Published in final edited form as:

Am J Geriatr Psychiatry. 2017 January ; 25(1): 64–72. doi:10.1016/j.jagp.2016.08.018.

Enhanced molecular aging in late-life depression: the Senescent Associated Secretory Phenotype

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Abstract

Objective—This study aims to investigate whether a systemic molecular pattern associated with aging (senescent-associated secretory phenotype – SASP) is elevated in adults with late-life depression (LLD), compared to never-depressed elderly comparison participants.

Design—Cross-sectional study.

Participants—We included 111 older adults (80 with LLD and 31 comparison participants) in this study.

Measurement—A panel of 22 SASP-related proteins was extracted from a previous multiplex protein panel performed in these participants. We conducted a principal component analysis to create the SASP index based on individual weights of each of protein.

Results—Participants with LLD showed a significantly increased SASP index compared to comparison participants, after controlling for age, depressive symptoms, medical comorbidity (CIRS-G) scores, gender, and cognitive performance ($F_{(1,98)}=7.3$, $p=0.008$). Correlation analyses revealed that the SASP index was positively correlated with age ($r=0.2$, $p=0.03$) and CIRS score ($r=0.27$, $p=0.005$), and negatively correlated with information processing speed ($r=-0.34$, $p=0.001$), executive function ($r=-0.27$, $p=0.004$) and global cognitive performance ($r=-0.28$, $p=0.007$).

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Disclosures:

The authors report no conflict of interest.

Conclusions—To the best of our knowledge, this is the first study to show that a set of proteins (i.e., SASP index) primarily associated with cellular aging, is abnormally regulated and elevated in LLD. These results suggest that individuals with LLD display enhanced aging-related molecular patterns that are associated with higher medical comorbidity and worse cognitive function. Finally, we provide a set of proteins that can serve as potential therapeutic targets and biomarkers to monitor the effects of therapeutic or preventative interventions in LLD.

Keywords

late-life depression; aging; senescent associated secretory phenotype; cognitive performance

Introduction

Late-life depression (LLD) is a common mental disorder in older adults¹. The occurrence of LLD is associated with increased risk of age-related disorders, e.g., cardiovascular, cerebrovascular, and neurodegenerative disorders². The exact neurobiological mechanisms of LLD are being characterized and likely involve the abnormal regulation and interaction of multiple biological processes, and structural and functional brain abnormalities³.

A key to understanding the neurobiology of LLD is how it interacts with aging-related brain and systemic biological changes. Understanding this interplay can provide insight into mechanisms by which LLD is associated with negative health outcomes common among older adults, such as higher risk of dementia, increased mortality, cardiovascular comorbidities, and disability^{4,5}. Recent studies have examined biomarkers related to cellular senescence in patients with major depression. In a large population-based study, leukocyte telomere length was significantly reduced in the participants with a current or history of depression⁶. Young and older depressed adults show heightened oxidative stress and pro-inflammatory states, increased endoplasmic reticulum stress, and loss of proteostatic control^{7,8}. In a large-scale gene expression study of brain tissue, most major depressive disorder (MDD)-related genes were positively correlated with age-dependent changes observed in control participants⁹, and notably showed greater age-related expression changes in MDD participants, demonstrating accelerated molecular processes in adult midlife MDD.

In an in vitro study, Coppé *et al*¹⁰ showed that different senescent fibroblast cell lineages actively secrete a common set of proteins that lead to cell cycle arrest and induce senescence in nearby cells. This set of “Senescent Associated Secretory Phenotype” (SASP) proteins include inflammatory and immune-modulatory cytokines and chemokines, growth factors, and cell surface molecules. Abnormal expression of SASP related proteins has been found in aging-associated disorders such as malignancies, osteoarthritis, and chronic obstructive pulmonary disease^{11–14}. Senescent glial cells, i.e., astrocytes and microglia, can also secrete SASP-related proteins and can induce senescent changes in the brain¹⁵.

Some clinical features that are common in individuals with LLD, such as comorbid medical illnesses, cerebrovascular changes, cognitive dysfunction, in particular, executive function and processing speed, and brain atrophy are also observed during the non-pathological aging process^{16–18}. However, these changes have a greater effect size in LLD compared to non-depressed age-matched individuals^{19,20}. No integrative mechanisms have been proposed so

far to explain these relationships. Therefore, we measured expression levels of proteins comprising the SASP index and compared values between LLD individuals and age-matched never depressed comparison participants. We hypothesized that LLD would present with an enhanced SASP profile compared to never-depressed older adults. We further evaluated whether the SASP profile is associated with demographic and clinical characteristics, cognitive performance, and brain structural neuroimaging markers in LLD participants. We hypothesized that the SASP index would significantly correlate with older age, higher medical comorbidity burden, greater cognitive dysfunction, and greater cerebrovascular disease (measured by white matter hyperintensities) and gray matter atrophy.

Methods

Participant recruitment and cognitive assessment

Data from 80 older adults with remitted LLD and 31 older adults with no previous history of major depression or other major psychiatric disorder (comparison group) were included in this analysis. All of the participants were enrolled in a research clinic based at the University of Pittsburgh's NIMH-sponsored Advanced Center for Intervention and Services Research for Late-Life Mood Disorders. All LLD participants had previously met DSM-IV criteria for current unipolar Major Depressive Disorder without psychotic features and were successfully treated to response (i.e., Hamilton Depression Rating of 10 or less for two consecutive weeks) in pharmacotherapy and/or interpersonal psychotherapy intervention trials.

Exclusion criteria for all participants encompassed substance abuse within the past year, unstable medical illness (precluding participation in clinical trials for depression), history of psychosis, bipolar disorder, neurologic disorder (including dementia) or significant head trauma (defined as loss of consciousness > 30 minutes). Written informed consent was provided before entering the neuroimaging study. The study was approved by the University of Pittsburgh Institutional Review Board.

After study recruitment (and following successful remission of mood symptoms for patients), participants underwent structural MRI and a detailed neuropsychiatric evaluation. The evaluation included the 17-item Hamilton Depression Rating Scale, neurologic examination, the Clinical Dementia Rating, the Informant Questionnaire on Cognitive Decline in the Elderly, medical history, and medication review. The University of Pittsburgh Alzheimer Disease Research Center comprehensive neuropsychological assessment was performed by trained examiners supervised by a senior neuropsychologist (MAB). The neuropsychological battery included, at least, two tests per domain, assessing language, visuoconstructional/visuospatial ability, attention/information processing speed, episodic delayed memory, and executive functions (See Supplementary Table 1 for the list of tests included in the battery). For this study, we then created a standardized score for each neuropsychological domain assessed in addition to a global score (represented by the mean score) based on the individual tests' Z-score to allow the comparison of the results across distinct cognitive domains.

Comparison participants were recruited from the community and underwent the same psychiatric and neuropsychological evaluation protocols as the LLD participants for the exclusion of current and past history of major depression (and other psychiatric disorders) and cognitive impairment.

Laboratory analysis: SASP development

After cognitive assessment, whole blood samples were withdrawn with EDTA tubes by antecubital venous puncture. Plasma samples were separated, aliquoted, and stored at -80°C . Plasma samples (750 μL) were sent to the Myriad RBM[®] laboratory (Austin, TX, USA) for biomarker measurements. We used the Human DiscoveryMAP[®] 250+ v2.0 assay, which simultaneously assesses 242 different protein analytes with a multiplex immunoassay panel (rbm.myriad.com). Details of the laboratory analysis can be found elsewhere⁷.

We extracted from the multiplex protein panel data for 22 out of the 24 protein markers that comprise the SASP profile based on the Coppé *et al* study¹⁰. Two markers (GRO(a,b,g) and βFGF) were not measured in the multiplex proteomic panel and were not available for this analysis. The SASP panel includes markers related to immune-inflammatory control, growth factors, cell surface molecules, and survival factors. Before the analysis, we performed log2 transformation of the protein concentration for all markers.

We calculated a SASP index for each participant based on the regression analysis of individual weights of biomarkers included in the SASP panel. For this, we initially carried out a principal component analysis (PCA) with all proteins included in the model. We extracted the individual weight of each biomarker based on its eigenvector value. Finally, we calculated the SASP index for each participant using a multiple linear regression model, in which SASP index was the dependent variable, the individual SASP biomarkers were the predictor variables, and the biomarker's weight was the regression coefficient for each SASP biomarker (equation 1):

$$SASP = \beta_1 x_{i1} + \dots + \beta_i x_{i1} + \varepsilon, i = 1, \dots, n \quad \text{Equation 1}$$

Structural neuroimaging

Magnetic Resonance (MR) acquisition—MR scanning was performed at 3.0 Tesla (n=64, LLD only) using a Siemens MAGNETOM Trio 3 Tesla Scanner (Siemens Medical Solutions USA, Malverne, PA), respectively. The protocol on the 3T scanner was as follows: 3D structural MR images were acquired at a sagittal orientation using 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE). MPRAGE (TR/TE=2300/2.98 ms, 256 slices, slice thickness 1.2 mm, flip angle = 9, in-plane resolution 1 mm $\times$ 1 mm). The T2-weighted FLAIR was acquired in the axial orientation (TR=9160 ms, TE=90 ms, TI=2500 ms, 48 slices, in-plane resolution 1mm $\times$ 1mm); section thickness was 3mm with no intersection gap, a 24cm field of view and a 192 $\times$ 256 pixel matrix.

We used a fully automated method for localizing and quantifying voxels as white matter hyperintensities (WMH) on the FLAIR images and then converted these values to a volume (1 voxel = 4.2mm³). Individual regions of white matter changes were summed to create a

variable representing total WMH burden for each participant and then were expressed as the ratio of total white matter hyperintensity volume (WMHV) by total white matter volume²¹. Normalized whole brain gray matter volume was calculated as the ratio of gray matter volume over whole brain volume. Gray matter volume and whole brain volume were estimated from the SPGR and MPRAGE images using standard processing streams; total intracranial volume was computed as the volume contained within the 'inner skull' using the brain extraction tool with an advanced option (-A) and gray matter volume was estimated using FAST (FMRIB's Automated Segmentation Tool) with a 3-tissue model (Gray, White, and CSF).

Statistical analysis

Differences in socio-demographic, cognitive and neuroimaging data were evaluated by independent t-tests (continuous variables) or chi-square test (dichotomous variables). We used an independent t-test to compare the SASP index (derived from PCA) between LLD and comparison participants. Pearson correlation analysis was carried out to evaluate correlations between SASP index, demographic, clinical, cognitive, and neuroimaging data. All analysis were done with the software SPSS v.21 for Windows.

Results

The clinical and neurocognitive characteristics, age and education level of LLD participants did not differ from those of comparison participants (table 1). There were more males in the comparison group and participants with LLD had worse cognitive performance in all assessed domains (table 1).

We observed a significant difference in the SASP index between groups ($t_{109}=4.3$, $p<0.001$; see Figure 1). The LLD participants had a significantly higher index compared to the comparison participants. The difference remained statistically significant after controlling for the covariates – age, education, depressive symptoms, Cumulative Illness Rating Scale-Geriatrics (CIRS-G) scores, gender, and cognitive performance ($F_{(1,98)}=7.3$, $p=0.008$). The Cohen's f^2 for the difference of SASP index between LLD and comparison groups was 0.18 $CI_{95\%}$ (0.03 – 0.37), indicating a small to moderate effect size. The raw values for individual biomarkers included in the SASP panel are presented in Supplementary Table 2.

Pearson correlation analyses revealed that the SASP index was positively correlated with age ($r=0.2$, $n=111$, $p=0.03$) and CIRS-G score ($r=0.27$, $n=111$, $p=0.005$), and negatively correlated with information processing speed ($r=-0.34$, $n=111$, $p=0.001$), executive function ($r=-0.27$, $n=111$, $p=0.004$) and global cognitive performance ($r=-0.28$, $n=111$, $p=0.007$). Given the large number of correlations carried out, we adjusted the p-value based on Bonferroni correction. After the Bonferroni correction ($p\text{-value} < 0.006$), age was not significantly correlated with SASP index. The significant correlations between CIRS-G scores and cognitive performance with SASP index persisted. The SASP index showed a significant negative correlation with GMV ($r=-0.27$, $n=64$, $p=0.03$). The correlation between the SASP index and WMH was not statistically significant ($r=0.09$, $n=64$, $p=0.49$). There were no additional significant correlations between the SASP index and other variables,

including lifetime duration of major depressive disorder, and length of current antidepressant treatment.

As the SASP index was significantly correlated with cognitive performance, we stratified the LLD sample according to cognitive status (cognitively normal [LLD+CN] and Mild Cognitive Impairment [LLD+MCI]). SASP index was significantly higher in the LLD+CN and LLD+MCI compared to the never depressed comparison participants ($F_{(2,96)} = 6.8$, $p = 0.002$), after adjustment for gender, age, HDRS-17, and CIRS-G scores. The Cohen's f^2 for the difference of SASP index between LLD+MCI, LLD+CN, and comparison groups was 0.21 $CI_{95\%}$ (0.05 – 0.42), indicating a moderate difference effect size (Cohen, 1988). Pairwise posthoc analysis with Bonferroni correction showed that LLD+MCI had highest levels of SASP, followed by LLD+CN and comparison individuals. There was no significant difference in the SASP index between LLD+CN and LLD+MCI (Figure 1). There were two outlier values among all individuals. Removing these outliers did not affect the results (*data not shown*).

Discussion

This is the first study to test a biomarker-based index related to aging in older adults with depression. We report, that the SASP index, an integrated value representing changes in proteins associated with a cellular senescent secretory phenotype¹⁰ was significantly higher in participants with remitted LLD (Figure 1). As expected, a higher SASP index was significantly correlated with older age and a greater number of medical comorbidities, including cardiovascular disease, measured by the CIRS-G scores. The results were independent of confounding variables like age, medical comorbidities, and depressive symptoms. Higher SASP index was also correlated with worse cognitive performance, in particular reduced executive function and information processing speed, and with greater gray matter atrophy. The effect size of the difference in SASP index between diagnostic groups varied from small to moderate, suggesting that SASP index difference may have a significant clinical relevance to differentiate subjects with LLD and non-depressed subjects, in particular those with cognitive impairment. Taken together, these results represent strong evidence that LLD is associated with an enhanced age-related molecular pattern which is, in turn, associated with clinical and structural brain aging phenotypes.

Aging is a complex, multifactorial process that leads to increased vulnerability to several systemic and brain disorders⁵. Although the prevalence of depression does not necessarily increase with aging, recent studies have shown a significant interaction between the neurobiological changes observed in depression and usual aging. Post-mortem studies have found a significant overlap of abnormal gene expression in major depressive disorder patients with genes whose expression is age-regulated^{9,22}. In addition, clinical studies, using an unbiased, data-driven, proteomic approach, have shown that major depression, together with the association of major depression and cognitive impairment, are both associated with abnormal regulation of biological pathways related to immune-inflammatory control, proteostasis, cell communication and signal transduction processes, and oxidative stress^{7,23,24}. These biological pathways have been implicated in the aging process, suggesting that depression across the lifespan is associated with aging-associated biological

abnormalities. The current study advances knowledge over previous findings by showing that a molecular pattern related to cellular aging that is measureable in blood samples is significantly enhanced in LLD, after controlling for confounding variables. Altogether, these results suggest that LLD is associated with enhanced aging-related biological abnormalities and may contribute to our understanding of the association of depression and negative health outcomes in older adults.

It should be noted that the LLD participants had blood drawn after remission of a major depressive episode and were in current treatment with antidepressants. The effect of antidepressants on SASP proteins is not known. Our results expand previous observations⁷ and can be viewed as an ongoing pathological change in LLD that persists or continues even after improvement in depressive symptoms and the ongoing use of antidepressants. Our results are consistent with the presence of biological “scar” in depression that render older adults with major depression more vulnerable to systemic illness, cognitive impairment and other negative health outcomes, which are not fully ameliorated despite successful antidepressant treatment²⁵.

The SASP index is comprised of a panel of biomarkers related to inflammation, growth factors and cell surface proteins. Previous studies have shown that some of these markers are abnormally regulated in LLD (e.g., increased levels of sTNFR2) or related to specific clinical characteristics, like cognitive impairment (e.g. angiogenin, IGFBP-6)^{7,26}. The current study extends these previous findings by providing an integrated view of changes related to a larger panel of biomarkers instead of addressing marker(s) in isolation. Furthermore, the PCA-based SASP index enabled us to assess the relative weight and direction of effects for the different proteins included in this biomarker assay (Figure 1). Given the dynamic nature of the neurobiology of LLD, our results suggest that changes in one biomarker may have a more significant impact compared to others. For example, an intervention that has a bigger impact on sTNFR2 compared to IL-6 may have a more pronounced effect on the neurobiology of LLD because the weight of sTNFR2 is greater than of IL-6. Thus, identifying the relative weights of the significant biomarkers may inform treatment choice at the level of the individual patient, thereby promoting personalized care. Finally, the SASP index, instead of a single biomarker, can be used as a surrogate marker to monitor the response to antidepressant treatment, and the biologic effects and the potential neuroprotective effect of interventions in this population.

The set of SASP proteins act in concert via p53, p38MAPK, and NFκB signaling pathways to induce its biological effects^{10,27}. Pharmacologic agents targeting one or more of these signaling pathways may have significant neuroprotective effects and impact long-term negative outcomes in LLD. In fact, agents currently used for the treatment of mood disorders can modulate these pathways, in particular p38MAPK, and NFκB²⁸. Long-term antidepressant treatment can reduce the risk of cancer-related mortality in older adults and the risk of all-cause dementia and Alzheimer’s disease^{29,30}. Long-term low-dose lithium treatment is associated with lower risk of dementia in individuals with mood disorders, and can delay cognitive decline in older adults with MCI^{31,32}. Therefore, the long-term use of antidepressants and mood stabilizers may promote neuroprotective effects in part by modulating the effect of proteins included in the SASP index. Finally, other drugs that

modulate SASP index proteins, or related signaling cascades (i.e., rapamycin) can be of interest not only for the treatment of the depressive episode but also for the long-term prevention of negative health outcomes in individuals with LLD³³.

Cognitive impairment is a common feature of depression in older adults and is associated with additive risk of progressing to dementia, increased disability and is associated with worse antidepressant response in older adults^{34,35}. The SASP index significantly correlated with worse cognitive performance, in particular in executive function and information processing speed. Also, participants with LLD+MCI had the highest levels of SASP, although not statistically different from those with LLD and normal cognitive performance. These findings are in line with recent studies showing that participants with LLD+MCI present broad neurobiological abnormalities and a steeper trajectory of decline in BDNF levels over two years of follow-up compared to participants with LLD and normal cognitive performance³⁶. Altogether, these findings suggest that cognitive impairment in LLD, in particular, executive dysfunction and slowed information processing speed, is associated with an enhanced aging molecular profile, and may indicate that there is a subgroup of depressed older individuals who are at increased risk of developing dementia over time.

There is a longstanding debate in the literature whether peripheral biomarker measures reflects changes observed in the brain³⁷. The SASP proteins can be produced and secreted by senescent glial cells and also activate neuronal intracellular cascades related to inflammation, metabolic control, cell growth and apoptosis¹⁵. Also, there is evidence that older adults with depression have increased blood-brain barrier permeability that allows the passage of molecules from the periphery to the central nervous system and vice-versa^{38,39}. Finally, there is the recent discovery that the brain lymphatic system provides strong evidence for a complex interplay between the brain and the periphery⁴⁰. Taken together, this evidence suggests that the abnormalities in SASP proteins observed in the periphery may reflect, at least in part, similar abnormality patterns in the brain of LLD participants.

Limitations

The current results should be viewed in light of several limitations. First, the SASP proteins were described from aging fibroblast research and may not encompass the whole complexity of the aging processes observed in living organisms. Nonetheless, these proteins, alone or in conjunction with one another, have been reported to be abnormally regulated in different aging-related conditions such as osteoarthritis, cancer, cardiovascular diseases, and are associated with negative health outcomes, such as increased risk of metastasis. Second, this is a cross-sectional study with correlational analyses that limits the interpretation of putative causal inferences. Third, despite being well characterized, our sample is relatively small, recruited from a single study center, and most participants were receiving antidepressant treatment. We also did not control for the effects of metabolic variables, like BMI, that might have a significant impact on the SASP protein. This could introduce significant bias in the analysis, in particular, related to the analysis of weights of individual markers composing the SASP index, and thus limits the generalization of results. Fourth, the neuroimaging results are restricted to the LLD individuals which limits the interpretation and generalization of the association between SASP and brain structural changes. Our findings are limited to older

adults with depression. However, it is possible that younger adults with major depression could also present with significant changes in SASP proteins, suggesting that SASP changes could represent a trait marker for major depression across the lifespan. Finally, it is important to evaluate whether our findings also extend to other mental illnesses (e.g. bipolar disorder, schizophrenia) and to determine the diagnostic specificity of SASP changes for major depression. Therefore, our results need to be replicated in other study samples, using a lifespan approach and with longitudinal and repeated biomarkers and clinical phenotype measures, that will allow us not only to confirm that changes in SASP proteins occur in LLD, but also to identify when such changes begin in depressed participants and how they associate with clinical and biological outcomes.

Conclusion

Our results provide strong evidence that individuals with LLD have an enhanced aging-related molecular pattern that is associated with higher medical comorbidity, worse executive function and information processing speed. Future studies are necessary to evaluate whether antidepressants, mood stabilizers, as well as other drugs (e.g. rapamycin, PPAR- γ modulators), can modulate the SASP index. Moreover, further research should address the mediating role of SASP modulation on therapeutic benefits of antidepressants and other neuroprotective agents. Finally, future studies should evaluate the prognostic role of SASP to identify LLD individuals at increased risk of negative outcomes, in particular, increased risk of dementia and death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by NIH grants P30MH090333 (Reynolds), MH080240 (Butters), MH093723 (Sibille), the UPMC Endowment in Geriatric Psychiatry (Reynolds), The John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry (Reynolds).

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Figure 1.

SASP index according to diagnostic group.

Data displayed as mean ± SE. Horizontal bar indicates the mean value for each group.

LLD: Late-life depression; LLD+NC: Late-life depression with normal cognitive performance; LLD+MCI: Late-life depression with mild cognitive impairment.

Table 1

Clinical and neurocognitive characteristics of the LLD and control participants. (Data are mean $\pm$ standard deviation)

	Diagnosis			
	LLD	Comparison group	Statistics	p-value
Demographic				
Age (years)	73.1 $\pm$ 6.0	72.7 $\pm$ 6.2	$t_{109}=0.36$	0.7
Education (years)	14.3 $\pm$ 2.8	14.9 $\pm$ 3.1	$t_{109}=1.05$	0.3
Gender	62/18	14/17		
Clinical Characteristics				
HDRS-17 (raw score)	4.7 $\pm$ 3.2	2.6 $\pm$ 2.5	$t_{109}=3.28$	0.001
CIRS-G (total score)	11.5 $\pm$ 3.7	8.0 $\pm$ 3.3	$t_{109}=4.53$	<0.001
LLD+CN/LLD +MCI	44/36	-	-	-
EOD/LOD	64/16	-	-	-
Single/Recurrent episodes	29/51	-	-	-
Duration of depressive disorder* (years)	29.2 $\pm$ 20.7	-	-	-
Antidepressant drug				
Venlafaxine	25	-	-	-
Escitalopram	19	-	-	-
Duloxetine	15	-	-	-
Citalopram	4	-	-	-
Fluoxetine	1	-	-	-
Venlafaxine + Citalopram	1	-	-	-
Venlafaxine + Bupropion	1	-	-	-
Bupropion + Citalopram	1	-	-	-
Mirtazapine + Nortryptiline	1	-	-	-
No	16	-	-	-
Cognitive Performance by Domain				
Processing Speed	-.23 $\pm$ 1.00	.16 $\pm$.54	$t_{109}= 2.03$	0.04
Language	-.03 $\pm$.66	.35 $\pm$.50	$t_{109}= 2.85$	0.005
Memory	.15 $\pm$.78	.70 $\pm$.62	$t_{109}= 3.46$	0.001
Visuospatial	-.45 $\pm$.69	.22 $\pm$.56	$t_{109}= 4.37$	<0.001
Executive	-.02 $\pm$.79	.50 $\pm$.46	$t_{109}= 3.44$	0.001
Global	-.13 $\pm$.56	.37 $\pm$.32	$t_{109}=4.55$	<0.001

HDRS-17: Hamilton Depression Rating Scale-17 items; CIRS-G: Cumulative Illness Rating Scale – Geriatrics; EOD: early onset depression; LOD: late-onset depression; LLD+NC: late-life depression and normal cognition; LLD+MCI: late-life depression and mild cognitive impairment.