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Citation for published version (APA):

Document status and date:
Published: 01/01/2019

DOI:
10.3233/JAD-180513

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

Depressive Symptoms in Mild Cognitive Impairment and the Risk of Dementia: A Systematic Review and Comparative Meta-Analysis of Clinical and Community-Based Studies

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Abstract.
Background: Affective symptoms are considered a risk factor or prodromal symptom for dementia. Recent reviews indicate that depressive symptoms predict progression from mild cognitive impairment (MCI) to dementia, but results need to be further explored.
Objective: To investigate the effect of depressive symptoms on the development of dementia in people with MCI, and explore potential sources of between-study variability, including study setting by a systematic review and meta-analysis.
Methods: Databases were searched for prospective studies defining people with MCI at baseline, investigating dementia at follow-up and giving information about depressive symptoms. Two authors independently extracted data from the studies and rated the methodological quality. Meta-analyses were conducted using random-effect models to yield pooled risk ratios (RR). Meta-regression analyses tested differences between clinical and community-based studies and other sources of heterogeneity.
Results: Thirty-five studies, representing 14,158 individuals with MCI, were included in the meta-analysis. Depressive symptoms in MCI predicted dementia in 15 community-based studies (RR = 1.69, 95% CI 1.49–1.93, $I^2 = 0.0\%$), but not in 20 clinical studies (RR = 1.02, 95% CI 0.92–1.14, $I^2 = 73.0\%$). Further investigation of this effect showed that the mean age of community-based studies was significantly higher than of clinical studies but neither this nor other study characteristics explained variability in study outcomes.
Conclusions: Depressive symptoms are associated with an increased risk of conversion from MCI to dementia in community-based studies. In contrast, evidence in clinical populations was insufficient with high heterogeneity.

Keywords: Dementia, depression, depressive symptoms, meta-analysis, mild cognitive impairment, risk factors, systematic review

INTRODUCTION

Mild cognitive impairment (MCI) is a well-known risk state for developing dementia, but the heterogeneity in underlying etiologies leading to cognitive

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impairment causes diversity in outcome. Importantly, not all individuals with MCI will develop dementia; a longitudinal study found that less than half of the individuals with amnestic MCI will develop dementia within ten years [1]. It is important to gain insight into easily-accessible factors that predict who will develop dementia and who will not. This might indicate potential for secondary prevention or, alternatively, lead to an earlier and more accurate diagnosis, give opportunities to start care and treatment timely, and to enable patients and their families to better anticipate their future.

Affective symptoms are considered a major risk factor or prodromal symptom for dementia in the general population [2–4]. However, their predictive value in persons with MCI is unknown as current results are conflicting. A recent review and meta-analysis of a broad range of potentially modifiable predictors of dementia in MCI found that there is evidence that depressive symptoms predict progression from MCI to dementia in community-based studies, but not in clinical studies [5]. However, the study was not specified for depressive symptoms, and hence only 13 studies were included and the associations were not further explored. Additionally, another recent review and meta-analysis found evidence that depressive symptoms increase the risk of progression from MCI to dementia, but heterogeneity was very high and not further explored [6].

The aim of this study is to systematically review the current evidence and perform a meta-analysis to investigate the effect of depressive symptoms on the development of dementia in persons with MCI. In addition, we investigate study characteristics that may explain the variability in study outcomes, especially differences between community-based and clinical studies.

METHODS

This study adhered to the PRISMA statement: Preferred Reporting Items for Systematic Reviews and Meta-Analyses [7].

Search strategy

We searched the PubMed, PsycINFO, EMBASE, and CINAHL databases for relevant studies published until March 31, 2018. The following search terms were used: 'human' and 'depression', 'anxiety', 'apathy', 'aggression', 'irritability',

'affective', 'mood', 'behavioral', 'neuropsychiatric', or 'behavioral and psychological symptoms of dementia' and 'mild cognitive impairment', 'MCI', 'amnestic', 'amnestic syndrome', 'memory impairment', 'mild cognitive decline', 'age-associated cognitive decline', 'AACD', 'age-associated memory impairment', 'AAMI', 'cognitive impairment no dementia', 'CIND', 'memory clinic', 'memory disorders clinic', 'dementia clinic' or 'memory disorder clinic' and 'follow-up studies', 'follow up studies', 'follow-up study', 'follow up study', 'follow up', or 'follow-up'. Neuropsychiatric symptoms such as anxiety and apathy were included in the search because of possible overlap with depressive symptoms and potential that associations were reported in sub-analyses. No search limits were applied.

Titles and abstracts of the retrieved studies were reviewed using the criteria specified below. Additionally, references of relevant publications were searched to identify additional studies.

Study selection

Studies were selected for further analysis if they fulfilled the following inclusion criteria: 1) prospective study; 2) defining individuals with MCI at baseline; 3) a diagnosis of dementia at follow-up according to any of the following criteria: Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (American Psychiatric Association, 1994), DSM 3rd Revised Edition (DSM-III-R) (American Psychiatric Association, 1987), the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1993), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA); 4) Available information on depressive symptoms or depression at baseline; and 5) A study cohort of 50 or more individuals.

We included all studies that defined MCI as subjective and/or objective cognitive impairment, without fulfilling dementia criteria. We included all subtypes of MCI, except for studies focusing on MCI in Parkinson's disease.

Data extraction

Two authors independently extracted the data from the studies. When available, we extracted both the number of individuals with and without baseline

depression or depressive symptoms (dichotomous variable) of converters and non-converters to dementia. We also extracted the reported risk measure including the 95% confidence interval. In addition, the following study characteristics were extracted: setting (clinical studies versus community-based studies), inclusion and exclusion criteria (specifically exclusion of a baseline major depressive disorder), MCI definition, measurement of depression, subject characteristics (e.g., gender, age, Mini-Mental State Examination (MMSE), education) and number of converters to dementia. Concerning the characteristic 'setting' the studies were divided into two types of studies: 1) Clinical studies: studies performed in a clinical setting (e.g., memory clinic); and 2) Community-based studies: studies performed in the general population.

In case the two authors disagreed, a third author reviewed the paper and consensus was reached. In case of incomplete data, authors were contacted and asked to complete or specify the data.

Assessment of methodological quality

To assess methodological quality, two reviewers rated each study according to a 19 items scale derived from a published method [8]. For the specific items, see Supplementary Table 1. In case of discrepancies between the reviewers, a third reviewer was asked to review and score to reach consensus. A median split and a split into tertiles of the total quality score classified studies into those with low, medium or high risk of bias.

Statistical analysis

Analyses were performed using STATA/MP version 12.1 for Mac OSX (StataCorp, Texas). Statistical significance was set at $p < 0.05$ in two-sided tests. The main outcome measure was the pooled risk ratio (RR) from random-effect models.

Unadjusted RR and standard errors (SE) were calculated directly from raw tables. For four studies raw data were not available and the reported risk measure was used. These risk measures were log-transformed and standard errors were calculated from the 95% confidence interval (CI). For two of these studies, only a hazard ratio (HR) was reported, but it was considered equivalent to the RR.

The amount of heterogeneity was calculated with the DerSimonian and Laird method, which is a method to estimate the variance between studies.

I^2 denotes the proportion of the observed variance between studies that reflects real differences rather than chance and was used next to the Q-statistic to assess heterogeneity. We performed meta-regression analyses to investigate possible sources of heterogeneity, i.e., sampling method (clinical versus community-based setting), baseline mean age of the cohort, baseline MMSE score, conversion rate, publication year, depression versus depressive symptoms, and whether studies used major depression as an exclusion criterion. Analyses were performed 1-by-1 for all variables, analyses were first performed on all studies and then for community and clinical studies separately. Publication bias was investigated using Egger's regression test and a visual inspection of the funnel plot.

RESULTS

Search results

A total of 5,470 publications were reviewed on title and abstract, of which 208 publications were selected for further scrutiny (Fig. 1). Additionally, 20 publications were retrieved through references. Of these 228 papers, 98 were excluded due to overlap in used literature databases. Additionally, from the remaining 130 papers, 8 were posters or correspondence letters, 18 gave no or unclear information about baseline depressive symptoms, 20 referred to the same cohort as another publication, 23 were excluded because of other reasons, and 26 publications were not included because not enough data were available. Concerning the publications reporting on the same cohort, the publication with the largest sample size was selected, if the sample size was the same then the study with the longest follow-up was selected. There was one exception, concerning the data of the Alzheimer's Disease Neuroimaging Initiative (ADNI); a recent study was selected fitting our research question most properly. Finally, 35 studies were included in the meta-analysis.

Study characteristics

In total, the 35 studies (Table 1) [9–43] included 14,158 individuals with MCI, of whom 7,855 (57.2%) were female (data missing for 1 study [41], $n = 429$). Of the 35 studies, fifteen were community-based studies ($n = 6,803$) and twenty ($n = 7,355$) were based

Table 1
Characteristics of studies included in the meta-analysis

Study		Setting	Sample size	MCI definition	Depression scale	Prevalence depression/ depressive symptoms (%)	Mean follow-up (y)	Mean age (y)	Mean education Mean MMSE	Mean MMSE (%)	Conversion rate
Tierney [36]	1999	Community	125	Symptomatic memory problems, no dementia	GDS-30	22.4	2	72.0	14.0	–	21.6
Visser [35]	2002	Community	63	'Minimal dementia'	clinical	11.1	2.3	79.5	7.3	22.5	53.0
Copeland [34]	2003	Community	123	CDR = 0.5	interview	43.8	3	72.2	14.9	29.1	20.3
Korf [33]	2004	Clinical	71	Petersen (close to)	MADRS	41.3	2.8	62.9	10.2	26.9	49.3
Modrego [31]	2004	Clinical	114	Petersen	GDS-30	36.0	3	72.8	–	–	51.7
Robert [37][1]	2006	Clinical	216	Petersen (close to)	MADRS	19.9	1	71.9	–	27.5	10.2
Teng [30]	2007	Clinical	51	Petersen	NPI	39.2	2.1	72.8	16.6	27.6	23.5
Artero [29]	2008	Community	2879	Petersen, MCI-revised[a]	CES-D	30.8	4	74.6	–	–	6.6
Houde [28]	2008	Clinical	60	Petersen	GDS-30	51.7	4.3	74.5	10.5	27.2	60.0
Fellows [27][2]	2008	Clinical	90	Petersen	GDS-30	57.8	3.3	73.7	10.7	27.5	56.0
Panza [26]	2008	Community	121	Petersen, without SMC as criterion	GDS-30	61.2	3.5	80.6	2.2	21.4	10.8
Robert [25][3]	2008	Clinical	214	Petersen (close to)	'lack of interest'	22.0	3	71.9	–	27.5	27.2
Devier [24][4]	2009	Clinical	148	86.5% Petersen (post-hoc)	HAM-D	22.3	3.9	67.1	15.0	27.5	26.4
Edwards [23]	2009	Clinical	521	aMCI, single non-memory MCI, mdMCI	clinical	38.1	1.6	72.8	13.0	26.3	67.0
Vicini Chilovi [22]	2009	Clinical	124	Petersen, MCI-revised[a]	GDS-15, NPI	47.6	2	71.3	7.5	26.6	22.6
Velayudhan [20]	2010	Community	103	Petersen	Cornell, NPI	29.4	4	79.4	10.6	26.3	31.0
Palmer [19][5]	2010	Clinical	131	Petersen	NPI	34.3	1.4	70.8	–	27.2	15.2
Ramakers [18]	2010	Clinical	263	GDS 2-3	HAM-D	51.6	5.4	66.9	–	27.6	34.2
Gallagher [17]	2011	Clinical	161	Petersen	BEHAVE-AD	25.5	2.25	73.7		25.4	43.0
Caracciolo [16]	2011	Community	160	Petersen + oCIND	'low mood'	36.0	3	–	–	–	31.3
Chan [15]	2011	Community	321	Petersen	NPI	16.8	2	77.3	3.0	24.3	15.9
Sikkes [14]	2011	Clinical	531	'Cognitive complaints'	Differed	10.0	1	69.6	10.0	27.5	13.0
Brodaty [13]	2012	Community	319	Petersen	NPI	12.4	2	79.0	11.6	27.6	4.7
Conde-Sala [12]	2012	Clinical	109	EADC	CAMDEX-R	53.8	5	74	–	21.3	39.4
Luck [43]	2012	Community	483	Petersen, MCI-revised[a]	GDS-15	13.9	3.7	80.1	–	26.0	24.2
Mauri [11][6]	2012	Clinical	208	Petersen	GDS-30	41.8	6	73.6	7.5	25.6	68.8
Steenland [42]	2012	Clinical	3010	NACC's definition	GDS-15, NPI-Q	35.3	2.5	74	–	27.2	39.0
Richard [41]	2013	Community	429	Petersen	CES-D	24.0	5.1	–	–	–	20.9
Brodaty [40]	2014	Clinical	185	Petersen, MCI-revised[a]	NPI	33	3	75.8	–	27.0	28.1
Van der Mussele [39][7]	2014	Clinical	183	Petersen	CSDD or GDS-30	22.4	3.8	74.9	10.9	26.0	59.6
Pink [38]	2015	Community	332	NPI-Q	NPI-Q	25.3	Median: 3	Median:82.1	Median: 12.0	–	35.2
Makizako [32]	2016	Community	732	>25 on MMSE, cognitive impairment, no functional dependency	GDS-15	16.1	2	71.8	11.3	–	4.5
Kida [21]	2016	Community	276	Cognitive complaints, objective impairment, preserved ADL	GDS-15	23.2	5.2 (incl. controls)	73.1	9.8	–	22.8
Myung [10]	2017	Clinical	961	NIA-AA definition	GDS-15	–	Median: 1.5	Median: 71	Median: 8	Median: 25	29.1
Moon [9]	2017	Community	337	Petersen	NPI-Q	22.3	1.9	71.8	16.2	28.1	15.4

CAMDEX-R, Cambridge Examination for Mental Disorders of the Elderly – revised; CES-D, Center for Epidemiological Studies Depression scale; CDR, clinical dementia rating scale; EADC, European AD Consortium; GDS, Global Deterioration Scale; GDS-15/GDS-30, Geriatric Depression Scale; CSDD, Cornell Scale for Depression in Dementia; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NACC, National Alzheimer's Coordinating Centre; NIA-AA, National Institute of Aging and Alzheimer's Association; NPI, Neuropsychiatric Inventory; SMC, subjective memory complaints. [a]Winblad et al., 2004 [57]. *Extra information about depression as an exclusion criterion in some of the studies:* [1]MADRS >20; [2]Yesavage Geriatric depression scale >16 (major depression); [3]MADRS >20; [4]'Current major affective disorder'; [5]'Patients with major depressive disorder if meaningful clinical improvement in cognition accompanying improvement in depression was observed within 6 months of antidepressants treatment initiation'; [6]GDS-30 >17; [7]CSDD ≥22 or GDS-30 ≥21; [8]GDS-15 ≥6.
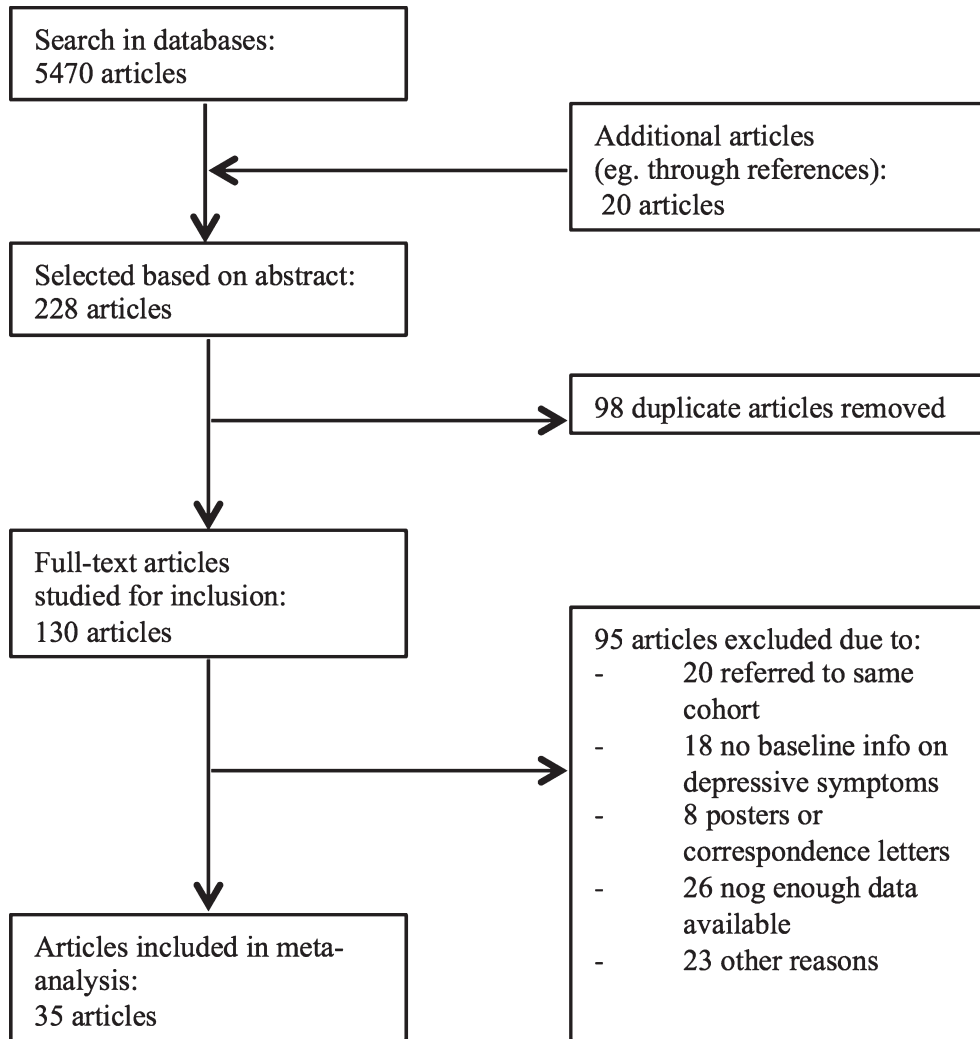
Fig. 1. Selection of studies.

on clinical samples. In 23 studies, MCI was defined according to the Petersen criteria [44] or minor variants thereof. The mean baseline age was 73.7 years (SD 4.2), mean MMSE score was 26.3 (SD 2.0) and mean education was 10.9 years (SD 3.8). In total, 3,509 (27.6%) MCI individuals showed depression or relevant depressive symptoms at baseline (not specified for 4 studies [11, 17, 41, 47], $n = 1,427$), 25.1% in community-based studies, and 32.5% in clinical studies.

In total, 3,208 (22.7%) individuals progressed from MCI to dementia during a mean follow-up period of 3.0 (SD 1.3) years. In 27 studies, it was specified whether the dementia was due to Alzheimer's disease, which was the case in 2,367 of 11,315 (20.9%) individuals.

Meta-analysis

Dementia developed in 1,043 (29.6%) individuals with MCI with depressive symptoms at baseline, compared to 1,833 (21.1%) MCI individuals without depressive symptoms at baseline (raw data missing for 4 studies [10, 16, 26, 40]). The accompanying pooled RR based on data from all 35 studies was 1.19 (95% CI = 1.07–1.32). When the two studies reporting HRs were excluded, the pooled RR was 1.22 (95% CI 1.06–1.41). When the four studies that reported ratios instead of raw data were excluded, the pooled RR was 1.22 (95%CI = 1.06–1.40).

There was significant heterogeneity across studies ($I^2 = 73.6\%$, $p < 0.001$). Since we expected sampling method (clinical versus community-based) to

partly explain differences between studies, we conducted meta-analysis stratified by sampling method. In community-based samples, the pooled risk ratio was 1.69 (95%CI = 1.49–1.93), compared to 1.02 (95%CI = 0.92–1.14) in clinical samples (Fig. 2). Additionally, heterogeneity was high in clinical studies (I^2 = 73.0%) but marginal in community-based studies (I^2 = 0.0%).

Exploratory analysis of additional variability in study outcomes

Studies were divided in two age groups: studies with a mean age ≥75 years (8 studies, n = 1927) and studies with a mean age <75 years (25 studies, n = 11087). The pooled risk ratio for studies with a mean age ≥75 years was 1.41 (95%CI = 1.12–1.77) and for studies with a mean age <75 years 1.16 (95%CI = 0.99–1.37). However, there was a large overlap between the community-based studies and the studies with a mean age ≥75 years, with a higher mean age in community-based studies than in clinical studies (76.4 versus 71.8, p < 0.001). To understand this effect further, we divided the community-based studies into those with a mean age ≥75 years or below. This showed slightly stronger associations in the younger cohorts (RR = 1.71, 95%CI = 1.38–2.14) versus the older cohorts (RR = 1.60, 95%CI = 1.32–1.93). The same analysis could not be performed in the clinical studies because only one of them had a mean age ≥75 years.

Multivariable meta-regression of all 35 studies suggested that only setting (clinical, community) significantly explained heterogeneity between studies (residual I^2 = 60.0%). In this model, community-based studies reported on average a 1.61-fold higher risk (95%CI = 1.24–2.09) as a function of depression compared with clinical studies. Adding mean age to this model did not substantially change results (RR = 1.58, 95%CI = 1.13–2.22, residual I^2 = 60.0%). Studies with a higher mean age did not convey a higher risk in this model (RR for age = 1.01, 95%CI = 0.97–1.05).

In an attempt to explain the variability in outcome in clinical studies, several meta-regression analyses were conducted (see Supplementary Table 2). Although all articles gave information on depression or depressive symptoms at baseline, in some clinical studies major depressive disorder was an exclusion criterion. There was no significant difference in the risk of progression to dementia in clinical studies with and without major depressive disorder as an exclusion criterion (Coef. 0.12, p = 0.627). Studies also differed in the way depression was defined, with some studies investigating depression according to clinical criteria and others as scoring above the cut-off on continuous symptom scales. Meta-regression analysis did not reveal any significant difference in outcome according to exposure definition (Coef. 0.20, p = 0.373). The Geriatric Depression Scale (GDS-15 or GDS-30) was the most commonly used scale (n = 9 out of 20 clinical studies) to measure depressive symptoms, but usage of the GDS versus other instruments did not result in a significantly different outcome (Coef. 0.02, p = 0.927). We further found no significant effect of other study characteristics: Peterson criteria for MCI (yes, no), clinical diagnosis of depression (yes, no), study quality (tertiles), mean MMSE score, mean follow-up duration, publication year, and conversion rate for explaining heterogeneity in clinical studies. Meta-regression analysis with the characteristic mean education was not possible, due to insufficient and possibly not comparable data.

Small sample effect

Visual inspection of the stratified funnel plots for community and clinical studies, as well as Egger's regression tests for community studies (bias coef. –0.860, SE 0.542, p = 0.137) and clinical studies (bias coef. –0.675, SE 0.783, p = 0.824), showed little evidence for small study effects.

Methodological quality

Meta-regression showed that studies with high or low risk of bias did not explain heterogeneity in study outcome. Dividing methodological quality scores into tertiles did not change this.

DISCUSSION

In a meta-analysis of 35 studies, representing almost 15,000 individuals with MCI, we found strong and consistent evidence that depressive symptoms predict a higher dementia risk in community-dwelling persons with MCI. The pooled risk ratio suggests a 1.69 times higher risk in depressed people with MCI for conversion to dementia with very low between-study heterogeneity. In contrast, the pooled risk was not increased in clinical cohorts with MCI, and heterogeneity in these studies was high. Other

Author	Year		Risk ratio (95% CI)	% Weight
Community				
Tierney	1999		0.99 (0.44, 2.21)	1.33
Visser	2002		1.14 (0.53, 2.48)	1.41
Copeland	2003		1.07 (0.51, 2.27)	1.48
Panza	2008		1.42 (0.48, 4.20)	0.80
Artero	2008		2.00 (1.52, 2.63)	4.54
Velayudhan	2010		1.44 (0.64, 3.25)	1.31
Chan	2011		1.87 (1.09, 3.21)	2.37
Caracciolo	2011		1.00 (0.50, 2.00)	1.67
Luck	2012		1.83 (1.29, 2.60)	3.77
Brodaty	2012		1.56 (0.36, 6.88)	0.46
Richard	2013		1.55 (0.98, 2.45)	2.89
Pink	2015		1.48 (1.10, 2.00)	4.28
Kida	2016		2.05 (1.15, 3.67)	2.16
Makizako	2016		2.26 (1.11, 4.63)	1.60
Moon	2017		2.36 (1.44, 3.85)	2.67
Subtotal (I-squared = 0.0%, p = 0.602)			1.69 (1.49, 1.93)	32.74
.				
Clinical				
Korf	2004		0.68 (0.41, 1.14)	2.54
Modrego	2004		2.60 (1.83, 3.69)	3.77
Robert	2006		1.88 (0.82, 4.32)	1.26
Teng	2007		3.10 (1.07, 8.95)	0.84
Robert	2008		1.56 (0.99, 2.45)	2.96
Fellows	2008		0.86 (0.59, 1.24)	3.63
Houde	2008		1.05 (0.69, 1.58)	3.23
Vicini Chilovi	2009		0.37 (0.17, 0.80)	1.40
Devier	2009		0.90 (0.46, 1.76)	1.75
Edwards	2009		1.05 (0.88, 1.24)	5.65
Ramakers	2010		0.78 (0.57, 1.08)	4.10
Palmer	2010		0.96 (0.36, 2.57)	0.94
Gallagher	2011		0.68 (0.42, 1.11)	2.69
Sikkes	2011		0.42 (0.14, 1.28)	0.76
Steenland	2012		1.18 (1.07, 1.31)	6.24
Conde-Sala	2012		0.71 (0.44, 1.14)	2.79
Mauri	2012		0.92 (0.76, 1.11)	5.44
Van der Mussele	2014		0.98 (0.73, 1.31)	4.37
Brodaty	2014		1.08 (0.98, 1.19)	6.29
Myung	2017		0.99 (0.96, 1.02)	6.61
Subtotal (I-squared = 73.0%, p = 0.000)			1.02 (0.92, 1.14)	67.26
.				
Overall (I-squared = 75.9%, p = 0.000)			1.19 (1.07, 1.32)	100.00

NOTE: Weights are from random effects analysis
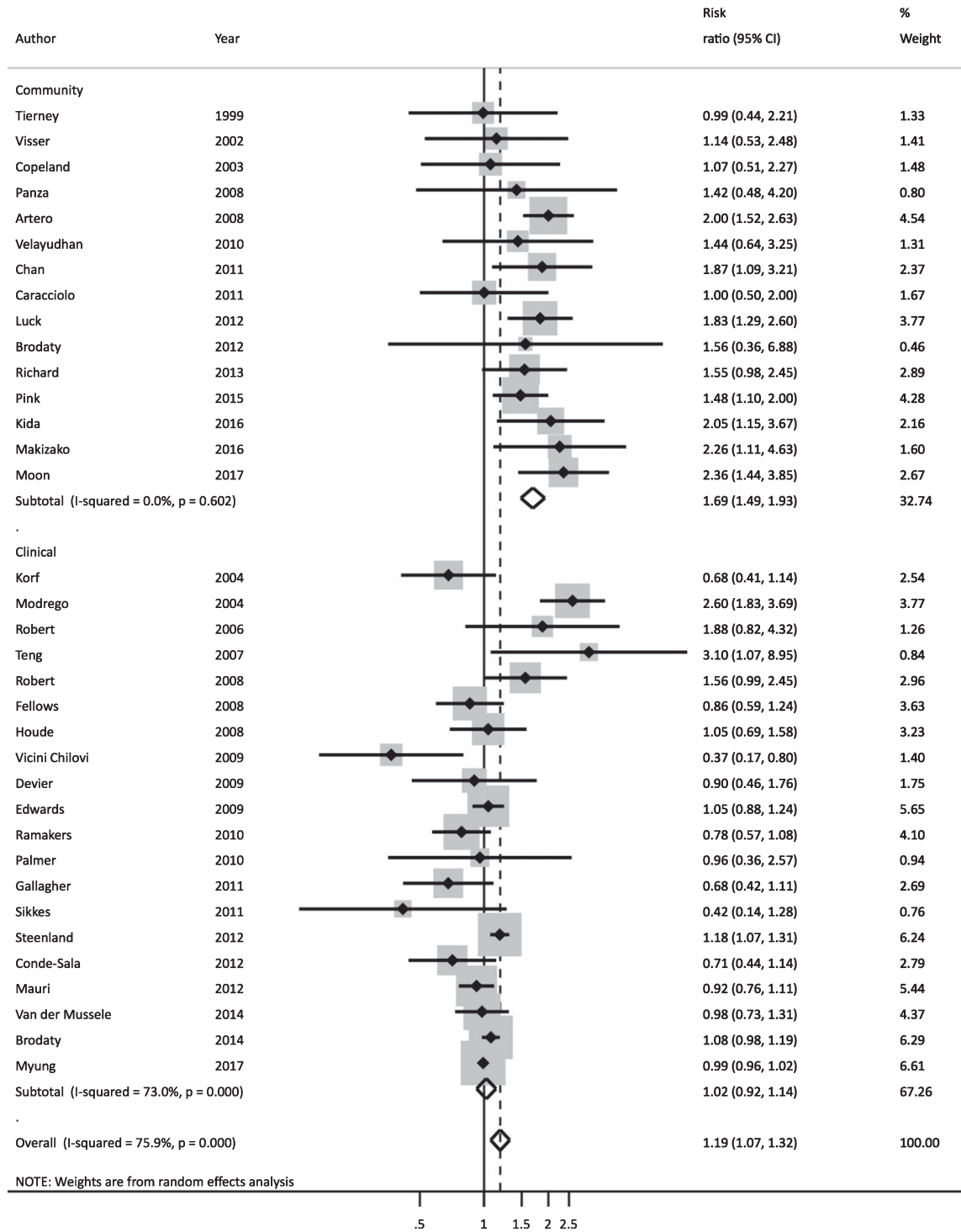
.5   1   1.5 2 2.5

Fig. 2. Pooled Risk Ratios for studies grouped by setting.

study characteristics did not explain the difference between clinical and community-based studies.

These findings give important insight into the robustness of the association between depression in MCI and risk of dementia conversion. A recent meta-analysis with a smaller total population [6] found depression to be associated with an increase in the risk but reported high variability in study outcomes. In the current study, an association with depression was only found in the community-based studies, which has also been shown in an earlier study by Cooper et al. [5]. The latter was, however, a smaller study (13 studies on depression compared to 35 in the present one), not focusing on depressive symptoms in particular. Importantly, our meta-regression analyses show that the difference between study settings is not explained by other study characteristics such as mean age, follow-up-duration, definition of MCI, or how depression was assessed.

The results of our study and these two studies also amplify two meta-analyses in cognitively healthy persons: a meta-analysis [2] studying the risk of dementia in cognitively healthy older adults with late-life depression in community-based prospective cohort studies found that late-life depression is associated with a 1.8-fold increased risk of incident all-cause dementia, and a meta-analysis [3] that found that cognitively-healthy persons with a history of major depression are more likely to be diagnosed with Alzheimer's disease later in life than persons without a history of major depression.

In clinical studies we could not find an association between depressive symptoms and the progression from MCI to dementia. A possible explanation is that heterogeneity in clinical studies was very high ($I^2 = 73.0\%$). An exploratory analysis indicated that age partly explains this heterogeneity. Another possible explanation for the heterogeneity might be that there are many different types of memory clinics in and outside hospitals with different populations (e.g., neurology, psychiatry, internal medicine). A study in a clinical population on neurobiological correlates of depressive symptoms in individuals with MCI and subjective memory impairment found that depressive symptoms are common, but not associated with pathological Alzheimer's disease biomarkers [47]. The authors suggest that in their clinical population depressive symptoms may drive the cognitive symptoms rather than being a mere correlate of neurodegenerative changes. This finding could also explain why some of the clinical studies in this meta-analysis found a negative relation between depressive symptoms and progression from MCI to dementia. Also, in clinical studies of individuals seeking help, one could expect the symptoms, whether being depressive symptoms or cognitive problems, to be more severe. This could lead to hypothetical subgroups of individuals with MCI with different subsets of symptoms and a different course and outcome. A recent study by Hanfelt el al. [48] on latent classes of MCI, in a clinical population, indeed found that seven latent classes of MCI differed significantly in clinical outcome. It could be that the heterogeneity in the clinical studies is a reflection of different classes with different outcomes, while in the community studies the homogeneity may indicate fewer classes or a different distribution.

The direction of the relation between depression and dementia in the community-based studies remains unclear. Different hypothesis are plausible and described in the literature, suggesting a causal or corollary effect or favoring reversed-causality [49, 50]. For instance, depressive symptoms may interact with, or provoke, the pathophysiological mechanism(s) of dementia, for example due to a cortisol-hippocampal pathway [49], resulting in a faster progression from MCI to dementia. Another hypothesis is that the progression from MCI to dementia itself leads to depressive symptoms, for example as an early symptom [51]. A quite similar hypothesis could be that the awareness of the patient that his or her cognitive functions are failing results in depressive symptoms. A fourth, and often postulated, hypothesis is the vascular depression hypothesis in which depression is associated with an increase in vascular risk factors and therefore an increased incidence of cognitive dysfunction due to cerebral small vessel disease [52]. Indeed, some studies suggest that cerebrovascular factors are the link between depressive symptoms and the progression from MCI to (vascular) dementia [41, 53]. Moreover, the meta-analysis of Diniz et al. found that, in case of late-life depression, the risk of vascular dementia is significantly higher than for Alzheimer's disease. Unfortunately, we were not able to perform a separate analysis focusing on vascular dementia due to insufficient data. Late-life dementia is often due to mixed brain pathologies (i.e., both vascular and Alzheimer's disease factors) [54]. Since depression has been strongly related to cerebrovascular disease including cerebral small vessel disease [55], stroke [56], and vascular dementia [2], its predictive value for dementia should be higher in populations that comprise more (mixed) vascular
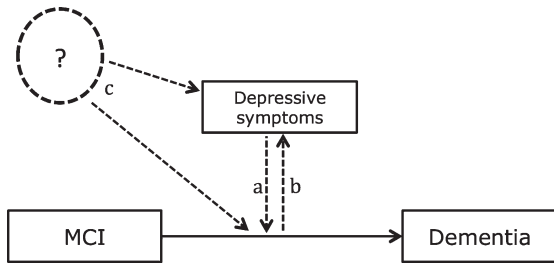
Fig. 3. Different hypotheses concerning the direction of relation between depressive symptoms and progression from MCI to dementia. a) Depressive symptoms influence the pathophysiological mechanisms of dementia. b) 1. The progression from MCI to dementia itself leads to depressive symptoms as an early symptom, 2. The awareness of failing cognitive functions leads to depressive symptoms.c) Another factor (e.g., vascular risk factors) leads to progression to dementia and to depressive symptoms.

pathologies. This might also explain the paralleling effect of age: since the mean age in community studies was higher than in the clinical studies, there may have been more vascular or mixed dementias in the community-studies. Of course, also a combination of these different hypotheses is possible in which different mechanisms operate in different (groups of) individuals (Fig. 3).

Although the direction of the association between depressive symptoms and dementia in the community studies is unclear, the present study does imply screening of depressive symptoms in MCI. The detection of depressive symptoms may lead to adequate treatment and a better quality of life, and may possibly modify the progression from MCI to dementia.

Strengths of this study are the comprehensive and broad search for the literature review, and the extensive analyses. However, the study has several limitations. First, useful studies may be missing because not all data were available in the published papers and not all authors of previous studies replied to our requests for additional data, for example because the authors were already retired. These studies were mainly studies with an earlier publication year. Furthermore, as noted before, we were able to include 35 studies, instead of the 13 and 18 studies included in earlier meta-analyses [5, 6]. Second, studies with different MCI definitions were included, although most studies used Petersen criteria [44] or criteria quite similar to Petersen criteria. Meta-regression findings showed that this did not affected our results. In addition, there was also heterogeneity in the depression scales, although meta-regression analysis indicated that this had no effect on the results. As stated earlier, heterogeneity in clinical studies was

high and we could only partly explain this heterogeneity. Also, more information on the type, course and any received treatment of depression and depressive symptoms, e.g., history of depression and age of onset, would have given more insight into the kind of association, but was unfortunately not available in enough studies to perform meta-regression analysis. More information on the type, course and any received treatment of the depressive symptoms could also have been useful to further understand the heterogeneity in the clinical studies.

In conclusion, we found strong evidence that depressive symptoms predict higher dementia risk in community-dwelling persons with MCI. More research is needed to identify the underlying mechanisms of this higher risk, particularly vascular risk factors should be taken into account and studies should differentiate between types of dementias. We found no significant association in clinical studies, but heterogeneity in these studies was very high.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0513r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-180513.

REFERENCES

[1] Visser PJ, Kester A, Jolles J, Verhey F (2006) Ten-year risk of dementia in subjects with mild cognitive impairment. *Neurology* **67**, 1201-1207.

[2] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds 3rd CF (2013) 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.

[3] 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.

[4] Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Munoz Sanchez JL, Anstey KJ, Brayne C, Dartigues JF, Engedal K, Kivipelto M, Ritchie K, Starr JM, Yaffe K, Irving K, Verhey FR, Kohler S (2015) Target risk factors for dementia prevention: A Systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry* **30**, 234-246.

[5] Cooper C, Sommerlad A, Lyketsos CG, Livingston G (2015) Modifiable predictors of dementia in mild cognitive impairment: A Systematic review and meta-analysis. *Am J Psychiatry* **172**, 323-334.

[6] Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS (2016) Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive

impairment: Systematic review and meta-analysis. *Int J Geriatr Psychiatry* **31**, 905-911.

[7] Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* **339**, b2535-b2535.

[8] Altman DG (2001) Systematic reviews of evaluations of prognostic variables. *BMJ* **323**, 224-228.

[9] Moon B, Kim S, Park YH, Lim JS, Youn YC, Kim S, Jang JW; Alzheimer's Disease Neuroimaging Initiative (2017) Depressive symptoms are associated with progression to dementia in patients with amyloid-positive mild cognitive impairment. *J Alzheimers Dis* **58**, 1255-1264.

[10] Myung W, Lee C, Park JH, Woo S, Kim S, Kim S, Chung JW, Kang HS, Lim S-W, Choi J, Na DL, Kim SY, Lee J-H, Han S-H, Choi SH, Kim SY, Carroll BJ, Kim DK (2017) Occupational attainment as risk factor for progression from mild cognitive impairment to Alzheimer's disease: A CREDOS study. *J Alzheimers Dis* **55**, 283-292.

[11] Mauri M, Sinforiani E, Zucchella C, Cuzzoni MG, Bono G (2012) Progression to dementia in a population with amnestic mild cognitive impairment: Clinical variables associated with conversion. *Funct Neurol* **27**, 49-54.

[12] Conde-Sala JL, Garre-Olmo J, Vilalta-Franch J, Llinas-Regla J, Turro-Garriga O, Lozano-Gallego M, Hernandez-Ferrandiz M, Pericot-Nierga I, Lopez-Pousa S (2012) Predictors of cognitive decline in Alzheimer's disease and mild cognitive impairment using the CAMCOG: A Five-year follow-up. *Int Psychogeriatr* **24**, 948-958.

[13] Brodaty H, Heffernan M, Draper B, Reppermund S, Kochan N, Slavin MJ, Trollor JN, Sachdev PS (2012) Neuropsychiatric symptoms in older people with and without cognitive impairment. *J Alzheimers Dis* **31**, 411-420.

[14] Sikkes SA, Visser PJ, Knol DL, de Lange-de Klerk ES, Tsolaki M, Frisoni GB, Nobili F, Spiru L, Rigaud AS, Frolich L, Rikkert MO, Soininen H, Touchon J, Wilcock G, Boada M, Hampel H, Bullock R, Vellas B, Pijnenburg YA, Scheltens P, Verhey FR, Uitdehaag BM (2011) Do instrumental activities of daily living predict dementia at 1- and 2-year follow-up? Findings from the Development of Screening guidelines and diagnostic Criteria for Predementia Alzheimer's disease study. *J Am Geriatr Soc* **59**, 2273-2281.

[15] Chan WC, Lam LC, Tam CW, Lui VW, Leung GT, Lee AT, Chan SS, Fung AW, Chiu HF, Chan WM (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.

[16] Caracciolo B, Backman L, Monastero R, Winblad B, Fratiglioni L (2011) 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 Neurosurg Psychiatry* **82**, 788-793.

[17] Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, Walsh B, Cunningham C, Lawlor BA (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.

[18] Ramakers IH, Visser PJ, Aalten P, Kester A, Jolles J, Verhey FR (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.

[19] Palmer K, Di Iulio F, Varsi AE, Gianni W, Sancesario G, Caltagirone C, Spalletta G (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.

[20] Velayudhan L, Poppe M, Archer N, Proitsi P, Brown RG, Lovestone S (2010) Risk of developing dementia in people with diabetes and mild cognitive impairment. *Br J Psychiatry* **196**, 36-40.

[21] Kida J, Nemoto K, Ikejima C, Bun S, Kakuma T, Mizukami K, Asada T (2016) Impact of depressive symptoms on conversion from mild cognitive impairment subtypes to Alzheimer's disease: A Community-based longitudinal study. *J Alzheimers Dis* **51**, 405-415.

[22] Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A (2009) Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* **27**, 390-398.

[23] Edwards ER, Spira AP, Barnes DE, Yaffe K (2009) Neuropsychiatric symptoms in mild cognitive impairment: Differences by subtype and progression to dementia. *Int J Geriatr Psychiatry* **24**, 716-722.

[24] Devier DJ, Pelton GH, Tabert MH, Liu X, Cuasay K, Eisenstadt R, Marder K, Stern Y, Devanand DP (2009) The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *Int J Geriatr Psychiatry* **24**, 1335-1342.

[25] Robert PH, Berr C, Volteau M, Bertogliati-Fileau C, Benoit M, Guerin O, Sarazin M, Legrain S, Dubois B (2008) Importance of lack of interest in patients with mild cognitive impairment. *Am J Geriatr Psychiatry* **16**, 770-776.

[26] Panza F, Capurso C, D'Introno A, Colacicco AM, Zenzola A, Menga R, Pistoia G, Santamato A, Scafato E, Gandin C, Capurso A, Solfrizzi V (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.

[27] Fellows L, Bergman H, Wolfson C, Chertkow H (2008) Can clinical data predict progression to dementia in amnestic mild cognitive impairment? *Can J Neurol Sci* **35**, 314-322.

[28] Houde M, Bergman H, Whitehead V, Chertkow H (2008) A predictive depression pattern in mild cognitive impairment. *Int J Geriatr Psychiatry* **23**, 1028-1033.

[29] Artero S, Ancelin ML, Portet F, Dupuy A, Berr C, Dartigues JF, Tzourio C, Rouaud O, Poncet M, Pasquier F, Auriacombe S, Touchon J, Ritchie K (2008) Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry* **79**, 979-984.

[30] Teng E, Lu PH, Cummings JL (2007) Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord* **24**, 253-259.

[31] Modrego PJ, Ferrandez 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.

[32] Makizako H, Shimada H, Doi T, Tsutsumimoto K, Hotta R, Nakakubo S, Makino K, Suzuki T (2016) Comorbid mild cognitive impairment and depressive symptoms predict future dementia in community older adults: A 24-month follow-up longitudinal study. *J Alzheimers Dis* **54**, 1473-1482.

[33] Korf ES, Wahlund LO, Visser PJ, Scheltens P (2004) Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology* **63**, 94-100.

[34] Copeland MP, Daly E, Hines V, Mastromauro C, Zaitchik D, Gunther J, Albert M (2003) Psychiatric symptomatology and prodromal Alzheimer's disease. *Alzheimer Dis Assoc Disord* **17**, 1-8.

[35]   Jelle Visser P, Verhey FR, Jolles J, Jonker C (2002) Course of minimal dementia and predictors of outcome. *Int J Geriatr Psychiatry* **17**, 835-841.

[36]   Tierney MC, Boyle E, Lam RE, Szalai JP (1999) Do depressive symptoms in memory-impaired elders predict probable Alzheimer's disease? *Aging Ment Health* **3**, 88-93.

[37]   Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, Legrain S, Dubois B (2006) 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 Neurosurg* **108**, 733-736.

[38]   Pink A, Stokin GB, Bartley MM, Roberts RO, Sochor O, Machulda MM, Krell-Roesch J, Knopman DS, Acosta JI, Christianson TJ, Pankratz VS, Mielke MM, Petersen RC, Geda YE (2015) Neuropsychiatric symptoms, APOE ε4, and the risk of incident dementia: A Population-based study. *Neurology* **84**, 935-943.

[39]   Van der Mussele S, Fransen E, Struyfs H, Luyckx J, Mariën P, Saerens J, Somers N, Goeman J, De Deyn PP, Engelborghs S (2014) Depression in mild cognitive impairment is associated with progression to Alzheimer's disease: A Longitudinal study. *J Alzheimers Dis* **42**, 1239-1250.

[40]   Brodaty H, Connors MH, Ames D, Woodward M (2014) Progression from mild cognitive impairment to dementia: A 3-year longitudinal study. *Aust N Z J Psychiatry* **48**, 1137-1142.

[41]   Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JJ, Mayeux R, Devanand D, Luchsinger JA (2013) Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurol* **70**, 374-382.

[42]   Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A (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.

[43]   Luck T, Luppa M, Wiese B, Maier W, van den Bussche H, Eisele M, Jessen F, Weeg D, Weyerer S, Pentzek M, Leicht H, Koehler M, Tebarth F, Olbrich J, Eifflaender-Gorfer S, Fuchs A, Koenig HH, Riedel-Heller SG, AgeCoDe Study Group (2012) Prediction of incident dementia: Impact of impairment in instrumental activities of daily living and mild cognitive impairment-results from the German study on ageing, cognition, and dementia in primary care patients. *Am J Geriatr Psychiatry* **20**, 943-954.

[44]   Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[45]   Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Scapicchio PL, Scafato E, Gandin C, Capurso A, Panza F (2007) Incident occurrence of depressive symptoms among patients with mild cognitive impairment - the Italian longitudinal study on aging. *Dement Geriatr Cogn Disord* **24**, 55-64.

[46]   Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Todarello O, Pellicani V, Santamato A, Scapicchio P, Maggi S, Scafato E, Gandin C, Capurso A, Solfrizzi V (2008) Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. *Dement Geriatr Cogn Disord* **25**, 336-346.

[47]   Auning E, Selnes P, Grambaite R, Šaltyte Benth J, Haram A, Løvli Stav A, Bjørnerud A, Hessen E, Hol PK, Muftuler løndalen A, Fladby T, Aarsland D (2015) Neurobiological correlates of depressive symptoms in people with subjective and mild cognitive impairment. *Acta Psychiatr Scand* **131**, 139-147.

[48]   Hanfelt JJ, Peng L, Goldstein FC, Lah JJ (2018) Latent classes of mild cognitive impairment are associated with clinical outcomes and neuropathology: Analysis of data from the National Alzheimer's Coordinating Center. *Neurobiol Dis* **117**, 62-71.

[49]   Byers AL, Yaffe K (2011) Depression and risk of developing dementia. *Nat Rev Neurol* **7**, 323-331.

[50]   Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, DeKosky ST, Becker JT (2008) Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci* **10**, 345-357.

[51]   Berger AK, Fratiglioni L, Forsell Y, Winblad B, Backman L (1999) The occurrence of depressive symptoms in the preclinical phase of AD: A Population-based study. *Neurology* **53**, 1998-2002.

[52]   Taylor WD, Aizenstein HJ, Alexopoulos GS (2013) The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry* **18**, 963-974.

[53]   Brodaty H, Luscombe G, Anstey KJ, Cramsie J, Andrews G, Peisah C (2003) Neuropsychological performance and dementia in depressed patients after 25-year follow-up: A Controlled study. *Psychol Med* **33**, 1263-1275.

[54]   Schneider JA, Arvanitakis Z, Bang W, Bennett DA (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* **69**, 2197-2204.

[55]   van Sloten TT, Sigurdsson S, van Buchem MA, Phillips CL, Jonsson P V, Ding J, Schram MT, Harris TB, Gudnason V, Launer LJ (2015) Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: The AGES-Reykjavik Study. *Am J Psychiatry* **172**, 570-578.

[56]   Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB (2011) Depression and risk of stroke morbidity and mortality: A Meta-analysis and systematic review. *JAMA* **306**, 1241-1249.

[57]   Winblad B, Palmer KKM (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.