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 studies1,5–9 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
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, but in contrast with clinical studies, about one person in four were not designed to diagnose MCI by the consensus criteria. For the sample has been carefully characterised, and we report long term outcomes internally consistent with the prevalence data.

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 “retro-fitting” the consensus criteria to epidemiological studies that were not designed to diagnose MCI by the consensus criteria. 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 and neuropsychological 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 was motivated by additional inquiries by our group.

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 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>
<thead>
<tr>
<th>Characteristics</th>
<th>NCI, n = 460</th>
<th>MCI-1, n = 19</th>
<th>MCI-2, n = 22</th>
<th>MCI-3, n = 36</th>
<th>MCI-4, n = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>75.7 (6.5)</td>
<td>77.7 (5.6)</td>
<td>77.9 (6.3)</td>
<td>76.9 (6.4)</td>
<td>77.1 (6.7)</td>
</tr>
<tr>
<td>% Female</td>
<td>60.6</td>
<td>47.4</td>
<td>45.4</td>
<td>50.0</td>
<td>48.7</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>11.2 (3.9)</td>
<td>10.0 (4.3)</td>
<td>10.9 (4.7)</td>
<td>10.3 (4.0)</td>
<td>10.8 (4.3)</td>
</tr>
<tr>
<td>% Residing in institutions</td>
<td>91</td>
<td>5.3</td>
<td>4.6</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Buschke Delayed Free Recall</td>
<td>10.0 (1.7)</td>
<td>7.1 (3.5)</td>
<td>6.5 (3.6)</td>
<td>7.4 (3.0)</td>
<td>7.1 (3.1)</td>
</tr>
</tbody>
</table>

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

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

*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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