Cand.Psych. Thesis

The AGES-Reykjavík Study: The Prevalence of Amnestic MCI in an Elderly Population

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ABSTRACT

Amnestic MCI (aMCI) has been consistently singled out as an important risk factor for Alzheimer´s dementia but few studies have investigated the multidomain amnestic subtype of MCI. The purpose of this study was first to estimate the prevalence of the two amnestic MCI subtypes, single domain and multidomain and second, to examine the associations of age, gender and education level with single- and multidomain amnestic MCI. A community sample of 2135 non-demented individuals aged 66 to 92 years, who participated in the AGES-Reykjavík longitudinal study, was examined. Standard scores for a battery of neuropsychological tests were calculated and participants who did not complete all tests or answer all relevant questions were removed from the sample, leaving 1557 participants. Criteria for amnestic MCI subtypes according to Winblad et al. (2004) were applied. Total amnestic MCI prevalence was estimated 13.8% and the prevalence of the subtypes single domain amnestic MCI and multidomain amnestic MCI was identical, at 6.9%. Amnestic MCI increased with age and men had a greater overall risk ratio, 1.3, of having aMCI, compared to women. Men between 66 and 69 years had a risk ratio of 6.9 for having single domain amnestic MCI compared to women in the same age group. Men under the age of 75 had a risk ratio of 2.1 of having single domain amnestic MCI, compared to women, whereas, among subjects 75 and older, there was no significant gender difference. Multidomain aMCI increased with age in a curvilinear fashion, but no relation to gender was observed. No direct relations of aMCI subtypes with education were observed but an interaction between education and aMCI subtypes was found, indicating that subjects with higher level of education tend to develop aMCI later in life, the difference being larger for multidomain type than single domain type. No other studies have reported such a large gender

difference in any type of MCI, although some studies do report greater male prevalence of aMCI. An age-gender interaction on the prevalence of aMCI has not been reported for MCI subtypes, though they have been observed for Alzheimer´s Disease (AD) (Letenneur et al., 1999).

THE AGES-REYKJAVÍK STUDY: THE PREVALENCE OF AMNESTIC MCI IN AN ELDERLY POPULATION

Introduction

Cognitive decline

As people age, they generally start noticing changes in their cognitive function. Often people complain of difficulties in remembering names and a slowing of their thought processes. These changes are considered normal. Some people, however, suffer a more serious cognitive deterioration, which may develop into dementia. Mild cognitive impairment (MCI) is often thought of as a transitional state between normal aging and dementia (Amieva et al., 2004). It is characterized by a cluster of measureable cognitive deficits, most often memory deficits, which are mild and do not interfere substantially with activities of daily living (ADL) nor result in inability to live independently. Subtypes of MCI can be classified based on the particular pattern of cognitive impairment. Although memory deficits are often central to this disorder, there are some cases where memory is relatively intact while other domains of cognition are affected, i.e. amnestic vs. non-amnestic MCI.

Dementia is a syndrome of severe cognitive decline. The diagnostic features include memory impairment and at least one of the following: aphasia, apraxia, agnosia or disturbances in executive functioning. The cognitive impairments should be severe enough to cause impairment in social and occupational functioning (APA, 2000). Numerous pathological changes in the central nervous system have been associated with both dementias in general and subtypes of dementia. Changes such as hippocampal atrophy (Wolf et al., 2003), neurofibrillary tangles and elevated levels of

certain amyloid and tau proteins in the cerebrospinal fluid (Petersen et al., 2006; Selkoe, 1991, 2004) have all been described in detail. These types of changes have also been found in MCI patients, albeit to a lesser extent (Grundman et al., 2004; Petersen et al., 2006; Rowe et al., 2007).

The effects of gender and age on cognitive decline are not yet clear. According to Amieva et al. (2004), the transition from MCI to dementia is related to age and size of temporal lobe but not to gender or education. Letenneur at al. (1999) found men to have a higher risk of developing Alzheimer´s dementia (AD) under the age of 80 while women had a higher risk after the age of 80 (after controlling for educational level). Thus, age and gender interactions may influence the outcome of prevalence studies, possibly explaining conflicting results pertaining to the relationship of gender and MCI prevalence (e.g. Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003a; Hanninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002; Lopez et al., 2003).

Education is an important factor influencing the outcome of cognitive tests as more educated subjects typically perform better than subjects with lower levels of education (Letenneur et al., 1999). Highly educated people also seem to develop MCI and dementia later in life (Amieva et al., 2005; Stern et al., 1994) whereas low educational levels are associated with a higher risk of MCI and Alzheimer's disease (AD; Di Carlo et al., 2007; Ganguli, Dodge, Shen, & DeKosky, 2004; Letenneur et al., 1999)..

Stern et al. (1994) proposed the hypothesis that people with a high educational level have a greater 'cognitive reserve capacity' than those with less education. This cognitive reserve may allow the individual to cope longer before dementia is clinically manifested. Amieva et al (2005) found that highly educated subjects performed better than those with a lower level of education on measures of visual

memory, verbal fluency and abstract thinking nine years prior to the onset of dementia. They, however, experienced a faster decline in the few years preceding dementia, so that their performance levels became similar to those of subjects with less education. These results seem to support the cognitive reserve hypothesis, as the nonlinear decline suggests a delay in the presentation of cognitive symptoms of pathology rather than a true protective effect of education against dementia.

Definition of MCI and subtypes

There have been many different definitions of the transitional state between normalcy and dementia in the elderly. Most definitions require a memory impairment and an absence of other cognitive decline (Stephan, Matthews, McKeith, Bond, & Brayne, 2007), such as *age-associated memory impairment* (AAMI). AAMI required subjective complaints of memory loss in people aged at least 50 years, not caused by specific medical conditions. Formal memory test performance must be at least one standard deviation below established means for young adults but other cognitive function should be normal (Richards, Touchon, Ledesert, & Richie, 1999). However, some definitions do not require a memory impairment, including *aging associated cognitive decline* (AACD; Levy, 1994), *mild cognitive decline* (Christensen et al.,1995; in DeCarli, 2003) and *cognitive impairment - no dementia* (CIND; Graham et al., 1997). Diagnostic criteria for AACD were proposed in 1994, by the task force of the International Psychogeriatric Association (IPA) in collaboration with the World Health Organization (WHO). To meet the criteria people must score at least one standard deviation below age- and education based standards on neuropsychological tests assessing multiple cognitive abilities (Hanninen et al., 1996). Mild cognitive decline is defined by the DSM-IV as 'an objectively identified decline in cognitive

functioning consequent to the aging process that is within normal limits, given the person's age,' but no defined diagnostic criteria exist and few epidemiological studies have used this definition (Panza et al., 2005). CIND was introduced by the Canadian Study of Health and Aging (CSHA) to classify all individuals with cognitive impairments (memory or other) that do not meet the criteria of dementia. This category includes subjects with impairment caused by medical or psychiatric conditions (ibid.).

The currently most widely adopted construct is *mild cognitive impairment* (MCI), introduced by Flicker, Ferris and Reisberg (1991) and later defined by Petersen et al. (1999) as a memory complaint (preferably corroborated by an informant), impaired memory on clinical assessment and preserved ADL, while failing to meet criteria for dementia. An earlier influential definition by Petersen (1995) required also normal general cognition and a score on the Clinical Dementia Rating (Morris, 1993) of 0.5. This will be referred to as the Mayo Clinic definition.

In 2001 a group of experts convened on the subject of MCI. They decided on a threefold division: MCI-amnestic, MCI-multiple domains slightly impaired and MCI-single nonmemory domain (Petersen et al., 2001). MCI-amnestic is defined by the criteria established by Petersen et al. (1999), while MCI-multiple domains slightly impaired requires impairment in at least two cognitive domains that may or may not include memory. Finally, MCI-single nonmemory domain includes subjects who show decline in only one cognitive domain, other than memory. This division has been widely adopted.

In 2003, the International Working Group on Mild Cognitive Impairment held its first symposium. The aim was to integrate clinical and epidemiological perspectives on MCI (Winblad et al., 2004). The agreed upon general MCI criteria

were: The patient is not normal and not demented according to the criteria of DSM IV or ICD 10. The patient is impaired on objective cognitive tasks according to self and/or informant report and/or there is evidence of decline over time on objective cognitive tasks. Basic ADL are preserved but there may be minimal impairment in complex instrumental functions. They also proposed that MCI be divided into four subgroups: single domain amnestic- or nonamnestic MCI and multidomain MCI with or without amnesia. Figure 1 shows the subtype classification process recommended by the International Working Group on Mild Cognitive Impairment.

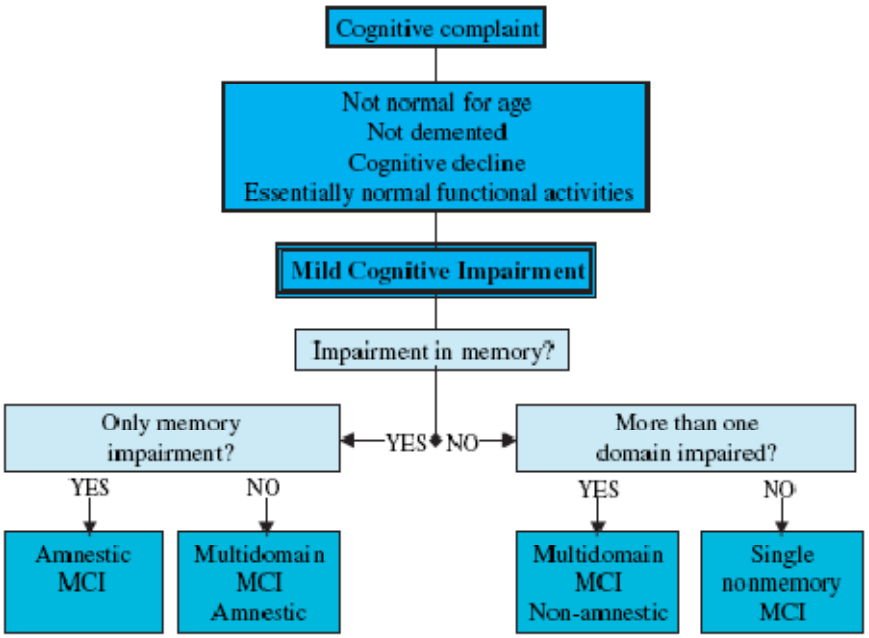

Figure 1: MCI classification process (Winblad et al., 2004)

In order to determine the specific subtype of MCI, comprehensive cognitive testing is necessary (Winblad et al., 2004). Winblad et al. recommend assessing episodic memory with, for example, a word list learning procedure (such as the CVLT) or paragraph recall. Other domains may also be tested if necessary, e.g.

language, executive function or visuospatial skills. Those subjects who score significantly lower than would be expected for their age would be considered impaired in that domain. Those subjects that are impaired in more than one domain would be classified as multidomain MCI with or without amnesia. Those who only show impairment in one domain would be considered having either single amnestic MCI or single nonmemory MCI, depending on whether memory was affected or some other cognitive domain. Artero et al (2006) showed that the revised criteria gave a significantly better prediction of transition to dementia than the previous MCI criteria. The new criteria were much more sensitive (95%) than the old criteria (5%) but rather less specific (66% compared to 91%). However, the predictive power was found to increase when amnestic and non-amnestic MCI subtypes were combined. For clarity, in this text, the term 'amnestic MCI' or 'aMCI' will be reserved for the combined subtypes of amnestic MCI while 'single domain amnestic MCI' or 'single domain aMCI' will denote the exclusively amnestic MCI subtype.

Very few studies have followed the fourfold division advocated by the International Working Group on MCI (see Figure 1). There is therefore a shortage of studies separately investigating the characteristics of multidomain amnestic MCI. Many have followed the threefold division advocated by Petersen et al. (2001; see above) or divided MCI in two subtypes: multidomain MCI vs. amnestic MCI. Amnestic MCI here usually represents single domain amnestic MCI and multidomain MCI often includes multidomain amnestic and non-amnestic subtypes. When appropriate, the terms of the authors will be replaced by the terminology of the International Working Group on MCI.

Prevalence of MCI

When comparing studies on MCI, one needs to be aware that studies published before the 2001 conference (Petersen et al., 2001) most likely define MCI principally as an impairment of memory, while later studies often include non-memory cognitive impairments, see above. Thus, prevalence estimates tend to be higher in later studies because of the inclusion of non-amnestic subjects. The estimated prevalence of MCI also varies depending on the study definition and the mean age of the sample. Even studies applying the same definition of MCI have failed to give a uniform answer to the question of MCI prevalence.

Working with data from the Leipzig Longitudinal Study of the Aged (LEILA75+), Busse et al. quoted figures for different study definitions of MCI ranging from 1 to 15% (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003c); other estimates rise to over 30% (Busse et al., 2003a; Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003b). Lopez et al. found an MCI prevalence of 19% (Cardivascular Health Study; 2003) while Artero et al. (2006) obtained an MCI prevalence of 16.6%, using the revised criteria. The combined prevalence of MCI in the Mayo Clinic Study of Aging was 15.2% (Roberts et al., 2008). Lastly, the Kungsholmen study found a total prevalence of MCI of 16.8% (Palmer, Bäckman, Winblad, & Fratiglioni, 2008).

Prevalence of amnestic MCI

The same precautions as above apply to the interpretation of amnestic MCI prevalence data on amnestic MCI as above. Studies employing the threefold division of MCI do not provide information on the prevalence of multidomain amnestic MCI nor on the prevalence of the combined amnestic subtypes (amnestic MCI) because

amnestic and non-amnestic subjects are included in the MCI-multiple domains slightly impaired subtype. However, combined prevalence estimates of amnestic MCI (single- and multidomain) should be more comparable to results using other memory based definitions, such as the Petersen (Petersen et al., 1999) definition and AACD than total MCI prevalence. Strict statistical definitions of amnestic MCI based on age-specific population memory tests tend to give higher estimates of prevalence than do definitions based on screening examinations or associated memory complaints verified by caregivers at interview (DeCarli, 2003).

Prevalence rates of combined amnestic MCI (single domain and multidomain types combined) differ considerably among studies: a Finnish study using the Mayo Clinic definition of MCI found a prevalence of 5.3% (Hanninen et al., 2002), the Californian Study on Health and Aging (CSHA) reported 3.0% aMCI prevalence after eliminating the requirement for a memory complaint and intact functional activity (Fisk, Merry, & Rockwood, 2003), the MoVies study in the United States (Ganguli et al., 2004) reported a prevalence rate of 3.2%, in a sample with mean age of 74.6 (SD: 5.3), the German LEILA +75 study reported 2.5% prevalence of amnestic MCI according to Petersen (1999) criteria (Busse et al., 2003c) and the Cardiovascular Health Study found a prevalence of 6% (Lopez et al., 2003).

Only one study seems to have estimated the prevalence of both subtypes of amnestic MCI suggested by the International Working Group on MCI (see above); using data from the LEILA+75 study, they reported 3% prevalence of single domain amnestic MCI (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). The ILSA study in Italy reported a prevalence rate of 3.2%[1] (Mayo Clinic criteria; Solfrizzi et al., 2004), Das et al. (2007) reported a 6.0% prevalence of single domain

[1] They ignored the criterion of subjective memory impairment.

amnestic aMCI in India, and DiCarlo found 7% in the Italian ILSA study (Di Carlo et al., 2007). Finally, Fisk et al. (2003) estimated a prevalence of single domain aMCI of 1.5%, based on clinical evaluation rather than a cutoff score on neuropsychological tests.

The one study that estimated the prevalence of multidomain amnestic MCI reported 0.9% prevalence in subjects 75 years and older (Busse et al., 2006). When criterion for subjective memory complaint was ignored the prevalence rose to 1.8%.

Memory complaint is usually a requirement of an amnestic MCI diagnosis. Formal studies of the prevalence of memory complaints within the community vary greatly, from 22% to 56% (DeCarli, 2003). Much of the variation relates to the average age of the population studied and the type of questions asked, but factors such as sex and educational achievement seem important as well. The high prevalence of complaints about memory problems from elderly people may reflect high rates of depressive symptoms (ibid.). Many studies have related memory complaints to subsequent development of dementia (Abdulrab & Heun, 2008). For example, Artero et al. (2006) found that subjects with a cognitive complaint verified by a proxy had a higher conversion rate to senile dementia (18% incidence over 3 years) than that observed in the general population. However, Palmer et al. (2008) reported that only half of future AD cases complained of memory problems three years before diagnosis.

Effects of age, gender and education

Age, educational level and gender have not been consistently related to MCI prevalence (Panza et al., 2005). Some studies have found MCI prevalence rates to increase with age (Hanninen et al., 2002; Lopez et al., 2003; Solfrizzi et al., 2004). For example Lopez et al. found prevalence to increase with age from 19% in

participants younger than 75 years to 29% in those older than 85 years, while others have not observed this trend (e.g. Busse et al., 2003a). A recent report from the Mayo Clinic Study of Aging found men to have a higher overall incidence of MCI than women, 17.7% in men compared to 13.4% in women (Roberts et al., 2008) in a sample aged 70 - 89 years, Ganguli et al. (2004) related male sex to amnestic MCI using data from the Pennsylvanian MoVies study, and two studies found AACD and AAMI to be more prevalent in men (Hanninen et al., 1996; Koivisto et al., 1995). Other studies have not observed this gender difference (Busse et al., 2003a; Hanninen et al., 2002; Solfrizzi et al., 2004). A higher educational level has sometimes been linked to a lower risk of MCI (Hanninen et al., 2002; Solfrizzi et al., 2004).

A recent study suggested that men are more likely to have the single domain amnestic type of MCI while women are more likely to have multiple domain types of MCI (Das et al., 2007).

Some studies suggest that patients with amnestic MCI are more likely than non-amnestic subtypes to progress to AD (Backman, Jones, Berger, Laukka, & Small, 2004; Petersen, 2004; Petersen et al., 2001). In most longitudinal studies of amnestic MCI (single and/or multiple domain), 10 to 15 percent per year progress to AD compared to an observed rate of 1–2% in the general population (Rountree et al., 2007). However, other studies have reported similar conversion rates to AD for all MCI subtypes, 14% per year for amnestic MCI and 13% per year for nonamnestic MCI (ibid.). It is believed that when individuals have impairments in domains other than memory, they may be more likely to progress to other dementias (Ries et al., 2008; Tabert et al., 2006) e.g. Lewy body dementia, frontotemporal dementia or primary progressive aphasia. But Palmer, Bäckman, Winblad, and Fratiglioni (2008) found multidomain MCI more predictive of AD than amnestic MCI. Finally, although

aMCI carries an increased risk of dementia, more than a quarter of aMCI cases are classified as normal after 5 years (Fisk et al., 2003).

Neuropsychological correlates of MCI

Attention and processing speed

Dannhauser et al. (2005) found that subjects with amnestic MCI had a clear deficit on a measure of divided attention and an attenuated prefrontal activation compared with age-matched controls. MCI subjects also perform worse than normals on the Digit Symbol Substitution Test (Nordlund et al., 2005) and Amieva (2004) found selective attention abilities, assessed by a Letter Cancellation Task (LCT), to be highly predictive of transition from MCI to dementia.

Measures of cognitive processing speed are frequently found to have moderate to large relations with age (Salthouse, 2000). Research suggests that speed of performance may reflect the efficiency of mental processes (Rypma & D'Esposito, 2000) such as memory. Slowing in speed of processing appears to more directly impact memory performance in individuals with the ε4 allele (O'Hara et al., 2008) which is a risk factor for AD. Slower speed of processing may therefore be an early indication of the memory deficits that are the hallmark of AD and amnestic MCI. However, changes in speed measures may be preceded by memory deficits by several years (Hall et al., 2001).

Memory

Memory is the central aspect of cognitive function in amnestic MCI. It is therefore not surprising that measures of memory relate closely to MCI in general and

amnestic MCI in particular. In a recent study using the Californian Verbal Learning Test (CVLT), MCI subjects displayed a pattern of deficits characterized by reduced learning, rapid forgetting, increased recency recall, elevated intrusion errors, and poor delayed recognition memory with increased false positives (Greenaway et al., 2006). This pattern closely resembled that of AD patients. MCI performance was significantly worse than that of controls and better than that of AD patients across memory indices. A discriminant function analysis revealed that delayed recall and total learning were most accurate in differentiating MCI, AD, and normal aging. Consistent with this, Nordlund et al. (2005) found a rather large decline in a measure of delayed logical memory in MCI subjects (η^2=0.15).

Using results from the French PAQUID study, Amieva et al. (2005) analyzed scores on the Benton Visual Retention Test which measures visual memory, the Isaacs Set Test which assesses verbal fluency and the Similarities subtest of the Wechsler Adult Intelligence Scale (WAIS) that measures abstract thinking. They found that scores on all measures were depressed several years before onset of AD. Backman et al. (2001) showed that episodic memory was impaired up to 6 years before the occurrence of dementia (The Kungsholmen project) while Hall et al. (2001) reported memory impairment 7 years before dementia diagnosis (The Bronx cohort study).

Memory usually declines with age. Episodic memory shows the greatest decline (Mitchell, Brown, & Murphy, 1990), while short term memory declines little (Nilsson, 2003) and procedural memory is unchanged (Fleischman, Wilson, Gabrieli, Bienias, & Bennett, 2004). Measures of immediate and delayed recall as well as recognition memory on the CVLT decline with age (Sigfúsdóttir, 2008). Semantic

knowledge, such as vocabulary, actually improves somewhat with age (Verhaeghen, 2003).

Men consistently achieve lower scores than women on tests of verbal memory (Kramer, Yaffe, Lengenfelder, & Delis, 2003). Lengenfelder et al. (2000) found that women used semantic clustering more efficiently than men, performing better on measures of semantic learning, immediate and delayed recall on the CVLT-II. These results were replicated by Sigfúsdóttir (2008). She also found that education was related to better performance on these measures. Women have been found to retain their memory function better with age than men in younger adulthood but this difference is not found at older ages (Kramer et al., 2003).

Executive functioning

The term *executive functioning* refers to those processes by which people optimize their performance on multicomponent tasks (Robbins et al., 1998). It is used to describe brain processes responsible for higher cognitive functions such as planning, cognitive flexibility, abstract thinking, rule acquisition, inhibition of inappropriate actions, and the selection of relevant sensory information. MCI subjects are impaired compared to normals on tests of cognitive planning but differences on tests of inhibition of prepotent responses (no-go accuracy, the Stroop effect, and negative priming) are not significant (Zhang, Han, Verhaeghen, & Nilsson, 2007). Nordlund et al (2005) reported non-significant differences on a Stroop task and the Wisconsin Card Sorting Test. However, the number of participants was rather small (24 in the smallest group), limiting the power of the statistical tests.

Use of strategy on tests of spatial working memory (CANTAB), spatial working memory span, attentional set shifting and planning decrease slightly with age

(Robbins et al., 1998). Another study using the AGES data found strategy use on the CANTAB, a measure of working memory (Digit Span Backward) and Stroop to decrease with age (Sigfúsdóttir, 2008) and increase with educational level. Women performed better on the Stroop task while men outperformed women on the spatial working memory task.

Study goals

Dementia develops over a long time; subtle symptoms appear many years before diagnostic criteria are met (Amieva et al., 2005; Hall et al., 2001). Due to increasing longevity, the prevalence of AD is expected to increase in coming decades. Early detection and intervention in persons with mild cognitive symptoms who are at risk for progressing to AD is therefore very important. Amnestic MCI has been consistently singled out as an important risk factor for AD (e.g. Winblad et al., 2004). There is a shortage of studies separately investigating the attributes of multidomain amnestic MCI. The main aims of this study were:

1. To describe the prevalence of the two subtypes of amnestic MCI in the Icelandic elderly population (older than 65 years).
2. To examine the associations of age, gender and education level with single- and multidomain aMCI.

Method

Participants

The Age Gene/Environment Susceptibility- Reykjavik Study (AGES)

The Age Gene/Environment Susceptibility- Reykjavik Study (AGES) is a joint effort of the Icelandic Heart Association and the National Institute on Aging, USA. It is aimed at investigating the contributions of environmental factors, genetic susceptibility and gene–environment interactions to the aging of the neurocognitive, cardiovascular, musculoskeletal, body composition and metabolic systems (Harris et al., 2007). The study commenced in 2002 and its first wave was finalized in February 2006. The participants are from a cohort of men and women, born in 1907–1935 and living in Reykjavik in 1966. The whole cohort, 30.795 people were invited to participate in study initiated in 1967 by the Icelandic Heart Association. Since 1967, cohort members have participated in up to six examinations, and have been under continuous surveillance for vital events. In 2002, surviving cohort members were re-invited to participate in the AGES-Reykjavik. The examination included a structured survey instrument, cognitive testing, and brain magnetic resonance imaging (MRI). Those participants who were unwilling or unable to come to the test site were tested at home. The response rate was 72%; the total number of participants amounted to 5764 (ibid.). The first wave of the AGES-Reykjavik study was completed in 2006 and the second wave is currently in progress.

The study sample

The participants are the first 2300 cohort members who completed the required examination. Inclusion criteria were: no home visit and no dementia. Those 56 participants who were unwilling or unable to come to the testing site were excluded from the study. Of those, 28 were demented, 18 had MCI, and 10 were cognitively unimpaired. Their age span was 67 to 95 years, but only 3 were under 80 years of age. In addition, one hundred demented participants were excluded from the study. Finally, nine participants were excluded because information on their educational status was missing. This left 2135 participants in the study, 897 men and 1238 women.

Data collection and consent

The current study is cross-sectional, using data from the first wave of the AGES study. Data collection methods are described in Harris et al. (2007). AGES-Reykjavik was approved by the Icelandic National Bioethics Committee (VSN 00-063), the Icelandic Data Protection Authority, and by the Institutional Review Board of the US National Institute on Aging, National Institutes of Health. Informed consent was signed by all participants. The current study was approved by the AGES steering committee.

Measurements

Mini Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, & McHugh, 1975) is a short screening test for cognitive dysfunction. It measures orientation, attention, memory, language and spatial perception. The maximum score is 30, reflecting perfect performance. MMSE has been found to have moderate to high reliability coefficients, demonstrate a high level of sensitivity for cognitive deficits in patients suffering from moderate to severe Alzheimer's disease, and reflect the cognitive decline typical of dementia patients (Tombaugh & McIntyre, 1992; in Tombaugh, McDowell, Kristjansson, & Hubley, 1996).

Digit Symbol Substitution Test (DSST)

The Digit Symbol Substitution Test is part of the Wechsler Adult Intelligence Scale-III (Wechsler, 1998). This is a measure of attention, perceptual speed, motor speed, visual scanning and memory. The subject is given a piece of paper with nine symbols corresponding with nine digits. Next on this piece of paper are three rows of digits with empty spaces below them. The subject is asked to fill in as many corresponding symbols as possible in 120 seconds but in the current study only 90 seconds were used. First a practice trial was given upon successful completion of which, the full test was administered. If the participant failed to complete the practice trial, the administration was discontinued.

Stroop Color-Word Test (SCWT)

Many versions of the SCWT exist and the number of stimuli varies between studies. In the current study, the version of Houx, Jolles and Vreeling was administered (1993). Participants were required to read out loud/name 40 stimuli (5x8) from an A4 sheet of paper. The test was in three parts; participants had two minutes to finish the first two parts and three minutes to finish the last part. The first two parts of the test measure cognitive processing speed while the last part measures executive functioning: the control of attention and inhibition of an automated response (reading words). In the first part the participant is required to read out loud the words: 'blue', 'green', 'red' and 'yellow', printed in black ink. In the second part subjects are asked to name the colors of squares in the same colors (blue/green/red/yellow). In the third part, the participant is required to name the color of the ink in which the words are printed, rather than reading the words. The task is made harder by the fact that the words themselves denote the same colors as before, but not the same as the color of the ink. For example, the word 'red' is written in blue ink and the participant is required to say 'red' while ignoring the meaning of the word. Total score on each part of the test was computed by subtracting the number of wrong answers from the total number of possible correct answers and then dividing by the time (in seconds) it took the subject to finish this part of the test. The higher the score, the better the performance.

Cambridge Neuropsychological Test Automated Battery - CANTAB

CANTAB is a computerized battery of tests of cognitive functioning. The current study makes use of two of these tests: Spatial Working Memory test and Motor Screening test (Robbins et al., 1994). A touch screen was employed. The

participants sat in front of the screen roughly 60 cm away from the screen, using the dominant hand to touch the screen.

Motor Screening test: The Motor Screening test is typically administered at the beginning of a test battery, and serves as a simple introduction to the touch screen for the subject. If a subject is unable to comply with the simple requirements of this test it is unlikely that they will be able to complete other tests successfully. This test therefore screens for visual, movement and comprehension difficulties. Administration time is around 3 minutes. Subjects must touch the flashing cross which is shown in different locations on the screen. This test has two outcome measures which measure the subject's speed of response and the accuracy of the subject's pointing.

Spatial Working Memory Test: SWM is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assesses heuristic strategy. This test is a sensitive measure of frontal lobe and 'executive' dysfunction. Administration time is around 8 minutes, depending on level of impairment. The test begins with four colored squares (boxes) being shown on the screen. The aim of this test is that, by touching the boxes and using a process of elimination, the subject should find one blue 'token' in each of a number of boxes and use them to fill up an empty column on the right hand side of the screen. The number of boxes is gradually increased, until it is necessary to search a total of eight boxes. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. The twenty-four outcome measures for SWM include errors (touching boxes that have been found to

be empty and revisiting boxes which have already been found to contain a token), a measure of strategy, and latency measures.

In the current study, the first trial is a practice trial with three boxes. The test administrator demonstrated how the test works and guided the participant through the test rules. Additionally, the test was modified so that instead of four trials for each number of boxes, (4, 6 and 8), a total of 12 trials, there were only two trials for each number of boxes, a total of 6 trials.

The California Verbal Memory Test (CVLT)

The California Verbal Memory Learning Test (Delis, Kramer, Kaplan, & Ober, 1987) is used to test immediate, delayed and recognition memory, learning, free recall, interference and the potential for semantic clustering to aid recall. The test involves the oral presentation of a 16-word list (list A) over four immediate recall trials (the full test includes five trials), followed by delayed free recall[2], cued recall and recognition memory trials for list A. The key variables in the current study are: (a) sum of correct recall over the first four trials, (b) learning curve over the first four trials, (c) delayed free recall, (e) delayed recognition memory, (f) false positives during testing of delayed recognition memory and (e) the ratio of delayed to immediate recall.

Pattern comparison

Pattern comparison measures visual processing speed. The participants compare two patterns and decide if they are different or the same (Salthouse & Babcock, 1991). The test is preceded by a practice trial with three pattern pairs,

[2] The full version includes an immediate recall trial of an interference list (list B), which was omitted.

followed by the actual test which consisted of two separately timed (30 s) administrations of (max) 30 pairs. The line patterns were connected lines in an invisible 4x4 matrix, with three, six, or nine line segments in each member of the pair. The examinee was to classify each pair as "same" or "different" as rapidly as possible. One half of the pairs in each page were same and one half were different. Pairs requiring a 'different' response were constructed by altering one line segment in one member of the pair. The total correct answers on both trials constitute the total score.

Digit Span Forward and Backward

This test is part of Wechsler Adult Intelligence Scale-III. Digits Forward measure attention and immediate memory whereas Digits Backward measure working memory/executive function (Wechsler, 1998). The participant is required to repeat the digits read out loud by the test administrator, in the same order as read (Digits Forward) or in the reverse order (Digits Backward). The test starts with two digits, then the number of digits increases up to a maximum of nine digits for Digits Forward, eight digits for Digits Backward. The participant got two trials for each number of digits. The test was discontinued when the participant failed two continuous same-number trials.

Questions on memory

The study includes questions from a questionnaire designed for the AGES study. There were six questions addressing subjective memory problems used in the current analysis (translated from Icelandic), the seventh question is from the Icelandic version of the Geriatric Depression Scale (Sheikh & Yesavage, 1986; Valdimarsdóttir, Jónsson, Einarsdóttir, & Tómasson, 2000):

1. Do you forget the names of your friends more often now than 12 months ago?
2. Do you forget where you put things more often now than 12 months ago?
3. Is it harder to find the right words now than 12 months ago?
4. Is it harder to find your way in familiar places now than 12 months ago?
5. Do you feel that your memory has gotten worse in the last 12 months?
6. Have you ever had your memory tested because you were worried about it?
7. Do you feel you have more problems with memory than most of your age peers? ('of your age peers' is an addition in the Icelandic version)

Quality control

There was strict quality control on all tests of cognitive function. At the end of each administration the trained test administrators evaluated the quality of the data. Any problems with administration were coded, making possible the elimination of flawed test scores before data analysis. All tests were normally distributed in the cohort and inter-rater reliability was very good - Spearman correlations for specific cognitive tests range from 0.96 - 0.99 (Saczynski et al., 2008) .

Implementation and data analysis

Study definition of amnestic MCI

In line with comparable studies, (Apostolova & Cummings, 2008), single domain amnestic MCI was defined as a score of 1.5 or more standard deviations below the mean on any of the following measures: immediate memory, learning curve, delayed memory (measured as ratio of delayed to immediate memory) or delayed recognition memory. In addition, participants had to answer at least one of

the seven questions on memory complaints affirmatively. Finally, to be classified as single domain amnestic MCI, participants had to be within normal range on all other cognitive measures.

Multidomain amnestic MCI was defined in the same way as single domain amnestic MCI, except that subjects had to score 1.5 or more standard deviations below the mean of at least one other cognitive measure besides memory.

As data on ADL of most subjects was not available, preserved ADL was not used as an inclusion criterion. Fisk, Merry, & Rockwood (2003) showed that the requirement of only minimal impairment in ADL can be removed without negative effects on the predictive validity, although naturally, prevalence estimates are increased. Defined this way, MCI covers all cognitive impairments milder than dementia, similar to CIND.

Variables

The current study includes measures relevant to the diagnosis and neuropsychological characteristics of MCI. Neuropsychological variables consist of items and/or composite scores on the MMSE, CVLT, DSST, Digit Span Forward and Backward, Figure Comparison, Modified Stroop Tests 1 to 3, as well as CANTAB motor speed and spatial working memory tests.

Calculation of standard scores

In studies of MCI, selected neuropsychological test norms are usually adjusted for age and education (Apostolova & Cummings, 2008). In this study we were interested in the variation of MCI with age and consequently did not wish to adjust

the scores with respect to age. On the other hand, men consistently achieve lower scores than women on tests of verbal memory (Kramer et al., 2003; Sigfúsdóttir, 2008). Therefore it was desirable to adjust the calculation of standard scores (z-scores) for gender so as not to overestimate the prevalence of amnestic MCI in men or conversely, underestimate the prevalence in women. Calculation of standard scores was therefore adjusted for gender and education.

Statistical analyses

Statistical analyses were performed using the SPSS (Statistical Package for Social Science) program version 13.0.

Results

Demographic characteristics and calculation of standard scores

Table 1 shows the mean and age of the participants, proportion having completed each level of education and mean scores on the MMSE, by gender. Age span was 66 to 92 years. The mean age of men and women is about the same, men are slightly more likely to have a higher education than women. The mean scores of men and women on the MMSE are similar, although statistically the difference is significant.

Table 1 Demographic characteristics of the sample.

Demographics N=2135	Men (897)	Women (1238)	Stat/sig
Age x (sd)	75,9 (5,44)	75,8 (5,60)	t=0.5(ns)
Education:			
elementary/secondary school high school/university	68% 32%	74% 26%	$\chi^2(1)=7.6$*
MMSE x (sd)	27,1 (2,18)	27,4 (2,14)	t=-3.2*

*The mean difference is significant at the 0.05 level

Standard scores were calculated using the original sample of 2135 participants, after removing invalid test scores[3]. Standard scores were calculated separately for men and women and two levels of education (elementary/secondary school vs. high

[3] If the participant did not finish the test, or had functional or perceptual disabilities that influenced performance on the test, test scores were considered invalid.

school/university). Table 2 shows the number of participants in each of the four groups. Standard scores were thus adjusted for the influence of gender and education.

Table 2: Number of participants in each of the four groups

Education	Men	Women
Low	611	911
High	286	327
Total	897	1238

1557 participants did not present any problems on the administration of any cognitive test and answered all relevant questions. These participants were therefore eligible for the application of the definition for amnestic MCI. Table 3 shows the demographic characteristics of this sample, which are similar to the whole sample. The age span was 66 to 92 years.

Table 3: Demographic characteristics of the sample

Demographics N=1557	Men (664)	Women (893)	Stat/sig
Age x (sd)	75,8 (5,46)	75,5 (5,48)	t=1.3(ns)
Education:			
elementary/secondary school	67%	73%	$\chi^2(1)=7.7$*
high school/university	33%	27%	
MMSE x (sd)	27,2 (2,04)	27,5 (2,07)	t=-2.8*

The sample was divided into five age groups for analytical purposes (see Table 4). The number of participants in each cell are not equal but enough for most

analytical purposes. Unfortunately there were fewer participants in the oldest age group (85+), which limits the power of the analysis to reach significance in this age group.

Table 4: Number of men and women in each of five age groups

Age-group	Men	Women	Total
-69	111	140	251
70-74	183	264	447
75-79	184	239	423
80-84	139	216	355
85+	47	34	81
Total	664	893	1557

Prevalence of amnestic MCI

Applying the criteria for amnestic MCI we obtained a prevalence of 6.9% for both single and multiple domain variants, resulting in a total of 13.8% prevalence of amnestic types MCI in the sample. In all, 216 subjects met the criteria, whereof half (108) were categorized as belonging to each type of amnestic MCI.

Age and gender differences

Amnestic MCI, both types combined: Table 5 shows the number of men and women in each age group who met criteria for either type of amnestic MCI. Women were, on the whole, less likely to have amnestic MCI ($\chi^2(1) = 5.5$, $p<0.05$), despite gender having been controlled for in the calculation of standard scores. The risk ratio of men compared to women was 1.3. A chi-square test on combined amnestic MCI types by gender and age group was significant only in the youngest age group,

suggesting that women younger than 69 are less likely than men to have either of the amnestic MCI ($\chi^2(1) = 7.7$, $p<0.01$). When age was dichotomized, women, age 74 and younger, were only half as likely as men to have amnestic MCI (4.7% of women vs. 9.9% of men; $\chi^2(1) = 7.1$, $p<0.01$), while for participants older than 74 there was no significant difference (18% for women vs. 21% for men; $\chi^2(1) = 1.3$, ns.). Thus, in the younger age group, men had a 2.1 times higher risk of aMCI than women. Finally, when calculated separately for single domain aMCI and multidomain aMCI it became clear that the difference was largely, if not completely, due to a large difference in proportional rates of men and women having single domain aMCI in this age group (see below).

Table 5: Number and proportions of men and women in each age group meeting criteria for amnestic MCI, both domains combined.

Age-group	Men	Women	Total
-69	13 (12%)	4 (3%)	17 (7%)
70-74	16 (9%)	15 (6%)	31 (7%)
75-79	27 (15%)	32 (13%)	59 (14%)
80-84	35 (25%)	42 (19%)	77 (22%)
85+	17 (36%)	15 (44%)	32 (40%)
Total	108 (16%)	108 (12%)	216 (14%)

Figure 2 shows how the proportions of combined amnestic MCI grow with age with the exception of men in the youngest group having higher proportional rates than men in the age group 70-74. This difference was not significant and is solely due to the high proportion of men in the youngest age group having single domain amnestic

MCI. Note that the higher proportion of women than men in the 85+ age group is not significant ($\chi^2(1) = 0.52$, ns.). No other differences in Table 5 reached significance.

Amnestic MCI prevalence increased with age ($r_{pb} = 0.27$, $p<0.01$). Test for curvilinearity was significant[4] (deviation from linearity: $\chi^2(3) = 19.417$, $p<0.005$).

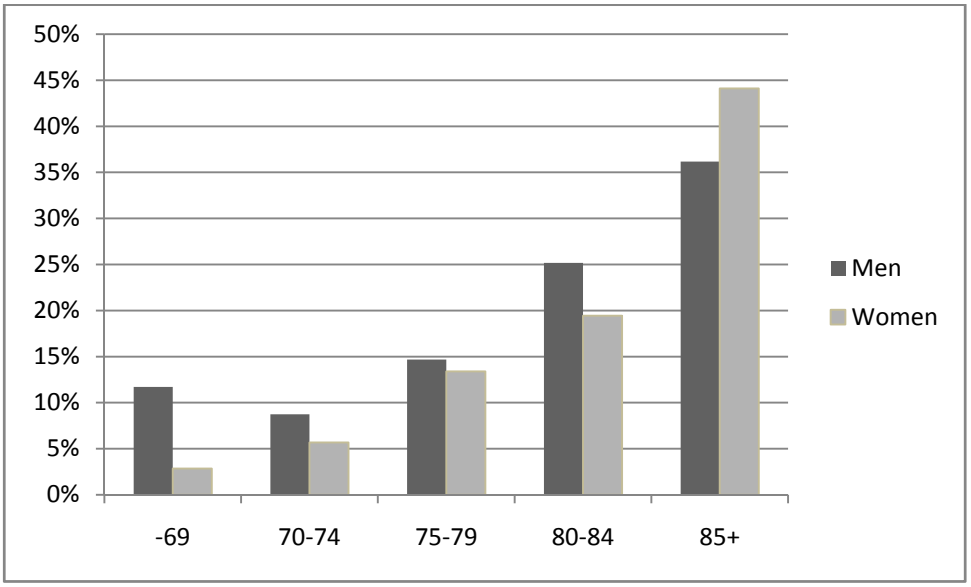

Figure 2: Proportion of men and women in each age group meeting criteria for amnestic MCI, types combined.

Single domain amnestic MCI: Table 6 shows the number and proportions of men and women in each age group who met criteria for single domain amnestic MCI. Prevalence increased linearly with age ($r_{pb} = 0.096$, $p<0.001$)[5]. Test for curvilinearity was not significant ($\chi^2(3) = 4.354$, ns.). Women were slightly less likely than men to have single domain amnestic MCI ($\chi^2(1) = 5.801$, $p<0,05$) but, controlling for age, the

[4] Chi-square for deviation from linearity obtained by subtracting the linear chi-square value from the Pearson chi-square value (Agresti, 2002; in Howell, 2007, pp. 289-290).

[5] The use of Pearsons r with ordinal variables by nominal or ordinal dichotomus variables is described by Agresti (2002; in Howell, 2007, pp. 289-290). In calculating the correlation between age and each type of aMCI, the type not included in the analysis was coded as 0. Thus, the aMCI variable was dichotomous; 0 for no aMCI or type a, and 1 for type b aMCI. In the case of combined types, type a and b were coded as 1.

difference was only significant in the age group under 69 years ($\chi^2(1) = 9.068$, $p<0.01$).

Table 6: Number and proportions of men and women in each age group meeting criteria for amnestic MCI, single domain

Age-group	Men	Women	Total
-69	11 (9.9%)	2 (1.4%)	13 (5.2%)
70-74	10 (5.5%)	8 (3.0%)	18 (4.0%)
75-79	15 (8.2%)	15 (6.3%)	30 (7.1%)
80-84	16 (12%)	22 (10%)	38 (11%)
85+	6 (13%)	3 (9%)	9 (11%)
Total	58 (8.7%)	50 (5.6%)	108 (6.9%)

Within the youngest age group, there was a significant negative correlation of gender with having single domain aMCI[6] ($\varphi = -0.19$, $p<0,05$), but not within the other age groups. Here, the risk ratio of men, compared to women, was 6.9. Thus, men under 70 yrs were almost seven times more likely to have single domain aMCI than women in the same age group! Among women, there was a significant relationship between age and single domain aMCI, the risk of single domain aMCI increasing with age ($r_{pb} = 0.13$, $p<0.001$; $d = 0.57$), but not among men ($r_{pb} = 0.06$, ns.). The lack of significant relationship for men may be due to a very high proportion of men in the youngest age group having single domain aMCI. None of the other gender differences observed in Table 6 were significant. Figure 3 shows how the proportion of men and women having single domain aMCI changes with age.

[6] aMCI was dichotomized, coded as 0 for no aMCI or multidomain aMCI or 1 for single domain MCI. Gender was coded 1 for male and 2 for female.

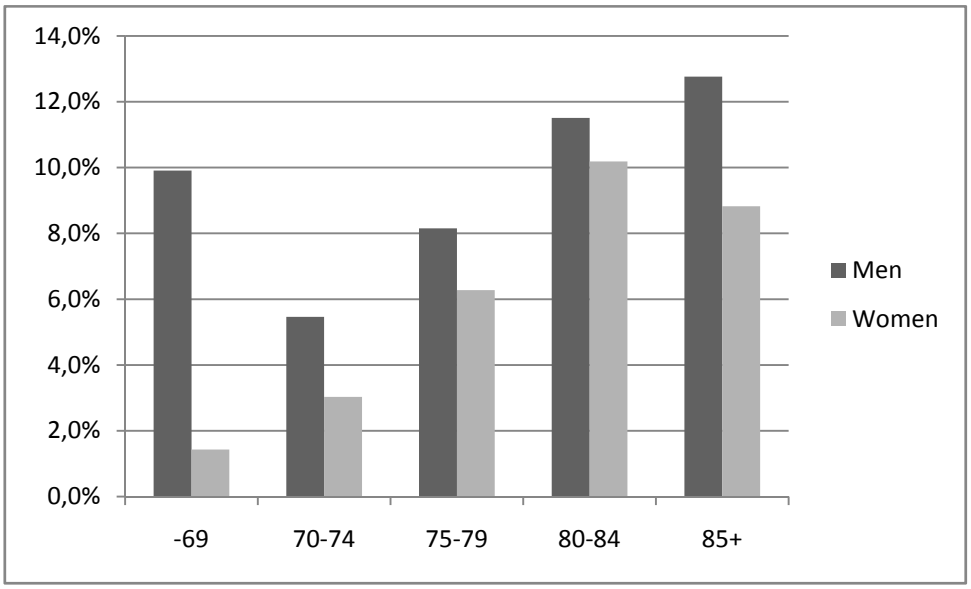

Figure 3: Proportion of men and women in each age group meeting criteria for amnestic MCI, single domain.

Multidomain amnestic MCI: Table 7 shows the number of men and women in each age group who met criteria for multidomain amnestic MCI.

Table 7: Number and proportions of men and women in each age group meeting criteria for amnestic MCI, multidomain

Age-group	Men	Women	Total
-69	2 (1.8%)	2 (1.4%)	4 (1.6%)
70-74	6 (3.3%)	7 (2.7%)	13 (2.9%)
75-79	12 (6.5%)	17 (7.1%)	29 (6.9%)
80-84	19 (14%)	20 (9.3%)	39 (11%)
85+	11 (23%)	12 (35%)	23 (28%)
Total	50 (7.5%)	58 (6.5%)	108 (6.9%)

There was no significant difference between the genders in overall multidomain aMCI prevalence ($\chi^2(1) = 0.632$, ns.), nor in any age group. However,

when calculated separately for women, subjects older than 84 were more likely to have multidomain aMCI than subjects younger than 84 ($\varphi = 0.232$, $p<0.001$).

In Figure 4 we see a steady rise in amnestic MCI, multidomain type, for both genders, rates seem to be growing faster in the older age groups than in the younger age groups. Prevalence increased linearly with age[7] ($r_{pb} = 0{,}21$, $p<0.001$) and chi-square test for curvilinearity was significant (deviation from linearity: $\chi 2(3) = 21.136$, $p<0.01$). This suggests that the nonlinear shape of the relationship between age and combined types of aMCI (see Figure 2) is accounted for by the multidomain type.

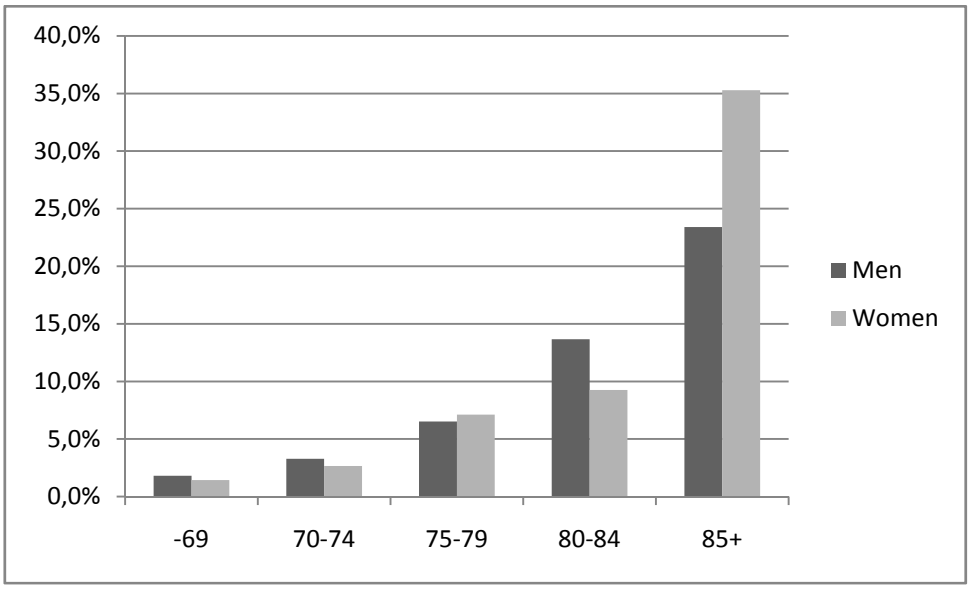

Figure 4: Proportion of men and women in each age group meeting criteria for amnestic MCI, multidomain.

Finally, there was a positive correlation between age and type of aMCI[8] ($\tau = 0.19$, $p<0.001$) suggesting that single domain aMCI subjects tend to be younger than multidomain aMCI subjects. Univariate ANOVA gave a significant effect for aMCI

[7] Coded 0 for nonamnestic or sdaMCI and 1 for mdaMCI.
[8] no aMCI coded as 0, single domain coded as 1 and multidomain coded as 2. Kendall´s tau was computed.

on age ($F(2)=46.979$, $p<0.001$) but neither the effect of gender ($F(1)=0.678$, ns.) nor gender-aMCI interaction was significant ($F(2)=1.750$, ns.). Post-hoc comparisons[9] reveal that mean age differences between all aMCI subtypes were significant ($p<0.01$), single domain aMCI subjects being older than subjects without aMCI and multidomain aMCI subjects being older than single domain aMCI. Chi-square test for curvilinearity for the relation between age and type of aMCI was significant (deviation from linearity: $\chi^2(7) = 24.938$, $p<0.005$).

Education effects

There was no significant relationship between the two education levels and aMCI ($\chi^2(2)=1.865$, ns.). However, a univariate analysis of variance revealed a significant interaction between aMCI subtype and education level on age ($F(2) = 3.9$, $p<0.05$) such that the mean ages of subjects with low educational attainment increased less going from no aMCI to single type aMCI to multiple domain aMCI, compared to that of subjects with a higher educational level (see Figure 5).

[9] Bonferroni adjustment for multiple comparisons

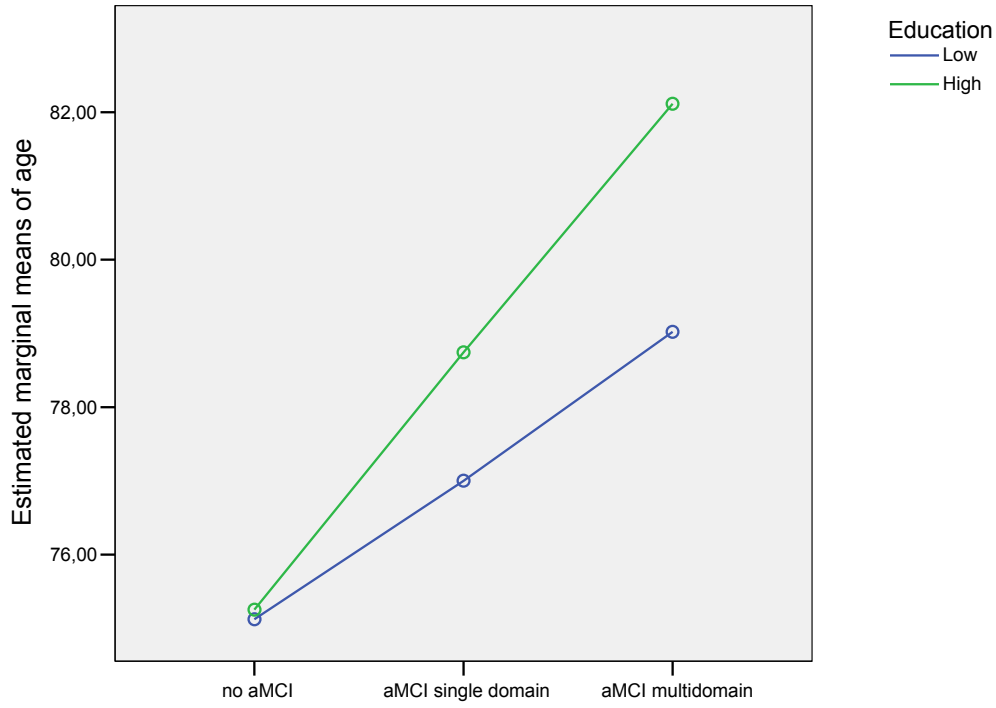

Figure 5: Interaction between educational level and aMCI subtypes on age.

Neuropsychological measures

In Table 8 we see that performance on measures of cognitive processing speed and attention is worse in participants meeting criteria for multi- than single domain aMCI, as should be expected. A one-way Anova was performed, yielding a significant difference between all three groups, no aMCI, single domain aMCI and multidomain aMCI. Post hoc comparisons[10] revealed that people with multidomain aMCI performed significantly worse than non aMCI and single domain aMCI on all

[10] All post hoc comparisons were corrected for multiple comparisons using Bonferroni adjustment

measures of speed and attention ($p<0.05$) and single domain MCI did not perform differently from non aMCI on any measures.

Table 8: Measures of cognitive processing speed and attention. Mean scores and SD in parentheses.

	No aMCI	Single domain aMCI	Multidomain aMCI
N	1341	108	108
Age	75.1	77.6	79.9
Figure_comparison	18 (5)	18.1 (4,5)	12.1 (4,6)
Stroop1	2.1 (0.4)	2.1 (0.3)	1.7 (0.4)
Stroop2	1.5 (0.3)	1.5 (0.2)	1.1 (0.3)
CANTAB Reaction time	1031.5 (302.2)	1002.8 (233.8)	1247.8 (428.6)
DSST total correct	31.4 (10.3)	30.8 (8.4)	20 (7.9)
Digit span forward	7.7 (2)	8.1 (1.9)	6.9 (1.6)

One-way analysis of variance also revealed the same pattern with measures of executive functions. The means and standard deviations of the three groups can be seen in Table 9.

Table 9: Measures of executive functions. Mean scores and SD in parentheses

	No aMCI	Single domain aMCI	Multidomain aMCI
Stroop3	0.4 (1.7)	0.5 (1.3)	0.2 (1.6)
Digit span backward	4.9 (2.1)	5 (1.8)	3.8 (2)
CANTAB Strategy errors	19.6 (2.2)	19.2 (1.9)	20.6 (2.1)

In Table 10 we see that multidomain aMCI perform worse than single domain aMCI on immediate and delayed recall and recognition discriminability. A one way Anova and Kruskal-Wallis test confirm that the groups differ on all measures of memory ($p<0.001$). Post hoc comparisons reveal that there are significant differences between all three groups on immediate and delayed recall and recognition discriminability ($p<0.05$). However, the learning curve of single domain aMCI is not different from that of multidomain aMCI and the difference between single domain MCI and multidomain MCI on the ratio of delayed to immediate memory was not significant.

Table 10: Measures of memory. Mean standard scores and SD in parentheses.

	No aMCI	Single domain aMCI	Multidomain aMCI
Immediate recall	0.2 (0.9)	-0.7 (0.9)	-1.1 (0.9)
Learning curve	0.1 (0.9)	-0.8 (1.1)	-0.8 (0.9)
Delayed recall	0.2 (0.9)	-0.9 (1)	-1.2 (0.9)
Recognition discriminability	0.2 (0.8)	-0.9 (1.1)	-1.2 (1.2)
Ratio delayed to immediate recall	0.1 (0.8)	-0.5 (1.5)	-0.7 (1.3)

Discussion

Prevalence of amnestic MCI and subtypes

We obtained a prevalence of 6.9% for both single and multiple domain variants, resulting in a total prevalence for amnestic types of MCI of 13.8%. This is considerably higher than the prevalences of 3-6% which have been reported in a number of other studies (Fisk et al., 2003; Ganguli et al., 2004; Hanninen et al., 2002; Lopez et al., 2003). However, Artero et al. reported a 16.8% prevalence of amnestic MCI (Artero et al., 2006), which is closer to our results. As discussed above, different estimates of prevalence often arise out of different study definitions and different age distribution of samples. The present study definition of aMCI did not exclude people on the basis of difficulties with daily life. Therefore, the findings may be more comparable to AACD with memory impairment, where impairments in activities of daily living (ADL) are not cause for exclusion. The prevalence of AACD w/memory impairment is around 9% (Busse et al., 2003a) among subjects older than 75 years, which is still lower than our estimate. However, AACD excludes people having had any present or past medical or psychiatric condition, or psychoactive substance use, that can cause cerebral dysfunction (Levy, 1994). Had they been included, the estimate might have been higher.

The prevalence of single domain aMCI varies considerably between studies, 3 -7% (Busse et al., 2003c; Das et al., 2007; Di Carlo et al., 2007). Fisk et al. (2003) reported 1.5% prevalence based on clinical evaluation rather than test scores, but clinical evaluation is known to produce lower estimates (DeCarli, 2003). Most of these estimates are slightly lower than in the current study, which again may perhaps be explained by this study not applying the criterion of mostly preserved ADL.

Only one study seems to have investigated the prevalence of multidomain amnestic MCI, obtaining an estimated prevalence of 0.9% in subjects 75 years and older (Busse et al., 2006) which is much lower than our estimate of 6.9%. Even when criteria were modified to include subjects who did not complain of cognitive problems, the estimate only rose to 1.8%. It is possible that the criterion of intact activities of daily living played a larger role in the classification of multidomain amnestic MCI; they are by definition more cognitively impaired than single domain aMCI and many of them may have been functionally impaired. This may be why Busse et al. obtained such a comparatively low prevalence of multidomain aMCI.

Age and gender differences

In the current study, amnestic MCI increased with age, a replication of the results of many other studies (Hanninen et al., 2002; Lopez et al., 2003; Solfrizzi et al., 2004). Men had a greater risk of aMCI overall than women, risk ratio 1.3. This is the same as the incidence risk ratio in a recent report from the Mayo Clinic Study of Aging where men had a higher incidence of MCI overall than women, in a sample aged 70 - 89 years (Roberts et al., 2008)[11]. They found an incidence of 17.7% in men compared to 13.4% in women but it is hard to compare these results with the current study, since Roberts and al. were measuring incidence of MCI (amnestic and non-amnestic), whereas we were measuring prevalence of amnestic MCI. However, the similarity of the male-to-female risk ratios is still intriguing.

We found that the gender difference was largely due to a large number of men in the youngest age group, 66-69 years, having single domain aMCI. These men had an incredible sevenfold risk of having single domain amnestic MCI compared to

[11] This information is from a conference abstract and therefore not complete. Note that incidence is usually lower than prevalence in chronic disorders.

women in the same age group. This is surprising, especially since no adjustments for age were made in calculation of the standard scores, which formed a basis for the MCI subgroup classification. Younger people were therefore classified on the same terms as older people, which should have depressed the prevalence estimates for the younger age groups (because younger people tend to perform better on tests of memory). Das et al. (Das et al., 2007) obtained similar results for single domain amnestic MCI in India (their subjects were younger than in the current study, but much poorer and therefore might age faster).

When age was dichotomized, women, age 74 and younger, were only half as likely as men to have amnestic MCI, while for participants older than 74 there was no significant gender difference. Thus, in the younger age group, men had a 2.1 times higher risk of having aMCI than women. In the oldest group (85+) prevalence of aMCI was slightly higher in women (44%) than in men (36%) but the difference was non-significant. These results are in line with Letenneur at al. (1999), who found men to have a higher risk of developing Alzheimer´s dementia under the age of 80, while women had a higher risk after the age of 80. As seen in Figure 2, more women than men in the oldest age group were classified as aMCI, but statistical significance was not reached. However, there were less than half as many participants in the oldest age group as in any of the other age groups, which affected the power of the statistical analysis. Other studies have not found age by gender interactions (Busse et al., 2003a; Hanninen et al., 2002; Solfrizzi et al., 2004).

Multidomain aMCI increased with age, in a curvilinear fashion, but no relation to gender was observed. Busse et al. did not report on the relationship of MCI subtypes with age (Busse et al., 2006).

Finally, there was a significant positive correlation between age and type of aMCI and a negative correlation between gender and type of aMCI, signifying that single domain aMCI subjects tend to be younger and male, while multidomain aMCI subjects tend to be older and female. This is in line with the above results. However, the correlation coefficient was much higher for the relation of age and type of aMCI than that for gender and type of aMCI (τ =0.19 vs. τ =-0.06). Thus, although a higher proportion of female subjects had multidomain aMCI (6.5%) than single domain aMCI (5.6%), multidomain aMCI was still more prevalent in men (7.5%). Looking at the graph for multidomain aMCI (Figure 4) we see that there is a great increase in the prevalence in women, 85 years and older, which was significant. If the mean age of the sample had been older, say around 80 years, the prevalence in women might have been significantly higher than in men, like the prevalence of AD in the older subjects of Letenneur et al. (1999).[12]

When comparing with other studies, the definition of aMCI is a confounding factor. Very few studies have investigated multidomain aMCI prevalence; most have combined amnestic and non-amnestic multidomain MCI. Therefore, the study definition of aMCI affects the age-gender pattern observed and complicates the comparison with other studies. Most studies have not found gender differences in the prevalence of MCI (Hanninen et al., 2002; Lopez et al., 2003; Solfrizzi et al., 2004). Where the ratio of subjects under 75 is high, as in the current study, memory impairments (amnestic MCI, AACD and AAMI) tend to be more prevalent in men than in women (Ganguli et al., 2004; Hanninen et al., 1996; Koivisto et al., 1995). Busse et al (2003a) used the Mayo Clinic definition, which roughly corresponds to

[12] However, had the sample been older we might have missed the great prevalence of single domain aMCI in men younger than 69. Letenneur et al had a similar age span but the sample was more than double the size of our sample, greatly increasing the power of the analysis in the older age groups.

single domain aMCI. They did not find gender differences in an older sample (75+). This is in line with our results for older subjects with single domain aMCI.

This is one of the first studies to separately estimate the prevalence of the two subtypes of amnestic MCI. There were no significant gender differences in prevalence of multidomain aMCI which increased with age in a curvilinear fashion. Busse et al. (Busse et al., 2006) did not report on the relationship of aMCI subtypes with age. We have observed that multidomain aMCI has distinct features from those of single domain aMCI: the prevalence of the single type increases linearly with age and it is more prevalent with men under 75, but no gender difference was observed in subjects, 75 and older. On the other hand, the multidomain type is not significantly affected by gender (although an insignificant trend toward greater female prevalence was observed in the oldest age group) and has a curvilinear positive relationship with age. The implications of the different shapes of the relationships with age are uncertain and deserve a separate study.

Education effects

There was no separate significant relationship between education and aMCI in this study but most studies do find a relationship between low education and aMCI (Panza et al., 2005). It is possible that the education range was too broadly defined in the current study, using only two education levels. However, we did find an interaction between aMCI subtype and education level on age, such that the mean ages of subjects with low educational attainment increased less going from no aMCI, through single type aMCI, to multiple domain aMCI, compared to that of subjects with a higher educational level (see Figure 5). This is in accordance with studies

showing that highly educated people tend to develop MCI and dementia later in life than people with lower levels of education (Amieva et al., 2005; Stern et al., 1994)

Neuropsychological measures

Multidomain aMCI is defined by performing subnormally on tests other than memory, while single domain aMCI is defined by normal performance on these tests. Thus, not surprisingly, that was the relationship found when test results were related to MCI classification. It is also self-evident that the aMCI groups perform worse than the non-aMCI group on measures of memory. The interesting part is how the two aMCI groups compare on measures of recall, that is, whether all measures of memory are similarly affected in the two groups. Single domain aMCI performed better than multidomain aMCI on immediate and delayed recall and recognition discrimination but the learning curve and ratio of delayed to immediate recall were not significantly different. This suggests that the main difference between the groups lies in poorer immediate recall in the multidomain aMCI subjects. Poor immediate recall would affect their total score on delayed recall and recognition discrimination but not their learning curve or the ratio of delayed to immediate recall.

Strengths of the current study

The AGES-Reykjavík study is large, population based and longitudinal in design. Although the current study is cross-sectional, the participants will continue to partake in regular examinations and neuropsychological testing. The study began over four decades ago and there already exist extensive data on their midlife lifestyle, past and present physical and mental health parameters (such as volumetric brain measurements, blood pressure, blood cholesterol, exercise etc.) as well as genetic

information. The study therefore provides a singular opportunity to investigate possible causal factors in amnestic MCI and dementia.

The present study is one of the first to estimate the prevalence of multidomain aMCI. The definition of multidomain aMCI is similar to the definition of AD in that it requires impairment in memory and in at least one other cognitive function (APA, 2000). It will be very interesting to follow the rate of conversion to AD for this MCI subtype in the next wave of the Reykjavik-AGES study, which is already underway.

Weaknesses of the study design

Ideally, the diagnosis of MCI should be an objective one, relying only on valid and reliable test results. However, cognitive tests are usually not administered unless a person presents with a complaint of cognitive problems or deterioration. A complaint of cognitive deterioration validates that test results reflect deterioration from a previous state, instead of a congenital cognitive deficiency. The drawback of relying on complaints is that as the cognitive deficiency becomes more serious, the patient´s insight diminishes and he may not realize the extent of his cognitive problems. In these cases, family members are usually the ones to call attention to the problem. Unfortunately, in the current study, information from family members on the participants´ cognitive state was not collected, unless participants failed the screening tests and underwent further neuropsychological testing and medical evaluation for possible dementia. Therefore, complaints from participants had to suffice for substantiating the test results and more severe cases of amnestic MCI might have been missed.

Another weakness of the study design is that the cognitive test battery was not complete as we did not measure visuospatial function or language. As a consequence

some multidomain aMCI subjects may have incorrectly classified as single domain aMCI and some may have been missed altogether.

A third possible weakness is that data on ADL was not available for most subjects and ADL was therefore not applicable as an inclusion/exclusion criterion. However, as mentioned above, eliminating this criterion does not seem to negatively affect the predictive validity of MCI (Fisk et al., 2003).

Future directions of study

It would be interesting to take a closer look at the large group of men, 66-69 years old, who are classified as having single domain aMCI and investigate possible causes of the high proportional prevalence, for instance statistics on physical health and psychiatric disorders, brain imaging and genotypic information. Further, it will be informative to see how many convert to AD or other types of MCI and how many remain with single domain MCI or revert to normal. Additionally, other subtypes of MCI should be investigated, as well as the relation of all subtypes to more detailed educational levels.

The next wave of AGES will provide information on the predictive power of the aMCI subtypes and concerning the relation of amnestic MCI subtypes to volumetric brain measurements and conversion to dementia.

The implications of the different shapes of the relationships of single domain vs. multidomain aMCI with age are uncertain and deserve a separate study.

Finally, it is clear that despite movement toward a consensus on the definition of MCI, variability in study definitions of MCI subtypes still impairs comparability of studies and thus hampers progress in the field. The development of more specific standards for measuring the prevalence of MCI would therefore be desirable, e.g.

regarding neuropsychological testing, statistical cutoff scores, and measures of subjective/objective memory impairment and ADL.

CONCLUSION

Total amnestic MCI prevalence was estimated 13.8% in a large sample of non-demented elderly Icelanders. The prevalence of the subtypes single domain amnestic MCI and multidomain amnestic MCI was identical, at 6.9%. These figures are higher than in most studies, but a part of the explanation may be that the definition used did not require minimal impairment in activities of daily life. Amnestic MCI increased with age and men had a greater overall risk ratio, 1.3 of aMCI compared to women. Men between 66 and 69 years had an astonishing sevenfold risk of having single domain amnestic MCI compared to women in the same age group. No other studies have reported such a large gender difference in any type of MCI, although some studies do report greater male prevalence of aMCI. Men under the age of 75 had a risk ratio of 2.1 of having single domain amnestic MCI, compared to women, whereas, among subjects 75 and older, there was no significant gender difference. This type of age-gender interaction has never before been reported for the prevalence of MCI subtypes, though similar age-gender interactions have been observed for Alzheimer´s dementia. Multidomain aMCI increased with age in a curvilinear fashion, but no relation to gender was observed. No relations of aMCI subtypes with education were observed, possibly due to a broad categorization of educational levels. However, an interaction between aMCI subtype and education level on age was found, such that the mean ages of subjects with low educational attainment increased less going from no aMCI, through single type aMCI to multiple domain aMCI, compared to that of subjects with a higher educational level. This is in line with studies showing that highly educated people tend to develop MCI and dementia later in life than people with lower levels of education.

Finally, age was related to aMCI subtype, such that single domain aMCI subjects tended to be younger while multidomain aMCI subjects tended to be older. Further investigation will be conducted concerning the relation of amnestic MCI subtypes to volumetric brain measurements and conversion to dementia.

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