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Cardiovascular Risk Factors as Differential Predictors of Incident Atypical and Typical Major Depressive Disorder in U.S. Adults

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Abbreviations: MDD = major depressive disorder; CVD = cardiovascular disease;; BMI = body mass index

Abstract

Objectives: While the association between major depressive disorder (MDD) and future cardiovascular disease (CVD) is established, less is known about the relationship between CVD risk factors and future depression, and no studies have examined MDD subtypes. Our objective was to determine whether hypertension, tobacco use, and body mass index (BMI) differentially predict atypical and typical MDD in a national sample of U.S. adults.

Methods: We examined prospective data from 22,915 adults with no depressive disorder history at baseline who participated in Wave 1 (2001-2002) and Wave 2 (2004-2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). CVD risk factors (Wave 1) and incident MDD subtypes (Wave 2) were determined by structured interviews.

Results: There were 252 atypical and 991 typical MDD cases. In fully-adjusted models, baseline hypertension (*OR*=0.58, 95% *CI*: 0.43-0.76), former tobacco use (*OR*=1.46, 95% *CI*: 1.20-1.78), and BMI (*OR*=1.32, 95% *CI*: 1.25-1.40; all *p*'s<0.001) predicted incident atypical MDD versus no MDD, whereas no CVD risk factor predicted incident typical MDD. Baseline hypertension (*OR*=0.52, 95% *CI*: 0.39-0.70), former tobacco use (*OR*=1.53, 95% *CI*: 1.22-1.93), and BMI (*OR*=1.26, 95% *CI*: 1.18-1.36; all *p*'s<0.001) also predicted incident atypical MDD versus typical MDD.

Conclusions: Our study is the first to report that CVD risk factors differentially predict MDD subtypes, with hypertension (protective factor), former tobacco use (risk factor), and BMI (risk factor) being stronger predictors of incident atypical versus typical MDD. Such evidence could provide insights into the etiologies of MDD subtypes and inform interventions tailored to MDD subtype.

Key Words: depressive disorder; atypical depression; hypertension; body mass index; tobacco use; prospective study

Introduction

Substantial evidence supports a relationship between depressive disorders or symptoms and atherosclerotic cardiovascular disease (CVD). Although more than 30 years of research has examined depression as a predictor of new-onset CVD (1), less attention has been given to the plausible reverse direction – CVD risk factors as predictors of new-onset depression. Consistent with the latter direction is the vascular depression hypothesis, which posits that late-life depression (onset after age 50) results from subclinical cerebrovascular disease due, in part, to CVD risk factors (2,3).

Findings of prospective studies suggest that some CVD risk factors may play a role in the etiology of depression. For instance, we observed that longitudinal increases in systolic blood pressure are associated with a future diagnosis of depression in elderly primary care patients (4); however, a meta-analysis of five prospective studies in the elderly detected no relationship between hypertension at baseline and future depression (5). In regards to smoking, a meta-analysis of seven prospective studies found that smokers at baseline have a 62% greater odds of subsequent depression than never smokers (6). With respect to obesity, a meta-analysis of 15 prospective studies revealed that obesity at baseline is associated with a 55% greater odds of later depression (7). A mechanism that could explain how hypertension, smoking, and obesity may contribute to depression onset is systemic inflammation, as these CVD risk factors promote inflammation (8–10) and inflammation has been implicated in the etiology of depression (11).

Because depression is a heterogeneous condition, it is possible that CVD risk factors may be stronger predictors of certain major depressive disorder (MDD) subtypes. One subtype that is a good candidate here is atypical MDD, which accounts for 15-40% of MDD cases (12,13). Among atypical MDD's key features are the reversed somatic-vegetative symptoms of hyperphagia (increased appetite/weight gain) and hypersomnia (excessive sleep), while typical

MDD is a broader category that consists of MDD with other features (e.g., anxious or melancholic (12–14). Recent studies have reported that atypical MDD, compared to typical or melancholic MDD, is associated with increased inflammatory activation, as indicated by elevated circulating levels of inflammatory markers (15–19). These findings suggest that systemic inflammation may play a larger role in the etiology of atypical MDD versus other MDD subtypes, raising the possibility that CVD risk factors, which promote inflammation, may be stronger predictors of incident atypical MDD. To date, no studies have examined if CVD risk factors differentially predict the development of MDD subtypes.

To address this knowledge gap, we examined prospective data collected from a large sample of the U.S. population in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Our objective was to determine whether hypertension, tobacco use, and elevated body mass index (BMI) differentially predict the onset of MDD subtypes. Specifically, we hypothesized that these CVD risk factors would be stronger predictors of incident atypical MDD than of incident typical MDD. Determining whether CVD risk factors differentially predict depressive disorder subtypes could (a) provide new insights into the etiologies of various MDD subtypes and (b) inform the development of novel prevention and treatment programs tailored to the MDD subtype.

Materials and Methods

Study Design and Sample

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a prospective cohort study with two waves of data collection. It was conducted by the National Institute on Alcohol Abuse and Alcoholism with the primary purpose to determine the prevalence of alcohol use disorders and their associated disabilities in the noninstitutionalized U.S. adult civilian population. Detailed descriptions of the NESARC sampling and interview

methods can be found elsewhere (20–22). At Wave 1 (2001-2002), 43,093 respondents (81.0% response rate) completed computer-assisted home interviews assessing substance use disorders, psychiatric disorders, and medical conditions. Three years later (mean = 36.6 months) at Wave 2 (2004-2005), 34,653 of the eligible Wave 1 respondents (86.7% response rate) completed a second home interview. Ethical approval for NESARC was provided by the U.S. Census Bureau and the U.S. Office of Management and Budget.

We applied four exclusion criteria to the Wave 2 sample. First, given our objective of predicting new-onset depression, we excluded respondents with a lifetime history of depressive disorders at Wave 1 (n = 6,884). Second, because CVD onset could result in CVD risk factor changes due to the initiation of new cardiovascular treatments and because the prevalence of depression is elevated following CVD onset (23), we excluded respondents with a CVD diagnosis at Wave 1 (n = 2,418). Third, due to the potential effects of pregnancy on both CVD risk factors and MDD, we excluded respondents who were pregnant within a year of the Wave 1 or 2 interviews (n = 1,527). Last, we excluded participants with missing data on any key variables (3.8%) – i.e., hypertension (n = 169), BMI (n = 651), and stressful life events (n = 89), leaving a final sample of 22,915 respondents.

Measures and Procedures

Cardiovascular Risk Factors

We examined three CVD risk factors assessed at Wave 1 as predictors of incident MDD subtypes: hypertension, tobacco use, and BMI. Hypertension was assessed with two questions. Part A asked, "In the past 12 months, have you had high blood pressure or hypertension?", and Part B asked, "Did a doctor or other health professional tell you that you had hypertension?" We coded respondents as positive for a self-reported physician diagnosis of hypertension if they answered "yes" to Parts A and B and coded respondents as negative if they answered "no" to

Part A. Although repeated blood pressure measurements is the gold standard for hypertension diagnosis, the hypertension awareness rate in the U.S. has been found to be as high as 74% (24).

The three-level lifetime tobacco use variable, created by NESARC personnel, consisted of history of cigarette, cigar, pipe, snuff, and chewing tobacco use. Respondents who reported using one or more tobacco products in the last year were coded as current tobacco users. Those who reported using at least one tobacco product more than once in the past but not in the last year were coded as former tobacco users, and those who reported never using tobacco products were coded as lifetime non-users. This NESARC variable possesses good reliability (25), and other investigations have observed high agreement between self-reported smoking and urinary cotinine levels (26,27).

We calculated BMI (kg/m^2) from self-reported height and weight. While measured BMI is more precise, evidence supports the use of self-reported BMI, as demonstrated by high correlations between measured and self-reported BMI, in epidemiologic studies examining relationships between factors (28).

Major Depressive Disorder and Subtypes

Lifetime MDD at baseline and incident MDD were determined by the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV), a fully structured diagnostic interview assessing mental disorders using DSM-IV criteria completed at both waves. This validated interview can be administered by experienced lay interviewers in clinical and general populations (29). We used the diagnostic variables coded by NESARC personnel that excluded illness-induced and substance-induced MDD and ruled out bereavement (21). Within the NESARC sample, the AUDIDIS-IV demonstrates good reliability and agreement with clinician evaluations (20,25).

From the Wave 2 NESARC variables, we used the NESARC coded two-level incident MDD outcome to create a three-level incident MDD subtype outcome. NESARC classified respondents, based on previous MDD history, into no incident MDD and incident MDD groups. To create our three-level outcome, we further classified respondents with incident MDD into atypical and typical MDD groups. The atypical MDD group consisted of respondents with both hyperphagia and hypersomnia. We coded individuals as having hyperphagia if they answered "yes" to either of the following AUDADIS-IV questions: "During that time when your mood was at its lowest/you enjoyed or cared the least about things, did you gain at least 2 pounds a week for several weeks or at least 10 pounds altogether within a month (other than when you were growing or pregnant)?" or "…did you find that you wanted to eat a lot more than usual for no special reason, most days for at least 2 weeks?" We coded respondents as having hypersomnia if they answered "yes" to the AUDADIS-IV question, "…did you sleep more than usual nearly every day for at least 2 weeks?" While other criteria for atypical MDD exist, using only the reversed somatic-vegetative symptoms demonstrates 78% sensitivity and 91% specificity and this valid approach (30) has been utilized in past studies (31–34). All other respondents with incident MDD were classified into the typical MDD group.

Covariates

The factors included as covariates in our models (all assessed at Wave 1) were selected because they are predictive of CVD risk factors and/or depression and, thus, are potential confounders of the relationships of interest (35,36). Our demographic-adjusted models included age, sex (0 = male, 1 = female), race/ethnicity, education level, cohabitation status, and unemployment status. We recoded race/ethnicity from a six-level variable to a four-level variable (0 = non-Hispanic White, 1 = non-Hispanic Black, 2 = Hispanic/Latino, 3 = Other) by combining the American Indian/Alaskan Native and Asian/Native Hawaiian categories with the Other

category due to low numbers of respondents in those categories. Education level was assessed by the question, "Highest grade or year of school completed?", from which we computed a four-level education level variable (0 = less than high school, 1 = high school or equivalent, 2 = some college or Associate's degree, 3 = Bachelor's degree or higher). Cohabitation status was assessed by asking, "What is your current marital status?" If respondents answered with "married" or "living with someone as if married", we coded them as cohabitating. We coded all others as not cohabitating. Unemployment status was assessed by asking, "Which describes your present situation?" If respondents answered with "unemployed or laid off and looking for work", "unemployed or laid off and not looking for work", or "unemployed and permanently disabled", we coded them as unemployed. We coded all other as not unemployed.

Our fully-adjusted models additionally included parental history of depression; lifetime anxiety, alcohol, and substance use disorders; and past-year stressful life events. If respondents indicated that their biological father or mother was depressed at any time, we coded them as positive for parental history of depression; otherwise, we coded them as negative. Respondents meeting criteria for panic disorder, agoraphobia, generalized anxiety disorder, or social phobia in the past year or prior (illness- and substance-induced disorders excluded) were coded as positive for lifetime anxiety disorder. Similarly, those meeting criteria for alcohol abuse or dependence were coded as positive for lifetime alcohol use disorder, and those meeting criteria for substance abuse or dependence (amphetamines, opioids, sedatives, tranquilizers, cocaine, inhalants/solvents, hallucinogens, cannabis, heroin, or other) were coded as positive for lifetime substance use disorder. Respondents not meeting criteria for each these disorders were coded as negative. Finally, respondents answered yes/no questions assessing whether they had experienced 12 stressful life events spanning health, social, job, and legal domains in the past year. From these data, we created a continuous past-year stressful life events variable ranging from 0-12 by summing the number of events reported (37).

Data Analysis

Before testing our hypothesis, we ran two logistic regression models examining the baseline CVD risk factors of hypertension, tobacco use, and BMI (z-scored) as simultaneous predictors of our two-level incident MDD outcome – no incident MDD (reference group) and incident MDD. Covariates in demographics-adjusted model were age, sex (male as the reference), race/ethnicity (3 dummy coded variables with non-Hispanic White as the reference), education level (3 dummy coded variables with less than high school as the reference), cohabitation status (not cohabitating as the reference), and unemployment status (not unemployed as the reference). Additional covariates in fully-adjusted model were parental history of depression (no parental history as the reference), lifetime anxiety disorder (no anxiety disorder as the reference), lifetime alcohol use disorder (no alcohol use disorder as the reference), lifetime substance use disorder (no substance use disorder as the reference), and past-year stressful life events. We selected these covariates, as they are potential confounders of the relationships of interest (35,36).

To test our hypothesis that CVD risk factors would be stronger predictors of incident atypical versus typical MDD, we ran four multinomial regression models examining the baseline CVD risk factors as simultaneous predictors of our three-level incident MDD subtype outcome (no incident MDD, incident atypical MDD, incident typical MDD). Two of these models used no incident MDD as the reference, and two used typical MDD as the reference. Covariates in demographics-adjusted and fully-adjusted models were the same as the logistic regression models described above.

All analyses were conducted with SAS statistical software, version 9.3. All models were adjusted for oversampling, selection probability, and nonresponse using the NESARC sample weights. Weighted analyses provide estimates for U.S. civilian noninstitutionalized population based on the 2000 Decennial Census (20).

Results

Baseline Cardiovascular Risk Factors and Incident Major Depression Disorder

At Wave 1 (see Table 1), there were 4,365 (19.1%) hypertension cases, 5,524 (24.1%) current tobacco users, and 4,417 (19.3%) former tobacco users. The mean BMI was 27.0 kg/m^2, which falls in the overweight range. At Wave 2, there were 1,243 (5.4%) incident MDD cases, of which 252 (20.3%) were atypical MDD and 991 (79.7%) were typical MDD.

Baseline Cardiovascular Risk Factors Predicting Three-Year Incidence of Major Depression Disorder

The demographics-adjusted logistic regression model revealed that baseline current tobacco use (*OR* = 1.13, 95% *CI*: 1.05-1.21, $p < 0.001$), former tobacco use (*OR* = 1.10, 95% *CI*: 1.00-1.21, $p = 0.047$), and z-scored BMI (*OR* = 1.12, 95% *CI*: 1.08-1.17, $p < 0.001$) predicted incident MDD; however, hypertension did not (*OR* = 0.99, 95% *CI*: 0.89-1.10, $p = 0.832$). In the fully-adjusted model, z-scored BMI (*OR* = 1.10, 95% CI: 1.06-1.15, $p < 0.001$) remained a predictor, whereas hypertension (*OR* = 0.97, 95% *CI*: 0.87-1.07, $p = 0.526$), current tobacco use (*OR* = 1.03, 95% *CI*: 0.96-1.11, $p = 0.397$), and former tobacco use (*OR* = 1.04, 95% *CI*: 0.95-1.14, $p = 0.362$) were not. Among the covariates in the fully-adjusted model (see Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/PSYMED/A465), increasing age, non-Hispanic Black, some college or Associate's degree, Bachelor's degree or higher, and cohabitating were independently associated with a lower odds of incident MDD, whereas female, Hispanic/Latino, other race/ethnicity, unemployed, parental history of MDD, lifetime anxiety disorder, and increasing number of past-year stressful life events were independently associated with a greater odds of incident MDD.

Baseline Cardiovascular Risk Factors Predicting Three-Year Incidence of Atypical and Typical Major Depression Disorder

As displayed in Table 2, the demographics-adjusted multinomial regression model using no incident MDD as the reference showed that baseline hypertension (42% lower odds), current tobacco use (25% greater odds), former tobacco use (52% greater odds), and z-scored BMI (35% greater odds per 1-*SD* increase) predicted incident atypical MDD versus no MDD. Additionally, baseline hypertension (12% greater odds), current tobacco use (10% greater odds), and z-scored BMI (6% greater odds per 1-*SD* increase) all predicted incident typical MDD versus no MDD. Former tobacco use did not predict incident typical MDD.

The fully-adjusted model using no incident MDD as the reference yielded some similar and some discrepant findings (see Table 2). In line with demographics-adjusted model, hypertension (42% lower odds), former tobacco use (46% greater odds), and z-scored BMI (32% greater odds per 1-*SD* increase) predicted incident atypical MDD versus no MDD. In contrast to demographics-adjusted model, current tobacco use no longer predicted incident atypical MDD, and none of the CVD risk factors predicted incident typical MDD.

Of greater relevance are the results of our models comparing atypical MDD to typical MDD presented in Table 3. In the demographics-adjusted model using incident typical MDD as the reference, baseline hypertension (48% lower odds), former tobacco use (49% greater odds), and z-scored BMI (27% greater odds per 1-*SD* increase) all predicted incident atypical MDD versus typical MDD. Current tobacco use did not predict incident atypical MDD. The fully-adjusted model using incident typical MDD as the reference yielded nearly identical results (see Table 3). As a set, these results indicate that CVD risk factors differentially predicted the MDD subtypes, with hypertension (negative relationship; protective factor), former tobacco use (positive relationship; risk factor), and BMI (positive relationship; risk factor) being stronger predictors of incident atypical MDD than of incident typical MDD.

As is shown in Supplemental Table 1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A465), the covariates predictive of incident typical MDD were nearly identical to those predictive of incident MDD, except that lifetime alcohol use disorder was independently associated with a greater odds of incident typical MDD. There were, however, notable differences for incident atypical MDD. Specifically, lifetime alcohol use disorder was independently associated with a lower odds, Hispanic/Latino was not associated, and high school or equivalent, some college or Associate's degree, and lifetime substance use disorder were independently associated with a greater odds of incident atypical MDD.

Discussion

Although past investigations have examined CVD risk factors as predictors of future depression, the present study is the first to test whether CVD risk factors differentially predict the development of MDD subtypes. In a large U.S national sample, we found partial support for our hypothesis that CVD risk factors would be stronger predictors of incident atypical versus typical MDD. Specifically, hypertension, former tobacco use, and BMI were: (a) predictors of incident atypical MDD but not typical MDD and (b) stronger predictors of incident atypical MDD than of typical MDD. While the associations of former tobacco use (46% greater odds) and BMI (32% greater odds per 1-*SD* increase) with incident atypical MDD were in the expected positive (risk factor) direction, the association for hypertension (42% lower odds) was in the negative (protective factor) direction. Current tobacco use did not predict either MDD subtype. Overall, the present findings suggest that certain CVD risk factors may play a greater role in the development of some MDD subtypes (atypical) but not others (typical).

Our findings that former tobacco use and elevated BMI were associated with greater odds of future atypical depression extend and refine existing evidence linking these CVD risk factors to future depression in general (6,7). Although the mechanisms underlying these associations are

unclear, systemic inflammation is a strong candidate. Both tobacco use (carbon monoxide causes endothelial dysfunction and inflammatory activation; 38) and obesity (adipose tissue directly produces inflammatory mediators; 39) can result in elevated levels of proinflammatory cytokines in circulation. These cytokines can then reach the brain via several routes, including leaky regions in the blood-brain barrier, active cytokine transport molecules, and afferent fibers of the vagus nerve (11). Once in the brain, this cytokine signal can be amplified and disrupt the function of several other systems implicated in depression – including the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic, norepinephrinergic, and dopaminergic neurotransmission (11) – which could give rise to the onset of depressive symptoms and disorders (40). Of note, recent research indicates that atypical MDD, versus other MDD subtypes, is associated with elevated levels of circulating inflammatory markers (see *Introduction*). Thus, it is possible that systemic inflammation specifically promotes the onset of this MDD subtype. Psychosocial factors could also be operating as mechanisms underlying the observed associations. In particular, obesity is associated with stigma/discrimination (41) and body image dissatisfaction (42), both of which could increase the risk of depression. Given our observational study design, unknown third factors could also account for the observed associations; however, we did adjust our models for several factors that could operate in this fashion, such as socioeconomic status (education level and unemployment status) and substance abuse (alcohol and other substance use disorders).

We also report two surprising results. One, our finding that hypertension was associated with a lower odds of incident atypical MDD conflicts with existing evidence of no association between this CVD risk factor and future depression in general (5). A potential explanation is that respondents with hypertension may have been followed more closely medically than those without hypertension and, thus, had a greater chance of being screened and treated for

depression, perhaps preventing the onset of a clinical disorder. Alternatively, the emotional-dampening hypothesis, which posits that elevated blood pressure is associated with decreased affect perception (43,44), may explain why hypertension appears to be a protective factor for atypical MDD. Two, it was also surprising that former tobacco use, but not current use, predicted incident atypical MDD. Of note, current tobacco use was a significant predictor in our demographic adjusted model (*OR* = 1.25). Given that this relationship was diminished but the direction remained the same in our fully-adjusted model (*OR* = 1.14), we suspect that adjustment for several factors likely related to current tobacco use (e.g., anxiety disorders, substance abuse, and past-year stressful life events) is responsible for this attenuation.

Although our findings are novel, there are limitations worthy of discussion. First, our CVD risk factor variables were based on respondent self-report. Though these self-report measures have been found to have acceptable validity (see *Measures and Procedures*), respondent inaccuracies may have resulted in an underestimation of true CVD risk factor-MDD subtype associations. Second, our tobacco use and hypertension variables were not continuous. Continuous measures – e.g., cumulative pack years and mean blood pressure levels – could provide more refined knowledge regarding the nature of the relationships. Third, only three CVD risk factors were measured at Wave 1 in NESARC. Examining other CVD risk factors (e.g., hypercholesterolemia) could provide further insights into the etiologies of MDD subtypes and, ultimately, inform interventions tailored to MDD subtype. Fourth, we did not have data pertaining to medical conditions and medications during the NESARC follow-up period, which could predict incident MDD. These limitations highlight the need for future prospective cohort studies with objective and comprehensive assessments of CVD risk factors to replicate and extend our findings. Our study does possess key methodological strengths, such as a large national sample, structured interview assessments of MDD, and the simultaneous examination of multiple CVD risk factors as predictors and MDD subtypes as outcomes.

Conclusions

Our study is the first to report that evidence that CVD risk factors differentially predict the incidence of MDD subtypes, with hypertension (protective factor), former tobacco use (risk factor), and BMI (risk factor) being stronger predictors of incident atypical MDD than of incident typical MDD. From a mechanistic perspective, this knowledge raises the possibility that CVD risk factors – such as tobacco use and obesity – may be involved in the etiology of atypical MDD, possibly due to their proinflammatory effects. From a clinical perspective, such mechanistic insights could ultimately inform the development of novel prevention and treatment programs tailored to the MDD subtype. To illustrate, if our findings are replicated in future studies, intervention programs designed to prevent or treat atypical MDD may incorporate aggressive screening and management of tobacco use and obesity into their protocols and test the efficacy of these components for depression outcomes.

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Table 1
Characteristics of Respondents (N = 22,915)

Baseline Covariates	
Age, years, mean (*SD*)	46.7 (17.3)
Women, %	51.5
Race/Ethnicity	
Non-Hispanic White, %	57.0
Non-Hispanic Black, %	19.6
Hispanic/Latino, %	18.8
Other, %	4.5
Education Level	
Less than High School, %	15.8
High School or Equivalent, %	29.1
Some College or Associate's Degree, %	29.7
Bachelor's Degree or Higher, %	25.4
Cohabitating, %	52.8
Unemployed, %	6.0
Parental History of Depression, %	15.3
Lifetime Anxiety Disorder, %	5.7
Lifetime Alcohol Use Disorder, %	26.1
Lifetime Substance Use Disorder, %	7.6
Number of Past-Year Stressful Life Events, mean, (*SD*)	1.4 (1.5)
Baseline Cardiovascular Risk Factors	
Hypertension, %	19.1
Tobacco Use	
Current, %	24.1
Former, %	19.3
Never, %	56.6
Body Mass Index, kg/m^2, mean, (*SD*)	27.0 (5.4)
Depressive Disorders	
Incident Major Depressive Disorder (MDD), %	5.4
Incident Atypical MDD, %	1.1
Incident Typical MDD, %	4.3

Table 2

Results of Demographic and Fully-Adjusted Multinomial Regression Models Examining Cardiovascular Risk Factors as Predictors of Incident Atypical and Typical Major Depressive Disorder (MDD) with No Incident MDD as the Reference Group

	Incident Atypical MDD				Incident Typical MDD			
	Demographic-Adjusted		Fully-Adjusted		Demographic-Adjusted		Fully-Adjusted	
	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**
No Hypertension	1.00	---	1.00	---	1.00	---	1.00	---
Hypertension	0.58 (0.43-0.77)	<0.001	0.58 (0.43-0.76)	<0.001	1.12 (1.01-1.24)	0.035	1.09 (0.98-1.21)	0.097
No Tobacco Use	1.00	---	1.00	---	1.00	---	1.00	---
Current Tobacco Use	1.25 (1.04-1.50)	0.016	1.14 (0.95-1.36)	0.165	1.10 (1.02-1.20)	0.016	1.01 (0.93-1.10)	0.835
Former Tobacco Use	1.52 (1.25-1.86)	<0.001	1.46 (1.20-1.78)	<0.001	1.01 (0.91-1.12)	0.878	0.95 (0.86-1.06)	0.375
Body Mass Index	1.35 (1.28-1.43)	<0.001	1.32 (1.25-1.40)	<0.001	1.06 (1.02-1.11)	0.010	1.05 (1.00-1.01)	0.057

Note. Body mass index was z-scored where 1 SD = 5.4 kg/m^2. Covariates in demographic-adjusted models model were age, sex, race/ethnicity, education level, cohabitation status, and unemployment status. The fully-adjusted models additionally included parental history of depression, lifetime anxiety disorder, lifetime alcohol use disorder, lifetime substance use disorder, and past-year stressful life events.

Table 3

Results of Demographic and Fully-Adjusted Multinomial Regression Models Examining Cardiovascular Risk Factors as Predictors of Incident Atypical and No Major Depressive Disorder (MDD) with Incident Typical MDD as the Reference Group

	Incident Atypical MDD				No Incident MDD			
	Demographic-Adjusted		Fully-Adjusted		Demographic-Adjusted		Fully-Adjusted	
	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**	***OR* (95% *CI*)**	***p*-value**
No Hypertension	1.00	---	1.00	---	1.00	---	1.00	---
Hypertension	0.52 (0.39-0.69)	<0.001	0.52 (0.39-0.70)	<0.001	0.90 (0.81-0.99)	0.035	0.92 (0.83-1.02)	0.097
No Tobacco Use	1.00	---	1.00	---	1.00	---	1.00	---
Current Tobacco Use	1.13 (0.92-1.39)	0.238	1.13 (0.91-1.40)	0.275	0.91 (0.84-0.98)	0.016	0.99 (0.91-1.08)	0.835
Former Tobacco Use	1.51 (1.21-1.89)	<0.001	1.53 (1.22-1.93)	<0.001	0.99 (0.90-1.10)	0.878	1.05 (0.95-1.16)	0.375
Body Mass Index	1.27 (1.19-1.37)	<0.001	1.26 (1.18-1.36)	<0.001	0.94 (0.90-0.99)	0.010	0.96 (0.91-1.00)	0.057

Note. Body mass index was z-scored where 1 SD = 5.4 kg/m2. Covariates in demographic-adjusted models model were age, sex, race/ethnicity, education level, cohabitation status, and unemployment status. The fully-adjusted models additionally included parental history of depression, lifetime anxiety disorder, lifetime alcohol use disorder, lifetime substance use disorder, and past-year stressful life events.