HHS Public Access

Author manuscript

Depress Anxiety. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Depress Anxiety. 2018 January ; 35(1): 10–17. doi:10.1002/da.22666.

Atypical Depression and Double Depression Predict New-Onset Cardiovascular Disease in U.S. Adults

Stephanie M. Case, MS[1], **Manisha Sawhney, PhD**[2], and **Jesse C. Stewart, PhD**[3]

[1]School of Psychological Sciences, University of Indianapolis, Indianapolis, IN

[2]Department of Psychology, Liffrig Family School of Education and Behavioral Sciences, University of Mary, Bismarck, ND

[3]Department of Psychology, Indiana University-Purdue University Indianapolis (IUPUI), Indianapolis, IN

Abstract

Background—Although depression is a risk factor for cardiovascular disease (CVD), it is unknown whether this risk varies across depressive disorder subtypes. Thus, we investigated atypical major depressive disorder (MDD) and double depression as predictors of new-onset CVD in a nationally representative sample of U.S. adults.

Methods—Prospective data from 28,726 adults initially free of CVD who participated in Wave 1 (2001–2002) and Wave 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were examined. Lifetime depressive disorder subtypes (Wave 1) and incident CVD (Wave 2) were determined by structured interviews.

Results—We identified 1,116 incident CVD cases. In demographics-adjusted models, the atypical MDD group had a higher odds of incident CVD than the no depression history (*OR*=2.19, 95% *CI*: 1.71–2.81, $p<.001$), dysthymic disorder only (*OR*=1.61, 95% *CI*: 1.08–2.39, $p=.019$), and nonatypical MDD (*OR*=1.46, 95% *CI*: 1.11–1.91, $p=.006$) groups. Likewise, the double depression group had a higher odds of incident CVD than the no depression history (*OR*=2.17, 95% *CI*: 1.92–2.45, $p<.001$), dysthymic disorder only (*OR*=1.59, 95% *CI*: 1.16–2.19, $p=.004$), and MDD only (*OR*=1.46, 95% *CI*: 1.20–1.77, $p<.001$) groups. Relationships were similar but attenuated after adjustment for CVD risk factors and anxiety disorders.

Conclusions—Adults with atypical MDD or double depression may be subgroups of the depressed population at particularly high risk of new-onset CVD. Thus, these subgroups may (a) be driving the overall depression-CVD relationship and (b) be in need of earlier and/or more intense CVD primary prevention efforts to reduce their excess CVD burden.

Corresponding Author: Jesse C. Stewart, Ph.D., Department of Psychology, Indiana University-Purdue University Indianapolis, 402 North Blackford Street, LD 100E, Indianapolis, IN 46202. Telephone: (317) 274-6761. Fax: (317) 274-6756. jstew@iupui.edu.

Conflicts of Interest and Source of Funding: NESARC is funded by the National Institute on Alcohol Abuse and Alcoholism with supplemental support from the National Institute on Drug Abuse. A portion of Dr. Stewart's time was supported by the National Heart, Lung, and Blood Institute under Award Number R01HL122245. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. None of the remaining authors has any possible conflicts of interest to declare.

Keywords

depressive disorder; arteriosclerosis; angina pectoris; myocardial infarction; epidemiologic studies; prospective studies

Introduction

Considerable evidence indicates that depression is an independent risk factor for cardiovascular disease (CVD) (Van der Kooy et al., 2007). However, it is unknown whether the CVD risk conferred by depression varies across disorder subtypes. Atypical depression accounts for 15–40% of depression cases, and among its key features are the reversed somatic-vegetative symptoms of hyperphagia and hypersomnia (APA, 2013; Grant et al., 2009; Quitkin, 2002). Adults with atypical depression, compared to those with nonatypical depression, have higher rates or levels of several CVD risk factors, including dyslipidemia, hypertension, diabetes, obesity, metabolic syndrome, physical inactivity, and systemic inflammation (Chou & Yu, 2013; Cizza et al., 2012; Glaus et al., 2013; Hickman, Khambaty, & Stewart, 2014; Lamers et al., 2013; Lasserre et al., 2014; Levitan et al., 2012; Niranjan, Corujo, Ziegelstein, & Nwulia, 2012; Rudolf, Greggersen, Kahl, Huppe, & Schweiger, 2014; Takeuchi, Nakao, Kachi, & Yano, 2013; van Reedt Dortland et al., 2010). Because of this higher risk factor burden, atypical depression may be a stronger predictor of CVD than nonatypical depression. The few existing studies, however, do not support this notion. Niranjan and colleagues (2012) found no difference in prevalent CVD between depressed adults with versus without atypical features, and atypical MDD symptoms were not associated with prevalent CVD in two other studies (Fraguas et al., 2007; Vogelzangs et al., 2010). A key limitation of all three studies, however, is their cross-sectional design, especially considering that reverse causality is plausible (Spijkerman et al., 2005) and could mask depression subtype differences.

Double depression refers to major depressive disorder (MDD) superimposed on dysthymia (Keller & Shapiro, 1982), a chronic, low-grade depressive disorder. About three quarters of patients with dysthymia have or will experience a major depressive episode and, thus, suffer from double depression (Hellerstein & Eipper, 2013). To date, associations of double depression with CVD risk markers or outcomes have not been examined. Nonetheless, double depression may be a stronger predictor of CVD due to its longer duration and higher recurrence rate than MDD alone and its greater symptom severity than dysthymia alone (Keller, Hirschfeld, & Hanks, 1997).

Because no studies have examined atypical or double depression as predictors of new-onset CVD, our primary aim was to address these key gaps. Our secondary aim was to evaluate whether these relationships are independent of anxiety disorders. As anxiety disorders are highly comorbid with depressive disorders (Kessler et al., 2003) and also predict incident CVD (Roest, Martens, de Jonge, & Denollet, 2010), it is important to adjust for them to isolate depression effects. We examined Wave 1 (2001–2002) and Wave 2 (2004–2005) data from a large, nationally representative sample of U.S. adults from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Materials and Methods

Study Design and Sample

NESARC is a prospective cohort study designed to determine the prevalence of alcohol use disorders and associated disabilities in the U.S. civilian noninstitutionalized population ≥18 years. Descriptions of study methods are provided elsewhere (Grant, et al., 2009; Grant et al., 2005; Hasin & Grant, 2015). NESARC received ethical approval from the U.S. Census Bureau and the U.S. Office of Management and Budget. At Wave 1, 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, 34,653 of the eligible Wave 1 respondents (86.7% response rate) completed a second home interview. A total of 3,134 Wave 1 respondents were not eligible for Wave 2 due to being deceased, deported, mentally or physically impaired, or on active duty in the armed forces. Respondents who participated in Waves 1 and 2, versus Wave 1 only, were younger (46.0 vs. 48.2 years) and more likely to be female (58.0% vs. 53.2%), to be non-Hispanic White (58.2% vs. 51.3%), to have a high school education or more (83.4% vs. 75.1%), and to have a lifetime depressive disorder (17.3% vs. 13.3%; all ps < .001). We applied three exclusion criteria to the Wave 2 sample. Respondents were excluded if: (1) CVD status at Wave 1 was positive (n=1,742) or missing (n=1,719), (2) CVD status at Wave 2 was missing (n=1,065), or (3) CVD risk factors at Wave 1 were missing (n=1,401). Characteristics of our final sample of 28,726 adults are shown in Table 1.

Measures and Procedures

Lifetime Depressive Disorder Subtypes—Lifetime dysthymic disorder and MDD were determined by the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV), a fully structured diagnostic interview administered by lay interviewers assessing mental disorders using DSM-IV criteria (Ruan et al., 2008). NESARC personnel coded diagnostic variables for the past year and prior to the past year. We used the NESARC variables that excluded illness-induced and substance-induced disorders and ruled out bereavement (Grant et al., 2005). The AUDADIS-IV has demonstrated good test-retest reliability for depressive disorders (Grant et al., 2003) and generally good agreement with clinician evaluations (Hasin & Grant, 2015).

From the NESARC variables, we computed two variables. Our first variable, *atypical depression*, had four levels: no depressive disorder, dysthymic disorder only, nonatypical MDD, and atypical MDD. First, we classified respondents into no depressive disorder history (never met criteria), lifetime dysthymic disorder only (past year or prior), and lifetime MDD (past year or prior) groups. Those who met criteria for both lifetime dysthymic disorder and MDD were placed into the MDD group. Then, we further classified respondents with lifetime MDD. 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 “During that time…, 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, "During that time…, did you sleep more than usual nearly every day for at least 2 weeks?" While other criteria for atypical MDD exist (APA, 2013), using only the reversed somatic-vegetative symptoms is a valid approach (Benazzi, 2002) and has been utilized in past studies (Blanco et al., 2012; Chou & Yu, 2013; Horwath, Johnson, Weissman, & Hornig, 1992; Matza, Revicki, Davidson, & Stewart, 2003).

Our second variable, *double depression*, also had four levels: no depressive disorder, dysthymic disorder only, MDD only, and double depression. The definitions for the no depressive disorder and dysthymic disorder groups were the same as above. Respondents with lifetime MDD were further classified into two groups: MDD only (if only lifetime MDD was present) and double depression (if both lifetime dysthymic disorder and MDD were present).

Incident Cardiovascular Disease—Using data from the NESARC Medical Conditions and Practices questionnaire administered at Wave 2, we computed an incident CVD variable comprised of new-onset arteriosclerosis, angina, or myocardial infarction (MI) based on self-reported physician diagnoses. In Part A, respondents were asked, "In the last 12 months, did you have: (1) hardening of the arteries or arteriosclerosis? (2) chest pain or angina pectoris? (3) a heart attack or myocardial infarction?" If the answer to Part A was "yes," in Part B respondents were asked, "Did a doctor or other health professional tell you that you had (name of condition)?" We coded respondents as positive for incident CVD if they answered "yes" to Parts A and B for at least one CVD question, and we coded respondents as negative if they answered "no" to all three Part A questions. Those who were coded as "unknown" for Part A or B for one or more questions and who did not answer "yes" to Part A and B for at least one question were coded as missing for incident CVD and were excluded. To compute a corresponding baseline CVD variable, we applied the same coding scheme to the identical Wave 1 CVD questions. Because our focus is predicting new-onset CVD, we included only respondents coded negative for baseline CVD.

Potential Confounders—The following variables – which could operate as potential confounders of depression-CVD associations (Luger, Suls, & Vander Weg, 2014; Luppino et al., 2010; Nouwen et al., 2010) – were included as control variables in the models: age (years), sex (0=male, 1=female), race/ethnicity, education level, hypertension, hypercholesterolemia, diabetes, tobacco use, body mass index (BMI), and lifetime anxiety disorder. These variables were based on self-reported data from Wave 1 except hypercholesterolemia and diabetes, which were assessed only at Wave 2. We recoded race/ethnicity into a four-level variable (0=non-Hispanic White, 1=non-Hispanic Black, 2=Hispanic or Latino, 3=Other). Next, we created three dummy-coded variables using non-Hispanic White as the reference category. Education level was assessed by the question, "Highest grade or year of school completed?" From these data, we computed a 4-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). Three dummy-coded variables using less than high school as the reference category were then created.

We coded respondents as positive for hypertension, hypercholesterolemia, and diabetes, respectively, if they answered “yes” to “In the past 12 months, have you had: (1) high blood pressure or hypertension? (2) high cholesterol? (3) diabetes or sugar diabetes?” and “yes” to “Did a doctor or other health professional tell you that you had (name of condition)?” We coded respondents as negative for each condition if they answered “no” to the first question. Those coded by NESARC personnel as “unknown” for either question were coded as missing for that condition and were excluded. We recoded NESARC’s tobacco use variable (current user, former user, lifetime nonuser) into a dichotomous variable (0=current nonuser, 1=current user). BMI (kg/m^2) was computed from self-reported height and weight.

We computed a lifetime anxiety disorder variable using AUDADIS-IV data collected at Wave 1. Respondents who were coded by NESARC personnel as meeting diagnostic 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. Those not meeting criteria for any of these disorders were coded as negative.

Data Analysis

We ran three sets of logistic regression analyses – demographics-adjusted, CVD risk factor-adjusted, and anxiety disorder-adjusted – examining the atypical depression variable as a predictor of incident CVD. For each set, we ran three models, each of which used a different reference category (1 = no depressive disorder, 2 = dysthymic disorder only, 3 = nonatypical MDD). Control variables in the demographics-adjusted models were age, sex, race/ethnicity, and education level. The CVD risk factor-adjusted models were further adjusted for hypertension, hypercholesterolemia, diabetes, tobacco use, and BMI. The anxiety disorder-adjusted models additionally included lifetime anxiety disorder. Finally, we ran an identical series of logistic regression analyses for the double depression variable. All selected control variables were significantly associated with the atypical depression and double depression variables.

Analyses were conducted with SAS statistical software, version 9.3. Models were weighted to account for oversampling, probabilities of selection, and nonresponse. Weighted analyses provide estimates for U.S. civilian noninstitutionalized population based on the 2000 Decennial Census (Hasin & Grant, 2015).

Results

Depressive Disorder Subtypes and Incident Cardiovascular Disease

The lifetime prevalence was 3.4% (964 cases) for atypical MDD and 3.1% (833 cases) for double depression. The degree of overlap between these two subtypes was modest, as the phi coefficient (r_ϕ) was 0.22, and 228 cases qualified for both atypical MDD and double depression. We identified 1,116 cases (3.9%) of incident CVD: 264 with arteriosclerosis only, 625 with angina only, 75 with MI only, 53 with arteriosclerosis and angina, 11 with arteriosclerosis and MI, 58 with angina and MI, and 30 with all three outcomes. Tables 2 and 3 display the number of CVD cases and the unadjusted case rate for each depressive disorder

subtype. Due to its smaller size, the dysthymic disorder only group had a low number of CVD cases, which reduced power for comparisons involving this group.

Atypical Depression as a Predictor of Incident Cardiovascular Disease

Demographics-adjusted logistic regression models (Table 2) revealed that respondents with atypical MDD had over twice the odds of incident CVD than those with no depressive disorder ($p<.001$). Although adults with dysthymic disorder only (37% greater odds; $p=.043$) or nonatypical MDD (51% greater odds; $p<.001$) were more likely to develop CVD than nondepressed adults, the magnitude of these associations was less than half of that for atypical MDD. These models also indicated that the odds of CVD in the atypical MDD group were greater than in the dysthymic disorder only (*OR*=1.61, 95% *CI*: 1.08–2.39, $p=.019$) and nonatypical MDD (*OR*=1.46, 95% *CI*: 1.11–1.91, $p=.006$) groups.

CVD risk factor-adjusted and anxiety disorder-adjusted models (Table 2) yielded a similar pattern of results, although associations were attenuated and some fell short of significance. Respondents with atypical MDD remained at the highest risk of incident CVD, with a 78% ($p<.001$) and 56% ($p=.001$) greater odds than nondepressed adults. However, comparisons of the atypical MDD group with the dysthymic disorder only group (CVD risk factor-adjusted *OR*=1.46, 95% *CI*: 0.97–2.18, $p=.068$; anxiety disorder-adjusted *OR*=1.39, 95% *CI*: 0.92–2.09, $p=.12$) and the nonatypical MDD group (CVD risk factor-adjusted *OR*=1.25, 95% *CI*: 0.94–1.65, $p=.13$; anxiety disorder-adjusted *OR*=1.22, 95% *CI*: 0.92–1.61, $p=.18$) were no longer significant. In the CVD risk factor-adjusted and anxiety disorder-adjusted models, nonatypical MDD also continued to predict incident CVD ($p<.001$ and $p=.004$), whereas dysthymic disorder did not ($p=.21$ and .48).

Double Depression as a Predictor of Incident Cardiovascular Disease

Demographics-adjusted models (Table 3) indicated that respondents those with double depression had more than twice the odds of incident CVD than nondepressed adults ($p<.001$). Dysthymic disorder only (36% greater odds; $p=.044$) and MDD only (49% greater odds; $p<.001$) also predicted incident CVD but these relationships were not as strong as that for double depression. The double depression group also had higher odds of incident CVD than the dysthymic disorder only (*OR*=1.59, 95% *CI*: 1.16–2.19, $p=.004$) and MDD only (*OR*=1.46, 95% *CI*: 1.20–1.77, $p<.001$) groups.

Although associations were again attenuated, the pattern of results was similar in the CVD risk factor-adjusted and anxiety disorder-adjusted models (Table 3). Adults with double depression remained at the highest odds of incident CVD. This group had a 95% ($p<.001$) and 65% ($p<.001$) greater odds than those in the no depressive disorder group, and comparisons with the dysthymic disorder only group (CVD risk factor-adjusted *OR*=1.61, 95% *CI*: 1.16–2.21, $p=.004$; anxiety disorder-adjusted *OR*=1.47, 95% *CI*: 1.07–2.02, $p=.018$) and the MDD only group (CVD risk factor-adjusted *OR*=1.42, 95% *CI*: 1.16–1.73, $p=.001$; anxiety disorder-adjusted *OR*=1.31, 95% *CI*: 1.08–1.59, $p=.006$) continued to be significant. In the CVD risk factor-adjusted and anxiety disorder-adjusted models, MDD only ($p<.001$ and $p=.016$) – but not dysthymic disorder only ($p=.22$ and .48) – remained a predictor of incident CVD.

Discussion

Our examination of the NESARC data indicates that atypical MDD and double depression are two depressive disorder subtypes that may be particularly strong predictors of new-onset CVD. With respect to atypical MDD, U.S. adults with a lifetime history of this subtype had a higher odds of incident CVD than those with no depression history, dysthymic disorder only, or nonatypical MDD in demographics-adjusted models. Although a similar pattern of results was observed in CVD risk factor-adjusted models, some comparisons fell short of significance. Concerning double depression, U.S. adults with a lifetime history of subtype had a higher odds of incident CVD than those with no depression history, dysthymic disorder only, or MDD only in both demographics- and CVD risk factor-adjusted models. Further adjustment for lifetime anxiety disorder attenuated associations but did not alter the pattern of results for either subtype. The modest degree of overlap between atypical MDD and double depression suggests that their associations with incident CVD likely reflect separate relationships; however, the 228 cases with both subtypes did contribute to both relationships. Collectively, our findings indicate that adults with atypical MDD or double depression may be subgroups of the depressed population at greatest risk of developing CVD and, thus, may be driving the overall depression-CVD relationship.

Our study addresses a key gap in the literature – i.e., the absence of prospective studies examining atypical depression or double depression as predictors of incident CVD. Our findings do conflict with three prior studies that observed no difference in prevalent CVD between depressed adults with versus without atypical features (Niranjan, et al., 2012) and no associations between atypical MDD symptoms and prevalent CVD (Fraguas, et al., 2007; Vogelzangs, et al., 2010). However, due to their cross-sectional design, reverse causality may have obscured depression subtype differences (Spijkerman, et al., 2005). To our knowledge, there are no previous studies that have examined associations between double depression and CVD risk markers or outcomes. Although one other prospective analysis of the NESARC data reported the association of lifetime MDD with CVD, the focus of that analysis was the bipolar disorder-incident CVD relationship, and depressive disorder subtypes were not examined (Goldstein, Schaffer, Wang, & Blanco, 2015).

There are multiple candidate mechanisms that could explain why atypical MDD may be a stronger predictor of incident CVD. Evidence suggests that conventional CVD risk factors are elevated in adults with atypical versus nonatypical depression (Chou & Yu, 2013; Cizza, et al., 2012; Glaus, et al., 2013; Lamers, et al., 2013; Levitan, et al., 2012; Niranjan, et al., 2012; Takeuchi, et al., 2013; van Reedt Dortland, et al., 2010). Moreover, atypical MDD has been found to predict incident obesity and increases in BMI, waist circumference, and fat mass over time (Lasserre, et al., 2014). In our models adjusting for Wave 1 CVD risk factors, associations were attenuated. However, because depressive disorders and CVD risk factors were assessed at the same point, the NESARC data cannot be used to determine whether the CVD risk factors were operating as confounders or mediators. Given that our objective was to provide unbiased estimates of the associations between depressive disorder subtypes and incident CVD, we chose to treat the CVD risk factors as potential confounders to be conservative. In addition to conventional CVD risk factors, other mechanisms may also be at work. Another candidate mechanism, which was not assessed in NESARC, is greater

systemic inflammation. Adults with atypical depression, versus those with nonatypical depression, have been found to have higher circulating levels of inflammatory markers predictive of CVD, such as C-reactive protein and interleukin-6 (Hickman, et al., 2014; Lamers, et al., 2013; Rudolf, et al., 2014). Two other candidate mechanisms are poor diet quality (Rahe et al., 2015) and low physical activity (Glaus, et al., 2013; Matza, et al., 2003). In addition to these biological and behavioral pathways, adults with atypical MDD may have greater lifetime exposure to depression, given that it is characterized by earlier age of onset, more severe symptoms, and a greater number of episodes (Blanco, et al., 2012; Matza, et al., 2003; Novick et al., 2005).

Less is known about the correlates of double depression that could be operating as underlying mechanisms. Like atypical depression, associations were attenuated after adjustment for conventional CVD risk factors, suggesting that they may partially explain the elevated CVD risk of this group. It is also plausible that double depression is a stronger predictor of incident CVD on account of its longer duration and higher recurrence rate than MDD alone and its greater symptom severity than dysthymia alone (Keller, et al., 1997), resulting in greater lifetime exposure to depression and the associated atherogenic biological and behavioral changes (Grippo & Johnson, 2002; Joynt, Whellan, & O'Connor, 2003). In addition, a smaller study found that patients with double depression reported greater hopelessness than patients with MDD or dysthymia (Joiner, Cook, Hersen, & Gordon, 2007). Hopelessness has been linked with greater subclinical atherosclerosis (Whipple et al., 2009) and an increased risk of CVD events (Everson et al., 1996), independent of depressive symptoms. Clearly, there is a need for studies examining associations of double depression with CVD outcomes and candidate mechanisms.

The present study has key strengths, including the longitudinal design, large nationally representative sample, and structured interview assessments of psychiatric disorders. NESARC is the largest and most comprehensive psychiatric epidemiologic survey conducted in the U.S (Hasin & Grant, 2015), and its prospective data allowed us to draw strong inferences regarding directionality. Our study also has limitations that should be considered. First, epidemiologic surveys often assess CVD by self-report of physician diagnoses. Supporting this approach, agreement between self-reported and medical record-ascertained CVD has been found to be acceptable to good (Barr, Tonkin, Welborn, & Shaw, 2009; Bergmann, Byers, Freedman, & Mokdad, 1998; Heckbert et al., 2004; Lampe, Walker, Lennon, Whincup, & Ebrahim, 1999; Machon et al., 2013; Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004). A recent study (Yasaitis, Berkman, & Chandra, 2015) comparing self-reported and Medicare claims-identified MIs did observe lower agreement than past studies; however, the authors speculated that this may have been due to their sample's older age and their narrower MI definition. Nonetheless, because some degree of misclassification occurs with self-reports of physician diagnoses, there is a need for future studies examining depressive disorder subtypes as predictors of incident CVD adjudicated by a review of medical records. Second, incident fatal CVD events were not captured. Respondents who died between Waves 1 and 2 of NESARC were excluded from the Wave 2 cohort, and information regarding cause of death is not available. While this could have compromised power, that does not appear to be the case, as we observed 1,116 cases of incident CVD. Third, some incident nonfatal MIs may have not have been detected because

the NESARC Wave 2 questions inquired about CVD diagnoses in the past 12 months only. This is less of a concern for arteriosclerosis and angina, as these are chronic conditions and not discrete events. Our composite incident CVD outcome also reduces the potential for misclassification, given that respondents who suffered nonfatal MIs between Waves 1 and 2, but prior to the past 12 months, may have also been diagnosed with one of the other CVD conditions during follow-up. Fourth, due to the limited temporal resolution of the diagnostic variables, our double depression definition did not take into account the order of onset or co-occurrence of dysthymic disorder and MDD. Future studies with diagnostic variables possessing greater temporal resolution are needed to examine the importance of these characteristics in predicting incident CVD. Fifth, although age ranged from 18 to 97 years in our sample, the mean age was only 45 years, and the follow-up period was only three years. Both of these factors likely contributed to the lower rate (3.9%) of incident CVD.

Conclusion

We report prospective evidence from a nationally representative sample indicating that U.S. adults with atypical MDD or double depression may be subgroups of the depressed population at particularly high risk of new-onset CVD who may be driving the depression-CVD relationship. With respect to research implications, our results suggest that clinical trials evaluating whether successful depression treatment reduces CVD risk should consider specifically recruiting patients with atypical MDD or double depression, as it is in these subgroups where most of the excess CVD risk seems to reside. Furthermore, our findings underscore the need to continue to test existing treatments (Fournier et al., 2013) or to develop new treatments to address residual depressive symptoms and syndromes, such as reversed somatic-vegetative symptoms and dysthymia. Concerning clinical practice, our results highlight the potential importance of depression screening that allows for depressive disorder subtyping. Finally, our findings raise the possibility that CVD primary prevention efforts should be initiated earlier and/or intensified among adults with atypical MDD or double depression to prevent or delay clinical CVD onset, thereby reducing the excess CVD burden of the depressed population.

Acknowledgments

NESARC is funded by the National Institute on Alcohol Abuse and Alcoholism with supplemental support from the National Institute on Drug Abuse. A portion of Dr. Stewart's time was supported by the National Heart, Lung, and Blood Institute under Award Number R01HL122245. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). Washington, DC: American Psychiatric Association; 2013.

Barr EL, Tonkin AM, Welborn TA, Shaw JE. Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. Internal Medicine Journal. 2009; 39:49–53. [PubMed: 19290982]

Benazzi F. Can only reversed vegetative symptoms define atypical depression? Europen Archives of Psychiatry and Clinical Neuroscience. 2002; 252:288–293.

Bergmann MM, Byers T, Freedman DS, Mokdad A. Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. American Journal of Epidemiology. 1998; 147:969–977. [PubMed: 9596475]

Blanco C, Vesga-Lopez O, Stewart JW, Liu SM, Grant BF, Hasin DS. Epidemiology of major depression with atypical features: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Journal of Clinical Psychiatry. 2012; 73:224–232. [PubMed: 21939615]

Chou KL, Yu KM. Atypical depressive symptoms and obesity in a national sample of older adults with major depressive disorder. Depression and Anxiety. 2013; 30:574–579. [PubMed: 23554014]

Cizza G, Ronsaville DS, Kleitz H, Eskandari F, Mistry S, Torvik S, Martinez PE. Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: the power study. PLoS One. 2012; 7:e28912. [PubMed: 22235252]

Everson SA, Goldberg DE, Kaplan GA, Cohen RD, Pukkala E, Tuomilehto J, Salonen JT. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosomatic Medicine. 1996; 58:113–121. [PubMed: 8849626]

Fournier JC, DeRubeis RJ, Hollon SD, Gallop R, Shelton RC, Amsterdam JD. Differential change in specific depressive symptoms during antidepressant medication or cognitive therapy. Behaviour Research and Therapy. 2013; 51:392–398. [PubMed: 23644038]

Fraguas R Jr, Iosifescu DV, Alpert J, Wisniewski SR, Barkin JL, Trivedi MH, Fava M. Major depressive disorder and comorbid cardiac disease: is there a depressive subtype with greater cardiovascular morbidity? Results from the STAR*D study. Psychosomatics. 2007; 48:418–425. [PubMed: 17878501]

Glaus J, Vandeleur C, Gholam-Rezaee M, Castelao E, Perrin M, Rothen S, Preisig M. Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. Acta Psychiatrica Scandinavica. 2013; 128:282–293. [PubMed: 23216242]

Goldstein BI, Schaffer A, Wang S, Blanco C. Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. Journal of Clinical Psychiatry. 2015; 76:163–169. [PubMed: 25742203]

Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. Drug and Alcohol Dependence. 2003; 71:7–16. [PubMed: 12821201]

Grant BF, Goldstein RB, Chou SP, Huang B, Stinson FS, Dawson DA, Compton WM. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Molecular Psychiatry. 2009; 14:1051–1066. [PubMed: 18427559]

Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou P, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Journal of Clinical Psychiatry. 2005; 66:1205–1215. [PubMed: 16259532]

Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. Neuroscience & Biobehavioral Reviews. 2002; 26:941–962. [PubMed: 12667498]

Hasin DS, Grant BF. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: review and summary of findings. Social Psychiatry abd Psychiatric Epidemiology. 2015; 50:1609–1640.

Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, Curb JD. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. American Journal of Epidemiology. 2004; 160:1152–1158. [PubMed: 15583367]

Hellerstein, DJ., Eipper, JW. Dysthymia and chronic depression. In: Mann, JJ.McGrath, PJ., Roose, SP., editors. Clinical handbook for the management of mood disorders. New York, NY: Cambridge University Press; 2013.

Hickman RJ, Khambaty T, Stewart JC. C-reactive protein is elevated in atypical but not nonatypical depression: data from the National Health and Nutrition Examination survey (NHANES) 1999–2004. Journal of Behavioral Medicine. 2014; 37:621–629. [PubMed: 23624671]

Horwath E, Johnson J, Weissman MM, Hornig CD. The validity of major depression with atypical features based on a community study. Journal of Affective disorders. 1992; 26:117–125. [PubMed: 1447429]

Joiner TE Jr, Cook JM, Hersen M, Gordon KH. Double depression in older adult psychiatric outpatients: hopelessness as a defining feature. Journal of Affective disorders. 2007; 101:235–238. [PubMed: 17475340]

Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. Biological Psychiatry. 2003; 54:248–261. [PubMed: 12893101]

Keller MB, Hirschfeld RM, Hanks D. Double depression: a distinctive subtype of unipolar depression. Journal of Affective disorders. 1997; 45:65–73. [PubMed: 9268776]

Keller MB, Shapiro RW. "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. American Journal of Psychiatry. 1982; 139:438–442. [PubMed: 7065289]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]

Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Molecular Psychiatry. 2013; 18:692–699. [PubMed: 23089630]

Lampe FC, Walker M, Lennon LT, Whincup PH, Ebrahim S. Validity of a self-reported history of doctor-diagnosed angina. Journal of Clinical Epidemiology. 1999; 52:73–81. [PubMed: 9973076]

Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, Preisig M. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. JAMA Psychiatry. 2014; 71:880–888. [PubMed: 24898270]

Levitan RD, Davis C, Kaplan AS, Arenovich T, Phillips DI, Ravindran AV. Obesity comorbidity in unipolar major depressive disorder: refining the core phenotype. Journal of Clinical Psychiatry. 2012; 73(8):1119–1124. [PubMed: 22687640]

Luger TM, Suls J, Vander Weg MW. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. Addictive Behaviors. 2014; 39:1418–1429. [PubMed: 24935795]

Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of General Psychiatry. 2010; 67:220–229. [PubMed: 20194822]

Machon M, Arriola L, Larranaga N, Amiano P, Moreno-Iribas C, Agudo A, Dorronsoro M. Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study. Journal of Epidemiology and Community Health. 2013; 67:71–75. [PubMed: 22577182]

Matza LS, Revicki DA, Davidson JR, Stewart JW. Depression with atypical features in the National Comorbidity Survey: classification, description, and consequences. Archives of General Psychiatry. 2003; 60:817–826. [PubMed: 12912765]

Niranjan A, Corujo A, Ziegelstein RC, Nwulia E. Depression and heart disease in US adults. General Hospital Psychiatry. 2012; 34:254–261. [PubMed: 22401707]

Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, Consoritum ER. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia. 2010; 53:2480–2486. [PubMed: 20711716]

Novick JS, Stewart JW, Wisniewski SR, Cook IA, Manev R, Nierenberg AA, Rush AJ. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D. Journal of Clinical Psychiatry. 2005; 66:1002–1011. [PubMed: 16086615]

Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. Journal of Clinical Epidemiology. 2004; 57:1096–1103. [PubMed: 15528061]

Quitkin FM. Depression with atypical features: diagnostic validity, prevalence, and treatment. The Primary Care Companion to the Journal of Clinical Psychiatry. 2002; 4:94–99.

Rahe C, Baune BT, Unrath M, Arolt V, Wellmann J, Wersching H, Berger K. Associations between depression subtypes, depression severity and diet quality: cross-sectional findings from the BiDirect Study. BMC Psychiatry. 2015; 15:38. [PubMed: 25886444]

Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. Journal of the American College of Cardiology. 2010; 56:38–46. [PubMed: 20620715]

Ruan WJ, Goldstein RB, Chou SP, Smith SM, Saha TD, Pickering RP, Grant BF. The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. Drug and Alcohol Dependence. 2008; 92:27–36. [PubMed: 17706375]

Rudolf S, Greggersen W, Kahl KG, Huppe M, Schweiger U. Elevated IL-6 levels in patients with atypical depression but not in patients with typical depression. Psychiatry Research. 2014; 217:34–38. [PubMed: 24673855]

Spijkerman T, de Jonge P, van den Brink RH, Jansen JH, May JF, Crijns HJ, Ormel J. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. General Hospital Psychiatry. 2005; 27:411–417. [PubMed: 16271655]

Takeuchi T, Nakao M, Kachi Y, Yano E. Association of metabolic syndrome with atypical features of depression in Japanese people. Psychiatry and Clinical Neurosciences. 2013; 67:532–539. [PubMed: 24152284]

Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. International Journal of Geriatric Psychiatry. 2007; 22:613–626. [PubMed: 17236251]

van Reedt Dortland A, Giltay E, van Veen T, van Pelt J, Zitman F, Penninx B. Associations between serum lipids and major depressive disorder: results from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Clinical Psychiatry. 2010; 71:729–736. [PubMed: 20021996]

Vogelzangs N, Seldenrijk A, Beekman AT, van Hout HP, de Jonge P, Penninx BW. Cardiovascular disease in persons with depressive and anxiety disorders. Journal of Affective disorders. 2010; 125:241–248. [PubMed: 20223521]

Whipple MO, Lewis TT, Sutton-Tyrrell K, Matthews KA, Barinas-Mitchell E, Powell LH, Everson-Rose SA. Hopelessness, depressive symptoms, and carotid atherosclerosis in women: the Study of Women's Health Across the Nation (SWAN) heart study. Stroke. 2009; 40:3166–3172. [PubMed: 19713542]

Yasaitis LC, Berkman LF, Chandra A. Comparison of self-reported and Medicare claims-identified acute myocardial infarction. Circulation. 2015; 131:1477–1485. [PubMed: 25747935]

Table 1

Characteristics of Respondents (N = 28,726)

Demographic Factors	
Age, years (*SD*)	44.8 (17.0)
Female, %	57.5
Race/Ethnicity	
Non-Hispanic White, %	58.2
Non-Hispanic Black, %	18.6
Hispanic/Latino, %	18.7
Other, %	4.5
Education Level	
Less than High School, %	15.2
High School or Equivalent, %	28.5
Some College or Associate's Degree, %	30.6
Bachelor's Degree or Higher, %	25.7
Cardiovascular Risk Factors	
Hypertension, %	18.2
Hypercholesterolemia, %	19.3
Diabetes, %	8.0
Tobacco Use, %	25.6
Body Mass Index, kg/m^2	27.0 (5.6)
Anxiety Disorders	
Lifetime Anxiety Disorder, %	10.5

Note. Continuous variables are presented as mean (standard deviation), and categorical variables are presented as percentage. Lifetime anxiety disorder consists of panic disorder, agoraphobia, generalized anxiety disorder, and social phobia.

Table 2

Logistic Regression Models Examining Atypical Depression as a Predictor of Incident Cardiovascular Disease

		Demographics-Adjusted Models		CVD Risk Factor-Adjusted Models		Anxiety Disorder-Adjusted Models	
	Incident CVD Cases (% of group)	***OR***	**95% *CI***	***OR***	**95% *CI***	***OR***	**95% *CI***
No Depressive Disorder (reference) *n* = 23,788 (82.8%)	903 (3.8%)	1.00	---	1.00	---	1.00	---
Dysthymic Disorder Only *n* = 227 (0.8%)	13 (5.7%)	1.37[a,d]	1.01–1.85	1.22	0.89–1.66	1.12	0.82–1.54
Nonatypical Major Depressive Disorder *n* = 3,747 (13.0%)	155 (4.1%)	1.51[a,d]	1.31–1.74	1.42[a]	1.23–1.65	1.28[a]	1.08–1.51
Atypical Major Depressive Disorder *n* = 964 (3.4%)	45 (4.7%)	2.19[a,b,c]	1.71–2.81	1.78[a]	1.37–2.30	1.56[a]	1.19–2.03

Note. *N* = 28,726 (1,116 incident CVD cases). Control variables in the demographic-adjusted models were age, sex, race/ethnicity, and education level. The CVD risk factor-adjusted models were further adjusted for hypertension, hypercholesterolemia, diabetes, tobacco use, and body mass index. The anxiety disorder-adjusted models also included lifetime anxiety disorder. CVD = cardiovascular disease. OR = odds ratio. CI = confidence interval.

[a]Significantly different from no depressive disorder ($p < .05$).

[b]Significantly different from dysthymic disorder only ($p < .05$).

[c]Significantly different from nonatypical major depressive disorder ($p < .05$).

[d]Significantly different from atypical major depressive disorder ($p < .05$).

Table 3

Logistic Regression Models Examining Double Depression as a Predictor of Incident Cardiovascular Disease

		Demographics-Adjusted Models		CVD Risk Factor-Adjusted Models		Anxiety Disorder-Adjusted Models	
	Incident CVD Cases (% of group)	***OR***	**95% *CI***	***OR***	**95% *CI***	***OR***	**95% *CI***
No Depressive Disorder (reference) *n* = 23,788 (82.8%)	903 (3.8%)	1.00	---	1.00	---	1.00	---
Dysthymic Disorder Only *n* = 227 (0.8%)	13 (5.7%)	1.36[a,d]	1.01–1.84	1.22[d]	0.89–1.66	1.12[d]	0.82–1.54
Major Depressive Disorder *n* = 3,828 (13.3%)	150 (3.9%)	1.49[a,d]	1.27–1.76	1.38[a,d]	1.16–1.63	1.26[a,d]	1.04–1.51
Double Depression *n* = 883 (3.1%)	50 (5.7%)	2.17[a,b,c]	1.92–2.45	1.95[a,b,c]	1.72–2.21	1.65[a,b,c]	1.46–1.87

Note. *N* = 28,726 (1,116 incident CVD cases). Control variables in the demographic-adjusted models were age, sex, race/ethnicity, and education level. The CVD risk factor-adjusted models were further adjusted for hypertension, hypercholesterolemia, diabetes, tobacco use, and body mass index. The anxiety disorder-adjusted models also included lifetime anxiety disorder. CVD = cardiovascular disease. OR = odds ratio. CI = confidence interval.

[a]Significantly different from no depressive disorder ($p < .05$).

[b]Significantly different from dysthymic disorder only ($p < .05$).

[c]Significantly different from major depressive disorder ($p < .05$).

[d]Significantly different from double depression ($p < .05$).