Review article

Mild cognitive impairment\(^1\) – a review of prevalence, incidence and outcome according to current approaches


Objective: Mild cognitive impairment is associated with an increased risk of developing dementia. However, agreement needs to be reached on clearly specified diagnostic criteria for mild cognitive impairment. The present paper critically reviews the different constructs of mild cognitive impairment on the basis of the available empirical evidence.

Method: All published papers on mild cognitive impairment during the last 15 years on Medline and other databases were reviewed.

Results: Age-specific prevalence and incidence rates according to the different constructs as well as the prognostic significance of the different constructs concerning the development of dementia are reported. Furthermore, a brief summary of recent research on possible risk factors for a negative course of mild cognitive impairment is provided.

Conclusion: As there is no construct to date that pools all efforts of defining mild cognitive impairment, the review provides suggestions for an agreement on constructive terminology and research practice.

Introduction

The discovery of the long preclinical phase of Alzheimer’s disease (AD) of up to 7 years (1) led to enhanced interest and research efforts in order to establish early diagnostic indices of dementia (2–4). In providing potential treatment options for delaying or, ideally, preventing further cognitive decline, the definition of high-risk populations is of utmost importance (5). Mild cognitive impairment is associated with an increased risk of developing dementia: patients develop dementia at a rate of 10–15%/year compared with healthy controls who develop dementia at a rate of 1–2%/year (6–8). However, data on the prevalence and incidence of mild cognitive impairment as well as the conversion rate to dementia, varies greatly according to the different definitional criteria applied. The rates of conversion to dementia reported in the literature for example vary from 1 to 25%/year (9), mainly because of the differences in criteria and assessment procedures applied. The current lack of agreement on terminology and specific diagnostic criteria poses problems both for clinicians in their work with patients and their families and for investigators studying the phenomenon. Furthermore, research into possible treatments for cognitive decline requires that agreement be reached on clearly specified high risk populations and their diagnostic criteria.

Aims of the study

This review aims at providing an overview of the research on the topic today. After a discussion of the diagnostic concepts, empirical data on their prevalence, incidence and outcome as well as the predictive utility of various measures are summarized.

Material and methods

The studies included in the present paper were found through a Medline, Psyclit and Psynex...
 search and by systematically checking through the bibliographies of relevant articles. Databanks were searched for relevant articles published during the last 15 years. The time criterion was chosen according to the publication of the proposed diagnostic criteria of age-associated memory impairment (AAMI) in 1986 (10). In providing the first operational definition it lead to increased research efforts to estimate the prevalence, incidence and outcome of mild cognitive impairment. Significant earlier writings concerning the conceptualization of mild cognitive impairment have been included in the review in order to follow the development of ideas historically where necessary. The major criterion for inclusion in this review was that the main focus of the study was on mild cognitive impairment.

Results

Critical review of research diagnostic criteria and constructs

Multiple terms have been applied in the literature to describe mild cognitive impairment in the older population associated with an increased risk of developing dementia. Four different areas can be identified as sources for defining mild cognitive impairment:

1. theoretical discussion of mild cognitive impairment in the medical literature
2. diagnostic manuals
3. dementia severity rating scales including a pre-clinical stage
4. application of additional concepts in empirical studies

Theoretical discussion of mild cognitive impairment in the medical literature

Benign senescent forgetfulness

The first attempt to differentiate between normal memory function, pathological memory processes and a mild form of memory loss was introduced into the medical literature as the term ‘benign senescent forgetfulness’ (BSF) by Kral (11). BSF (as opposed to malignant forgetfulness which bears the essential characteristics of the amnestic syndrome) is defined as ‘the inability of the subjects to recall relatively unimportant data and parts of an experience, like a name, a place or a date, whereas the experience of which the forgotten data form a part can be recalled’ (11). It is described as a ‘senium naturale’ (11) and believed to be caused by physiological ageing. Its impact on research was limited until the 1980s, when advancing population ages led to further discussion and renewed interest in studying mild cognitive impairment in the older population. Two studies with follow-up periods of 3 and 3.7 years yielded conversion rates to dementia of 9% (12) and 37% for people classified according to BSF (13). The clinical description of benign senescent forgetfulness as proposed by Kral can be seen as a starting point for further defining mild cognitive impairment operationally.

Age-associated memory impairment and its modifications

The construct of AAMI was introduced by Crook et al. (1986) in order to describe ‘memory loss that may occur in healthy, elderly individuals in the later decades of life’ (10). The criteria include age 50+, memory test performance 1 SD below the mean established for younger adults on a standardized test of secondary memory, complaints of memory loss and evidence of adequate intellectual functioning. A wide range of exclusion criteria are defined in order to rule out the possibility of memory changes because of medical or psychiatric conditions such as delirium, stroke, AD, inflammatory brain disease, depression, history of alcoholism, medical conditions that can produce cognitive deterioration, and use of psychotropic drugs.

Although this was the first attempt to operationally define mild cognitive impairment, almost all of the criteria have been criticized (14, 15). As O’Brien & Levy (16) pointed out, the age criterion fails to address discontinuity in normal ageing functions between early and late old age. Instead of using normative values established for younger adults several authors have suggested applying age and education standardized normal values (15–17), or, ideally, comparing present memory with an internal and retrospective measure of original cognitive functioning (14). Some authors recommended excluding individuals whose general intelligence was below average and suggested setting an upper limit of the IQ score (18). Subjective memory complaints have been criticized for having multiple and complex determinants (17, 19). It has also been suggested that a wider range of cognitive measures should be included in addition to the assessment of memory performance (14, 15). Finally, whereas the inclusion criteria appear to be overinclusive, the exclusion criteria have been criticised for being over-restrictive because of multimorbidity in older age which does not affect memory performance (18). Thus, the construct is unlikely to identify homogenous samples and is too broad a clinical entity to be useful (16, 17, 20–24).
Whereas the older term ‘benign’ by Kral had been criticized because memory problems could prove distressing for many elderly people (17), the term ‘impairment’ was disapproved of for being overly pejorative in suggesting a disease rather than a borderline condition (15, 25). Consequently, the discussion of the construct in the literature relates to the question as to whether AAMI is a clinical diagnostic entity which needs to be treated or rather a phenomenon of normal ageing (20). Although a wide range of compounds for treatment are already under development by the pharmaceutical industry (26), it is debatable what the target level should be for improving function in the elderly (14).

The prevalence rate for age associated memory impairment (AAMI) for subjects 65 years and older varies greatly from 7% (27) to 38% (28), mainly because of unstandardized methodology as well as varying definitions of AAMI. Earlier reviews found a prevalence rate as high as 35–98% on the basis of the literature and archival data (29). An annual incidence rate of 6.6 per 1000 person-years has been reported for people 65 years and older (30).

Annual conversion rates to dementia for individuals classified according to the AAMI criteria vary between 1 and 3% (31–33) and 24% (34).

In addressing the criticism of the original AAMI construct, several suggestions for its modification have been proposed (17, 18). Blackford and La Rue (1989) introduced three different subtypes of objective memory impairment (18). The term AAMI was retained for the first subtype, which corresponds to its original usage. With reference to the mean of young adults, this category also included individuals with test performance above average (18). Two more subtypes were defined psychometrically: age-consistent memory impairment (ACMI) and ‘late-life-forgetfulness’ (LLF). ACMI identified individuals ‘whose memories appear to be ageing in accord with normative expectations’, which is defined as a test performance 1 SD within the age specific mean on 75% of administered tests (18). In contrast, LLF classified individuals ‘whose scores are mildly but quite consistently below average’, which is defined as a test performance 1–2 SD below the age-specific mean on 50% of administered tests (18). According to the authors this category is likely to be of greatest interest to clinicians. Furthermore, the authors proposed minor changes in the inclusion and exclusion criteria of the original AAMI construct. They suggested an upper age limit of 79 years because of the lack of normative data for people in the ninth decade and above (18, 35). In addition, the medical exclusion criteria were relaxed slightly to include individuals with adequately treated hypothyroidism, hypertension and insulin-dependent diabetes.

However, 10–20% of subjects perform with such variability on different memory tests that they cannot be classified according to the ACMI–LLF scheme (25). Furthermore, the reference points are restricted to age specific rather than age and education specific norms. To our knowledge, no epidemiological study concerning the predictive value of the subtypes has been conducted.

Ageing-associated cognitive decline

In addressing the criticism concerning the AAMI construct and its revisions a new category termed ‘ageing-associated cognitive decline’ (AACC) has been suggested (36). As decline may have its onset earlier in life, no age restriction is included. However, the duration of at least 6 months is introduced to decrease the chance of including reversible forms. There should be a report by the individual or a reliable informant that cognitive function has declined. Decline in any of five broad cognitive domains is regarded sufficient for diagnosis, defined as 1 SD below the mean value for the appropriate age and education-matched population. The cognitive domains include memory and learning, attention and concentration, thinking, language and visuospatial functioning. Where available, gender-, race- or culture-specific norms are also to be taken into consideration. The decline should not be the result of any present or past medical or psychiatric condition, or psychoactive substance use, that can cause cerebral dysfunction (36, 37).

Two population-based studies have examined the prevalence of AACC to date, reporting a prevalence rate of 27% for subjects 65 years and older (28) and a prevalence rate of 21% for subjects 60 years and older (38). When applying both criteria to the same sample, only about half of the participants (54%) classified according to AAMI also met criteria for the AACC and the AACC cases showed more extensive cognitive impairment (39). The prevalence of AACC is lower than that of AAMI, mainly because of the application of age and education-specific norms. Thus, AACC might differentiate a more restricted, pathological subgroup for research and clinical setting. To our knowledge, the only population-based study applying the AACC criteria to date reported a 29% conversion rate to dementia within 3 years (38). A clinical study applying criteria comparable with those of the AACC concept yielded an annual conversion rate to AD of 14% (40).
Diagnostic manuals

Age-related cognitive decline and mild cognitive disorder

Slightly different terms have been included in the diagnostic manuals. In the DSM-IV ‘age-related cognitive decline’ (ARCD) (780.9), has been included as a V-code suggesting that these patients require clinical attention, but there is no reference to a diagnosis nor a disease (41). Although the inclusion of mild cognitive impairment in the diagnostic manuals broadens the spectrum of cognitive changes, it also implies the preliminary status of its definition to date. ARCD is suggested, when there is ‘an objectively identified decline in cognitive functioning related to the ageing process that is within normal limits given the person’s age. Individuals with this condition may report problems remembering names or appointments or may experience difficulty in solving complex problems.’ The impairment should not be attributable to mental or neurological disorders (41). No specific psychometric criteria are proposed (42). A prevalence rate of 8% for people aged 65 and over has been reported (43) and 28% of ARCD cases developed dementia after 2 years of follow-up (40).

In the ICD-10 the category ‘mild cognitive disorder’ (MCD) (F 06.70) has been included as a provisional definition (44). Although the definition is slightly narrower than the one in the DSM-IV (45), weak correlations among its components call an underlying presence of a syndrome into question (46). In contrast to the constructs mentioned above, the category MCD includes cases with impairment caused by medical or psychiatric conditions. However, a prevalence rate of only 4% for people 70 years and older has been reported (46) and people with a diagnosis of MCD are more distinguished by anxiety, depression and neuroticism than by cognitive deficits (47). The authors went as far as to relate MCD to neurotic, stress-related and somatoform disorders. One population-based study revealed that 12% of MCD-classified cases according to ICD-10 developed dementia after a follow-up period of approximately 4 years (47).

Dementia severity rating scales including a preclinical stage

Mild cognitive decline, questionable dementia, minimal dementia, limited cognitive disturbance

In order to psychometrically stage dementia, several scales have been developed: for instance, the Global Deterioration Scale (GDS) (48), the Cognitive Dementia Rating Scale (CDR) (49), the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (50), and the Comprehensive Assessment and Referral Evaluation (CARE) (51). All scales include a preclinical form of dementia, referred to as mild cognitive decline for the GDS (GDS = 3), questionable dementia for CDR (CDR = 0.5), minimal dementia according to CAMDEX, limited cognitive disturbance according to CARE. Although the scales are widely applied, many authors use the corresponding terms interchangeably and often without clear reference to the psychometrics behind them (52, 53). This adds to the confusion given the slight differences in the constructs of preclinical dementia stages (19). Moreover, the Consortium for the Establishment of Registries in Alzheimer’s Disease (CERAD) proposed the term possible dementia prodrome (PDP) for a score of 0.5 on the CDR (54).

Using the CAMDEX, a prevalence rate of 16% for people aged 65 years and over (55) and an annual incidence rate of 54 per 1000 person-years has been found for minimal dementia (56). Fifteen per cent of people aged 65 years and over (55) and 15–25% of people aged 75 years and older classified according to CAMDEX develop overt dementia after 1 year (55, 57–59).

According to the CDR a much lower prevalence rate of 3% (52) and an annual incidence rate of 12–15 per 1000 person-years has been given for people 65 years and older (53). Annual rates of conversion to dementia vary between 6% (60) and 16% (61).

A prevalence rate of 22% has been given according to GDS = 3 (31) and annual rates of conversion to dementia vary between 1 and 4% (31, 62), and 40% (63).

However, operational criteria for the cognitive testing included in the dementia severity rating scales remain unspecified. Consequently, studies using the same scale can still vary greatly according to the definition of cases. Moreover, scales including the criterion of slight psychosocial impairment not interfering with everyday life prove to be less sensitive and might overlook cases which would be included because of poor cognitive performance alone. For example, the CAMDEX requires ‘occasional errors in everyday tasks’ in defining the minimal dementia stage (57).

Application of additional concepts in empirical studies

Mild cognitive impairment (MCI) and CIND

Research practice leads to working definitions of mild cognitive impairment, thereby further increasing the number of definitions in use. The term MCI, for example, is used by several research
centres (6, 63–65). The definitional criteria include complaint of memory, normal activities of daily living, normal general cognitive function, abnormal memory function for age and education (1–2 SD), and absence of dementia (4). Prevalence rates of 15% for people 75 years and older (66) and only 3% for people 60 years and older have been reported (38).

MCI has been characterized as an early stage of AD (65), but the rate of conversion to AD varies between studies mainly because of differences in assessment procedures, sample composition and definition of cases. Clinical studies reported a conversion rate of 10–15%/year (e.g. 61, 67, 68), whereas annual rates of up to 40% have also been given (63). A recent population-based study revealed 11% conversion rate within a 3-year period, calling the predictive validity for the onset of dementia in the general population into question (38).

At the Current Concepts in MCI Conference in 1999 subclassifications for MCI were suggested based on the recognized heterogeneity in the use of the term (69). Three subsets of MCI were proposed: ‘MCI-amnestic’, ‘MCI-multiple domains slightly impaired’ and ‘MCI-single non-memory domain’. According to the redefinition of MCI only ‘MCI-amnestic’ was evaluated in the recent study by Ritchie et al. (38).

Finally, a term that often appears in research reports is the category ‘cognitively impaired, not demented’ (CIND) (70, 71), classifying all cognitively impaired cases, which do not satisfy the criteria for dementia. The CIND classification usually includes cases with impairment caused by medical or psychiatric conditions. Mild cognitive impairment as discussed above is then treated as a subcategory among these cases. Problems arise, when prevalence and incidence rates are not calculated according to the different subcategories covered by the broad term of ‘cognitive impairment, no dementia’.

Prevalence of mild cognitive impairment

Research on the prevalence of mild cognitive impairment has produced inconsistent data mainly because of different definitional criteria as well as different sampling and assessment procedures. Population-based studies indicate that the prevalence of mild cognitive impairment is more than double that of dementia (65). However, as described above, the prevalence rates are highly dependent on the diagnostic criteria applied. For example, in applying current diagnostic criteria to the same study sample, Schröder and coworkers found varying prevalence rates according to the different diagnostic criteria applied (72).

Education, age and gender are not consistently related to the prevalence of mild cognitive impairment. Higher prevalence rates for low level of education (73) as well as the opposite pattern (28) have been reported. An increase in the prevalence after the age of 65, but a lack of continued rise after the age of 85 has been found (43, 71), in contrast to the finding of a general decline with age (74). No difference in the prevalence rates between men and women (66, 71), and also higher prevalence rates for men have been reported (28). Higher prevalence rates have been found in institutions compared with community dwellings (71), and in rural vs. urban areas (43).

Age-specific prevalence rates per annum according to the different diagnostic criteria are given in Table 1. Only population-based studies are included.

Incidence of mild cognitive impairment

Few incidence studies have been carried out so far. An average incidence rate of 12 (75) to 15 (53) per 1000 person-years has been reported for people 65 years and older. For people 75 years and above, the incidence rate of 54 per 1000 person-years (56) has been estimated. Comparison of incidence rates across studies is difficult because of differences in diagnostic criteria, sample composition, follow-up periods and neuropsychological measures.

Similar to dementia, incidence rates of mild cognitive impairment seem to increase with age (56) and are higher for people with lower education (75). In contrast to the epidemiology of dementia, a tendency of higher incidence rates of mild cognitive impairment for men compared with women has been reported (75). However, the number of incidence studies to date is too small to draw any conclusions about the relation of incidence of mild cognitive impairment to age, gender and education.

Age-specific incidence rates of mild cognitive impairment in population-based studies are given in Table 2.

The course of mild cognitive impairment

Longitudinal studies with repeated assessment over lengthy periods in large community samples are needed if the course and outcome of mild cognitive impairment is to be traced correctly (57). Data on the rate of conversion to dementia reported in the literature varies greatly (8). This variability could be occurring for several reasons: different entry and follow-up criteria, differences in the length of
In the follow-up period, sample composition (hospital vs. community, volunteer cohort vs. probability sample), sample size, drop-out rates, as well as differences in outcome measures and assessment procedures (60). Three types of longitudinal studies can be identified according to sample composition: volunteer, clinical and population-based studies, with sample sizes ranging from $n = 16$ (76) to
Predictors of conversion to AD

In order to answer the question, as to which subjects with mild cognitive impairment might be more likely to progress at an accelerated rate and may thereby represent a meaningful clinical subgroup, the predictive validity of several factors has been evaluated. It is out of the scope of the present review to report a detailed evaluation of the many diagnostic indices under investigation, yet a brief review of recent findings and lines of inquiry is given.

First, the predictive utility of neuropsychological measures has been discussed controversially (61, 81). Memory impairment, especially deficits in verbal episodic memory and in tests assessing delayed recall, has been reported as one of the earliest and most sensitive precursors of conversion to dementia (59, 61, 81). However, memory deficits have also been found in normal elderly people, confirming that mild cognitive impairment might fluctuate over time and is far too heterogeneous to define a specific circumscribed diagnostic category of high predictive validity. Discrepancies on the original definition have been challenged of defining mild cognitive impairment. Some of the terms are only of historic interest because modifications of their original definition have been introduced. A historic term certainly is ‘BSF’ by Kral, although some authors have advised returning closer to his original ideas in modern definitions (16, 36). The original definition of AAMI as introduced by Crook (1986) has been strongly criticized as well as subclassified according to Blackford and La Rue (18). The existence of a discrete diagnostic entity has been challenged recently (24, 35, 46, 91–93). The authors argue, that cognitive impairment might fluctuate over time and is far too heterogeneous to define a specific circumscribed diagnostic category of high predictive validity.

Incidence rates of dementia among individuals with mild cognitive impairment are elevated compared with the incidence of dementia in the general population (77), thus confirming that mild cognitive impairment comprises a high-risk population. However, conversion rates to dementia vary to a greater extent according to the different constructs applied than according to age and sample composition (see Table 3). In fact, there does not seem to be any age effect at all.

Most studies yielding conversion rates to dementia or AD per annum below 10% applied BSF (12) AAMI (31–33), MCD (47), GDS = 3 (62) and CDR (60, 65).

Conversion rates above 10% have been found in most studies applying the criteria of MCI (78–80), CAMDEX (57–59), AACD (38), and ARCD (40), thus having higher predictive validity. However, in the latter study operational criteria were used, which are comparable with those of AACD.

Discussion

There is no construct to date that pools all efforts of defining mild cognitive impairment. Some of the terms are only of historic interest because modifications of their original definition have been introduced. A historic term certainly is ‘BSF’ by Kral, although some authors have advised returning closer to his original ideas in modern definitions (16, 36). The original definition of AAMI as introduced by Crook (1986) has been strongly criticized as well as subclassified according to Blackford and La Rue (18). The existence of a discrete diagnostic entity has been challenged recently (24, 35, 46, 91–93). The authors argue, that cognitive impairment might fluctuate over time and is far too heterogeneous to define a specific circumscribed diagnostic category of high predictive validity.

Incidence rates of dementia among individuals with mild cognitive impairment are elevated compared with the general population, confirming that...
Table 3. Outcome of mild cognitive impairment

<table>
<thead>
<tr>
<th>First author</th>
<th>Diagnostic criteria</th>
<th>Age range/ mean (S.D)</th>
<th>N in fup</th>
<th>follow-up period in years</th>
<th>Outcome in follow-up period</th>
<th>Outcome per annum (calculated by the authors)</th>
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<td><strong>50+ Volunteers</strong></td>
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<tr>
<td>Morris (2001)</td>
<td>MCI</td>
<td>45+</td>
<td>227</td>
<td>5.1</td>
<td>43% AD</td>
<td>8%</td>
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<td>Clinical studies</td>
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<tr>
<td>Colis (1997)</td>
<td>ARCD/AACD</td>
<td>62.2 (8.8)</td>
<td>18</td>
<td>2</td>
<td>28% AD</td>
<td>14%</td>
</tr>
<tr>
<td>Devanand (1997)</td>
<td>Questionable dementia [CDR = 0.5]</td>
<td>66.2 (10.0)</td>
<td>75</td>
<td>2.5</td>
<td>41% dementia</td>
<td>16%</td>
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<tr>
<td>Jelic (2000)</td>
<td>MCI</td>
<td>47–69</td>
<td>27</td>
<td>1.8</td>
<td>52% AD</td>
<td>29%</td>
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<td></td>
<td>(1 SD below age appropriate mean)</td>
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<td><strong>60+ Volunteers</strong></td>
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<tr>
<td>Nielsen (1998)</td>
<td>AAMI</td>
<td>60–77</td>
<td>44</td>
<td>3.5</td>
<td>2.3% dementia</td>
<td>(2.3% VD)</td>
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<tr>
<td>Daly (2000)</td>
<td>Questionable dementia [CDR = 0.5]</td>
<td>65+</td>
<td>123</td>
<td>3</td>
<td>19% AD</td>
<td>6%</td>
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<td>Clinical studies</td>
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<td>O’Brien (1992)</td>
<td>BSF</td>
<td>68</td>
<td>3</td>
<td>9%</td>
<td>dementia</td>
<td>3%</td>
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<tr>
<td>Coria (1992)</td>
<td>AAMI</td>
<td>58–89</td>
<td>22</td>
<td>1.5</td>
<td>36% AD</td>
<td>24%</td>
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<tr>
<td>Rubin (1989)</td>
<td>Questionable dementia [CDR = 0.5]</td>
<td>64–82</td>
<td>16</td>
<td>7</td>
<td>69% dementia</td>
<td>10%</td>
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<tr>
<td>Tierney (1996)</td>
<td>GDS = 2 or 3</td>
<td>71.5 (7.8)</td>
<td>123</td>
<td>2</td>
<td>24% AD</td>
<td>12%</td>
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<tr>
<td>Reisberg (1986)</td>
<td>GDS = 3</td>
<td>68–85</td>
<td>32</td>
<td>3.6</td>
<td>16% AD</td>
<td>4%</td>
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<tr>
<td>Flicker (1991)</td>
<td>GDS = 3</td>
<td>71.3 (1.4)</td>
<td>20</td>
<td>2.1</td>
<td>80% dementia</td>
<td>40%</td>
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<tr>
<td>Bozoki (2001)</td>
<td>MCI</td>
<td>68.4 (7.2)</td>
<td>48</td>
<td>2</td>
<td>33% AD</td>
<td>17%</td>
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<td></td>
<td>(1 SD below age and education appropriate mean)</td>
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<tr>
<td>Jack (1999)</td>
<td>MCI</td>
<td>77.7 (6.8)</td>
<td>80</td>
<td>2.7</td>
<td>34% AD</td>
<td>13%</td>
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<td></td>
<td>(1.5 SD below age and education matched controls)</td>
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<td><strong>Population-based studies</strong></td>
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<tr>
<td>Hänninen (1995)</td>
<td>AAMI</td>
<td>60–77</td>
<td>176</td>
<td>3.6</td>
<td>9% dementia</td>
<td>3%</td>
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<tr>
<td>Snowdon (1984)</td>
<td>AAMI [GDS = 3]</td>
<td>65+</td>
<td>27</td>
<td>8</td>
<td>7% dementia</td>
<td>1%</td>
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<tr>
<td>Cooper (1996)</td>
<td>Minimal dementia [CAMDEX]</td>
<td>65+</td>
<td>67</td>
<td>2.3</td>
<td>34% dementia</td>
<td>15%</td>
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<tr>
<td>Ritchie (2001)</td>
<td>AACC MCI</td>
<td>60+</td>
<td>174</td>
<td>3</td>
<td>29% 11% dementia</td>
<td>10%</td>
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<td><strong>70+ Volunteers</strong></td>
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<tr>
<td>Katzmann (1989)</td>
<td>BSF</td>
<td>75–85</td>
<td>73</td>
<td>3.75</td>
<td>37% dementia</td>
<td>10%</td>
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<td>Clinical studies</td>
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<tr>
<td>Petersen (1999) see also Smith (1996)</td>
<td>MCI [1 SD below age and education matched controls]</td>
<td>80.9 (1.0)</td>
<td>76</td>
<td>4</td>
<td>12% AD per year</td>
<td>12%</td>
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<td><strong>Population-based studies</strong></td>
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<tr>
<td>Christensen (1997)</td>
<td>MCD according to ICD-10</td>
<td>70–97</td>
<td>25</td>
<td>3.6</td>
<td>12% dementia</td>
<td>3%</td>
</tr>
<tr>
<td>O’Connor (1991)</td>
<td>MMSE &lt; 26 and minimal dementia [CAMDEX]</td>
<td>75+</td>
<td>24</td>
<td>2</td>
<td>50% dementia</td>
<td>25%</td>
</tr>
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mild cognitive impairment comprises a high-risk population. However, a true comparison of conversion rates among studies is difficult partly because of varying follow-up periods. Incidence rates per annum, as have been calculated by the authors for the purpose of the present review can be criticized. Therefore, analogous to dementia the use of the person-years at risk method for analysis of conversion rates is recommended, where incidence rates are estimated as the number of cases of dementia divided by person-years at risk. Studies should then be compared according to sampling, because higher conversion rates because of highly selective samples could be expected in clinical studies. A comparison of conversion rates according to age-groups is suggested, because differing rates could be assumed analogous to the incidence of dementia.

In order to evaluate the predictive power of the different approaches, constructs need to be compared empirically in a prospective fashion, ideally in applying different criteria to the same sample (35, 38, 70). Different studies, referring to the same approach still vary greatly because of definition of cases and assessment procedures applied. This obscures a true comparison of studies by concept and calls for more consistent criteria to be adopted. For example, agreement need to be reached concerning the choice of tests with appropriately referenced norms (17) and the mnemonic and non-mnemonic capacities evaluated for diagnosis. As the number and choice of tests is critical for the identification of cases (28), the definition of a specific battery of tests for use in defining and detecting mild cognitive impairment has been suggested (25).

Longer periods of observation and a larger number of incidence cases are necessary to determine the rate of progression in mildly impaired individuals (65, 88, 89). To our knowledge, only five studies with a sample size of \( n > 100 \) individuals with mild cognitive impairment have been conducted worldwide to examine the course and outcome of mild cognitive impairment longitudinally (32, 38, 60, 65, 68). In determining the onset, course and outcome of the different stages in the course of the illness prospective longitudinal studies are needed monitoring cognitive performance in a healthy cohort of the elderly and, ideally, following those subjects until their death (90).

Among the concepts attempting to cover a high-risk population, MCI and the use of CAMDEX show the greatest conversion rates to dementia in most studies to date. MCI proves to be highly predictive in most clinical studies and its operational criteria have proved to be highly applicable in a clinical setting. CAMDEX proves to be highly predictive in most population-based studies, yet its operational criteria remain unclear. In addition, it must be assumed that CAMDEX is less sensitive because the beginning of slight psychosocial impairment without interference with everyday life is included in its criteria, consequently defining a more impaired subgroup which can be more likely to convert to dementia. In fact, some studies preselected subjects by applying the CAMDEX only to those scoring below 26 on the MMSE (57, 58). Thus, CAMDEX might overlook very mild cases, which might be included because of cognitive testing alone.

The definition of AACD seems to be one of the best operational constructs to date (36). Its comprehensive and clearly defined research diagnostic criteria, which take into account age and education-specific norms, might prove superior in differentiating a meaningful subgroup from an elderly population (28, 39). Moreover, the criterion of deficits in cognitive domains other than memory has been supported by recent research on the prediction of AD (60, 79). However, as subjective memory impairment is less useful in the prediction of conversion to dementia, it seems preferable to omit this as a criterion or restrict complaints to the perception of informants, which has proved to be of better prognostic value. Although the high predictive power of AACD might be assumed theoretically, its true predictive validity remains to be confirmed in further empirical outcome studies. The recent subclassifications of MCI seem to be close to the concept of AACD (69). A true comparison of these concepts should be grounded

<table>
<thead>
<tr>
<th>First author</th>
<th>Diagnostic criteria</th>
<th>Age range/mean(S.D.)</th>
<th>N in fup</th>
<th>follow-up period in years</th>
<th>Outcome in follow-up period</th>
<th>Outcome per annum (calculated by the authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paykel (1998)</td>
<td>MMSE &lt; 26 and minimal dementia (CAMDEX)</td>
<td>75+</td>
<td>22</td>
<td>2.4</td>
<td>41% dementia</td>
<td>17%</td>
</tr>
<tr>
<td>Visser (1999)</td>
<td>Minimal dementia (CAMDEX)</td>
<td>65–85 78.8 (4.8)</td>
<td>20</td>
<td>3</td>
<td>45% AD</td>
<td>15%</td>
</tr>
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</table>
on empirical evidence. Moreover, a test of any concept should be based on longitudinal prospective studies, as a retrospective application of criteria to existing databases can be manipulated to provide any results desired.

To summarize, it is advisable to consider the categories of AACD and the subclassifications of MCI in future revisions of the diagnostic manuals. In order to establish the differences between those cases who develop dementia and those who do not show further decline, additional measures should be further investigated in order to increase the accuracy of any concept of mild cognitive impairment in the prediction of dementia (20). The parallel investigation of neuropsychological, sociodemographic and genetic indices allows an evaluation of the impact of the different pathogenetic mechanisms involved and an examination of the links between genetic and epigenetic factors.

In our view, agreement on terminology for mild cognitive impairment can only be reached if researchers are aware of the parallel use of different terms for the same spectrum of cognitive functioning, as well as the use of the same term with different operational criteria. One step towards agreement on terminology would be that investigators are explicit regarding the classification of their subjects and do not refer to terms that have been replaced by new designations or modifications in definition. Given an agreement on constructive terminology and research practice, the field of dementia research will benefit greatly from further investigating the nature and outcome of mild cognitive impairment. Increasing the accuracy in detecting dementia in an early phase will help to administer and further develop effective pharmacological and behavioural interventions for delaying the onset and progression of the disease.

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