SHORT REPORT

Outcomes of incident mild cognitive impairment in relation to case definition

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Definitions of mild cognitive impairment (MCI) vary, yielding conflicting results. For example, case definitions affect prevalence but not outcomes in prevalent cases. Our objective was to determine whether variation in case definitions affects outcomes in incident cases of MCI. The 5 year risks of death, institutionalisation, and dementia were evaluated in clinically examined incident MCI cases in the Canadian Study of Health and Aging. The definition of MCI was varied so as to include or relax combinations of diagnostic features from consensus criteria. Relative risks (RR) of each adverse outcome were highest in MCI case definitions that required subjective memory complaints (for example, RR of dementia = 26.4–38.7). Although each MCI definition conferred an increased risk of dementia, for each case definition 20–30% of survivors had no cognitive impairment at follow up. In this population based study, MCI represented a transitional state, but was heterogeneous, with substantial proportions recovering, regardless of how MCI was defined. Factors associated with recovery and non-progression in MCI require elucidation.

Mild cognitive impairment (MCI) is common and important.[1 2] Classically defined MCI,[3 4] reflecting largely the experience of memory clinics, implies a progression to dementia that is gradual but relentless amongst those who survive long enough. By contrast, population based studies[1 5–9] show that an important proportion of people diagnosed with MCI are either stable or recover.[10].

To help understand which factors might account for outcomes other than relentless progression to dementia, we previously evaluated the impact of key features of the diagnostic criteria of MCI on outcomes in the Canadian Study of Health and Aging (CSHA).[1] In prevalent cases, we found that the strict definition of MCI (that is, people with a subjective memory complaint who had objective memory deficits and no functional impairment) yielded the lowest prevalence (1.03%) of MCI. Relaxing various diagnostic features (except for an objective memory deficit) increased the prevalence (to 3.02%). Regardless of the case definition, however, about 25% of people with MCI at baseline had a consensus diagnosis of no cognitive impairment (NCI) 5 years later.

Compared with prevalent cases, incident cases are more likely to represent transition states, and hence would show a greater progression to dementia. Moreover, the transition to MCI within a population based sample might better simulate the clinical situation, in which patients seek help for newly identified problems. We therefore evaluated the effect on outcomes of varying the case definition of incident MCI in the CSHA.

METHODS

The population based CSHA cohort, as described elsewhere,[1 2 11–13] was assembled from 1991 to 1992 (CSHA-1) and re-assessed at 5 (CSHA-2) and 10 (CSHA-3) years. MCI was not an initial diagnostic category, but was derived from the clinical database, which specifically included a clinically diagnosed "cognitive impairment, no dementia" (CIND) category.[1 2] Subjects were required to have memory impairment but no other cognitive impairment on neuropsychological testing. They could not have a consensus diagnosis of dementia and could not have problems in self care activities. Four overlapping MCI subgroups were created by varying the requirements for subjective memory complaints and intact instrumental activities of daily living (IADL) (MCI-1, memory complaints and intact IADL; MCI-2, memory complaints and some IADL impairment; MCI-3, no memory complaints and intact IADL; MCI-4, no memory complaints and some IADL impairment).[1]

Participants

The cohort included the 460 people who had NCI at CSHA-1 and who were evaluated by clinical and neuropsychological examination at CSHA-2, where they had diagnoses either of NCI or MCI. The four MCI case definitions identified groups of 19–39 people (table 1). Vital status is known for all subjects. Of the 368 who were alive at CSHA-3, six could not be contacted (1.6%), 25 refused (6.8%), and 29 (7.8%) did not complete the clinical assessment.

Analysis

The 5 year outcomes following CSHA-2 included death, incident institutionalisation, and a diagnosis of dementia for survivors. The assumption of proportional hazards was tested and verified, and the Cox regression model was used. Relative risks (RR) were adjusted for age, sex, and education. Direct statistical comparison of the MCI groups is not possible as the groups overlap. The CSHA was approved by the ethics committees of all participating institutions and the secondary analysis by the Capital District Health Authority, Halifax, Nova Scotia.

RESULTS

There was little difference in the clinical and demographic characteristics of the various MCI groupings (table 1).

People with incident MCI, however defined, were not at increased risks of death or institutionalisation, but all MCI survivors were at increased risk of dementia after 5 years (table 2). There were no significant differences between groups in the proportions lost to follow up or the reasons for their being lost.

Abbreviations: CIND, cognitive impairment, no dementia; CSHA, Canadian Study of Health and Aging; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; NCI, no cognitive impairment; RR, relative risks

Table 1 Characteristics of subjects with NCI and four incident MCI subgroups at CSHA-2

Characteristics	NCI, n = 460	MCI-1, n = 19	MCI-2, n = 22	MCI-3, n = 36	MCI-4, n = 39
Mean age (SD)	75.7 (6.5)	77.7 (5.6)	77.9 (6.3)	76.9 (6.4)	77.1 (6.7)
% Female	60.6	47.4	45.4	50.0	48.7
Mean years of education (SD)	11.2 (3.9)	10.0 (4.3)	10.9 (4.7)	10.3 (4.0)	10.8 (4.3)
% Residing in institutions	9.1	5.3	4.6	2.8	2.6
Buschke Delayed Free Recall	10.0 (1.7)	7.1 (3.5)	6.5 (3.6)	7.4 (3.0)	7.1 (3.1)

While the small number of subjects means large, overlapping confidence intervals, the risk of dementia was highest for MCI case definitions that required subjective memory complaints (that is, MCI-1, MCI-2). The proportion of survivors with dementia was also highest in these groups while the proportion with CIND was lowest. Regardless of the case definition, however, 20–30% of survivors with MCI had NCI after 5 years.

DISCUSSION

In this population based study, incident MCI was associated with an increased risk of dementia, regardless of the case definition. In keeping with other population estimates,[4–7], but in contrast with clinical studies, about one person in four with incident MCI had NCI 5 years later.

Our study must be interpreted with caution. Although population based at inception, by the 10 year follow up the cohort is no longer representative and the small numbers of cases yield large confidence intervals. On the other hand, while the numerators are small, the denominators are large, the sample has been carefully characterised, and we report long term outcomes internally consistent with the prevalence data.[1 14]

There are many reasons why population based samples are more likely to improve, while clinical samples typically show uniform progression. As Petersen has pointed out, there are important conceptual and practical difficulties in ''retrofitting'' the consensus criteria to epidemiological studies that were not designed to diagnose MCI by the consensus criteria.[15] Pragmatically, not all relevant variables might be available, or those that are available might be incompletely specified. Conceptually, the consensus criteria incorporate clinical judgment and are not derived just from test cut points. In that context, we note that the CSHA criteria for MCI, CIND, and ''dementia'' each incorporated clinical judgment that was based on extensive clinical[12] and neuropsychological[13] evaluations.

An additional issue in population studies of MCI is the impact of screening which is particularly relevant in considering the role of a subjective memory complaint. An analogy exists in cancer epidemiology, in which lead time and length biases are recognised as distorting the impact of screening.[16]. People with slowly progressive cancer are more likely to be detected by screening than are those in whom cancer progresses rapidly. They have a more favourable prognosis, either because their disease was detected earlier in its course (lead time bias) or because their illness is more slowly progressive (length bias). Either bias allows both a higher likelihood of screening (especially with relevant symptoms) and a higher likelihood of survival. In our sample, the two MCI definitions with a subjective memory complaint had a higher, clinic-study-like rate of progression to dementia. Thus, it is possible to imagine grades of risk, with the lowest risk being no subjective or objective impairment, followed by an increased risk from objective memory impairment without a subjective complaint, to objective memory impairment *and* a subjective complaint that motivates a person to become a patient. What determines the latter remains unclear. Memory complaints, memory impairment, and IADL impairment are unlikely to be the only factors contributing to a continuum of risk for the development and progression of cognitive decline.[17] At least three studies of mild Alzheimer's disease have reported that many cases (about one in seven) show only slow progression.[18–20] In short, stable or slowly progressive MCI might be part of a spectrum of slowly progressive cognitive disorders. Learning again from cancer epidemiology, it would clearly be preferable to investigate a phenomenon with continuously distributed exposures and outcomes rather than binary ones.

CONCLUSIONS

In elderly people, MCI represents a transitional state between NCI and dementia, but remains heterogeneous in its composition and outcomes. People with MCI come from a larger CIND pool[2] and while there is merit in refining the MCI definition to identify people at increased risk, it should not be so narrowly circumscribed that it simply (and circularly) identifies very mild Alzheimer's disease. A definition that yields heterogeneous outcomes is unlikely to be circular and represents potential opportunity to evaluate modifiable components. Prognostic factors, including those that are associated with improvement, require further elucidation and are motivating additional inquiries by our group.

Table 2 Relative risk estimates (adjusted for age, sex, education) for institutionalisation, death, and development of dementia after 5 years, for subjects in each incident amnestic MCI subgroup compared to subjects with NCI

	Diagnosis (no. of survivors with diagnostic data)				
	NCI (n = 287)	MCI-1 (n = 9)	MCI-2 (n = 10)	MCI-3 (n = 20)	MCI-4 (n = 21)
RR of death*	–	2.0 (0.7–5.5)	1.8 (0.7–4.7)	1.5 (0.7–3.3)	1.5 (0.7–3.1)
RR of institutionalisation*	–	1.1 (0.5–2.2)	1.3 (0.8–2.1)	1.3 (0.7–2.3)	1.3 (0.8–2.0)
RR of dementia for survivors*	–	38.7 (6.7–223.6)	26.4 (5.6–124.9)	6.6 (2.3–19.2)	6.2 (2.2–17.8)
% NCI	61.0	22.2	20.0	30.0	28.6
% CIND	28.6	0.0	10.0	30.0	33.3
% Dementia	10.4	77.8	70.0	40.0	38.1

*Values in parentheses are 95% confidence intervals.
The proportions of various incident amnestic MCI subgroup survivors with no cognitive impairment (NCI), cognitive impairment, no dementia (CIND), and dementia after 5 years are shown.

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