Occurrence of medical co-morbidity in mild cognitive impairment: implications for generalisation of MCI research

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Abstract

Background: diagnosis of mild cognitive impairment (MCI) typically excludes individuals with medical co-morbidity. Interest in MCI screening raises the questions of what are the best criteria to identify a representative sample and what factors are associated with MCI progression to dementia.

Objectives: to compare the pattern of disease co-morbidity across different cognitive groups and to examine the role of health co-morbidity as a risk factor for dementia progression from MCI.

Methods: individuals from the MRC Cognitive Function and Ageing Study were classified as having no cognitive impairment (NCI), MCI, other cognitive impairment no dementia (OCIND) or dementia. At 2 years dementia status was assessed.

Findings: over 50% of individuals in each group reported one or more medical condition. The pattern of disease prevalence was similar in the NCI, MCI and OCIND groups. Anaemia was the only health factor associated with an increased risk of dementia progression from MCI.

Conclusion: classification of MCI using medical exclusions would exclude the majority of the population from a MCI diagnosis. This has implications for treatment decisions and clinical trial recruitment. This could not only make recruitment more difficult but also limit the generalisability of trial results. Medical co-morbidity does not help to distinguish progressive from non-progressive MCI.

Keywords: mild cognitive impairment (MCI), health-related co-morbidity, dementia risk, elderly

Introduction

Poor health has been associated with an increased risk of cognitive decline and may also be a risk factor for Alzheimer’s disease (AD) and vascular dementia. Examining health status in cognitively impaired older adults may be important in identifying the underlying pathogenesis of cognitive decline, and if helpful in predicting dementia risk might be relevant to the development of strategies to delay the onset of dementia. Accounting for health and its risk factors in cognitively impaired older individuals is also important for clinical trial enrolment and decision-making about treatment, particularly in the presence of co-morbidity given the risks associated with polypharmacy.

The term mild cognitive impairment (MCI) is widely used to describe a state of increased dementia risk between ageing without impaired cognitive function and dementia. Although not always explicitly stated a MCI diagnosis is often made following medical exclusion [1–3]. In screening protocols however, the exclusion of co-morbid conditions
may adversely affect selection of the population at risk. Interest in screening for MCI raises the question of what are the best eligibility criteria to identify a representative MCI sample. While clinically significant medical abnormalities can compromise participant safety, expose individuals to undue risk or significantly interfere with trial procedures and outcomes, too strict inclusion criteria can affect sample representativeness (to the population at risk) and trial validity. The implication of medical exclusion on case diagnosis is not known and determining the representativeness of participants selected for trials requires knowledge of disease prevalence in the general population and in individuals with MCI. Furthermore determining those individuals in whom cognitive impairment can be ameliorated through alternative channels such as uncompensated diabetes, hyperthyroidism or hyponatraemia is important for exclusion from clinical trials.

The annual conversion rate from MCI to dementia varies from 5 to 10% according to the definition used. Not all individuals with MCI progress to dementia, with some individuals remaining stable or reverting to normal [4, 5]. Markers are now being sought to distinguish progressive from non-progressive forms of MCI. Longitudinal studies have found that poor health in mid-life can increase risk of cognitive decline and dementia in late life [6, 7]. In some studies, poor health is found to elevate risk of dementia progression from MCI [8–10]. Associations are not always robust, however, and may depend on the timing of health measurement (mid-life versus later life), study sample (clinic versus population based) and MCI diagnostic criteria (amnestic versus non-amnestic). Whether poor health status can be used to inform the subdivision between progressive and non-progressive MCI may be of value in defining dementia risk in MCI cohorts.

The aim of this study is to compare the pattern of major disease co-morbidity across the spectrum of age-associated cognitive changes including normal, MCI, OCIND and demented groups. We also examined the role of health co-morbidity as a risk factor for 2-year incident dementia across the different cognitive states.

## Methods

### Participants

Participants were from MRC CFAS (see [http://www.cfas.ac.uk](http://www.cfas.ac.uk)) [11]. Baseline interviewing began in 1991. Individuals aged 65 years or older were randomly selected from the Family Health Service Authority lists in five areas of the UK including centres in Cambridgeshire, Gwynedd, Newcastle, Nottingham and Oxford. In total, 13,004 participants completed the screening interview undertaken by a trained interviewer at the participants’ place of residence. Information on demographic and socio-demographic status, functional ability, self report health status and cognitive performance measured using the Mini Mental State Examination (MMSE) [12], and selected items from the Geriatric Mental State (GMS) Automated Geriatric Examination for Computer-Assisted Taxonomy (AGECAT) [13] were collected. A sub-sample of approximately 20% (n = 2,640) of respondents were selected based on age, centre and cognitive ability to complete a more detailed assessment. This included the organicity sections of the AGECAT and the Cambridge Cognitive Examination (CAMCOG) [14]. All individuals were also asked to provide details of an informant, and the History and Aetiology Schedule was completed for as many as possible. The study was approved by the local ethics committee for each centre and informed consent obtained from all participants before interview. Data from the initial prevalence screen, first assessment and 2-year follow-up interviews (Data Version 8.2) were used in this analysis.

### Health co-morbidity index

Health status was determined based on self or an informant report of the presence of a condition. From the baseline interview 10 conditions common in the older population were selected including: pernicious anaemia, Parkinson’s disease (PD), breathing difficulties, angina, hypertension, diabetes mellitus, peripheral vascular disease (PVD: intermittent claudication), transient ischaemic attack (TIA), self-reported history of stroke or heart attack. Angina and PVD were derived from the Rose Angina Scale [15]. A co-morbidity score (range 0–10) was defined as the number of health conditions present.

### Dementia

Dementia status was derived using the full AGECAT diagnostic algorithm [13], defined as an AGECAT organicity rating case level of 3 or above. This is reported to be equivalent to dementia as diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [16, 17]. In total, 8.8% (9.8% age standardised rate) had a case level diagnosis of dementia with a proportional rate) had a case level diagnosis of dementia with a proportional.
Medical co-morbidity in mild cognitive impairment

week with washing, cooking and dressing, or if the individual was housebound) and, (4) objective memory and/or non-memory impairment (based on age-adjusted CAMCOG cut-off values derived from composite memory and non-memory scores). To be classified as NCI, individuals had to fulfill the following criteria: (i) normal general cognitive functioning; (ii) no severe functional impairment; (iii) normal memory and non-memory test performance and (iv) not demented. The OCIND group included all non-normal individuals who failed to fulfil MCI criteria [21]. At first assessment interview 608 individuals fulfilled criteria for NCI, 319 MCI and 580 OCIND.

Analysis

Summary statistics (means and medians, weighted for study design) were used to compare baseline demographic characteristics across cognitive groups. ANOVA was used to test for group differences in age, cognitive status (MMSE) and educational attainment. The population prevalence (95% confidence interval: 95% CI) of each health condition stratified by cognitive status was calculated. Group differences in disease prevalence were tested using the Chi-squared statistic. Post hoc comparisons of prevalence were tested using logistic regression weighted for study design, with the MCI group as the referent. The pattern of disease and medical co-morbidity was also examined in the A-MCI, N-MCI and M-MCI groups to test whether collapsing across each subtype to form the MCI group was driving the results. Age standardised prevalence estimates were also calculated using 5-year age groups (including 64–69, 70–74, 75–79, 80–84 and 85 + years). This controlled for the baseline differences in the age structure across the different cognitive groups. The association between each health condition and dementia progression was evaluated using univariate and multivariate (age, gender and education) logistic regression models (weighted for attrition) in the NCI, MCI and OCIND groups. Analyses were undertaken using Stata Version 10.0.

Results

Socio-demographic characteristics

Baseline prevalence and socio-demographic characteristics for each cognitive group by disease co-morbidity status are shown in Table 1. Most of the sample (50.1%, back-weighted) was not cognitively impaired. Overall, the dementia group was the oldest in both the disease and no-disease co-morbidity conditions (all P < 0.0001). There were no other group differences in age. In both the disease and no-disease co-morbidity conditions the NCI group had a higher level of education than all other groups.

Health co-morbidity across cognitive groups

Table 2 shows the prevalence of each health condition in the NCI, MCI, OCIND and dementia groups. Age standardisation did not substantially change prevalence estimates (data not shown) and unstandardised estimates are used for all further analysis. Overall, hypertension was the most common condition, being present in over 20% of individuals in each cognitive group. PD was the least common condition being present in less than 5% of individuals in each cognitive group. There was a high degree of similarity in disease prevalence across the different cognitive groups, except that stroke and PD were significantly more

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Table 1. Baseline demographic characteristics (weighted for study design) of the different cognitive groups stratified by disease status (including those individuals who do not report any of the health conditions and individuals who report one or more of the health conditions)

<table>
<thead>
<tr>
<th>Health Condition</th>
<th>NCI (n = 608)</th>
<th>MCI (n = 319)</th>
<th>OCIND (n = 580)</th>
<th>Dementia (n = 587)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population prevalence (95% CI)</td>
<td>50.1 (47.1–53.2)</td>
<td>16.4 (14.3–18.8)</td>
<td>24.7 (22.2–27.3)</td>
<td>8.8 (7.8–9.8)</td>
</tr>
<tr>
<td>Age standardised prevalence (95% CI)</td>
<td>43.6 (40.8–46.4)</td>
<td>14.5 (12.5–16.4)</td>
<td>21.5 (19.3–23.7)</td>
<td>7.7 (6.6–8.6)</td>
</tr>
<tr>
<td>% Progressed to dementia at 2 years (95% CI)</td>
<td>0.7 (0.3–1.5)</td>
<td>5.6 (3.0–10.0)</td>
<td>7.7 (4.2–13.8)</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No health conditions</th>
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<tbody>
<tr>
<td>Mean age (q1, q3), years</td>
<td>72.6* (68.76)</td>
<td>74.2* (68.79)</td>
<td>73.0* (68.78)</td>
<td>81.9 (79.87)</td>
</tr>
<tr>
<td>Mean education (q1, q3), years</td>
<td>11.1* (9.12)</td>
<td>9.9*** (9.10)</td>
<td>9.5** (9.10)</td>
<td>9.7 (9.10)</td>
</tr>
<tr>
<td>% Female (q3)**</td>
<td>54.0 (141)</td>
<td>58.4 (68)</td>
<td>57.6 (143)</td>
<td>73.2 (111)</td>
</tr>
<tr>
<td>Mean MMSE [q2 (q1,q3)]</td>
<td>27.6* (26,29)</td>
<td>26.1*** (25,28)</td>
<td>25.4*** (24,28)</td>
<td>20.1** (17,24)</td>
</tr>
</tbody>
</table>

One or more health conditions

<table>
<thead>
<tr>
<th>Health Condition</th>
<th>NCI (n = 608)</th>
<th>MCI (n = 319)</th>
<th>OCIND (n = 580)</th>
<th>Dementia (n = 587)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (q1, q3), years</td>
<td>73.5* (69,78)</td>
<td>72.5* (68,77)</td>
<td>73.0* (68,76)</td>
<td>79.8 (74,84)</td>
</tr>
<tr>
<td>Mean education (q1, q3), years</td>
<td>10.4 (9.11)</td>
<td>9.6** (9.10)</td>
<td>9.6** (9.10)</td>
<td>9.1** (9.9)</td>
</tr>
<tr>
<td>% Female (q3)**</td>
<td>54.2 (204)</td>
<td>53.3 (126)</td>
<td>60.6 (226)</td>
<td>60.1 (101)</td>
</tr>
<tr>
<td>Mean MMSE [q2 (q1,q3)]</td>
<td>27.4* (26,29)</td>
<td>26.2*** (25,28)</td>
<td>25.4*** (24,28)</td>
<td>19.3** (16,22)</td>
</tr>
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</table>

All estimates (means, SDs, medians and quartiles) are population weighted.

n, number of observations; q2, Quartile 2 (50th percentile); q1, Quartile 1 (25th percentile); q3, Quartile 3 (75th percentile); NCI, no cognitive impairment; MCI, mild cognitive impairment; OCIND, other cognitive impairment no dementia.*A proportion of which have other psychiatric co-morbidity.

Some individuals in each group are missing the co-morbidity score.

*Significantly different from the dementia group.

**Significantly different from the NCI group.
were similarly prevalent across MCI subtypes. Alternatively, all other conditions were more prevalent in the M-MCI compared to the N-MCI group. Otherwise, all other group differences were significant.

**Discussion**

The findings confirm previous reports of a high prevalence of disease co-morbidity in the older population [22]. In all groups, fewer than 50% reported no medical conditions with a large number of individuals reporting between one and three conditions. Disease prevalence, however, differed between the demented and non-demented groups. Generally there was no association between single-risk factors and incident dementia in MCI. Disease status was predictive of 2-year incident dementia in the MCI group only when co-morbidity was associated with anaemia.

While the pattern of disease prevalence was similar in the NCI, MCI and OCIND groups, individuals with dementia were more likely to have medical co-morbidity related to stroke and PD. This is not unexpected as each of these conditions is known to increase in incidence with age.
An important focus of MCI research is the identification of improved methods of classification to differentiate MCI cases at risk of dementia progression from those who are not [29]. Medical co-morbidity may affect dementia progression in MCI cohorts. It has been hypothesised that heterogeneity in the outcome of MCI may be linked to the presence of co-morbid disease [30]. Previous studies have, however, been inconclusive in identifying medical risk factors for incident dementia in MCI groups. Only atrial fibrillation and low folate levels have been associated with an increased risk of dementia progression in MCI [31]. Disparate results are possibly due to differences in MCI case selection criteria, sample age (young-old versus oldest-old), disease severity levels, measurement of risk factors and study populations (clinic samples with ranging emphasis versus population based). In this study, only anaemia increased risk of dementia in individuals with MCI. Anaemia has not, however, been consistently associated with cognitive decline and dementia risk [32, 33]: not all studies find an association, including a previous study using the CFAS cohort. One possible reason for a lack of an association in otherwise non-demented samples may be due to a wash-out effect on the relationship when the different cognitive groups (i.e. normal, MCI and OCIND) are combined for analysis. Given that the prevalence of anaemia was similar across all groups, the results suggest that one mechanism by which anaemia impacts dementia risk in MCI could be due to compromised compensatory processes in the MCI state. Indeed, in MCI the pathology underlying cognitive symptoms (e.g. AD or vascular pathology) may make it difficult for the brain to compensate for the additional insult (i.e. low-oxygen supply) caused by the anaemia. In contrast, in the NCI and OCIND states neuropathology would be unlikely to be as great and, therefore, compensatory mechanisms would be expected to be more efficient. This needs to be tested.

Conclusions

Medical co-morbidity is an important aspect of ageing. There is relatively little difference across the different cognitive groups apart from increased stroke and PD in dementia. Trends of co-morbidity and treatment need to be updated, especially as patterns of disease and medication use are important considerations for clinical trial design with regard to issues of polypharmacy and sample representativeness. Most published MCI case definitions do not explicitly state medical exclusion criteria although these are routinely employed in the diagnosis of MCI and tend to relate to psychiatric and vascular co-morbidity [3]. In clinical trials, strict eligibility criteria are typically necessary when the isolated effect of an agent is to be tested and for safety reasons. However, the results suggest that strict eligibility criteria could result in insufficient or biased case identification as less than 50% of individuals across any group report no medical co-morbidities. As such clinical trial samples will not reflect the population for whom the treatment is being sought. Trials must be designed with careful consideration and general agreement of inclusion/exclusion criteria for MCI, and should only be restricted to those individuals who are most likely to be affected favourably by the treatment [3].

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Key points

- Clinical trials in older aged populations typically exclude individuals with common medical co-morbidities.
- MCI sample characteristics will change depending on the medical exclusions applied for a case diagnosis.
- Strict eligibility criteria could result in insufficient or biased MCI case identification, especially in clinical trials, restricting the generalisability of results.
- Medical co-morbidity does not appear to increase the risk of dementia progression in individuals with MCI.


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Author contributions
B.S., E.M. and C.B. developed and designed the project and obtained funding. E.M. and G.S. provided statistical expertise. B.S. completed the literature review. All authors took part in preparation of the manuscript and provided critical intellectual interpretation and manuscript revision. All authors read and approved the final manuscript. The statistical analysis was carried out by B.S., G.S. and E.M.

Conflicts of interest
None declared.

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References


Assessing quality-of-life in older people in care homes

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Abstract

Background: many measures of Quality-of-Life (QoL) may not be suitable for older people in care homes, and do not cover the most relevant domains for individuals.

Objective: to describe QoL of older people living in care homes using the SEIQoL-DW and the two 10-point rating scales, and to describe how people were using these measures.

Design: we used quantitative methods to describe QoL, and qualitative methods to explore residents’ experiences of completing the measures.

Setting: three care homes in the United Kingdom.

Sample: twenty residents.

Methods: residents completed the measures in interviews. We report descriptive statistics for QoL, the most important QoL domains for residents, completion rates and experiences of administering the instruments.

Results: the most important QoL domains identified in the SEIQoL-DW were leisure activities; family; relationships; social life; independence and peace and contentment. Physical limitations and difficulty in understanding the instructions and concepts made completing it a challenge. The SEIQoL index was strongly correlated with a single 10-point rating of current QoL (rho = 0.67, P = 0.007).