Mild Cognitive Impairment in the Population and Physical Health: Data on 1,435 Individuals Aged 75 to 95

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Background. The physical health correlates of mild cognitive impairment (MCI) in the older individual are poorly known. The aim of this study was to investigate the relationship between physical health and MCI with population data.

Methods. Subjects were 1,435 nondemented 75- to 95-year-old subjects. MCI was defined as scoring one standard deviation below age- and education-specific means on the Mini-Mental State Examination. MCI was consistently associated with indicators of poorer health in logistic regression models with adjustment for potential confounders.

Results. The adjusted odds ratios for those with two, three, four, or more somatic symptoms compared with those with one or no symptoms were 1.3 (95% confidence intervals 1.0 to 1.9) and 2.1 (1.2 to 4.5; *p* for trend < .004); for those with poor self-rated health the odds ratio was 1.9 (1.4 to 2.6); for those with one, two, or more chronic diseases compared with those with no chronic diseases, the odds ratios were 1.3 (0.9 to 1.9) and 3.0 (1.2 to 7.6; *p* for trend = .02); and for those dying during the 3-year follow-up period the odds ratio was 1.5 (1.1 to 2.2).

Conclusions. MCI is associated with poor physical health, leading to the hypothesis of a causal relationship between physical diseases and MCI in older populations.

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Conclusions. MCI is associated with poor physical health, leading to the hypothesis of a causal relationship between physical diseases and MCI in older populations.

Cognitive impairment and dementia are major public health issues. Dementia-associated disability accounts for the largest proportion of disability in daily activities in the older population (1), and it has been estimated that the proportion of disability that is due to cognitive impairment will increase by 60% in the next 40 years (2). The recent availability of drugs that improve cognitive impairment that is due to neurodegenerative diseases (3) has kindled new interest in research on the milder degrees of cognitive deterioration that are not severe enough to qualify as, but might be prodromal of, dementia [mild cognitive impairment (MCI)]. However, it is still unclear whether the majority of persons with MCI are affected by a neurodegenerative disorder in its initial phase or whether other conditions are at stake.

Some observations suggest that poor physical health might be involved in the very early stages of cognitive deterioration. Literature data indicate that subjects with clinically evident nonneurological conditions can show selective or general cognitive problems (4–8), suggesting that the origin of their cognitive disturbance might not be primarily neurological. In epidemiological populations, general vascular and cerebrovascular disease (9) as well as greater mortality (10–13) have been reported to be frequently associated with MCI. Studies specifically focusing on health in MCI subjects are, however, not available.

Moreover, methodological problems have hampered research on this issue. All the authors agree that MCI should be defined as cognitive performance below normal in the absence of dementia, but a number of definitions of normality have been used. It has often been suggested that normality should be defined on the basis of the subject’s age and educational background (14). However, this has rarely been accomplished.

The aim of the present study is to test the hypothesis that MCI in the older individual is associated with poorer health. Global indicators of health and a definition of MCI that takes into account age and education will be used.

Methods

Study Population and Design

These data come from a study initiated in 1987 (the Kungsholmen Project) and aimed at assessing the prevalence and incidence of dementia in the general population (15). A detailed description of subject recruitment, evaluation, and follow-up can be found elsewhere (15). Here we briefly summarize the issues most relevant to the present study.

The project was originally conceived as a two-phase (screening and clinical examination) door-to-door survey aimed at detecting the prevalence of dementia in those 2,368 subjects born in 1912 or earlier who lived in the Kungsholmen district, Stockholm. In the screening phase, potentially demented subjects were identified with a cogni-
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Cognitive test [Swedish version of the Mini-Mental State Examination (MMSE)] (16). These subjects underwent clinical examination and detailed neuropsychological testing to confirm dementia on the basis of the criteria of the American Psychiatric Association’s Diagnostic and Statistical Manual, third edition.

Of the 2,368 subjects, 267 had died or changed address before the screening examination. Of the 2,101 eligible subjects, 291 (14%) refused the interview. Of the 1,810 screened subjects, 385 scored under the cutoff for dementia screening (23/24) on the MMSE. These and a stratified (by age and gender) random sample of 354 subjects taken from all those scoring above the cutoff underwent clinical examination (15). One hundred and ten subjects could not (dead or moved) or would not (refusal) undergo the clinical examination. At the end of the clinical examination phase, 225 subjects were identified as having definite or questionable dementia and 1,475 were considered to be not demented (15).

A few of the 1,475 nondemented subjects were excluded for the following reasons: score lower than 20 on the MMSE (n = 31), unknown education (n = 6), and age over 95 years (n = 3). Therefore the study population consisted of 1,435 nondemented individuals aged 75 to 95 years.

Definition of MCI

Two definitions of MCI were tested, both based on MMSE score and taking into account the effect of age and education on MMSE. Subjects with acute confusional state (delirium) were retested after remission of the condition.

The first definition was based on simple stratification, with no modeling of the age and education effect, and the second was based on a statistical model. MCI was thus defined as achieving an MMSE score of

(a) one standard deviation below the mean of age- and education-defined strata. Seven age strata were defined (75–76, 77–78, 79–80, 81–83, 84–86, 87–89, and 90–95 years) for each of the two education strata. The strata were chosen to minimize cohort effects and to allow sufficient numerosity (always greater than 30) in each of the strata. The age- and education-specific means and standard deviations were computed for each age and education strata. Subjects with below one standard deviation from the mean were defined as MCI. Cutoffs separating MCI from non-MCI subjects were generally lower for the less educated in most age strata and decreased with advancing age for both education strata. Cutoffs were set for high education at 26/27 from 75 to 78 years of age, 25/26 from 79 to 86 years of age, 24/25 from 87 to 89 years of age, 23/24 from 90 to 95 years of age, and for low education at 25/26 from 75 to 76 years of age, 24/25 from 77 to 86 years of age, and 23/24 from 87 to 95 years of age. The distribution of subjects by MCI, age, MMSE score, and education is shown in Fig. 1.

(b) one standard deviation below the age- and education-specific mean computed from a statistical model. The relationship of MMSE score to age was first explored with a generalized additive model (locally weighted regression). This technique provides a model representation of the relationship but does not assume any specific shape (17). The analysis indicated that the relationship of MMSE score to age followed a linear decline until approximately age 90. Around the age of 90 the slope became steeper and the relationship stayed linear but with a steeper slope up to age 95. This pattern held for both high and low education. For highly educated subjects, the expected MMSE scores computed on the basis of the model ranged from MMSE = 27.8 at 75 years of age, to MMSE = 26.3 at 90 years of age, to MMSE = 25.5 at 95 years of age. The values for subjects with a lower education were 0.8 points lower than those for highly educated subjects at any age. On the basis of this model, the expected MMSE score for each education stratum at every year of age, and the residual (i.e., the deviation from the expected MMSE scores) and standardized residual

![Figure 1. Distribution of subjects by mild cognitive impairment (MCI) and educational level. Age and Mini-Mental State Examination (MMSE) scores are jittered for better visualization. Open circles: no MCI; filled circles: MCI. The line denotes the cutoff scores. The occasional overflow of open circles below and of solid circles above the cutoff is due to jittering.](https://academic.oup.com/biomedgerontology/article-abstract/55/6/M322/2948067)
were computed for each subject. MCIs were defined as those subjects whose standardized residuals were lower than −1. The resulting cutoffs for high education were 26/27 at 75 years of age, 25/26 from 76 to 86 years of age, 24/25 from 87 to 93 years of age, and 23/24 from 94 to 95 years of age, and for low education 25/26 from 75 to 77 years of age, 24/25 from 78 to 88 years of age, 23/24 from 89 to 94 years of age, and 22/23 at 95 years of age. It should be underlined that this approach assumed a Gaussian distribution of MMSE score by levels of age and education. Although this is not true in the general adult population for the ceiling effect of the MMSE, in our own study of old and not highly educated subjects, the distribution of MMSE scores was very close to normal.

Both definitions set the ideal MCI prevalence at 15.9% of the study population. This figure is close to that found by Graham and colleagues (16.8%) in a population sample of over 10,000 older subjects (18).

We tested definitions of MCI by carrying out parallel analyses of the association of MCI with physical health. The results reported in the tables in the next section refer to the latter. Following diseases were recorded: cancer (ICD-8: 140 to 208 and 230 to 239), coronary heart disease (myocardial infarction, angina, and chronic ischemic heart disease, ICD-8: 410 to 414), and diabetes mellitus (ICD-8: 250). Information on vital status up to 3 years after the screening examination was obtained from official registers. Categories were made for the number of somatic symptoms (0 to 1, 2 to 3, and 4 to 5) and chronic diseases (0, 1, and 2 to 3) on the basis of the numerosity of the levels and of exploratory analysis of their association with MCI.

Missing values never exceeded 0.9% of the total population for any one variable.

**Statistical Analysis**

Differences of means between groups were tested with the Student’s t test, and of proportions with the chi-square test. The association of MCI with health variables was assessed with odds ratios and 95% confidence intervals computed in logistic regression models in which MCI and health variables were entered as categorical variables. We adjusted for factors potentially affecting cognition by entering the former in the models. We tested the dose-response effect (i.e., the poorer the health, the greater its association with MCI) by entering the appropriate health variable (somatic symptoms and chronic diseases) as a three-level continuous variable (test for trend).

**Results**

The distribution of MCI by age and education strata is shown in Table 1. The prevalence of MCI was close to the theoretical value of 15.9% for most strata (11% to 19%), except for the 85- to 89-year-old low-education stratum. The prevalence of MCI was not different across age (p = .56) and education (p = .10) strata.

Table 2 shows that, as expected, non-MCI and MCI subjects were not different with respect to age and education. However, MCI subjects were more often depressed, more often had cerebrovascular disease, and were more often disabled. Psychotropic drug use was similar in the two groups.

Health indicators were chosen to be representative of the organ systems more frequently affected by disease in older individuals: chest and heart discomfort (heart), shortness of breath (lung), digestion troubles (gastroenteric system), joint pain (musculoskeletal system), and poor appetite (general state of health). Subjects were asked concerning the presence or absence of the symptom. Self-rated health was assessed as a subjective judgement on a 6-point Likert scale, and subjects were divided into those with good health (those very satisfied with health, i.e., the maximum score on the scale) and those with poorer health (all the others). Chronic diseases other than cerebrovascular were ascertained with the same procedure used for the latter. The following diseases were recorded: cancer (ICD-8: 140 to 208 and 230 to 239), coronary heart disease (myocardial infarction, angina, and chronic ischemic heart disease, ICD-8: 410 to 414), and diabetes mellitus (ICD-8: 250). Information on vital status up to 3 years after the screening examination was obtained from official registers.

Factors potentially affecting cognition.— Symptomatic depression was defined as the subjective symptom report of often feeling lonely and often being in a low mood. In a subsample of 354 individuals of the present study with MMSE of 24 or higher who were evaluated with the full clinical protocol, this definition was shown to capture 76% of those with moderate to severe depression (score greater than 1.0 on the pertinent subscale of the Comprehensive Psychopathological Rating Scale) (19). We ascertained cerebrovascular disease (stroke and transient ischemic attack, International Classification of Diseases, 8th ed. [ICD-8]: 430 to 438) through the Computerised Stockholm Inpatient Registry System by reviewing the hospital discharge diagnoses from 1969 to the date of screening examination for the entire population. We ascertained use of psychotropic drugs (neuroleptics, benzodiazepines, antidepressants, and other sedatives) through interviews and by asking to see medicine bottles, prescriptions, and medicine lists. Disability in basic activities of daily living was defined in relation to dependency in bathing, dressing, toileting, continence, feeding, and walking (20).
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Table 1. Distribution of Mild Cognitive Impairment by Age and Education Among 1,435 Nondemented Subjects Aged 75 to 95 Years

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Education</th>
<th>No MCI</th>
<th>MCI</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>High School and University</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>39/304 (13%)</td>
<td>49/334 (15%)</td>
<td>88/638 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80–84</td>
<td>39/261 (15%)</td>
<td>33/245 (14%)</td>
<td>72/506 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85–89</td>
<td>30/114 (26%)</td>
<td>12/96 (13%)</td>
<td>42/210 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–95</td>
<td>8/43 (19%)</td>
<td>4/38 (11%)</td>
<td>12/81 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>116/722 (16%)</td>
<td>98/713 (14%)</td>
<td>214/1435 (15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Sociodemographic and Clinical Features According to Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th></th>
<th>No MCI (n = 1221)</th>
<th>MCI (n = 214)</th>
<th>Total (n = 1435)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>27.4 ± 1.3</td>
<td>23.8 ± 1.5</td>
<td>26.9 ± 1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sociodemographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>80.8 ± 4.5</td>
<td>81.4 ± 4.7</td>
<td>80.9 ± 4.5</td>
<td>.080</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>911 (75%)</td>
<td>170 (79%)</td>
<td>1081 (75%)</td>
<td>.131</td>
</tr>
<tr>
<td>Education (primary school)</td>
<td>606 (50%)</td>
<td>116 (54%)</td>
<td>722 (50%)</td>
<td>.217</td>
</tr>
<tr>
<td>Living in nursing home</td>
<td>50 (4%)</td>
<td>14 (7%)</td>
<td>64 (5%)</td>
<td>.110</td>
</tr>
<tr>
<td>Factors potentially affecting cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic depression</td>
<td>85 (7%)</td>
<td>23 (11%)</td>
<td>108 (8%)</td>
<td>.053</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>67 (6%)</td>
<td>24 (11%)</td>
<td>91 (6%)</td>
<td>.002</td>
</tr>
<tr>
<td>Psychotropic drug use</td>
<td>450 (37%)</td>
<td>78 (36%)</td>
<td>528 (37%)</td>
<td>.910</td>
</tr>
<tr>
<td>Disability (one or more basic function lost)</td>
<td>266 (22%)</td>
<td>74 (35%)</td>
<td>340 (24%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Notes: Values represent mean ± standard deviation or numbers (%). p denotes significance on χ² or t test.

Discussion

The data indicate that, at the population level, mild, nondementing cognitive impairment is associated with poorer health. The results highlight the need of a better definition of the relative contribution of physical and brain factors in the causation of MCI in the individual patient and in populations.

The influence of body health on brain function is well known in the clinical practice, and acute confusional states (i.e., delirium) occurring during physical diseases have been extensively studied. However, the data are more sparse on the role of physical diseases on milder and stabilized dearrangements of cognition. Some studies have shown an assoc-
According to the definition of MCI that we used, the gap between the cutoff for the youngest (75-year-old) and most-educated group and that for the oldest (95-year-old) and least-educated group was 3 to 4 MMSE points. This difference is usually regarded as clinically meaningful (3), supporting the opportunity to correct for age and education in MCI studies.

Some notes of caution in the interpretation of these results need to be underlined.

The definition of MCI that we have used is a statistical one and does not account for a possible increase of the condition with older age. In a population-based study, Barker and colleagues (23) have reported that the prevalence of MCI (defined as age-associated memory impairment) (24) was 16% among those aged 50 to 64 years and 24% among those aged 65 to 79 years. Although our own definitions and those of Barker and colleagues are hardly comparable, it is possible that, mainly in the older ages, some truly MCI individuals might have been incorrectly classified as non-MCI by our definition. This prompts a couple of considerations. First, our definition might represent a conservative estimate of the prevalence of MCI, which might indeed (at least in older age) be greater. Second, because the concept of MCI has been operationalized in clinical series to identify a group of individuals at risk for the development of Alzheimer’s disease (25), further epidemiological work will need to validate our population-based definition towards such an outcome. This might lead to a broader definition of MCI in the older ages (identifying a greater proportion of affected individuals) and to a narrower one in the younger ages.

We have chosen to use a number of different markers, both objective and subjective, to capture health status. Taken individually, none of these is probably sufficiently accurate to measure the health status of the older person. However, which indicator is a better descriptor of health is a matter of considerable debate. Despite meaningful attempts (26), the frequent co-occurrence of multiple chronic conditions and their different severities make the operational definition of a unique health marker a particularly difficult task.

Table 3. Association of Health Indicators With Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th></th>
<th>No MCI</th>
<th>MCI</th>
<th>Crude Association</th>
<th>Adjusted Association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>OR (95% C.I.)</td>
<td>p</td>
</tr>
<tr>
<td>Number of somatic symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>829 (68)</td>
<td>124 (58)</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td>2–3</td>
<td>352 (29)</td>
<td>75 (35)</td>
<td>1.42 1.04 to 1.95</td>
<td>1.30 1.00 to 1.87</td>
</tr>
<tr>
<td>4–5</td>
<td>40 (3)</td>
<td>15 (7)</td>
<td>2.51 1.35 to 4.67</td>
<td>2.12 1.24 to 4.51</td>
</tr>
<tr>
<td>Self-rated health*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>691 (57)</td>
<td>80 (38)</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td>Poorer</td>
<td>520 (43)</td>
<td>132 (62)</td>
<td>2.19 1.61 to 2.94</td>
<td>1.94 1.41 to 2.63</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>983 (81)</td>
<td>157 (73)</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td>1</td>
<td>222 (18)</td>
<td>50 (23)</td>
<td>1.41 1.00 to 2.00</td>
<td>1.30 .91 to 1.86</td>
</tr>
<tr>
<td>2–3</td>
<td>16 (1)</td>
<td>7 (3)</td>
<td>2.74 1.11 to 6.76</td>
<td>3.03 1.20 to 7.64</td>
</tr>
<tr>
<td>Vital status after 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>992 (81)</td>
<td>152 (7)</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td>Dead</td>
<td>229 (19)</td>
<td>62 (29)</td>
<td>1.77 1.27 to 2.45</td>
<td>1.50 1.06 to 2.11</td>
</tr>
</tbody>
</table>

Notes: OR = odds ratio, C.I. = confidence interval. Adjusted association: for symptomatic depression, cerebrovascular disease, psychotropic drug use, and disability, p denotes significance of the increase of odds ratios (adjusted test for trend) throughout levels of somatic symptoms and chronic diseases and significance of the odds ratio for death and self-rating of health. Percentages may not add up to 100 because of rounding off.

*Information was missing for 12 subjects.
Some chronic diseases and conditions that can have adverse effects on cognition could not be appropriately ascertained in this study. This is the case of hypothyroidism and vitamin B12 deficiency, for which we have no information. The prevalence of diabetes might also be underestimated. It is likely that only the most severe cases of diabetes were recorded in hospital discharge charts. It should be emphasized that, in the light of the known association of hypothyroidism, vitamin B12 deficiency, and diabetes with poorer cognition, an appropriate ascertainment of these conditions might further strengthen the present findings. Hypertension was very seldom (3.5%) reported in the hospital charts. However, both high (27) and low (28) blood pressure have been shown to be associated with poor cognitive performance in this and other populations. The role of hypertension in cognition still needs to be elucidated.

In the nondemented cases, the MMSE has relatively poor sensitivity in the detection of different levels of cognitive performance, and this property might have introduced a large amount of error in the definition of MCI. In fact, a 1-point change of the age- and education-specific cutoff for MCI in our population caused a substantial number of subjects to shift from one MCI category to the other. For this reason, we have tested the working hypothesis with two independent definitions of MCI that allowed for different cutoffs; results obtained were very similar.

Last, the relevance of brain degenerative changes as potential causative factors in a portion of MCI subjects should be taken into account. Observations on clinical series of patients seen for memory disturbances indicate that a high proportion of these subjects develop dementia, often with the clinical features of Alzheimer’s disease, within a few years (9% to 24% per year) (29–31). Although the conversion to dementia of conditions of cognitive impairment similar to MCI is lower (2.5% to 4% per year) in epidemiological settings (32–34), the contribution of degenerative factors to MCI in the population should be further investigated.

The concept of MCI is currently undergoing definition. The operational definition that is gaining increasing popularity is that of Petersen and colleagues (25). This is meant to capture amnestic MCI cases as well as cases that are due to other causes (poor physical health, brain vascular disease, depression, sensory problems, comorbidity, etc.) needs to be operationalized. This will allow researchers to clarify the relationship of the amnestic with other subgroups of MCI and to outline their natural history. We believe that the results of the present study contribute to this deed.

Acknowledgments

This study was financially supported by the Swedish Medical Research Council, the Swedish Council for Social Research, the Swedish Municipal Pension Institute, the Gun and Bertil Stohne Foundation, and by a grant of the IRCCS San Giovanni di Dio – FBF, Brescia. We thank Marco Trabucchi, Angelo Bianchetti, and Renzo Rozzini for their constant support and encouragement. Luigi Ferrucci, INRCA “I Fratricini”, Firenze, and Cristina Geroldi, MD, gave valuable comments on the manuscript. Samantha Galuzzi, MD, helped in the revision of the manuscript. We thank all the members of the Kungsholmen Project Study Group for their co-operation.

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Received April 26, 1999
Accepted September 6, 1999
Decision Editor: William B. Ershler, MD