RESEARCH ARTICLE

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Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis

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Objective: There is a long-standing debate in the literature whether depressive symptoms increase the risk of dementia in older with mild cognitive impairment (MCI). We aim to conduct a meta-analysis of studies that evaluated the risk of dementia in subjects with MCI and depressive symptoms compared with subjects with MCI and no depressive symptoms.

Methods: We calculated the relative risk of progression to dementia in subjects with MCI and depressive symptoms compared with subjects with MCI and no depressive symptoms using a generic inverse variance method with random effect models.

Results: Eighteen studies were included in the meta-analysis, with a sample size of 10,861 MCI subjects. The pooled relative risk of progressing to dementia was 1.28 $CI_{95\%}$ [1.09–1.52] ($p = 0.003$) in the group of MCI subjects with depressive symptoms compared with the MCI subjects with no depressive symptoms.

Discussion: Our results provide additional evidence that depressive symptoms determine an additive risk effect to the progression to dementia in subjects with MCI. The comorbidity between depression and cognitive impairment can be an intervention target for prevention of dementia in MCI subjects.

Additional supporting information may be found in the online version of this article:

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Introduction

Mild cognitive impairment (MCI) is a common disorder in the elderly (Forlenza *et al.*, 2013). It is defined by the objective impairment of one or more cognitive domains, with no or minimal impairments of the performance on instrumental activities of daily living and no global cognitive impairment (Albert *et al.*, 2011). Older adults with MCI are at increased risk of progressing to Alzheimer's disease (AD) and other dementia syndromes. The risk is greater in those who present with abnormalities in biomarkers related to clinical AD, for example, reduced cerebrospinal amyloid-β level, increased brain deposition of amyloid-β in molecular imaging, or hippocampal atrophy in structural neuroimaging (Forlenza *et al.*, 2010).

Depressive disorders are very common in older adults and have a complex relationship with neurocognitive disorders (Panza *et al.*, 2010). History of major depression in young and older adults significantly increase the risk of Alzheimer's disease and vascular dementia (Ownby *et al.*, 2006; Diniz *et al.*, 2013a, 2013b) and MCI (Geda *et al.*, 2014). The occurrence of depressive symptoms in subjects with MCI has been associated with higher risk of progression to dementia compared with

MCI subjects with no depressive symptoms (Modrego and Ferrández, 2004). However, the relationship is controversial as case-control and cohort study did not find a significant association (Rosenberg *et al.*, 2013; Steenland *et al.*, 2012) or even found a protective effect of depressive symptoms in the progression from MCI to dementia (Vicini Chilovi *et al.*, 2009). Such inconsistent results may be due to several reasons. Methodological differences among studies, such as study settings, patients' recruitment, depressive symptoms assessments, evaluation of cognition, and follow-up length can explain, in part, the different results. (Table 1)

It is important to understand if depressive symptoms moderate the risk of progression from MCI to dementia. This can lead to the development of tailored interventions aiming the prevention of dementia in this group of patients. For example, long-term antidepressant use was associated with reduced risk of dementia in a registry-based study (Kessing *et al.*, 2011). Donepezil treatment reduced the risk of cognitive decline and progression to dementia in subjects with MCI and depression, in particular in the first year of treatment (Reynolds *et al.*, 2011). Antidepressants or low-dose lithium carbonate can modulate the metabolism of the amyloid protein precursor and reduce the production of amyloid-β peptides, thus being potentially protective against the development of dementia (Diniz *et al.*, 2013a, 2013b).

Therefore, we aim to carry out a systematic review and meta-analysis of the literature to evaluate whether the presence of depressive symptoms increases the risk of dementia in older adults with MCI.

Methods

This meta-analysis followed the preferred reporting items for systematic review and meta-analysis guidelines for conducting and reporting systematic reviews (Moher *et al.*, 2009).

Search strategy

We conducted a comprehensive search of potentially relevant articles that reported the association between depressive symptoms and the risk of progression of dementia in older adults with MCI. Literature search was performed using the electronic databases Medline, Scopus, and PsycINFO. These are the largest databases with comprehensive coverage and indexing of biomedical journals worldwide. We also carried out a careful review of references from reviews and original studies to search for additional relevant publications. The literature search was conducted in November 2014 and updated in February 2015. The search was limited to articles published after 01/01/1999, and there was no language restriction. The reason for the limitation of search dates was because the operationalization of the diagnostic criteria for MCI was first established in the year of 1999 (Petersen, 1999).

We conducted research in the electronic database with the following terms: (mild cognitive impairment or cognitive impairment no dementia), (depression or depressive), (dementia or Alzheimer's disease), and (risk, conversion, or progression). These terms were used according to the Medical Subject Heading.

Study selection and quality assessment

The criteria for inclusion of studies for data extraction were the following:

1 Longitudinal studies;
2 Diagnosis of MCI according to the criteria of the Mayo Clinic (Petersen, 1999; Petersen, 2001) or other diagnostic criteria validated for the diagnosis of MCI in the initial evaluation;
3 Information about the presence of depressive symptoms at baseline assessment and the progression to dementia in the longitudinal evaluation;

Study quality was performed using the scale "Newcastle-Ottawa Scale for Quality Assessment of Observational Studies" (Wells *et al.*, 2013). This scale assesses methodological aspects of non-randomized observational studies such as selection criteria for inclusion of cases and controls, comparability of population ascertainment of exposure to risk, quality of case ascertainment, and outcome assessment.

Two investigators (R. J. M. and G. M.) independently reviewed the title and abstract of each article retrieved from the literature search to identify potentially relevant studies. The selected articles were revised to verify whether they fulfilled the inclusion criteria for data extraction. If there was any disagreement in the study selection, a third investigator (B. S. D.) made the final decision on the inclusion of the selected article. If different publications reported data from the same population, we included the data from a publication with the larger sample size.

Data extraction and statistical analysis

Data were extracted by two independent investigators (R. J. M. and G. M.) using a standardized data extraction form. The following data were extracted for each study:

Table 1 Summary of included study characteristics

Study	Study design	Follow-up (years)	MCI criteria	Depression criteria	Dementia criteria	Depression assessment	Age (years) (MCI + depression group)	Gender (% female) (MCI + depression group)	Age (years) (MCI + no depression group)	Gender (% female) (MCI + no depression group)
Artero *et al.*, 2008	Cohort	4	Winblad *et al.*, 2004	CES-D >16 MINI	DSM-IV TR	CES-D	—	—	—	—
Beaudreau *et al.*, 2013	Cohort	3.5	CIND: Ebly *et al.*, 1995	NPI ≥ 1	DSM-IV	NPI	—	—	—	—
Chan *et al.*, 2011	Cohort	2	Petersen, 2004	NPI ≥ 1 (Dysphoria / Depresison subitem)	DSM-IV TR	NPI (chinese version)	—	—	—	—
Vicini Chilovi *et al.*, 2009	Case-control	2	Petersen, 2004	DSM-IV	McKhann, 1984	DSM-IV	70.8 ± 7.6	65.8%	71.6 ± 8.5	62.7%
Gallagher *et al.*, 2011	Case-control	2.25	Petersen *et al.*, 1999	BEHAVE-AD	DSM-IV	BEHAVE-AD	—	—	—	—
Houde *et al.*, 2008	Case-control	4.3	Petersen *et al.*, 2001	GDS > 10	Not specified	GDS-30	—	—	—	—
Lee *et al.*, 2012	Case-control	2	Petersen *et al.*, 1999	NPI ≥ 1 (Dysphoria / Depresison subitem)	Not specified	NPI	75.0 ± 6.8	34%	75.3 ± 6.9	34%
Modrego and Ferrández, 2004	Cohort	3	Petersen *et al.*, 1999	DSM-IV GDS ≥ 10	DSM-IV	GDS	73.4 ± 4.5	—	72.3 ± 5.6	—
Palmer *et al.*, 2007	Cohort	3.4	Petersen *et al.*, 2001	CPRS between 2 to 6	McKhann, 1984	CPRS	—	—	—	—
Palmer *et al.*, 2010	Case-control	4	Petersen *et al.*, 2001	NPI > 2 (depression/ dysphoria subitem)	McKhann, 1984	NPI	69.3 ± 5.6	50%	71.6 ± 6.8	36%
Panza *et al.*, 2008	Cohort	3.5	Petersen *et al.*, 1999	GDS ≥ 10	DSM-III-R	GDS-30	80.8 ± 2.4	58%	80.4 ± 2.7	38%
Peters *et al.*, 2013	Cohort	3.3	CIND: Ebly *et al.*, 1995	NPI ≥ 1	DSM-III-R	NPI	—	—	—	—
Pink *et al.*, 2015	Cohort	3	Petersen *et al.*, 2011	NPI	DSM-IV	NPI	81.7 IQR (76.1 – 84.2)	47%	82.1 IQR (77.7 – 85.0)	46%
Ramakers *et al.*, 2010	Case-control	10	Petersen *et al.*, 1999	HAMD > 10	DSM-IV	HDRS	—	—	—	—
Richard *et al.*, 2012	Case-control	2.7	Petersen *et al.*, 1999 Petersen, 2004	GDS-15 ≥ 6	Not specified	GDS-15	72.8 ± 7.5	37%	75.9 ± 6.6	36%
Richard *et al.*, 2013	Cohort	5.4	Petersen *et al.*, 1999	CES-D ≥ 4	DSM-III R	CES-D	77.7 ± 7.2	64%	76.7 ± 7.0	78%
Rosenberg *et al.*, 2013	Cohort	1.58	Petersen *et al.*, 2001	DSM-IV	McKhann, 1984	NPI and GDS	—	—	—	—
Steenland *et al.*, 2012	Cohort	2.6	Petersen *et al.*, 2001	DSM-IV	McKhann, 1984	NPI and GDS-30	—	—	—	—

CPRS, Comprehensive Psychopathological Rating Scale; CES-D, Center for Epidemiology Scales-Depression; MINI, Mini International Neuropsychiatric Interview; NPI, Neuropsychiatric inventory; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment.

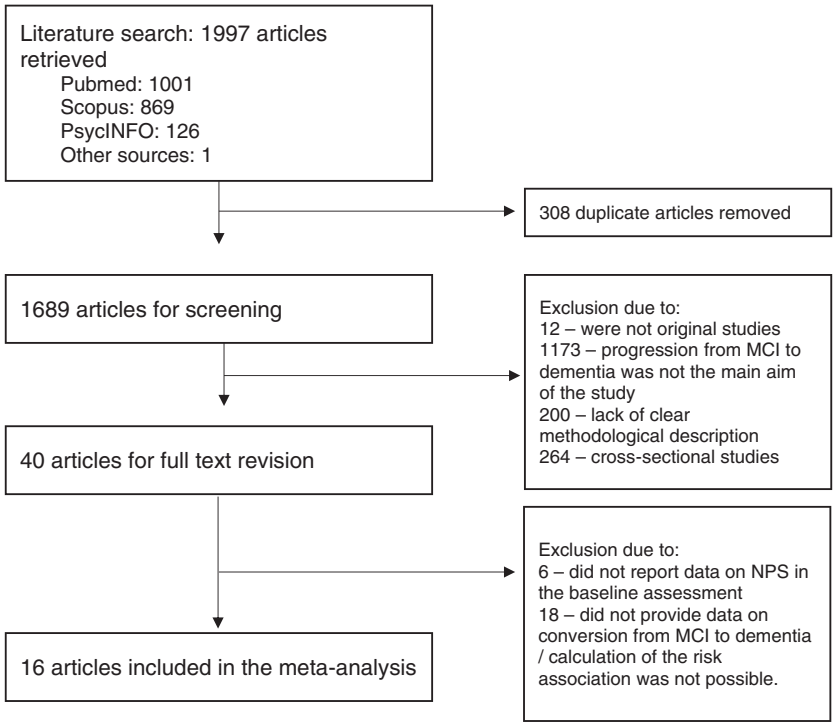

Figure 1 Flowchart of the article selection and inclusion in the meta-analysis.

year of publication, country, study design, depression assessment method, demographic variables, sample size, and the risk of dementia in the MCI subjects.

We calculated the pooled relative risk (RR) for progression to dementia in MCI subjects with depressive symptoms compared with those without depressive symptoms. We assessed heterogeneity in the analysis with the *Q*-test and I^2 index. If the *p*-value was equal to or below 0.05 in the *Q*-test and/or the I^2 index was higher than 50%, the pooled analysis was considered significantly heterogeneous. Random or fixed effect model was used based on the statistical evidence of heterogeneity in the analysis. We performed sensitivity analyses by excluding one study at a time and recalculating the overall effect to evaluate whether the pooled RR was biased by any individual study.

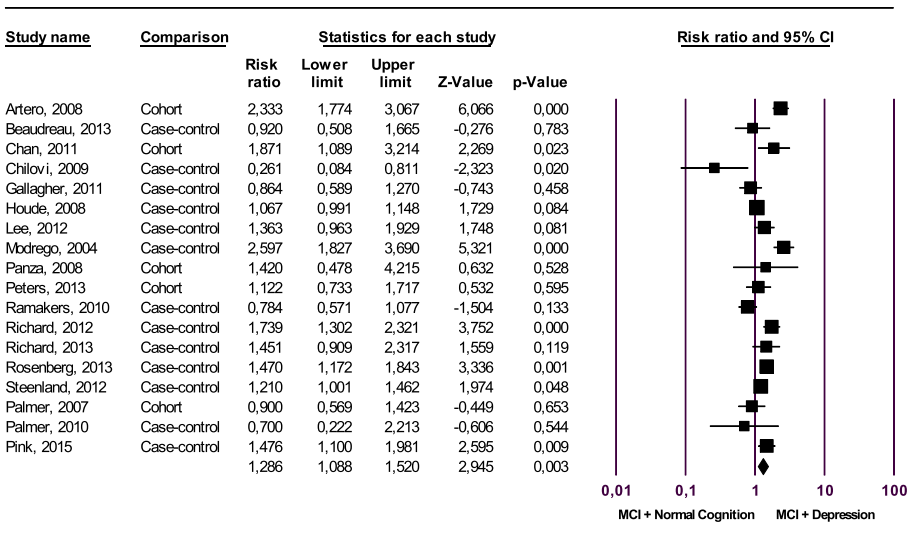

Figure 2 Forest plot for the risk of dementia in subjects with mild cognitive impairment and depression.

We addressed whether mean follow-up was a significant covariate for the risk of progression to dementia in this analysis with a mixed effect meta-regression model (method of moments). Publication bias was ascertained by visual inspection of a funnel plot and the classic fail-safe N analysis. All analyses were performed with the Comprehensive Meta-Analysis Software version 2.2 for Windows (Englewood, NJ, USA).

Results

Eighteen studies met criteria for inclusion in the meta-analysis (13 case-control and 5 cohort studies), with a sample size of 10,861 MCI subjects. Figure 1 shows the flowchart for study search and selection for inclusion in the meta-analysis.

Because of high heterogeneity in the analysis ($Q = 86.9$, df = 17, $p < 0.001$; $I^2 = 80\%$), we carried out all analyses with random effect models. The pooled RR of progressing to dementia was 1.28 $CI_{95\%}$ [1.09–1.52] ($p = 0.003$) in the group of MCI subjects with depressive symptoms compared with the MCI subjects with no depressive symptoms. Figure 2 shows the forest plot for the pooled RR. Sensitivity analysis did not reveal a significant impact in the pooled RR after removing any specific study from the analysis.

Mixed effect meta-regression analysis (method of moments) did not show that mean follow-up time (point estimate = −0.02, SE = 0.08, $p = 0.7$) nor study quality (point estimate = −0.09, SE = 0.05, $p = 0.1$) were significant moderators of the pooled RR. Visual inspection of the funnel plot and the classic fail-safe N analysis showed evidence of significant publication bias in the studies included in the meta-analysis ($p < 0.001$) (Supporting Information Figure S1).

Discussion

In the present meta-analysis, we found that the pooled RR of progressing to dementia is 28% higher in MCI subjects with depressive symptoms compared with those without depressive symptoms. This result suggests that the co-occurrence of depressive symptoms in subjects with MCI has an additive risk for progression to AD. This study provides additional support to the growing body of evidence linking depression in older adults and risk of cognitive decline and dementia.

Depression and neurocognitive disorder have a complex and bidirectional relationship. Cognitive dysfunction is common during a depressive syndrome in younger and older adults, usually persists after antidepressant response, and is associated with worse short-term and long-term prognosis (Koenig *et al.*, 2015; Rock *et al.*, 2014). Depression increases the risk of incident MCI, AD, and vascular dementia (Diniz *et al.*, 2013a, 2013b; Geda *et al.*, 2014; Steffens *et al.*, 2014). The finding that higher depressive symptoms increases the risk of progression from MCI to dementia suggests that depressive symptoms can be considered genuine state markers risk instead of an affective or behavioral reaction to the perception of progressive cognitive decline in older adults. Nonetheless, it is worth noting that several epidemiologic studies did not find evidence of increment of depressive symptoms in the years preceding the diagnosis of dementia (Wilson *et al.*, 2008), suggesting that depressive symptoms are trait markers for the risk of dementia in older adults with or without MCI.

Subgroup analysis showed a distinct pattern for the association between depression and the risk of progression to dementia according to the study setting. The risk was significantly increased in the case-control studies, while not in the cohort studies. Different study setting is one of the possible explanations of the large variability of the progression rates from MCI to dementia (Petersen *et al.*, 2014). Clinical and case-control studies usually show higher progression rates in contrast to cohort and population-based studies. Case-control studies usually suffer from sampling and recruitment biases that can lead to inclusion of more diseased individuals and inflating the association between two conditions. Therefore, differences in the pooled RR observed in the current meta-analysis can be due to methodological differences between case-control and cohort studies included.

The present results be viewed with caution. The studies included in the meta-analysis were methodologically heterogeneous; depressive symptoms were assessed by different scales (e.g., GDS) or by subitems of scales that evaluated global neuropsychiatric symptoms (e.g., NPI); and the psychiatric history of the subjects was poorly characterized (e.g. no information on presence of past episodes). These factors can lead to large variability in the estimates of depressive symptoms and of the association between depression and the risk of progression to dementia in different studies. We did not address the association of depression and specific MCI subtypes. Previous studies showed that progression rates to dementia differ according to the MCI subtype, with amnestic multiple-domain MCI showing the highest risk (Forlenza *et al.*, 2009). Therefore, the relationship between depression and MCI may differ according to the MCI subtype. We did not address the moderating role of genetic factors in the risk of dementia in MCI + depression subjects.

However, a large community-based study found that the presence of APOEε4 found that moderates the risk of dementia in subjects with MCI and depression (Geda *et al.*, 2006). Additional studies are necessary to address the role of apolipoprotein E (APOE) and other genetic markers as moderating variables of the risk of dementia in subjects with MCI and depression. We found a significant evidence for publication bias in the studies included in the meta-analysis. This may lead to an over estimation of the risk of dementia in the meta-analysis because non-significant results might have not be published and, thus, not be included in the current analysis. Finally, we did not evaluate the association between other neuropsychiatric symptoms and the risk of dementia. Nonetheless, recent studies showed that neuropsychiatric symptoms like anxiety and apathy can also increase the risk of progression to dementia in subjects with MCI (Vicini Chilovi *et al.*, 2009)

Depression and mild cognitive impairment are heterogeneous conditions and secondary to abnormalities in several neurobiological cascades. A recent study showed that subjects with late-life depression (LLD) and cognitive impairment showed significant abnormalities in several biological pathways related to immune-inflammatory control, neurotrophic cascades, protein homeostasis, lipid metabolism, and clotting processes (Diniz *et al.*, 2015). Another study showed a progressive and significant decline in peripheral brain-derived neurotrophic factor (BDNF) levels in subjects with LLD and cognitive decline compared with subjects with LLD and no cognitive impairment or healthy older subjects (Diniz *et al.*, 2015). Similar abnormalities have been observed in subjects with Alzheimer's disease and mild cognitive impairment and can predict the progression from MCI to AD (Forlenza *et al.*, 2015; Ray *et al.*, 2007). Thus, we can hypothesize that depression and MCI share several biological abnormalities that help to explain the elevated risk of progression to AD in older adults with depression and mild cognitive impairment. Despite that the current work did not directly evaluate any biological marker, future studies need to include the assessment of biomarkers to evaluate whether abnormalities in distinct biological cascades can improve the identification of subjects with depression and MCI at higher risk to progress to AD upon follow-up.

In conclusion, our results reinforce the association of depressive symptoms and the risk of dementia in older adults. We showed that subjects with MCI and depression have a greater risk of progressing to dementia upon follow-up. The current study provides a strong rationale for the need of studies aiming to treat depression in subjects with MCI and to evaluate whether depression treatment can reduce such risk in these individuals.

Conflict of interest

None declared.Key points

- There is a complex relationship between depressive symptoms and cognitive decline in older adults
- Depressive symptoms determine an additive risk for progression to dementia in subjects with mild cognitive impairment.
- The comorbidity between depressive symptoms and mild cognitive impairment can be a target to interventions aiming the prevention of dementia in older adults.

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References

Albert MS, DeKosky ST, Dickson D, *et al.* 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**: 270–279. DOI:10.1016/j.jalz.2011.03.008.

Artero S, Ancelin ML, Portet F, *et al.* 2008. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry* **79**: 979–984. DOI:10.1136/jnnp.2007.136903.

Beaudreau SA, Kaci Fairchild J, Spira AP, Lazzeroni LC, O'Hara R. 2013. Neuropsychiatric symptoms, apolipoprotein E gene, and risk of progression to cognitive impairment, no dementia and dementia: the Aging, Demographics, and Memory Study (ADAMS). *Int J Geriatr Psychiatry* **28**: 672–680. DOI:10.1002/gps.3868.

Chan WC, Lam LC, Tam CW, *et al.* 2011. Neuropsychiatric symptoms are associated with increased risks of progression to dementia: a 2-year prospective study of 321 Chinese older persons with mild cognitive impairment. *Age Ageing* **40**: 30–35. DOI:10.1093/ageing/afq151.

Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. 2013a. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* **202**: 329–335. DOI:10.1192/bjp.bp.112.118307.

Diniz BS, Machado-Vieira R, Forlenza OV. 2013b. Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders. *Neuropsychiatr Dis Treat* **9**: 493–500. DOI:10.2147/NDT.S33086.

Diniz BS, Reynolds CF 3rd, Begley A, *et al.* 2014. Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: a longitudinal study. *J Psychiatr Res* **49**: 96–101. DOI:10.1016/j.jpsychires.2013.11.004.

Diniz BS, Sibille E, Ding Y, *et al.* 2015. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. *Mol Psychiatry* **20**: 594–601. DOI:10.1038/mp.2014.76.

Ebly EM, Hogan DB, Parhad IM. 1995. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. *Arch Neurol* **52**: 612–619.

Forlenza OV, Diniz BS, Gattaz WF. 2010. Diagnosis and biomarkers of predementia in Alzheimer's disease. *BMC Med* **8**: 89. DOI:10.1186/1741-7015-8-89.

Forlenza OV, Diniz BS, Nunes PV, *et al.* 2009. Diagnostic transitions in mild cognitive impairment subtypes. *Int Psychogeriatr* **21**: 1088–1095. DOI:10.1017/S1041610209990792.

Forlenza OV, Diniz BS, Stella F, Teixeira AL, Gattaz WF. 2013. Mild cognitive impairment. Part 1: clinical characteristics and predictors of dementia. *Rev Bras Psiquiatr* **35**: 178–185.

Forlenza OV, Diniz BS, Teixeira AL, *et al.* 2015. Lower cerebrospinal fluid concentration of brain-derived neurotrophic factor predicts progression from mild cognitive impairment to Alzheimer's disease. *Neuromolecular Med* **17**: 326–332. DOI:10.1007/s12017-015-8361-y.

Gallagher D, Coen R, Kilroy D, *et al.* 2011. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int J Geriatr Psychiatry* **26**: 166–172. DOI:10.1002/gps.2509.

Geda YE, Knopman DS, Mrazek DA, *et al.* 2006. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Arch Neurol* **63**: 435–440.

Geda YE, Roberts RO, Mielke MM, *et al.* 2014. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry* **171**: 572–581. DOI:10.1176/appi.ajp.2014.13060821.

Houde M, Bergman H, Whitehead V, Chertkow H. 2008. A predictive depression pattern in mild cognitive impairment. *Int J Geriatr Psychiatry* **23**: 1028–1033. DOI:10.1002/gps.2028.

Kessing LV, Forman JL, Andersen PK. 2011. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *Int Clin Psychopharmacol* **26**: 316–322. DOI:10.1097/YIC.0b013e32834ace0f.

Koenig AM, DeLozier IJ, Zmuda MD, *et al.* 2015. Neuropsychological functioning in the acute and remitted states of late-life depression. *J Alzheimers Dis* **45**: 175–185. DOI:10.3233/JAD-148006.

Lee GJ, Lu PH, Hua X, *et al.* 2012. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatry* **71**: 814–821. DOI:10.1016/j.biopsych.2011.12.024.

McKhann G, Drachman D, Folstein M, *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of vDepartment of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**: 939–944.

Modrego PJ, Ferrández J. 2004. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol* **61**: 1290–1293.

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* **62**: 1006–1012. DOI:10.1016/j.jclinepi.2009.06.005.

Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. 2006. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* **63**: 530–538.

Palmer K, Berger AK, Monastero R, *et al.* 2007. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* **68**: 1596–1602.

Palmer K, Di Iulio F, Varsi AE, *et al.* 2010. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimers Dis* **20**: 175–183. DOI:10.3233/JAD-2010-1352.

Panza F, Capurso C, D'Introno A, *et al.* 2008. 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* **23**: 726–734. DOI:10.1002/gps.1967.

Panza F, Frisardi V, Capurso C, *et al.* 2010. Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am J Geriatr Psychiatry* **18**: 98–116. DOI:10.1097/JGP.0b013e3181b0fa13.

Peters ME, Rosenberg PB, Steinberg M, *et al.* 2013. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the cache county study. *Am J Geriatr Psychiatry* **21**: 1116–1124. DOI:10.1016/j.jagp.2013.01.049.

Petersen RC. 2004. Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**: 183–194.

Petersen RC, Caracciolo B, Brayne C, *et al.* 2014. Mild cognitive impairment: a concept in evolution. *J Intern Med* **275**: 214–228. DOI:10.1111/joim.12190.

Petersen RC, Doody R, Kurz A, *et al.* 2001. Current concepts in mild cognitive impairment. *Arch Neurol* **58**: 1985–1992.

Petersen RC, Smith GE, Waring SC, *et al.* 1999. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**: 303–308.

Pink A, Stokin GB, Bartley MM, *et al.*. 2015. Neuropsychiatric symptoms, APOE ε4, and the risk of incident dementia: a population-based study. *Neurology* **84**: 935–943. DOI:10.1212/WNL.0000000000001307.

Ramakers IH, Visser PJ, Aalten P, *et al.* 2010. Affective symptoms as predictors of Alzheimer's disease in subjects with mild cognitive impairment: a 10-year follow-up study. *Psychol Med* **40**: 1193–1201. DOI:10.1017/S0033291709991577.

Ray S, Britschgi M, Herbert C, *et al.* 2007. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* **13**: 1359–1362.

Reynolds CF 3rd, Butters MA, Lopez O, *et al.* 2011. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Arch Gen Psychiatry* **68**: 51–60. DOI:10.1001/archgenpsychiatry.2010.184.

Richard E, Reitz C, Honig LH, *et al.* 2013. Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurol* **70**: 374–382.

Richard E, Schmand B, Eikelenboom P, *et al.* 2012. Symptoms of apathy are associated with progression from mild cognitive impairment to Alzheimer's disease in non-depressed subjects. *Dement Geriatr Cogn Disord* **33**: 204–209. DOI:10.1159/000338239.

Rock PL, Roiser JP, Riedel WJ, Blackwell AD. 2014. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* **44**: 2029–2040. DOI:10.1017/S0033291713002535.

Rosenberg PB, Mielke MM, Appleby BS, *et al.* 2013. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry* **21**: 685–695. DOI:10.1016/j.jagp.2013.01.006.

Steenland K, Karnes C, Seals R, *et al.* 2012. Late-life depression as a risk factor for mild cognitive impairment or Alzheimer's disease in 30 US Alzheimer's disease centers. *J Alzheimers Dis* **31**: 265–275. DOI:10.3233/JAD-2012-111922.

Steffens DC, McQuoid DR, Potter GG. 2014. Amnestic mild cognitive impairment and incident dementia and Alzheimer's disease in geriatric depression. *Int Psychogeriatr* **26**: 2029–2036. DOI:10.1017/S1041610214001446.

Vicini Chilovi B, Conti M, Zanetti M, *et al.* 2009. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* **27**: 390–398. DOI:10.1159/000210045.

Wilson RS, Arnold SE, Beck TL, Bienias JL, Bennett DA. 2008. Change in depressive symptoms during the prodromal phase of Alzheimer disease. *Arch Gen Psychiatry* **65**: 439–445. DOI:10.1001/archpsyc.65.4.439.

Winblad B, Palmer K, Kivipelto M, *et al.* 2004. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med.* **256**: 240–246.

Wells GA SB, O'Connell D, Peterson J, *et al.* 2013. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. In: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.