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Are Depressive Symptoms in Mild Cognitive Impairment Predictive of Conversion to Dementia?

Ellen De Roeck[1,3], Ingrid Ponjaert-Kristoffersen[1], Marc Bosmans[1], Peter Paul De Deyn[2,3], Sebastiaan Engelborghs[2,3], Eva Dierckx[1,4]

[1] Developmental and Lifespan Psychology, Vrije Universiteit Brussel, Brussels, Belgium
[2] Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium
[3] Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium
[4] Alexian Brothers Hospital, Tienen, Belgium

Authors:

Ellen De Roeck
Campus Drie Eiken, room D.T.652, Universiteitsplein 1, 2610 Wilrijk, Belgium

Prof. Dr. Ingrid Ponjaert-Kristoffersen
Faculty of Psychology and Educational Sciences, Pleinlaan 2, 1050 Brussels, Belgium

Marc Bosmans
Kielstraat 6 bus 1, 3910 Neerpelt, Belgium

Prof. Dr. Peter Paul De Deyn
Campus Drie Eiken, room D.T.698, Universiteitsplein 1, 2610 Wilrijk, Belgium

Prof. Dr. Sebastiaan Engelborghs
Campus Drie Eiken, room D.T.651, Universiteitsplein 1, 2610 Wilrijk , Belgium

Corresponding author:

Prof. Dr. Eva Dierckx
Faculty of Psychology and Educational Sciences, Pleinlaan 2, 1050 Brussels, Belgium
Phone: + 32 2 629 36 22, Fax: + 32-2-629 25 32, E-mail: eva.dierckx@vub.ac.be

Abstract

Background: Depressive symptoms are common in amnestic mild cognitive impairment (aMCI) The association between depressive symptoms and conversion to dementia is not yet clear. This longitudinal study was conducted to ascertain whether depressive symptoms in aMCI patients are predictive of conversion to dementia.

Method: 35 aMCI patients participated in this study. All participants underwent cognitive testing and were administered the geriatric depression scale (GDS) to determine the presence of depressive symptoms. A score equaling or higher than 11 on the GDS was taken as the cutoff point for presence of significant depressive symptoms. Conversion to dementia was assessed at follow-up visits after 1.5, 4 and 10 years.

Results: 31.4% of the patients reported depressive symptoms at baseline. None of the cognitive measures revealed a significant difference at baseline between patients with and without depressive symptoms. After 1.5, 4 and 10 years respectively 6, 14 and 23 patients had converted to dementia. Although the GDS scores at baseline did not predict conversion to dementia, the cognitive measures and more specifically a verbal cued recall task (the memory impairment scale-plus) was a good predictor for conversion.

Conclusion: Based on this dataset, the presence of depressive symptoms in aMCI patients is not predictive of conversion to dementia.

Keywords: depressive symptoms, depression, mild cognitive impairment, dementia, conversion, Alzheimer's disease,

Running title: Depressive symptoms predictive of conversion?

Introduction

In clinical practice, the early detection of Alzheimer's disease (AD) has focused primarily on the mild cognitive impairment (MCI) phase. MCI is often seen as an intermediate stage between normal aging and dementia. In the amnestic form of MCI (aMCI), objective and subjective memory complaints are dominant. It often occurs that aMCI is a prodromal phase of AD (Dubois *et al.*, 2014).

Many studies have shown that depressive symptoms are common in MCI, with depression being present in about 16% to 27% of the MCI patients (Lee *et al.*, 2007; Van der Mussele *et al.*, 2014). Research on the association between depression and AD however, has provided us with inconsistent findings regarding the temporal and directional association of both disorders. In some studies, older adults with depressive symptoms had an increased risk of developing AD (Ownby *et al.*, 2006; Saczynski *et al.*, 2010; Sacuiu *et al.*, 2015), whereas in other research, individuals with AD had an increased risk of developing depression (Chen *et al.*, 1999; Vinkers, *et al.*, 2004). Some researchers even did not find any association between depression and incident dementia (Luppa *et al.*, 2013). So, in sum, the role of depression and depressive symptoms as an early prodromal clinical manifestation of dementia, as a risk factor and / or as a reaction to cognitive decline is still a matter of debate (Panza *et al.*, 2010).

The main aim of the present study was to investigate whether depressive symptoms in aMCI patients could predict conversion to dementia. More specifically the following research questions were raised: (1) do depressive symptoms in aMCI patients allow for an accurate prediction of conversion to dementia, after 1.5, 4 and 10 years of follow-up; (2) are there significant differences in baseline depressive symptoms and scores on cognitive measures between aMCI patients with a diagnosis of dementia at follow-up (i.e., converters) and those without (i.e., non-converters)?

Methods

Participants

All patients were recruited from the Memory Clinic of Hospital Network Antwerp and were diagnosed with aMCI after a diagnostic work-up consisting of a general physical and neurological examination, blood screening, structural neuroimaging and a neuropsychological assessment. To establish a diagnosis of aMCI, Petersen's criteria (Petersen *et al.*, 1999) were applied. These consist of (1) a subjective memory complaint ideally corroborated by an informant, (2) an objective memory impairment for age and education, (3) essentially preserved general cognitive functions (4) largely intact functional activities, and (5) not demented.

The inclusion criteria for our study were: (1) a diagnosis of aMCI at the Memory Clinic of Hospital Network Antwerp (2) age equal to or above 64 years, (3) no history of neurological diseases or comorbid neurological disorder and (4) no psychiatric illness. Because of a lack of an uniform definition and clinical diagnostic criteria for aMCI, all aMCI patients were diagnosed by clinicians in the same center in order to preserve homogeneity in this diagnostic group.

Materials and procedure

To avoid circular reasoning, (i.e. the same tests are used to diagnose a disease and then to predict the diagnosis), it is important to point out that the cognitive screening tests used in this study are different from the tests used in the neuropsychological assessment for the diagnosis of aMCI/dementia..

At baseline (1) the Dutch version of the Cambridge Cognitive Examination. (CAMCOG) (Derix, *et al.*, 1992; Roth *et al.*, 1986), a global cognitive screening test, (2) the

Mini Mental Status Examination (MMSE) (Folstein, *et al.*, 1975), a short screening instrument for cognitive functions, (3) the 30 items Geriatric Depression Scale (GDS) (Yesavage, 1988), a self-report questionnaire to assess depressive symptoms, (4) the Memory Impairment Screen (MIS-plus) (Dierckx *et al.*, 2007) (Dutch version of the original MIS) consisting of six to-be-learned words instead of the original four), and (5) the Visual Association Test (VAT) (Lindeboom and Schmand, 2003), a visual cued recall task, were administered to all patients.

The GDS is a self-report questionnaire specifically designed to screen for depressive symptoms in the elderly. Scores range from 0 to 30, with higher scores indicating a greater likelihood of depression. A cutoff score of 11 is generally used to distinguish between the presence and absence of significant depressive symptoms (Yesavage, 1988).

The patients were subsequently divided into two groups based on their GDS scores. Patients who obtained a GDS score equaling 11 or higher were labeled as the *MCI patients with depressive symptoms* group, while patients with a GDS score below 11 were labeled as the *MCI patients without depressive symptoms* group.

After 1.5, 4 and 10 years, clinical data were used to establish a follow-up diagnosis. A diagnosis of dementia was established in the same center and by the same clinicians who initially established the diagnosis of aMCI. A dementia diagnosis was made according to DSM-IV criteria (American Psychiatric Association, 1994). Probable AD dementia was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA criteria) (McKhann *et al.*, 1984). In this way a group of converters (i.e., diagnosis of dementia at follow-up) and a group of non-converters (i.e., no diagnosis of dementia at follow-up) could be distinguished.

The local ethics committees approved the study and a written informed consent was obtained from all patients.

Statistical analysis

Data were analyzed using SPSS Statistics 22 (IBM Corp., 2013) and a criterion alpha of .05 was used throughout all analyses. First baseline scores between participants that had follow-up and that had not were compared with non-parametric Mann–Whitney U tests for each follow-up moment. Non-parametric tests were chosen because of the small sample sizes. Then aMCI patients with and without depressive symptoms at baseline were compared for baseline demographics and cognitive measures by means of Mann–Whitney U tests (age, education and all cognitive measures) or chi-square analysis (gender). Differences in baseline GDS, CAMCOG, MMSE, MIS-plus, and VAT scores between converters to dementia and non-converters were studied with non-parametric Mann–Whitney U tests, after both 1.5 and 4 years. Additionally binary logistic regression analysis was performed to explore whether depressive symptoms at baseline could predict conversion to dementia in general and to AD dementia in specific in aMCI patients, both after 1.5 and 4 year of follow-up. Due to the small sample size of the non-converted group after 10 years, no further analyses were done between converters to dementia in general and non-converters. Subsequently an 'AD group' consisting of converters to AD and a 'non-AD group' consisting of converters to other types of dementia. By means of non-parametric Mann–Whitney U tests the differences in baseline GDS, CAMCOG, MMSE, MIS-plus, and VAT scores were studied.

Finally, survival analyses were done. The association between aMCI at baseline and dementia was studied separately for conversion to dementia in general and for conversion to AD after 10 years of follow-up. The associations were studied using Tarone-Ware $\chi 2$ tests

comparing estimates of the Kaplan–Meier survival estimates of aMCI patients with depressive symptoms and those aMCI patients without depressive symptoms at baseline. Because of the promising findings with the MIS-plus to predict conversion to AD, the Kaplan–Meier analyses were reperformed to compare aMCI patients who scored below the cutoff of the MIS-plus (5 or 6) and those with aMCI who scored under the cutoff of the MIS-plus (4 or less) at baseline. Finally a figure was made using GraphPad Prism version 6.05 for Windows

Results

Baseline characteristics of aMCI patients with and without follow-up (table 1).

A total of 35 aMCI completed the baseline neuropsychological examination for this study. An even number of male (54.3%) and female participants participated with a mean age of 75.31 (5.98), ranging from 64 to 91. Mean scolarity, calculated as the mean number of years of education as from the age of six years, was 11.77 (3.26) years (range 8-18).

Data analysis showed that 11.43%, 22.86% and 28.29% of the participants were not followed up after 1.5, 4 and 10 years respectively. The differences between the participants that were followed up and those that dropped out are described for each follow-up moment in table 1. Only baseline MMSE scores differed significantly between patients who were follow-up after 1.5 year and those who were not.

Table 1. Differences in baseline scores of MCI patients who received follow-up and drop outs at 1.5, 4 and 10 years follow-up

	1.5 year			4 years			10 years		
	follow-up (n=31)	no follow-up (n=4)		follow-up (n=27)	no follow-up (n=8)		follow-up (n=25)	no follow-up (n=10)	
	Mean (sd)	Mean (sd)	p	Mean (sd)	Mean (sd)	p	Mean (sd)	Mean (sd)	p
GDS	8.32 (4.86)	11.25 (5.19)	.254	7.93 (4.51)	11.13 (5.69)	.166	8.52 (4.45)	9.00 (6.16)	.928
MMSE	25.61 (2.20)	22.50 (2.38)	.032	25.56 (2.28)	24.25 (2.71)	.269	25.08 (1.98)	25.70 (3.33)	.397
CAMCOG	89.48 (6.02)	84.25 (7.93)	.194	89.78 (6.02)	85.88 (6.92)	.206	88.80 (5.70)	89.10 (8.10)	.627
MIS-plus	3.52 (2.17)	1.25 (0.50)	.073	3.52 (2.23)	2.38 (1.69)	.154	3.16 (2.25)	3.50 (2.07)	.788
VAT	3.45 (2.06)	2.50 (1.73)	.379	3.67 (2.06)	2.25 (1.58)	.080	3.40 (2.04)	3.20 (2.10)	.788

Baseline demographics and cognitive scores of aMCI patients with and without depressive symptoms (table 2).

When applying the cutoff of 11 on the GDS, 31.4% of aMCI patients reported depressive symptoms at baseline. At baseline, aMCI patients with and without depressive symptoms did not significantly differ in age and years of education. None of the cognitive measures revealed a significant difference at baseline between aMCI patients with and without depressive symptoms.

Table 2. Baseline demographics and cognitive functioning of aMCI patients with and without depressive symptoms

	aMCI with depressive symptoms (n=11)	aMCI without depressive symptoms (n=24)	
	Mean (SD)	Mean (SD)	p
Age	74.74 (5.52)	75.58(6.28)	.662[1]
Gender	45.45 % male	58.33 % male	.716[2]
Education	11.64 (2.94)	11.83 (3.46)	.958[1]
CAMCOG	87.64 (6.30)	89.46 (6.43)	.430[1]
MMSE	25.00 (2.28)	25.38 (2.50)	.687[1]
MIS-plus	3.09 (2.51)	3.33 (2.06)	.662[1]
VAT	2.91 (2.26)	3.54 (1.93)	.451[1]
GDS	14.73 (2.41)	5.88 (2.72)	.000[1]

1 Mann– Whitney U tests
2 chi square

Differences in baseline cognitive scores and depressive symptoms between converters and non-converters (table 3).

After 1.5 years, 31 out of 35 aMCI patients were reassessed and 6 fulfilled criteria for probable AD, while 25 had not (yet) converted to dementia. The conversion rate was 19.35 %.

According to a binary logistic regression analysis, GDS scores at baseline were not able to predict conversion to AD (*Wald* $X^2(1) = 2{,}397$, $p = .122$).

Converters scored higher on the GDS at baseline than non-converters although this difference was not statistically significant. Concerning the cognitive measures, converters performed significantly worse on the MIS-plus, the VAT and CAMCOG (see Table 3).

A forward binary logistic regression using the GDS, CAMCOG, MMSE, MIS-plus and VAT as predictive variables showed that the MIS-plus was the best predictor for conversion to AD dementia after 1.5 years (*Wald* $X^2(1)=2{,}973$, p=.085).

After 4 years, the available clinical data from 27 out of 35 aMCI patients were evaluated and 14 fulfilled criteria for dementia (12 converted to AD and 2 to non-specified dementia), while 13 had (still) not converted to dementia. The conversion rate was 51.85 %. According to a binary logistic regression analysis, GDS scores at baseline, again, could not predict conversion to dementia (*Wald* $X^2(1) = .123$, $p = .726$) nor to AD dementia (*Wald* $X^2(1) = .263$, $p = .608$).

There was no significant difference in the presence of depressive symptoms at baseline between converters and non-converters. Converters again performed significantly worse on the MIS-plus, VAT and CAMCOG. This meant that converters performed worse at baseline, mainly on cognitive measures of memory (table 3).

Forward binary logistic regression analyses using GDS, CAMCOG, MMSE, MIS-plus and VAT as predictive variables (first modeled all together and subsequently all separately) showed that the MIS-plus is the best predictor of conversion to dementia and to AD dementia after 4 years (respectively *Wald* $X^2(1)=8{,}880$, $p=.003$ and *Wald* $X^2(1)=5.056$, $p=.025$).

Table 3. Differences in cognitive measures and depressive symptoms at baseline in converters and non-converters after 1.5 years and 4 years.

	after 1.5 years	after 4 years

	non-converters (n=25)	converters (n=6)		non-converters (n=13)	converters (n=14)	
	mean (sd)	mean (sd)	p	mean (sd)	mean (sd)	p
GDS	7.64 (4.91)	11.17 (3.76)	.067	7.62 (5.11)	8.21 (4.06)	.650
MMSE	25.84 (2.30)	24.67 (1.51)	.158	26.38 (2.26)	24.79 (2.09)	.068
CAMCOG	90.56 (5.70)	85.00 (5.59)	.046	92.23 (5.75)	87.50 (5.52)	.048
MIS-plus	4.20 (1.80)	0.67 (0.82)	.000	5.15 (1.14)	2.00 (1.96)	.000
VAT	3.92 (1.87)	1.50 (1.76)	.012	4.69 (1.32)	2.71 (2.20)	.019

Finally after 10 years the clinical data of 25 out of 35 aMCI patients were evaluated and 23 fulfilled criteria for dementia (15 converted to AD dementia, 7 to non-specified dementia and 1 to Parkinson's disease dementia), while 2 had (still) not converted to dementia. The conversion rate was 92 %. Due to the small non-converter group no further analyses were done on conversion to dementia in general. In table 4 the group that converted to AD is compared with the non-AD group (converters to other types of dementia). There was no significant difference in the presence of depressive symptoms at baseline between the AD group and non-AD group. The AD patients scored worse on the MIS-plus, however this difference did not reach significance.

Table 4 Comparison between non-AD and AD groups after 10 years

	non-AD group (n=8)	AD group (n=15)	
	mean (sd)	mean (sd)	p
GDS	9.38 (5.07)	8.27 (3.90)	.591
MMSE	24.13 (1.46)	25.33 (1.99)	.169
CAMCOG	89.75 (3.92)	87.53 (6.35)	.294
MIS-plus	4.25 (2.12)	2.27 (2.02)	.065
VAT	4.25 (1.28)	2.73 (2.22)	.131

Survival analyses

Similar as with the binary logistic regression, the Kaplan Meier model showed that depressive symptoms were not predictive for conversion to dementia in general (*Tarone ware*

$X^2(1)=0.157$, $p=.692$), nor for conversion to AD dementia (*Tarone ware* $X^2(1)=0.749$, $p=.387$). In contrast, the model showed that the MIS-plus is a good predictor of conversion to AD over time (*Tarone ware* $X^2(1) = 9.648$, $p=.002$) (figure 1).

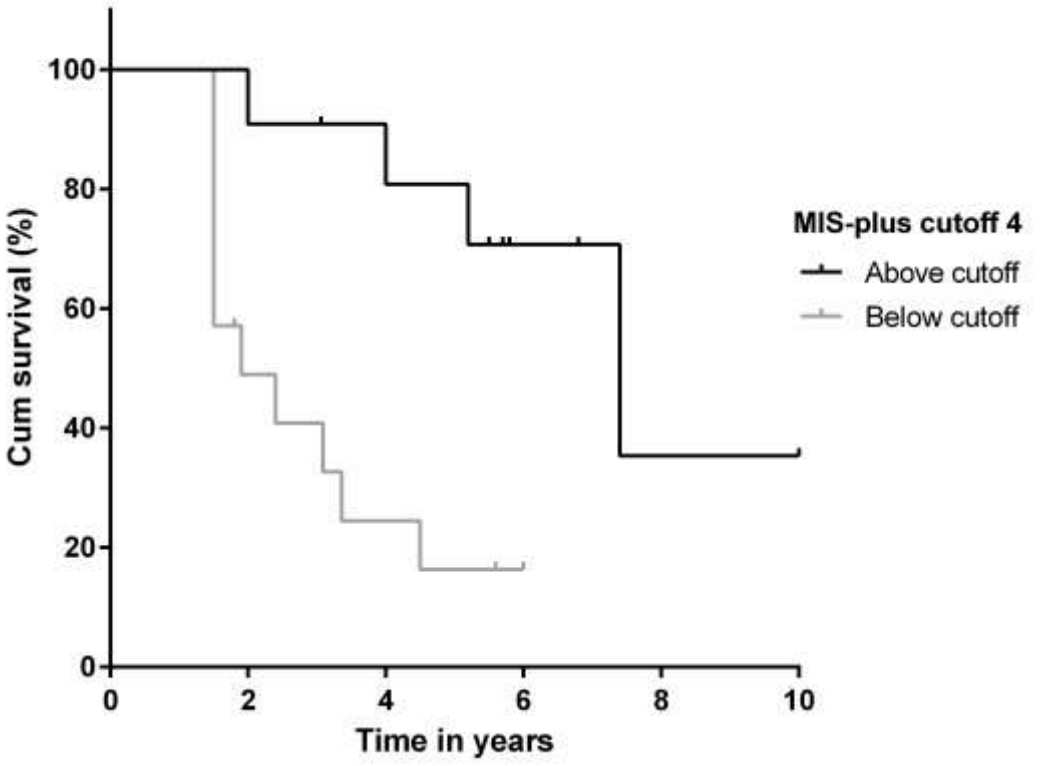

Figure 1 Progression to AD dementia in aMCI patients with scores above and below the MIS-plus cutoff of 4.

Discussion

The current study aimed to explore the relationship between depressive symptoms and the risk of developing dementia in MCI patients. More specifically, this study wanted to investigate whether conversion to dementia could be predicted after 1.5, 4 and 10 years of follow-up based on the presence of depressive symptoms in amnestic mild cognitive impairment (aMCI) patients.

Our results are in accordance with previous studies showing that depressive symptoms are common in MCI patients. While in this study 31.4% of aMCI patients reported significant depressive symptoms, other studies including population based studies reported prevalence rates ranging between 3% and 63% with a median of 15.7% (Panza *et al.*, 2010). This wide variation in reported prevalence rates might be the result of differences in the use of diagnostic criteria and the operationalization of depression and depressive symptoms among studies as well as the contribution of possible selection biases (memory clinic versus population-based studies).

After 1.5, 4 and 10 years the conversion rate from aMCI to dementia was respectively 19% (whereof 19% to AD), 52% (whereof 44% to AD) and 92% (whereof 60% to AD). Compared to other studies (Mitchell and Shiri-Feshki, 2009) this is a rather high conversion rate. This might be due a possible selection bias given the setting (memory clinic).In these settings, in most cases, the symptoms of cognitive decline are already manifest in patients and a degenerative process has been started. Besides this, it might be the case that stable or "progressed to normal" aMCI patients were represented in the missing data as they stopped coming to the clinic for follow-up.

Concerning the prediction of conversion to dementia after 1.5 years, our results show that the presence of depressive symptoms in aMCI patients is not predictive of conversion to dementia. However the converters reported slightly more depressive symptoms then the non-converters. So it is plausible that with a larger sample size this difference would have been stastiscally significant. Although there was a significant difference between converters and non-converters on the cognitive tasks, these could also not predict conversion to dementia.

Regarding the prediction of conversion to dementia and AD dementia after 4 and 10 years our results indicate that the presence of depressive symptoms in aMCI patients is not predictive of conversion to dementia nor to AD dementia. In contrast the cognitive measures and specifically memory tasks could predict dementia and AD dementia.

Our results are in contrast with a recent meta-analysis of longitudinal studies (Gao *et al.*, 2013) that concluded that depression is a major risk factor for incidence of dementia However, from the four studies investigating the link between depression and AD, only two found a significant difference in the incidence of AD dementia in subjects with depression. Although most studies published to date support the assumption that there is an increased risk of dementia in people with depression, approximately 25% of published studies fail to find this association (da Silva *et al.*, 2013). A 3-year and 8-year prospective study failed to show a clear significant association between depression and incident dementia and thus do not support the assumption that depressive symptoms predict cognitive decline either (Luppa *et al.*, 2013).

These discrepancies might be attributed to methodological differences between studies (e.g., sample size, definition and operationalization of depression, follow-up time) but might as well be explained by the impact of specific characteristics of depression influencing the association with dementia. Greater severity of depressive symptoms has been found to be an important characteristic influencing the risk of dementia (Chen *et al.*, 2008; Saczynski *et al.*,

2010; Van der Mussele *et al.*, 2014). Age at onset of depression (early- and late-life depression) has also been explored. While early-life depression has consistently been found to increase the risk of developing dementia in late life (Sacuiu *et al.*, 2015), studies investigating late-life depression have left us with contradictory findings (da Silva *et al.*, 2013).

Though, this conflicting evidence might also be due to differences in follow-up term. As proposed by different researchers (Banks *et al.*, 2014; Gaugler *et al.*, 2014; Van der Mussele *et al.*, 2014), it is reasonable that depressive symptoms form an early manifestation of the pathological process of dementia. So, it is possible that depressive symptoms in aMCI patients worsen when they are progressing to dementia with even a higher incidence at the moment of conversion to dementia. In this way, depressive symptoms are only predictive during a limited time frame. Our results indeed indicate that depressive symptoms are more predictive, however not yet significant, after 1.5 years then after 4 years of follow-up. In accordance with this hypothesis, Banks and colleagues (2014) found that MCI patients who progressed to dementia had increased self-reported depression.

This study also explored differences in baseline cognitive functioning between converters and non-converters, and tested whether these cognitive measures allow for a reliable prediction of conversion to dementia. There was a significant difference between converters and non-converters on memory tasks (i.e., CAMCOG, VAT and MIS-plus), with converters performing worse. This is in accordance with research on memory performance wherein it is found that so called prodromal AD patients obtain lower scores on tests of cued recall (e.g., the VAT and MIS-plus), and free recall (e.g., the memory tests of the CAMCOG) (Conde-Sala *et al.*, 2012; Dierckx *et al.*, 2009).

The guidelines from IWG-2 group (Dubois *et al.*, 2014) state that for typical AD pathology the clinical phenotype is recognized by an early and significant episodic memory impairment of the hippocampal type preferably measured with a free and cued recall task.

Indeed, in our study the MIS-plus was a good predictor of conversion from aMCI to dementia and more specifically to AD dementia. So, our results are also in accordance with studies supporting the hypothesis that cued recall tasks, like the VAT and the MIS-plus, are better predictors of conversion to AD than other measures of memory, for instance a free recall task (Dierckx *et al.*, 2009). Moreover, impairment on cued recall seems strongly associated with AD biomarkers in cerebrospinal fluid (Wagner *et al.*, 2012) which might be promising for the development of screening instruments to capture the clinical phenotype of AD in an early stage.

Some study limitations merit mentioning. First, this study has a small sample size (N=35) in combination with a rather high dropout rate over ten years. This might leave the study underpowered. Indeed, in a recent study with a much larger sample size (N=183) of MCI patients at baseline, the presence of significant depressive symptoms was associated with progression to AD (Van der Mussele et al., 2014). Second, the lack of an uniform operationalization of depression or depressive symptoms in MCI patients limits the comparability of our study with other studies.

Third, this study did not take into account the psychiatric history of the patients. As a consequence we cannot estimate the impact of early-life depressive symptoms or duration of the depressive symptoms on conversion, while studies have shown that the onset and duration of depression are important factors in determining the risk of developing dementia (da Silva et al., 2013). Besides this, only depression was assessed in this study. However, it has been shown that also other psychiatric symptoms and conditions like for example apathy, which shares a lot of characteristics with depression, might be a risk factor for the conversion to AD (Robert et al., 2006). Future research should take into account the psychiatric history of the patient and as well as duration of depressive symptoms or apathy as independent variables. In conclusion, this study showed that (1) depressive symptoms were common in this sample of

aMCI patients, and that (2) the presence of depressive symptoms at baseline, as measured by means of the GDS, is not predictive of conversion to dementia nor to AD dementia and that (3) especially the verbal cued recall task (MIS-plus) was able to predict conversion to dementia, specifically AD dementia in aMCI patients. However, future prospective, longitudinal studies with larger sample sizes of MCI patients should be used. Although depressive symptoms are one of the most prevalent neuropsychiatric symptoms in MCI and AD patients, other neuropsychiatric symptoms, e.g. apathy, should be studied in light of an early diagnosis of AD.

Conflict of interest

None

Description of author's roles

E. De Roeck conducted analyses, and wrote portions of the paper. I. Ponjaert-Kristoffersen supervised the execution of the study and contributed to the study's design. M. Bosmans wrote portions of the paper. P. P. De Deyn supervised the execution of the study. S. Engelborghs supervised the analysis, and interpretation of data and writing of this article. E. Dierckx designed the study, collected data, and supervised the analysis, and interpretation of data and writing of this article.

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