The symptom of low mood in the prodromal stage of mild cognitive impairment and dementia: a cohort study of a community dwelling elderly population

B Caracciolo,[1] L Bäckman,[1,2] R Monastero,[3] B Winblad,[1] L Fratiglioni[1,2]

[1]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden
[2]Stockholm Gerontology Research Center, Stockholm, Sweden
[3]Department of Clinical Neuroscience, Section of Neurology, University of Palermo, Palermo, Italy

Correspondence to
B Caracciolo, Aging Research Center, Karolinska Institutet, Gävlegatan 16, Stockholm 113 30, Sweden;
barbara.caracciolo@ki.se

Received 22 July 2010
Revised 13 September 2010
Accepted 8 November 2010

ABSTRACT

Objective To investigate the symptom of low mood as a predictor of mild cognitive impairment (MCI) and its progression to dementia, taking into account: (i) MCI severity, (ii) time of assessment and (iii) interaction with other factors.

Methods 764 cognitively healthy elderly subjects living in the community, from the Kungsholmen Project. Participants were assessed by direct interview to detect low mood. Subjects were then followed for 6 years to identify those who developed MCI. People with incident MCI were followed for a further 3 years to assess progression to dementia.

Results People with low mood at baseline had a 2.7-fold (95% CI 1.9 to 3.7) increased risk of developing MCI at follow-up. The association was stronger for amnestic MCI (aMCI: HR 5.8; 95% CI 3.1 to 10.9) compared with global cognitive impairment (other cognitive impairment no dementia, oCIND: HR 2.2; 95% CI 1.5 to 3.3). ApoE-ε4 interacted with low mood in a synergistic fashion, increasing the risk of aMCI, while no interaction with psychiatric, vascular, frailty related or psychosocial factors was observed. Low mood at baseline, as opposed to low mood co-occurring with MCI, was associated with a 5.3-fold (95% CI 1.2 to 23.3) increased risk of progression to dementia in aMCI. In contrast, no association was found in oCIND.

Conclusion Low mood was more strongly associated with aMCI than with global cognitive impairment. Progression towards dementia was predicted only by low mood manifest in the prodromal stage of MCI. These findings indicate that low mood is particularly prominent in the very early stages of cognitive decline.

INTRODUCTION

Depression is the most studied neuropsychiatric feature of mild cognitive impairment and its association with cognitive deterioration has been shown both cross sectionally and longitudinally.[1] Prevalence of depression is higher in mild cognitive impairment (MCI) and dementia than in cognitively healthy subjects.[2] Subclinical syndromes of depression and isolated depressive symptoms are more common than clinical depression in both MCI and dementia. Interestingly, the most prevalent symptom of depression in MCI is low mood whereas in dementia apathy is predominant.[1] Longitudinally, depressive symptoms in cognitively healthy persons have been consistently associated with the development of MCI.[3–7] In contrast, studies on the progression of MCI towards dementia have produced conflicting evidence. Out of 10 studies,[4 8–16] three found that depressive symptoms increased the risk of progressing to dementia[4 14 16]; two reported an association only in women or for isolated symptoms[12 13]; three found no association[10 11 15]; and two recent studies reported that the presence of depressive symptoms decreased the risk of developing dementia.[8 9]

The discrepancy between studies on MCI development and studies on MCI progression may have alternative explanations. First, depressive symptoms may have a different role in different stages of the cognitive decline process. Specifically, symptoms of depression that are the expression of underlying neurodegenerative pathology[17] may be prominent during the transition between healthy cognition and initial cognitive impairment but lose their importance in more advanced stages of cognitive decline. Thus depressive symptoms may be differentially related to MCI types of different severity that represent different stages of the dementing process. In amnestic MCI (aMCI),[18 19] for instance, memory deficits are present in the background of otherwise preserved global cognitive functioning whereas in other definitional categories, such as other cognitive impairment no dementia (oCIND),[20 21] cognitive functioning is globally compromised although not yet to a degree sufficient to fulfil the criteria for a diagnosis of dementia. Therefore, oCIND can be interpreted as a more advanced stage of cognitive impairment compared with aMCI.

Secondly, most studies investigating the progression of MCI to dementia have focused on depressive symptoms co-occurring with MCI. Indeed, if low mood is an early feature of dementia related neuropathology, its onset should precede the stages when cognitive impairment becomes manifest, first as MCI and later as dementia. When MCI or dementia is detectable, depressive symptoms could also result from a subjective reaction to the cognitive problems, leading to reverse causality. Therefore, as depressive symptoms may be due to different mechanisms, they may have different odds of progressing towards dementia in people with MCI. Heterogeneity of depressive symptoms might also result in different responses to antidepressant drugs. It has been shown that depressive symptoms in MCI are particularly resistant to treatment.[16] For these reasons, it is important to pay special attention to the time of assessment of the depressive symptoms when studying the association with MCI and the impact on progression from MCI to dementia.

Thirdly, depression as a prodromal feature of cognitive impairment might have characteristics that do not coincide with the typical depressive syndrome, as described by depression interviews, scales and questionnaires. Indeed, isolated depressive symptoms are common in MCI and low mood is the most prevalent symptom.[1] Moreover, in a recent clinically based study, low mood predicted progression of MCI to Alzheimer's disease (AD) better than scores from a depression scale.[13]

Finally, to understand the nature of the relationship between depressive symptoms and MCI, it is important to unfold the pattern of interactions with other factors (eg, genetic, psychiatric vascular, frailty related and psychosocial) that are relevant for both depression and MCI and that might modify their association.

The present paper aimed at investigating the symptom of low mood as a predictor of MCI and its progression to dementia in the framework of a large community based study of the elderly, taking into account: (i) MCI severity, (ii) time of assessment and (iii) interaction with other factors.

METHODS

Study population

Data were gathered from the Kungsholmen Project, a community based prospective study of persons aged 75 years and above, who lived in Kungsholmen, Stockholm, Sweden, at the end of 1987.[22] As illustrated in figure 1, out of 1700 participants at baseline (1987–1989) 40 were excluded due to very low global cognitive status or unknown educational background. To obtain a cognitively healthy cohort, we further excluded: (a) prevalent dementia cases (n=225); and (b) all prevalent MCI cases (n=337). Of the remaining 1098 persons, 199 (18%) died and 135 (12%) moved or discontinued their participation before the first follow-up examination. The resulting 764 cognitively healthy cohort members were followed for 6 years, during which two clinical examinations took place with an interval of 3 years (first follow-up 1994–1996; second follow-up 1997–1998). To ascertain progression towards dementia, incident MCI cases were followed for 3 further years (third follow-up 1999–2000).

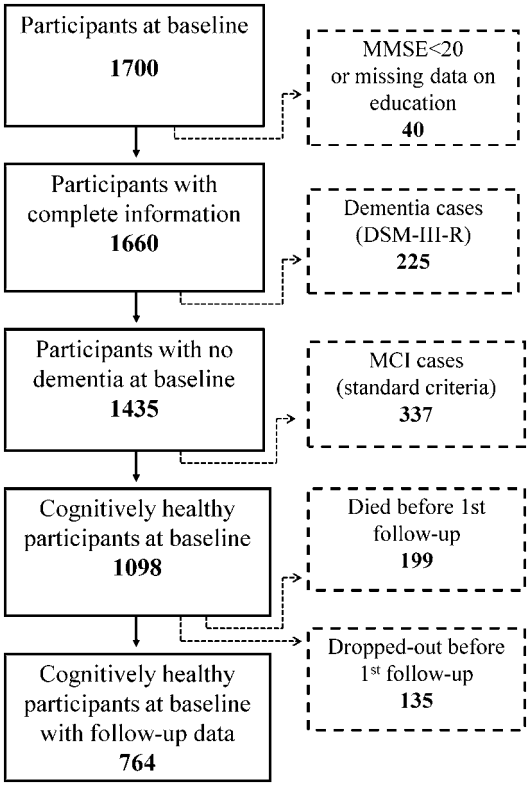

Figure 1 Study population: identification of the cognitively healthy cohort at baseline with follow-up data. MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Between the first and the second follow-up examinations, 28 (30%) cases died and six (6%) refused or moved. Between the second and third follow-up examinations, 23 (35%) cases died and four (6%) refused or moved.

All phases of the Kungsholmen Project have been approved by the ethics committee of Karolinska Institutet, and informed consent was obtained from all participants.

Data collection

All study participants underwent a comprehensive clinical, medical, cognitive and psychosocial examination both at baseline and at the follow-ups, as described in detail elsewhere.[20 22] Information on medical history was taken from the inpatient register system which encompasses all hospitals in Stockholm from 1969 onwards. The International Classification of Disease, 8th revision (ICD-8) was used in the register system until 1986[23]; from 1987, the ICD-9th revision (ICD-9) was used.[24] Information on drug use (in the preceding 2 weeks) and blood samples were collected at each examination.

Low mood symptom

We defined the symptom of low mood as a report of perceived sadness. At baseline, nurses assessed mental health as part of a general health status interview consisting of questions with yes/no answers. The questionnaire investigated different health related symptoms and included items on depressive symptoms, such as low mood, anxiety, feelings of loneliness, sleeping disturbances, reduced appetite and tiredness. All of these symptoms except loss of appetite loaded on the same factor, as shown by a factor analysis with varimax rotation performed at baseline. Low mood had the highest loadings on this depression factor (0.81), followed by feeling lonely (0.70) and anxiety (0.64).

At the follow-ups, all patients underwent a structured psychiatric interview performed by physicians and based on the Comprehensive Psychopathological Rating Scale.[25] Report of perceived sadness was drawn from the Comprehensive Psychopathological Rating Scale interview, and was graded in degree of severity from 0 (no perceived sadness) to 6 (extreme sadness).[26] The item was used both as an ordinal variable and as a categorical variable. In the latter case, the item was dichotomised into low mood, for all scores exceeding 0, versus no low mood, for a score equal to 0.

Definition of MCI

People with MCI included all non-demented participants who fulfilled aMCI[18 19] or oCIND[20 21] criteria. aMCI was defined according to standard criteria[18 19] and operationalised according to previous research[20] as follows: (1) memory complaints were assessed based on memory problems reported by the subjects or informants; (2) normal general cognitive function was defined as scoring above the minus 1 SD cut-off for the age and education adjusted Mini-Mental State Examination mean (MMSE)[27]; (3) absence of dementia was verified by clinical examination; (4) normal activities of daily living was characterised by no impairment in Katz' Activities of Daily Living scale[28]; and (5) objective memory impairment was defined as scoring 1.5 SD

below the age and education adjusted mean in a verbal memory task (free recall of slowly and rapidly presented words).[29] All cases with global cognitive impairment that did not fulfil criteria for dementia were classified as oCIND[21] and operationalised according to previous research[20] as follows: (1) impaired general cognitive function, defined as scoring 1 SD or more below age and education adjusted means on the MMSE derived from the dementia free population at baseline; and (2) absence of dementia, verified by clinical examination. aMCI and oCIND were mutually exclusive in the present study.

Diagnosis of dementia

Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R) criteria,[30] following a three step procedure, as described in detail elsewhere.[22] The dementia diagnoses for dead subjects were made by physicians consulting clinical records and death certificates.[31]

In the present study, a broad category, including all dementia cases, regardless of dementia type, was considered. However, AD was the most common form of dementia detected, accounting for nearly 80% of all cases.

Covariates

Medical conditions derived from the inpatient register database were: history of psychosis (ICD-8 and ICD-9 codes 291–298) which included episodic mood disorders; history of cerebrovascular disease (ICD-8 and ICD-9 codes 430–438); history of heart disease (ICD-8 or ICD-9 codes 410–414 and 427–428); hip fracture (ICD-8 and ICD-9 codes 820, 821); and diabetes (ICD-8 and ICD-9 code 250). Data on diabetes were integrated with information from other sources, as descried elsewhere.[32] High blood pressure was defined as ≥180 arterial blood pressure (ie, systolic Korotkoff phase I and diastolic phase V). Multimorbidity was defined as having two or more chronic conditions. Polypharmacy was defined as the use of more than five drugs.[33] Psychotropic drug use was defined as using one versus none of the following psychoactive drugs: neuroleptics (ATC code: N05A), anxiolytics (ATC code: N05B), other tranquilisers, hypnotics (ATC code: N05C) and antidepressants (ATC code: N06A). APOE genotyping was carried out using a standard PCR[34] and dichotomised as having at least one ApoE-ε4 allele versus having none. Social network was coded according to previous research as a four level ordinal variable (extensive/moderate/limited/poor social network).[35]

Data analysis

Incidence of MCI among cognitively healthy people

The cognitively healthy cohort was followed for 6 years to detect new cases of MCI. Subjects were considered at risk of MCI until they: (i) were classified for the first time as MCI or demented; (ii) dropped out of the study due to refusal or moving; or (iii) died.

Differences in subject characteristics were tested with Pearson's χ^2. Independent Cox models were used to estimate the HR and 95% CIs of developing MCI in relation to baseline low mood. For cases of MCI detected at the first wave of examinations, the baseline for low mood exposure was set at the study baseline. For cases of MCI detected at the second wave of examinations, the baseline for low mood exposure was set at the second wave (first follow-up). The relative risks of MCI in relation to baseline low mood were comparable between the two waves; therefore, Cox regression analysis was performed using data from both waves. In order to preserve the 3 year follow-up exposure for MCI, baseline low mood and all other variables varying with time were entered as time dependent variables. Low mood co-occurring with incident MCI (follow-up low mood) was used as a covariate. Multiplicative interactions were tested within Cox regression. To test for additive interactions, the attributable proportion due to interaction was calculated together with 95% CI.[36]

Incidence of dementia among cognitively healthy people

Dementia that developed in cognitively healthy people not previously classified as MCI was used as a competitive outcome and the relation with low mood was analysed with the same methodology described above.

Evolution of MCI

Persons who developed MCI were followed for 3 further years to assess their progression towards dementia. Independent Cox regression models were run to evaluate the HR and 95% CI of dementia in subjects with MCI in relation to baseline and follow-up low mood. Adjustment and interactions with other covariates were tested as described above.

Missing values were imputed with Multiple Imputation based on available information on other covariates,[37] using Stata 9.0. All other analyses were performed using SPSS, with an α level of $p<0.05$.

RESULTS

Incidence of MCI among cognitively healthy people

During the 3711.5 person years (minimum 1.2; maximum 8.2) of follow-up, 160 persons developed MCI. Of these, 40 were classified as aMCI and 120 as oCIND. Characteristics of the cohort and the cases are shown in table 1. Fifty-three per cent (n=21) of aMCI and 31% (n=37) of oCIND occurred in people with baseline low mood. When considering aMCI and oCIND together, the incidence of MCI in people with baseline low mood was about 2.5 times higher than that detected among people without baseline low mood, and this ratio was constant across the two waves of examinations (figure 2). Cox regression analysis performed using data from both waves confirmed the increased risk of all outcomes in relation to the presence of baseline low mood although the association was stronger for aMCI. Adjustment for socioeconomic characteristics and other covariates, including follow-up low mood, history of psychosis, psychotropic drug use, ApoE-ε4 allele, history of cerebrovascular disease, heart disease, diabetes, high blood pressure, hip fracture, multimorbidity and polypharmacy, did not substantially change

Table 1 Study population and incident cases of amnestic mild cognitive impairment, other cognitive impairment no dementia and overall mild cognitive impairment by age, gender, and education

Characteristic	Study population	Incident cases		
		aMCI (n=40)	oCIND (n=120)	All-MCI (n=160)
Age (years), baseline				
75–79	367 (48)	19 (48)	61 (51)	80 (50)
80+	397 (52)	21 (52)	59 (49)	80 (50)
Gender				
Women	576 (75)	29 (73)	92 (77)	121 (76)
Men	188 (25)	11 (28)	28 (23)	39 (24)
Education				
High	403 (53)	27 (68)	55 (46)	82 (51)
Low	361 (47)	13 (32)	65 (54)	78 (49)

Values are n (%).
All-MCI, overall mild cognitive impairment; aMCI, amnestic mild cognitive impairment; oCIND, other cognitive impairment no dementia.

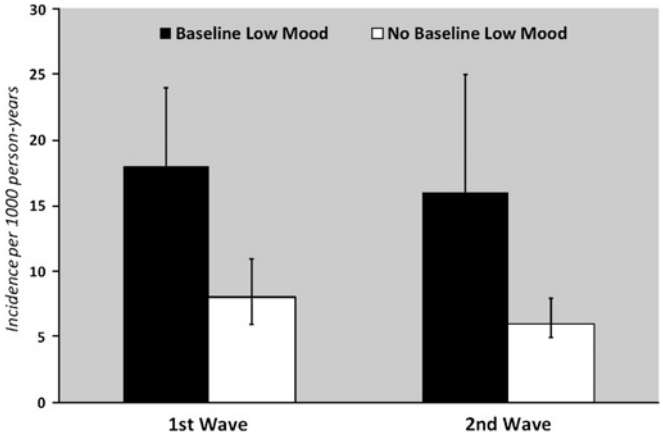

Figure 2 Crude incidence rates (IR) per 1000 person years and 95% CIs of all mild cognitive impairment in subjects with and without low mood at baseline. Data are shown for the first and second wave of examinations separately.

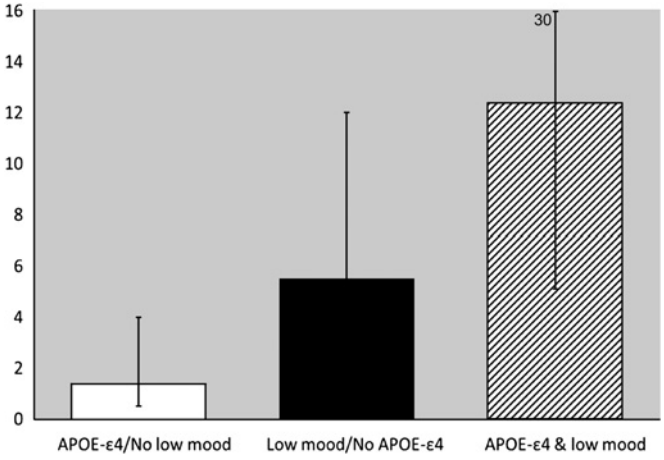

Figure 3 HRs with 95% CIs of amnestic mild cognitive impairment in relation to ApoE-ε4 and baseline low mood. Subjects with no low mood at baseline and without any ε4 allele were used as reference. Data are adjusted for age, sex and education.

the results and HRs remained stable even after multi-adjustment (table 2).

Stratified analyses showed that the increased risk of aMCI and oCIND associated with baseline low mood was not substantially modified by follow-up low mood or by the other factors (as listed above). However, an additive interaction was found between baseline low mood and ApoE-ε4 allele for the risk of developing aMCI (attributable proportion: 0.5, 95% CI 0.1 to 0.96) (figure 3) but not for the risk of developing oCIND. No other interactions were observed.

Incidence of dementia among cognitively healthy people

During the follow-up, 158 cognitively healthy persons developed dementia, bypassing MCI. In these people, the HR for low mood was 1.6 (95% CI 1.1 to 2.3) after adjustment for age, sex and education. Further adjustment for the other covariates did not affect the relationship with baseline low mood. However, the association was no longer significant after adjustment for follow-up low mood (HR 1.4, 95% CI 0.9 to 2.0) and in the multi-adjusted model (HR 1.3, 95% CI 0.9 to 1.9).

Evolution of MCI

During the 1354.8 person years (minimum 0.7; maximum 4.5) of follow-up, 50 people with MCI progressed to dementia. Eleven cases of dementia occurred in people with aMCI and 39 cases of dementia occurred in people with oCIND. Among the aMCI persons who progressed to dementia, eight (70%) had baseline low mood, detected before the development of aMCI, and three (27%) had follow-up low mood, which was detected at the time of aMCI classification. Among the oCIND that progressed to dementia, 14 (33%) had baseline low mood and six (15%) had follow-up low mood. Cox regression analysis confirmed the association of baseline low mood with an increased risk of progression to dementia in people with aMCI (table 3).The association was strengthened after further adjustment for ApoE-ε4 allele. Adjustment for other factors did not substantially change the association. On the other hand, follow-up low mood was not associated with an increased risk of progression to dementia in people with aMCI (table 3). Progression to dementia in people with oCIND was not linked to baseline or follow-up low mood (table 3).

DISCUSSION

In our large, prospective, community based study, low mood reported 3 years before MCI detection substantially increased the risk of developing MCI. In particular, low mood was associated with a 5.8-fold increased risk of aMCI, a 2.2-fold increased risk of oCIND and a 2.7-fold increased risk of all-MCI, after adjustment for sociodemographic factors. These findings are in line with previous evidence from other longitudinal studies which found an association between baseline depressive symptoms and incident MCI, with estimates ranging from 1.2- to 16-fold increased risk of MCI.[3–7]

The excess risk of aMCI associated with low mood was almost triple that for oCIND (HR 5.8 vs 2.2), suggesting the

Table 2 HRs and 95% CIs of amnestic mild cognitive impairment, other cognitive impairment no dementia and overall mild cognitive impairment in relation to baseline low mood (3 years before mild cognitive impairment detection)

	aMCI (n=40) HR (95% CI)	oCIND (n=120) HR (95% CI)	All-MCI (n=160) HR (95% CI)
Basic adjustment*	5.8 (3.1 to 10.9)	2.2 (1.5 to 3.3)	2.7 (1.9 to 3.7)
Basic adjustment + follow-up LM†	5.5 (2.9 to 10.6)	2.2 (1.5 to 3.3)	2.6 (1.9 to 3.7)
Multi-adjustment‡	6.2 (3.1 to 12.6)	2.2 (1.3 to 3.2)	2.6 (1.8 to 3.7)

*Adjusted for: age, sex, education.
†Adjusted for: age, sex, education and low mood assessed at the same time of MCI detection (follow-up LM).
‡Simultaneous adjustment for age, sex, education, history of psychosis, psychotropic drug use, follow-up LM, ApoE-ε4 allele, history of cerebrovascular disease, heart disease, diabetes, high blood pressure, hip fracture, multimorbidity and polypharmacy.
All-MCI, overall mild cognitive impairment; aMCI, amnestic mild cognitive impairment; LM, low mood; oCIND, other cognitive impairment no dementia.

Table 3 HRs and 95% CIs for 3 year progression of amnestic mild cognitive impairment, other cognitive impairment no dementia and overall mild cognitive impairment to dementia in relation to low mood 3 years before detection of cognitive impairment (baseline LM) and to low mood reported at the time of detection of cognitive impairment (follow-up LM)

		Dementia (n = 50)	
		HR (95% CI) for baseline LM	HR (95% CI) for follow-up LM
aMCI	Basic adjustment*	5.3 (1.2 to 23.3)	1.2 (0.3 to 5.2)
	Basic + ApoE-ε4†	5.9 (1.4 to 25.0)	1.1 (0.5 to 2.0)
oCIND	Basic adjustment*	1.1 (0.5 to 2.1)	1.0 (0.5 to 2.1)
	Basic + ApoE-ε4†	1.0 (0.5 to 2.1)	1.1 (0.5 to 2.3)
All-MCI	Basic adjustment*	1.4 (0.8 to 2.4)	1.0 (0.5 to 2.0)
	Basic + ApoE-ε4†	1.4 (0.8 to 2.4)	1.1 (0.5 to 2.0)

*Adjusted for: age, sex, education.
†Adjusted for: age, sex, education and ApoE-ε4 allelic status.
All-MCI, overall mild cognitive impairment; aMCI, amnestic mild cognitive impairment; LM, low mood; oCIND, other cognitive impairment no dementia.

presence of a gradient in the relationship between low mood and cognitive impairment severity. Indeed, in our study, the definition of aMCI excluded people with global cognitive impairment (MMSE mean 26). On the other hand, oCIND included more severely impaired cases with global cognitive impairment (MMSE mean 21) who did not fulfil criteria for dementia. In addition, we also observed a group of people that rapidly progressed to dementia, bypassing MCI (MMSE mean 8), for whom the excess risk associated with low mood was 60%, lower than that observed in both aMCI and oCIND.

Interestingly, we found a synergistic action of low mood and ApoE-ε4, with increased risk of aMCI in people with both baseline low mood and at least one ApoE-ε4 allele. This is in line with results from a study on primary care patients[5] and supports the hypothesis that low mood may be related to AD-type neuropathology.[17 38] Conversely, none of the other factors considered in our investigation interacted with low mood. In particular, no modification of the relationship of baseline low mood with MCI was observed by taking into account history of psychosis, psychotropic drug use and vascular factors. Indeed, low mood in prodromal MCI can be independent from history of depression.[5] It has also been observed that depressive symptoms in MCI are particularly resistant to treatment.[16 39] On the other hand, the lack of interaction of low mood with vascular factors confirms previous findings from the Cardiovascular Health Study and does not support the 'vascular depression hypothesis'.[6]

Low mood was associated with a 5.3-fold increased risk of progression to dementia in people with aMCI. This finding is in line with some progression studies of MCI[4 12–14 16] and is at odds with others.[8–11 15] Indeed, most of the studies that found no association or an inverse association focused on depressive symptoms measured at the same time of MCI detection.[8 9 11 15] We showed that only low mood measured at baseline, 3 years before the detection of MCI, predicted subsequent progression of MCI to dementia. Conversely, low mood that co-occurred with MCI did not predict further progression to dementia. This result supports the hypothesis that the symptom of low mood may be relevant in the prodromal stage of MCI, losing its importance in more advanced stages when cognitive deficits are already manifested. Our findings do not confirm previous evidence from a report based on the Religious Order Study[10] which found no increase in depressive symptoms in the prodromal stage of dementia. Indeed, the generalisability of those results has been questioned, as religious order people might have higher resilience against depressive symptoms.[40]

Our study has many strengths, including the community based design; the longitudinal assessment of the relationship between low mood and cognitive impairment; comparison of the impact of low mood on different types and degrees of severity of cognitive impairment; comparison of different times of assessment of low mood in relation to progression of MCI to dementia; and the thorough assessment of the interaction of low mood with other factors. However, there are some limitations. First, it is difficult to disentangle the directionality of the association between low mood and cognitive impairment even in the framework of a longitudinal study. Reverse causation is always possible. Indeed, people might have performed poorly in the cognitive tests because they were depressed at the time of assessment. This could have generated a spurious association with baseline low mood if those people with low mood at the time of MCI detection were already depressed at baseline. However, we controlled for this possibility and found no evidence of confounding between baseline low mood and follow-up low mood. Secondly, the assessment of low mood was performed in different settings between the first and the second wave of examinations. Nonetheless, the figures regarding the occurrence of MCI in relation to low mood at the two measuring occasions are very similar, pointing to a substantial stability of the construct of low mood across different measurements. Thirdly, grading of severity of low mood was not available for all participants. However, available information showed that the symptom was mild in most (91%) people with low mood who developed MCI. Fourthly, the cross sectional assessment of low mood did not provide any information on duration. Nonetheless, the majority of people with MCI who reported low mood at baseline were euthymic on the subsequent 3 year follow-up examination. Fifthly, we used dementia as an outcome rather than dementia type. This was done considering the relatively small sample of MCI persons who progressed to dementia. However, in our population, nearly 80% of all diagnoses of dementia were classified as probable or possible AD. Future investigations should try to expand our findings using dementia type as an outcome. Finally, in the present cohort there was a group of people who developed dementia without previously being classified as MCI. It is likely that the association between low mood and cognitive decline would have been further strengthened by using a follow-up interval short enough to observe the transitional stage of MCI in all subjects who developed dementia.

Our results showed that low mood is a predictor of MCI development and its progression towards dementia, and confirmed our working hypothesis that low mood may be more closely related to early, rather than advanced, stages of cognitive decline. There are different possible explanations for this finding. One explanation could be that low mood is a risk factor for cognitive impairment and particularly memory functioning, which would likely be mediated by the interplay between psychosocial stress and the activity of the adrenocortico axis, where imbalance has known effects on neurogenesis and hippocampal physiology.[41] Another possible explanation is that low mood and MCI share a common neuropathogenic substrate. In this case, the narrow time frame that we observed for the relationship between low mood and cognitive decline would be explained by the stage of the underlying neurodegenerative process. In earlier stages, when cognitive deterioration is not yet manifest, low mood could be one behavioural sign of neurodegeneration, as in the concept of 'amyloid-associated

depression'.[17] In more advanced stages, when neurodegeneration has become more pervasive, MCI could represent a later manifestation of the process leading to dementia.

In conclusion, although further studies are needed to disentangle the relative contribution of possible underlying mechanisms, cognitively healthy elderly subjects presenting with the symptom of low mood should be closely monitored as they are at increased risk of MCI and subsequent progression to dementia.

Acknowledgements We thank all staff of the Kungsholmen Project for their collaboration on data collection and management.

Funding This study was supported by grants from the Swedish Council for Working Life and Social Research, Regional Agreement on Medical Training and Clinical Research (ALF) between Stockholm County Council and Karolinska Institutet, and the Swedish Brain Power Initiative. Private funding from Stiftelsen Gamla Tjänarinnor and Gun and Bertil Stohnes Foundation was also provided.

Competing interests None.

Ethics approval This study was conducted with the approval of the ethics committee of Karolinska Institutet, Stockholm, Sweden.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Monastero R,** Mangialasche F, Camarda C, *et al*. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. *J Alzheimers Dis* 2009;**18**:11—30.
2. **Geda YE,** Roberts RO, Knopman DS, *et al*. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry* 2008;**65**:1193—8.
3. **Rosenberg PB,** Mielke MM, Xue QL, *et al*. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *Am J Geriatr Psychiatry* 2010;**18**:204—11.
4. **Stepaniuk J,** Ritchie LJ, Tuokko H. Neuropsychiatric impairments as predictors of mild cognitive impairment, dementia, and Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2008;**23**:326—33.
5. **Geda YE,** Knopman DS, Mrazek DA, *et al*. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Arch Neurol* 2006;**63**:435—40.
6. **Barnes DE,** Alexopoulos GS, Lopez OL, *et al*. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Arch Gen Psychiatry* 2006;**63**:273—9.
7. **Lopez OL,** Jagust WJ, Dulberg C, *et al*. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003;**60**:1394—9.
8. **Ramakers IH,** Visser PJ, Aalten P, *et al*. Affective symptoms as predictors of Alzheimer's disease in subjects with mild cognitive impairment: a 10-year follow-up study. *Psychol Med* 2010;**40**:1193—201.
9. **Vicini CB,** Conti M, Zanetti M, *et al*. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* 2009;**27**:390—8.
10. **Wilson RS,** Arnold SE, Beck TL, *et al*. Change in depressive symptoms during the prodromal phase of Alzheimer disease. *Arch Gen Psychiatry* 2008;**65**:439—45.
11. **Panza F,** Capurso C, D'Introno A, *et al*. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. *Int J Geriatr Psychiatry* 2008;**23**:726—34.
12. **Artero S,** Ancelin ML, Portet F, *et al*. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry* 2008;**79**:979—84.
13. **Houde M,** Bergman H, Whitehead V, *et al*. A predictive depression pattern in mild cognitive impairment. *Int J Geriatr Psychiatry* 2008;**23**:1028—33.
14. **Gabryelewicz T,** Styczynska M, Luczywek E, *et al*. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *Int J Geriatr Psychiatry* 2007;**22**:563—7.
15. **Palmer K,** Berger AK, Monastero R, *et al*. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* 2007;**68**:1596—602.
16. **Modrego PJ,** Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol* 2004;**61**:1290—3.
17. **Sun X,** Steffens DC, Au R, *et al*. Amyloid-associated depression: a prodromal depression of Alzheimer disease? *Arch Gen Psychiatry* 2008;**65**:542—50.
18. **Petersen RC,** Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;**56**:303—8.
19. **Petersen RC,** Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005;**62**:1160—3.
20. **Caracciolo B,** Palmer K, Monastero R, *et al*. Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. *Neurology* 2008;**70**:1778—85.
21. **Larrieu S,** Letenneur L, Orgogozo JM, *et al*. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology* 2002;**59**:1594—9.
22. **Fratiglioni L,** Viitanen M, Backman L, *et al*. Occurrence of dementia in advanced age: the study design of the Kungsholmen Project. *Neuroepidemiology* 1992;**11** (Suppl 1):29—36.
23. **WHO.** *International Classification of Disease, Injuries, and Cause of Death, 8th revision (ICD-8)*. Geneva: World Health Organization, 1967.
24. **WHO.** *International Classification of Disease, Injuries, and Cause of Death, 9th revision (ICD-9)*. Geneva: World Health Organization, 1987.
25. **Asberg M,** Schalling D. Construction of a new psychiatric rating instrument, the Comprehensive Psychopathological Rating Scale (CPRS). *Prog Neuropsychopharmacol* 1979;**3**:405—12.
26. **Berger AK,** Fratiglioni L, Forsell Y, *et al*. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology* 1999;**53**:1998—2002.
27. **Folstein MF,** Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189—98.
28. **Katz S.** Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* 1983;**31**:721—7.
29. **Wahlin A,** Backman L, Winblad B. Free recall and recognition of slowly and rapidly presented words in very old age: a community-based study. *Exp Aging Res* 1995;**21**:251—71.
30. **APA.** *Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R)*. Washington, DC: American Psychiatric Association, 1987.
31. **Fratiglioni L,** Viitanen M, von Strauss E, *et al*. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology* 1997;**48**:132—8.
32. **Xu WL,** Qiu CX, Wahlin A, *et al*. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004;**63**:1181—6.
33. **Monastero R,** Palmer K, Qiu C, *et al*. Heterogeneity in risk factors for cognitive impairment, no dementia: population-based longitudinal study from the Kungsholmen Project. *Am J Geriatr Psychiatry* 2007;**15**:60—9.
34. **Basun H,** Corder EH, Guo Z, *et al*. Apolipoprotein E polymorphism and stroke in a population sample aged 75 years or more. *Stroke* 1996;**27**:1310—15.
35. **Fratiglioni L,** Wang HX, Ericsson K, *et al*. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 2000;**355**:1315—19.
36. **Padyukov L,** Silva C, Stolt P, *et al*. A gene—environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004;**50**:3085—92.
37. **Rubin DB.** *Multiple Imputation for Nonresponse in Surveys*. New York: Wiley, 1987.
38. **Kim J,** Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron* 2009;**63**:287—303.
39. **Bhalla RK,** Butters MA, Becker JT, *et al*. Patterns of mild cognitive impairment after treatment of depression in the elderly. *Am J Geriatr Psychiatry* 2009;**17**:308—16.
40. **Modrego PJ.** Depression in the prodromal phase of Alzheimer disease and the reverse causal hypothesis. *Arch Gen Psychiatry* 2009;**66**:107.
41. **Videbech P,** Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* 2004;**161**:1957—66.