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Brief Report

Intima-media thickness and age of first depressive episode

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ABSTRACT

Background: Late life depression, including patients with vascular depression, has been associated with higher levels of intima-media thickness (IMT). Although individuals with vascular depression tend to report a later onset of depression, the relationship of IMT and age of first depressive episode is uncertain in younger adults. We therefore investigated the relationship between IMT and age of first depressive episode in a sample of 202 adults (age range 40–81 years) with major depression (MDD).
Methods: Depression status was assessed using the Structured Clinical Interview Schedule and the Hamilton Depression Rating Scale. Patients underwent a physical examination in which a medical history was obtained. IMT was measured from the left and right common carotid arteries. Simple regression analyses were used to investigate the association between IMT and self-reported age of first depressive episode.
Results: IMT was associated with a later onset of first major depressive episode ($b = .225$, $P = .0005$) and this association remained significant after controlling for age, Framingham Stroke Risk Profile, smoking pack years, physical activity, high- and low-density lipoprotein, body mass index, triglyceride levels, and history of chronic medical conditions ($b = .142$, $P = .028$). Each .10 mm increase in IMT was associated with a 2.6-year later reported occurrence of first major depressive episode (MDE). Similarly, higher levels of IMT were associated with fewer previous MDEs ($b = -.149$, $P = .020$) and this effect remained significant in our multivariate model ($b = -.140$, $P = .030$). In contrast, IMT was not associated with current depressive severity ($b = -.024$, $P = .720$).
Conclusions: Greater levels of IMT are associated with a later onset of depression and fewer previous depressive episodes among middle-aged and older adults, independent of cardiovascular co-morbidities. These findings provide preliminary evidence that increased vascular burden may be associated with a later onset of depression.

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1. Introduction

Major depression (MDD) is one of the primary causes of disability in the United States (Simon, 2003) and is associated with significant cardiovascular morbidity (Barnes et al., 2006). Individuals experiencing MDD in later life exhibit a greater prevalence of *vascular depression* (Mast et al., 2008), characterized by poorer vascular health, cognitive decrements, and a later onset of first depressive episode, typically occurring after age 50 (Kim et al., 2006). Recent studies have demonstrated that individuals with a later onset of first MDE exhibit greater intima-media thickness (IMT), a marker of systemic atherosclerosis, compared with controls (Chen et al., 2006).

Despite evidence that individuals with vascular depression exhibit a later onset of first depressive episode and greater vascular burden, the mechanisms responsible for the characteristic later onset of this disorder have received little attention. It has been hypothesized that poorer vascular health results in greater white matter damage, resulting in dysregulation of the frontal-striatal systems of the brain (Alexopoulos et al., 2008), which are critical for modulation of affect (Gunning-Dixon et al., 2008; Davidson et al., 2002). Although a relationship between poorer vascular health and white matter damage has been demonstrated in healthy adults (Jeerakathil et al., 2004; Herrmann et al., 2008) and individuals with MDD (Chen et al., 2006), to our knowledge, the relationship between vascular health and age of first MDE has not been studied. We therefore investigated the relationship between IMT and age of first MDE among 202 middle-aged and older adults with MDD.

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Abbreviations: HRSD, Hamilton rating scale for depression; IMT, intima-media thickness; MDD, major depression; MDE, major depressive episode; SBP, systolic blood pressure.

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2. Methods

2.1. Study design

The sample examined in this report represents baseline data obtained from a subset of individuals from a larger clinical trial of exercise and medication among middle-aged and older adults with MDD (Blumenthal et al., 2007). Exclusion criteria included a primary psychiatric diagnosis other than MDD, medical contra-indications preventing participation in either the exercise or medication arm of the larger study (i.e., sertraline), and current treatment for MDD. No patient was on an anti-depressant at the time of this assessment. Participants were recruited from October 2000 to September 2005 and the study protocol was approved by a Duke Institutional Review Board.

2.2. Cerebrovascular risk factors

2.2.1. Framingham stroke risk profile

A modified version of the Framingham Stroke Risk Profile (FSRP), a risk assessment tool used to assess the risk of incident stroke, was used an index of cerebrovascular risk (Dagostino et al., 1994). Risk factors used to assess stroke risk include systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation (Dagostino et al., 1994). Details of our cerebrovascular risk factor and IMT assessments have been previously reported (Smith et al., 2007). Because age served as a covariate in our statistical analyses, it was not included in calculating Framingham Stroke Risk Profile scores. Furthermore, left ventricular hypertrophy, a component of the original Framingham Stroke Risk Profile score, was not used in the current analysis because this information was not obtained for any participant.

2.2.2. Serum cholesterol

High-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol were assessed enzymatically (LabCorp, Research Triangle Park, NC). HDL-C was estimated by assay of the supernatant remaining after precipitation of serum LDL with dextran sulfate plus magnesium chloride. Participants fasted for 12 h prior to this assessment.

2.3. Measures of vascular health

2.3.1. Intima-media thickness (IMT) in carotid arteries

Carotid artery IMT was assessed by high-resolution B-mode ultrasound using an Acuson Aspen (Mountain View, CA) vascular imaging system with 10 MHz linear array transducer. Ultrasound examinations of the far wall of the left and right common carotid arteries were used to acquire longitudinal images spanning 2 cm proximal to the carotid bulb. IMT of the far wall of the left and right common carotid arteries was measured over a 1 cm segment using Carotid Analyzer 5.0.5 (Medical Imaging Applications LLC, Iowa City, IA) edge detection software. Far wall measurements only were utilized as near wall measurements have been shown to have limited reliability (Wendelhag et al., 1991). Because left and right-sided IMT values were similar (mean left-sided IMT = .63 mm, SD = .15 mm; mean right-sided IMT = .63 mm, SD = .15 mm) and substantially intercorrelated ($r = .57$, $P < .0001$), these values were averaged to create one IMT value for each participant.

2.4. Assessment of depression

2.4.1. Structured clinical interview for the DSM-IV

The presence of MDD was determined by a trained clinical psychologist using the Structured Clinical Interview for the DSM-IV (SCID) (American Psychiatric Association, 2004). All participants met criteria for MDD based on Diagnostic and Statistical Manual-IV (American Psychiatric Association, 2004).

2.4.2. Hamilton rating scale for depression

Depression severity was assessed using the Hamilton Rating Scale for Depression (HRSD) (Williams, 1988), a 17-item clinical rating scale that assesses the severity of depressive symptoms such as changes in appetite, sleep, and depressed mood.

2.4.3. Age of onset of first MDE and number of previous MDEs

The SCID was supplemented with additional questions pertaining to the onset and treatment of the current MDE, as well as any prior MDEs. Previous MDEs were indexed as 0, 1, 2, or ≥ 3 MDEs prior to the current episode.

2.5. Statistical analysis

2.5.1. Data analysis

In order to determine the relationship between IMT, reported age of first MDE, and number of previous depressive episodes, we first examined the bivariate correlations between IMT and our depression variables. We then constructed two regression models in order to examine these relationships while controlling for relevant cardiovascular co-morbidities. In order to control for the effects of age in our analysis, IMT was examined as a dependent variable. Within these models, age at first MDE and number of previous MDEs were our predictors of interest while current age and cardiovascular co-morbidities served as covariates. Cardiovascular co-morbidities included the Framingham Stroke Risk Profile, current and previous smoking packs-per-year (PPY), physical activity (GODIN) (Godin and Shephard, 1985), body-mass index (BMI), HDL and LDL cholesterol, triglycerides, and history of chronic disease (e.g., stroke, cancer, and/or arthritis). As a supplementary analysis, we examined the association between IMT and depression severity, indexed by the HRSD. In this model, HRSD scores served as the predictor of interest with IMT as the dependent variable, controlling for cardiovascular co-morbidities. Multiple imputation based on the parametric maximum likelihood regression was used to account for missing data. Missing data was minimal (Harrell, 2001), with only 7 individuals (3.5%) missing IMT data and 5 (2.5%) missing data on age of first depressive episode. Model assumptions of additivity, linearity, and distribution of residuals were evaluated and found to be adequate before analysis.

3. Results

3.1. Sample characteristics

Participants ranged in age from 40 to 81 years of age (mean age = 51.7 years, SD = 7.6). As shown in Table 1, the majority of participants were female (75.7%) and Caucasian (67.8%), and almost half were college-educated (49.5%). Participants were in generally good health, as indexed by relatively low levels of FSRP (mean FSRP = 5.39, SD = 3.2), SBP (mean SBP = 124.2 mmHg, SD = 17.4), LDL cholesterol (mean LDL = 122.5 mg/dL, SD = 32.9), IMT (mean IMT = 0.63 mm, SD = .13), and higher HDL cholesterol (mean HDL = 56.9 mg/dL, SD = 16.0). The sample was relatively free of other co-morbidities such as diabetes (6.9%), arthritis (21.8%), current tobacco use (15.8%), history of cancer (5.5%), and history of stroke (2%).

3.2. Relationship of IMT, age of first MDE, and number of previous MDEs

In an unadjusted bivariate analysis, higher levels of IMT were associated with later ages of first MDE ($b = .225$, $P = .0005$) (Fig. 1).

Table 1
Background characteristics.

Variable	Mean	SD
Age (year)	51.6	7.5
Gender (male), *n* (%)	48 (24)	
Caucasians, *n* (%)	134 (68)	
Education (college graduate), *n* (%)	100 (51)	
HRSD	17	4.3
Married, *n* (%)	75	49
IMT (mm)	0.63	0.13
Current smoker, *n* (%)	32 (16)	
Previous smoker (excluding current use), *n* (%)	65 (38)	
SBP (mmHg)	124	18
DBP (mmHg)	79	10
BP-lowering medications, *n* (%)	47 (23)	
Total cholesterol (mg/dL)	207	41
LDL total (mg/dL)	122	33
HDL total (mg/dL)	56.9	15.8
Lipid-lowering medications, *n* (%)	17 (8)	
BMI (kg/m^2)	30.1	7.1
GODIN Exercise	9.5	10.3
Framingham Risk Profile Score	5.4	3.2
Age of first depressive episode (year)	38.3	13.6
Previous depressive episodes, *n* (%)		
(0)	69 (34.2)	
(1)	48 (23.8)	
(2)	15 (7.4)	
($\geq$3)	70 (34.7)	

Note: HRSD indicates Hamilton rating scale for depression; IMT indicates intima-medial thickness; SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; mmHg indicates millimeters of mercury; LDL indicated low-density lipoprotein; HDL indicates high-density lipoprotein; BMI indicated body mass index.