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Relationship between novel inflammatory biomarker galectin-3 and depression symptom severity in a large community-based sample

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Abstract

Major depressive disorder is associated with pro-inflammatory markers, such as cytokines TNF-alpha, IL-6, IL-1ß, and C-reactive protein. Galectin-3 is a novel emerging biomarker with pro-

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Contributors: All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Darlene R. King, M.D. contributed to the analysis and interpretation of data for the work. She collaborated with Jayme M. Palka, Ph.D. to perform statistical analyses. She drafted the work and revised it critically for important intellectual content. She edited multiple versions of the manuscript. Damilola C. Salako, M.D. assisted with the acquisition and analysis of data. She contributed to drafting the work. Samia Kate Arthur-Bentil, M.D. reviewed and edited multiple versions of the manuscript. Arielle E. Rubin, M.D. assisted with the acquisition and analysis of data. Jay B. Italiya, M.D. assisted with the acquisition and analysis of data. Jenny S. Tan, M.D., Kaylee Davis-Bordovsky, M.D., and Matthew Faubion, M.D., wrote portions of, as well as, reviewed and edited multiple versions of the manuscript. Dimitri G. Macris, M.D. assisted with the acquisition and analysis of data. Hunter K. Neely, M.D. reviewed and edited the manuscript. Jayme M. Palka, Ph.D. performed the statistical analyses, helped write, review and edit multiple versions of the manuscript. Justin L. Grodin, M.D., M.P.H. contributed to the conception of the work and the acquisition of the data for the work. He also reviewed and edited the manuscript. Carol S. North, M.D. contributed to the conception of the work, the acquisition, the analysis and interpretation of the data for the work. Dr. North helped write, reviewed and edited multiple versions of the manuscript. E. Sherwood Brown, M.D., Ph.D. designed the study and contributed to the conception of the work, the acquisition, the analysis and interpretation of the data for the work. Dr. Brown reviewed and edited multiple versions of the manuscript. He provided final approval of the version to be published.

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Conflict of Interest

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inflammatory properties. It is a saccharide binding protein distributed throughout many tissues with varying functions and is a predictor of poor outcomes in patients with heart failure and stroke. However, its role as a predictor in depressive symptom severity remains undefined. Data from the community-based Dallas Heart Study (n = 2554) were examined using a multiple linear regression analysis to evaluate the relationship between galectin-3 and depressive symptom severity as assessed with Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scores. Additional covariates included age, sex, race/ethnicity, body mass index (BMI), years of education, serum creatinine, history of diabetes, and smoking history. Galectin-3 levels statistically significantly predicted QIDS-SR depressive symptom severity (β = 0.055, p = .015). Female sex, smoking status, and BMI were found to be statistically significant positive predictors of depression severity, while age, years of education, non-Hispanic White race, and Hispanic ethnicity were negative predictors of depressive symptom severity. In this large sample, higher galectin-3 levels were associated with higher levels of depressive symptoms. The findings suggest that galectin-3 may be a new and useful inflammatory biomarker associated with depression.

1. INTRODUCTION

Major depressive disorder (MDD) is the most common psychiatric disorder and a leading source of disability worldwide (North and Yutzy, 2018). The inflammatory model of MDD provides a well-known proposed mechanism for the development of depressive symptoms. It includes etiologies such as the cytokine hypothesis. Neurobiological correlates supporting these theories include elevated levels of inflammatory markers (IL-1ß, IL-6, tumor necrosis factor-α, and C-reactive protein) in certain patients with MDD (McGorry et al., 2014). Activation of the brain's innate immune system has been shown to induce depressive-like behavior in mice (Dantzer and Kelley, 2007). Additionally, cytokines are known to affect neurotransmitter production through their action on indoleamine 2,3-dioxygenase (IDO), generating neurotoxic metabolites to activate glutamatergic receptors in the brain (Dantzer and Kelley, 2007). Mice with elevated IDO have altered levels of brain serotonin neurotransmission and depressive-like behavior (Dantzer and Kelley, 2007). Overall, there is a robust connection between cytokines, inflammation, and the development of depressive symptoms. Research is ongoing to identify additional inflammatory mediators of MDD. Such biomarkers may elucidate unknown mechanisms of MDD as well as lead to potential drug targets in the future (Duman, 2013).

A novel inflammatory biomarker is galectin-3 protein (gal3). Gal3 is part of a family of β-galactoside-binding lectins. It is widely distributed in many tissues and is associated with systemic inflammation (Burguillos et al., 2015; Dumic et al., 2006). In the cytoplasm, gal3 promotes cell survival. In the nucleus, it regulates gene expression, and in the extracellular space, it modulates cell-to-cell communication. Of interest, are proposed mechanisms for gal3 mediating inflammation and host defense through the same cytokines that are also implicated in MDD (Dong et al., 2018). Gal3 binds to IL-4, and the administration of a neutralizing antibody against gal3 decreases the expression of other neuroinflammatory markers including IL-1ß, IL-6, TNF-α, and NOS2 (Yip et al., 2017). Gal3 is positively correlated with obesity and inflammation as measured by inflammatory markers IL-6 and CRP (Pang et al., 2016). The effects of gal3 on neurons are not well understood. Some

suggest it may play a detrimental role in exacerbating inflammation immediately after a cerebral ischemic infarct, while other studies suggest gal3 may help with neurogenesis (Shin, 2013; Venkatraman et al., 2018). Levels of gal3 were elevated in patients with Alzheimer's disease compared with healthy controls (Wang et al., 2015). Gal3 secretion is associated with macrophage and fibroblast activation and subsequent inflammation and fibrosis (de Boer et al., 2012; Dumic et al., 2006). Macrophage and fibroblast production of gal3 has been studied in experimental models of cardiac (Sharma et al., 2004), renal (Henderson et al., 2008), and hepatic fibrosis (Henderson et al., 2006). As all of these conditions are associated with depression and neurocognitive dysfunction, further investigation is warranted into whether there is an association between depression and gal3 (Cannon et al., 2017; Hackett et al., 2014; Halaris, 2013).

A cross-sectional study analyzed gal3 and depression in participants with type 1 diabetes (ages 18–59, n= 283). Those with type 1 diabetes and depression had significantly higher levels of serum gal3 versus those with only type 1 diabetes (Melin et al., 2018). However, these findings must be interpreted in the context of other distinct mechanisms implicated in type 1 diabetes that may not be applicable to the general population with MDD. Such mechanisms include impaired glucoregulatory mechanisms, insulin resistance, autoimmune activation of cytokines, and unique psychosocial stressors (Wang et al., 2019). To date, there are no studies of gal3 levels in patients with MDD alone.

We evaluated the relationship between gal3 and depressive symptom severity using a large, multi-ethnic sample that includes males and females. It was hypothesized that gal3 would be a positive predictor of depressive symptomatology. Given the large and diverse sample, we explored the influence of sex and race/ethnicity on the association of gal3 and depressive symptoms.

2. EXPERIMENTAL PROCEDURES

The Dallas Heart Study (DHS) is a community-based cohort study conducted from 2000–2009 to examine differences in cardiovascular health among ethnic groups. The study is a population-based probability sample of Dallas County in which detailed socioeconomic, biomarker, and imaging data were collected from participants. As such, this study sample is not limited to patients with cardiac disease, but rather allows inferences at the general population level. African-American participants were intentionally oversampled (50% of the sample) to provide sufficient power to analyze findings relevant to this group. DHS was conducted in two phases. DHS-1 refers to the first collection of the community-based sample from Dallas County between 2000 and 2002. The design and details of the first phase have been described in detail (Victor et al., 2004). A second phase (DHS-2) was conducted from 2007–2009. Details of the second phase can be found in a prior report (Hlis et al., 2018). This second phase included a depression assessment. Thus the current report consists of a cross sectional analysis of the data from DHS-2.

Participants

Participants in this study were selected from the DHS-2 cohort which included surviving members of DHS-1 plus new participants to replenish subjects lost to attrition in order to

maintain sample size. DHS-2 participants (n = 3401) completed a demographic survey, provided blood samples, underwent structural neuroimaging, and completed the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al., 2003). Longitudinal data are not available for every DHS-2 participant. Additionally, blood samples were not collected in DHS-1. As biomarker data from blood samples is the focus of the present study, we utilized only a cross-section of the data, including only those who participated in DHS-2. All participants signed written informed consents approved by The University of Texas Southwestern Medical Center Institutional Review Board.

Inclusion criteria

To be included in the current analysis, participants were required to have gal3 levels and QIDS-SR data. Participants were excluded from the analytic sample if they had missing covariate data or history of cardiac arrest, myocardial infarction, or stroke. Due to the known association of galectin with cardiovascular illnesses, these participants were excluded while the analysis controlled for Diabetes Mellitus which is associated with inflammation. In addition, because gal3 levels are influenced by creatinine clearance, creatinine levels were controlled for in the regression model. Of the initial sample of 3401 participants, 375 (11.00%) were missing a valid QIDS-SR score, 208 (6.10%) were missing a valid gal3 level, 164 (4.82%) had a history of cardiac arrest, myocardial infarction, and/or stroke, and 266 (7.82%) had missing covariate data. Based on these criteria, 2554 participants were included in the final analytic sample (Table 1).

As a preliminary step, independent samples t-tests were conducted to determine whether the included and excluded groups differed demographically. Results from the independent samples t-tests used to compare the included (n = 2719) and excluded (n = 682) groups suggested that the two groups were statistically significantly different on all demographic variables aside from BMI, sex, and smoking status (Table 1). However, these differences were small in magnitude (i.e., $|d| < 0.25$) and deemed negligible.

Variables

Depressive symptom severity.—The QIDS-SR is a 16-item self-report questionnaire administered in English or Spanish that directly assesses depressive symptom severity over the past seven days for the nine major depressive symptoms listed in DSM-5 criteria for MDD. The QIDS-SR yields a total score with a possible range of zero to 27 (Rush et al., 2003). The instrument has acceptable psychometric properties and correlates highly with other frequently used and well-validated depression symptom self-report measures (Trivedi et al., 2004). It has been shown to be reliable and valid across race, age and language groups (e.g., coefficient alpha = 0.88) (Lamoureux et al., 2010; Rush et al., 2003). The QIDS was developed to improve on the available clinician and patient rating scales such as Patient Health Questionnaire-9, Beck Depression Inventory, and Hamilton Rating Scale for Depression in 4 distinct ways. It provides equivalent weightings (0–3) for each symptom item, provides clearly stated anchors that estimate the frequency and severity of symptoms, includes all DSM-*5* criterion items required to diagnose a major depressive episode, and provides matched clinician and patient ratings. Psychometric validation of the QIDS-SR has been documented in multiple studies which have shown its ability in being able to reliably

discriminate between individuals with and without a current major depressive episode (Suris et al., 2016).

Gal3 biomarker.—Plasma gal3 levels were collected in both DHS-1 and DHS-2. Blood samples were collected by venipuncture, EDTA tubes were used for storage, and samples were kept at 4°C for less than 4 hours before undergoing centrifugation (1430 g for 15 minutes). Plasma was extracted from the sample, frozen, and then stored at −70°C until measurements were taken. Plasma gal3 levels were detected from plasma samples using the Architect Galectin- 3 assay (Abbot Diagnostics, Abbott Park, Illinois), which is a quantitative chemiluminescent microparticle immunoassay. The assay has quantification limit of ≤ 4 ng/mL and value range from 4.0 – 114.90 ng/ml. Support for measurement of gal3 was provided by Abbott Diagnostics.

Demographic and laboratory data.—Additional covariates included sex, ethnicity, age, BMI, years of education, smoking status, history of diabetes, and serum creatinine levels. Serum creatinine values are a commonly used and accepted biomarker of renal function (Gowda et al., 2010). Renal dysfunction is a confounder causing elevated gal3 levels through lower clearance (Drechsler et al., 2015; Tang et al., 2011). Serum creatinine levels were collected to account for the confounding effect of renal dysfunction on galectin levels. These samples were collected in DHS-2 as part of a standard chemistry screen. Standard reference values range from 0.72 mg/dL to 1.18 in men and 0.55 to 1.02 in women (Ceriotti et al., 2008). BMI was selected as a covariate to account for effects of elevated BMI on gal3 levels, as prior research suggests that participants with BMI over 30 have a resting chronic low-grade inflammatory state with increased levels of gal3 produced by adipocyte cells (Weigert et al., 2010). Smoking status was selected as a covariate to account for the known relationship between smoking history and gal3, as gal3 expression is also increased in the lungs in smokers compared to non-smokers with chronic obstructive pulmonary disease (Pilette et al., 2007).

Statistical analysis

Two multiple linear regression models were analyzed to determine the predictive ability of gal3 on QIDS-SR score. Relevant demographic and health information (i.e., age, years of education, sex, race/ethnicity, serum creatinine level, BMI, history of diabetes, and smoking status) were included in both models as covariates. Gal3, age, years of education, serum creatinine level, and BMI were analyzed as continuous covariates while sex (male/female), race/ethnicity (black, white, and Hispanic), history of diabetes (yes/no), and smoking status (non-smoker, past/current smoker) were analyzed as nominal covariates. Additionally, while the first model did not include any plausible interaction terms, two interaction terms were added to the second model: gal3 × sex, gal3 × race/ethnicity. Both skew and kurtosis were within acceptable ranges (a value of +/− 2 for skewness and a value of +/−7 for kurtosis) for all variables except gal3 and creatinine (Rigdon, 1997). As such, these two variables were log transformed prior to being included in analyses. Additionally, categorical variables were dummy coded prior to analyses with the following reference categories: male (sex), non-Hispanic black (race/ethnicity), history of (diabetes), and non-smoker (smoking status). All

analyses were conducted using IBM SPSS Statistics version 25.0 (Armonk, NY: IBM Corp.). Results with *p*-values < .05 were considered statistically significant.

3. RESULTS

Demographic features of the participants included in the study are summarized in Table 1. Participants were primarily female (60.1%), non-Hispanic black (50.2%) and had no smoking history (55.1%). Mean age was 49.60 ± 11.09 years and mean years of education was 12.71 ± 2.14. Average QIDS-SR score was 5.50 ± 3.82 (range of 0–24) and the average gal3 level was 14.76 ± 5.23 (range 4–114 ng/ml). Approximately 11% of participants reporting using antidepressant medication.

Table 2 presents results for the first multiple linear regression in which the predictive ability of gal3 on QIDS-SR, while controlling for covariates, was examined. After excluding cases with missing data on one or more variables included in the analysis (i.e., listwise deletion), a total of $n = 2554$ participants remained. Omnibus results were first checked to determine whether the overall model was statistically significant [$F(10, 2543) = 23.671$, $p < .001$, $R^2 = 0.085$] before proceeding to an examination of individual predictors. Cumulatively, the predictors accounted for approximately 9% of variance observed in total QIDS-SR score. Importantly, gal3 was found to be a statistically significant predictor of QIDS-SR scores [$\beta = 0.055$, $p = .015$] such that an increase in gal3 levels is expected to result in an increase in QIDS-SR score. To further examine this important effect, the structure coefficient for gal3 was calculated ($r_s = 0.310$). This suggests that gal3 was able to uniquely account for approximately 10% of the obtained R^2 effect. All included covariates statistically significantly predicted QIDS-SR score with the exception of creatinine and history of diabetes which were statistically non-significant [$\beta = -0.002$, $p = .934$; $\beta = -0.008$, $p = .685$, respectively]. Most notable was the effect of sex on QIDS-SR score [$\beta = 0.168$, $p < .001$] suggesting that on average, women score nearly one-fifths of a standard deviation higher than men on the QIDS-SR. Results also indicated that in comparison to non-Hispanic black participants, both non-Hispanic white [$\beta = -0.47$, $p = .027$] and Hispanic [$\beta = -0.055$, $p = .010$] participants have lower QIDS-SR scores, on average.

An additional exploratory multiple regression analysis was conducted to control for medication use – a dichotomous variable indicating whether the participant was using any antidepressants (yes/no) – as medication use groups had statistically significant differences in gal3 levels [$t(2552) = -5.033$, $p < .001$] with higher levels shown in the anti-depressant use group. Gal3 remained a statistically significant predictor ($p = .035$) of QIDS score. Finally, two interaction terms were explored (gal3 × sex, gal3 × ethnicity). Neither of the interaction terms were found to be statistically significant ($p = .461$ and .706, respectively); therefore, results for models including these terms are not presented.

4. DISCUSSION

The pathophysiology of MDD is heterogeneous and complex. Multiple subtypes of MDD are recognized and the literature proposes many distinct but often overlapping causative etiologies (Hasler, 2010). This community-based sample from DHS-2 found that gal3

statistically significantly predicted depression symptom severity as measured by the QIDS-SR. This result demonstrates, for the first time, the association between gal3 and depression in a large sample. Our results suggest a potential bridge between the pro-inflammatory action of gal3 and the presence of depressive symptoms in a large, multi-ethnic population. A major strength of this study is the large, community-based sample with available demographic data. While gal3 has been implicated in mediating inflammation, with studies examining its role in heart failure, heart rate variability, coronary artery disease, cerebral ischemic infarct, neurodegeneration, brain tumors, dementia, and anxiety, its relationship to depression had not been explored (Cannon et al., 2017; Hackett et al., 2014; Halaris, 2013; Shin, 2013; Wang et al., 2015; Stajic, 2019). Substantial research supports a role of gal3 in inflammatory processes of cardiovascular and ischemic brain disease (Chen et al., 2015; Maiolino et al., 2015; Walther et al., 2000), and there is a greater prevalence of depression in these populations (Hackett et al., 2014; Halaris, 2013). In addition, gal3 predicts poor outcomes for patients with heart failure, coronary artery disease, and stroke (Cannon et al., 2017; Hackett et al., 2014; Halaris, 2013). Furthermore, gal3 is implicated in a Our results suggest gal3 as a novel biomarker in the inflammatory hypothesis of depressive symptomatology. In addition, elevated levels of these cytokines predict poorer response to selective serotonin reuptake inhibitor treatment (Majd et al., 2019). The inflammatory neural changes caused by cytokines are diverse, including alterations in vagal function and aberrant blood brain barrier permeability (Majd et al., 2019). Gal3 has pleiotropic effects in central nervous system inflammation, including a pro-inflammatory role, remodeling capacity in damaged CNS tissues, microglial activation and proliferation, and IL-4 mediated macrophage polarization (Burguillos et al., 2015; Shin, 2013). Studies have shown gal3 exerting cytokine-like regulatory actions in brain-resident immune cells via the JAK-STAT pathway, suggesting its action as an endogenous danger-signaling molecule under pathological conditions of the brain (Jeon et al., 2010). In cerebral ischemia models, gal3-dependent TLR-4 activation induced sustained microglia activation, prolonging inflammatory events in the brain (Burguillos et al., 2015). In patients with traumatic brain injury, gal3 may act as an alarmin, binding to TLR-4 and promoting inflammation and neuronal loss (Yip et al., 2017). TLR-4 has a regulatory role in immune response of the brain to stress and TLR-4 activation is suggested to play a role in the pathophysiology of depression via upregulation of pro-inflammatory cytokines and glutamate/γ-aminobutyric acid (GABA) transmission imbalance (Aboul-Fotouh et al., 2018; Garate et al., 2011). Eritoran is an investigational drug for sepsis and due to its structural similarity to gram-negative bacterial lipopolysaccharide lipid A, it acts as a TLR-4 antagonist. Eritoran was studied in a chronic restraint stress (CRS) model of depression in rats and its administration ameliorated CRS-induced depressive-like symptoms via blockade of the TLR-4 neuroinflammatory response to stress (Aboul-Fotouh et al., 2018). The exact mechanistic pathway by which gal3 might contribute to depressive symptoms has yet to be explored. Stajic et al studied the role of gal3 modulation of anxiety in mice and found that gal3 deletion in mice subjected to LPS neuroinflammation prevented increased IL-6, was protective against decreased BDNF, showed a decline in immunoreactivity, and decreased the effect of neuroinflammation on anxiety. LPS induced neuroinflammation in mice have shown decreased exploratory locomotor activity, anhedonia, and anxiety-like behavior. These findings provide a possible mechanistic link between gal-3 and depressive

symptomatology. Our findings open up various directions for future study regarding the role of gal3 in depression as well as adding to the broader discussion of an inflammatory model of depression. Further study of gal3 in depression may elucidate a novel inflammatory pathway involved in depressive symptomatology, such as that of the TLR-4 cascade.

Younger age was associated with higher QIDS-SR score, consistent with prior findings suggesting decreasing prevalence of depressive disorders with increasing age, at least up to age 65 (because individuals of age greater than 65 were included in the DHS study) (Byers et al., 2010). Greater number of years of education shows protective effects against depression for some populations; this was supported in our community-based sample as a lower number of years of education was associated with a higher QIDS-SR score (Bauldry, 2015). As expected, female sex was associated with a higher QIDS-SR score, a finding corroborated by previous research indicating sex differences in depression (Hasin et al., 2005; McCarter, 2008). A history of smoking and higher BMI were also significant predictors in our analyses of QIDS-SR. This is consistent with prior findings suggesting strong links between smoking and depression severity (Pratt and Brody, 2010), as well as BMI and depression severity (Mannan et al., 2016). This is further consistent with the inflammatory model of depression, as these factors cause both CNS and peripheral inflammation (Majd et al., 2019).

The study has several limitations. The cross-sectional design of DHS-2 offered a substantial amount of data at a single time point, thereby circumventing analysis of trends over time. Further, although our results indicate that gal3 levels are elevated in the presence of depressive symptoms, this study was unable to determine the causal mechanism of this relationship. Additionally, our available depression measure, the QIDS-SR, provides self-report data only for current symptoms. It does not provide MDD diagnosis, or allow for a determination of depression subtypes. The data set lacks information on the onset, duration, and potential mood co-morbidities of the self-reported depressive symptoms. In terms of the population with elevated gal3, this study does not address if these depressed individuals are similar or different than those with alternative inflammatory biomarkers. CRP levels were measured during DHS-2; Huckvale et al.(Huckvale et al., 2020) found that QIDS and CRP are statistically non-significantly related ($r = .035$; $p = .105$) in the DHS-2 sample. Although our analytic sample differs somewhat from Huckvale et al. due to differing exclusion/inclusion criteria, we found the same ($r = 0.038$, $p = .111$). We were unable to include additional immune biomarkers in our model as these data were not collected by DHS. This inhibits our ability to make conclusions about gal3 in relation to other more well-known biomarkers of inflammation. This study does not compare the severity of depressive symptoms in individuals with elevated gal3 vs alternative inflammatory biomarkers nor does it address the comorbidities these populations share. In addition, because our use of serum creatinine to control for renal function is limited by low sensitivity of creatinine in early stages of renal dysfunction, a more exact measure would be creatinine clearance or glomerular filtration rate. However, the serum creatinine estimate is consistent with prior studies evaluating effects of renal function and gal3 levels (Drechsler et al., 2015).

Overall, this study demonstrated that depressive symptom severity is statistically significantly associated with gal3 levels adjusted for age, sex, ethnicity, smoking history,

history of diabetes, education level, BMI, and serum creatinine in a general population sample without comorbid cardiac arrest, myocardial infarction, or stroke histories. Further study is needed to better clarify the mechanism(s) underlying the relationship between gal3 and depressive symptom severity. Future studies should also explore whether gal3 predicts antidepressant response and whether it decreases as depressive symptoms improve.

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Highlights

- Depression is associated with inflammatory markers
- Galectin-3 is an inflammatory biomarker associated with cognitive disorders
- Galectin-3 levels and depressive symptom severity were assessed in a community sample
- Galectin-3 levels statistically significantly predicted depressive symptom severity
- Galectin-3 appears to be a novel inflammatory biomarker associated with depression

Table 1

Descriptive Statistics for Included and Excluded Participants

	Listwise Deletion									
	Missing		Excluded		Included		Independent Samples *t*-Test			
	Freq.	%	Mean	SD	Mean	SD	*df*	*t*	*p*	*d*
QIDS-SR	375	11.0	5.87	4.39	5.50	3.82	610.34	1.879	.060	0.09
Galectin	208	6.1	16.08	6.92	14.76	5.23	828.92	4.529	< .001	0.22
Education	96	2.8	12.23	2.36	12.71	2.14	1136.46	−4.984	< .001	−0.21
Age	0	0.0	51.10	11.22	49.60	11.09	3399	3.404	.001	0.13
BMI	27	0.8	30.87	7.45	31.29	7.43	3372	−1.436	.151	−0.06
Creatinine	84	2.5	1.02	0.84	0.91	0.39	861.04	3.269	.001	0.17
							Chi-Square Test			
	Freq.	%	Freq.	%	Freq.	%	*df*	χ^2	*p*	
Sex	0	0.0	-	-	-	-	1	3.101	.078	-
Male	-	-	367	43.3	1019	39.9	-	-	-	
Female	-	-	480	56.7	1535	60.1	-	-	-	
Ethnicity[a]	104	3.1	-	-	-	-	2	33.430	< .001	-
Black	-	-	448	60.3	1283	50.2	-	-	-	
White	-	-	181	24.4	908	35.6	-	-	-	
Hispanic	-	-	114	15.3	363	14.2	-	-	-	
Smoking	123	3.6	-	-	-	-	1	0.958	.328	-
Never	-	-	384	53.0	1407	55.1	-	-	-	
Past/Current	-	-	340	47.0	1147	44.9	-	-	-	
Diabetes	0	0.0	-	-	-	-	1	5.553	.018	-
Yes	-	-	157	18.5	386	15.1	-	-	-	
No	-	-	690	81.5	2168	84.9	-	-	-	
Anti-depressant use	0	0.0					1	0.013	.909	
Yes	-	-	91	10.7	278	10.9				
No	-	-	756	89.3	2276	89.1				

Note.

[a]Statistically significant group differences found between frequency of Black and White participants [$\chi^2(1) = 33.077$, $p < .001$] and White and Hispanic participants [$\chi^2(1) = 11.494$, $p = .001$] in the excluded and included groups. Valid listwise $n = 2554$.

Table 2

Multiple Linear Regression Results

	B	SE	β	*p*	95% CI	
Galectin-3	0.732	0.301	0.055	.015	0.143	1.322
Age	−0.033	0.007	−0.096	< .001	−0.047	−0.019
Years of Education	−0.270	0.038	−0.151	< .001	−0.345	−0.196
Creatinine	−0.028	0.341	−0.002	.934	−0.697	0.640
BMI	0.036	0.010	0.069	.001	0.015	0.056
Sex (male vs female)	1.312	0.185	0.168	< .001	0.950	1.673
Ethnicity (Non-Hispanic white)	−0.376	0.169	−0.047	.027	−0.708	−0.044
Ethnicity (Hispanic)	−0.606	0.236	−0.055	.010	−1.069	−0.142
Smoking status (non-smoker)	0.590	0.150	0.077	< .001	0.296	0.885
Diabetes	−0.087	0.215	−0.008	.685	−0.508	0.334

Note $F(10, 2543) = 23.671$, $p < .001$, $R^2 = .085$. Reference groups are: male (sex), non-Hispanic black (ethnicity), non-smoker (smoking status), and history of diabetes (yes). Gal3 and creatinine were log transformed prior to analyses. Total $n = 2554$.