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Amyloid Pathologies Modulate the Associations of Minimal Depressive Symptoms With Cognitive Impairments in Older Adults Without Dementia

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ABSTRACT

BACKGROUND: The relationship between depression and Alzheimer's disease (AD) is complex and still not well understood. We aimed to examine the roles of the AD core pathologies in modulating the associations of minimal depressive symptoms (MDSs) with cognitive impairments.

METHODS: A total of 721 participants who had measures of cognition, depressive symptoms, and cerebrospinal fluid AD biomarkers were included from the CABLE (Chinese Alzheimer's Biomarker and LifestylE) study. Causal mediation analyses with 10,000 bootstrapped iterations were conducted to explore the mediation effects of AD pathologies on cognition. The ADNI (Alzheimer's Disease Neuroimaging Initiative) was used 1) to replicate the mediation effects and 2) to examine the longitudinal relationships of MDSs with amyloid pathology and incident AD risk.

RESULTS: In CABLE, MDSs were associated with poorer global cognition ($p = .006$) and higher amyloid burden as indicated by cerebrospinal fluid amyloid markers ($p < .0001$). The influence of MDSs on cognition was partially mediated by amyloid pathology (a maximum of 85%). The mediation effects were replicated in 725 elderly persons without dementia (age, mean ± SD = 73.5 ± 6.9 years; 301 female subjects [42%]) in ADNI, such that the mediation percentage varied from 10% to 30% for general cognition, memory, and executive functions. Longitudinal analyses revealed a bidirectional relationship between MDSs and amyloid pathology ($p = .01$). MDSs were associated with 83% increased risk of developing AD dementia (hazard ratio = 1.83, $p < .01$).

CONCLUSIONS: Overall, amyloid pathology might partially mediate and magnify the influences of MDSs on cognitive impairments and AD risk.

Keywords: Alzheimer's disease, Amyloid, Cerebrospinal fluid, Cognition, Minimal depressive symptoms, Tau

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Alzheimer's disease (AD) is pathologically characterized by aberrant amyloid deposition and tau phosphorylation, and it manifests clinically as cognitive and behavioral impairments. Neuropsychiatric symptoms (NPSs) in nondementia stage were associated with an increased risk of AD (1,2), suggesting that NPSs could be promising intervention targets for primary prevention. As common NPSs in older adults without dementia, depressive symptoms were proposed to be markers for prognostic utility of AD (3). Nonetheless, the causal relationship between depressive symptoms and AD has long been disputed. Recently, it was proposed that there were reverse causal relationships between depression and AD core biomarkers (4,5). It was shown that individuals with mild cognitive impairment (MCI) with cerebral amyloid-β (Aβ) burden had a higher risk of having depression compared with those without Aβ burden (5,6). However, another two cross-sectional studies reported no significant correlations between depression and Aβ pathology in nondementia samples (4,7). A longitudinal study by Donovan *et al.* found that higher Aβ burden was associated with increased anxious-depressive symptoms over time in older adults without cognitive impairment (8). Instead, Perin *et al.* reported that incident risk of depression was not increased in Aβ-positive cognitively normal adults (9). Elucidating the causal relationships of depressive symptoms with AD core pathology can not only provide clues for molecular pathways linking depression to AD but help clarify whether depressive symptoms could be a good target for intervention or prevention strategies to reduce AD risk.

In the natural course of depressive symptoms, individuals could experience a range of effects, from "minimal symptoms" to "subclinical symptoms" to major depression (10–12). Investigators have shown that subclinical or major depression could significantly elevate the risk of cognitive impairments or AD (13). However, how minimal depressive symptoms (MDSs), a more common but readily neglected phenomenon, could contribute to AD has not been a subject of much study. In addition, although depressive symptoms and amyloid burden were revealed to contribute to cognitive decline independently

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(14,15), it is still disputable whether amyloid could modulate the relationships of depressive symptoms with cognitive functions (14–16). Herein, we aimed 1) to explore the relationships of MDSs with cognition, cerebrospinal fluid (CSF) AD biomarkers, and AD risk; 2) to test whether the influences of MDS on cognition were mediated by AD core pathology; these analyses were conducted based on the CABLE (Chinese Alzheimer's Biomarker and LifestylE) study and ADNI (Alzheimer's Disease Neuroimaging Initiative); and 3) to examine the longitudinal associations between MDSs and amyloid pathology to reflect the causal relationship.

METHODS AND MATERIALS

Participants

A total of 721 adults without dementia who were northern Han Chinese were gathered from the CABLE study (17). Since 2017, CABLE has been a large-scale study aiming to explore AD's risk factors and biomarkers in the Han Chinese population. Participants were recruited from Qingdao Municipal Hospital, Shandong, China. Inclusion criteria comprised 1) self-reported Han Chinese in origin and 2) age between 40 and 90 years. The exclusion criteria were 1) major neurological disorders, such as infection, trauma, epilepsy, or multiple sclerosis; 2) major psychological disorders, such as major depressive disorder or general anxiety disorder; 3) malignant tumors; and 4) genetic disorders. All participants underwent neuropsychological examinations and biological sample (blood and CSF sample) collection by doctors with standardized training via a structured questionnaire and an electronic medical record system. The CABLE study was approved by the institutional review board of Qingdao Municipal Hospital, and written informed consent was obtained from all participants or their guardians in accordance with the Declaration of Helsinki.

To validate the findings from CABLE and to test the causal relationships, data from 932 adults without dementia were downloaded from the ADNI database (adni.loni.usc.edu). ADNI is designed to test clinical, imaging, genetic, and biochemical biomarkers of AD. The participants are adults aged 55 to 90 years. Detailed information can be found at http://www.adni-info.org (18–20). Each ADNI participant underwent an in-person interview for health and neuropsychological assessments at baseline and at annual follow-up (Figure S1). To exclude those diagnosed with depression, baseline diagnosis information in medical history and medication records was searched, with terms including "depression" and "depress." Finally, 207 participants who were found to have current depression at baseline were excluded, leaving 725 participants for analyses. The ADNI was approved by institutional review boards of all participating institutions, and written informed consent was obtained from all participants or their guardians according to the Declaration of Helsinki.

Measurement of Neuropsychiatric Symptoms

To assess the depressive symptoms of participants, the 17-item version of the Hamilton Depression Rating Scale and the Geriatric Depression Scale were employed in CABLE and ADNI, respectively. Participants were categorized according to their scores into a normal group (absence of symptoms) and an MDS group. MDSs were defined by a Hamilton Depression Rating Scale score ≥ 1 and ≤ 7 in CABLE or a Geriatric Depression Scale score ≥ 1 and ≤ 7 in ADNI, in accordance with previous publications (10–12). As for the evaluation of anxiety symptoms, Hamilton Anxiety Rating Scale was used in CABLE. The records about scores of Neuropsychiatric Inventory (Neuropsychiatric Inventory file) or Neuropsychiatric Inventory Questionnaire (Neuropsychiatric Inventory-Q file) were downloaded from ADNI. Minimal anxiety symptoms (MASs) were defined by a score ≥ 1 and < 7 on the Hamilton Anxiety Rating Scale in CABLE.

Cognitive Measures

In CABLE, a Chinese version of the Mini-Mental State Examination (MMSE) was used to assess the global cognitive function. In ADNI, cognitive functions were examined using multiple scales, including the global cognition by MMSE and the cognitive section of Alzheimer's Disease Assessment Scale and cognitive domains (executive and memory functions) by reviewing the neuropsychological batteries to identify items that could be considered indicators of these two domains (21,22).

Measurements of CSF AD Biomarkers

In CABLE, CSF was collected by lumbar puncture into 10-mL polypropylene tubes that were then sent to the lab within 2 hours. CSF were centrifuged at 2000*g* for 10 minutes. Before testing, the thaw/freezing cycle was controlled not to surpass 2 cycles. CSF levels of $A\beta_{1-42}$, $A\beta_{1-40}$, tau, and phosphorylated tau_{181} (p-tau_{181}) were determined with the enzyme-linked immunosorbent assay kit (Innotest; Fujirebio, Ghent, Belgium) on the microplate reader (Multiskan MK3; Thermo Fisher Scientific, Waltham, MA). The within-batch precision values were $<5\%$ for all proteins. The interbatch coefficients of variation were $< 15\%$ (9% for $A\beta_{1-42}$, 3.6% for $A\beta_{1-40}$, 12.2% for tau, and 10.9% p-tau_{181}). Aβ42 was expressed as ratio to Aβ40 to assess the pathologic species while accounting for individual differences in amyloid production. Total tau (t-tau) and p-tau_{181} were expressed in ratio to Aβ42 because they were reported as better predictors of cerebral Aβ deposition (23,24) and cognitive decline (25–28) than those expressed alone.

In ADNI, CSF procedural protocols have been described previously (29). In brief, CSF $A\beta_{1-42}$, tau, and p-tau_{181} concentrations (pg/mL) were measured using the INNO-BIA AlzBio3 immunoassay (Innogenetics-Fujirebio, Ghent, Belgium). The within-batch precision values were $<10\%$ (5.1%–7.8% for $A\beta_{1-42}$, 4.4%–9.8% for tau, and 5.1%–8.8% for p-tau_{181}). Meanwhile, CSF AD core biomarkers were analyzed by an evolving technology called electrochemiluminescence immunoassays (Elecsys; Roche Diagnostics, F. Hoffmann-La Roche, Basel, Switzerland) on a fully automated Elecsys cobas e 601 instrument (F. Hoffmann-La Roche) (provided in UPENNBIOMK9.csv file). These measurements are for explorative research use only. We used these data for sensitivity analyses to lower the measurement bias. The CSF biomarker statuses established by these cutoffs were proven to be highly concordant with positron emission tomography (PET) classification in ADNI (30). The participant had

assessments of these CSF biomarkers at baseline and at annual follow-up.

APOE ε4 Genotyping

DNA was extracted from overnight fasting blood samples with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and amplified by the polymerase chain reaction with forward primers 5′-ACGGCTGTCCAAGGAGCTG-3′ (rs429358) and 5′-CTCCGCGATGCCGATGAC-3′ (rs7412). The extracted DNA was separated and stored at −80°C until the *APOE* ε4 genotyping was performed via restriction fragment length polymorphism technology.

Statistical Analyses

R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 7.00 (GraphPad Software, San Diego, CA) were used for statistical analyses and figure preparation. A p value $< .05$ was considered significant except where specifically noted. We used χ^2 tests (for categorical variables) and Mann-Whitney U test (for continuous variables) to test the difference of baseline characteristics. The values of dependent variables in linear regression models were normalized using the "car" package in R software.

First, we tested the relationships of MDSs with cognition and cerebrospinal fluid (CSF) AD biomarkers. CABLE participants were categorized into four groups: normal, only MASs, only MDSs, and MDSs plus MASs. Linear regressions were used to explore the cross-sectional relationships of MDSs (independent variable) with CSF AD biomarkers and global cognition (continuous, dependent variables). Interaction analyses for sex and *APOE* ε4 status were performed to investigate whether strata effects existed ($p < .1$), in which cases stratified analyses were performed. Furthermore, the relationship between MDSs and incident probable AD was studied by calculating cumulative incidence by the Kaplan-Meier method. Hazard ratio with 95% confidence interval was estimated using the time-dependent Cox proportional hazards model. Individuals who did not develop AD or who were lost to follow-up were censored at the time of their last evaluation. The dependent measure was time from entry into the cohort to AD diagnosis. The "lm," "survival," "ggplot2," "ggpubr," "magrittr," and "survminer" packages in R version 3.5.1 software were used to conduct the above analyses.

Next, to examine whether the association between MDSs and cognition was mediated by AD pathology, linear regression models were fitted based on the methods proposed by Baron and Kenny (31). The first equation regressed the mediator (CSF AD biomarkers) on the independent variable (MDSs). The second equation regressed the dependent variable (cognitive score) on the independent variable. Considering the close relationship between cognitive score and clinical diagnosis (MCI vs. healthy control subjects [HC]), diagnosis was not included as a covariate in the analyses with MMSE as the dependent variable. The third equation regressed the dependent variable on both the independent variable and the mediator variable. Mediation effects were established if the following criteria were simultaneously reached: 1) MDSs were significantly related to CSF AD biomarkers; 2) MDSs were significantly related to cognitive measures; 3) CSF AD biomarkers were significantly related to cognitive measures; and 4) the association between MDSs and cognition was attenuated when CSF AD biomarkers (the mediator) were added in the regression model. Furthermore, the attenuation or indirect effect was estimated, with the significance determined using 10,000 bootstrapped iterations, where each path of the model was controlled for age, sex, education, and *APOE* ε4 status. The "lm," "mediate," and "car" packages in R version 3.5.1 software were used to perform the above analyses.

Finally, the linear mixed-effects models were used to depict the longitudinal relationship between MDSs and amyloid markers. Specifically, we separately treated amyloid deposition (Geriatric Depression Scale score as the dependent variable) and MDSs (CSF AD biomarkers as the dependent variable) as independent variables. Participants with CSF $A\beta_{1-42}$ concentration < 976.6 pg/mL as measured by Elecsys were considered A positive (A+) and otherwise A negative (A−). The CSF biomarker status established by the cutoff was proven to be highly concordant with PET classification in ADNI (30). The linear mixed-effects models had random intercepts and slopes for time and an unstructured covariance matrix for the random effects, and they included the interaction between time (continuous) and the dependent variable (A+ vs. A− or MDSs vs. normal) as a predictor. Covariates include age, sex, education, and *APOE* ε4 status in all analyses. The "nlme," "ggplot2," and "car" packages in R version 3.5.1 software were used to conduct the above analyses.

RESULTS

Characteristics of Participants

As for CABLE, a total of 721 individuals (505 HC and 216 MCI) free of dementia and major psychological diseases were included. The mean age of the study sample was 62.4 (±10.3) years, and 58.4% were female. Participants with MDSs tended to be male and *APOE* ε4 positive, and they had lower global cognition measures and higher burden of cerebral amyloid deposition (Table 1). As for ADNI, a total of 725 individuals without dementia (295 HC and 430 MCI) or depression were included. The study sample was older (mean age, 73.5 years) and had more educational years (mean, 16.1 years) than CABLE participants. Individuals with MDSs tended to be female and younger. Similarly, they also had lower cognitive scores and higher cerebral amyloid burden by CSF markers (Table 1).

Associations of MDSs With Cognitive Measures and CSF AD Biomarkers

In the CABLE sample, individuals with more depressive or anxiety symptoms had lower global cognitive measures and greater cerebral amyloid deposition, as indicated by lower levels of $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$, and higher ratios of p-tau/$A\beta_{1-42}$ and $tau_{181}/A\beta_{1-42}$ (Table S1). The associations remained significant after controlling for age, sex, education, *APOE* ε4 status, and cognitive score. No potential interaction effect due to sex or *APOE* ε4 status was found ($p > .1$).

Given that a significant positive correlation between depressive symptoms and anxiety symptoms exists ($p < 2.2 \times 10^{-16}$), we conducted secondary analyses that categorized the

Table 1. Characteristics of Participants in CABLE and ADNI

Characteristic	CABLE				ADNI[a]			
	Total	Normal	MDSs[a]	*p* Value[b]	Total	Normal	MDSs	*p* Value[b]
n	721	595	126	–	725	265	460	–
Age, Years, Mean ± SD	62.4 ± 10.3	62.2 ± 10.2	63.0 ± 10.7	.36	73.5 ± 6.9	74.2 ± 6.3	73.0 ± 7.2	.04
Sex, n_{Male}/n_{Female}	300/421	239/356	65/61	.02	289/436	150/115	139/321	<.0001
Education, Years, Mean ± SD	9.7 ± 4.4	9.7 ± 4.4	9.3 ± 4.5	.49	16.1 ± 2.7	16.3 ± 2.6	16.1 ± 2.8	.33
Positive *APOE* ε4 Carrier Status, *n* (%)	112 (15.4)	101 (17.0)	11 (7.9)	.01	301 (41.5)	97 (36.6%)	204 (44.3%)	.04
MMSE Score, Mean ± SD	27.2 ± 3.2	27.3 ± 3.0	26.4 ± 3.9	<.01	28.2 ± 1.8	28.5 ± 1.6	28.0 ± 1.9	.002
ADAS Score, Mean ± SD	–	–	–	–	13.4 ± 6.8	11.9 ± 6.5	14.3 ± 6.9	<.0001
MEM, Mean ± SD	–	–	–	–	0.52 ± 0.76	0.72 ± 0.77	0.40 ± 0.73	<.0001
EF, Mean ± SD	–	–	–	–	0.45 ± 0.85	0.63 ± 0.87	0.35 ± 0.82	<.0001
Depressive Symptoms[c]	0 (0–0)	0 (0–0)	2 (1–3)	<.0001	1.24 ± 1.32	0.00 ± 0.00	1.96 ± 1.16	<.0001
CSF AD Biomarkers and Ratios, Mean ± SD								
Aβ42	152.1 ± 61.5	157.6 ± 62.6	126.2 ± 48.6	<.0001	183.4 ± 53.9	191.3 ± 55.0	178.8 ± 52.8	.003
Aβ40	6187 ± 2550	6155 ± 2515	6338 ± 2716	.42	–	–	–	–
P-tau	37.6 ± 8.8	37.6 ± 9.0	37.4 ± 8.2	.72	36.4 ± 21.3	35.0 ± 19.7	37.2 ± 22.1	.24
Tau	172.2 ± 68.4	172.9 ± 69.1	168.5 ± 65.3	.69	82.2 ± 48.6	76.3 ± 40.3	85.6 ± 52.5	.06
Aβ42/Aβ40 ratio	0.028 ± 0.013	0.028 ± 0.012	0.024 ± 0.016	<.0001	–	–	–	–
P-tau/Aβ42 ratio	0.271 ± 0.091	0.261 ± 0.087	0.318 ± 0.095	<.0001	0.24 ± 0.19	0.46 ± 0.35	0.57 ± 0.48	<.01
Tau/Aβ42 ratio	1.230 ± 0.573	1.187 ± 0.547	1.434 ± 0.646	<.0001	0.53 ± 0.44	0.22 ± 0.17	0.25 ± 0.20	.04

ADAS, Alzheimer's Disease Assessment Scale; ADNI, Alzheimer's Disease Neuroimaging Initiative; CABLE, Chinese Alzheimer's Biomarker and Lifestyle Study; CSF, cerebrospinal fluid; EF, executive function; GDS, Geriatric Depression Scale; HAMD, Hamilton Depression Rating Scale; MDSs, minimal depressive symptoms; MEM, memory function; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau.

[a]MDSs was defined as 1 ≤ HAMD score ≤ 7 in CABLE and 1 ≤ GDS score ≤ 7 in ADNI.

[b]The significance of difference among groups was examined by the Mann-Whitney *U* test (for continuous variables) and Pearson's χ^2 test (for categorical variables).

[c]HAMD (median, 25% & 75% percentile) was used in CABLE and GDS (mean ± SD) was used in ADNI to evaluate the depressive symptoms.

total sample into four subgroups: normal group, MAS-only group, MDS-only group, and a group with both minimal depressive and anxiety symptoms. We found that the burden of cerebral amyloid deposition was significantly higher in the MDS and MDS+MAS groups, but not in the MAS group, compared with their HC counterparts (Figure 1A–D). Moreover, the association with MDSs remained significant after adjusting for MASs, whereas the association with minimal anxiety disappeared after adjusting for MDSs (Table S1). All the above findings suggested that MDSs, but not minimal anxiety, were an independent contributor to amyloid pathology. No significant association with CSF tau proteins was found (Table 2).

Causal Mediation Analyses

The above findings suggested that MDSs were not only a significant risk factor for cognitive impairment, but also a potential modulator of amyloid pathology. We next investigated whether MDSs contribute to cognitive impairments via modulating amyloid pathology. We found that the relationship between MDSs and global cognitive impairment was mediated by amyloid pathology, including Aβ42/Aβ40 (Figure 2A), p-tau/Aβ42 (Figure 2B), and tau/Aβ42 (Figure 2C). The effect was considered partial mediation with the proportion of mediation varying from 6.4% to 85%.

Replication in ADNI

The mediation effects were further replicated in ADNI. In the first regression, MDSs were significantly associated with higher levels of CSF Aβ42 (p = .016) and tau/Aβ42 (p = .012). In the second equation, MDSs showed a significant association with poorer global cognition measured by the Alzheimer's Disease Assessment Scale (p = .03). Finally, in the third equation, when the amyloid indicator and MDSs were simultaneously included in the model, the influences of depression on global cognition remained but were significantly attenuated. Overall, we found that the relationship between MDSs and global cognitive impairment was partially mediated by amyloid pathology, including Aβ42 (Figure 2D), and tau/Aβ42 (Figure 2E), but not p-tau/Aβ42 (Figure 2F). Besides, similar results were concluded for global cognition and cognitive domains, including memory and executive functions (Figure 3). The proportion of mediation varied from 1% to 26% (p < .05). The above associations did not change after further adding anxiety score as a covariate. Moreover, the analyses using Elecsys assay data further validated the above findings, such that the relationships between MDSs and cognitive measures, including global cognition (proportion = 10%–20%), memory function (proportion = 15%–25%), and executive function (proportion = 15%–25%), were mediated by amyloid pathologies, indicated by CSF levels of Aβ42 (Figure S2A), tau/Aβ42 (Figure S2B), and p-tau/Aβ42 (Figure S2C).

These findings further supported the hypothesis that amyloid pathology could at least partially modulate the influences of depressive symptoms on cognitive functions. To verify this "mediation effect" hypothesis, we conducted

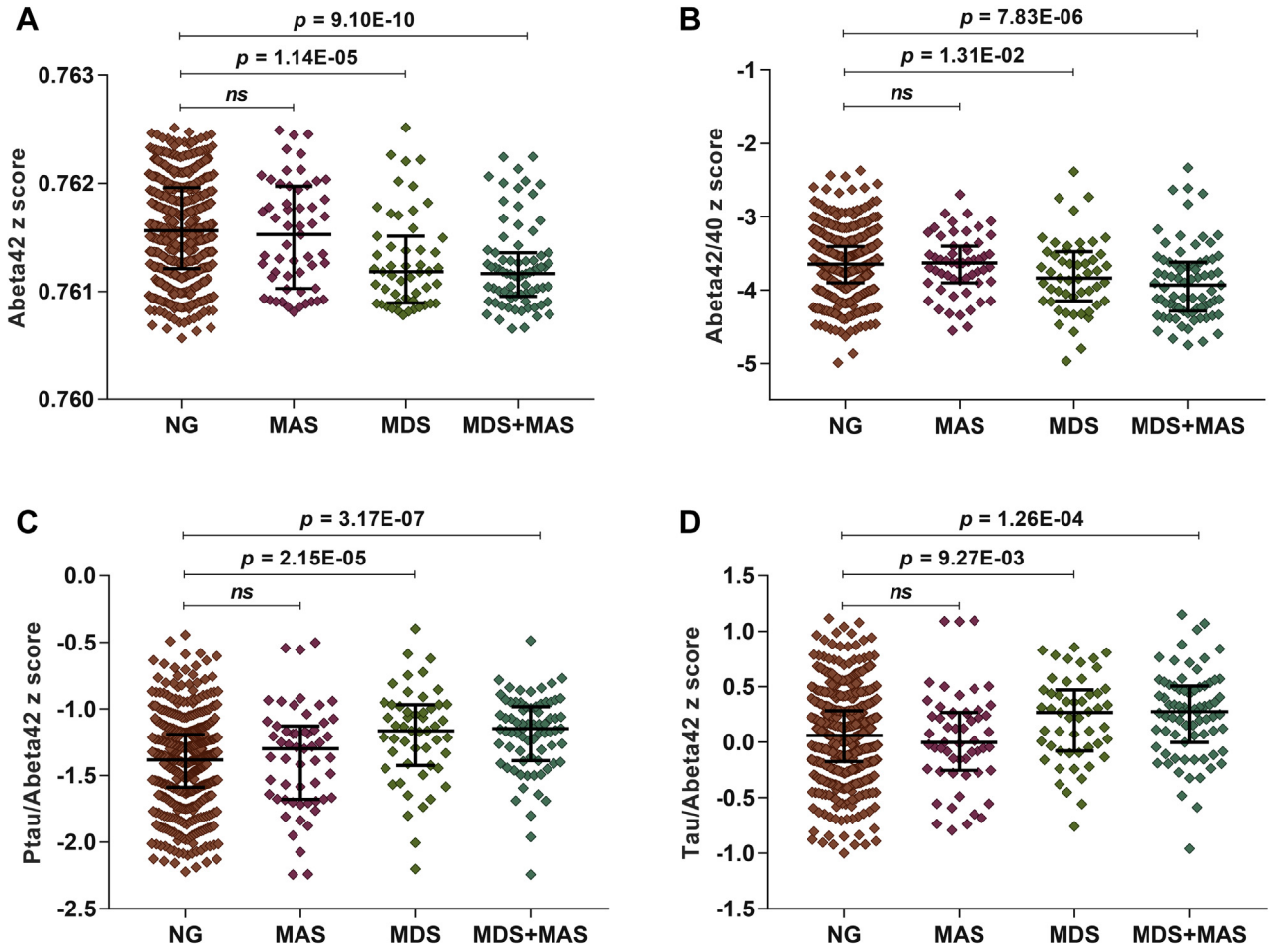

Figure 1. Associations of depression and anxiety symptoms with cerebrospinal fluid indicators of amyloid deposition. We categorized the total sample into four subgroups: normal group (NG), minimal depressive symptoms–only (MDS), minimal anxiety symptoms–only (MAS), and a combination of both MDS and MAS (MDS+MAS). We found that cerebrospinal fluid indicators of cerebral amyloid deposition, including **(A)** amyloid β 42 (Abeta42), **(B)** amyloid β 42/amyloid β 40 ratio (Abeta42/40), **(C)** phosphorylated tau/amyloid β 42 (Ptau/Abeta42) ratio, and **(D)** tau/amyloid β 42 (Tau/Abeta42) ratio, were significantly higher in the MDS and MDS+MAS groups, but not in the MAS group, compared with those of their normal counterparts. ns, nonsignificant.

subgroup analyses according to Aβ pathological status (A+ vs. A−). As expected, the influences of MDS on cognition were only significant or much stronger in the A+ group (Table S2).

Longitudinal Relationship Between MDSs and Amyloid Pathology

A total of 686 and 724 individuals were respectively included to explore the longitudinal relationship between MDSs and

Table 2. The Associations of Minimal Depressive and Anxiety Symptoms With CSF AD Biomarkers

Dependent Variable	*n*	Effect	Aβ42	P-tau	Tau	Aβ42/Aβ40	Tau/Aβ42	P-tau/Aβ42
MDSs Only	51	β	-2.93×10^{-4}	2.43×10^{-3}	-2.28×10^{-3}	-1.53×10^{-1}	1.41×10^{-1}	2.01×10^{-1}
		p Value	1.14×10^{-5}[a]	6.42×10^{-1}	5.67×10^{-1}	1.31×10^{-2}[a]	9.27×10^{-3}[a]	2.15×10^{-5}[a]
MASs Only	55	β	-4.87×10^{-5}	6.20×10^{-4}	-4.18×10^{-3}	-5.83×10^{-3}	-3.86×10^{-2}	2.40×10^{-2}
		p Value	4.48×10^{-1}	9.02×10^{-1}	2.78×10^{-1}	9.22×10^{-1}	4.62×10^{-1}	5.98×10^{-1}
MDSs Plus MASs	75	β	-3.48×10^{-4}	-3.98×10^{-3}	-3.20×10^{-3}	-2.34×10^{-1}	1.77×10^{-1}	2.05×10^{-1}
		p Value	9.10×10^{-10}[a]	3.68×10^{-1}	3.42×10^{-1}	7.83×10^{-6}[a]	1.26×10^{-4}[a]	3.17×10^{-7}[a]

All models were adjusted for age, sex, education, *APOE* ε4 status, and diagnosis at baseline.

Aβ, amyloid β; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MASs, minimal anxiety symptoms; MDSs, minimal depressive symptoms; p-tau, phosphorylated tau.

[a]Statistically significant.

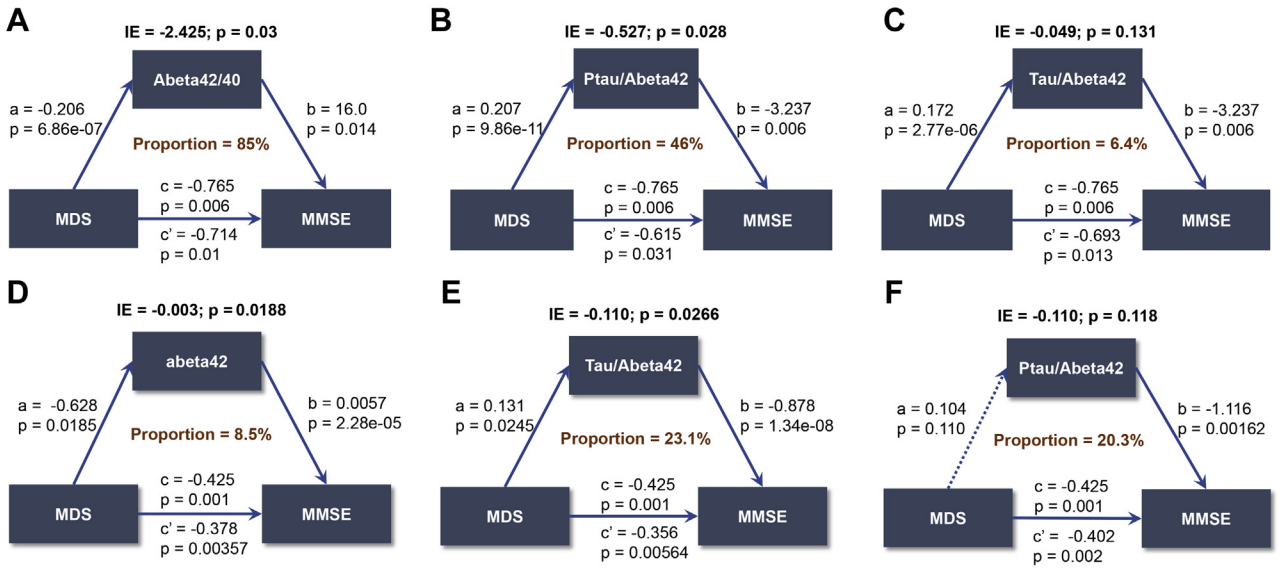

Figure 2. Mediation analyses with Mini-Mental State Examination (MMSE) as cognitive outcome. In CABLE (Chinese Alzheimer's Biomarker and Lifestyle Study), the relationship between minimal depressive symptoms (MDSs) and global cognitive impairment was mediated by amyloid pathology indicated by **(A)** amyloid β 42/amyloid β 40 ratio (Abeta42/40), **(B)** phosphorylated tau/amyloid β 42 (Ptau/Abeta42), and **(C)** tau/amyloid β 42 (Tau/Abeta42) ratios. The above findings were validated in ADNI (Alzheimer's Disease Neuroimaging Initiative), indicated by **(D)** amyloid β 42 (Abeta42) and **(E)** Tau/Abeta42 ratio rather than Ptau/Abeta42 **(F)**. IE, indirect effect.

amyloid pathology (Table S3). Compared with the A− group, individuals in the A+ group showed faster elevation of depressive symptoms (β = .08, SE = .03, interaction with time p = .006) (Figure 4A), after controlling for age, sex, education, *APOE* ε4 status, and clinical diagnosis. Interestingly, we also found that individuals with MDSs displayed faster elevation of CSF tau/Aβ42 levels (β = .018, SE = .008, interaction with time p = .010) (Figure 4B), after controlling for age, sex, education, *APOE* ε4 status, clinical diagnosis, and anxiety score.

MDSs and Incident AD Risk

In the cohort for incident AD dementia, 323 participants were included (follow-up duration: mean ± SD = 2.9 ± 2.2 years; maximum = 9 years; age, mean ± SD = 75.1 ± 6.9 years, 104 female subjects [32%]), among whom 120 participants (37%) developed probable AD dementia. Compared with normal participants, those with MDSs were associated with an average of 83% increased risk of developing AD dementia (hazard ratio = 1.83, 95% confidence interval = 1.18–2.83, p = .007). The significance was compromised after adjusting for age, sex, education, *APOE* ε4 status, and clinical diagnosis (MCI vs. HC) (hazard ratio = 1.52, 95% confidence interval = 0.97–2.39; p = .069) (Figure 4C).

DISCUSSION

The present study found that in adults without dementia 1) mild depressive symptoms could significantly elevate the risk of cognitive impairment and AD; 2) MDSs predicted greater cerebral amyloid burden; 3) the influence of MDSs on cognition was partially mediated by amyloid pathology; and 4) the causal relationship between depressive symptoms and amyloid pathology might be bidirectional. These findings consolidated the close relationships of depressive symptoms with amyloid pathology and cognition, supporting the hypothesis that affective dysregulation domains of mild behavioral impairment, as reflected by clusters of NPSs, represent early manifestations of preclinical AD (32,33).

Based on the above findings, it could also be reasonably inferred that amyloid pathology could modulate the relationship of depressive symptoms with cognition via at least two ways: mediation effects or magnifying effects. For mediation effects, MDSs lead to cognitive impairments by contributing to cerebral amyloid deposition. The mediation effects were replicated, but the percentage seemed different in two cohorts, possibly because of the difference in measuring AD biomarkers and depressive symptoms. For magnifying effects, the deleterious impacts on cognitive impairments could be magnified by a vicious cycle formed by MDSs and amyloid pathology. These effects will finally increase the risk of AD dementia (Figure 4D). Future studies are still warranted to elucidate the temporal relationship for depressive symptoms, amyloid abnormality in CSF, and amyloid deposition by PET.

Our results are consistent with recent findings from longitudinal cohort studies that linked depression to amyloid pathology in a population without dementia (7,8), in spite of some negative findings based on cross-sectional design (4,7). The Harvard Aging Brain Study enrolled 270 cognitively normal elderly individuals who had baseline amyloid Pittsburgh compound B PET measures and were assessed at follow-up for depressive or anxiety symptoms by the Geriatric Depression Scale. After a mean follow-up period of 3.8 years, it was found that higher amyloid burden at baseline predicted emerging depression-anxiety symptoms (8). Similarly, the Mayo Clinic Study of Aging recruited 1038 HC individuals who underwent Pittsburgh compound B PET scans and completed the Beck Depression Inventory-II and Beck Anxiety Inventory. It also observed an informative association between increased

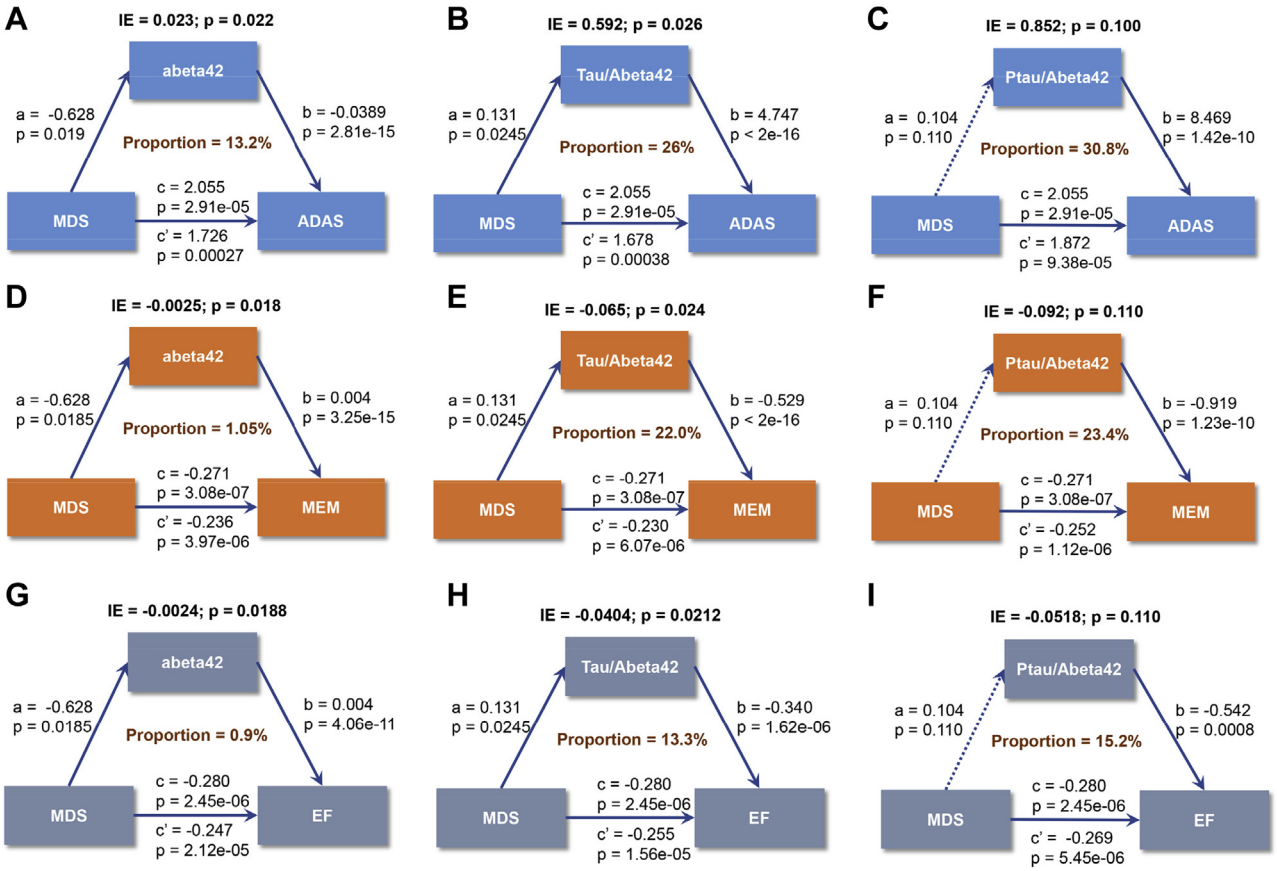

Figure 3. Mediation analyses with Alzheimer's Disease Assessment Scale (ADAS) and cognitive domains as cognitive outcomes. The relationship between minimal depressive symptoms (MDSs) and cognitive measures, including **(A–C)** global cognition measured by ADAS as well as **(D–F)** cognitive domain of memory (MEM) and **(G–I)** executive function (EF) was mediated by amyloid pathology, including **(A, D, G)** amyloid β 42 and **(B, E, H)** tau/amyloid β 42 (Tau/Abeta42) ratio, but not phosphorylated tau/amyloid β 42 (Ptau/Abeta42) ratio **(C, F, I)**. IE, indirect effect.

depression-anxiety scores and elevated cortical amyloid deposition (7). Additionally, Australian Imaging Biomarkers and Lifestyle study found that sex or *APOE* ε4 moderated the relationship between Aβ and the severity of depressive symptoms in cognitively normal older individuals (34), while we failed to identify potential interaction effects of these variables in the present study.

Moreover, it was found that the presence of depressive symptoms contributed to greater cognitive impairments in individuals who were A+ with MCI (35,36). The combination of depression diagnosis and AD biomarker accelerated the onset of driving problems in cognitively normal older adults (37). All these findings highlighted the synergetic roles of depressive symptoms and amyloid pathology, which was consistent with the above-mentioned hypothesis. In the present study, we not only revealed that MDSs contributed to cognitive dysfunction independent of amyloid burden but also found a mediation effect of amyloid pathology using two different cohorts. These are consistent with previous findings that amyloid burden, depressive symptoms (14,15,32), and their interaction effects (16) could contribute to cognitive decline.

We did not identify the effects of MDSs on cognitive functions that were mediated by tau proteins. However, this needs to be cautiously explained, especially considering that tau pathologies could lead to cognitive decline independent of amyloid status, and a recent tau-PET study reported that depression diagnosis was associated with tau but not amyloid pathology in cognitively normal individuals (38). The difference might be derived from the depression severity and biomarker measurement approach. In addition, we failed to reveal significant associations of amyloid burden in CSF with anxiety symptoms, which were indicated as early markers of AD pathology (39,40). The negative findings here might be explained by the fact that the severity of anxiety is minimal and depressive symptom was included as a covariate in the model.

It is also interesting to observe a higher percentage of MDSs in male subjects compared with female subjects in CABLE, which seemed contrary to the common belief that men are less prone to depression. We guessed that this finding might be due to higher exposure to social pressure or job stress of men in China, though we did not identify an interaction or subgroup effect stratified by sex. Some might also wonder whether the difference of age range in two datasets might influence the

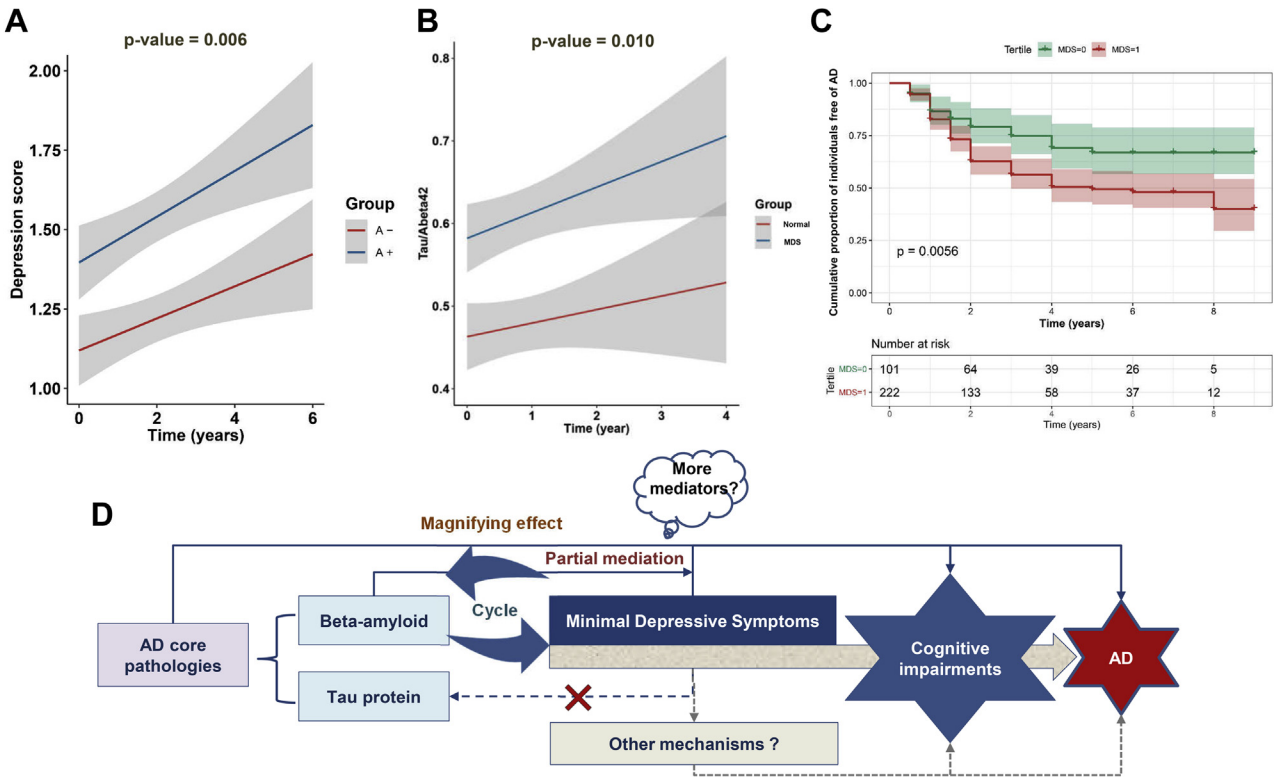

Figure 4. Longitudinal relationships between minimal depressive symptoms (MDSs), cerebrospinal fluid amyloid markers, and Alzheimer's disease (AD) risk. **(A)** Individuals in the amyloid β_{1-42}–positive (A+) group showed faster elevation of depressive symptoms, **(B)** and individuals with MDSs displayed faster elevation of cerebrospinal fluid tau/amyloid β 42 (Tau/Abeta42) levels. These findings implied a bidirectional relationship between depressive symptoms and amyloid pathology. Compared with normal participants, those with MDSs were associated with an average of 83% increased risk of developing AD dementia. **(C)** A schematic graph depicting associations among depression, AD core pathology, and cognition. Based on the present study, it could be reasonably inferred that the relationships between neuropsychiatric symptoms and amyloid pathology (but not tau protein) might be bidirectional in a closed loop. Amyloid pathology acted not only as an independent contributor to elevated depressive symptoms, but also as a key mediator for influences of depression on cognitive impairments. **(D)** The mediation effect is deemed partial and future studies are warranted to explore whether there are more mediators via which depression contributed to AD. A−, amyloid β_{1-42}–negative group.

results. To avoid the confounding bias due to age, all analyses were controlled for age and still we did not identify any interaction effects of age in either cohort.

The mechanisms by which depression was involved in regulating amyloid pathology are still unclear. Possible pathways might include a dysfunctional hypothalamic-pituitary-adrenal axis (41), an altered GABA (gamma-aminobutyric acid) system (42), increased neuroinflammatory cytokines (43), or disordered brain-derived neurotrophic factor (41), all of which were shared in impaired conditions observed in both depression and AD (41,44). The roles of these pathways or genetic signals (45) in mediating influences of MDSs on amyloid pathology warrant further investigation because they are potential targets of early intervention to prevent AD.

There are limitations in this study. First, the generalizability of our conclusions might be restricted by the sources of the study populations of CABLE and ADNI, which recruited participants from hospitals and volunteers, respectively. More large-scale community-based longitudinal studies are warranted to validate these associations. Second, the studied samples were restricted to those with the mildest symptoms of depression. The effect size of depressive symptoms might be underestimated given that the severity of the condition was low. Third, we used CSF biomarkers of amyloid deposition but not PET imaging in the cross-sectional analyses, which might introduce some bias. Instead, we used three different CSF biomarker ratios in CABLE. Fourth, both HC and MCI were included in the present analyses to maximize the sample size, but this, however, might introduce bias owing to population heterogeneity. Fifth, the depressive scores measured by scales only reflected the short-term condition around baseline and cannot represent the situation during the follow-up. The natural history of depression, i.e., age-of-onset, exposure duration, and confounding effects from other components of mild behavioral impairment, should be considered in future studies. Finally, the MMSE that was used to indicate the general cognition in CABLE was a relatively crude scale. We instead replicated the primary findings using more comprehensive cognitive scales in ADNI.

To sum up, the present study indicated that amyloid pathology acted not only as an independent contributor to elevated depressive symptoms but also as a key mediator for the influences of MDSs on cognitive impairments and AD risk. These findings support the hypothesis that emerging MDSs

represent an early manifestation of preclinical AD and could be used to help define high-risk population who are suitable for early prevention of the disease.

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The replication and longitudinal data used herein were accessed from the ADNI database (adni.loni.usc.edu), for which the investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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