Journal of Affective Disorders 280 (2021) 77–84

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Associations of the Rate of Change in Geriatric Depression Scale with Amyloid and Cerebral Glucose Metabolism in Cognitively Normal Older Adults: A Longitudinal Study

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ARTICLE INFO

Keywords:
Geriatric Depression Scale
Alzheimer's disease
amyloid
tau
cerebral glucose metabolism

ABSTRACT

Background: Depression is considered a psychological risk factor for Alzheimer's disease (AD). We sought to examine the differential associations of depression severity with cognitive decline, clinical progression to mild cognitive impairment (MCI) or AD, and neuroimaging markers of AD in cognitively normal older adults.

Methods: A total of 522 cognitively normal (CN) participants who underwent assessments for depression (longitudinal geriatric depression scale [GDS]) and cognitive assessments were included from the Alzheimer Disease Neuroimaging Initiative (ADNI) cohort. The cross-sectional and longitudinal associations of the rate of change in GDS with amyloid-β (Aβ)-positron emission tomography (PET), tau-PET, and 18F-fluorodeoxyglucose (FDG)-PET were explored. Kaplan-Meier survival curves of clinical progression and Aβ accumulation were plotted based on mean annual changes in GDS. Mediation analyses were utilized to explore the mediation effects of AD markers.

Results: Higher rate of increase in GDS was associated with faster cognitive decline and higher risk of progression to MCI or AD. Moreover, the rate of change in GDS was significantly associated with Aβ accumulation and cerebral glucose metabolism. The influences of the rate of change in GDS on cognition and clinical progression were partially mediated by Aβ accumulation and cerebral glucose metabolism.

Limitations: GDS is a self-reported questionnaire and not the same as a clinical diagnosis of depression.

Conclusions: The cognitive and clinical consequences of changes in depressive symptoms partly stem from Aβ accumulation and cerebral glucose metabolism, which increases our understanding of how depressive symptoms may increase vulnerability to dementia.

Introduction

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder and the most common cause of dementia (Hodson, 2018). The cognitive impairment might be present decades before AD onset. The accumulation of amyloid-β (Aβ) and tau may occured in the preclinical stage of AD (van der Kant et al., 2020). The term "preclinical" was felt to encompass this AD stage best. Secondary prevention of AD (preventive interventions targeting at-risk individuals) is clinically relevant in the absence of effective treatments. In previous studies, depression was reported as a potential risk indicator of dementia and AD (Geda et al., 2014; Kivipelto et al., 2018). Depression symptoms can predict incident mild cognitive impairment (MCI) in cognitively normal (CN) persons in several population-based cohort studies, which had a similar or greater

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[#] The longitudinal data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI 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.

https://doi.org/10.1016/j.jad.2020.10.078
Received 14 July 2020; Received in revised form 9 September 2020; Accepted 31 October 2020
Available online 5 November 2020

predictive ability compared with structural Magnetic Resonance Imaging (MRI) and genetic methods (Donovan et al., 2014; Geda et al., 2014; Steenland et al., 2012). The roles of depressive symptoms may differ across time and disease stage, and exploring the differential mechanisms may contribute to the accurate classification and treatment of individuals at risk for AD. Previous studies have established that positron emission tomography (PET)-based molecular (e.g., Aβ and tau) imaging is a valid in vivo surrogate for AD pathology (Clark et al., 2012; Fleisher et al., 2011; Ikonomovic et al., 2008; Jack et al., 2018; Josephs et al., 2016; Seo et al., 2017). PET-based assessment of the spatiotemporal progression of AD pathology (Aβ and tau) has revealed consistent patterns across sporadic AD patients (van der Kant et al., 2020). Several clinical imaging cohort studies found that higher baseline Aβ was associated with worsening depressive symptoms over time (Babulal et al., 2016; Donovan et al., 2018; Harrington et al., 2017). In major depressive disorder, the impaired cerebral glucose metabolism (cingulate gyrus and superior frontal gyrus) of ^{18}F-fluorodeoxyglucose (FDG) has also been reported (Wei et al., 2016). PET imaging has great potential to serve as a biomarker to identify individuals with high risk of AD (Jack et al., 2018). In order to improve secondary prevention of AD, it is necessary to perform long-term monitoring of depressive symptoms and explore the trajectories of AD-related neuroimaging markers. In this study, we sought to evaluate the cross-sectional and longitudinal associations of the rate of change in the geriatric depression scale (GDS) with cognitive function and neuroimaging markers of AD in cognitively normal older adults. We also sought to explore whether the Aβ pathology, tau pathology, and cerebral glucose metabolism mediated the associations between the rate of change in GDS and cognition and clinical progression to MCI or AD. Based on previous studies, we hypothesized that the cognitive and clinical consequences of changes in depressive symptoms would stem from AD pathologies and cerebral glucose metabolism.

Methods

Subjects

A total of 522 cognitively normal (CN) participants (mean ± SD age, 73.6 ± 5.98 years) from Alzheimer Disease Neuroimaging Initiative (ADNI)- 1, ADNI-2, and ADNI-GO were included in the present study. All participants had no prior psychiatric history. They underwent assessments of depressive symptoms at least two times. The specific ADNI diagnostic criteria for distinguishing CN, MCI, and AD participants were summarized in Supplementary Table 4 (Petersen et al., 2010; Thomas et al., 2019).

Measurement of neuropsychiatric symptoms

The 15-item Geriatric Depression Scale (GDS-15) was used to assess depressive symptoms in participants. A higher score indicates an elevated level of depressive symptoms, and score ≥ 6 is the cutoff for clinically significant depression. During the screening process, all participants scored below the cutoff for clinically significant depression in the follow-up period (4.21 ± 2.67 years). Neuropsychiatric Inventory Questionnaire (NPI-Q) was used to assess anxiety symptoms (score 1 on anxiety domain) at baseline.

Cognitive measures

Cognitive measures in our study were ADNI memory (ADNI-MEM) and ADNI executive function (ADNI-EF). Memory and executive functions were reported useful for the detection of cognitive decline in older adults who have depressive symptoms (Shimada et al., 2014). The ADNI-MEM was developed from the Rey Auditory Verbal Learning Test, Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), Logical Memory Test, and Mini-Mental State Examination (MMSE) (Crane et al., 2012). ADNI-EF consists of Category Fluency-animals, Category Fluency-vegetables, Trail-Making Test parts A and B, Digit Span Backwards, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution, and 5 Clock Drawing items (circle, symbol, numbers, hands, time) (Gibbons et al., 2012).

Clinical disease progression

All participants were classified into either stable group or group of clinical disease progression (cognitive impairment). Participants were designated as having clinical disease progression if their clinical classification changed (CN participants converted to MCI or AD at follow-up). If the above criteria have not been met at follow-up, participants were deemed stable (Jack et al., 2004).

APOE 4 genotyping

Polymerase chain reaction (PCR) amplification, Hhal restriction enzyme digestion, and standard gel resolution and visualization processes were used to carry out *APOE* genotyping in ADNI-1 (Hixson and Vernier, 1990; Reymer et al., 1995). LGC Genomics (Beverly, MA, USA) and Prevention Genetics (Marshfield, WI, USA) were used to carry out *APOE* genotyping in ADNI-2 and ADNI-GO (Hawkins et al., 2002; Myakishev et al., 2001). Quality-controlled genotyping data were obtained from the ADNI database (http://adni.loni.usc.edu). Participants were classified as *APOE ε4* non-carriers (0), carriers of one *APOE ε4* allele (1), and carriers of two *APOE ε4* alleles (2).

PET imaging

University of California (UC) Berkeley datasets for PET imaging (18F-AV45 amyloid-PET, representing the Aβ deposition; 18F-AV1451 tau-PET, representing the tau deposition; 18F-fluorodeoxyglucose (FDG)-PET, representing the cerebral glucose metabolism) were downloaded from LONI (http://adni.loni.usc.edu). Summary 18F-AV45 cortical standard uptake volume ratios (SUVR) (normalized by composite reference regions: whole cerebellum, brainstem/pons, and eroded subcortical white matter) were used to evaluate longitudinal changes in Aβ deposition (Landau et al., 2015). Summary 18F-AV45 cortical SUVR (normalized by the whole cerebellum) were utilized to assess baseline Aβ, and the recommended cutoff value to distinguish the Aβ-PET-positive from negative patients was 1.11 (Yu et al., 2019). Six regions of interest (ROIs) (amygdala, entorhinal cortex, fusiform, parahippocampal, and inferior temporal and middle temporal gyri) were averaged together into a composite ROI, which was used in tau-PET analyses (Jack et al., 2017). Three ROIs (angular, temporal, and posterior cingulate) were averaged together into a composite ROI, which was used in FDG-PET analyses, and the recommended cutoff value to distinguish the FDG-PET-positive from negative patients was 1.21 (Jagust et al., 2010; Jagust et al., 2009). Unified imaging protocol and subject assessment, as well as meticulous data quality control were employed to calculate the PET data in ADNI.

Statistical analyses

Linear mixed models were utilized to compute longitudinal rates of change in the GDS, Aβ-PET, tau-PET, and FDG-PET. These models were adjusted for age, sex, education (years), and *APOE4* status. All models were fitted with the lmer function in the lme4 package in R, version 3.6.2. Using these models, we estimated the mean rates of change (by the sim function in the arm package with 10 000 replicates) for the whole samples (Josephs et al., 2017). Chi-square tests (for categorical variables) and Pearson correlation tests (for continuous variables) were used to compare the baseline demographic and clinical characteristics, as well as the mean rates of change. The associations of baseline Aβ and cerebral glucose metabolism (negative vs. positive) with mean annual

changes in GDS were tested using linear regression models adjusted for age, sex, education (years), and *APOE4* status. P < 0.05 was considered significant.

Kaplan-Meier survival curves of clinical progression (progress from CN to MCI or AD) and Aβ accumulation were plotted based on mean annual changes in GDS (lower half vs. upper half). The log-rank test was used to compare the survival distribution of subgroups with different GDS change rates. Cox proportional hazards models were used to test the predictive abilities of the GDS change rate for clinical progression and Aβ accumulation. In addition, we performed mediation analyses to test and quantify the mediation effects of PET imaging on the associations of the GDS change rate with cognitive decline and clinical progression, in which we used bootstrapping (10,000 iterations) methods to estimate the 95% CI (Baron and Kenny, 1986). All the mediation models were adjusted for age, sex, education, and *APOE4* status. The "survival", "survminer", "ggplot2", "mediation", "lm", and "glm" packages in R 3.6.2 software were used to perform the above analyses.

Results

Characteristics of participants

A total of 522 CN participants who underwent assessments of depressive symptoms at least two times were included (Supplementary Figure 1). The participants were aged 55 to 91 (mean ± SD age, 73.6 ± 5.98) years. The study population had a female proportion of 48.8%, 16.5 ± 2.59 years of education, and an APOE4 positive percentage of 31.6%. The mean (SD) change rate in GDS was 0.96 per year (SD = 1.09). Participants with greater change rates in GDS had worse cognitive performance (ADNI-MEM, p=0.024; ADNI-MEM, p=0.007) (Table 1). A higher rate of increase in GDS was associated with poorer executive function at baseline (R = -0.10, p = 0.023) (Figure 1B) and faster cognitive decline during follow-up (ADNI-MEM: R = -0.13, p = 0.002; ADNI-EF: R = -0.17, p = 6.7e-05) (Figure 1C and Figure 1D). In addition, NPIQ was available for 333 participants (anxiety: 19). The rate of change in GDS did not differ significantly between anxious and non-anxious subjects (Supplementary Table 3).

Table 1
Baseline characteristics of participants in the study

Characteristics	Mean annual changes in GDS[#]				
	Total	p value[§]	Lower half	Upper half	p value[*]
N.	522		260	262	
Age (mean ± SD, year)	73.6 ± 5.98	0.335087	73.6 ± 5.97	73.6 ± 6.00	0.934
Sex (M/F)	267/255	0.542158	137/123	130/132	0.483
Education (mean ± SD, year)	16.5 ± 2.59	0.694045	16.4 ± 2.62	16.5 ± 2.57	0.674
APOE4 carrier status (%)	165 (31.6%)	0.150196	79 (30.4%)	86 (32.8%)	0.555
ADNI_MEM (mean ± SD)	1.01 ± 0.56	0.086817	1.06 ± 0.54	0.95 ± 0.58	**0.024**
ADNI_EF (mean ± SD)	0.83 ± 0.80	**0.022908**	0.92 ± 0.79	0.74 ± 0.80	**0.007**
Mean annual changes in GDS (mean ± SD)	0.96 ± 1.09		-0.03 ± 0.02	0.03 ± 0.04	

Abbreviations: GDS, Geriatric depression scale; MEM, Memory Function; EF, Executive Function; Prevalence of each allele type is provided for each of the subsamples.

[#] GDS score ≥ 6 is the cutoff for clinically significant depression; The GDS score < 6 in the follow-up period (4.21 ± 2.67 years).

[§] Pearson correlation tests (for continuous variables).

[*] The significance of difference among groups was examined by Mann-Whitney U test (for continuous variable) and Pearson's Chi-squared test (for categorical variable).

Cross-sectional analyses

In the cross-sectional analyses, 295 CN with cross-sectional data of Aβ-PET, 79 CN with cross-sectional data of tau-PET, and 345 CN with cross-sectional data of FDG-PET were included (Supplementary Figure 1). The results suggested that the rate of change in GDS was significantly associated with baseline Aβ (R = 0.14, p = 0.014) (Figure 2A). Aβ-PET-positive was associated with a significant increase in GDS (Figure 2B). Significant associations were not found between the GDS change rate and baseline tau or baseline cerebral glucose metabolism (Supplementary Figure 2 and Figure 3).

Longitudinal analyses

In the longitudinal analyses, 225 CN with follow-up data of Aβ-PET, 43 CN with follow-up data of tau-PET, and 201 CN with follow-up data of FDG-PET were included (Supplementary Figure 1). The results suggested that a higher rate of increase in GDS was significantly associated with a higher rate of increase in Aβ deposition (R = 0.19, p = 0.0053) (Figure 3A). A higher rate of increase in GDS was significantly associated with a higher rate of decline in cerebral glucose metabolism (R = -0.20, p = 0.0043) (Figure 3C). Significant association was not found between the rate of change in GDS and the rate of change in tau deposition (R = 0.29, p = 0.061) (Supplementary Figure 2).

In Kaplan-Meier survival analyses, a higher rate of increase in GDS (upper-half group) was significantly associated with shorter estimated time of clinical progression, compared with the lower-half group (plog-rank = 0.0004) (Figure 1E). In the Cox regression model (adjusted for age, sex, years of education, and APOE4 status), individuals in the upper-half group had a higher risk of progression to MCI or AD (hazard ratio (HR) 1.78, 95% confidence intervals (CI) 1.19–2.64, p = 0.004446) (Supplementary Table 1). In addition, CN participants in the upper-half group had a higher risk of progression to Aβ-PET-positive than those in the lower-half group (plog-rank = 0.04; Figure 3B). Cox regression model showed a robust result with HR = 2.23, 95% CI = (1.01–4.95), p = 0.047645 (Supplementary Table 2). However, we did not detect any differences in the risk of progression to FDG-PET-positive between upper-half group and. lower-half group (plog-rank = 0.4000) (Supplementary Figure 3).

Causal mediation analyses

In the mediation analyses, we investigated whether these AD markers mediated the influences of the rate of change in GDS on cognition and clinical progression. After controlling for a range of potential confounders (age, sex, years of education, and *APOE4* status), 22.24% of the total association of the rate of change in GDS with the decline in ADNI-MEM scores (Figure 4A), and 11.9% of the total association with the clinical progression (Figure 4C), were attributed to baseline Aβ. Moreover, 17.64% of the total association of the rate of change in GDS with the decline in ADNI-MEM scores was attributed to longitudinal changes in Aβ deposition (Figure 4D). As for cerebral glucose metabolism, 33.25% of the total association of the rate of change in GDS with the decline in ADNI-MEM scores (Figure 5A), 21.60% of the total association with the ADNI-EF decline (Figure 5B) and 34.40% of the total association with clinical progression (Figure 5C), were attributed to longitudinal changes in cerebral glucose metabolism. We did not found the relationships between the rate of change in GDS and cognition (ADNI-MEM and ADNI-EF), or the rate of change in GDS and clinical progression were mediated by baseline cerebral glucose metabolism (Supplementary Figure 4).

Discussion

The present results indicated that the rate of increase in GDS was not only a potential modulator of cognitive function, but also a significant

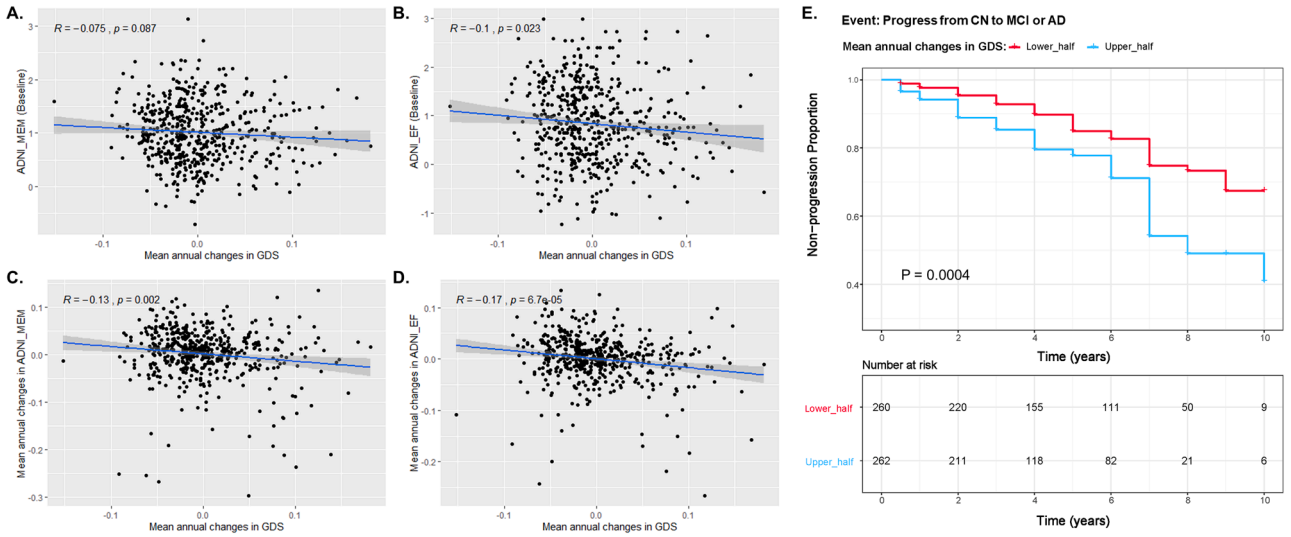

Figure 1. Associations of the rate of change in GDS with cognition and clinical progression. Higher rates of increase in GDS was associated with poor executive function at baseline (R = -0.10, p = 0.023) (B) and faster cognitive decline during follow-up (ADNI-MEM: R = -0.13, p = 0.002; ADNI-EF: R = -0.17, p = 6.7e-05) (C and D). Kaplan-Meier survival analysis suggested that the higher rate of increase in GDS (upper-half group) was significantly associated with the shorter estimated time of clinical progression, compared with the lower-half group (plog-rank = 0.0004) (E).

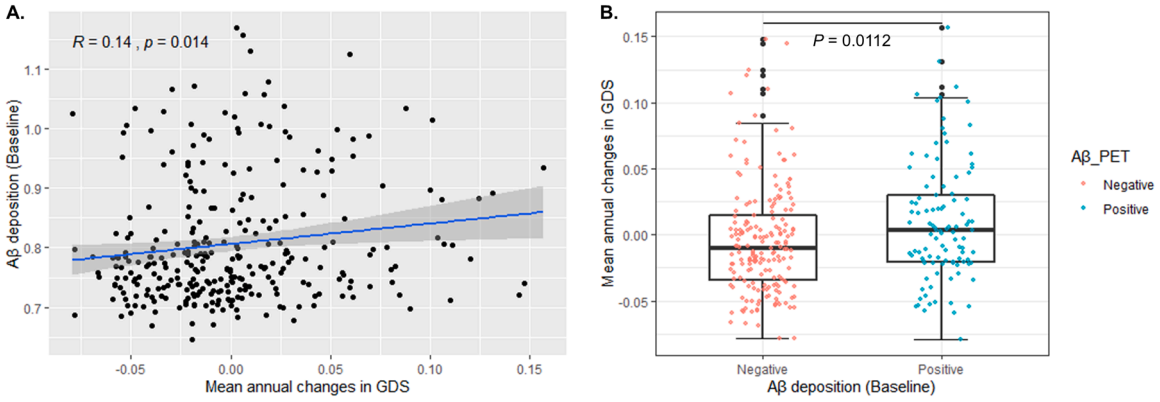

Figure 2. Associations of the rate of change in GDS with baseline Aβ. The baseline Aβ deposition is associated with the rate of change in GDS (R = 0.14, P = 0.014) (A); Aβ-PET- positive is associated with a significant increase in GDS (P = 0.0112), P-value in the plot was computed from linear regression model after adjusting for age, sex, years of education, and *APOE4* status (B).

risk factor for clinical progression. The influences of the rate of change in GDS on cognition and clinical progression were partially mediated by baseline Aβ and the rate of change in glucose metabolism of the brain. In addition, the association of the rate of change in GDS with subsequent memory decline is partially attributed to the changes in Aβ deposition. All these associations were found before the onset of clinically significant depression.

During the evaluation of depressive symptoms, the GDS-15 scores represented a stable and enduring trait explaining between-person differences in depression severity (Gana et al., 2017). Previous studies suggested that depression could trigger cognitive decline and incipient AD (Gracia-Garcia et al., 2015; Herbert and Lucassen, 2016; Santabarbara et al., 2019). We provide further evidence that the associations of changes in depressive symptoms with cognition and clinical progression were revealed before the onset of clinically significant depression. Neuroimaging evidence indicated that depressive symptoms were associated with abnormal functioning of cognition-related brain networks. The configurations of these networks can change between individuals and over time, which may contribute to explaining the variable presentation and fluctuating course of depressive symptoms (Rayner et al., 2016).

The pathological bases of these relationships are still unclear. Several cohort studies have examined linkages between depressive symptoms and the pathology of AD (evaluated by PET imaging) in CN individuals. They found that the higher baseline Aβ was associated with aggravated depressive symptoms (Babulal et al., 2016; Donovan et al., 2018; Harrington et al., 2017). Consistent with these studies, our findings point to Aβ-related structural and/or functional changes as possible etiological bases for changes in depressive symptoms (Babulal et al., 2016; Donovan et al., 2018; Harrington et al., 2017). Moreover, we further found that Aβ, not tau, partly mediated the associations between depressive symptoms and cognitive changes. The accumulation of neurotoxic oligomeric aggregates of Aβ is an important pathological event in AD, starting decades before dementia (Bateman et al., 2012; Jansen et al., 2015; van der Kant et al., 2020). Previous studies suggested that amygdala-hippocampal network played an crucial role in emotional regulation disorders, including depression (Leal et al., 2017). Aβ oligomers can enhance long-term synaptic depression, inhibit long-term potentiation, and decrease synapse number (atrophy) in relevant brain regions. They can further affect the activity in functionally coupled limbic and neocortical areas, resulting in changes in depressive symptoms and cognitive decline (Leal et al., 2017; Selkoe and Hardy, 2016;

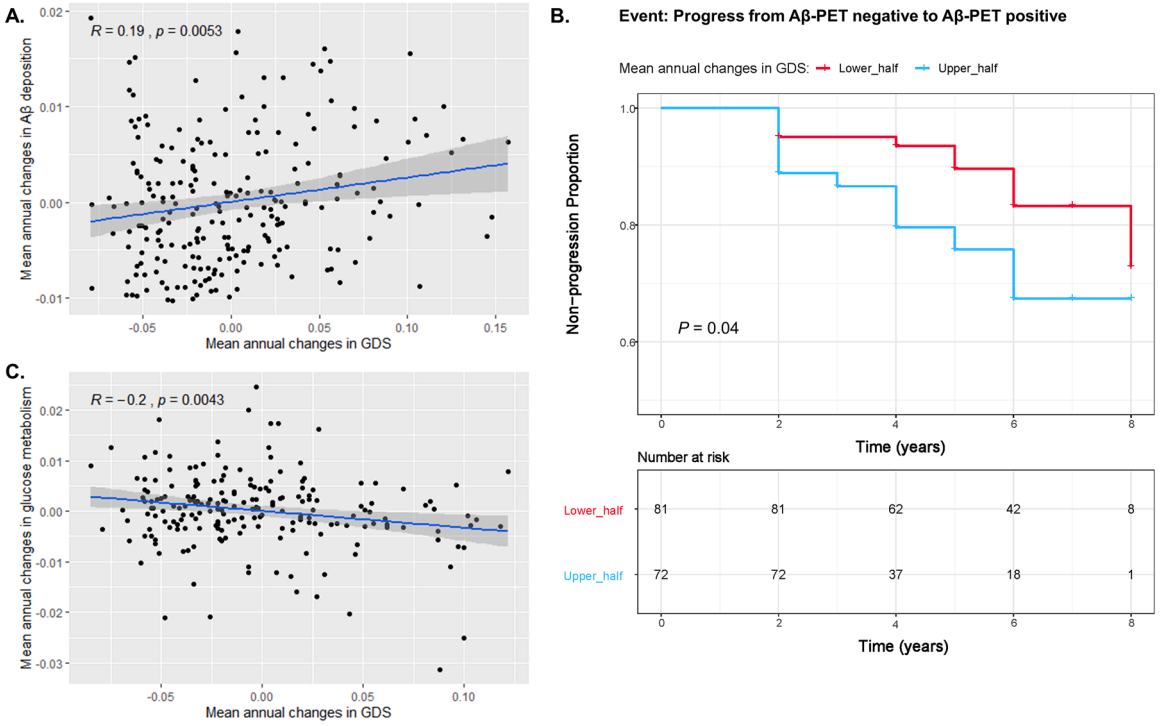

Figure 3. Associations of the rate of change in GDS with longitudinal changes in Aβ deposition and cerebral glucose metabolism. The rate of change in GDS was significantly associated with the rate of changes in Aβ (R = 0.19, p = 0.0053) (A) and in cerebral glucose metabolism (R = -0.20, p = 0.0043) (C). Kaplan-Meier survival analysis suggested that the higher rate of increase in GDS (upper-half group) was significantly associated with the shorter estimated time of progression to Aβ-positive, compared with the lower-half group (plog-rank = 0.04) (B).

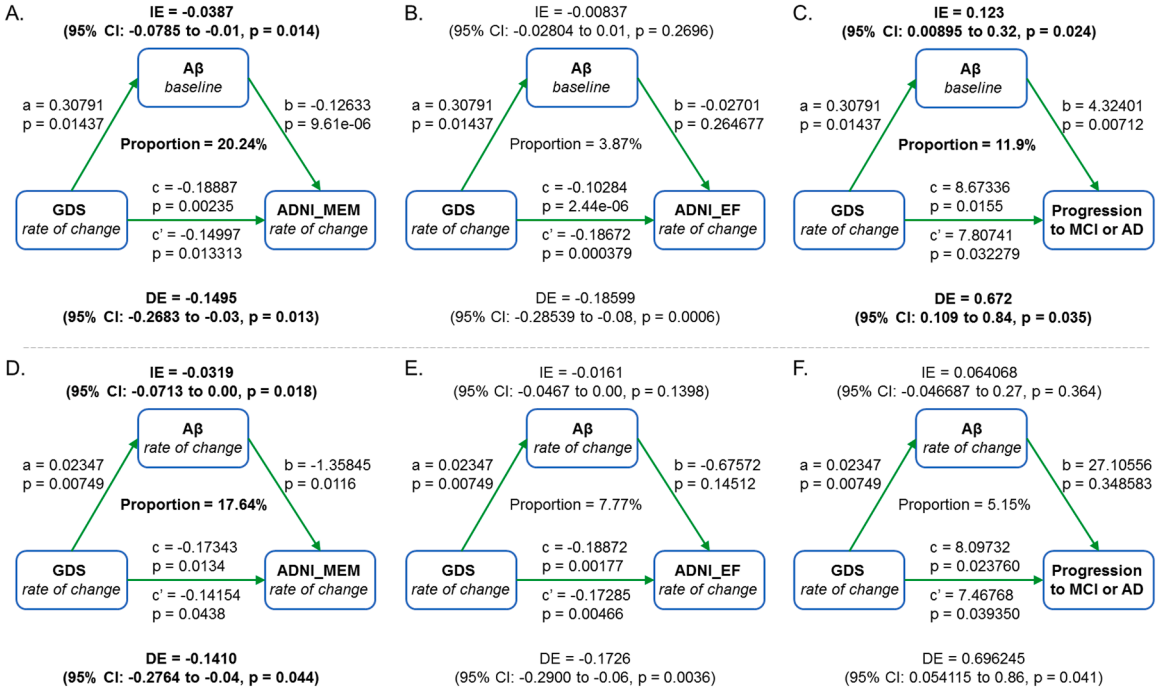

Figure 4. Mediation effects of baseline Aβ and longitudinal changes in Aβ deposition on the associations of the rate of change in GDS with cognition and clinical progression. After controlling for a range of potential confounders (age, sex, years of education, and *APOE4* status), 22.24% of the total association of the rate of change in GDS with ADNI-MEM decline (A), and 11.9% of the total association with the clinical progression (C), was attributed to baseline Aβ. Moreover, 17.64% of the total association of the rate of change in GDS with the ADNI-MEM decline was attributed to longitudinal changes in Aβ deposition (D).

Sperling et al., 2019; Tu et al., 2014). In addition, Aβ clearance-related anti-inflammatory cytokine, the Transforming-Growth-Factor-β1 (TGF-β1), has also been reported to correlate with depression severity (Caraci et al., 2018; Wyss-Coray et al., 2001). Also, depressive symptoms can increase glucocorticoid production, and related stress response may cause an increase of Aβ (mainly by increasing steady-state levels of

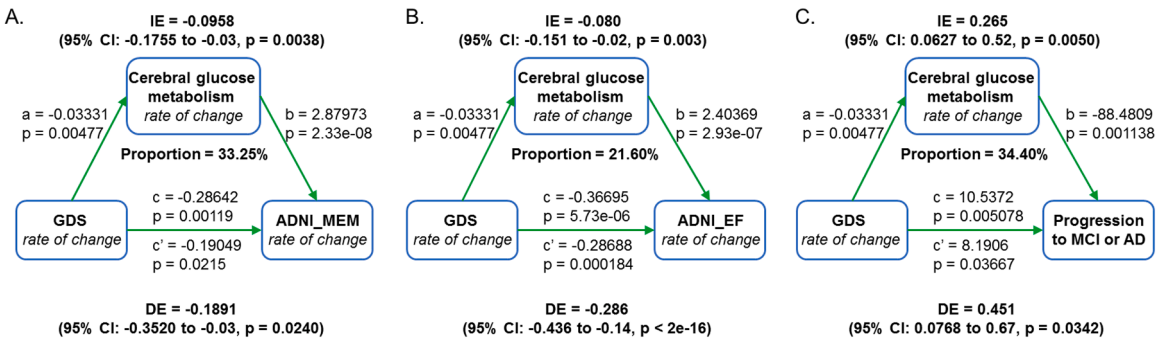

Figure 5. Mediation effects of longitudinal changes in cerebral glucose metabolism on the associations of the rate of change in GDS with cognition and clinical progression. After controlling for a range of potential confounders (age, sex, years of education, and *APOE4* status), 33.25% of the total association of the rate of change in GDS with ADNI-MEM decline (A), 21.60% of the total association with the ADNI-EF decline (B) and 34.40% of the total association with the clinical progression (C), was attributed to longitudinal changes in cerebral glucose metabolism.

amyloid precursor protein (APP) and the β-APP cleaving enzyme) (Byers and Yaffe, 2011; Green et al., 2006). Additionally, depressive symptoms may directly influence the amyloidogenic processing through the serotonergic system (Byers and Yaffe, 2011).

FDG-PET is a biomarker of neurodegeneration or neuronal injury, and has been evaluated by AT(N) (b-amyloid deposition [A], pathologic tau [T], and neurodegeneration [N]) system (Jack et al., 2018; Yu et al., 2019). The impairment in cerebral glucose metabolism may occurred before cognitive dysfunction and pathological alteration. A hypothesis states that multiple pathogenic cascades originating from the impaired cerebral glucose metabolism can result in neuronal degeneration and subsequent cognitive decline (Chen and Zhong, 2013). In addition, cross-sectional studies have shown that depression is associated with cerebral glucose hypometabolism (including the frontal gyri, cingulate gyrus, temporal gyri, insula, inferior parietal lobules, and occipital gyrus et al.) (Baeken et al., 2018; Hosokawa et al., 2009; Martinot et al., 1990; Su et al., 2018). Our results suggest that the worsening of depressive symptoms is accompanied by a decrease in glucose metabolism in ROIs. Previous study revealed that functional connections (including inferior parietal lobule, posterior cingulate cortex, and dorsolateral prefrontal cortex et al.) may be a potential marker for the cognitive vulnerability to depression (Sun et al., 2018). The glucose hypometabolism can cause a subcortical connectivity lesion, which may allow the depressive mood to weaken cognitive regulation (Su et al., 2018).

Major strengths of our study include the longitudinal assessments of GDS and neuroimaging markers, population-based design, and causal mediation analyses. Our findings suggested that the management of depression severity may help delay or slow progressive cognitive decline and clinical progression. In participants with elevated depressive symptoms, Aβ deposition and impaired cerebral glucose metabolism may act together to contribute to cognitive decline and clinical progression. The Aβ-PET and FDG-PET may be useful for monitoring depressive symptoms and then predicting cognitive trajectories.

Limitations

There are limitations in this study. First, the GDS total score was chosen to evaluate the severity of depressive symptoms in the present study, which is a self-reported questionnaire and not the same as a clinical diagnosis of depression. Second, the ADNI database is not specifically designed for depression. The ADNI protocol specially excluded patients with clinically significant depressive symptom at baseline. Therefore, our study was limited to minimal to mild depressive symptoms. Third, considering that a substantial number of participants may die during a long follow-up, the Cox model may provides a less accurate risk estimation (Berry et al., 2010). Fourth, we did not control for other potential confounding factors (e.g., other genetic factors, vascular risk factors, and socioeconomic status et al.) in our analyses. Fifth, this study was conducted with modest samples sizes, and the generalizability of our conclusions might be restricted by sources of studied populations of ADNI which recruited participants from volunteers. Further large-scale community-based longitudinal studies are warranted to validate these associations..

Conclusion

The present study indicated that the worsening depressive symptoms in cognitively normal older adults, in addition to progressive cognitive decline, may herald the acceleration of progression to MCI or AD, as well as indicating potentially increased rate of Aβ deposition and decreased rate of cerebral glucose metabolism. The cognitive and clinical consequences of changes in depressive symptoms partly stem from Aβ accumulation and cerebral glucose metabolism, which increases our understanding of how depressive symptoms may increase vulnerability to dementia. The management of fluctuating course of depressive symptoms may help improve cognitive outcomes. Furthermore, Aβ-PET and FDG-PET may play important roles in monitoring depressive symptoms and assessing the risk of cognitive decline.

Author statement

Contributions: JTY, QD and LT conceptualized and designed the study. ZTW, XNS, YHM and YNO conducted the study. ZTW and XNS analyzed and extracted data. ZTW and JTY wrote the first draft of the manuscript. All authors reviewed the manuscript.

Funding: This study was supported by grants from the National Natural Science Foundation of China (91849126), the National Key R&D Program of China (2018YFC1314702), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgement

Data collection and sharing for ADNI data section was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following:

AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.10.078.

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