Association of Molecular Senescence Markers in Late-Life Depression With Clinical Characteristics and Treatment Outcome

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Abstract

IMPORTANCE Many older adults with depression do not experience remission with antidepressant treatment, and markers of cellular senescence in late-life depression (LLD) are associated with greater severity of depression, greater executive dysfunction, and higher medical illness burden. Since these clinical characteristics are associated with remission in LLD, molecular and cellular senescence abnormalities could be a possible biological mechanism underlying poor treatment response in this population.

OBJECTIVE To examine whether the senescence-associated secretory phenotype (SASP) index was associated with the likelihood of remission from a depressive episode in older adults.

DESIGN, SETTING, AND PARTICIPANTS A nonrandomized, open-label clinical trial was conducted between August 2009 and August 2014 in Pittsburgh, Pennsylvania; St Louis, Missouri; and Toronto, Ontario, Canada, with older adults in a current major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) diagnostic criteria. Data from biomarker analyses were reported according to the clinical trial archived plasma samples run in March 2021. Data were analyzed from June to November 2021.

EXPOSURE Venlafaxine extended release (dose ranging from 37.5 mg to 300 mg daily) for up to 12 weeks.

MAIN OUTCOMES AND MEASURES The association between a composite biomarker-based index (SASP index) and treatment remission in older adults with major depression was measured using clinical data and blood samples.

RESULTS There were 416 participants with a mean (SD) age of 60.02 (7.13) years; 64% (265 participants) were self-reported female, and the mean (SD) Montgomery-Asberg Depression Rating Scale score was 26.6 (5.7). Higher SASP index scores were independently associated with higher rates of nonremission, with an increase of 1 unit in the SASP index score increasing the odds of nonremission by 19% (adjusted odds ratio, 1.19; 95% CI, 1.05-1.35; P = .006). In contrast, no individual SASP factors were associated with remission in LLD.

CONCLUSIONS AND RELEVANCE Using clinical data and blood samples from a nonrandomized clinical trial, the results of this study suggest that molecular and cellular senescence, as measured with the SASP index, is associated with worse treatment outcomes in LLD. Combining this index score reflecting interrelated biological processes with other molecular, clinical, and neuroimaging markers may be useful in evaluating antidepressant treatment outcomes. These findings inform a path forward for geroscience-guided interventions targeting senescence to improve remission rates in LLD.
Introduction

Achieving response and remission in older adults with major depressive disorder (late-life depression [LLD]) is a major clinical challenge. Treatment response and remission rates in LLD are approximately 50% after first-line antidepressant treatment. Nonremission leads to persistent depressive symptoms, a source of depleted psychological well-being, increased disability, accelerated cognitive decline, and premature mortality in older adults. Therefore, identifying mechanisms and factors associated with treatment outcomes is key for improving therapeutics and for a priori identification of individuals for whom antidepressant treatment would be more effective. A recent meta-analysis identified higher baseline depression severity, comorbid anxiety, and executive dysfunction as the most important clinical variables associated with poor treatment response in LLD. Other studies have also identified cardiovascular risk factors (eg, metabolic syndrome), cerebrovascular disease, brain structural changes, physical comorbidity, and frailty as variables associated with poor treatment response. Some of these variables are common in depression across the lifespan (eg, comorbid anxiety and depression severity), but others are geriatric specific (eg, cerebrovascular disease burden and executive dysfunction), suggesting that remission with treatment in LLD may have specific mechanisms that are associated with age-related brain and systemic aging processes.

From a geroscience perspective, identifying and targeting biological processes associated with biological aging can ideally prevent, or at a minimum delay, the onset and progression of multiple chronic diseases and adverse age-related health outcomes that are typically observed in older adults. Previous works have suggested the involvement of biological aging and cellular senescence abnormalities in the biological mechanisms of LLD. For example, abnormalities in proteostasis control, heightened proinflammatory status, mitochondrial dysfunction, insulin resistance, and metabolic dysregulation have been described in LLD. They are associated with cognitive impairment, physical comorbidity burden, and higher mortality risk. Cellular senescence and changes in its cellular secretome (ie, the senescence-associated secretory phenotype or SASP) are other important hallmarks of biological aging. The SASP factors comprise several signaling proteins associated with inflammatory control, tissue remodeling, cell growth, cell cycle control, and metabolic regulation. They act in concert in different tissues and cell types, propagating prosenescence signals, leading to cellular senescence changes in neighboring cells and distant tissues. Reflecting these multiple interrelated biological pathways and functions, examining them as a biomarker-composite index may be more robust than examining each individual factor separately for examining disease outcomes, much as polygenic risk scores are more predictive than a single source of genetic variation. For example, recent studies have shown that a SASP index, including 22 SASP factors, is substantially elevated in LLD and associated with the severity of depressive symptoms, executive dysfunction, the burden of physical comorbidity, and markers of worse brain health.

Biological mechanisms of aging itself may drive LLD treatment outcomes. A genome-wide association study, including 184 individuals treated with venlafaxine extended release (XR), has identified 8 loci associated with treatment remission in LLD. The most common biological pathways associated with these genes were proteostasis regulation (eg, ubiquitin-proteasome system) and vascular health. Another recent study including 64 older adults with LLD, investigated the transcriptomic profile associated with remission with escitalopram and memantine treatment and showed that both medications strongly modulated inflammatory responses. Other biological pathways associated with remission were cellular proliferation, apoptosis (escitalopram only), cellular clearance, metabolism, and cytoskeletal dynamics (escitalopram and memantine). These studies point to processes implicated in accelerated biological aging (ie, immunoinflammatory...
response, cellular proliferation and apoptosis, and metabolic control) as mechanisms and variables associated with treatment response and remission in LLD. 16

Thus, we undertook an analysis to evaluate whether SASP factors, systemic indicators of abnormal cellular senescence, were associated with treatment remission in a large sample of older adults with LLD. Our primary hypothesis was that a higher composite score of SASP factors (the SASP index) would be associated with treatment resistance (ie, nonremission to venlafaxine XR treatment). We also evaluated the association between the SASP index and demographic and clinical characteristics.

Methods

In this nonrandomized controlled trial, we analyzed blood samples and clinical data from participants in the open-label phase of the Incomplete Response in Late-Life Depression: Getting to Remission (IRLGREY) Study, a 3-site trial in which treatment remission was assessed prospectively. 26 This study reports secondary data analyses focusing on the association between blood-based biomarkers and treatment remission according to data available from the IRLGREY study. The prespecified primary and secondary outcomes have been previously published. 26, 27 Participants provided written informed consent, and ethics approval was obtained from the institutional review boards at the Centre for Addiction and Mental Health in Toronto, the University of Pittsburgh, and Washington University in St Louis. This study follows the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline. The trial protocol is available in Supplement 1.

Study Sample

The IRLGREY study, conducted between August 2009 and August 2014, has been described in detail previously. 26 Participants were aged 60 years or older and had current nonpsychotic major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) diagnostic criteria 28 with a score of 15 or higher on the Montgomery-Asberg Depression Rating Scale (MADRS). 29 The diagnosis of MDD and the presence of a major depressive episode were confirmed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-IV-TR), Research Version, Patient Edition. 30 Exclusions were lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, other psychotic disorders, or current psychotic symptoms; clinical history of dementia; alcohol or substance use disorder in the past 6 months; imminent suicide risk; unstable physical illness; or contraindication to venlafaxine XR.

Intervention

Participants were treated for up to 12 weeks openly with venlafaxine XR. Participants started at 37.5 mg per day and flexibly titrated as needed up to 300 mg per day following a standardized protocol as published previously. 26

Outcome Measure and Additional Demographic and Clinical Variables

Depression symptom severity was measured by the MADRS score assessed at study baseline, week 1, week 2, and every 2 weeks thereafter for 12 weeks, with remission defined as MADRS scores of 10 or below for 2 consecutive assessments at phase end.

Demographic (age, self-reported sex, self-reported race [Black, White], years of education) and anthropometric (weight, height) data were obtained in the baseline assessment. Race was assessed in this study because it is a social variable that can influence access to treatment and the antidepressant remission rates. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured while sitting after at least 5 minutes of resting. Systolic and diastolic blood pressure values are the mean of 2 measurements taken 5 minutes apart. Physical comorbidity burden was assessed with the Cumulative Illness Rating Scale–Geriatrics. 31
Information about the participant’s history, including the length of the current depressive episode, age of onset of the first depressive episode, depressive episode recurrence, and presence of comorbid anxiety disorder, was obtained during the SCID-IV-TR interview. In addition, the MDD was classified as early-onset depression (EOD) or late-onset depression (LOD) depending on whether the first depressive episode happened before or after the age of 60 years.

A neuropsychological test battery was administered before starting venlafaxine XR. Executive function was evaluated using 2 tests from the Delis-Kaplan Executive Function System—the Color-Word Interference task (measuring response inhibition) and the Trail Making Test (measuring set-shifting and cognitive flexibility). The Color-Word Interference condition 3, called inhibition, assesses the ability to inhibit an automatic response (ie, reading words); instead, participants must produce a response that requires more effort (ie, naming the colors of words). The Trail Making Test condition 4 (also known as the Number-Letter Switching condition) requires participants to switch back and forth between connecting numbers and letters (ie, 1-A, 2-B, to 16-P). Condition 5 is a motor speed condition in which participants trace over a dotted line connecting circles on the page as quickly as possible to gauge their motor drawing speed. Comparing performance on condition 4 (which assesses cognitive flexibility) with performance on condition 5 (which assesses motor speed) removes the motor speed element from the test score to ascertain cognitive flexibility; thus, to evaluate set-shifting performance, we used the Delis-Kaplan Executive Function System normed scaled score (with a mean [SD] score of 10 [3]) for the difference in speeds between condition 4 and condition 5. All tests were scored according to published age-adjusted norms for each test, and additional details about the neuropsychological testing and scoring can be found elsewhere.

SASP Factors
Blood was collected by venipuncture with EDTA tubes after overnight fasting and processed immediately after collection. Plasma was obtained from the blood by centrifugation at 3000 g for 10 minutes at 4 °C. Plasma was separated, aliquoted, and stored in a −80 °C freezer until the laboratory analysis.

The SASP factors were analyzed by a customized multiplex assay (R&D System) using the Luminox 100/200 platform (Luminex). All the experiments were performed according to the manufacturer’s instructions. All the biomarkers were analyzed using the same assay batch, and the coefficient of variation was less than 10% for all analytes. All samples were analyzed on the same day to reduce variability across laboratory experiments.

The SASP factors included in the SASP index are the IGFBP6, IGFBP2, CCL4, interleukin-1β, granulocyte-macrophage-colony-stimulating factor, placental growth factor, angiogenin, migration inhibitory factor-1, macrophage inflammatory protein (MIP)-1α, chemokine growth-regulated protein α, interleukin-6, human monocyte chemoattractant protein-4, glycoprotein 130, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, interleukin-8, MIP-3α, osteoprotegerin, metallopeptidase inhibitor-1, urokinase-type plasminogen activator receptor, tumor necrosis factor (TNF) receptor-1, and TNF receptor-Ⅱ. We selected the candidate SASP proteins included in our analyses according to previous preclinical studies focused on the changes in the secretome pattern of senescent cells and our previous publications. The raw data were log2 transformed and standardized to the z score. We calculated the SASP index score for each participant according to the following regression formula: SASP index = \( \beta_1 x_1 + \ldots + \beta_2 x_2 \), where \( \beta \) is the individual weight and \( x \) is the standardized value of each biomarker included in the SASP index. The weight for each factor was derived from a previous publication from our group using an independent and clinically heterogeneous sample of older adults with and without a history of MDD (eTable 1 in Supplement 2). The SASP index mean was centered at 0, with an SD of 1 in the whole sample.

Statistical Analysis
First, we conducted a descriptive analysis of all the continuous variables and the visual inspection of P-P plots to evaluate whether they followed a normal distribution. The variables that did not show
a normal distribution were log-transformed. Then, we performed 2-sided $t$ tests to assess the association between demographic variables (eg, sex) or characteristics of the MDD (eg, LOD vs EOD) and the SASP index scores. We also performed Pearson correlation analyses to evaluate the association between SASP index scores, baseline demographics, clinical data, and executive function performance data.

We evaluated whether treatment outcome (nonremission vs remission) was associated with differences in SASP index score or other baseline demographic, clinical, and executive function performance data using $t$ tests. Analyses of covariance were done to evaluate the relevance of potential covariates on the association between treatment outcome and the SASP index score. Finally, we performed a logistic regression analysis to assess potential variables associated with treatment outcome to venlafaxine XR (treatment resistance as the reference group). First, we evaluated whether the SASP index scores baseline demographic, clinical, and executive function performance data were associated with treatment resistance in unadjusted models (a total of 12 analyses were run in the unadjusted logistic regression analyses). Then, variables that were significantly associated with treatment resistance in the unadjusted model (ie, variables with $P < .05$) were entered simultaneously in the model (adjusted model). We did not test the interaction between the SASP index and covariates in the logistic regression models. We used the Hosmer-Lemeshow test to evaluate the goodness-of-fit of the model. We also did the same set of analyses with each SASP factor. All analyses were performed using Stata statistical software version 17 for Windows (StataCorp). Data were analyzed from June to November 2021.

Results

SASP Index and Baseline Characteristics

Participants totaled 416 and were included in this analysis if they had complete data from baseline and at least 1 follow-up visit, plus baseline biomarker data. Participants’ mean (SD) age was 60.0 (7.1) years, 64% (265 participants) were self-reported female, and the mean (SD) MADRS score was 26.6 (5.7). Table 1 shows the demographic and clinical characteristics of the sample, broken down by their remission status.

The 103 participants with LOD had significantly higher SASP index scores than the 313 participants with EOD (mean [SD], 0.39 [0.16] vs −0.05 [0.10]; $t_{414} = 2.25$; $P = .02$). Self-reported male sex was significantly associated with higher SASP index scores (mean [SD], 0.41 [0.12] for male vs −0.13 [0.11] for female; $t_{414} = 3.16$; $P = .002$). In the full sample, higher SASP index scores were associated with older age ($r = 0.22$; $P < .001$), higher physical comorbidity burden ($r = 0.37$; $P < .001$), higher BMI ($r = 0.23$; $P < .001$), higher systolic blood pressure ($r = 0.11$; $P = .02$), and worse performance on executive function tests (set shifting score $r = −0.16$; $P = .001$; inhibition score, $r = −0.19$; $P < .001$; inhibition-switching score, $r = −0.19$; $P < .001$) (Figure 2). The SASP index scores were not significantly associated with MADRS scores ($r = −0.03$; $P = .53$), duration of the current depressive episode ($r = 0.07$; $P = .14$), educational level ($r = −0.09$; $P = .07$), or diastolic blood pressure measures ($r = −0.02$; $P = .60$).

SASP Index and Treatment Outcomes With Venlafaxine XR

With open-label treatment with venlafaxine XR, 176 participants achieved remission (remission group) and 240 did not (nonremission group). Participants in the nonremission group were more frequently male, had higher pretreatment MADRS scores, longer current depressive episode, higher diastolic blood pressure, and higher SASP index scores than those in the remission group (Table 1). The association between the SASP index scores and nonremission remained significant ($F_{5.407} = 5.37; P = .02$) after controlling for the effect of sex ($F_{5.407} = 8.36; P = .004$), baseline depressive symptoms ($F_{5.407} = 0.05; P = .80$), length of the current depressive episode ($F_{5.407} = 1.09; P = .29$), and diastolic blood pressure levels ($F_{5.407} = 1.73; P = .19$) (Figure 1). Since sex and age of onset were associated with SASP index, we also tested whether they were moderators of the association.
between treatment outcome and SASP index. Neither sex ($F_{3,412} = 2.81; P = .09$) nor age of onset of MDD ($F_{3,412} = 0.04; P = .84$) significantly moderated the association between treatment outcomes and the SASP index.

Since the SASP index includes 22 independent biomarkers, we also explored the association between each biomarker and remission status. We found that the MIP-3α and TNFRII were significantly higher in those with nonremission (eTable 1 in Supplement 2). However, this association did not remain significant after controlling for the covariates (sex, severity of baseline depressive symptoms, length of current depressive episode, and diastolic blood pressure) (eTable 1 in Supplement 2).

In the logistic regression analysis, a higher SASP index score was associated with a higher risk of nonremission, with an increase of 1 unit of the SASP index scores, increasing the risk of nonremission by 16% (odds ratio [OR], 1.16; 95% CI, 1.06-1.30; Wald = 6.47; $P = .01$). In the adjusted model, including sex, MADRS scores, and cognitive inhibition and set-shifting scores, the SASP index scores remained independently associated with a 19% higher risk of nonremission of the major depressive episode (OR, 1.19; 95% CI, 1.05-1.35; Wald = 7.48; $P = .006$) (Table 2). We also evaluated the association between each 22 independent SASP biomarkers and treatment outcomes. Again, the only biomarker that was associated with nonremission was the MIP-3α (OR, 1.11; 95% CI, 1.00-1.23; Wald = 4.08; $P = .045$). However, this association did not remain significant in the adjusted model (OR, 1.09; 95% CI, 0.98-1.22; Wald = 2.46; $P = .12$) (eTable 2 in Supplement 2).

### Table 1. Sample Characteristics According to Treatment Outcome After Treatment With Venlafaxine Extended Release

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%) by treatment outcome</th>
<th>Statistics</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonremission (n = 240)</td>
<td>Remission (n = 176)</td>
<td></td>
</tr>
<tr>
<td><strong>Self-reported sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>139 (58)</td>
<td>126 (72)</td>
<td>$\chi^2 = 7.74$</td>
</tr>
<tr>
<td>Male</td>
<td>101 (42)</td>
<td>50 (28)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>68.6 (6.9)</td>
<td>69.7 (7.4)</td>
<td>$t_{414} = 1.54$</td>
</tr>
<tr>
<td><strong>Education, mean (SD), y</strong></td>
<td>14.2 (2.8)</td>
<td>14.7 (2.8)</td>
<td>$t_{414} = 1.65$</td>
</tr>
<tr>
<td><strong>Self-reported race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>29 (12)</td>
<td>17 (10)</td>
<td>$\chi^2 = 0.35$</td>
</tr>
<tr>
<td>White</td>
<td>211 (88)</td>
<td>159 (90)</td>
<td></td>
</tr>
<tr>
<td><strong>Montgomery-Asberg Depression Rating Scale score, mean (SD)</strong></td>
<td>27.7 (5.7)</td>
<td>25.1 (5.4)</td>
<td>$t_{414} = 4.72$</td>
</tr>
<tr>
<td><strong>Duration of current major depressive episode, mean (SD), d</strong></td>
<td>342 (673)</td>
<td>215 (508.8)</td>
<td>$t_{414} = 2.10$</td>
</tr>
<tr>
<td><strong>Comorbid anxiety diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>139 (58)</td>
<td>104 (59)</td>
<td>$\chi^2 = 0.24$</td>
</tr>
<tr>
<td>Yes</td>
<td>101 (42)</td>
<td>72 (41)</td>
<td></td>
</tr>
<tr>
<td><strong>Age of onset of major depressive disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late onset depression</td>
<td>68 (28)</td>
<td>51 (29)</td>
<td>$\chi^2 = 2.91$</td>
</tr>
<tr>
<td>Early onset depression</td>
<td>172 (72)</td>
<td>126 (71)</td>
<td></td>
</tr>
<tr>
<td><strong>CIRS-G, Cumulative Illness Rating Scale--Geriatric total score, mean (SD)</strong></td>
<td>10.1 (4.6)</td>
<td>9.6 (4.2)</td>
<td>$t_{414} = 1.18$</td>
</tr>
<tr>
<td><strong>Body mass index, mean (SD)</strong></td>
<td>29.8 (7.3)</td>
<td>29.6 (6.0)</td>
<td>$t_{414} = 0.25$</td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD), mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133.4 (19.4)</td>
<td>130.3 (18.7)</td>
<td>$t_{414} = 0.92$</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.5 (11.6)</td>
<td>74.7 (11.5)</td>
<td>$t_{414} = 2.40$</td>
</tr>
<tr>
<td>Set shifting score, mean (SD)</td>
<td>8.5 (4.1)</td>
<td>8.9 (4.1)</td>
<td>$t_{414} = 0.93$</td>
</tr>
<tr>
<td>Response inhibition score, mean (SD)</td>
<td>10.4 (3.1)</td>
<td>10.2 (2.9)</td>
<td>$t_{414} = 0.65$</td>
</tr>
<tr>
<td>Response inhibition-shifting score, mean (SD)</td>
<td>9.9 (3.4)</td>
<td>10.2 (3.7)</td>
<td>$t_{414} = 1.01$</td>
</tr>
<tr>
<td>Senescence-associated secretory phenotype index score, mean (SD)</td>
<td>0.25 (0.10)</td>
<td>−0.19 (0.14)</td>
<td>$t_{414} = 2.58$</td>
</tr>
</tbody>
</table>

* Body mass index is calculated as weight in kilograms divided by height in meters squared.
Discussion

In this nonrandomized controlled trial, we explored whether circulating molecular markers of cellular senescence (SASP factors) were prospectively associated with nonremission to venlafaxine treatment in a large sample of older adults with MDD. A higher SASP index composite score was a significant and independent variable associated with nonremission in this population. By contrast, none of the individual SASP biomarkers was independently associated with remission status. We also showed that higher SASP index scores were associated with specific characteristics of the depressive episode as a geriatric syndrome, namely, later age of onset, a higher burden of medical comorbidity, and executive dysfunction. This is important because it demonstrates that the key interrelated biological processes of aging called senescence may underlie many cases of LLD, particularly in the context of poor treatment response. This finding is concordant with research on late-life neuropsychiatric disorders and could lead to geriatric-specific solutions to improve treatment outcomes in mental disorders by interrogating and intervening at the level of cellular aging.\(^{36,37}\)

Inflammatory markers constitute a significant component of the SASP index,\(^{38}\) and several studies have addressed whether inflammatory markers are associated with antidepressant treatment outcomes, with mixed results. For example, in an early study of younger adults with MDD treated with escitalopram for 12 weeks, higher serum TNF-α was associated with a worse treatment response.\(^{39}\) However, in 2 other studies, plasma levels of TNF-α, TNF-α receptors, or other inflammatory biomarkers (eg, C-reactive protein, interleukin-6) did not project response or remission to treatment with sertraline, transcranial direct current stimulation, or omega-3 fatty acid.\(^{40,41}\) In a study of 52 young participants with MDD treated with venlafaxine, none of 7 inflammatory markers were individually associated with treatment response.\(^{42}\) However, recent meta-analyses\(^{43,44}\) suggested that higher levels of interleukin-8 and C-reactive protein are associated with worse treatment response in MDD, although these associations had small effect sizes. All these studies evaluated whether individual biomarkers were associated with outcome; none assessed whether a composite index was associated with antidepressant treatment outcome, and they focused mostly on a young and middle-aged adult population.

Like these other studies, none of our individual inflammatory (or other) biomarkers was associated with remission with antidepressant treatment. By contrast, when all these biomarkers were incorporated into a single composite index (SASP index) associated with different pathways affected by pathological aging processes (eg, inflammation, metabolic control, cell growth, and tissue remodeling), the SASP index showed a robust association with remission in LLD. Our findings,
thus, provide evidence that moving beyond the 1 disease, 1 molecule paradigm by incorporating multiple biomarkers reflecting different biological pathways into a composite index can be more powerful in informing the biological mechanisms associated with treatment outcomes for psychiatric disorders. Other examples in psychiatry include the development of polygenic risk scores to investigate the mechanisms and biological variables associated with treatment response in major depression.\textsuperscript{45-47}

Previous works have explored the association between telomere length, a robust marker of cellular senescence, and MDD across the lifespan. Overall, there is evidence of shorter leukocyte telomere length in patients with MDD, with mild to moderate effect size (Cohen $d = -0.205$).\textsuperscript{48} Also, a recent study\textsuperscript{49} reported a substantial association between the severity of the depressive episode in LLD and shorter leukocyte telomere length. A few small clinical trials\textsuperscript{50-52} evaluated whether leukocyte telomere length was associated with treatment response or remission in MDD, with mixed results. None of these studies included older adults with LLD, a population more vulnerable to age-related biological abnormalities.\textsuperscript{53} Our previous study\textsuperscript{18} evaluated the association of molecular and cellular senescence with the outcome of protocolized antidepressant treatment in a large sample of older patients with MDD. We focused on well-established circulating SASP factors.\textsuperscript{15-17} Our finding that a higher SASP index score, reflecting more intense molecular and cellular senescence abnormalities, is associated with treatment outcome supports the hypothesis that enhanced

Figure 2. Scatterplots of the Association Between Senescence-Associated Secretory Phenotype (SASP) Index Scores, Age, Medical Comorbidity Burden and Executive Function Performance

Dots indicate each individual included in the analysis; shaded area indicates 95% CI for the linear trend; line indicates linear trend. CIRS-G indicates Cumulative Illness Rating Scale–Geriatrics.
age-related biological changes render older individuals with LLD less prone to achieve remission of the depressive episode.

These previous results and our congruent findings suggest that molecular and cellular senescence abnormalities may be a common mechanism negatively associated with treatment outcomes indirectly and directly. Cellular senescence and the SASP are viewed as responses to different stressors that lead to cell dysfunction (e.g., DNA damage and loss of proteostasis). The accumulation of senescent cells leads to a gradual loss of the capacity of tissues to optimally compensate homeostatic function against deleterious stimuli and recover normal function even after removing the noxious stimuli. The accumulation of senescent cells in different tissues and SASP factors systemically can lead to the incidence of various age-related diseases and worse medical outcomes. In the context of our study, we can speculate that a higher SASP index is a general indicator of systemic and brain dysfunction that leads to a worse response to antidepressants. Moreover, these poor outcomes observed in LLD can also reflect a broader process of unhealthy aging that can be identified by an elevated SASP index. Interventions and lifestyle modifications, including increased physical activity, improved dietary patterns, and good management of chronic medical conditions, contribute to improved general health, possibly by regulating different age-related biological processes and slowing of molecular and cellular senescence. Importantly, these lifestyle and behavioral factors are protective against the development of depressive symptoms and can be used as adjunctive treatment options to improve treatment response in older adults with major depression, but also can be useful for the prevention of other age-related outcomes commonly observed in this population. Finally, geroscience-guided interventions, such as using senolytic drugs that specifically clear senescence cells aiming to reduce or mitigate cellular senescence and the harmful effects of SASP factors, could be used to improve antidepressant treatment outcomes in LLD. Such strategies have recently showed promising results to mitigate anxiety and cognitive impairment after chronic stress in different animal models.

Table 2. Logistic Regression to Determine Factors Associated With Treatment Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Wald</th>
<th>P value</th>
<th>Adjusted* OR (95% CI)</th>
<th>Wald</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senescence-associated secretory phenotype index score</td>
<td>1.16 (1.06-1.30)</td>
<td>6.47</td>
<td>.01</td>
<td>1.19 (1.05-1.35)</td>
<td>7.48</td>
<td>.005</td>
</tr>
<tr>
<td>Self-reported sex</td>
<td>2.06 (1.26-3.37)</td>
<td>8.24</td>
<td>.004</td>
<td>1.86 (1.23-3.11)</td>
<td>8.00</td>
<td>.005</td>
</tr>
<tr>
<td>MADRS score</td>
<td>0.908 (0.87-0.95)</td>
<td>19.99</td>
<td>&lt;.001</td>
<td>1.10 (1.06-1.14)</td>
<td>23.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of MDE</td>
<td>1.000 (0.99-1.00)</td>
<td>3.55</td>
<td>.06</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age</td>
<td>1.007 (0.97-1.04)</td>
<td>1.41</td>
<td>.11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Self-reported race</td>
<td>1.099 (0.51-2.37)</td>
<td>0.58</td>
<td>.81</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Years of education</td>
<td>1.077 (0.99-1.17)</td>
<td>2.915</td>
<td>.09</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CIRS-G</td>
<td>.956 (0.90-1.01)</td>
<td>2.501</td>
<td>.11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Set shifting</td>
<td>1.117 (1.00-1.24)</td>
<td>4.246</td>
<td>.04</td>
<td>1.06 (1.00-1.13)</td>
<td>3.87</td>
<td>.05</td>
</tr>
<tr>
<td>Response inhibition</td>
<td>.867 (0.78-0.96)</td>
<td>7.702</td>
<td>.006</td>
<td>1.10 (1.01-1.19)</td>
<td>5.21</td>
<td>.02</td>
</tr>
<tr>
<td>Response inhibition-shifting</td>
<td>1.077 (0.99-1.18)</td>
<td>2.741</td>
<td>.01</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comorbid anxiety diagnosis</td>
<td>.941 (0.59-1.49)</td>
<td>0.66</td>
<td>.79</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.000 (0.99-1.01)</td>
<td>.001</td>
<td>.98</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diastolic</td>
<td>.983 (0.96-1.01)</td>
<td>1.763</td>
<td>.18</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMI*</td>
<td>1.014 (0.98-1.05)</td>
<td>.562</td>
<td>.453</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale-Geriatric; MADRS, Montgomery-Asberg Depression Rating Scale; MDE, current major depressive episode; NA, not applicable; OR, odds ratio.

* Adjusted by self-reported male sex, MADRS scores, and scores on cognitive inhibition and set-shifting tasks. OR greater than 1.0 indicates a higher risk of nonremission status.

** Body mass index is calculated as weight in kilograms divided by height in meters squared.
Several variables were significantly associated with a higher SASP index among the LLD participants. Self-reported sex was associated with the SASP index scores, with male participants having higher SASP index scores than female participants. A meta-analysis showed that biological sex was not significantly associated with leukocyte telomere length and MDD. Our study offers additional evidence that biological sex can be significantly associated with biological hallmarks of aging in LLD, with male individuals showing a higher SASP index score. This finding could explain the higher risk of poorer outcomes, such as higher mortality, in older male individuals with MDD compared with female individuals. Several lines of evidence suggest that patients with late-onset depression and early-onset depression have distinct biological mechanisms and long-term, age-related outcomes (eg, more rapid cognitive decline in LOD vs EOD). In our study, participants with LOD had higher SASP than EOD, again providing additional evidence for potential distinct mechanisms between these 2 subgroups of LLD.

Strengths and Limitations
Our study has some strengths (eg, a large sample and the use of protocolized antidepressant treatment to prospectively characterize outcome) and limitations. First and foremost, all participants were treated with venlafaxine XR, and we cannot distinguish whether the association between higher SASP index scores and nonremission is specific to venlafaxine or reflects a more general effect of molecular and cellular senescence on treatment remission in LLD. We did not have a specific measure of vascular risk scores in this sample, but a more systemic measure of medical burden (the Cumulative Illness Rating Scale–Geriatrics), and we may not have more detailed information about the association between the SASP index and vascular risk factors. Also, our sample mainly included White participants, and our results may not be generalizable to other racial or ethnic groups. Another potential limitation was the inclusion of participants who have a history of alcohol use disorder as long as it was in remission for at least 6 months. This duration may not be sufficient to rule out the impact of alcohol use disorder on senescence markers. However, we have previously reported on the absence of association between previous or current alcohol use and SASP index. Thus, it is unlikely that the inclusion of participants with a history of alcohol use disorder influenced the current results.

Conclusions
In conclusion, our findings suggest that molecular and cellular senescence, as measured with the SASP index, is significantly associated with worse treatment outcomes in LLD. Our study also demonstrates that a composite index, integrating biomarkers reflecting distinct but interrelated biological processes, is superior to any single biomarkers in the association with treatment remission in LLD. Our findings can inform a path forward for geroscience-guided interventions targeting senescence to improve remission rates in LLD.

ARTICLE INFORMATION
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Author Contributions: Drs Diniz and Lenze had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Reynolds, Butters, Lenze.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Diniz, Mendes-Silva, Lenze.

Critical revision of the manuscript for important intellectual content: Diniz, Mulsant, Reynolds, Blumberger, Karp, Butters, Vieira, Tseng, Lenze.

Statistical analysis: Diniz, Tseng.

Obtained funding: Diniz, Mulsant, Reynolds, Lenze.

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Supervision: Mulsant, Karp.

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REFERENCES


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Association of Molecular Senescence Markers in Late-Life Depression With Treatment Outcome


SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
eTable 1. Comparison Between Individual SASP Factors Between Nonremission vs Remission Groups
eTable 2. Logistic Regression of Each Individual SASP Factor to Predict Treatment Outcome