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Antidepressant use and Subclinical Measures of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—Antidepressants are commonly prescribed medications used in primary care. The cardiovascular safety profile of anti-depressant medications, in terms of subclinical atherosclerosis, is under-examined.

Methods—6,814 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) were examined. At baseline, the mean age was 62 years with four race/ethnic groups represented: European-(38%), Hispanic-(23%), African-(28%) and Chinese-Americans (11%). Antidepressants were sub-grouped as serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and “other” (bupropion, nefazodone, trazodone, mirtazapine). After adjusting for potential confounders, we estimated the association between antidepressant use and the following measures of subclinical atherosclerosis: coronary artery calcium (CAC), the ankle-brachial index (ABI), and carotid intima-media thickness (cIMT), both cross-sectionally and prospectively.

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Results—A total of 324 participants were exposed to SSRIs, 88 to TCAs, 41 to SNRIs and 123 to “other” antidepressants. For CAC incidence, the fully-adjusted longitudinal analyses revealed no consistent associations with SSRIs[RR: 0.99(0.71, 1.37)], SNRIs[RR=0.49(0.13, 1.86)], TCAs[RR=0.94(0.50, 1.77)], other antidepressant [RR=0.87(0.73, 1.03)] exposure and subclinical disease. Similar null results were obtained in the cross-sectional and longitudinal exposure to antidepressants with changes in baseline CAC>0, ABI and cIMT.

Conclusions—The results of the current study do not support an association between antidepressants and subclinical atherosclerosis.

Keywords

Multi-Ethnic Study of Atherosclerosis; antidepressant medication; sub-clinical disease; coronary artery calcium

Introduction

Antidepressants are among the most commonly prescribed medications given by primary care providers[,] . Antidepressants are classified based on their postulated mechanism of action: serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and other antidepressants with mixed dopaminergic and serotoninergic modulation such as bupropion, trazodone and mirtrazapine, among others. In general, and especially serotonin reuptake inhibitors (SSRIs), these medications have been associated with a reduction of major heart disease events[,] and are considered to be a safe treatment for patients with known atherosclerotic risk factors. Conversely, there is evidence that TCAs and tetracyclic antidepressants like mirtazapine have been associated with cardiotoxic effects that affect conduction and rhythm[,] . There are also reports that link SSRIs with increased risk of hemorrhagic stroke among postmenopausal women[-]. Furthermore, open-label trials of 12 weeks duration and a meta-analysis have reported an association of exposure to SNRIs with increased blood pressure compared to non-SNRIs users[,] . Even though such studies have suggested that antidepressants, especially SSRIs, are not associated with higher risk of atherosclerotic disease[,] , other studies have reported an association between antidepressants and CVD, especially sudden cardiac death. To date, little is known about the association of different classes of antidepressants with measures of subclinical atherosclerotic disease in patients without a history of cardiovascular events.

Subclinical atherosclerosis is associated with incident CVD and is considered to be a chronic progressive inflammatory disease[,] . Risk factors thought to contribute to the development of atherosclerosis include genetics, diabetes, obesity, smoking, dyslipidemia, physical inactivity, systematic inflammation, and negative emotional states such as depression and anxiety[-]. Subclinical markers of atherosclerosis include coronary calcium (CAC), the ankle-brachial index (ABI) and carotid intima-media thickness (cIMT) [among others] which are measured with computed tomography, a hand-held Doppler and B-mode ultrasound respectively[,] .

Since there is paucity in the literature, and to better understand the safety profile of antidepressants for sub-clinical CVD, we conducted a longitudinal study among a diverse cohort of participants free from cardiovascular disease at baseline and with repeat measures of subclinical measures of atherosclerosis at regular intervals. In this study we tested the hypothesis that individuals exposed to different classes of antidepressants would show a protective association with different measures of subclinical atherosclerosis as measured by CAC, ABI and cIMT.

Methods

Study Population

The design and goals of the MESA have been described in previous literature. Briefly, the MESA is a multi-site cohort study that included 6,814 participants with the principal objective of identifying risk factors for the progression of subclinical atherosclerosis to clinical CVD. The MESA cohort includes men and women ages 45-84 years recruited in 2000-2002 from 6 field centers (Columbia University, New York; Johns Hopkins University, Baltimore; Northwestern University, Chicago; University of California, Los Angeles; University of Minnesota, Minneapolis-St. Paul; and Wake Forest University, Winston Salem) and followed for approximately 10 years. All participants were free from known CVD at baseline. Approximately 38% of the participants are European-American, 28% African-American, 23% Hispanic-American, and 11% Chinese-American. All field centers and the data coordinating center had independent institutional review board approval.

Data Collection

Standardized questionnaires were used at each clinic visit to collect demographics, ethnicity, educational attainment, income and health insurance status. Information about medications, and antidepressant medications in particular, was collected through a previously validated medication inventory approach during each examination[-]. The medication inventory approach is more accurate than self-report for assessing baseline exposure to medications in a cohort study. The use of antidepressant medications was classified according to their pharmacological properties into SSRIs, SNRIs, TCAs, and “other” antidepressants (bupropion, nefazodone, trazodone, mirtrazapine). A total of 501 (7.3%) participants reported taking anti-depressant medications at baseline. These are standard categories and are considered exhaustive within the current classification of antidepressants[,] . Concordance use of antidepressant was also determined between baseline and follow-up visits. Between the first and second MESA exams, on average 18 months apart, the concordance was 79% for non-TCA use and 65% for TCA use, indicating reasonably consistent antidepressant use over time.

Covariates included systolic blood pressure, body mass index (kg/m^2) (BMI), total cholesterol, HDL cholesterol, C-reactive protein, interleukin-6 and fibrinogen. Psychologic variables included depressive symptom severity as reported by the Center for Epidemiologic Studies Depression scale (CES-D) and anxiety state reported by the Spielberger State-Trait Anxiety Inventory (STAI). Behavioral variables included smoking and alcohol use (never, former, current), and self-reported physical activity. Additional covariates included the

presence of diabetes defined by the 2003 American Diabetes Association's criteria of fasting plasma glucose>126 mg/dl or taking medication for diabetes, lipid-lowering medications, anti-hypertensive medications and aspirin use.

Measures of Subclinical Atherosclerosis

Coronary Artery Calcium (CAC)—CAC was measured using electron-beam computed tomography or multi-detector computed tomography. CAC is a strong predictor of coronary heart disease and provides predictive information for cardiovascular events. At Exam 1 each participant was scanned twice consecutively and the results averaged. At Exam 5 only one scan was performed. Scans were read independently at a centralized reading center (22,23). The amount of calcium was quantified using the Agatston scoring method (24). Calcium scores were adjusted using a standard calcium phantom (25). CAC presence was defined as an Agatston score>0.

Ankle-Brachial Index (ABI)—The ABI was measured at a number of MESA exams, including both exam 1 and 5, as the ratio of the systolic blood pressure in the ankle to that in the arm, as described by previous MESA reports . The participant's ABI was the lower of the left and right legs. Participants with abnormal high ABI >1.40 in either leg were excluded from the analyses because of the possibility of stiff ankle arteries that may lead to an artificially elevated systolic blood pressure . A low-ABI was defined as<0.9, while normal was 0.90-1.40. A low-ABI has been recognized as a good indicator of systemic atherosclerosis and preclinical CVD as well as a good predictor of cardiovascular disease .

Carotid Intima-Media Thickness (cIMT)—At the baseline exam and 10 years later (at exam 5), B-mode ultrasound was used to image the near and far walls of the left distal common carotid artery using a Logiq-700 ultrasound system (General Electric Medical Systems, 13-MHz transducer). The literature has described that one standard deviation increase in cIMT is significantly associated with myocardial infarction and stroke, establishing that high measures of cIMT a good predictor cardiovascular events. Images were read at the University of Wisconsin, and the exact position of the measures at follow-up was determined using anatomical landmarks. All readings were done centrally at the University of Wisconsin and blinded to participant characteristics.

Statistical Analyses

Continuous variables were described by means/standard deviations (SD) and categorical variables were described as frequencies/percentages where applicable (Table 1). Both unadjusted and adjusted analyses were performed for all estimates of association between antidepressant medications and subclinical CVD.

After initial unadjusted analysis, we used a staged model approach with model 1 controlling for demographics only. Model 2 additionally controlled for biological, psychological and behavioral covariates. Model 3 was fully adjusted, additionally controlling for medications and comorbidities. Absolute differences and prevalence ratios (PR) were estimated by linear and prevalence ratio regression models, respectively to determine the effect size of

antidepressant exposure with continuous and dichotomous measures of subclinical atherosclerosis.

We also examined the longitudinal association of antidepressant use with subclinical measures of atherosclerosis. The longitudinal association was determined using a generalized linear model to determine the association of antidepressant exposure at baseline with measures of subclinical atherosclerosis over a 10 year period of study follow-up. Relative risk was calculated for CAC incidence and linear regression estimates were reported for change in CAC, in continuous ABI, and in changes in left distal common carotid mean IMT.

Results

The mean age of participants was 62.1 (10.2) and 56% were women (Table 1). The mean CES-D score was 7.5 (7.5) and the mean STAI state score was 15.8 (4.5). Of the 501 participants taking anti-depressants at baseline, 56% (324) reported taking a SSRI, 15% (88) reported taking a TCA, 7% (41) reported taking a SNRI and 21% (123) reporting taking “other” antidepressant (bupropion, nefazodone, trazodone and/or mirtrazapine). Anti-hypertensive medications were the most frequently used concomitant medication in our sample. Thirty nine percent of SSRI users, 37% of SNRI users, 50% of TCA users, and 38% of users of “other” antidepressant were also taking an antihypertensive medication. Table 1 summarizes these findings.

Additional matched controlled analyses between those with significant (CES-D>16) and normal depressive symptoms Vs. those exposed and not exposed to antidepressants, did not show a significant difference between the mean scores of the different measures of subclinical disease. Table 2 summarized this analyses.

Coronary Artery Calcium (CAC)

Compared to non-antidepressant medication users, in fully adjusted models, there were no significant cross-sectional associations between SSRIs, TCAs, SNRIs and “other” antidepressant users with the presence of CAC (Table 2). Similarly, there was no significant association between antidepressant medications and CAC measured as a continuous variable [log(CAC)] (Table 3).

In the longitudinal analyses, in fully adjusted models, there was no significant relationship between exposure to SSRIs, TCAs, SNRIs and “other” antidepressants with incident CAC (change from CAC=0 at baseline) (Table 4). Compared to non-antidepressant users, there was also no significant relationship between exposure to antidepressants and changes in CAC>0 at baseline (Table 4).

Ankle Brachial Index (ABI)

In the fully adjusted model there was no significant association between exposure to SSRIs, TCAs and SNRIs with the ABI as a continuous variable (Table 3), but there was a significant positive association between “other” antidepressant exposure (β=0.023;95%CI:0.004,0.04) with continuous ABI measures (Table 3).

In longitudinal analyses (Table 4), the fully adjusted model showed no association between "other" antidepressant exposure and change in ABI from baseline over the 10-year observation period. There were also no significant associations between SSRIs, TCAs and SNRIs and change in ABI during the 10-year observation period. Table 4 summarizes these findings.

Carotid Intima-Media Thickness (cIMT)

The estimates of the cross-sectional association in the fully adjusted models were non-significant for the associations between SSRIs, TCAs, SNRIs or for "other" antidepressants and the left distal common carotid mean IMT compared to non-antidepressant medication use (Table 3).

Similarly, the longitudinal analyses in the fully adjusted models (Table 4) showed non-significant findings on the associations between SSRIs, TCAs, SNRIs and "other" antidepressant medication with left distal common carotid mean IMT compared to non-antidepressant medication use.

Discussion

In this longitudinal study of MESA participants free from clinical cardiovascular disease at baseline, there were no significant associations between antidepressant use and measures of subclinical atherosclerosis. The single, cross-sectional association between "other" anti-depressant use and ABI was compatible with chance given that we tested 4 medication classes, 2 time-points, and 3 measures of sub-clinical CVD (24 tests). Furthermore, the longitudinal association between these two variables was non-significant, leading us to presume that it was not a real association.

To our knowledge, this is the first study that included longitudinal analyses of different antidepressants that are commonly used in primary care settings with subclinical measures of atherosclerosis. A previous report from the Look AHEAD clinical trial, which studied the long-term health outcomes of a comprehensive weight loss intervention among patients with diabetes and obesity, found a significant cross-sectional association of antidepressant use with low-ABI that was non-significant after controlling for multiple covariates. The association of antidepressants with low-ABI was not reported in the longitudinal analysis of the Look AHEAD clinical trial. Additionally, in the Look AHEAD study the association between different classes of antidepressants and ABI measures was not reported.

Depressive and anxiety disorders are well-described risk factors for the development of CVD[9] . In this study we controlled for symptoms of depression and anxiety, yet the scales that were used (CES-D and STAI) are not frequently used in clinical practice and participants in the MESA cohort were not assessed with structure clinical interviews to discern a diagnosis of a major depressive or anxiety disorder. Even though, cross-sectional studies have demonstrated an association between depressive and anxiety disorders with subclinical atherosclerosis as measured by the ABI, our manuscript was not intended to study the association of depressive symptoms with subclinical measures of atherosclerosis. To what extent the use of antidepressants might protect against the development of

atherosclerosis remains to be further examined. The literature has reported an association between antidepressant exposure and cardiovascular events such as sudden cardiac death. In our study, we did not test for the association of antidepressant use and cardiovascular events since our main focus was to test the association of antidepressants with subclinical measures of atherosclerosis. Also, our study did not have the power to test for the association of antidepressant exposure and cardiovascular events.

Studies in rodents have shown that SSRIs reduce atherosclerotic changes in the endothelium as measured by decreased expression in cell adhesion molecules (VCAM-1). In humans, a randomized clinical trial demonstrated that patients with congestive heart failure taking sertraline, an SSRI, had a reduction in the expression of cell endothelial adhesion molecules (VCAM and ICAM) after a 3 month exposure compared to patients receiving placebo indicating a possible anti-inflammatory effect. On the other hand, a cross-sectional population study from the Netherlands found no association between SSRIs, TCAs or "other" antidepressants with measures of ABI. Our longitudinal study further complements the literature by demonstrating a null relationship between SSRIs, SNRIs, TCAs and "other" antidepressants not only with measures of ABI, but also measures of CAC and cIMT over a 10-year observational period.

Our study has some limitations. We are not able to examine the association between different doses of antidepressants and measures of subclinical atherosclerosis. Additionally, we did not have information of pre-baseline exposure to antidepressants to have a continuous parameter for temporal exposure, that means we did not have duration of exposure prior to baseline assessments. Antidepressant exposure was too rare to estimate dose or agent specific associations. Because of the prevalence use of antidepressants was low, the power to detect associations is accordingly limited. The study was, in addition, observational and thus residual confounding in our estimates is possible.

However, this study has many strengths including: longitudinal data, presence of multiple classes of antidepressants, having gold-standard measures of subclinical atherosclerosis, and the multi-ethnic nature of our sample. Additionally, this study could adjust for a broad range of potential confounders, including a number of covariates that may be important in this context.

In conclusion, we found no significant associations between different classes of antidepressants and any measure of subclinical atherosclerosis. Clinical trials are needed to demonstrate any definitive statement of medication safety, but such trials seem unlikely given the current evidence. However, given its longitudinal component, this study does provide a moderate to high level of evidence that these medications are not strongly associated with subclinical atherosclerosis.

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Table 1

Participant characteristics by baseline use of antidepressant medications. Data from the Multi-Ethnic Study of Atherosclerosis (MESA).

	SSRIs (n=324)	TCAs (n=88)	SNRIs (n=41)	Other (n=123)	No Antidepressant (n=6298)
Age (years)	61	62	60	57	62
Male	30%	20%	34%	41%	49%
Race/Ethnicity Caucasian	63%	58%	78%	74%	36%
Chinese	5%	3%	2%	1%	12%
African-American	13%	20%	2%	12%	29%
Hispanic	19%	18%	17%	13%	22%
Education <High School	11%	15%	7%	7%	19%
High School	45%	56%	51%	47%	47%
College	23%	11%	10%	22%	17%
Graduate School	21%	18%	32%	25%	18%
Household Income <$25K	30%	37%	21%	25%	32%
≥ $25K and < $50	33%	31%	21%	30%	29%
≥ $50K and < $100	24%	29%	38%	28%	26%
≥ $100K	13%	2%	21%	17%	14%
No Health Insurance	4%	5%	12%	5%	9%
BMI (kg/m^2)	29	30	30	29	28
Total Cholesterol (mg/dL)	200	192	193	191	194
HDL Cholesterol (mg/dL)	54	53	52	52	51
Systolic BP (mmHG)	124	124	130	121	127
C-reactive protein (mg/dl)	4.9	6.1	4.4	4.2	3.7
Fibrinogen Antigen (mg/dl)	346	360	342	337	347
IL-6 (pg/mL)	1.67	1.95	1.76	1.54	1.54

	SSRIs (n=324)	TCAs (n=88)	SNRIs (n=41)	Other (n=123)	No Antidepressant (n=6298)
Depression Score (CES-D)	11	10	11	12	7
Anxiety Score (STAI)	18	17	18	19	16
Smoking: Current	12%	19%	17%	20%	13%
Former	42%	40%	44%	43%	36%
Alcohol Consumption: Current	57%	50%	66%	50%	55%
Former	28%	27%	24%	39%	24%
Intentional Exercise (met-min/wk)	1680	1312	1119	1474	1548
Diabetes	13%	16%	10%	8%	13%
Lipid Lowering Medications	23%	25%	34%	23%	16%
Antihypertensive Medications	39%	50%	37%	38%	37%
Aspirin Use	26%	24%	39%	32%	25%
Coronary Artery Calcium					
Prevalent CAC>0	46%	44%	51%	37%	50%
incident CAC>0	28%	23%	14%	26%	26%
ABI Baseline	1.12	1.12	1.11	1.14	1.11
Change E1 to E5	-0.014	-0.016	-0.024	-0.005	-0.007
Carotid IMT (mm) Baseline	0.74	0.73	0.67	0.70	0.76
Change E1 to E5	0.11	0.13	0.10	0.10	0.11

IL-6= Interleukin-6; CES-D: Center for Epidemiologic Studies Depression Scale; STAI=Spielberger Trait Anxiety; CCA=Common Carotid Artery; IMT=Intima-Media Thickness; ABI=Ankle-Brachial Index.

Table 2

Mean Differences of Subclinical Measures of Atherosclerosis among participants exposed to antidepressants and CES-D symptoms

CES-D> 16	Sub-Clinical Measure of Atherosclerosis	N	Mean	SD	Minimum	Maximum
No Antidepressants & Not depressed	CCA IMT (mm)	5578	0.874	0.195	0.400	2.453
	ANKLE-BRACHIAL INDEX	5592	1.114	0.122	0.306	1.983
	CAC Score	5655	150.238	424.993	0.000	6315.910
No Antidepressants & Depressed	CCA IMT (mm)	635	0.858	0.192	0.470	1.858
	ANKLE-BRACHIALINDEX	632	1.104	0.115	0.607	1.888
	CAC Score	641	127.418	394.309	0.000	4506.495
On Antidepressants & Not depressed	CCA IMT (mm)	379	0.845	0.183	0.475	1.625
	ANKLE-BRACHIAL INDEX	377	1.122	0.105	0.712	1.455
	CAC Score	384	131.011	376.286	0.000	2333.970
On Antidepressantsm & Depressed	CCA IMT (mm)	119	0.852	0.194	0.530	1.528
	ANKLE-BRACHIAL INDEX	119	1.108	0.125	0.452	1.500
	CAC Score	119	109.897	292.459	0.000	1697.730

CES-D: Center of Epidemiologic Studies Depression Scale; CCA-IMT: Common Carotid Artery-Intima Media Thickness; CAC: Coronary Artery Calcification; SD: Standard Deviation

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Table 3

Cross-Sectional Association of antidepressants with subclinical atherosclerosis

	SSRIs PR (95% CI)	TCAs PR (95% CI)	SNRIs PR (95% CI)	Other PR (95% CI)	Non Users
Coronary Artery Calcium Prevalence (CAC>0)					
Model 1	1.05 (0.95, 1.15)	0.99 (0.82, 1.20)	1.05 (0.82, 1.34)	0.87 (0.73, 1.04)	Ref
Model 2	1.04 (0.94, 1.14)	0.99 (0.83, 1.19)	1.03 (0.86, 1.25)	0.88 (0.74, 1.05)	Ref
Model 3	1.01 (0.92, 1.11)	0.95 (0.78, 1.14)	0.98 (0.82, 1.17)	0.87 (0.73, 1.03)	Ref
Coronary Artery Calcium Amount: log(CAC) among those with CAC>0					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	-0.04 (-0.33, 0.25)	0.20 (-0.36, 0.75)	-0.02 (-0.80, 0.75)	-0.09 (-0.62, 0.43)	Ref
Model 2	-0.10 (-0.39, 0.20)	0.23 (-0.32, 0.78)	-0.19 (-0.96, 0.58)	-0.07 (-0.59, 0.46)	Ref
Model 3	-0.17 (-0.47, 0.12)	0.17 (-0.38, 0.72)	-0.28 (-1.05, 0.48)	-0.09 (-0.61, 0.43)	Ref
Continuous ABI *excludes participants with ABI > 1.40*					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	0.005 (-0.01, 0.02)	0.014 (-0.01, 0.04)	-0.018 (-0.05, 0.02)	0.017 (-0.003, 0.04)	Ref
Model 2	0.007 (-0.01, 0.02)	0.016 (-0.01, 0.04)	-0.013 (-0.05, 0.02)	*0.022 (0.003, 0.04)* ‡	Ref
Model 3	0.009 (-0.003, 0.02)	0.019 (-0.004, 0.04)	-0.010 (-0.04, 0.02)	*0.023 (0.004, 0.04)* ‡	Ref
Carotid IMT (left distal common carotid mean IMT)					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	0.011 (-0.02, 0.05)	-0.026 (-0.10, 0.04)	-0.027 (-0.13, 0.08)	0.00 (-0.05, 0.05)	Ref
Model 2	-0.000 (-0.03, 0.03)	-0.028 (-0.10, 0.04)	-0.035 (-0.14, 0.07)	-0.001 (-0.05, 0.05)	Ref
Model 3	-0.002 (-0.04, 0.03)	-0.031 (-0.10, 0.04)	-0.038 (-0.14, 0.06)	-0.004 (-0.06, 0.05)	Ref

Model 1 (Demographics): Age, gender, ethnicity, education, income, health insurance; **Model 2 (Biological, Psychological & Behaviors)**: BMI, total cholesterol, HDL cholesterol, systolic blood pressure, CRP, IL-6, Fibrinogen, CES-D, STAI, smoking, alcohol use, and physical activity; **Model 3: Medications and Comorbidities**: Diabetes, lipid-lowering medication, antihypertensives, aspirin use. **CAC**: Coronary calcium. **ABI**: Ankle-brachial index. **IMT**: intima-media thickness. **SSRIs**: Serotonin reuptake inhibitors. **TCAs**: Tricyclic antidepressants. **SNRIs**: Serotonin-norepinephrine reuptake inhibitors. **Other**= bupropion, nefazadone, trazodone, mirtrazapine. **PR**: prevalence ratio

$^{\neq}p<0.05$

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Table 4

Longitudinal Association of antidepressants with subclinical atherosclerosis

Coronary Artery Calcium Incidence (CAC>0)					
	SSRIs RR (95% CI)	**TCAs RR (95% CI)**	**SNRIs RR (95% CI)**	**Other RR (95% CI)**	**Non Users**
Model 1	1.07 (0.81, 1.42)	0.88 (0.48, 1.64)	0.52 (0.14, 1.94)	1.02 (0.65, 1.60)	Ref
Model 2	0.99 (0.72, 1.37)	0.93 (0.50, 1.73)	0.49 (0.13, 1.86)	1.11 (0.70, 1.76)	Ref
Model 3	0.99 (0.71, 1.37)	0.94 (0.50, 1.77)	0.49 (0.13, 1.86)	1.10 (0.69, 1.76)	Ref
Change in CAC Amount (Agatston; among those with CAC>0 at baseline)					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	3 (-123, 128)	149 (-95, 394)	-187 (-552, 178)	-1 (-216, 214)	Ref
Model 2	-36 (-164, 92)	124 (-120, 369)	-258 (-622, 106)	-34 (-249, 181)	Ref
Model 3	-54 (-178, 70)	137 (-101, 374)	-220 (-574, 133)	-58 (-266, 151)	Ref
Change in Continuous ABI *excludes participants with ABI > 1.40*					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	-0.01 (-0.03, 0.01)	-0.004 (-0.04, 0.03)	-0.01 (-0.06, 0.04)	-0.004 (-0.03, 0.02)	Ref
Model 2	-0.01 (-0.03, 0.01)	-0.001 (-0.04, 0.03)	-0.01 (-0.06, 0.04)	-0.004 (-0.03, 0.02)	Ref
Model 3	-0.01 (-0.03, 0.01)	-0.004 (-0.04, 0.03)	-0.01 (-0.06, 0.04)	-0.005 (-0.03, 0.02)	Ref
Change in Carotid IMT (left distal common carotid mean IMT)					
	SSRIs Coef (95% CI)	TCAs Coef (95% CI)	SNRIs Coef (95% CI)	Other Coef (95% CI)	Non Users
Model 1	-0.003 (-0.03, 0.03)	0.03 (-0.03, 0.08)	-0.01 (-0.10, 0.08)	-0.002 (-0.05, 0.04)	Ref
Model 2	-0.007 (-0.04, 0.02)	0.03 (-0.03, 0.09)	-0.01 (-0.10, 0.08)	-0.002 (-0.05, 0.04)	Ref
Model 3	-0.009 (-0.04, 0.02)	0.03 (-0.03, 0.09)	-0.02 (-0.10, 0.07)	0.001 (-0.04, 0.05)	Ref

Model 1 (Demographics): Age, gender, ethnicity, education, income, health insurance; **Model 2 (Biological, Psychological & Behaviors)**: BMI, total cholesterol, HDL cholesterol, systolic blood pressure, CRP, IL-6, Fibrinogen, CES-D, STAI, smoking, alcohol use, and physical activity; **Model 3 (Medications and Comorbidities)**: Diabetes, lipid-lowering medication, antihypertensives, aspirin use. **CAC**: Coronary calcium. **ABI**: Ankle-brachial index. **IMT**: intima-media thickness. **SSRIs**: Serotonin reuptake inhibitors. **TCAs**: Tricyclic antidepressants. **SNRIs**: Serotonin-norepinephrine reuptake inhibitors. **Other**= bupropion, nefazadone, trazodone, mirtrazapine. **RR**: relative risk

$^{\neq}p<0.05$