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Depressive Symptoms Are Not Associated with Predementia Cerebrospinal Fluid Amyloid Pathology

Cecilia Magdalena Eriksson[a, b, c] Bjørn-Eivind Kirsebom[d, e] Ragna Espenes[d, e] Nikias Siafarikas[a] Knut Waterloo[d, e] Arvid Rongve[f, g] Per Selnes[c, h, i] Dag Aarsland[c, j, k] Tormod Fladby[c, h, i] Erik Hessen[b, c]

[a]Department of Geriatric Psychiatry, Akershus University Hospital, Nordbyhagen, Norway; [b]Institute of Psychology, University of Oslo, Oslo, Norway; [c]Department of Neurology, Akershus University Hospital, Nordbyhagen, Norway; [d]Department of Neurology, University Hospital of North Norway, Tromsø, Norway; [e]Department of Psychology, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway; [f]Department of Research and Innovation, Helse Fonna, Haugesund, Norway; [g]Department of Clinical Medicine, University of Bergen, Bergen, Norway; [h]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway; [i]Faculty of Medicine, University of Oslo, Oslo, Norway; [j]Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway; [k]Institute of Psychiatry, Psychology and Neuroscience, King's College, SE5 8AF London, London, UK

Keywords

Depression · Alzheimer's disease · Subjective cognitive decline · Mild cognitive impairment · Cerebrospinal fluid biomarkers · Amyloid $A\beta_{42/40}$ ratio

Abstract

Introduction: Depressive symptoms are associated with Alzheimer's disease (AD), but their neurobiological and neuropsychological correlates remain poorly understood. We investigate if depressive symptoms are associated with amyloid (Aβ) pathology and cognition in predementia AD. ***Methods:*** We included subjective cognitive decline (SCD, n = 160) and mild cognitive impairment (MCI, n = 192) from the dementia disease initiation cohort. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS-15). Aβ pathology was determined using cerebrospinal fluid (CSF) $A\beta_{42/40}$ ratio. Associations between depressive symptoms and cognition were assessed with logistic regression. ***Results:*** Only the Aβ negative MCI group (MCI-Aβ–) was associated with depressive symptoms (odds ratio [OR] = 2.65, $p = 0.005$). Depressive symptoms were associated with worse memory in MCI-Aβ– (OR = 0.94, $p = 0.039$), but with better performance in MCI-Aβ+ (OR = 1.103, $p = 0.001$). ***Conclusion:*** Our results suggest that depressive symptoms in MCI are neither associated with Aβ pathology, nor AD-associated memory impairment. However, memory impairment in non-AD MCI may relate to depressive symptoms.

karger@karger.com
www.karger.com/dee

Correspondence to:
Cecilia Magdalena Eriksson, eriksson-magdalena@hotmail.com

Introduction

Depression and Alzheimer's disease (AD) are common and often co-occur in older adults. Both are major public health problems causing disability and impaired quality of life among patients and caregivers [1]. Prevalence's of depression in dementia due to AD have been reported ranging from 5 to 48% [2]. Some studies also find that depression is frequent at the proposed prodromal mild cognitive impairment (MCI) stage of AD [3]. Findings indicate that depressive symptoms may be a risk factor [4] or a prodromal facet of AD [5] and relate to an increased progression rate to dementia. Moreover, depressive symptoms and the experience of subjective cognitive decline (SCD) in cognitively normal individuals have been linked to independent risk of future MCI and dementia due to AD [6]. However, the role of depression and its neurobiological correlates on the AD continuum are still poorly understood. Associations of depressive symptoms to AD pathology, neuroinflammation and cerebrovascular lesions have been discussed, but findings are inconclusive. Depressive symptoms have shown associations to both more and fewer signs of AD pathology in PET and structural MRI studies [5, 7–10]. It has been suggested that depressive symptoms may be linked to risk of vascular dementia (VaD) rather than AD [11]. For cerebrospinal fluid (CSF) AD markers, no significant associations to depressive symptoms have been demonstrated in neither mild dementia [12, 13], MCI [14] nor SCD [13, 15]. Similarly, in a previous study from our group, based on a small cohort, increasing depressive symptoms were associated with less severe CSF AD-specific changes in patients with SCD and MCI [7].

Only a few studies have investigated associations between depressive symptoms and Aß-pathology in predementia cases and interpretation has been hampered by small sample sizes and older adults. Moreover, MCI may include patients with considerably varying underlying or comorbid diseases, including depression and vascular pathology [16]. To shed light on the putative role of depressive symptoms in predementia AD, we assessed the associations of depressive symptoms and Aß-pathology as determined by CSF $A\beta_{42/40}$ ratio in a large cross-sectional sample of participants (n = 352) with SCD (n = 160) and MCI (n = 192). In addition, we also measured the associations between depressive symptoms and neuropsychological performance in the presence or absence of Aß-pathology in both SCD and MCI. As far as we know no previous research have investigated the role of depression and neuropsychological performance with a more sensitive and specific marker ($A\beta_{42/40}$ ratio) in a younger cohort with SCD or MCI.

Methods

Subjects

A total of 352 participants recruited between 2013 and 2020 were included from the Norwegian national multicenter study dementia disease initiation. The sample comprised SCD (n = 160) and MCI (n = 192) cases. Inclusion criteria were ages 40–80 years and a native language of Norwegian, Swedish, or Danish. Exclusion criteria were brain trauma or disorder, including clinical stroke, dementia, severe psychiatric and/or somatic disease that may account for symptoms, intellectual disability or other development disorders. For a detailed description of the cohort, see Fladby et al. [17].

Assessment

MCI was classified according to the NIA-AA criteria, which require the presence of subjective cognitive impairment or decline in combination with lower performance than expected in one or more cognitive domains, yet preserved independence in functional ability and not fulfilling the criteria of dementia [18]. Participants were classified as SCD according to the SCD-I framework, which requires normal objective cognitive performance on standardized neuropsychological tests while experiencing a subjective decline in any cognitive domain [6]. The criterion for MCI was a score of 1.5 standard deviations or more below the normative mean on at least one of the cognitive domains included in the cognitive test battery: Delayed verbal recall (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] word list test) [19, 20], divided attention (Trail Making Test part B (TMT-B) [21, 22], language/verbal fluency (Controlled Oral Word Association Test (COWAT) [22, 23], and visuoperception (Visual Object and Space Perception Battery [VOSP] silhouettes) [24]. Symptoms of depression were assessed using a 15-item version of the Geriatric Depression scale (GDS-15). We used the recommended cut off ≥6 to indicate symptoms of depression [25].

Amyloid CSF Measurement and Study Design

CSF samples were obtained by lumbar puncture using a standardized protocol. Lumbar puncture was performed before noon, and CSF was collected in polypropylene tubes (Thermo Nunc) and centrifuged within 4 h at 2,000 *g* for 10 min at room temperature. The supernatant was transferred to new tubes and frozen at −80°C prior to analysis. All CSF samples were analyzed at the Clinical Molecular Biology (EpiGen), Medical Division, Akershus University Hospital, and samples from other sites were frozen before sending to this laboratory. The QuickPlex SQ 120 system from MesoScale Discovery (MSD, MD, USA) was used to measure $A\beta_{42}$ and $A\beta_{40}$ in a multiplex setup using V-plex Ab Peptide Panel 1 (6E10) kit (K15200E–1). The analyses were carried out according to the manufacturers' procedures. The concentration ratio of CSF $A\beta_{42}$ to $A\beta_{40}$ ($A\beta_{42/40}$ ratio) have

Table 1. Between-group comparisons of demographic, clinical and neuropsychological data

Variables	SCD groups			MCI groups		
	SCD Aβ– (*n* = 109)	SCD Aβ+ (*n* = 51)	*t*/U/χ^2, d/η^2, (*p* value)	MCI Aβ– (*n* = 93)	MCI Aβ+ (*n* = 99)	*t*/U/χ^2, d/η^2, (*p* value)
Age, mean (SD), years	60.0 (8.4)	69.0 (6.7)	*t* = 6.66, d = 1.29 (<**0.001**)	61.1 (66.8)	66.8 (7.8)	*t* = 4.51, d = 0.65 (<**0.001**)
Female, *n* (%)	57 (52.3)	26 (51.0)	χ^2 = 0.02, (n.s.)	51 (54.8)	47 (47.5)	χ^2 = 1.0, (n.s.)
Education years, mean (SD)	14.0 (2.9)	13.7 (3.1)	*t* = 0.60, (n.s.)	13.5 (3.1), 15,4 (3,6)	13.7 (3.4)	*t* = 0.40, (n.s.)
MMSE, median (IQR)	30 (1)	29 (2)	U = 2,216, η^2 = 0.03 (<**0.05**)	29 (3)	27 (3)	U = 2,221, η^2 = 0.21 **(<0.001)**
CERAD Recall T, mean (SD)	49.9 (8.7) *n* = 108	48.2 (11.2)	*t* = 1.02, (n.s.)	37.1 (10.8)	32.0 (9.5) *n* = 97	*t* = 3.56, d = 0.52 **(<0.001)**
TMT-B T, mean (SD)	50.7 (8.1)	48.4 (9.7) *n* = 50	*t* = 1.61, (n.s.)	41.2 (13.4) *n* = 89	39.0 (12.0) *n* = 92	*t* = 1.17, (n.s.)
COWAT T, mean (SD)	51.8 (9.0) *n* = 108	53.6 (9.7) *n* = 49	*t* = 1.11, (n.s.)	42.3 (9.3)	45.6 (10.0) *n* = 98	*t* = 2.36, d = 0.34 **(<0.05)**
VOSP T, mean (SD)	53.0 (10.5) *n* = 103	51.6 (8.0) *n* = 49	*t* = 0.79, (n.s.)	45.3 (11.6) *n* = 88	43.8 (11.3) *n* = 95	*t* = 0.89, (n.s.)
A/T pathology, *n* (%)						
A–/T–	103 (94.5)	–		81 (87.1)	–	
A–/T+	6 (5.5)	–		12 (12.9)	–	
A+T–	–	20 (39.2)		–	29 (29.3)	
A+T+	–	31 (60.8)		–	70 (70.7)	

SCD, subjective cognitive decline; MCI, mild cognitive impairment; Aβ+/–, presence or absence of amyloid pathology; *n*, sample size; SD, standard deviation; IQR, interquartile range; n.s., nonsignificant results; *t*, *t* test statistic, T, T-scores; U, Mann-Whitney U statistic; d, Cohen's d; A–, Aβ negative; A+, Aβ positive; T–, tau pathology negative; T+, tau pathology positive; –, no cases.

shown to improve diagnostic accuracy of Aβ plaque pathology as compared to using $A\beta_{42}$ alone [26] and was therefore used to determine Aβ plaque pathology. An optimum cut-off for $A\beta_{42/40}$ ratio at ≤0.077 was determined following using receiver operating curve analysis using visual read of [18F]-flutemetamol PET scans as the standard of truth [27]. SCD and MCI participants were assigned to four subgroups according to Aβ status: (1) SCD Aβ– (*n* = 109), (2) SCD Aβ+ (*n* = 51), (3) MCI Aβ– (*n* = 93), (4) MCI Aβ+ (*n* = 99). In addition, we tally cases with or without tau-tangle pathology as measured by CSF phosphorylated tau181 (Innotest, Fujirebio, Ghent, Belgium) (p-tau181 with an inhouse laboratory cut-off at ≥65). These are grouped as positive or negative for either amyloid and tau-tangle pathology yielding four different groupings: A–/T–, A–/T+, A+/T–, and A+/T+. See Table 1 for details.

Statistics

Statistical procedures were performed with R version 4.0.2 [28] and plots were created with the ggplot2 package [29]. First, descriptive comparisons between SCD Aβ+/– and MCI Aβ+/– groups were performed. Independent sample *t* tests were used for continuous variables with assumed normal distributions, whereas Mann-Whitney U tests were used for non-normal distributions. The binary variable "sex" was analyzed with a χ^2 test. Effect sizes for *t* tests (Cohen's d) and Mann-Whitney U (η^2) were reported for significant between-group differences ($p < 0.05$). Next, logistic regression was used to assess the likelihood of having symptoms of depression (GDS-15 ≥ 6) in the four different symptom groups specified in the method section (SCD Aβ–, SCD Aβ+, MCI Aβ–, and MCI Aβ+). Initially, the demographic variables age, sex and years of education were assessed in separate univariate regression models. Significant associations then passed to multivariate regression models. We also evaluated similar analyses for A/T groups; however, A/T group numbers were deemed to low within the SCD and MCI groups for reliable statistical analyses. Lastly, univariate logistic regression models were fitted to assess the association of cognitive domains (i.e., memory recall, executive functions, verbal fluency, and visuoperception) with symptoms of depression within Aβ+/– SCD and MCI groups.

Adjustment for multiple testing (Bonferroni-Holm) for the latter analyses was only considered if >1 cognitive tests were significantly associated with symptoms of depression within the pertinent symptom group (i.e., SCD/MCI Aβ+/–). Results from the logistic regression models are presented with odds ratios (ORs), 95% confidence intervals (CIs) and *p* values.

Table 2. Univariate and multivariate logistic regression models, associations between demographics and symptom groups to symptoms of depression (GDS ≥6)

	Univariate models		
	OR	95% CI	*p* value
Age	0.962	0.927–0.998	**0.038**
Years of education	0.907	0.810–1.009	0.078
Sex	0.938	0.483–1.819	0.849
SCD Aβ–	0.950	0.448–1.906	0.888
SCD Aβ+	0.282	0.045–0.965	0.088
MCI Aβ–	2.910	1.476–5.717	**0.002**
MCI Aβ+	0.507	0.200–1.125	0.118
	Multivariate model		
	OR	95% CI	*p* value
MCI Aβ–	2.651	1.327–5.265	**0.005**
Age	0.970	0.934–1.007	0.112

GDS, Geriatric Depression Scale; SCD, subjective cognitive decline; MCI, mild cognitive impairment; Aβ+/–, presence or absence of amyloid pathology; OR, odds ratio; CI, confidence interval. Significant results ($p < 0.05$) are highlighted in bold.

Results

Between-Group Comparisons in Cognition and Demographics

Between-group comparisons are detailed in Table 1. When comparing depressive symptoms in the SCD and MCI, independent of Aβ status, no significant differences were found between the groups ($p = 0.126$). SCD Aβ+ cases had slightly lower scores on MMSE as compared to SCD Aβ– ($p < 0.05$) but performed similarly on other cognitive measures. MCI Aβ+ cases performed worse on both the MMSE ($p < 0.001$) and CERAD recall tests as compared to MCI Aβ– ($p < 0.001$), were similar on the TMT-B and VOSP silhouettes test but performed slightly better than MCI Aβ– on the COWAT verbal fluency test ($p < 05$). Both the SCD Aβ+ ($p < 0.001$) and MCI Aβ+ ($p < 0.001$) groups were older than their respective Aβ– groups. No differences in education or sex distributions between groups were found.

Likelihood of Having Depressive Symptoms in SCD and MCI Groups

The logistic regression models are detailed in Table 2 and comparisons of frequencies of GDS ≥6 between groups are shown in Figure 1. The initial univariate logistic regression models showed that lower age (OR = 0.962, $p = 0.038$) was associated with depressive symptoms, and that only the MCI Aβ– group had significantly higher likelihood of having depressive symptoms (OR = 2.910, $p = 0.002$). A subsequent multivariate logistic regression model found that the MCI Aβ– was associated with symptoms of depression (OR = 2.651, $p = 0.005$), after adjusting for the effects of age (OR = 0.970, $p = 0.112$). Also, in the SCD group, depressive symptoms were more common in the Aβ– (11%) compared to the Aβ+ (3.9%), but the difference was not significant.

Associations between Cognitive Domains and Depressive Symptoms within SCD and MCI Groups

The logistic regression models pertaining to cognitive tests are detailed in Table 3 and illustrated in Figure 2. No associations between symptoms of depression and performance on the cognitive tests were demonstrated within the SCD Aβ– and SCD Aβ+ groups. Within the MCI Aβ– group, lower CERAD memory recall performance was associated with symptoms of depression (OR = 0.939, $p = 0.039$). In contrast, higher CERAD memory recall performance was associated with symptoms of depression within the MCI Aβ+ group (mean age: 64, SD: 7.37; mean education: 15.4, SD: 3.6) (OR = 1.103, $p = 0.001$). The MCI Aβ+ (mean age: 67, SD: 7.86; mean education, 13.6, SD: 3.41) group without depressive symptoms were older with less education.

Discussion

In this cross-sectional study, we investigated the relationship between depressive symptoms and Aβ pathology in SCD and MCI. We found that depressive symptoms were significantly higher in the MCI Aβ– group compared to the MCI Aβ+ but there was no significant association of Aβ in the SCD Aβ–/+ groups. Moreover, whereas poorer memory recall was associated with symptoms of depression in the MCI Aβ–, better memory recall was related to symptoms of depression in the MCI Aβ+ group.

While many have suggested pertinent roles of depression in the AD-continuum, the association between AD-pathology and depressive symptoms has been conflicting. Studies have suggested that clinical depression may have pertinent roles in the AD-continuum, as risk factor (depression early in life) [4], as part of the prodrome of AD [3, 5] and also in the dementia phase of AD [30]. However, most studies do not find relationships between AD pathology and depressive symptoms in preclinical, prodromal, or even mild dementia [31].

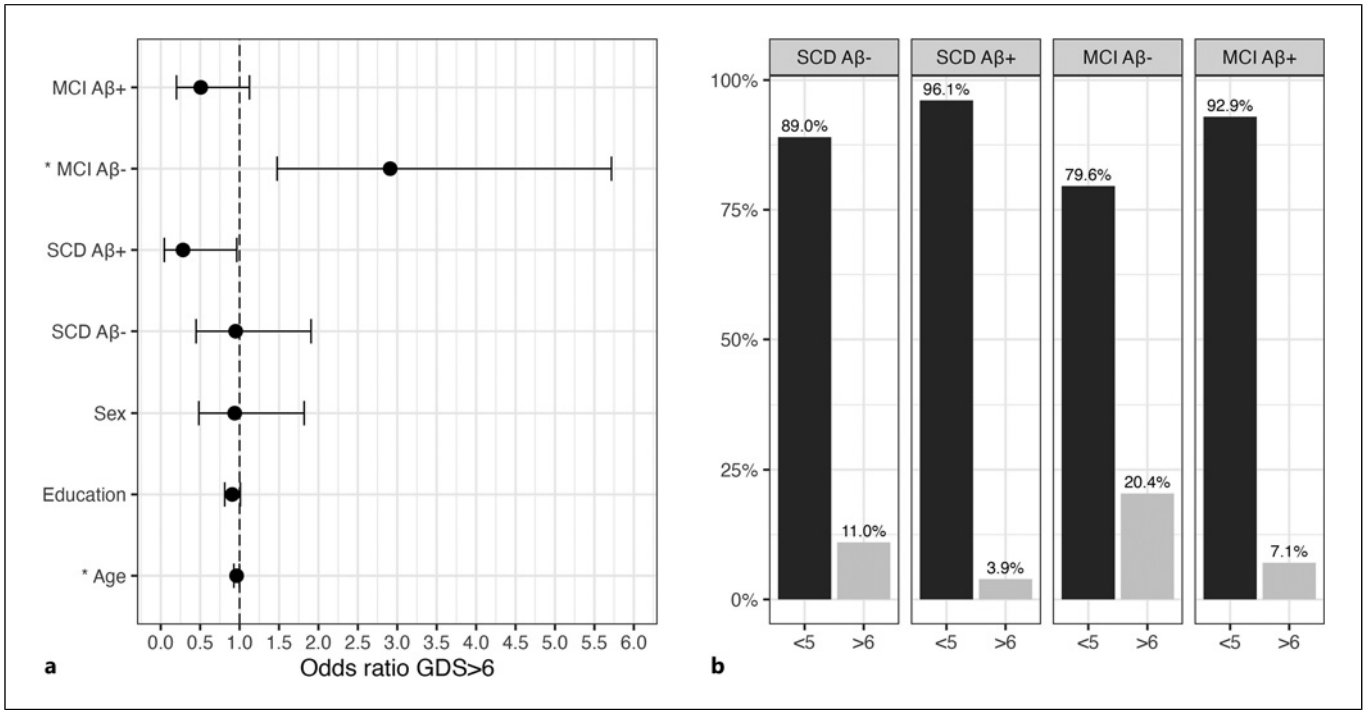

Fig. 1. Shows the associations between Aβ pathology and depressive symptoms in SCD and MCI cases. **a** Logistic regression odds ratios (ORs) (95% CI) associated with symptoms of depression (GDS-15 scores ≥6) * indicates variables included in the final multivariate analyses. Vertical dotted line as reference for OR = 1. **b** Relative percentages of GDS-15 scores ≥6 between groups.

Table 3. Univariate logistic regression models, associations with cognitive tests and symptoms of depression (GDS ≥6) within symptom groups

	SCD Aβ–	SCD Aβ+	MCI Aβ–	MCI Aβ+
CERAD word list recall T-scores	1.007 (0.936–1.082) $p = 0.842$	1.045 (0.919–1.082) $p = 0.536$	0.939 (0.877–0.992) **$p = 0.039$**	1.103 (1.026–1.195) **$p = 0.001$**
TMT-B T-scores	0.939 (0.856–1.017) $p = 0.146$	1.113 (0.954–1.337) $p = 0.193$	1.007 (0.967–1.051) $p = 0.741$	0.967 (0.905- 1.032) $p = 0.315$
COWAT T-scores	1.054 (0.988–1.129) $p = 0.111$	0.893 (0.701–1.054) $p = 0.249$	1.014 (0.960–1.072) $p = 0.600$	0.964 (0.885–1.042) $p = 0.369$
VOSP Silhouettes T-scores	1.057 (0.987–1.464) $p = 0.144$	1.168 (0.972–1.499) $p = 0.127$	1.021 (0.973–1.074) $p = 0.407$	1.023 (0.955–1.107) $p = 0.545$

Results are given as OR (95% CI) and *p* values. GDS, Geriatric Depression Scale; SCD, subjective cognitive decline; MCI, mild cognitive impairment; Aβ+/–, presence or absence of amyloid pathology; CERAD, consortium to establish a registry for Alzheimer's Disease; TMT-B, Trail Making Test part B; COWAT, controlled oral word association test; VOSP, visual object and space perception battery; OR, odds ratio; CI, confidence interval. Significant results ($p < 0.05$) are highlighted in bold.

Our study investigated general depressive symptoms as measured by the GDS-15, but more specific neuropsychiatric symptoms (NPSs) may be more common in the AD-continuum [32] and since depressive symptoms did not seem to be related to our MCI Aβ+ cases other NPS might have been reported more frequently in our

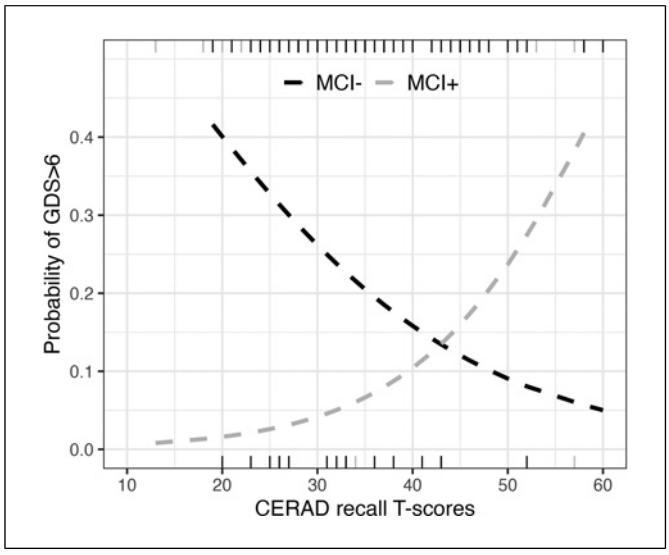

Fig. 2. Visual representation of the significant CERAD word list memory recall associations with probability for symptoms of depression (GDS >6) in MCI Aβ+ (gray dotted line) and mild MCI Aβ− (black dotted line), respectively.

group. According to Aalten, Verhey, Boziki, Bullock, Byrne, Camus, Caputo, Collins, De Deyn, and Elina [33] apathy is the most common and persistent symptom in AD. Apathy has also been associated with MCI and an increased risk of developing AD dementia. A longitudinal study found that amnestic MCI patients with apathy, not depression, had a 7-fold risk to progression to AD, indicating an important role in conversion [34]. Further, one small study found that increased apathy in MCI is associated with greater amyloid burden as measured by PiB PET [35].

Moreover, it has been reported that amyloid positive individuals may have a later age of onset of first major depressive episode and less total number of major depressive episodes than amyloid negative individuals [36]. However, in this present study we did not control for the age of onset thereby making it difficult to draw any conclusion of possible subtypes of late life depression. Also, at a more advanced stage of MCI Aβ+ some patients may become less aware of their impairments [37] and thereby reporting fewer depressive symptoms. Lack of awareness has also been negatively associated with high scores on the Geriatric Depression scale [38]. There might also be some difficulties for some patients in the MCI Aβ+ to report depressive symptoms due to problems of recall. In one study, poorer memory was associated with fewer self-reported depressive symptoms on the Beck Depression Scale (BDI).

While the MCI Aβ+ cases did not have significantly increased depressive symptoms, increased depressive symptoms in this group were associated with better memory performance. This may be related to the fact that these cases were both younger and more educated compared to MCI Aβ+ without depressive symptoms. Higher educational attainment has been related to increased cognitive reserve, were some individuals are more resilient to neuropathology and remain clinically intact for longer periods [39]. Associations of depressive symptoms with non-AD MCI (MCI Aβ−) pathology suggest that depressive symptoms may be driven by other than AD typical mechanisms. Although depression is primarily a mood disorder, cognitive complaints and impairments are frequently associated with depression and are referred to in the ICD 10 criteria of depression [40]. Indeed, we demonstrated that depressive symptoms in the MCI Aβ− group were associated with lower scores on delayed verbal recall. This is in accord with findings suggesting that individuals with MCI and depression perform poorer on memory tasks than nondepressed patients with MCI [41]. Moreover, studies also show that depressive symptoms may have an adverse effect on immediate recall of new information. Conradi, Ormel, and De Jonge [42] reported that cognitive problems were present in 85–94% during a depressive episode but lowered to 39–44% during remission. This suggests that remission of depressive symptoms may improve cognitive functions. Thus, some of the patients in our MCI Aß− group may show improvements in memory performance coinciding with remission.

Self-reported depressive symptoms may in some cases be better explained by other factors such as psychosocial or environmental factors or other biological factors. In the elderly, depressive symptoms may have many causes, for instance loss of relatives and friends, social isolation, bereavement, poor physical health, and low economic status [43].

Some studies have also indicated that depressive symptoms may be associated with vascular disease and VaD [44] and in particular in comparison with AD dementia [45, 46]. While some studies have shown that depressive symptoms may be linked to MCI [2, 3], less is known about the role of depressive symptoms in MCI due to cerebrovascular pathology as compared to MCI due to AD. Thus, some of the MCI Aβ− cases may comprise MCI due to VaD rather than AD.

We found no significant associations with depressive symptoms in neither Aβ+ nor Aβ− SCD patients. Importantly, this suggests that increased depressive

symptoms are not a primary characteristic of preclinical AD. These findings are generally in line with previous reports [7, 13], indicating that depressive symptoms may not be associated with AD pathology in neither preclinical nor prodromal stages. Moreover, a recent large multicohort study (that also includes cases from the DDI cohort) found that amyloid pathology was associated with lower frequency of depressive symptoms, particularly in memory clinic recruited SCD cases, and no association in cases recruited from community samples [15] suggesting that medical help-seeking SCD with symptoms of depression to a large degree may represent a non-AD condition. Indeed, we have previously reported that medical help seeking due to SCD in DDI seems to represent Aβ– cases with depressive symptoms, and nondepressed Aβ+ cases [47]. There are multifactorial causes of subjective cognitive difficulties and a high prevalence rate of such difficulties in the general population, ranging from 25 to 50% [48]. Even in memory clinic cohorts, SCD tends to be a benign condition with low association to pathological AD markers and low frequency of progression to dementia [49]. Evidence of amyloid plaque pathology in SCD has been shown as a predictor for future cognitive decline [50]. This suggests that biomarkers play an essential role in identifying patients with the highest risk of developing future MCI and dementia due to AD. This is of importance since the magnitude of depressive symptoms between SCD Aβ+ and SCD Aβ– did not differ in our study, and the presence or absence of depressive symptoms does not seem a viable marker of SCD due to preclinical AD. While both the MCI and SCD Aβ+ cases are more likely to develop future cognitive impairment and dementia due to AD than their Aβ– counterparts, the role of depressive symptoms in both SCD and MCI cases without amyloid pathology need to be further assessed through longitudinal studies. Of note, there may be role of depression in the context of vascular lesions in non-AD MCI that should be investigated. Moreover, while A/T groupings were deemed to low within in our SCD and MCI subjects for reliable statistical analyses. We also note that while more MCI cases (70.7%) had concurrent CSF determined amyloid and tau-tangle pathology (A+/T+), MCI diagnoses (60.8%) were also more frequent in the A+/T-group. This suggests that cognitive impairment is associated not only with increased CSF tau concentrations. Indeed, observed percentages of clinical impairment within these groups align with recent reports suggesting that CSF tau concentrations could point to AD-subtypes [51], rather than solely as a measure of disease severity. These AD-subtypes are reported to be associated with differing pathophysiological processes involving e.g., synaptic plasticity and innate immune activation [51, 52]. To our knowledge, degree of psychiatric symptoms, including depression, has not been assessed in relationship to these proposed subtypes. And while unfortunately not feasible in the present work, we aim to assess this question in the future when more cases have been recruited in the DDI cohort. The result from our study highlight that depressive symptoms may not be a defining feature of preclinical and prodromal AD, and the use of CSF biomarkers may guide clinicians in selecting appropriate therapeutic interventions such as antidepressant therapy in the case of clinical depression or cholinesterase inhibitors in the case of AD.

This study has some limitations. First, the cross-sectional design does not allow us to measure the potential relationship between baseline depressive symptoms and future changes in CSF AD markers or cognition. A future longitudinal study in our research group is planned to assess these relationships. This will add information about the potential clinical relevance of the present findings. Second, we assessed depressive symptoms with the GDS-15 scale. This is a self-report questionnaire where responses might be compromised by both cognitive decline and depressive symptoms. Third, we examined the relationship between depressive symptoms and CSF AD biomarkers in predementia cases, but not the relation between other NPSs that might be of importance [34].

Conclusion

This cross-sectional study found a significant association between symptoms of depression and MCI without Aβ pathology, but not with MCI with Aβ pathology. Longitudinally studies are needed to determine both the functional consequences and the biological mechanisms of depressive symptoms in persons with mild cognitive impairment.

Statement of Ethics

All subjects signed informed consent before taking part in the study and the regional medical research ethics committee, Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK) approved the study. The REK-approval number is 2013/150. All further study conduct was in line with the guidelines provided by the Helsinki Declaration of 1964, revised 2013 and the Norwegian Health and Research act.

Conflict of Interest Statement

Cecilia Magdalena Eriksson, Arvid Rongve, Nikias Siafarikas, Ragna Espenes, Erik Hessen, and Knut Waterloo have no disclosures. Bjørn-Eivind Kirsebom has served as a consultant for Biogen and on an advisory board for Eisai. Tormod Fladby has served as a consultant and on an advisory board for Biogen and Eisai. Per Selnes has served as a consultant for Roche. Dr. Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, Evonik, Roche Diagnostics, and GE Health, and served as paid consultant for H. Lundbeck, Eisai, Heptares, Mentis Cura, Eli Lilly, Cognetivity, Enterin, Acadia, EIP Pharma, and Biogen.

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Author Contributions

All authors, Cecilia Magdalena Eriksson, Bjørn-Eivind Kirsebom, Ragna Espenes, Nikias Siafarikas, Knut Waterloo, Arvid Rongve, Per Selnes, Dag Aarsland, Tormod Fladby, and Erik Hessen have given final approval of the version being published. C.M.E.: conceptualization, writing – original draft, investigation, and methodology. B.-E.K: formal analysis, visualization, and writing – review and editing. R.E., N.S., K.W., A.R., and P.S.: investigation, writing – review and editing. D.A. and T.F.: supervision, conceptualization, and writing – review and editing. E.H.: supervision, conceptualization, writing – review and editing, and methodology.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants.

Corresponding author [C.M.E.] can, upon reasonable request, have excess to data. The data are stored securely using protected databases.

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