Five-Year Follow-up of Cognitive Impairment With No Dementia

Holly Tuokko, PhD; Robert Frerichs, MSc; Janice Graham, PhD; Kenneth Rockwood, MD; Betsy Kristjansson, PhD; John Fisk, PhD; Howard Bergman, MD; Al Kozma, PhD; Ian McDowell, PhD

Context: The importance of early identification of dementia has prompted numerous investigations of mild cognitive impairment and the preclinical stages of progressive degenerative disorders. To date, there is limited information from large-scale studies regarding outcomes of persons specifically identified with cognitive impairment but no dementia (CIND).

Objectives: To investigate outcomes for persons with no cognitive impairment (NCI) or CIND, focusing on its etiologic subcategories, from the Canadian Study of Health and Aging (CSHA) and to examine the predictive validity of a set of core features thought to be early manifestations of subsequent dementia.

Design: Five-year, longitudinal follow-up of all persons without dementia examined during the first phase of the CSHA in 1991.

Setting: Community and institutional settings.

Participants: Population-based sample of 883 persons with NCI and 801 persons with CIND at the first phase of the CSHA. At follow-up, 517 persons with NCI (59%) and 327 persons with CIND (41%) were alive and received clinical diagnoses.

Main Outcome Measures: Mortality, institutionalization, and clinical diagnoses using the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria for dementia.

Results: Persons with CIND were more likely than those with NCI to die (49% vs 30%), to be admitted to facility care (29% vs 14%), or to receive diagnoses of dementia (47% vs 15%) at follow-up. Those subsequently diagnosed as having dementia were more likely to have had impaired memory, informant-reported change in memory, and functional impairment at baseline.

Conclusions: Persons with CIND were more likely to have a negative outcome than persons with NCI during a 5-year interval. This was true across etiologic subcategories and suggests that the use of specific diagnostic criteria sets does not improve our identification of those who develop dementia compared with a broader, more inclusive approach. More factors contributed to the prediction of all forms of dementia than to AD, but the most accurate prediction was for those who remained dementia free.

Arch Neurol. 2003;60:577-582
neuropsychologists, (2) informant-based report of cognitive decline, and (3) performance in activities of daily living. It was anticipated that memory functioning would be the strongest contributor, but rather than seek the best predictor, our aim was to delineate the predictive utility of the entire set of criteria.

**METHODS**

**SAMPLE**

The CSHA is an ongoing, national, multicenter study of the epidemiology of dementia in persons 65 years and older. In 1991, a representative population sample (N = 10,263) was drawn from provincial electoral records in Ontario and from health insurance records in all other Canadian provinces. The CSHA included people provincial electoral records in Ontario and from health insurance records. The CSHA is an ongoing, national, multicenter study of the epidemiology of dementia in persons 65 years and older. In 1991, a representative population sample (N = 10,263) was drawn from provincial electoral records in Ontario and from health insurance records in all other Canadian provinces. The CSHA included people provincial electoral records in Ontario and from health insurance records.

**OUTCOME MEASURES**

Outcome measures included death, institutional admission, and cognitive status. For participants who had died before CSHA-2, the date and cause of death were obtained from the relevant sources. Only persons who were not in institutional care at the CSHA-1 clinical examination. We excluded (1) people with dementia at CSHA-1 (community n = 402; institution n = 730), (2) persons who screened positive at CSHA-1 but were not clinically assessed (ie, refused or lost to follow-up) (n = 508), and (3) participants from Newfoundland for whom provincial ethical guidelines precluded their participation in CSHA-2 (n = 395). Those who did not participate in CSHA-2 (ie, refusals or lost to follow-up) and those who screened positive at CSHA-2 but were not clinically examined were retained and compared with those who participated (Table 1).

**CORE CRITERIA (PREDICTORS)**

The first core criterion was informant-based report of cognitive decline. An informant was interviewed about the cognitive and medical status of the participant using the Cambridge Examination for Mental Disorders (CAMDEX)—section H. Items referring to general mental functioning and memory were selected for analysis.

---

**Table 1. Description of Participants Diagnosed as Having NCI and CIND in CSHA-1**

<table>
<thead>
<tr>
<th>Characteristics at CSHA-1</th>
<th>NCI (n = 833)</th>
<th>NCI in CSHA-2</th>
<th>NCI in CSHA-2</th>
<th>All CIND</th>
<th>Dead at CSHA-2</th>
<th>Not in CSHA-2</th>
<th>CIND in CSHA-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>78.99</td>
<td>81.55</td>
<td>79.00</td>
<td>77.69</td>
<td>80.61</td>
<td>82.35</td>
<td>78.80</td>
</tr>
<tr>
<td>Screening 3MS score, mean (SD)</td>
<td>81.19</td>
<td>78.44</td>
<td>79.74</td>
<td>82.67</td>
<td>70.95</td>
<td>69.48</td>
<td>71.03</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>9.29</td>
<td>8.9</td>
<td>9.07</td>
<td>9.54</td>
<td>8.23</td>
<td>8.23</td>
<td>8.80</td>
</tr>
<tr>
<td>FLS, mean (SD)</td>
<td>0.38</td>
<td>0.51</td>
<td>0.45</td>
<td>0.31</td>
<td>1.08</td>
<td>1.20</td>
<td>0.62</td>
</tr>
<tr>
<td>Reporting &quot;very good/pretty good&quot; health, %</td>
<td>78.2</td>
<td>66.5</td>
<td>75.5</td>
<td>83.7</td>
<td>71.6</td>
<td>64.6</td>
<td>80.3</td>
</tr>
<tr>
<td>Female, %</td>
<td>61.5</td>
<td>55.9</td>
<td>67.0</td>
<td>63.2</td>
<td>61.2</td>
<td>56.9</td>
<td>64.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** CIND, cognitive impairment, no dementia; CSHA, Canadian Study of Health and Aging; NCI, no cognitive impairment.

*Only the community participants were administered the screening Modified Mini-Mental State Examination (3MS), self-rating of health, and the Functional Limitation Scale score (FLS).
The second core criterion was objective memory (or other cognitive) deficits. A neuropsychologist evaluated participants’ performance (n = 1352) on 12 cognitive measures and identified mild-to-severe impairment of short-term and/or long-term memory and other cognitive domains.9 For those who did not receive the neuropsychological examination (n = 332), this judgment was made on the basis of the 3MS administered by the nurse.

The third core criterion was activities of daily living. The Functional Limitation Scale score (FLS)1 was derived from reported changes in everyday activities from the CAMDEX–section H12 and the participant’s history taken at clinical examination.

The fourth core criterion was self-rating of health. Participants rated their health status on a scale from 1 (very good) to 5 (very poor).

**ANALYSES**

Outcomes

Initially, diagnostic outcomes were tabulated only for those participants who were alive and took part in CSHA-2. Subsequently, those who had died were included in the analyses. Three sources of information were used to estimate the dementia status of persons who died before CSHA-2: (1) death certificates citing dementia as an underlying or contributing cause of death (n = 34); (2) a positive answer to the question “Was [the deceased] ever diagnosed with memory problems, for example Alzheimer’s disease or senile dementia?” asked of a knowledgeable informant (n = 51); and (3) a probability of greater than 0.95 of dementia before death based on a predictive algorithm (n = 177).13 This algorithm was derived on the CSHA-1 sample and validated on a subsample of CSHA participants who died within 5 months of undergoing the CSHA-1 clinical examination.14 Those who met one or more of these criteria were classified as having had dementia (n = 198). Of the 263 NCI persons and the 392 CIND persons who died before CSHA-2, 32 and 35 persons, respectively, did not have data concerning their dementia status.

**Evaluation of Core Features**

A hierarchical logistic regression analysis was performed to assess the predictive value of the core features (ie, objective memory or other cognitive deficits, informant-based report of cognitive decline, and FLS) thought to be indicative of early manifestations of dementia. The core features were entered as blocks in the following order: (1) memory impairment, (2) impairment in other cognitive domains, (3) reported change in mental or general mental functioning, and (4) FLS. All analyses were conducted using SPSS-X statistical software (SPSS Inc, Chicago, Ill).

**RESULTS**

**OUTCOMES**

Death

People identified with CIND at CSHA-1 had a much higher probability of dying than those who had NCI. By CSHA-2, 48.9% of the CIND persons had died, and 29.8% of the NCI persons had died (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.9-2.8). Of the original CSHA-1 clinical sample, 59% of those with NCI and 41% of those with CIND were alive and took part in CSHA-2 (Table 1). The NCI persons participating in CSHA-2 were significantly younger (P < .001), had a higher 3MS screening score (P < .001), and had better self-reported health (P < .001) than those NCI persons who had died. Among those with CIND at CSHA-1, those who participated in CSHA-2 were younger (P < .001) and in better health (P = .01) than those who had died.

**Institutional Admission**

Follow-up data concerning institutional admission were available for approximately 70% of participants who resided in the community at CSHA-1 (n = 1684) (1152; NCI persons = 708 and CIND persons = 444). We found that 29% of people with CIND at CSHA-1 were institutionalized at CSHA-2, whereas 14% of people with NCI at CSHA-1 were institutionalized at CSHA-2 (OR, 2.5; 95% CI, 1.9-3.3).

**Progression to Dementia**

Overall, persons with CIND were 5 times more likely to develop dementia or AD by CSHA-2 than persons with NCI (OR for dementia, 5.3; 95% CI, 3.8-7.4; OR for AD, 5.0; 95% CI, 3.4-7.3). The proportion of those progressing to AD (n = 159) vs all other forms of dementia (n = 71) did not differ between those with NCI and CIND at CSHA-1 (OR, 0.8; 95% CI, 0.4-1.5; Table 2). When the data on dementia status for the decedents were included, estimates for dementia outcome yielded similar findings (NCI persons = 18%; CIND persons = 43%).

For both the NCI and CIND groups, cognitive decline was associated with older age, lower 3MS score, lower education, and more functional disability at baseline (Table 3). Those with NCI who progressed to CIND were more likely to report fair or poor health at CSHA-1 than those who remained unimpaired (P < .05).

Table 4 shows the diagnostic outcomes by subcategory of CIND. Although the percentages vary modestly among groups, dementia was not a more frequent outcome for any one subcategory (P > .25).

**EVALUATION OF CORE FEATURES**

The logistic regression analysis, shown in Table 5, included 662 persons (424 NCI persons, 238 CIND persons) for whom no data were missing on the predictor variables for identifying persons who develop demen-
tia. With all of the core features included in the equation, 78.6% of the cases were correctly classified: 93% of persons remaining without dementia over time and 32% of those who developed dementia after 5 years.

Persons identified with memory impairment at CSHA-1 were 3 times more likely to develop dementia than persons without memory impairment (OR, 3.2; 95% CI, 2.1-5.0). The presence of other cognitive impairment did not contribute to the equation. Similarly, those with family report of memory impairment were twice as likely to develop dementia as those whose families reported no impairment (OR, 2.1; 95% CI, 1.3-3.2), but a family report of change in general mental functioning did not contribute significantly (OR, 1.6; 95% CI, 1.0-2.5). Impairment in activities of daily living at CSHA-1 was related to the probability of having dementia at CSHA-2 (OR, 1.2; 95% CI, 1.1-1.5); this means that the likelihood of having dementia increased by 1.2 with impairment in each activity. The overall results did not differ when age, education, and sex were entered into the model.

When the same analyses were performed using only cases with AD (n=106), 83.4% of cases were correctly classified: 93% of persons remaining without dementia over time and 32% of those who developed dementia after 5 years.

### Table 3. Description of CSHA-1 Participants Diagnosed as Having NCI, CIND, and Dementia at CSHA-2*

<table>
<thead>
<tr>
<th>Characteristics at CSHA-1</th>
<th>NCI at CSHA-1 (n = 517)</th>
<th>CIND at CSHA-1 (n = 327)</th>
<th>Dementia at CSHA-2 (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76.1 A (6.1)</td>
<td>78.6 B (6.9)</td>
<td>82.2 C (5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Screening 3MS Score, mean (SD)</td>
<td>85.6 A (10.5)</td>
<td>79.3 B (9.6)</td>
<td>77.3 C (9.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>10.1 A (4.1)</td>
<td>9.0 B (4.1)</td>
<td>8.5 B (3.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>FLS, mean (SD)</td>
<td>0.24 A (0.6)</td>
<td>0.33 AB (0.7)</td>
<td>0.58 B (1.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Reporting “very good/pretty good” health, %</td>
<td>86.9 A (6.0)</td>
<td>77.0 B (6.7)</td>
<td>69.3 AB (9.1)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

**Abbreviations:** CIND, cognitive impairment, no dementia; CSHA, Canadian Study of Health and Aging; NCI, no cognitive impairment.

**P** values that do not share common letters (eg, A, B, C) differ at **P**/H11021 <.05 in post hoc difference comparisons.

### Table 4. Status at CSHA-2 for Participants Diagnosed Within the Subcategories of CIND in CSHA-1

<table>
<thead>
<tr>
<th>CIND Subclassification at CSHA-1</th>
<th>Status at CSHA-2, %</th>
<th>Dead</th>
<th>Nonparticipant</th>
<th>NCI</th>
<th>CIND</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium (n = 10)</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Long-term alcohol or other drug use (n = 56)</td>
<td>44.6</td>
<td>17.9</td>
<td>7.1</td>
<td>14.3</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>Depression (n = 63)</td>
<td>50.8</td>
<td>11.1</td>
<td>2</td>
<td>20.6</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder (n = 50)</td>
<td>34</td>
<td>10</td>
<td>2</td>
<td>36</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>AAMI* (n = 210)</td>
<td>51.4</td>
<td>9.5</td>
<td>7.1</td>
<td>9.0</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Mental retardation (n = 19)</td>
<td>26.3</td>
<td>0</td>
<td>5.3</td>
<td>47.4</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>Other† (n = 197)</td>
<td>49.9</td>
<td>10.1</td>
<td>4.8</td>
<td>15.9</td>
<td>19.2</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AAMI, age-associated memory impairment; CIND, cognitive impairment, no dementia; CSHA, Canadian Study of Health and Aging; NCI, no cognitive impairment.

*Not defined by criteria; relabeled as circumscribed memory impairment by Graham et al.1
†Includes cerebrovascular, general vascular, Parkinson disease, multiple sclerosis, epilepsy, brain tumor, sociocultural, social isolation, and sensory loss.

### Table 5. Final Step in the Hierarchical Logistic Regression Predicting Dementia or No Dementia at CSHA-2 From Core Features

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Wald</th>
<th>P Value</th>
<th>R*</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician observed memory impairment</td>
<td>1.16</td>
<td>27.17</td>
<td>&lt;.001</td>
<td>0.20</td>
<td>3.20 (2.07-4.95)</td>
</tr>
<tr>
<td>Clinician observed impaired cognition</td>
<td>0.31</td>
<td>1.93</td>
<td>.16</td>
<td>0.00</td>
<td>1.37 (0.88-2.13)</td>
</tr>
<tr>
<td>Informant report of change in memory</td>
<td>0.72</td>
<td>10.79</td>
<td>.001</td>
<td>0.12</td>
<td>2.06 (1.34-3.17)</td>
</tr>
<tr>
<td>Reported Functional Limitations Scale score</td>
<td>0.45</td>
<td>3.76</td>
<td>.53</td>
<td>0.05</td>
<td>1.56 (1.00-2.45)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CSHA, Canadian Study of Health and Aging; OR, odds ratio.

*The total **R** was 0.44 and **R**^2 was 0.19.
classified (97% of persons remaining without dementia over time and 16% of the cases classified with AD). People identified with memory impairment were approximately 4 times more likely to develop AD than persons without memory impairment (OR, 3.9; 95% CI, 2.4-6.5), whereas those with family report of change in memory were twice as likely to develop AD than those without family-reported memory impairment (OR, 2.3; 95% CI, 1.4-3.8).

Data from the CSHA indicate that persons with CIND were more likely than persons with NCI to have died, entered an institution, or progressed to dementia at 5-year follow-up. Despite the heterogeneity of the CIND category, rates of progression to dementia were not substantially different among etiologically defined subgroups; decline seemed prevalent and nonspecific. These progression conversion rates to dementia refer to the percentage of the sample being followed up in each study. They are not population estimates and should not be interpreted as incidence rates.

Our finding that 14.5% (or 17.8% including decrease in cognition) of persons with NCI progress to dementia during 5 years is similar to other reports in the literature. In our study, just less than half of the CIND cases progressed to dementia or AD during 5 years; this is similar to rates shown in other studies with follow-up intervals of 4 to 5 years (47.6%-68.8%). Perhaps the most striking feature of our results is the consistency in the rates of progression to dementia across subgroups of CIND formed on the basis of presumed cause. That is, not only did those persons with apparent AAMI or circumscribed memory impairment develop dementia but also did those with cognitive impairment attributable to other identifiable disorders, such as depression, long-term alcohol use, mental retardation, and vascular conditions. Much emphasis has been placed on the development of sets of criteria for identifying specific entities, similar to our AAMI/CMI group (eg, MCI), predictive of dementia. Our results suggest that this approach may not be prognostically relevant.

There are several methodologic and conceptual factors that need to be considered when evaluating the results. First, the diagnosis of CIND at CSHA-1 was based on clinical judgment rather than reliance on formal inclusion criteria. This approach is broad and inclusive. In fact, previous research has demonstrated that few of the CSHA-1 CIND diagnoses were captured when criteria sets were applied to the data post hoc. This suggests that existing diagnostic criteria sets may be hindering our broader understanding of cognitive impairment rather than aiding it. As yet, it seems that criteria sets do not improve our identifications of those who develop dementia over this broader, population-based approach.

For these reasons, it was important for us to examine those criteria that have been identified in the literature as early manifestations of subsequent dementia. Of the core features examined, memory impairment, informant report of change in memory, and functional disability were significantly related to the diagnosis of dementia at CSHA-2. This is not surprising because these criteria are central to the diagnosis of dementia but, like other recent investigations, draw attention to the importance of functional impairment. The neuropsychologist’s observation of other cognitive impairment and the informant report of impairment of general mental functioning did not contribute to the diagnosis of dementia. Although the base rate of occurrence is low, cases exist in which cognitive impairments other than memory impairment are the first manifestation of a dementia. For this reason, it may still be clinically worthwhile to note other cognitive impairment when assessing persons who may be developing dementia.

The relative importance of the criteria we examined changed when analyses were restricted to include only AD. Only indicators of memory impairment contributed significantly to the prediction model. This speaks to the questions posed by Ritchie and Touchon regarding the implications of identified cognitive impairment and suggests that different predictors are related to different forms of dementia. The MCI criteria that focus on memory impairment may be most useful in identifying those likely to manifest AD, whereas criteria that include a broader range of features (eg, aging-associated cognitive decline) may be more predictive of dementia in general.

Although 87.6% of cases were correctly classified using the criteria, the identification of dementia or AD using our prediction models was poor. The value of the model lies in the identification of a subset of cognitively healthy individuals who have a high likelihood of maintaining intact cognitive functioning during a 5-year interval. These people may contribute to our understanding of the spectrum of cognitive functioning in older adults through the development of more robust normative and control samples. Alternatively, factors other than cognitive performance may prove to be most important in the prediction of dementia.

A related conceptual issue is whether it is cognitive impairment or cognitive loss that is predictive of future decline. In our study, persons classified as having CIND exhibited poor cognitive performance at a specific point. However, it is possible that it is not level of impairment in cognition that will predict dementia but the rate at which a person is experiencing cognitive decline. If so, we may need to focus more actively on applying methods for assessing reliable change because they account for variability in performance due to measurement error and practice effects. The effectiveness of these alternative approaches is yet to be determined.

There are numerous possible limitations to our study, including the manner in which we chose to operationalize the core criteria; the limited sample (ie, subset only) used to examine the utility of the core criteria for predicting dementia; the length of interval between the 2 phases of the CSHA (ie, 5 years), which may be insufficient to adequately detect progression to dementia over time; and the narrow range of criteria examined as predictors.

Despite these potential limitations to our study, our findings underscore the importance of CIND-related constructs in terms of their relevance to the identification of poor outcomes. The findings suggest that different predictors may be indicative of different forms of dementia.
but challenge the prognostic relevance of specific criteria sets. To move beyond the restrictions imposed by this limited approach, we need to reevaluate how we conceptualize and study these issues.

Accepted for publication July 17, 2002.

Author contributions: Study concept and design (Drs Tuokko, Graham, Kristjansson, Fisk, Kozma, and McDowell); acquisition of data (Drs Tuokko, Graham, Rockwood, Kristjansson, Fisk, Bergman, Kozma, and McDowell and Mr Frerichs); drafting of the manuscript (Dr Tuokko and Mr Frerichs); critical revision of the manuscript for important intellectual content (Drs Tuokko, Graham, Rockwood, Kristjansson, Fisk, Bergman, Kozma, and McDowell and Mr Frerichs); statistical expertise (Drs Tuokko, Graham, and Rockwood and Mr Frerichs); obtained funding (Drs Tuokko, Rockwood, Fisk, Kozma, and McDowell); administrative, technical, and material support (Drs Tuokko, Graham, Rockwood, Kristjansson, and McDowell); study supervision (Dr Tuokko).

The CSHA was funded by the Seniors’ Independence Research Program through the National Health Research and Development Program (NHRDP) of Health Canada (project 6606-3954-MC[S]). Additional funding was provided by Pfizer Canada Incorporated through the Medical Research Council/Pharmaceutical Manufacturers Association of Canada Health Activity Program, NHRDP (project 6603-1417-302 [R]), Bayer Incorporated, and the British Columbia Health Research Foundation (projects 38 [93-2] and 34 [96-1]). The Alzheimer’s Society of British Columbia provided funding to support Mr Frerichs and Alzheimer Canada provided funding to support Dr Kristjansson in the preparation of the manuscript.

The study was coordinated through the University of Ottawa and the Division of Aging and Seniors, Health Canada. We thank David Hogan, MD, for his comments and feedback.

Corresponding author and reprints: Holly Tuokko, PhD, University of Victoria, Centre on Aging, Sedgewick Building, Room A104, PO Box 1700 STN CSC, Victoria, British Columbia V8W 2Y2, Canada (e-mail: htuokko@uvic.ca).

REFERENCES


