

RESEARCH ARTICLE

Depressive symptoms and CSF Alzheimer's disease biomarkers in relation to clinical symptom onset of mild cognitive impairment

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Abstract

Introduction: We sought to examine whether depressive symptoms and level of Alzheimer's disease (AD) pathology are independently or interactively associated with the risk of progression to mild cognitive impairment (MCI).

Methods: The study included a total of 216 participants from the Biomarkers for Older Controls at Risk for Alzheimer's Disease study, a cohort of individuals who were cognitively normal at baseline (mean age = 57) and followed for more than 20 years (mean = 12.7 years), who had baseline Hamilton Depression Scale (HAM-D) scores and cerebrospinal fluid (CSF) amyloid beta ($A\beta$)₁₋₄₂, t-tau, and p-tau measures available.

Results: Cox regression demonstrated that baseline HAM-D and CSF AD biomarkers were both associated with time to onset of MCI. There was an interaction between HAM-D scores and markers of AD pathology, in which depression was associated with time of onset in participants with low levels of AD pathology (hazard ratio = 0.64; 95% confidence interval = 0.43–0.95; $P = .026$).

Discussion: The effect of depressive symptoms on progression to clinical symptoms of MCI may be most evident among individuals with low levels of AD pathology.

KEYWORDS

Alzheimer's disease, amyloid, cerebrospinal fluid, depression, mild behavioral impairment, mild cognitive impairment, p-tau, t-tau, vascular disease

1 | INTRODUCTION

Neuropsychiatric symptoms such as depression, anxiety, and apathy are increasingly recognized as risk factors for dementia and mild cognitive impairment (MCI), the early symptomatic phase of Alzheimer's disease (AD).¹ In particular, late-life subsyndromal depressive symptoms, as opposed to depressive symptoms earlier in life, have been associated with a higher risk of progression to MCI^{2,3} and dementia.^{4,5} Neu-

ropsychiatric symptoms even at low, subsyndromal severity, occurring in advance of, or in concert with MCI, have been referred to as mild behavioral impairment.⁶

Previous work directly examining the association between depressive symptoms and the two pathological hallmarks of AD, amyloid beta ($A\beta$) and tau, in cognitively normal subjects has produced mixed results, with some studies reporting an association between subsyndromal depressive symptoms and AD biomarkers,⁷⁻⁹ and others reporting

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mixed findings⁷ or no association.^{9,10} It also remains unclear whether depressive symptoms and AD pathology during the preclinical phase of AD interact with one another, or independently alter risk for subsequent cognitive decline, as few prospective studies have examined this issue. Gatchel et al. reported an association between increasing depressive symptoms and greater cognitive decline among older adults (mean age, 73.5 years) with high but not low amyloid, as measured by positron emission tomography (PET).¹¹ However, participants had a mean age of 73.5 at baseline, the impact of tau was not addressed, and the longitudinal follow-up was relatively limited (mean, 3.9 years). By comparison, a retrospective neuropathological study by Wilson et al. among individuals with a mean baseline age of 76.6 years found that while both markers of AD pathology and depressive symptoms were independently associated with cognitive decline, neuropathologic markers were not related to levels of depression over time, and depressive symptoms did not alter the relationship between neuropathology and longitudinal cognitive trajectories.^{12,13} However, AD-related pathological processes occur up to decades before the onset of cognitive symptoms,¹⁴ and these early changes may not be accounted for in these studies that included primarily older adults. Thus, a further understanding of early non-cognitive symptoms among middle-aged individuals is needed.

To our knowledge, no previous study has assessed the interaction among biomarkers of AD pathology, depressive symptoms at middle age, and the risk of progression from normal cognition to MCI. Our primary objective was to examine the combined effects of depression and AD pathology, as measured by cerebrospinal fluid (CSF) biomarkers of amyloid and tau, on risk of progression from normal cognition to onset of clinical symptoms of MCI. We also sought to examine the relationship between baseline depressive symptoms and the short-term rate of change in CSF AD biomarkers.

2 | METHODS

2.1 | Study design and participant selection

Data for these analyses were derived from the Biomarkers for Older Controls at Risk for Alzheimer's Disease (BIOCARD) study, which was designed to recruit and follow a cohort of cognitively normal individuals to identify variables that could predict the subsequent development of mild to moderate symptoms of AD. By design, approximately 75% of the participants had a first-degree relative with dementia due to AD.

The BIOCARD study was initiated at the National Institutes of Health (NIH) in 1995. Recruitment procedures and baseline evaluations have previously been described in detail.¹⁵ Briefly, recruitment was conducted by staff at the National Institutes of Mental Health Geriatric Psychiatry Branch, with enrollment occurring between 1995 and 2005. At their baseline visit, participants completed a comprehensive evaluation consisting of a physical, neurological, and psychiatric examination; neuropsychological testing; an electrocardiogram; and standard laboratory studies. Individuals were excluded from participation if they were cognitively impaired or had significant medical

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources. While depressive symptoms and high burden of Alzheimer's disease pathology have both been associated with cognitive decline, it is unknown whether the two factors independently or synergistically alter the risk of progression to mild cognitive impairment and dementia.
2. Interpretation: Our findings suggest that the effect of depressive symptoms on progression to mild cognitive impairment may be most evident among individuals with low levels of AD pathology, and that this association may occur through mechanisms outside of the amyloid and tau pathway.
3. Future directions: Further understanding of how mechanisms outside the amyloid and tau pathway relate to depressive symptoms and cognitive decline is needed.

HIGHLIGHTS

- Low-severity depressive symptoms among cognitively normal, primarily middle-aged individuals were associated with an increased risk of progression to clinical symptom onset of mild cognitive impairment in individuals who "low Alzheimer's disease (AD) pathology" at baseline.
- Higher baseline Hamilton Depression Scale was associated with more rapid rate of decline in cerebrospinal fluid amyloid beta ($A\beta$)₁₋₄₂ and increase in the ratio of CSF tau/ $A\beta$ ₁₋₄₂.
- Exploratory comparisons indicate that individuals with "low AD pathology" who progressed to mild cognitive impairment/dementia had higher rates of hypertension and higher white matter hyperintensity volumes relative to those who remained normal.
- The effect of depressive symptoms on progression to mild cognitive impairment may be most evident among individuals with low levels of AD pathology, and this association may occur through mechanisms outside of the amyloid and tau pathway.

problems such as severe cardiovascular disease (eg, atrial fibrillation), chronic neurologic disorders (eg, epilepsy, multiple sclerosis), or severe cerebrovascular disease (based on magnetic resonance imaging [MRI] scan).

After providing written informed consent, a total of 349 individuals were enrolled in the study. While the initial study was at the NIH, participants were administered a comprehensive neuropsychological

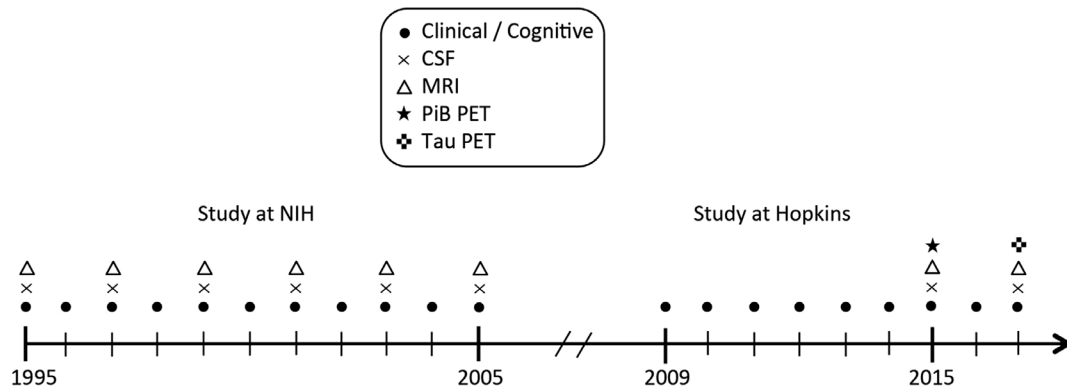


FIGURE 1 Schematic representation of study design. Shown are types of data collected each year for the Biomarkers for Older Controls at Risk for Alzheimer's Disease study between 1995 and 2017. The Hamilton Depression Scale (HAM-D) was collected as part of clinical/cognitive assessments conducted at the NIH. First-available HAM-D scores were used in these analyses. Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; NIH, National Institutes of Health; PiB PET, positron emission tomography using Pittsburgh compound B

battery annually. MRI scans, CSF samples, and blood specimens were obtained approximately every 2 years.

The study was stopped in 2005 for administrative reasons and resumed in 2009 at the Johns Hopkins School of Medicine where annual clinical and cognitive assessments and blood draws were reinstated. Additional biomarker collection was subsequently initiated (see Figure 1). The analyses presented here are based on data from 216 subjects who were cognitively normal at baseline, and had CSF available within 1 year of their baseline (ie, first available) depression score (mean [standard deviation (SD)] 35.4 [83.6] days between baseline depression score and most proximal CSF). The analyses included depression and CSF data that were collected while the study was at the NIH, and clinical follow-up data through November 2017. Subjects were excluded if: (1) they had not yet re-enrolled or withdrew after the study was resumed at Johns Hopkins in 2009 ($n = 28$); (2) the estimated age of onset of clinical symptoms was determined to be at or before baseline, based on the report of the subject and an informant ($n = 12$); (3) they were missing baseline Hamilton Depression Scale (HAM-D) scores ($n = 6$); (4) they did not have CSF within 1 year of their baseline HAM-D score ($n = 83$); and (5) subjects were missing follow-up diagnosis ($n = 4$).

2.2 | Clinical and cognitive assessments

A comprehensive neuropsychological battery covering all major cognitive domains, including memory, executive function, language, visuospatial ability, attention, speed of processing, and psychomotor speed was completed annually (see Albert et al.¹⁵ for the complete battery). A consensus diagnosis for each study visit was established by the staff of the BIOCARD Clinical Core at Johns Hopkins, prospectively starting in 2009, and retrospectively for subjects evaluated at the NIH.

Consensus diagnosis procedures have previously been described in detail elsewhere.¹⁵ Briefly, for each case a syndromic diagnosis is first established using (1) clinical data pertaining to the individual's medical, neurological, and psychiatric status; (2) reports of changes in cognition by the individual and by collateral sources (based on the Clinical

Dementia Rating scale [CDR]);¹⁶ and (3) evidence of cognitive decline based on longitudinal neuropsychological test performance and comparison to published norms. If a subject was deemed to be impaired, a decision about the likely etiology of the syndrome was made. More than one etiology could be endorsed for each subject (eg, AD and vascular disease). The consensus diagnosis procedures followed the diagnostic recommendations incorporated in the National Institute on Aging-Alzheimer's Association workgroup reports for the diagnosis of MCI¹⁷ and dementia due to AD.¹⁸ The clinical diagnosis was established without knowledge of CSF biomarker data.

A diagnosis of "impaired not MCI" was made for individuals with contrasting information between the CDR¹⁶ interview and the cognitive test scores. As in prior publications, these participants were included in the group of cognitively normal individuals (as they do not meet criteria for MCI) and excluded in sensitivity analyses.

Our main outcome variable was based on the estimated age of onset of clinical symptoms of MCI. Age of clinical symptom onset was established based primarily on reports of clinical symptoms reported during the CDR interview, conducted with both the subject and the collateral source. See section 2 of supporting information for additional details regarding diagnostic procedures.

2.3 | Depression assessments

Depressive symptomatology was measured at baseline with the HAM-D.¹⁹ The HAM-D is one of the most widely used scales for assessing depressive symptom severity.²⁰ It is a clinician-administered scale consisting of 21 items that measures somatic and affective symptoms of depression. Scores of 0 to 7 are generally considered to be normal.²¹ Staff conducting the consensus diagnosis were blinded to HAM-D scores of the participants. In these analyses, HAM-D scores were treated as a continuous measure and also dichotomized by median split, creating two groups: HAM-D >1 and HAM-D 0-1. Previous analyses using method of categorization have found that subjects with HAM-D >1 were more likely to progress to MCI within 7 years than those with HAM-D 0-1.²

2.4 | CSF assessments

CSF samples used in the present analyses were collected between 1995 and 2005 and were analyzed with a kit (xMAP-based AlzBio3; Innogenetics) run on a suspension array system (Bio-Plex 200; Bio-Rad). Each participant had all samples (run in triplicate) analyzed on the same plate (see section 3 in supporting information for details regarding the CSF assay). Additional details have been previously published elsewhere.²²

Using all eligible baseline CSF measures, a dichotomous AD biomarker indicator variable, “high AD pathology,” was created to reflect low $A\beta_{1-42}$ and high p-tau or low $A\beta_{1-42}$ and high t-tau, based on tertiles. In previous analyses using this method of classification, the comparable “high AD pathology” group has been associated with greater cognitive decline than groups with more normal levels of CSF AD biomarkers.²³ “Low” $A\beta_{1-42}$ was defined as $A\beta_{1-42}$ in the lower one third of the distribution, while “high” t-tau or p-tau was defined as the upper one third of the distribution. This results in a group similar to the “Stage 2” hypothetical preclinical AD group, defined by abnormal biomarkers for both amyloid and tau, which has been proposed to be one of three successive stages for categorizing cognitively normal individuals along the spectrum of preclinical AD.²³ Individuals who did not meet criteria for “high AD pathology” are referred to as “low AD pathology.” Note that the primary goal of these groupings was to identify “high” versus “low” pathology for statistical purposes, and not to categorize individuals as biomarker normal versus abnormal, which would require clinically validated cut-points.

2.5 | Vascular risk factors

Baseline vascular risk factors were established by medical records or by self-report. A composite vascular risk score was calculated by summing five dichotomous vascular risk factors (each coded as 0 = absent or 1 = recent/remote), as previously published:²⁴ hypertension, hypercholesterolemia, diabetes, current smoking (in the past 30 days), and obesity (body mass index > 30 kg/m²).

2.6 | White matter hyperintensity volume

Global baseline white matter hyperintensity (WMH) volume, a marker of small-vessel cerebrovascular disease, was quantified from axial fluid-attenuated inversion recovery (FLAIR) images obtained with a 1.5T GE MRI scanner (TR = 9002, TE = 157.5, field of view [FOV] = 256 × 256, thickness/gap = 5.0/0.0 mm, flip angle = 90, 28 slices) using a previously described automated method.²⁵

2.7 | Statistical analysis

Group differences in demographics and baseline characteristics were compared to t-tests for continuous variables and chi-square tests for dichotomous variables. Cox regression models (ie, proportional hazard models) were used to determine whether the relationship between

baseline HAM-D scores and time to clinical symptom onset was modified by the presence of AD pathology, as measured by the “high AD pathology” indicator variable. The models were designed to compare two groups, based on the diagnosis at their last visit: (1) participants who remained cognitively normal and (2) participants who were normal at baseline but were diagnosed with MCI or dementia at their last follow-up. The outcome variable was the time to MCI clinical symptom onset, for the participants who progressed to MCI or dementia. All models were adjusted for left truncation because individuals were required to be symptom free at baseline, and the last date of diagnosis was used as the censoring time. The predictors were HAM-D score (continuous or dichotomous), the “high AD pathology” indicator, and the HAM-D × “high AD pathology” interaction term, which was of primary interest. The model was run with the “high AD pathology” indicator defined by CSF $A\beta_{1-42}$ and t-tau, and then with the “high AD pathology” indicator defined by CSF $A\beta_{1-42}$ and p-tau. Models were adjusted for age, education, and sex.

Linear mixed effects regression models were used to examine whether baseline HAM-D scores were associated with rate of change in the CSF biomarkers over time. Separate models were run for each of the CSF biomarkers and their ratios, including $A\beta_{1-42}$, t-tau, p-tau, t-tau/ $A\beta_{1-42}$, and p-tau/ $A\beta_{1-42}$, which served as the dependent variables. The models were specified with a random intercept and slope. All CSF variables were standardized before model fitting; the ratios of t-tau/ $A\beta_{1-42}$, and p-tau/ $A\beta_{1-42}$ were log-transformed, to reduce skewness, before standardization. Predictors included baseline age, sex, baseline HAM-D score, time (in years), and the interaction of each predictor with time. In these models, we were primarily interested in the HAM-D score × time interaction, which tests whether the rate of change in a CSF biomarker over time differs as a function of baseline HAM-D scores.

To examine vascular factors as a possible mechanism for the association between depressive symptoms and risk of clinical symptom onset, we compared measures related to vascular risk in the subset of individuals with “low AD pathology.” For these analyses, comparisons were made with t-tests or Kruskal-Wallis rank tests for continuous variables and chi-square tests or Fisher’s exact tests for dichotomous variables, depending on the distribution of the variables.

All analyses were run in Stata (version 16.1). Significance was set at $P < .05$.

3 | RESULTS

Table 1 shows the baseline characteristics for participants included in the analysis. Of the 216 individuals with HAM-D and CSF data at baseline, 169 have remained cognitively normal (mean [SD] time from baseline HAM-D to last diagnosis, 14.3 [4.2] years), and 47 subsequently developed symptoms of MCI or dementia (mean [SD] time from baseline HAM-D to age of clinical symptom onset, 6.8 [4.1] years). Subjects who progressed to MCI/dementia were older, had higher CSF t-tau and p-tau levels, and lower CSF $A\beta_{1-42}$ levels at baseline compared to those who remained cognitively normal (all $P < .005$, Table 1).

TABLE 1 Baseline characteristics of all participants in the analyses and stratified by diagnostic outcomes

	All subjects in analyses (n = 216)	Remain normal (n = 169)	Progress to MCI/dementia (n = 47)	P-value
Age at baseline HAM-D, mean (SD)	57.0 (9.8)	55.2 (9.3)	63.4 (9.0)	<.001
Female sex, N (%)	86 (39.8%)	65 (38.5%)	21 (44.7%)	.44
Years of education, mean (SD)	17.2 (2.3)	17.2 (2.4)	17.4 (2.2)	.68
APOE 4, N (%)	76 (35.2%)	55 (32.5%)	21 (44.7%)	.123
White ethnicity, N (%)	210 (97.2%)	166 (98.2%)	44 (93.6%)	.089
MMSE score at baseline HAM-D, mean (SD)	29.5 (0.8)	29.6 (0.8)	29.5 (0.9)	.37
Baseline HAM-D score, mean (SD)	2.3 (3.0)	2.2 (3.0)	2.5 (3.0)	.56
Baseline HAM-D score > 1, N (%)	103 (47.7%)	78 (46.2%)	25 (53.2%)	.39
CSF A β_{1-42} , mean (SD), pg/mL	399.6 (98.9)	409.2 (91.8)	365.1 (115.6)	.007
CSF t-tau, mean (SD), pg/mL	68.2 (30.2)	64.3 (26.2)	82.5 (38.6)	<.001
CSF p-tau, mean (SD), pg/mL	35.3 (15.8)	33.7 (13.2)	41.0 (22.0)	.005
CSF t-tau/A β_{1-42} , mean (SD), pg/mL	0.19 (0.17)	0.17 (0.14)	0.28 (0.22)	<.001
CSF p-tau/A β_{1-42} , mean (SD), pg/mL	0.10 (0.11)	0.09 (0.10)	0.15 (0.14)	.003
"High AD pathology" defined by A β_{1-42} and tau, N (%)	27 (12.5)	12 (7.1)	15 (31.9)	<.001
"High AD pathology" defined by A β_{1-42} and p-tau, N (%)	27 (12.5)	12 (7.1)	15 (31.9)	<.001

P-values are for the comparisons between individuals who remain normal versus those who progress to MCI or dementia over the course of follow-up.

Abbreviations: A β_{1-42} , amyloid 1-42; AD, Alzheimer's disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; HAM-D, Hamilton Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; SD, standard deviation; t-tau, total tau

Descriptive statistics for participants who progressed to MCI/dementia, stratified by AD pathology category, are shown in Tables S3a and S3b in supporting information. Notably, individuals with "low AD pathology" had higher mean baseline HAM-D scores and higher proportion of baseline HAM-D score >1 (all $P \leq .03$) compared to those with "high AD pathology." Participants with "low AD pathology" were more likely to be diagnosed with MCI/dementia due to a non-AD or depressive etiology relative to those with "high AD pathology" (both $P = .01$) (Table S3a). Among individuals who progressed to MCI/dementia with "low AD pathology," there were no differences in baseline CSF biomarkers between those with a HAM-D score of 0-1 ($N = 11$) versus HAM-D > 1 ($N = 21$, Tables S4a and S4b in supporting information). All three baseline CSF biomarkers were significantly different between groups with low versus high AD pathology (all $P < .001$; Table S6 in supporting information).

3.1 | Relationship between HAM-D and CSF biomarkers of AD and time to onset of clinical symptoms of MCI

Our primary analyses examined the combined effects of depression and AD pathology, as measured by CSF biomarkers of amyloid and tau, on risk of progression from normal cognition to onset of clinical symptoms of MCI. Results of the Cox regression models, adjusted for age, sex, and education, are shown in Table 2. Kaplan-Meier plots for unadjusted models are shown in Figure 2 (AD pathology status defined by CSF A β_{1-42} and p-tau) and Figure S1 in supporting information

(AD pathology status defined by CSF A β_{1-42} and t-tau). When coded dichotomously, baseline HAM-D scores > 1 were associated with an increased risk of clinical symptom onset of MCI associated with an increased risk of clinical symptom onset of MCI (both $P < .05$), whereas this association did not reach significance when HAM-D scores were coded continuously (both $P < .11$). "High AD pathology" was associated with an increased risk of clinical symptom onset of MCI in all models (all $P < .001$). There was also an interaction between baseline HAM-D scores and the "high AD pathology" indicator (all $P < .03$), indicating that higher baseline HAM-D scores were significantly associated with increased risk of clinical symptom onset among individuals with "low AD pathology," which was not the case for individuals who had "high AD pathology." The pattern of results was identical when apolipoprotein E (APOE)4 was included as an additional model covariate (Table S7 in supporting information).

In line with our primary findings, in a sensitivity analysis that only included individuals with "low AD pathology," HAM-D scores were associated with risk of progression, despite the smaller sample size (Table 3). The pattern of results was similar when APOE4 was included as an additional covariate (Table S8 in supporting information). Within the "high AD pathology" group, the difference in risk of progression to MCI between HAM-D 0-1 and HAM-D >1 was not statistically significant in unadjusted models; however, the sample size of the group ($N = 27$) and number of outcomes ($N = 15$) were too small for reliable comparisons, particularly with covariates included.

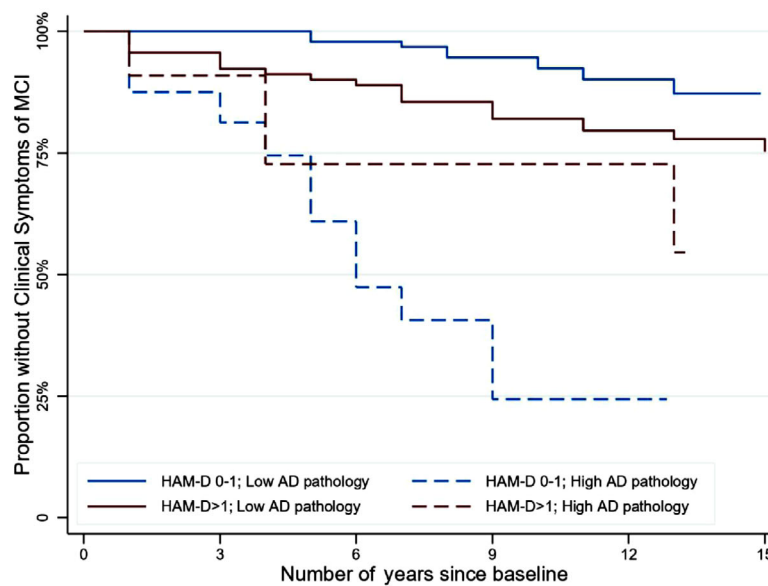
The pattern of results was similar when subjects with a diagnosis of "impaired not MCI" were excluded from the analyses, although in these models, both the dichotomous and continuous baseline HAM-D scores

TABLE 2 Hazard ratios for baseline HAM-D scores and “high AD pathology” indicators in relation to time to onset of clinical symptoms of MCI

Variable	AD pathology group defined by $A\beta_{1-42}$ and t-tau			AD pathology group defined by $A\beta_{1-42}$ and p-tau		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
HAM-D continuous	1.08	0.98-1.19	.101	1.09	0.99-1.19	.078
“High AD pathology” indicator	5.78	2.44-13.62	<.001	6.45	2.78-14.98	<.001
HAM-D continuous × “High AD pathology” indicator	0.64	0.43-0.95	.026	0.61	0.41-0.92	.017
HAM-D dichotomous (0-1 vs >1)	2.16	1.02-4.56	.043	2.20	1.05-4.64	.038
“High AD pathology” indicator	7.48	3.08-18.17	<.001	7.87	3.28-18.90	<.001
HAM-D dichotomous × “High AD pathology” indicator	0.11	0.03-0.43	.002	0.11	0.03-0.43	.002

All models adjusted for age, education, sex. N = 216.

Abbreviations: AD = Alzheimer’s Disease; CI, confidence interval; HAM-D, Hamilton Depression Scale; High AD pathology, evidence of CSF $A\beta_{1-42}$ levels in the lower one third of distribution of participants and having tau or p-tau levels in the upper one-third of the distribution; MCI, mild cognitive impairment.



	Number at risk					
	0	3	6	9	12	15
HAM-D 0-1; Low AD pathology	97	97	92	85	76	35
HAM-D 0-1; High AD pathology	16	14	9	5	3	1
HAM-D >1; Low AD pathology	92	86	80	73	65	30
HAM-D >1; High AD pathology	11	10	7	7	7	2

FIGURE 2 Kaplan-Meier plot of time to onset of clinical symptoms of mild cognitive impairment based on unadjusted Cox regression model. Unadjusted comparisons of the HAM-D 0-1 versus HAM-D >1 groups are not significant. The y-axis represents the proportion of subjects remaining without symptoms. Abbreviations: HAM-D, Hamilton depression scale, score 0-1 vs >1 based on median split; High AD pathology, high $A\beta_{1-42}$ and high p-tau, based on tertiles. “Low” $A\beta_{1-42}$ was defined as $A\beta_{1-42}$ in the lower one third of the distribution, while “high” p-tau was defined as the upper one third of the distribution; Low AD pathology, group consisting of individuals who did not meet criteria for “high AD pathology.” The pattern of results for “high AD pathology” defined by $A\beta_{1-42}$ in the lower one third of the distribution and t-tau in the upper one third of the distribution was similar, and can be found in Figure S1 in supporting information

TABLE 3 Hazard ratios for baseline HAM-D scores in relation to time to onset of clinical symptoms of MCI or dementia in individuals with “low AD pathology”

Variable	“Low AD pathology” defined by t-tau			“Low AD pathology” defined by p-tau		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
HAM-D continuous	1.09	0.99-1.21	.073	1.10	1.00-1.22	.051
HAM-D dichotomous (0-1 vs >1)	2.14	1.00-4.61	.051	2.15	1.00-4.61	.05

All models are adjusted for age, education, and sex. N = 189.

Abbreviations: AD, Alzheimer’s disease; CI, confidence interval; HAM-D = Hamilton Depression Scale; p-tau = phosphorylated tau; t-tau = total tau

TABLE 4 Relationship between baseline HAM-D scores and rate of change in CSF biomarkers, as indicated by the baseline HAM-D score x time interaction terms

CSF Measure	HAM-D continuous			HAM-D dichotomous		
	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value
A β ₁₋₄₂	-0.010	-0.02-0.0007	.034	-0.06	-0.11-0.003	.036
T-tau	0.0003	-0.007-0.008	.938	-0.004	-0.05-0.04	.868
P-tau	0.006	-0.007-0.02	.364	0.04	-0.03-0.11	.274
Log(T-tau/ A β ₁₋₄₂)	0.003	0.0005-0.0062	.017	0.011	-0.007-0.030	.228
Log(P-tau/ A β ₁₋₄₂)	0.005	-0.0002-0.011	.057	0.029	-0.003-0.061	.080

All models adjusted for age and sex and their interaction terms with time. N = 579 longitudinal data points from 216 subjects. The mean number of timepoints per subject was 2.7 (SD = 1.6).

Abbreviations: A β ₁₋₄₂ = amyloid 1-42; CI, confidence interval; CSF, cerebrospinal fluid; HAM-D = Hamilton depression scale; MCI, mild cognitive impairment; p-tau = phosphorylated tau; t-tau = total tau

were significantly associated with risk of progression (all $P < .05$) in the main models (section 4 in in supporting information).

individuals with HAM-D scores of 0–1 versus HAM-D scores > 1 (Tables S4a and 4b in supporting information).

3.2 | Relationship between baseline HAM-D and rate of change in CSF AD biomarkers

Of the 216 subjects included in the linear mixed effects regression analyses, 147 subjects (68%) had multiple (ie, 2+) CSF measures collected over time. Individuals with multiple CSF measurements on average had 3.47 (SD = 1.41) CSF measures, with a mean of 4.33 (SD = 2.64) years between first and last CSF measure. Higher baseline HAM-D scores were associated with a more rapid rate of decline in CSF A β ₁₋₄₂ (for continuous HAM-D scores, $P = .034$; for dichotomous HAM-D scores, $P = .036$). Continuous HAM-D scores were also associated with a more rapid increase in the ratio of CSF t-tau/A β ₁₋₄₂ ($P = .017$) over time, with a similar trend for CSF p-tau/A β ₁₋₄₂ ($P = .057$); however, these effects were not significant for the dichotomous baseline HAM-D models. Baseline HAM-D scores were not associated with rate of change in CSF t-tau or p-tau (Table 4).

3.3 | Exploratory analysis of measures related to vascular risk

Findings from our primary analysis suggested a stronger relationship between depressive symptoms and progression to clinical symptoms of MCI in individuals with “low AD pathology” (Tables 2 and 3). To examine vascular risk as a potential non-AD mechanism for the association between depressive symptoms and progression to MCI/dementia, exploratory comparisons of baseline vascular risk in individuals with “low AD pathology” were conducted. Within this subgroup, individuals who progressed to MCI/dementia had higher rates of hypertension and higher WMH volumes relative to those who remained normal (both $P < .003$; Table S5 in supporting information). Among individuals with “low AD pathology,” there were no differences in a composite vascular risk score, or in the presence of various vascular risk factors including hypertension, high cholesterol, diabetes, and smoking status between

4 | DISCUSSION

The primary finding in the present study was a significant interaction between baseline depressive symptoms and level of AD pathology, as measured by CSF, indicating that higher baseline HAM-D scores were significantly associated with increased risk of clinical symptom onset among individuals with “low AD pathology,” but not in “high AD pathology.” A possible explanation is that, among individuals with higher levels of AD pathology, the effects of depression on the risk of progression to MCI are overshadowed by the well-established risks incurred by the presence of a high burden of AD pathology.^{22,26} In individuals with low AD pathology, however, depressive symptoms may serve as an additional risk factor for cognitive symptom onset.

To our knowledge, this is the first study investigating the interaction between depressive symptoms and CSF AD biomarkers on risk of progression from normal cognition to the onset of clinical symptoms of MCI. Our findings extend previous studies that have examined the interaction between subsyndromal depressive symptoms and AD pathology on prospective or retrospective cognitive decline. Similar to Wilson et al., a retrospective neuropathological study of 582 subjects without cognitive impairment at baseline,¹² we found that depressive symptoms and AD neuropathology were associated with cognitive decline. However, they did not find any evidence of an interaction between depressive symptoms and neuropathology associated with dementia (including AD- and vascular-related pathology). In contrast, Gatchel et al., a longitudinal study of 276 participants followed for an average of 4.4 years found that increasing depressive symptoms were associated with worsening cognition in individuals with higher but not lower cortical amyloid burden, as measured by PET.¹¹ While the findings of Gatchel et al. point to an interaction between depression and AD biomarkers on cognition, it should be noted that their primary outcome was cognitive performance rather than clinical progression, which accounts for functional decline and clinically meaningful change. Additionally, only 6.5% of the cohort in Gatchel et al. progressed to MCI

or dementia, as opposed to 22% of the present cohort and 70.1% in Wilson et al. Our study also had a longer follow-up time, used different definitions for AD pathology, and examined depressive symptoms and AD pathology in mid-life as opposed to late-life. Because AD pathology accumulates with age,²⁷ differences in findings may be explained by the younger age of our cohort at the time of AD pathology assessment (mean age = 57 years), as opposed to 73.5 years in Gatchel et al. and 87.6 years in Wilson et al.

The specific mechanisms through which depressive symptoms affect clinical symptom onset are unclear. Previous work directly examining the association between depressive symptoms and the two pathological hallmarks of AD, A β and tau, in cognitively normal subjects has produced mixed results. While cross-sectional studies have not found evidence of an association between subsyndromal depressive symptoms and amyloid,⁷⁻⁹ one has reported an association between depressive symptoms and greater inferior temporal lobe tau on PET.⁹ In longitudinal studies, higher baseline amyloid burden on PET imaging was reported by Donovan et al.,¹⁰ while Babulal et al. found that higher ratios of CSF tau/A β ₁₋₄₂⁷ were associated with greater increase in depressive symptoms at 1 year follow-up. The findings in Babulal et al. were mixed, however, as the association was only observed between CSF tau/A β ₁₋₄₂ and depressive symptoms measured by the Profile of Mood States–Short Form (POMS-SF) depression subscale,²⁸ but not when depressive symptoms were measured by Geriatric Depression Scale (GDS).²⁹ These mixed findings may be explained by the more comprehensive nature of the POMS-SF over the GDS, which includes a wider range of symptoms. It may also be reflective of a weak association between CSF AD biomarkers and depressive symptoms in the setting of a relatively short period of follow-up, leading to limitations in replicating the results with different measures.

Though our finding that depressive symptom severity at baseline was associated with greater rate of change in CSF A β ₁₋₄₂ and CSF t-tau/A β ₁₋₄₂ over time (with marginal effects for CSF p-tau/A β ₁₋₄₂) is consistent with previously proposed hypotheses that the association between depressive symptoms and progression to MCI/dementia is mediated by AD pathology,^{30,31} our results do not demonstrate a mediation effect. To address this question directly, future studies examining longitudinal depressive symptoms and longitudinal AD biomarkers are needed. We therefore hesitate to draw any conclusions from this finding given the limitations of a having a relatively small sample size, the short period of CSF biomarker follow-up, and only evaluating baseline depression assessments. Additionally, in line with the hypothesis that the relationship between depressive symptoms and progression to MCI is not mediated by AD pathology, there was no evidence that depressive symptoms were associated with higher baseline levels of AD pathology in the exploratory analysis of “low AD pathology” participants who progressed to MCI/dementia. Taken together with our previous finding that depressive symptoms are associated with increased risk of MCI symptom onset within 7 years, but not after 7 years,² it is possible that in individuals with low AD pathology, the relationship between depression and cognitive decline is mediated through mechanisms outside of amyloid and tau.

For example, in our exploratory analysis, we found that among individuals who progress to MCI/dementia, those with “low AD pathology” had higher prevalence of non-AD pathologies or other etiologies contributing to their clinical impairment, relative to individuals with “high AD pathology.” Though depression itself can contribute to cognitive impairment, only 19% of the cohort with “low AD pathology” were diagnosed with MCI/dementia attributable to depression as a primary contributing etiology. With regards to vascular risk factors, we found that in individuals with “low AD pathology,” those who do progress to MCI/dementia had higher prevalence of hypertension and higher mean WMH volume. This is consistent with previous evidence that depression may be a risk factor and/or prodrome for vascular dementia,^{32,33} and that late-life depressive symptoms are associated with higher risk for vascular dementia.³⁴ More investigation into the association between depressive symptoms and vascular risk factors in the presence and absence of AD pathology on progression to MCI/dementia is needed.

Many older adults with cognitive impairment have non-AD pathologies.^{35,36} For example, there is considerable evidence that pathologies outside of the amyloid-tau pathway are seen in amnesic MCI and dementia in older patients. In community-based autopsy studies of older adults, the prevalence of mixed dementia pathologies ranges from 10% to 74%.³⁷ A *post mortem* autopsy study of individuals diagnosed with AD dementia based on clinical information found that only 41% of cases were attributable to AD pathology.³⁸ Many different etiologies outside of amyloid and tau have been proposed as the underlying mechanism for the association between depressive symptoms and dementia. Proposed mechanisms have included vascular factors, hypothalamic-pituitary-adrenal axis dysfunction, inflammation, neurotrophin deficiency, impairments in neurotransmitter systems, genetic factors,³⁰ and TDP-43 proteinopathy.³⁹

This study has several strengths, including the long duration of follow-up (mean = 12.7 years, maximum = 21.6 years). It includes a relatively large number of well-characterized, cognitively normal individuals who were primarily in middle age at baseline. These findings, however, should also be interpreted within the context of their limitations. The participants were primarily well-educated, White, and had very low severity of depressive symptoms at baseline, which limits its generalizability. Depressive symptoms were only examined at a single time point, and the impact of fluctuations of depressive symptoms cannot be ruled out. Although these analyses included a total of 216 participants, the number of individuals who progressed to MCI or dementia in each AD pathology subgroup was relatively low (high AD pathology $n = 15$, low AD pathology = 32); these results should therefore be replicated in future studies. The follow-up time for serial CSF measurements was short, with an average of 4.3 years. Additionally, CSF biomarkers are reflective of global changes in A β ₁₋₄₂ and tau, and brain-region-specific effects of amyloid and tau cannot be ruled out. Future studies using PET imaging examining the relationship between AD biomarkers and depressive symptoms across multiple time points may help address these limitations.

In summary, low-severity depressive symptoms among cognitively normal, primarily middle-aged individuals were associated with an

increased risk of progression to clinical symptom onset of MCI in individuals with low AD pathology. These results suggest that the effect of depression on progression to MCI may be most evident among individuals with low levels of AD pathology, and that this association may occur through mechanisms outside of the amyloid and tau pathway.

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CONFLICTS OF INTEREST

Dr. Marilyn Albert is an advisor to Eli Lilly. The following authors report no competing interests: Dr. Carol Chan, Dr. Anja Soldan, Dr. Corinne Pettigrew, Ms. Jiangxia Wang, Dr. Paul Rosenberg.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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