Reviews in Clinical Gerontology 2013 23; 317–356
© Cambridge University Press 2013 doi:10.1017/S0959259813000129

Mild cognitive impairment and mood: a systematic review

Jennifer A Yates, Linda Clare and Robert T Woods
Dementia Services Development Centre, Bangor University, Bangor, UK

Summary

This systematic review, with meta-analyses conducted where data were available, aimed to investigate the prevalence of symptoms of depression and anxiety in mild cognitive impairment (MCI), and to establish how symptoms of depression and anxiety relate to the progression from no cognitive impairment to MCI, and from MCI to dementia. Sixty studies were included in the review. Meta-analyses indicated that symptoms of depression and anxiety were more prevalent in people with MCI than in people with normal cognitive function, and increased the risk of progression from no cognitive impairment to MCI. There were mixed results regarding the effect of such symptoms on progression from MCI to dementia. The findings highlight the need for more research in this area, which can inform attempts to slow or halt the progression of cognitive impairment in later life, with resulting benefits for quality of life.

Key words: depression, anxiety, memory, meta-analysis, neuropsychiatric symptoms.

Introduction

Mild cognitive impairment (MCI) is a concept that has been developed in an attempt to describe a proposed transitional state that may exist between age-appropriate levels of cognitive functioning and pathological cognitive decline.[1] In general, core elements of the MCI classification are a subjective memory complaint, an objective memory impairment, typically demonstrated by performance on a battery of neuropsychological tests, intact general cognitive function and intact activities of daily living (ADLs). MCI is a broad term encompassing several subtypes. A primary distinction is made between single-domain MCI, where only one aspect of cognitive functioning is impaired, and multiple-domain MCI, which involves impairment in more than one aspect of cognitive functioning. A secondary division can then be made into amnestic MCI, where memory is impaired, or non-amnestic MCI, in which only aspects of cognitive functioning other than memory, such as executive function, are impaired. Thus for example, individuals classified as having multiple domain amnestic subtype MCI experience impairments in both memory and other cognitive functions.

However, controversy surrounds the concept of MCI. At least sixteen variations on the criteria used to classify MCI have been identified and these differ in the extent to which they include each of the elements described above.[2] It is also unclear whether the subtypes identified under the broad umbrella term of MCI are truly distinct categories and how they work together. Furthermore, although MCI is often seen as a transitional state between normal ageing and pathological decline, or even as a prodrome of dementia, not everyone who has been diagnosed with MCI will convert to having dementia. Indeed, in one study, 12% of participants classified as having MCI improved and 53% remained stable over 3 years.[3] A separate study found after 2.7 years 19.5% of participants had improved to a normal level of cognitive functioning and 61% of participants remained at a stable level of cognitive functioning.[4] The concept is also controversial due to the heterogeneity of aetiologies that may underlie the cognitive changes experienced in MCI, such as vascular changes or Alzheimer's pathology. This heterogeneity prevents the development of a set of specific diagnostic criteria[5] such as those used in making a dementia diagnosis. A small post-mortem study revealed that there was no single type of pathology across all cases of MCI, suggesting that it would be unwise to conceptualize MCI simply as a prodromal form of Alzheimer's disease.[6]

Nevertheless, the concept of MCI is useful for identifying individuals who may be at increased risk of progression to a diagnosis of dementia. People classified as having MCI are more likely than individuals without cognitive impairment to

Address for correspondence: Miss Jennifer Yates, Dementia Services Development Centre, 45 College Road, Bangor Gwynedd LL57 2DG
Email: j.yates@bangor.ac.uk

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

progress to a diagnosis of dementia, at a rate of 10–15% compared with 1–2% per year.[7] Individuals at an early stage of cognitive decline may benefit from implementing strategies to cope with cognitive change, which could help to increase independence and quality of life. Given the increased risk of progressing to dementia from MCI, it is important to understand any associated factors that may contribute to the development of MCI.

One important factor associated with MCI is mood, in particular low mood or high levels of anxiety.[8–10] Possible explanations for this association include the suggestions that worries may compete for cognitive resources, leaving less capacity for cognitive functioning,[11] or that symptoms of anxiety may lead individuals to be more vigilant towards their cognitive functioning and more aware of subtle changes in their cognitive function. Depression is related to cognitive disturbances in older people who are ageing normally[12] although it is unclear in which direction the relationship operates. On the one hand, depression might lead to reduced cognitive functioning, but on the other hand, individuals classified as having MCI may be at risk of developing symptoms of depression or anxiety.[13] It is possible that both explanations could occur concurrently, indicating a circular relationship between mood and MCI. On discovering a cognitive impairment, an individual may become anxious with regard to how his or her cognitive functioning may change in the future and what implications any changes might have. It is important to examine the nature of the association between MCI and mood, and a systematic review is an appropriate way to synthesize existing literature in this area.

This review aims to answer the following questions:

(1) Are people with MCI more likely to show low mood or increased anxiety than people with normal cognitive function, and does this vary by MCI subtype?
(2) What is the temporal relationship between mood problems and the development of MCI?
(3) Does the presence of low mood or increased anxiety in people with MCI increase the risk of progression to dementia?

Search methods

A search of the electronic databases PsycINFO, PubMed, Science Direct and Web of Knowledge was conducted on 17 November 2012 using the terms 'mild cognitive impairment', 'MCI' and 'cognitive impairment' combined with 'depress*', 'anxi*', 'neuropsychiatric symptoms', 'NPS' and 'mood'. The terms 'depress*' and 'anxi*' were used as these are the aspects of mood that this review is addressing. The term 'neuropsychiatric symptoms' was included as it is frequently used in a way that encompasses the concepts of anxiety and depression, especially in studies that have used the Neuropsychiatric Inventory (NPI) to assess mood. Other terms used to describe cognitive impairment, such as 'cognitive impairment no dementia' (CIND) were not included as the aim was to achieve a consistent population of individuals with MCI. Studies were included if they considered symptoms or diagnoses of depression or anxiety in older people who, according to the study authors, met criteria for MCI. The search process is shown in Fig. 1. All titles and abstracts identified in the initial database search were assessed. Full articles were retrieved if the title and abstract suggested that the study both considered symptoms of anxiety or depression and classified participants as having MCI. Further studies were identified through the reference sections of selected studies. There was no restriction on the definition of MCI. As the term MCI was not widely used before 1991 there was no limit set on the year of publication as it was thought that there would not be papers published before this date.[14] Only quantitative studies published in English were included. Conceptual studies and review articles were excluded.

Methodological quality was assessed using a checklist adapted from the QUADAS tool (Quality Assessment of Diagnostic Accuracy Studies[15]). The QUADAS tool was developed for use in systematic reviews and was adapted by the present authors to allow for studies of varied methodologies through the omission of several items. The original tool has 14 items, seven of which were not applicable to this review, and were omitted. The primary reviewer identified the studies, extracted the relevant data and conducted the quality assessment. Ten per cent of the studies were randomly selected for review for quality assessment by a secondary reviewer.

Statistical analysis

Random effects meta-analyses were conducted where possible to synthesize results of similar studies, which reported usable data, using MIX 2.0

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

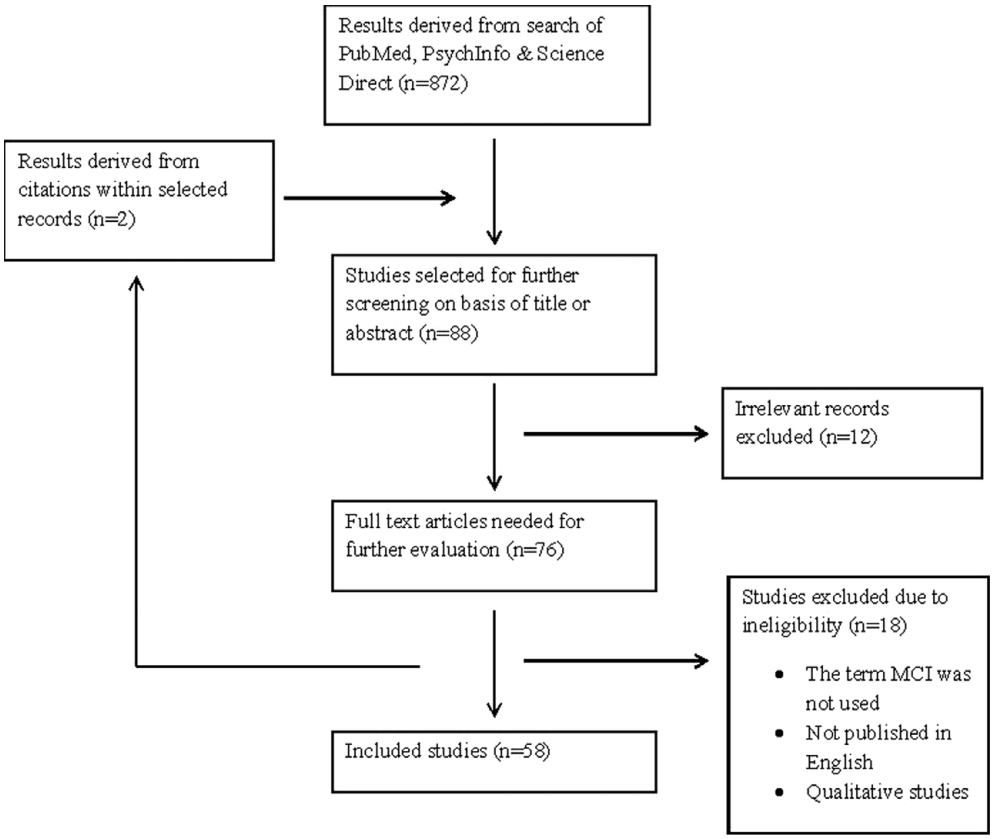


Figure 1. The process used for selecting studies to be included in the review

Pro software. Heterogeneity ranged from moderate to high for the analyses. Odds ratios were examined to address research question (RQ) 1. Odds ratios were either taken directly from the study reports or calculated from frequencies presented in the results sections of study reports. Hazard ratios were examined to address RQ2 and these were either taken directly from study reports or calculated from data given in the results sections. Relative risk ratios were examined to address RQ3 and were either obtained directly from study reports or calculated from available data.

Results

Sixty studies were included in this review. Studies focusing on cognitive changes in people with mood problems are summarized in Table 1. Studies investigating changes in mood in participants classified as having MCI are summarized in Table 2. Forty-four studies found a significant positive association between MCI and depression or anxiety, with one study finding a negative association between depression and MCI.[16]

Quality assessment

Table 3 shows the quality score for each study The score in each case represents the number of unmet criteria, and hence lower scores indicate higher quality. Fifteen studies met all seven quality criteria, eighteen studies failed to meet one, eighteen studies failed to meet two, eight studies failed to meet three, and only one study failed to meet four.[17]

Participant characteristics

The included studies describe either clinical or community samples. In the clinical studies the concept of MCI was applied to individuals

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Studies investigating the occurrence of MCI in participants with mood problems*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Adler *et al.* (2004)	34 with depression including 18 with MCI; age: 73.4 (6.5)	Cross-sectional study	A cut-off score of less than 46 on the Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, multi-infarct dementia, and dementias of other aetiology according to DSM-III-R and ICD-10 (SIDAM)	Not used	Depression	Hamilton Depression Scale (HMD; Hamilton, 1967)	MCI is frequent in depressed older adults, particularly those with late onset of depression. However, depression and the severity of affective symptoms had no relevant impact on cognitive performance and its course. MCI had no negative impact on recovery from depression
Barnes *et al.* (2006)	2220 Mean age: 74	Prospective, population based longitudinal study, part of the Cardiovascular Health Study	Individuals not meeting dementia criteria who exhibited poor cognitive function that reflected a decline from a prior level	Modified Mini-Mental State Examination (3MS) was used and the average score across participants was 95.2 (2.9)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)	41% of participants were described as having low levels of depressive symptoms and 20% were described as having moderate/high levels of depressive symptoms. 13% of participants developed MCI. More depressive symptoms increased the risk of MCI
Bhalla *et al.* (2009)	109 non-MCI meeting criteria for depression; age: 74.7 (5.6) 65 non-MCI, never depressed; age: 74.0 (5.6)	Cross-sectional study	Petersen criteria (Petersen, 2004)	Depressed: 28.2 (1.9) Non-depressed: 28.9 (1.2)	Instrumental activities of daily living Depression	Hamilton Depression Scale (HMD; Hamilton, 1967)	Significantly more depressed patients had a cognitive diagnosis than non-depressed patients

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Brodaty *et al.* (2012)	799 including 319 MCI; age: 79.01 (4.7) 480 NCI; age: 78.41 (4.72)	Longitudinal	Petersen *et al.*,(1997; 2004)	MCI: 27.61 (1.6) NCI: 28.45 (1.22)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	NPS were significantly associated with the amnestic-multiple-domain MCI subtype. There were no significant relationships between level of NPS at baseline and progression from MCI to dementia
Caracciolo *et al.* (2012)	764 Age: 75+	Longitudinal	Petersen *et al.* (1999; 2005)	Not specified	Depression	Self-report of perceived sadness	53% of incident cases of MCI occurred in those with low mood over 6 years. Incidence of MCI in baseline low mood was 2.5 times higher than in people without low mood. 50 people with MCI progressed to dementia and 70% of these had baseline low mood
Cherbuin *et al.* (2009)	18 MCI	Longitudinal	Petersen *et al.* (1999) criteria	29.11 (0.83)	Anxiety Depression	Goldberg Anxiety and Depression Scales (GAS; Goldberg & Hillier, 1979)	Taking anxiety and anti-depression medication was significantly predictive of progression to MCI from NCI over four years. 71% of those with MCI at wave one reverted to NCI by wave two. A self-report of anxiety or depression was only mildly predictive of MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Dotson *et al.* (2010)	1239 aged 55.5 (18.8)	Longitudinal study as part of the Baltimore Longitudinal Study of Aging	Petersen criteria (Petersen, 2004) where MCI was diagnosed by impairment on a single domain or multiple domains without significant functional loss	Not used	Depression	Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)	88 participants were found to have MCI. MCI was not related to the recurrence of elevated depressive symptoms
Geda *et al.* (2006)	840 normal older people Age: 78.0	Longitudinal	Petersen criteria (Petersen, 2004)	28.0	Depression	15-item Geriatric Depression Scale (GDS-15; Yesavage *et al.*, 1982)	17% of participants developed depression, of which 13.3% developed MCI, compared with 4.9% of participants without depression. The risk of MCI was greater for newly developed depression than a life history of depression. The incidence of MCI did not increase with increasing severity of depression

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Goveas *et al.* (2011)	6376 aged 65–79	Prospective cohort study	Petersen criteria (Petersen *et al.*, 1992), poor performance on at least one CERAD test, some decline in IADLs, intact ADLs, absence of other conditions that may explain decline in cognitive function and no dementia	Modified Mini-Mental State Examination (3MS) was used. Depressive disorder: 95.0 (4.7) No depressive disorder: 96.0 (3.9)	Depressive disorders	Burnam screening algorithm (Using six items from the Center for Epidemiologic Studies Depression Scale [CES-D; Radloff, 1977] and two items from the National Institute of Mental Health's Diagnostic Interview Schedule [DIS])	Depressive disorder was associated with a greater risk of incident MCI
Kumar *et al.* (2006)	29 MCI; age: 62.65 (1.36) 520 Controls; age: 62.55 (1.46)	Cross-sectional study derived from the PATH Through Life Project	Consensus clinical judgement using Petersen (1999) criteria used to define MCI	Not used	Depression Physical disability	Goldberg Depression Scale (Goldberg *et al.*, 1988) PRIME-MD Patient Health Questionnaire (PHQ) depression section (Spitzer *et al.*, 1999).	Participants with MCI are more likely to have a lack of energy, feel slowed up, and feel worse in the mornings. A higher depression score and a DSM-IV diagnosis for minor depression were significant predictors for MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Lee *et al.* (2006)	129 meeting DSM-IV criteria for major depression aged 68.0 (6.4)	Longitudinal	Performance 1.5 SD below mean levels on one or more of eight memory measures	27.7 (2.1)	Depression	Duke Depression Evaluation Schedule (Landerman *et al.*, 1989). Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)	55.2% of participants had MCI at baseline and 44.8% had MCI at 1 year. 59.4% remained stable MCI and 26.7% progressed from NCI to MCI. Having MCI at baseline increased risk of having MCI at 1 year by four times even when no longer depressed
Panza *et al.* (2008)	139 MCI 2824 Controls Age: 73.4 (5.69)	Longitudinal	Petersen *et al.* (1999) criteria but without requirement for subjective memory complaints	26.5 (2.2)	Depression	Geriatric Depression Scale (GDS-30; Yesavage *et al.*, 1982)	Over 3.5 years there were 113 new cases of MCI but there were no significant associations found between depressive symptoms and the rate of incident MCI
Shahnawaz *et al.* (2012)	767 total participants; age: 78.53 (4.68) including 299 MCI	Cross-sectional of community dwellers	Winblad *et al.* (2004) criteria	MMSE was not used	Depression Psychological distress (which primarily focuses on depression and anxiety)	15-item Geriatric Depression Scale (GDS-15; Yesavage *et al.*, 1982) Kessler Psychological Distress Scale (K10; Kessler *et al.*, 1994).	A significantly greater proportion of participants with clinically relevant depressive symptoms (GDS>6) met criteria for MCI than non-depressed participants (57.4% compared to 37.8%). Depressive symptoms were significantly associated with the amnestic MCI subtype (aMCI)

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 1. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Spira *et al.* (2012)	302 Age: 86.9 (2.1)	Longitudinal population based	Petersen *et al.* (1999) criteria	Not specified	Depression	Geriatric Depression Scale 15 item version (GDS-15; Yesavage *et al.*, 1982)	41.5% or participants were found to have MCI. 70% of those with elevated depressive symptoms had MCI
Steenland *et al.* (2012)	3010 MCI 5845 Control Age: 73.0 (10.0)	Longitudinal	National Alzheimer's Co-ordinating Center Codebook (2006)	28.3 (2.0)	Depression	Clinician Interview GDS-5 (GDS-5; Yesavage *et al.*, 1982) NPI-Q (NPI; Cummings *et al.*, 1994)	Depression throughout the study was associated with progression from not cognitively impaired to having MCI, with 15% progressing. 38% of those with MCI progressed to having AD over 2.6 years. Past depression was not related to an increased risk of MCI
Wilson *et al.* (2007)	1256 not cognitively impaired at baseline Age: 76.8 (7.7)	Longitudinal	Bennett *et al.* (2002) criteria	28.7 (1.5)	Chronic distress Depression	Distress was assessed using six items from the Neuroticism scale of the NEO Five-Factor (Costa & McRae, 1992) Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)	482 participants developed MCI over 12 years. The risk of MCI increased by approximately 2% for each point increase on the distress score. The risk of MCI increased by approximately 6% for each depression symptom on the CES-D. The association between depression and MCI did not remain significant when distress was controlled for

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Studies investigating symptoms of mood in participants with MCI*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Artero *et al.* (2008)	6892 including 2882 MCI Age: 74.2 (5.6)	Longitudinal study	Winblad *et al.* (2004) criteria	MMSE was not used	Depressive symptoms	Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) Mini International Neuropsychological Interview (MINI)	6.6% progressed to dementia, 56.5% remained stable with MCI and 37% reverted to normal cognitive functioning. Depressive symptoms were present in participants with MCI and subclinical depressive symptoms increased the risk of progression from MCI to dementia in female participants
Baiyewu *et al.* (2012)	53 MCI Age: 80.9 (5.6)	Longitudinal study	Informant or clinician detected impairment in cognition, cognitive test scores 1.5 SD below a normative reference and normal ADLs	17.3 (3.0)	Neuropsychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	90.6% of participants with MCI had any NPI symptom in the past 4 weeks. The most frequent symptom measured by the NPI was depression (45.3%). Anxiety was less common (18.9%)

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Chan *et al.* (2003)	333 Dementia; age: 81.8 (7.1) 121 MCI; age: 78.4 (6.3)	Prospective observational cohort study	1.5 SD below the mean on any one test or 1 SD below the mean on two tests or more. No requirement for a subjective memory complaint, and the diagnosis was not limited to an objective memory complaint, but instead an objective impairment on cognitive function was used	Dementia: 16.9 (7.2) MCI: 24.1 (3.2)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) The Behavior Symptom Rating Scale (BSRS; Rabins, 1994)	47% of patients with MCI had at least one behavioural/psychiatric symptom. Symptoms experienced by patients with MCI were associated with IADL and ADL difficulties
Clement *et al.* (2009)	30 MCI; age: 65.97 (10.43) 27 control; age: 68.19 (8.37)	Cross-sectional study	Petersen *et al.* (2001) criteria	MMSE was not used	Psychiatric symptoms	Indices de Detresse Psychologique (French translation of Psychiatric Symptom Index; Illfield *et al.*, 1976) Geriatric Depression Scale (Yesavage *et al.*, 1982)	A main group effect for depression and anxiety was found for participants with MCI compared to healthy controls. Participants with MCI showed more mood disturbances

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Collie *et al.* (2002)	23 MCI; age: 65.9 (5.4) 23 control; age: 67.8 (7.8)	Cross-sectional study as part of an ongoing longitudinal study	Impaired cognitive function on three consecutive behavioural assessments	MCI: 28.8 (1.1) Control: 28.1 (1.4)	Anxiety Depression	Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) The State-Trait Anxiety Inventory (STAI)	Participants with MCI experienced higher levels of state anxiety than control participants. Few subjects remained consistently impaired across all three assessments (13%)
Devier *et al.* (2009)	148 MCI; age: 67. 1 (9.9) 63 Control; age: 65.7 (9.3)	Longitudinal study	Subjective memory complaint and impaired performance on measures of delayed recall and preferably an informant's confirmation of memory decline	MCI: 27.5 (2.2) Control: 29.4 (0.8)	Anxiety Depression	The State-Trait Anxiety Inventory (STAI) Hamilton Depression Scale (HMD; Hamilton, 1967)	Mean anxiety and depression scores were higher for participants with MCI than for control participants. 26.4% of participants converted from MCI to AD. Depression was not a significant predictor for conversion. Higher trait anxiety was significantly associated with a lower risk of developing AD

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Di Iulio *et al.* (2010)	119 AD; age: 74.4 (7.0) 68 md-MCI; age: 71.0 (6.5) 58 a-MCI; age: 7.1 (6.5) 107 Control; age: 68.1 (8.2)	Cross-sectional study	Petersen criteria (Petersen, 2004)	AD: 22.6 (3.2) md-MCI: 26.6 (2.0) a-MCI: 28.0 (1.8) Control: 28.5 (1.6)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	Participants with md-MCI had similar levels of depressive symptoms to those with AD, with 75% of md-MCI having clinically significant depressive symptoms. However, symptoms were more likely to be less severe in md-MCI than in AD. Apathy symptoms increased as the severity of cognitive symptoms increased
Edwards *et al.* (2009)	521 with MCI aged over 50 years	Longitudinal study	MCI was defined using a neuropsy-chological battery and included diagnoses or amnestic disorder and cognitive impairment no dementia (CIND) according to DSM III-R and DSM IV	Three or less NPS: 26.4 (2.7) Four or more NPS: 26.0 (2.7)	Functional status Neuropsychi-atric symptoms	Clinical evaluation to determine NPS	Participants with high levels of NPS were more likely to have amnestic MCI than those with low levels of NPS. Depression was twice as frequent in patients with amnestic MCI. 75% of participants had at least one NPS

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Elfgren *et al.* (2010)	24 with subjective memory complaint; age: 56.6 (8.3) 22 with MCI; age: 61.3 (6.3) 13 with dementia; age: 62.4 (9.5) from out-patient memory clinic	3-year cohort study of people presenting with subjective memory complaints	Subjective memory complaint, impaired memory function, preserved general cognitive abilities, normal ADLs, no dementia	SMC: 29.1 (1.1) MCI: 27.9 (1.4) Dementia: 22.2 (2.8)	Depression Anxiety	Montgomery-Asberg depression scale (MADRS; Montgomery & Asberg, 1979) Anxiety measured through self-report and clinical signs	High prevalence of psychosocial stress and anxiety amongst participants with a subjective memory complaint
Fernandez-Martinez *et al.* (2010)	485 total participants, including 91 MCI; age: 74.19 50 Control; age: 74.55	Longitudinal	Petersen *et al.* (1999) criteria	MCI: 26.4 Control: 28.6	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	70.3% of people with MCI had at least one symptom on the NPI compared to 42% of control participants. 33% of those with MCI had depression compared to 8% of control participants and these differences were significant
Forsell *et al.* (2003)	89 MCI; age: 83.1 (2.5) 353 Non-MCI; age: 84.3 (3.5)	Population-based study (the Kungsholmen Project)	Subjects with MMSE scores 1SD below age/education-specific means	MCI: 22.6 (1.5) Non-MCI: 25.6 (2.7)	Psychiatric symptoms including depression, anxiety and psychotic symptoms	Comprehensive Psychopatho-logical Rating Scale (CPRS) DSM-III-R	Memory complaints, suspiciousness, anxiety syndromes, social withdrawal, worrying over trifles and loss of initiative were more often found in people with MCI than non-MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Gabryelewicz *et al.* (2006)	105 community-dwelling individuals with MCI; age: 69.3 (7.2)	Longitudinal study	Criteria similar to those set out by Petersen (1997): memory complaint, normal activities of daily living, objective memory impairment or an impairment in another area of cognitive function, normal global cognitive functioning and no dementia	27.2 (1.8)	Depression	Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)	The mean MADRS score was significantly higher in participants who progressed to dementia than those who remained stable
Gallagher *et al.* (2011)	161 MCI; age: 73.7 (7.1)	Cross-sectional study	Petersen criteria (Petersen, 2004)	Convertors: 24.7 (2.5) Stable MCI: 26.0 (2.4)	Neuropsychiatric symptoms	Behavioural Pathology in AD Rating Scale (BEHAVE-AD; Reisberg *et al.*, 1996)	76% of participants had at least one NPS with anxiety being the most common at 52%. The total BEHAVE-AD score correlated with clinical severity and cognitive status. The annual rate of conversion was 19%

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Gallassi *et al.* (2007)	49 MCI aged 71.06 (8.07)	Cross-sectional study	Petersen *et al.* (2001) and Winblad *et al.* (2004) criteria	27.29 (2.31)	Depression Anxiety	Beck Depression Inventory (BDI; Beck *et al.*, 1961) Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) The State-Trait Anxiety Inventory (STAI; Spielberg *et al.*, 1980)	Significantly more participants with MCI had symptoms of depression according to the NPI than participants with no cognitive impairment who had subjective cognitive complaints. No differences were found between groups on the BDI and STAI
Geda *et al.* (2008)	319 MCI; age: 70–91 1590 Non-MCI; age: 70–91	Cross-sectional case control study comparing MCI with normal cognition	Petersen criteria (Petersen, 2004)	MMSE was not used	Neuro-psychiatric symptoms	Neuropsychiatric Inventory Questionnaire (NPI-Q; Cummings *et al.*, 1994)	51% of participants with MCI compared to 27% of participants with normal cognition had at least one neuropsychiatric symptom

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Hidaka *et al.* (2012)	1888 community-dwelling; age: 73 (6.0)	Cross-sectional study	Cognitive complaints, objective impairment 1.5 SD below norms on at least one of five measures of cognition, preserved ADLs and no dementia	MMSE was not used	Depression	Geriatric Depression Scale, 15 item version (GDS-15; Yesavage *et al.*, 1982)	19.5% of the sample had MCI. 26.3% of those with MCI also had depression compared with 18.0% of those with normal cognition. There was no difference found between the different subtypes of MCI and the prevalence of depression, but the multiple domain subtype was more prevalent in those with depression compared to those without depression
Huddon *et al.* (2008)	33 Control; age: 66.2 (9.9) 18 a-MCI/D+; age: 65.1 (11.1) 26 a-MCI; age: 65.2 (8.0)	Cross-sectional study	Petersen criteria (Petersen, 2004)	MMSE was not used	Depressive symptoms	Geriatric Depression Scale, five item version (GDS-5; Hoyl *et al.*, 1999)	a-MCI/D+ made more errors on tests of cognitive function and were slower on tests of inhibition than controls or a-MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Houde *et al.* (2008)	60 MCI aged 74.5 (6.5)	Longitudinal study	Petersen *et al.* (2001) criteria	27.1 (1.9)	Depression	Geriatric Depression Scale (Yesavage *et al.*, 1982)	After a mean follow-up of 4.3 years 60% progressed to dementia, equivalent to a 14% annual conversion rate. 53% of those who progressed had depression at baseline. There was no difference between levels of depression at baseline between those who progressed to dementia and those who remained stable MCI
Hwang *et al.* (2004)	28 MCI aged 73.4 (6.4)	Cross-sectional study	Petersen *et al.* (1999) criteria	28.7 (1.3)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	A significant difference in total NPI score was found between MCI and healthy controls. 25% of those with MCI had symptoms measured by the NPI and frequent symptoms included dysphoria, apathy, irritability and anxiety
Johnson *et al.* (2012)	105 with MCI aged 67.0 (14.44)	Longitudinal study	Petersen *et al.* (1999) criteria	MMSE was not used	Depressive symptoms	Geriatric Depression Scale (Yesavage *et al.*, 1982)	33 participants had non-amnestic MCI and 72 participants had amnestic MCI. 51% of those with non-amnestic MCI had depression compared with 33% of those with amnestic MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Kruger *et al.* (2012)	83 MCI aged 80.0 (7.7)	Longitudinal study	Winblad *et al.* (2004) criteria	MMSE was not used	Depressive symptoms	Geriatric Depression Scale (Yesavage *et al.*, 1982)	Participants with MCI reported more depressive symptoms on the GDS than healthy controls (4.7 *vs* 3.2). Each point increase on the GDS was associated with a 14% increase in the odds of an MCI diagnosis
Lopez *et al.* (2005)	228 MCI; age: 70.1 (9.1) 427 AD; age: 73.2 (8.1)	Cross-sectional study	Memory performance 1.5 SD below age/education means, ADLs may be slightly impaired	MCI: 25.9 (2.1) AD 23.5 (1.9)	Neuro-psychiatric symptoms Depression	Semi-structured CERAD Interview Hamilton Depression Rating Scale (HMD; Hamilton, 1967)	The proportion of MCI participants with major depression and aggression was similar to the proportion in early AD
Luppa *et al.* (2012)	1006 Age: 81.5 (4.8) including 198 MCI	Cross-sectional study	Winblad *et al.*, (2004) criteria	Not specified	Depressive symptoms	Center for Epi-demiological Studies Depression Scale (CES-D; Radloff, 1977)	Participants with MCI showed an increased risk of depressive symptoms but only the multiple domain or non-amnestic subtypes

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Lyketsos *et al.* (2002)	320 MCI; age: 75 (5.0) 362 Dementia; age: 77 (5.0)	Cross-sectional study derived from the longitudinal Cardiovascular Health Study	Cognitive decline not meeting DSM-IV criteria for dementia that was 1.5 SD below same age and education level means on standardised tests	Modified Mini-Mental State Examination was used but no figures are given	Neuropsychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	Just under half of participants with MCI exhibited neuropsychiatric symptoms
McDougall *et al.* (2006)	265 from SeniorWISE study Age: 75	A baseline study as part of a larger clinical trial	Criteria used were: having cognitive decline, memory impairment, no dementia, essentially normal activities of daily living, and cognitive complaints not normal for the age of the individual	Participants were required to have a score of >23, although those falling just below the cut-off, but scoring well on other measures were accepted	Health Anxiety Depression Memory complaints Memory performance Instrumental activities of daily living	Health Scale (from the Multilevel Assessment Instrument) The State-Trait Anxiety Inventory (STAI) Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977)	As memory performance decreased, symptoms of anxiety and depression increased. Individuals with poorer memory function performed significantly worse on the DAFS

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
McIlvane *et al.* (2008)	46 MCI Age: 77.3 (7.1) 29 Care partners	Cross-sectional study	Performance one to two SD below expectations for estimated premorbid intellect with no dementia	26.3 (3.14)	Psychologic well-being Perceptions of Illness Coping Perceptions of Need for Help and Caregiving Service Use and Needs	Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) Life Satisfaction Index-Z (LSI-Z; Wood *et al.*, 1969) Short Form Health Survey (SF-36; Ware & Sherbourne, 1992)	Relatively low depressive symptoms, high life satisfaction, high mastery and high mental and physical quality of life were found. More emotion and problem focused coping was used in comparison to dysfunctional coping. Participants minimized their risk for AD and endorsed the effectiveness of health promotion activities to prevent AD. Participants reported relatively little stress in relation to memory problems
Muangpaisan *et al.* (2008)	77 MCI; age: 63.7 (7.3) 30 non-MCI; age: 66.3 (7.9)	Population-based study	Petersen's criteria (Petersen *et al.*, 1999), showing impairment on at least one measure of memory, clinician's judgement based on use of the Clinical Dementia Rating Scale (CDR; score of 0.5) and Global Deterioration Scale (GDS; Reisberg *et al.*, 1982) score of 3	Thai version Mini Mental State Examination (TMSE) was used. Patients with scores of <24 were excluded. MCI: 26.5 (1.6) Non-MCI: 28.1 (1.8)	Neuropsychiatric symptoms Financial status	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) Financial status was self-reported on the balance of income and expenditure	Patients with MCI had significantly higher levels of dysphoria, anxiety and night-time behaviours, and a tendency to suffer from a higher degree of apathy. Male patients had a higher percentage of dysphoria and anxiety symptoms. Patients who reported a poor financial status had a higher percentage of dysphoria and anxiety symptoms

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Palmer *et al.* (2007)	47 MCI 185 Control Age: 84.0 (5.1)	Longitudinal population-based study	Subjective memory complaint, no dementia, intact ADLs, objective evidence of cognitive impairment on neuropsychological tests	Not specified	Neuropsychiatric symptoms	Comprehensive Psychopathological Rating Scale (CPRS)	Participants with MCI were four times more likely to have one clinically significant psychiatric symptom compared with NCI participants. The presence of mood-related depressive symptoms did not increase risk of progression from MCI to dementia over 3 years. For each increase in the number of anxiety symptoms the risk of progression from MCI to dementia almost doubled
Palmer *et al.* (2010)	131 MCI Age: 70.8 (6.5)	Longitudinal study	Petersen criteria (Petersen, 2004)	27.2 (2.0)	Depression Apathy Neuropsychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) Structured interview	36.6% of participants had depression but this was not found to increase the risk of conversion to AD. 10.7% of participants had apathy, with a 20% increase in risk of conversion to AD with each point increase for apathy on the NPI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Panza *et al.* (2008)	1445 including 139 MCI	Longitudinal study	Petersen *et al.* (1999) criteria	Not specified	Depressive symptoms	Geriatric Depression Scale (Yesavage *et al.*, 1982)	15 participants with MCI progressed to dementia over 3.5 years. Of these, 9 had a GDS score >10. A significant association between depressive symptoms and rates of conversion to dementia in MCI was not found
Ramakers *et al.* (2009)	263 MCI Age: 66.9 (7.7)	Longitudinal study	MCI was broadly defined as a score of 2 or 3 on the Global Deterioration Scale (GDS; Reisberg *et al.*, 1982). The amnestic subtype was further defined as a score 1.5 SD below the reference population on the Auditory Verbal Learning Test	27.6 (2.1)	Depression	Hamilton Depression Scale (HMD; Hamilton, 1967)	Depression was associated with a lower risk of MCI when MCI was defined according to the broad definition of MCI but not when the amnestic subtype was used
Ravaglia *et al.* (2008)	72 MCI; age: 78.1 (8.3) 595 Control; age: 72.3 (5.6)	Longitudinal population-based study	Winblad *et al.*, (2004) criteria but without requirement for subjective memory complaints	MCI: 21.4 (2.1) Control: 28.5 (1.3)	Depression	Geriatric Depression Scale (Yesavage *et al.*, 1982)	The prevalence of depression in MCI was 44% which was almost two times that of the control participants

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Robert *et al.* (2006)	251 a-MCI Age: 71.9 (5.4)	Cross-sectional study derived from the PAQUID Study	Memory complaints, at least one error on the MMSE three word recall task, or a score of <29 on the Isaac-Set Test (Isaacs *et al.*, 1973)	Individuals who developed dementia of Alzheimer type (DAT): 26.9 (1.1) Stable MCI: 27.6 (1.3)	Anxiety Depression	Goldberg Anxiety Scale (GAS; Goldberg & Hillier, 1979) Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)	The proportion of conversion from MCI to dementia of Alzheimer type (DAT) was higher for participants with symptoms of apathy. 91.7% of the participants who developed DAT had at least one symptom of apathy compared to 26.4% of non-converted participants
Robert *et al.* (2002)	19 Control; age: 70.68 (8.21) 24 MCI; age: 71.67 (5.92) 12 PD; age: 64.1 (11.9) 60 AD; age: 74.90 (7.11)	Reliability and validity assessment of the Apathy Inventory	ICD-10 criteria	Control: 29 MCI: 28.2 (1.06) PD: 27.2 (3.5) AD: 22.55 (3.98)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	Scores on these measures for participants with MCI were between the scores for those with AD and control participants. The largest difference between the control participants and participants with MCI was for the lack of initiative dimension
Rosenberg *et al.* (2012)	1779 MCI Age: 75.4 (9.6)	Multi-centre population study	Objective or subjective evidence of cognitive impairment but no significant functional impairment to meet criteria for dementia	27.8 (7.5)	Neuro-psychiatric symptoms Depression	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) 15-item Geriatric Depression Scale (GDS-15; Yesavage *et al.*, 1982)	Participants with greater levels of executive dysfunction had increased symptoms of NPS. 27.3% of participants had depressive symptoms

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Rozzini *et al.* (2007)	94 a-MCI; age: 71.7 (8.3) 26 na-MCI; age: 68.8	Longitudinal clinic-based	Artero *et al.* (2006)	a-MCI: 26.2 (1.8) na-MCI: 27.4 (1.8)	Anxiety Neuropsychiatric symptoms Depression	Geriatric Depression Scale 15 item version (GDS-15; Yesavage et al., 1982) Hamilton Anxiety Scale (Hamilton, 1967) Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	83% of those with a-MCI and 73% of those with na-MCI had depressive symptoms. 75% of those with a-MCI and 73% of those with na-MCI had symptoms of anxiety. 99 participants were re-evaluated 1 year later and 42 of these had progressed to dementia
Rozzini *et al.* (2009)	57 out-patients with cognitive complaints Age: 71.2 (7.3)	Validation of Geriatric Anxiety Inventory	Cognitive complaint, no dementia, change from normal functioning in IADL/ADL, preserved general functioning, cognitive functioning 1.5 SD below means	27.7 (1.9)	Anxiety Neuropsychiatric symptoms Depression	Geriatric Anxiety Inventory (Pachana *et al.*, 2007) Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) Geriatric Depression Scale (Yesavage *et al.*, 1982) Anxiety Status Inventory (Zung, 1971)	44 participants had MCI and anxiety. Those with anxiety showed more behavioural and psychological disturbances, more depressive symptoms and were more compromised in instrumental activities of daily living. Executive functions were independently related to anxiety disorders in participants.

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Ryu *et al.* (2011)	241 MCI Age: 72.9 (5.7)	Population-based study	Petersen's criteria (Petersen, 2004) of cognitive concern expressed by an informant or the participant, cognitive impairment in one domain or more, intact activities of daily living, and no dementia	22.5 (3.3)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) Korean version of the Geriatric Depression Scale (GDS-K; Cho *et al.*, 1999) Quality of Life-AD (QoL-AD; Logsdon *et al.*, 1999)	At 6-month follow-up 46.6% of participants had at least one NPS with 30.9% having clinically significant symptoms. Those with more symptoms at baseline were more likely to have persistent symptoms and a poorer quality of life. Depression, anxiety and sleep disturbances were the most common symptoms
Solfrizi *et al.* (2007)	2963 including 139 MCI	Longitudinal community	Petersen *et al.* (1999) criteria but without requirement for subjective memory complaints	Those scoring high on depression: 21.3 (4.2) Without depression: 21.7 (4.2)	Depression	Geriatric Depression Scale (Yesavage *et al.*, 1982)	63.3% of participants with MCI had high levels of depression. 36 participants completed a second analysis and all scored highly on the measure of depression
Teng *et al.* (2007)	51 MCI Age of those who progressed to AD: 75.8 (6.0) Age of those who did not progress to AD: 71.9 (7.3)	Longitudinal clinic-based	Petersen *et al.* (2004) criteria	Those who progressed to AD: 26.3 (2.8) Those who did not progress to AD: 28.0 (1.7)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994)	12 participants progressed to AD over 2.1 years. Baseline NPI symptoms were higher in those who progressed than in those who did not. Participants who progressed were more likely to have depression but this was not significant after corrections

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Van der Linde *et al.* (2010)	389 MCI aged 73.8 (0.43)	MRC-CFAS Longitudinal	Subjective memory complaint, performance on tests of memory or other cognitive domains below 16th percentile, no impairment in general cognitive function	25.4 (0.14)	Behavioural and psychological symptoms	Structured interviews with participants and informants which include the Cambridge Mental Disorders of the Elderly Examination (CAMDEX; Roth *et al.*, 1986)	Depression increased as cognitive function worsened but there was no difference between those with MCI and healthy controls in the prevalence of anxiety. 61% of participants with MCI had depression
Vicini Chilovi *et al.* (2009)	124 including 50 without depression; age: 71.6 (8.5) 38 with depression; age: 70.8 (7.6)	Longitudinal clinic-based	Winblad *et al.* (2004) criteria	Without depression: 26.8 (1.9) With depression: 26.7 (1.8)	Depression	DSM-IV Criteria Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) Geriatric Depression Scale 15 item version (GDS-15; Yesavage *et al.*, 1982) Hamilton Anxiety Scale (Hamilton, 1967)	24% of those with MCI but not depression progressed from MCI to dementia. 7.9% of those with MCI and depression progressed to dementia. Depression appeared to have a protective effect on progression from MCI to dementia

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 2. *Continued*

Name and year	Participants, n, and mean age	Design	Definition of MCI used	MMSE	Symptoms assessed	Measures used in assessment	Results
Zhang *et al.* (2012)	38 MCI Age: 71.0 (8.0) 49 controls	Observational	Petersen *et al.* (1999) criteria	28.0 (1.0)	Neuro-psychiatric symptoms	Neuropsychiatric Inventory Chinese Version (Xie *et al.*, 2004)	81.6% of participants with MCI had at least one NPS. Common symptoms were depression (28.9%) and anxiety (26.3%)
Zihl *et al.* (2009)	24 MCI; age: 65.8 (5.8) 50 Depressed; age: 64.1 (6.4) 20 Control; age: 63.4 (1.0)	Cross-sectional study	Winblad *et al.* (2004) revised diagnostic criteria	MCI: 27.8 (1.8) Depressed: 28.3 (1.6) Control: 29.8 (0.4)	Depressive symptoms	Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)	Participants with MCI and participants with depression plus cognitive impairments have a very similar neuropsychological pattern in the domains of attention, memory and executive functions. Cognitive dysfunction remained in participants with depression even after remission of depressive symptomology

Table 3. *Quality assessment of included studies*

	Representative sample	Was an appropriate sample size used?	Acceptable classification of MCI	Acceptable measures of mood	No confounding factors	Reporting of withdrawals	Statistical methods appropriate for the study design	Score
Adler *et al.* (2004)	✗	✗	√	√	N/A	✗	√	3
Artero *et al.* (2008)	√	√	√	√	√	✗	√	1
Baiyewu *et al.* (2012)	√	✗	✗	√	√	√	√	2
Barnes *et al.* (2006)	√	√	✗	√	√	✗	√	2
Bhalla *et al.* (2009)	✗	√	√	√	✗	N/A	√	1
Brodaty *et al.* (2012)	√	√	√	√	√	√	√	0
Caracciolo *et al.* (2012)	√	√	√	√	√	✗	√	1
Chan *et al.* (2003)	√	√	√	√	√	N/A	√	0
Cherbuin *et al.* (2009)	√	√	√	√	√	✗	√	1
Clement *et al.* (2009)	✗	✗	√	√	✗	N/A	√	3
Collie *et al.* (2002)	√	√	√	√	√	✗	√	1
Devier *et al.* (2009)	✗	√	✗	√	✗	√	√	3
Di Iulio *et al.* (2010)	✗	√	√	√	✗	N/A	√	2
Dotson *et al.* (2010)	√	√	√	√	√	✗	√	1
Edwards *et al.* (2009)	✗	√	√	✗	N/A	✗	√	3
Elfgren *et al.* (2010)	✗	✗	√	√	√	√	√	2
Fernandez-Martinez *et al.* (2010)	✗	√	√	√	✗	N/A	√	2
Forsell *et al.* (2003)	√	√	✗	√	√	N/A	√	1
Gabryelewicz *et al.* (2006)	√	√	√	√	N/A	√	✗	1
Gallagher *et al.* (2011)	✗	√	√	✗	N/A	✗	√	3
Gallassi *et al.* (2007)	✗	√	√	√	✗	N/A	✗	3
Geda *et al.* (2006)	√	√	√	✗	N/A	✗	√	2
Geda *et al.* (2008)	√	√	√	✗	N/A	N/A	√	1
Goveas *et al.* (2011)	✗	√	√	√	√	✗	√	2
Hidaka *et al.* (2012)	√	√	√	✗	N/A	√	√	1
Huddon *et al.* (2008)	✗	√	√	✗	√	N/A	√	2
Houde *et al.* (2008)	✗	√	√	√	N/A	N/A	✗	2
Hwang *et al.* (2004)	✗	√	√	√	√	N/A	√	1

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 3. *Continued*

	Representative sample	Was an appropriate sample size used?	Acceptable classification of MCI	Acceptable measures of mood	No confounding factors	Reporting of withdrawals	Statistical methods appropriate for the study design	Score
Johnson *et al.* (2012)	√	√	√	√	√	N/A	√	0
Kruger *et al.* (2012)	√	√	√	√	✗	N/A	√	1
Kumar *et al.* (2006)	√	√	√	√	√	N/A	√	0
Lee *et al.* (2006)	✗	√	✗	√	✗	✗	√	4
Lopez *et al.* (2005)	✗	√	√	√	✗	N/A	√	2
Luppa *et al.* (2012)	√	√	√	√	√	N/A	√	0
Lyketsos *et al.* (2002)	√	√	√	√	√	✗	√	1
McDougall *et al.* (2006)	√	√	√	√	✗	N/A	√	1
McIlvane *et al.* (2008)	✗	✗	✗	√	N/A	N/A	√	3
Muangpaisan *et al.* (2008)	√	√	√	√	√	N/A	√	0
Palmer *et al.* (2007)	√	√	√	√	√	√	√	0
Palmer *et al.* (2010)	√	√	√	√	√	√	√	0
Panza *et al.* (2008)	√	√	√	√	√	√	√	0
Panza *et al.* (2008)	√	√	√	√	√	√	√	0
Ramakers *et al.* (2009)	✗	√	✗	√	N/A	√	√	2
Ravaglia *et al.* (2008)	√	√	√	√	√	√	√	0
Robert *et al.* (2002)	✗	√	√	√	√	N/A	√	1
Robert *et al.* (2006)	✗	√	✗	√	√	√	√	2
Rosenberg *et al.* (2011)	√	√	√	√	√	N/A	√	0
Rozzini *et al.* (2007)	✗	√	√	√	√	✗	√	2
Rozzini *et al.* (2009)	✗	√	√	√	N/A	N/A	√	1
Ryu *et al.* (2011)	√	√	√	√	√	✗	√	1
Shahnawaz *et al.* (2012)	√	√	√	√	√	N/A	√	0
Solfrizi *et al.* (2007)	√	√	√	√	√	N/A	√	0
Spira *et al.* (2012)	✗	√	√	✗	N/A	✗	√	3
Steenland *et al.* (2012)	✗	√	√	√	√	✗	√	2
Teng *et al.* (2007)	✗	√	√	√	N/A	✗	√	2
Van der Linde *et al.* (2010)	√	√	√	√	√	N/A	√	0
Vicini Chilovi *et al.* (2009)	✗	√	√	√	N/A	✗	√	2

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

Table 3. *Continued*

	Representative sample	Was an appropriate sample size used?	Acceptable classification of MCI	Acceptable measures of mood	No confounding factors	Reporting of withdrawals	Statistical methods appropriate for the study design	Score
Wilson *et al.* (2007)	✗	√	√	√	N/A	✗	√	2
Zhang *et al.* (2012)	✗	√	√	√	√	N/A	√	1
Zihl *et al.* (2009)	✗	√	√	√	√	✗	√	2

Key
√ Criterion met
✗ Criterion not met
N/A Criterion not applicable

presenting at memory clinics or experiencing memory problems, whether self-referred or referred by General Practitioners (GPs). In the community studies MCI criteria were applied to samples of older people drawn from the general population.

Mean MMSE scores were specified for the majority of the clinical studies, although in some cases the Modified Mini Mental State Exam (3MS) was used instead,[8,18,19] and in one case the Thai version of the MMSE was used.[20] Mean MMSE scores ranged from 22.5[21] to 28.7[22] and the mean across studies where data were available was 27.2 for the clinical studies. Mean MMSE scores were given for nine of the twenty-four community samples and ranged from 17.3[23] to 28.8.[24] The mean across studies where data were available was 25.8 for community samples.

The number of participants ranged from 18[25] to 8855.[26] In studies where data regarding the age of participants were available, the age of participants ranged from 55.5 to 86.9 years (mean across studies: 72.6 years).

MCI definitions used

Various classification systems for MCI were used. Twenty-seven studies used the Petersen *et al.*[7,27,28] criteria which require a subjective memory complaint, deficits in cognitive function compared with age and education norms, intact activities of daily living and intact global cognition, and stipulate that the individual should not meet criteria for dementia.

Twenty-two studies used criteria similar to those of Petersen *et al.*[7,27,28] in terms of deficits on neuropsychological test batteries. One study required a deficit of 1.5SD (standard deviation) below the mean on any single test or 1SD below the mean on two or more tests of cognitive function.[13] Other research required that participants had an MMSE score of 1SD below age- and education-specific means.[29] Other studies[30–32] did not specify the cut-off scores for the neuropsychological tests used. Of the twenty-two studies, ten required a subjective memory complaint in order to classify participants as having MCI.[32–34]

ICD-10 criteria that refer to mild cognitive disorder[35] were used in one study. These criteria require that an individual must have difficulties in new learning, memory, concentration, thinking, or language, and stipulate that there should be abnormality or decline in performance on neuropsychological tests.

Seven studies[36,37] used revised diagnostic criteria for MCI.[38] These criteria specify that an individual should not meet criteria for dementia and should show cognitive decline through a subjective memory complaint in conjunction with deficits on objective cognitive tests. Basic ADLs should be preserved and complex instrumental functions should be minimally impaired.

Criteria used in one study were derived from previous investigations of the same sample.[39] The National Alzheimer's Co-ordinating Center Codebook (2006), which is a comprehensive assessment that considers an individual's cognitive functioning along with health and demographic factors, was used in another study.[26]

Definitions of mood

The studies reviewed used several terms to describe mood. Most studies directly investigated either depression[8,10] or anxiety.[31] Several studies investigated both anxiety and depression.[26,30]

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

The term 'neuropsychiatric symptoms' was used in nineteen of the studies.[19,21,40] Neuropsychiatric symptoms are typically measured with the NPI and the term encompasses symptoms in the domains of delusions, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and night time behaviours, and appetite and eating disorders. This review is concerned with depression/dysphoria and anxiety, and so measurements of these aspects of neuropsychiatric symptoms were considered where information was given. One study referred to 'psychosocial stress'.[34] The term refers to patient reports of experiences of daily stress during the last three months. This was included here due to its association with anxiety.

Selection of measures for assessment of mood

A range of measures was used to assess mood. Five studies[9,32,41–43] used the Hamilton Depression Scale (HAM-D). Sixteen studies[13,19,40,44] used the Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994). In addition, two studies[45,46] used the shortened form of the NPI, the Neuropsychiatric Inventory Questionnaire (NPI-Q). Seven studies[8,18,24,30,47–49] used the Center for Epidemiologic Studies Depression Scale (CES-D;). Four studies[34,50–52] used the Montgomery Asberg Depression Scale (MADRS). Nine studies used the full version of the Geriatric Depression Scale (GDS-30), six studies used the 15-item version of the Geriatric Depression Scale (GDS-15), two studies[26,53] used the shortened five-item version (GDS-5) and one study[21] used the Korean version (GDS-K). One study used the Comprehensive Psychopathological Rating Scale,[29] which contains mostly self-report items but also includes some observer-rated items, and another used the BEHAVE-AD scale.[54] One study used the Goldberg Depression Scale and the depression section of the PRIME-MD Patient Health Questionnaire (PHQ).[55] One study used a self-report rating of perceived sadness.[56]

Several measures were used to assess anxiety, such as the State-Trait Anxiety Inventory (STAI)[30] and the Goldberg Anxiety Scale (GAS).[51] One study used both the Geriatric Anxiety Inventory (GAI) and the Anxiety Status Inventory (ASI).[31]

Relationship between MCI and mood

A meta-analysis was conducted to investigate whether people with MCI were more likely to have low mood than those who are not cognitively impaired (Fig. 2) and this shows that the odds of having depressive symptoms are increased in people with a classification of MCI (odds ratio (OR) = 3.23; 95% CI: 2.00–5.22).

A further meta-analysis (Fig. 3) was conducted to ascertain whether symptoms of anxiety were more prevalent in people classified as having MCI than in those without cognitive impairment. In seven of the eight studies included in this analysis, the odds of having symptoms of anxiety are increased by 1.43 to 3.6 if an individual is classified as having MCI. One study[22] showed an increase in the odds of having symptoms of anxiety of 16.5. The overall result shows an increase in the likelihood of symptoms of anxiety in people with MCI (OR = 2.50; 95% CI: 1.69–3.71).

Four studies examined the relationship between the subtype of MCI and symptoms of depression or anxiety. Individuals with multiple-domain MCI experienced a similar frequency of depressive symptoms to individuals with Alzheimer's disease, which is greater than older people with normal cognitive functioning, although the symptoms were likely to be milder.[44] One study showed that more individuals with non-amnestic MCI than individuals with the amnestic subtype of MCI had depressive symptoms,[55] whereas another reported there were similar levels of symptoms of depression and anxiety for the amnestic and non-amnestic subtypes.[57]

Temporal relationship

Follow up times ranged from 2.1 years[58] to 12 years.[39] Three studies commented on the effect of the time of onset of mood problems. Two studies reported that the risk of MCI was greater for people with newly developed depression rather than a life history of depression[9,10] and one study found that past depression was not related to an increase in the risk of incident MCI.[26]

Several studies investigated the progression from not cognitively impaired to a classification of MCI, and five studies showed that depressive symptoms or low mood increased the risk of being classified as having MCI. Those with low mood were 2.5 times more likely to progress to a classification of MCI over 6 years.[56] Two studies concluded that

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

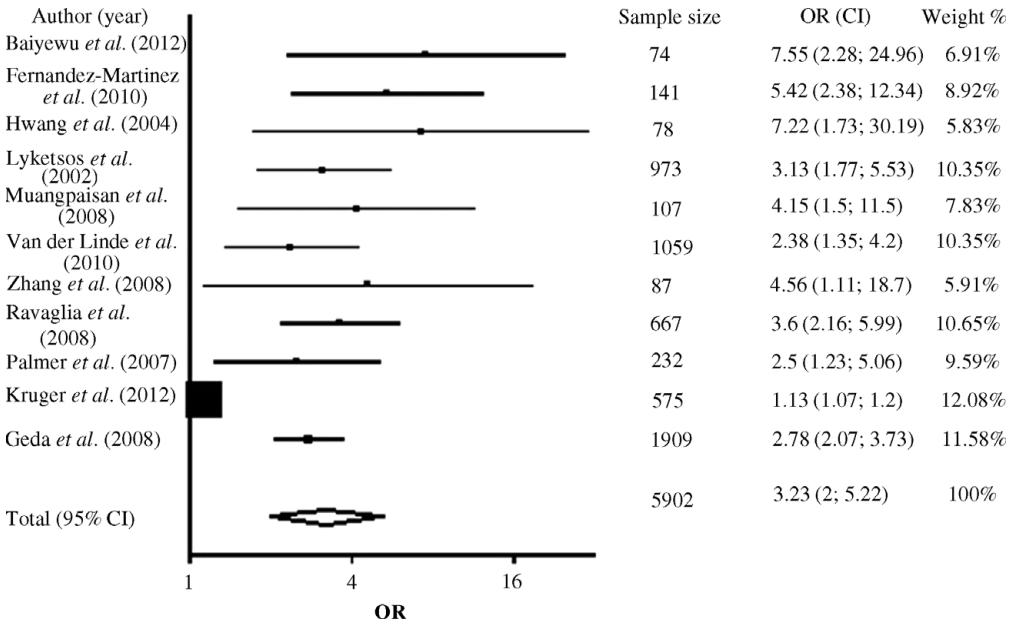


Figure 2. The odds of having depressive symptoms in individuals with MCI

a diagnosis of depression was associated with a greater incidence of MCI.[18,59] Taking medication for symptoms of anxiety or depression was found to be significantly predictive of a progression from not cognitively impaired to MCI over 4 years.[25] Self-report of anxiety or depression was only mildly predictive of MCI. One study followed participants for 3.5 years and found no significant association between depressive symptoms and the rate of incident MCI.[60] A further study reported that the risk of MCI increased by approximately 6% for each symptom of depression endorsed by participants, but this did not remain significant when proneness to distress was controlled for.[39] A meta-analysis was conducted using studies where data were available to examine the risk of progressing from not cognitively impaired to having MCI when symptoms of depression are present. Figure 4 shows an increase in the risk of progression from no cognitive impairment to MCI when depressive symptoms are present (hazard ratio (HR) = 2.40; 95% CI: 1.91–3.02).

Progression from MCI to dementia

Eight studies investigated the risk of progression from MCI to dementia over time and most found that depression was not a risk factor. Only one study found that a higher score on measures of depression was significantly more frequent in individuals who progress from MCI to dementia.[50] One study found that whilst there was no difference in the baseline levels of depressive symptoms between individuals who progressed to dementia and those who did not, the persistence of depressive symptoms increased risk of progression.[61] A further study followed participants for 2.1 years and found that baseline NPI scores for depression were higher in those who progressed from MCI to dementia than in those who continued to be classified as having MCI, although this did not remain significant after correction for multiple comparisons.[58] A protective effect of depression on the progression from MCI to dementia has also been reported.[16] A meta-analysis was conducted using studies where data were available to examine the effect of depressive symptoms on the risk of progression to dementia from MCI. Figure 5 shows an overall increase in risk of progressing from MCI to dementia when depressive symptoms are present (relative risk (RR) = 1.14; 95% CI: 0.77–1.68).

Only a small number of studies considered anxiety and it was not possible to conduct a meta-analysis to examine the effect of anxiety on progression from MCI to dementia. One study found that as the number of anxiety symptoms

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

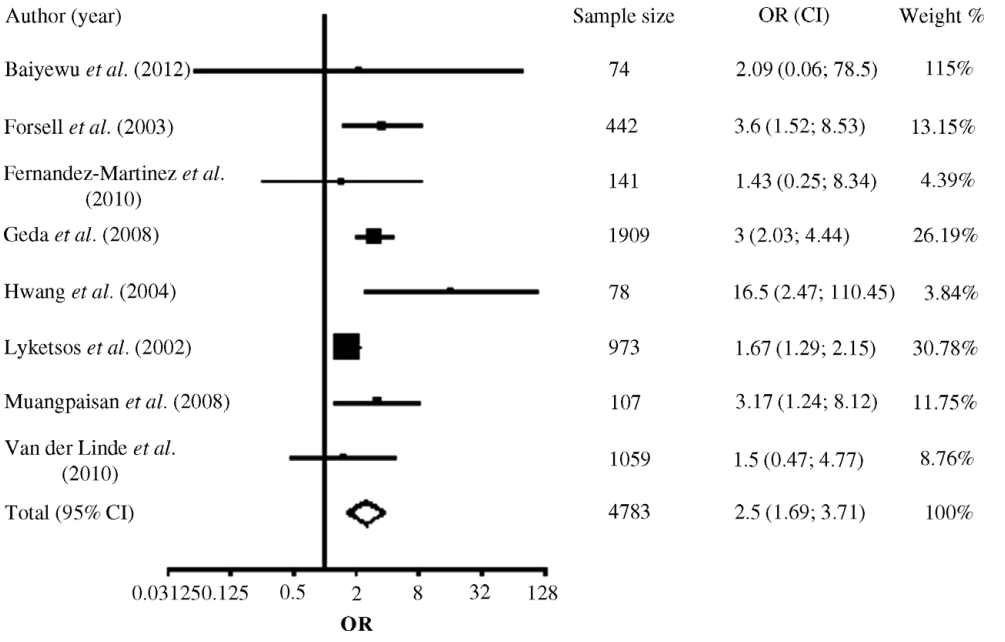


Figure 3. The odds of having symptoms of anxiety in individuals with MCI

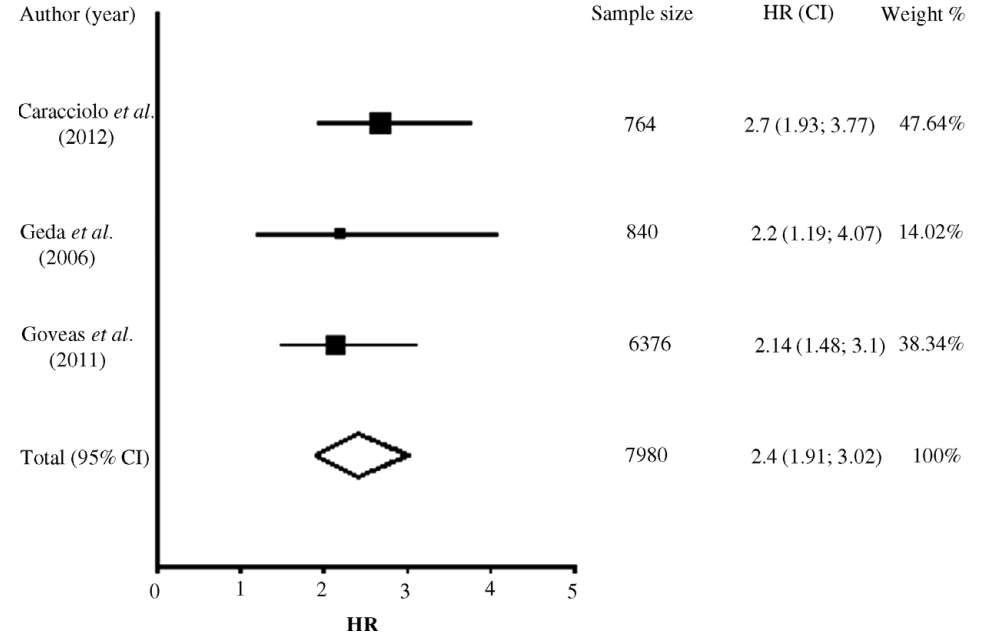


Figure 4. The effect of depressive symptoms on risk of progression from not cognitively impaired to a classification of MCI

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

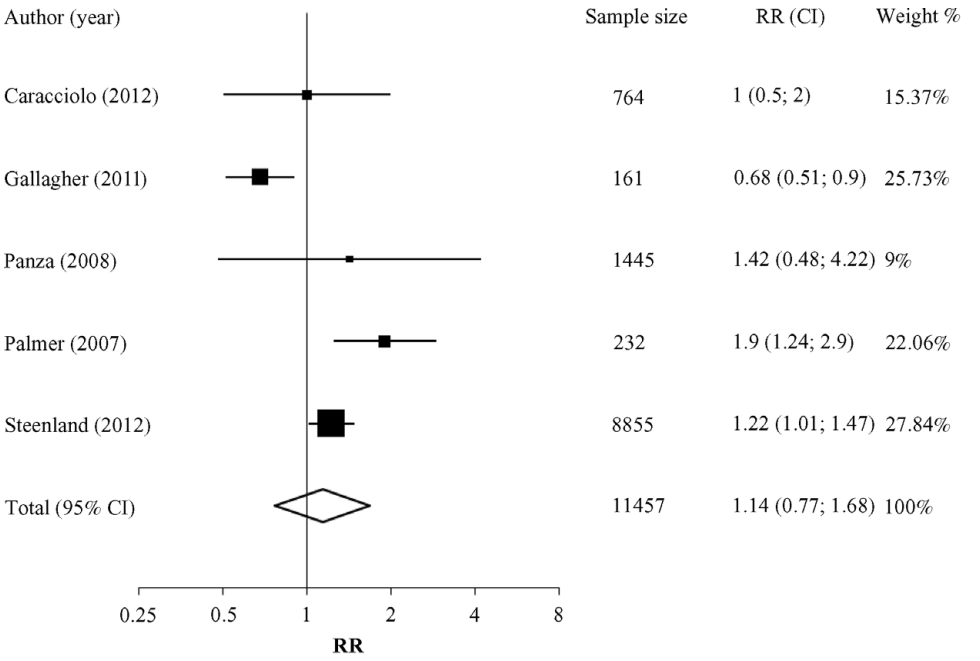


Figure 5. The effect of depressive symptoms on risk of progression from a classification of MCI to a diagnosis of dementia

increased, the risk of progression from MCI to dementia almost doubled.[12] However, another study found that higher levels of trait anxiety were significantly associated with a lower risk of conversion to Alzheimer's disease.[54]

Discussion

This review aimed to explore the relationship between mood and MCI through investigating whether symptoms of depression and anxiety are more likely in individuals who have been classified as having MCI, and examining the effect of such symptoms on the risk of progression from no cognitive impairment to MCI, or from MCI to dementia. To the best of our knowledge, this review is the first to synthesize studies investigating mood and MCI, assess the effects of mood on progression, and conduct meta-analyses using available data to clarify the relationships explored.

The meta-analyses showed that symptoms of depression or anxiety were more common in people classified as having MCI compared with people with normal cognitive functioning. Having symptoms of depression increased the risk of progression from not cognitively impaired to MCI, and from MCI to dementia. Data were not available to calculate whether there was an increase in risk associated with symptoms of anxiety.

There are several issues that should be considered when interpreting the findings of this review. Firstly, the source of the study population can be problematic when applying the concept of MCI. Clinical samples tend to be drawn from individuals who have presented at memory clinics for a detailed assessment, allowing the identification of subtle difficulties, whereas when applying MCI criteria retrospectively in community samples, individuals with more subtle impairments may not be identified and so results may be biased towards those who show a greater level of impairment.[62] It has been suggested that there are differences between clinical samples and community samples in the rate of conversion from MCI to dementia,[63] with research showing that 15% of clinical samples but only 7.5% of community dwellers converted to dementia.[64]

MMSE scores were provided for the majority of the studies reviewed and whilst most scores fall within expected ranges, some studies report MMSE scores that are much lower that would be

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

anticipated for individuals who have been classified as having MCI.[29] It could be suggested that individuals showing this level of cognitive function may be more impaired than other individuals who have been classified as having MCI and hence may not be directly comparable.

A number of studies included a small number of participants[31,34] and these may not be as representative of the MCI population as studies using larger samples.[18,26] The age of participants in the included studies was within the expected range except for one study in which the youngest participants were aged 55.5 years.[47] This is younger than would be expected, as studies investigating MCI typically consider participants who are over 65 years old.

Several different definitions of MCI were used in the included studies. A recent study found that the application of different classification systems resulted in the same individuals being concurrently classed as having MCI according to certain definitions and healthy according to others,[1] highlighting the need for agreement on which definition to use. The heterogeneity of the definitions of MCI used in the included studies could suggest that participants from different studies may not have the same levels or types of cognitive impairment.

The majority of studies included in this review either did not specify which subtype of MCI was investigated, or included only participants with the amnestic subtype. This may mean that individuals with other subtypes were unaccounted for, or where the subtype of MCI was not specified, participant groups could be considered to be overly heterogeneous, which may have attenuated any effects. The subtype of MCI investigated may also have an impact on the relationship between MCI and depression or anxiety. Only four of the studies included in this review investigated the effect of MCI subtype, and the results were mixed.

Several of the included studies required a subjective memory complaint as part of the MCI definition, although there is controversy as to the usefulness of this. Research has recommended that subjective memory complaint should not be a diagnostic criterion because it lacks accuracy.[65] Instead objective evidence for the stability or decline of cognitive function over time should be sought. Corroboration by an informant is not a requirement, but it is valuable as it can help to ensure the accuracy of the subjective memory complaint. Furthermore, increased levels of subjective memory complaints were found to be correlated with increased levels of anxiety and depression, independent of whether an individual was classified as having MCI, suggesting that mood may influence the accuracy with which people appraise their memory. The presence of depression may inflate memory problems by enhancing negative attributions.[14] The association between subjective memory complaints and depression is stronger than the association between subjective memory complaints and objective memory impairments.[66] It has been shown that including subjective memory complaint in the criteria for MCI classification does not increase predictive ability.[64] Subjective memory complaints may therefore be unnecessary and could potentially contribute to identification of more false positives or false negatives.[65]

The findings may also have been affected by the use of several different measures of mood. The NPI is well established for use with individuals who have impairments in cognitive functioning; however, the shortened version of the NPI (NPI-Q) should be interpreted with caution as it contains fewer questions than the original NPI. In addition, both versions of the NPI are based on informant report rather than being directly administered to the participant, which could allow for symptoms to be wrongly estimated or misattributed.

A further issue is the overlapping nature of depression and anxiety. These frequently co-exist and may interact with each other. Research has found that anxiety symptoms were significantly and directly associated with depressive symptoms. In one study, taken together, symptoms of anxiety and depression were associated with a decline in cognitive function but the association did not hold for depressive symptoms alone.[67] Therefore, studies that consider only depression or anxiety may be missing participants with milder symptoms of one mood problem that interact with symptoms of the other.

The use of neuropsychological tests to quantify cognitive functioning is not straightforward. Neuropsychological models of memory indicate that there are several different systems of memory, with different processes and modalities involved. However, memory impairments are often treated much more simply in the context of MCI. Aspects and processes of memory may be affected in MCI in different ways, with some preserved

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

and others impaired. In addition, depression or anxiety may differentially affect some aspects or processes compared with others. The use of neuropsychological tests is complex as different tests assess different aspects of memory and use different modalities, and therefore the results of tests may not be directly comparable. In addition, interpreting the results from neuropsychological tests is difficult as simple cut-off scores are not used. Instead, individual performance is assessed in relation to age- and education-specific norms.[68] Relying on one single test may be problematic, and research suggests that instead of requiring marked impairment on one single test it may be more appropriate to focus on a pattern of performance across a range of tests that indicate milder, but more widespread impairment.[69,70]

The review highlights additional issues that should be considered. This review only included articles published in English and so relevant articles published in other languages may have been missed. One article published in Spanish was excluded. In addition, this review only included published items as the search methods did not reveal any unpublished literature; hence there may be a publication bias towards studies that have found an association between MCI and mood.

This review has several implications. From a theoretical viewpoint the review demonstrates that systems for classifying MCI should take symptoms of depression and anxiety into account. At present, classification systems often exclude individuals with mood problems, which may distort prevalence and incidence rates for MCI. In a practical sense, there is a need to help individuals overcome symptoms of depression and anxiety. At present the direction of the relationship between symptoms of depression or anxiety and MCI has not been established, but this review has shown that the odds of having MCI are increased in those with depressive symptoms. Further research may be able to clarify this relationship and hence allow interventions to be targeted accordingly. This review has implications for clinical practice, general practitioners and front-line medical staff who need to recognize subtle symptoms in older people, in relation to both mood and cognitive function, and to encourage older people to talk about their concerns.

This review has demonstrated that evidence exists for a relationship between MCI and mood. Whilst the direction of the relationship cannot be firmly established at the moment, there is scope for further investigation involving participants with either mood problems, cognitive impairment, or both. The findings of this review also suggest that symptoms of depression may have an effect on the progression of cognitive impairment, and such findings could be used to increase awareness amongst older people and general practitioners. More knowledge in this area may provide a foundation for attempts to slow or prevent progression from MCI to dementia in order to afford a better quality of life for those affected by cognitive impairment and their families.

Conflicts of interest

The authors declared no conflicts of interest.

Funding

This study was funded by Economic and Social Research Council (ESRC) grant RES-060-250060.

References

1 Matthews FE, Stephan BCM, McKeith IG, Bond J, Brayne C. Two year progression from mild cognitive impairment to dementia: To what extent do different definitions agree? *J Am Geriatrics Soc* 2008; **56**: 1424–33.

2 Stephan BCM, Brayne C, McKeith IG, Bond J, Matthews FE. Mild cognitive impairment in the older population: Who is missed and does it matter? *Int J Geriatric Psychiatry* 2008; **23**: 863–71.

3 Wahlund LO, Pihlstrand E, Jonhagen M. Mild cognitive impairment: Experience from a memory clinic. *Acta Neurologica Scandinavica* 2003; **107**: 21–24.

4 Wolf H, Grunwald M, Ecke GM, Zedlick D, Bettin S, Dannenberg C. The prognosis of mild cognitive impairment in the elderly. *J Neural Transmission* 1998; **54**: 31–50.

5 Dubois B, Albert ML. Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurology* 2004; **3**: 246–48.

6 Stephan BCM, Matthews FE, Hunter S, Savva GM, Bond J. Neuropathological profile of mild cognitive impairment from a population perspective. *Alzheimer's Disease Associated Disorders* 2012; **26**: 205–12.

7 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV *et al.* Current concepts in mild cognitive impairment. *Archives Neurology* 2001; **58**: 1985–92.

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

8 Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Archives Gen Psychiatry* 2006; **63**: 273–79.

9 Bhalla RK, Butters MA, Becker JT, Houck PR, Snitz BE, Lopez OL *et al.* Patterns of mild cognitive impairment after treatment of depression in the elderly. *Am J Geriatric Psychiatry* 2009; **17**: 308–16.

10 Geda YE, Knopman DS, Mrazek DA, Jicha GA, Smith GE, Negash S *et al.* Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Archives Neurology* 2006; **63**: 435–40.

11 Butters MA, Bhalla RK, Andreescu C, Wetherell JL, Mantella R, Begley AE *et al.* Changes in neuropsychological functioning following treatment for late-life generalised anxiety disorder. *Br J Psychiatry* 2011; **199**: 211–18.

12 Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* 2007; **68**: 1596–602.

13 Chan DC, Kasper JD, Black BS, Rabins PV. Prevalence and correlates of behavioral and psychiatric symptoms in community-dwelling elders with dementia or mild cognitive impairment: the Memory and Medical Care Study. *Int J Geriatric Psychiatry* 2003; **18**: 174–82.

14 Roberts JL, Clare L, Woods RT. Subjective memory complaints and awareness of memory functioning in mild cognitive impairment: A systematic review. *Dementia and Geriatric Cognitive Disorders* 2009; **28**: 95–109.

15 Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Meth* 2003; **3**: 25.

16 Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dementia and Geriatric Cognitive Disorders* 2009; **27**: 390–98.

17 Lee JS, Potter GG, Wagner HR, Welsh-Bohmer KA, Steffens D. Persistent mild cognitive impairment in geriatric depression. *Int Psychogeriatrics* 2006; **19**: 125–35.

18 Goveas JS, Espeland MA, Woods NF, Wassertheil-Smoller S, Kotchen JM. Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: the Women's Health Initiative Memory Study. *J Am Geriatrics Soc* 2011; **59**: 57–66.

19 Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002; **288**: 1475–83.

20 Muangpaisan W, Intalapaporn S, Assantachai P. Neuropsychiatric symptoms in the community-based patients with mild cognitive impairment and the influence of demographic factors. *Int J Geriatric Psychiatry* 2008; **23**: 699–703.

21 Ryu SH, Ha JH, Park DH, Yu J, Livingston G. Persistence of neuropsychiatric symptoms over six months in mild cognitive impairment in community-dwelling Korean elderly. *Int Psychogeriatrics* 2011; **23**: 214–20.

22 Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL. Mild cognitive impairment I associated with characteristic neuropsychiatric symptoms. *Alzheimer's Disease and Associated Disorders* 2004; **18**: 17–21.

23 Baiyewu O, Unverzagt FW, Ogunniyi A, Smith-Gamble V, Gureje O, Lane KA *et al.* Behavioural symptoms in community-dwelling elderly Nigerians with dementia, mild cognitive impairment and normal cognition. *Int J Geriatric Psychology* 2012; **27**: 931–39.

24 Collie A, Maruff P, Currie J. Behavioral characterization of mild cognitive impairment. *J Clin Exp Neuropsychol* 2002; **24**: 720–33.

25 Cherbuin N, Reglade-Meslin C, Kumar R, Jacomb P, Easteal S, Christensen H *et al.* Risk factors of transition from normal cognition to mild cognitive disorder: The PATH through Life Study. *Dementia Geriatric Cognitive Disorders* 2009; **28**: 47–55.

26 Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A. Late-life depression as a risk factor for mild cognitive impairment or Alzheimer's disease in 30 US Alzheimer's disease centers. *J Alzheimer's Disease* 2012; **31**: 265–75.

27 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Int Med* 2004; **256**: 183–94.

28 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. *Archives Neurology* 1999; **56**: 303–8.

29 Forsell Y, Palmer K, Fratiglioni L. Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. *Acta Neurologica Scandinavica Suppl* 2003; **179**: 25–28.

30 McDougall GJ, Becker H, Arheart KL. Older adults in the SeniorWISE Study at risk for mild cognitive impairment. *Archives Psychiatric Nursing* 2006; **20**: 126–34.

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

31 Rozzini L, Chilovi BV, Peli M, Conti M, Rozzini R, Trabucchi M *et al.* Anxiety symptoms in mild cognitive impairment. *Int J Geriatric Psychiatry* 2009; **24**: 300–5.

32 Devier DJ, Pelton GH, Tabert MH, Liu X, Cuasay K, Eisenstadt R *et al.* The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *Int J Geriatric Psychiatry* 2009; **24**: 1335–42.

33 Hidaka S, Ikejima C, Kodama C, Nose M, Yamashita F, Sasaki M *et al.* Prevalence of depression and depressive symptoms among older Japanese people: comorbidity of mild cognitive impairment and depression. *Int J Geriatric Psychiatry* 2012; **27**: 271–79.

34 Elfgren C, Gustafson L, Vestberg S, Passant U. Subjective memory complaints, neuropsychological performance and psychiatric variables in memory clinic attendees: a 3-year follow-up study. *Archives Gerontology Geriatrics* 2010; **51**: e110–14.

35 Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O *et al.* The Apathy Inventory: Assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatric Psychiatry* 2002; **17**: 1099–105.

36 Kruger TM, Abner EL, Mendiondo M, Schmitt FA, Smith CD, Jicha GA. Differential reports of pain and depression differentiate mild cognitive impairment from cognitively intact elderly participants. *J Geriatric Psychiatry Neurol* 2012; **25**: 107–12.

37 Luppa M, Sikorski C, Luck T, Weyerer S, Villringer A, Konig HH *et al.* Prevalence and risk factors of depressive symptoms in latest life – results of the Leipzig Longitudinal Study of the Aged (Leila 75+). *Int J Geriatric Psychiatry* 2012; **27**: 286–95.

38 Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO. Mild cognitive impairment – beyond controversies, towards a consensus: Report of the International Working Group on mild cognitive impairment. *J Internal Med* 2004; **256**: 240–46.

39 Wilson RS, Schneider JA, Boyle PA, Arnold SE, Tang Y, Bennett DA. Chronic distress and incidence of mild cognitive impairment. *Neurology* 2007; **68**: 2085–92.

40 Palmer K, Di Iulio F, Varsi AE, Gianni W, Sancesario G, Caltagirone C *et al.* Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimer's Disease* 2010; **20**: 175–83.

41 Adler G, Chwalek K, Jajcevic A. Six-month course of mild cognitive impairment and affective symptoms in late-life depression. *European Psychiatry* 2004; **19**: 502–5.

42 Lopez OL, Becker JT, Jagust WJ, Fitzpatrick A, Carlson MC, DeKosky ST *et al.* Neuropsychological characteristics of mild cognitive impairment subgroups. *J Neurol Neurosurgery Psychiatry* 2006; **77**: 159–65.

43 Ramakers IH, Visser PJ, Aalten P, Kester A, Jolles J, Verhey FR. Affective symptoms as predictors of Alzheimer's disease in subjects with mild cognitive impairment: A 10-year follow-up study. *Psychological Med* 2009; **40**: 1193–201.

44 Di Iulio F, Palmer K, Blundo C, Casini AR, Gianni W, Caltagirone C *et al.* Occurrence of neuropsychiatric symptoms and psychiatric disorders in mild Alzheimer's disease and mild cognitive impairment subtypes. *Int Psychogeriatrics* 2010; **22**: 629–40.

45 Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatric Psychiatry* 2013; **21**: 685–95.

46 Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJ, Pankratz VS *et al.* Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Archives Gen Psychiatry* 2008; **65**: 1193–98.

47 Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* 2010; **75**: 27–34.

48 McIlvane JM, Popa MA, Robinson B, Houseweart K, Haley WE. Perceptions of illness, coping, and well-being in persons with mild cognitive impairment and their care partners. *Alzheimer Disease Associated Disorders* 2008; **22**: 284–92.

49 Artero S, Ancelin M-L, Portet F, Dupuy A, Berr C, Dartigues J-F *et al.* Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurgery Psychiatry* 2008; **79**: 979–84.

50 Gabryelewicz T, Styczynska M, Luczywek E, Barczak A, Pfeffer A, Androsiuk W *et al.* The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *Int J Geriatric Psychiatry* 2007; **22**: 563–67.

51 Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M *et al.* Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: A one-year follow-up study. *Clin Neurol Neurosurgery* 2006; **108**: 733–36.

52 Zihl J, Reppermund S, Thum S, Unger K. Neuropsychological profiles in MCI and in depression: Differential cognitive dysfunction patterns or similar final common pathway disorder? *J Psychiatric Res* 2010; **44**: 647–54.

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press

53 Huddon C, Belleville S, Gauthier S. The association between depressive and cognitive symptoms in amnestic mild cognitive impairment. *Int Psychogeriatrics* 2008; **20**: 710–23.
54 Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D *et al.* Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int J Geriatric Psychiatry* 2011; **26**: 166–72.
55 Johnson LA, Mauer C, Jahn D, Song M, Wyshywaniuk L, Hall JR *et al.* Cognitive differences among depressed and non-depressed MCI participants: A project FRONTIER study. *Int J Geriatric Psychiatry* 2012; **28**: 377–82.
56 Caracciolo B, Backman L, Monastero R, Winblad B, Fratiglioni L. The symptom of low mood in the prodromal stage of mild cognitive impairment and dementia: a cohort study of a community dwelling elderly population. *J Neurol Neurosurgery Psychiatry* 2011; **82**: 788–93.
57 Rozzini L, Vicini Chilovi B, Conti M, Delrio I, Borroni B, Trabucchi M *et al.* Neuropsychiatric symptoms in amnestic and non-amnestic mild cognitive impairment. *Dementia Geriatric Cognitive Disorders* 2008; **25**: 32–36.
58 Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dementia Geriatric Cognitive Disorders* 2007; **24**: 253–59.
59 Kumar R, Jorm AF, Parslow RA, Sachdev PS. Depression in mild cognitive impairment in a community sample of individuals 60–64 years old. *Int Psychogeriatrics* 2006; **18**: 471–80.
60 Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ *et al.* Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. *Dementia Geriatric Cognitive Disorders* 2008; **25**: 336–46.
61 Houde M, Bergman H, Whitehead V, Chertkow H. A predictive depression pattern in mild cognitive impairment. *Int J Geriatric Psychiatry* 2008; **23**: 1028–33.
62 Chertkow H. Mild cognitive impairment. *Canadian Alzheimer Disease Review* 2002; **5**: 15–20.
63 Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. *Int Psychogeriatrics* 2004; **16**: 129–40.
64 Baars MAE, van Boxtel MPJ, Dijkstra JB, Visser PJ, van den Akker M. Predictive value of mild cognitive impairment for dementia. *Dementia Geriatric Cognitive Disorders* 2009; **27**: 173–81.
65 Lenehan ME, Klekociuk SZ, Summers MJ. Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): is it time to abandon subjective memory complaint as an MCI diagnostic criterion? *Int Psychogeriatrics* 2012; **24**: 1–10.
66 Minett TS, Da Silva RV, Ortiz KZ, Bertolucci PH. Subjective memory complaints in an elderly sample: A cross sectional study. *Int J Geriatric Psychiatry* 2007; **23**: 49–54.
67 Stillman AN, Rowe KC, Arndt S, Moser DJ. Anxious symptoms and cognitive function in non-demented older adults: An inverse relationship. *Int J Geriatric Psychiatry* 2012; **27**: 792–98.
68 Clare L. Neuropsychological Assessment. In Woods R, Clare L (eds), *Handbook of the Clinical Psychology of Ageing*, 2nd edn, pp. 363–83. England: John Wiley & Sons Ltd 2008.
69 Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatric Psychiatry* 2009; **17**: 368–75.
70 Fisk JD, Rockwood K. Outcomes of incident mild cognitive impairment in relation to case definition. *J Neurol Neurosurgery Psychiatry* 2005; **76**: 1175–77.

https://doi.org/10.1017/S0959259813000129 Published online by Cambridge University Press