the understanding of the various causes of CIND, helps with predicting the outcome of CIND, and may ultimately identify pathways to specifically manage each subtypes of CIND.

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Appendix 1.

Diagnostic Checklist for NCI, CIND, and dementia (adapted from the DSM-III-R diagnostic criteria for dementia) [8]

Criteria	Yes	No
1 There is impairment in		
a short-term memory, or	☐	☐
b long-term memory	☐	☐
2 There is impairment in at least one of the following higher cortical function such as:		
a insight and judgement	☐	☐
b language problems or aphasia	☐	☐
c apraxia	☐	☐
d agnosia	☐	☐
e constructional difficulty	☐	☐
f personality change	☐	☐
3 Criteria 1 or 2 interfere with at least one of (a) work or IADL		
a social activities	☐	☐
b relationships with others	☐	☐
4 Impairment occur outside episodes of delirium	☐	☐
5 No evidence (from history, physical examination) of specific organic factor(s) that can be etiologically related to the disturbance	☐	☐
6 No other mental disorders (such as major depression) that could explain the change in cognitive function	☐	☐

For ‘No Cognitive Impairment’ (NCI), criteria 1–3 must be all ‘no’.

For Dementia, all criteria 1–6 must be ‘yes’.

For ‘Cognitively Impaired Not Demented’ (CIND) at least one of criteria 1 or 2 is ‘yes’, but not all criteria 1–6.

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