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Recurrent Depression, Cardiovascular Disease, and Diabetes among Middle-Aged and Older Adult Women

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Abstract

Background—The goal of this study was to investigate the concurrent and prospective relationships between a history of single and recurrent Major Depression Disorder (MDD) and the medical conditions of cardiovascular disease (CVD) and diabetes using a community sample of middle- and older-aged women.

Methods—Data from women (*n*=557 at baseline; *mean* age=55.7 yrs.) participating in a two-wave longitudinal study (5-year interval) were used to examine associations between single and recurrent MDD, assessed with a structured clinical interview, and three self-report indicators of CVD (heart attack or myocardial infarction, stroke, angina), major CVD risk markers (hypertension, high cholesterol), and diabetes. Analyses were conducted to evaluate hypotheses which proposed that recurrent depression would be significantly associated with the three medical outcomes, but not single episode MDD.

Results—After controlling for a range of important covariates (e.g., BMI, smoking, alcohol use), cross-sectional analyses indicated that recurrent MDD, but not single episode MDD, significantly predicted CVD risk and diabetes. Prospective analyses indicated that recurrent MDD, but not single episode MDD, increased the risk for CVD and diabetes.

Limitations—The sample was a predominantly white, middle-class sample so generalizability of findings may be limited for minorities and men. Reliance on self-report data may have biased the findings.

Conclusions—These findings suggest the benefits of measuring single versus recurrent MDD when investigating the risk of depression on chronic diseases. Findings also suggest the importance of identifying individuals suffering from recurrent MDD early in their lifespan with the goal of preventing future depressive episodes.

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Contributors
Michael Windle designed the study and wrote the protocol. Rebecca Windle supervised data collection. Rebecca Windle managed the literature searches. Michael Windle undertook the statistical analyses. Michael Windle and Rebecca Windle co-wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest
Authors Michael Windle and Rebecca Windle report no conflict of interest.

Keywords

Depression; CVD; Diabetes; Hypertension; Cholesterol

Introduction

As the US population is disproportionately "graying", it becomes increasingly important to understand the complex interrelationships among mental disorders and medical conditions. A specific research area that has garnered increasing attention is the link between depression and cardiovascular disease (CVD) and other medical conditions (e.g., diabetes) (Chapman et al., 2005; Duivis et al., 2011; Mezuk et al., 2008). Depression, CVD, and diabetes are highly prevalent conditions and are also highly comorbid. Studies investigating the prevalence of Major Depressive Disorder (MDD) among representative samples in the US have found lifetime rates on the order of 15%, with women having a significantly higher prevalence of lifetime MDD relative to men (Hassin et al., 2005; Kessler et al., 2005). Wassertheil-Smoller et al. (2004) reported data from the Women's Health Initiative indicating that 15.8% of the women in this sample reported high levels of current depressive symptoms and 12.3% reported a history of depressed mood. Diabetes has a similarly high prevalence among adults. The Centers for Disease Control and Prevention (CDC, 2011) estimated a prevalence rate among adults 20 years and older at 11.3% for diagnosed and undiagnosed diabetes. The rate in men was 11.8% and in women it was 10.8%. Type 2 diabetes accounted for 90–95% of all cases in adults. Finally, heart disease is the leading cause of death among both males (25.4%) and females (24.5%) in the US (CDC, 2008a; 2008b). Thus, as would be expected, coronary diseases and coronary risk factors are quite high in the general population. For example, data from the 2011 National Health Interview Survey (CDC, 2012) indicated that 6.3% of respondents reported coronary disease (i.e., coronary heart disease, angina pectoris, and/or heart attack), 24.3% reported hypertension, and 2.6% reported a stroke. These percentages increased with increasing age of the participants.

While each of these conditions independently account for high levels of morbidity, there are also high rates of co-occurrence among them. For example, individuals with Type 2 diabetes have almost twice the rate of depression relative to those without diabetes (19.1% versus 10.7%, respectively) (Roy and Lloyd, 2012), and depression is associated with a 60% increased risk of Type 2 diabetes (Mezuk et al., 2008). Current depression, along with a history of depression, have been linked to cardiac events and subclinical coronary disease both concurrently and longitudinally (Jones et al., 2003; Rowan et al., 2005; Rozanski et al., 1999; Wagner et al., 2006). Cardiovascular disease is a frequent complication of Type 2 diabetes (Howard and Magee, 2000). Adults with diabetes are 2–4 times more likely to have heart disease or a stroke than people without diabetes (Gregg et al., 2012). Furthermore, women with diabetes have a significantly higher relative risk of fatal coronary heart disease than do men with diabetes (Huxley et al., 2006). However, while CVD and diabetes often co-occur, the majority of people (approximately 75%) in the national population who have diabetes *do not* have current CVD (Gregg et al., 2012). Furthermore, research suggests the potential important link between depression and diabetes independent of CVD (Mazuk et al., 2008; Roy and Lloyd, 2012).

Although meta-analyses and systematic reviews have demonstrated significant associations between depression and manifestations of CVD (Pan et al., 2011; Rugulies, 2002; Wuslin, 2004) and diabetes (Anderson et al., 2001; de Groot et al., 2001; Mezuk et al., 2008), respectively, only a limited number of studies have focused on the different effects single episode MDD versus recurrent MDD may have on CVD and diabetes. For instance, with a sample of 336 middle-aged women, Jones et al. (2003) reported that recurrent MDD was

associated with a two-fold increase in plaque, a biomarker for carotid atherosclerosis. In contrast, single episode MDD did not significantly predict increases in plaque. The findings of Wagner et al. (2009) indicated that recurrent depression among postmenopausal women with Type 2 diabetes was associated with vasoconstriction and endothelial dysfunction, but not among those with a history of single episode MDD. In a prospective study with a younger-aged sample, Copeland et al. (2012) reported that recurrent MDD was associated prospectively with higher levels of C-reactive protein, an immune system marker for cardiovascular and metabolic diseases in middle and older adulthood (Duivis et al., 2011). Limitations of the current literature on single episode versus recurrent MDD include restrictions on comparisons between these two MDD groups versus comparisons to a control group (Monroe and Harkness, 2011), and mostly cross-sectional (versus longitudinal) research designs (Holzel et al., 2011).

One of the challenges of investigating the associations between depression and CVD and diabetes is the potential confounding or “third” variable influences that may attenuate or eliminate the bivariate associations. Review articles and meta-analyses have catalogued a number of these factors, including sociodemographic variables (e.g., socioeconomic status), co-occurring conditions (e.g., overweight or obesity), lifestyle factors (e.g., tobacco and alcohol use), and stressful life events (Chapman et al., 2005; Rugulies, 2002; Wuslin, 2004). Mixed evidence has also been indicated for the role of anxiety disorders as possibly influential in relation to CVD. Some studies have supported this association (Frasure-Smith and Lesperance, 2008; Martens et al., 2010; Goodwin et al., 2009) whereas others have not (Jones et al., 2003). Given the high co-occurrence rate of depression and anxiety disorders, it is beneficial to evaluate the independent contributions of these mental health disorders to CVD and diabetes.

A second challenge to the study of associations between MDD and CVD and diabetes pertains to the direction of effects (Keyes, 2004; Ren et al., 2011). That is, the causal status of the relationship between depression and CVD (and other chronic diseases) could be bidirectional, contingent on when one is conducting assessments on respondents (e.g., prior to or after a cardiac event). For example, depression could be a consequence of CVD or other chronic disorders as individuals attempt to cope with potentially debilitating conditions and functional limitations. Alternatively, depression may contribute to a set of mediating conditions such as increased platelets and inflammation that may directly (e.g., by impacting plaque build-up) or indirectly (e.g., by reducing sleep or level of social support due to unpleasant depressive symptom expression) contribute to the occurrence of a cardiac event. It is also possible that common factors contribute to depression and CVD and diabetes (e.g., obesity). In the current study, due to the sample characteristics (i.e., a community [vs. clinical] sample of women) and the few new MDD onset cases that occurred between waves of measurement, the primary focus was on MDD as a predictor of chronic medical conditions rather than the reverse, or the study of bidirectional influences.

In the current study, we used two-wave panel data with a community sample of women to investigate both concurrent and prospective associations between single-episode and recurrent MDD and indicators of CVD (heart attack, stroke, angina), CVD-risk factors (hypertension, high cholesterol), and diabetes. In doing so, we controlled for a range of potential confounding factors (e.g., BMI, alcohol use, cigarette use, and stressful life events) that have been associated with CVD, diabetes, and depression, so as to rule out these third variable causes as explanations for any significant relationships between depression and CVD and diabetes. Likewise, because some studies have suggested that anxiety disorders are associated with coronary heart disease (Martens et al., 2010), we also controlled for lifetime anxiety disorders. On the basis of the literature reviewed previously, we hypothesized that after controlling for significant covariates, recurrent depression would

significantly predict CVD, CVD risk, and diabetes both in the cross-sectional and longitudinal analyses, but that single episode MDD would not significantly predict these outcomes.

METHOD

Participants

The data used in this study were collected as part of a larger, multi-wave panel design initially focused on risk factors for adolescent and young adult substance use and mental health (see Windle et al., 2005). The first four waves of the study, conducted at six-month intervals during adolescence for the initial target sample, involved primary caregivers (principally mothers) as reporters on child behaviors (e.g., behavior problems) and family variables (e.g., family income, family history of alcoholism) that the participating child may not know. The Waves 5–7 assessments occurred at three, five-year intervals and the primary targets for study were expanded to include not only the adolescents as they transitioned to young and middle adulthood, but also the parents of these adult children. This paper focuses on the women's (mothers') data collected at Waves 6 and 7 because data on medical conditions were collected only at these waves. The sample included 557 women at Wave 6 and 506 women at Wave 7. Descriptive statistics for the sample are provided in Table 1.

Procedure

During the adolescent phase (i.e., Waves 1–4), target adolescents were recruited and surveyed in their high school settings and the participation rate was 76%; primary caregivers participated via a brief mail survey. One-on-one interviews were conducted at Waves 5 and 6 either in the subjects' homes or at the host institute of the investigators. Subjects were paid $40 to complete an interview that lasted approximately two hours. Computer-assisted personal interviews were used to collect data. At Wave 7, due to budgetary cuts, mail surveys were completed by parents and returned in self-addressed, stamped envelopes.

This longitudinal study was reviewed and approved by the Institutional Review Board of the University at Buffalo. Signed informed consent was obtained from participants prior to each wave of assessment.

Measures

Parental sociodemographic variables—In their individual interviews and the completion of mail surveys, participants were asked about their age, number of years of education completed, family income, and other status indicators (e.g., marital and occupational status).

CVD, CVD-Risk, and Diabetes—Six items regarding medical conditions were used from the Behavioral Risk Factor Surveillance System Survey Questionnaire developed by the Centers for Disease Control and Prevention (CDC, 2004). At Waves 6 and 7, participants were asked if a doctor ever told them that they had each of the following medical conditions: heart attack (or myocardial infarction), angina, stroke, hypertension, high cholesterol, and diabetes. Three different indexes were used in the analyses: cardiovascular disease (CVD) with indicators of heart attack, angina, or stroke; CVD risk for hypertension or high cholesterol; and the single item of diabetes. For CVD and CVD risk, scores greater than one were recoded to 1; therefore there were three binary outcomes.

Psychiatric Disorders—*DSM-IV* disorders were derived via personal interviews at Waves 5 and 6 using the World Health Organization Composite International Diagnostic Interview (WHO-CIDI; WHO, 1997). Reliability data for the WHO-CIDI have been

reported (WHO, 1997) and the disorders used in this study included major depressive disorders, both single and recurrent, and the summation of the following anxiety disorders: social anxiety disorder, generalized anxiety disorder, panic disorder, and simple phobias. The WHO-CIDI interview, or interviews with minor modifications that are similar to it, have been used extensively in epidemiologic studies in the United States (Kessler et al., 2005) and internationally (Andrade et al., 2003).

Body Mass Index—Self-reports of current height and weight were requested from each participant and these indicators were then used to calculate a body-mass index (BMI) via standard conversion formulas (weight in kilograms was divided by height in meters squared). Self-reported BMI correlates highly with more finely calibrated instruments (Cronk and Roche, 1982).

Alcohol use—Alcohol use was measured with a standard quantity frequency index (QFI) that assessed beer, wine, and hard liquor consumption in the past 6 months (Armor and Polich, 1982). Respondents were asked how often they usually had each beverage in the last 6 months (1 = never to 7 = every day) and, when they had the beverage, on average how much they usually drank (10-point scale from 1 = none to 10 = more than 8 cans, bottles, or glasses, depending on the beverage). A QFI of 0.5 ounces of ethanol is equal to 1 drink. In order to conform more closely to the assumption of distributional normality, we applied a logarithmic transformation to the resulting consumption values. (The specific transformation for the quantity-frequency measure of alcohol consumption involved adding 10 to the original value and then taking the natural logarithm of the summed value.)

Cigarette use—Participants were requested to rate the frequency of last 30-days cigarette use using a seven-point Likert scale that ranged from never used to used every day. The validity of self-reports of tobacco and other substance use has been supported in numerous research studies (Oetting and Beauvais, 1990; Winters et al., 1991) and the correlation between last 30 day cigarette use and last six-month cigarette use was *Pearson* $r=0.98, p < .001$.

Stressful Life Events—At each wave of measurement participants completed an adaptation of the Holmes and Rahe scale (1967) to assess stressful life events using two timeframes—last year and the three years preceding the last year. There were a total of 46 events that can be scored as an aggregate measure of stressors with events covering domains of work stressors, interpersonal stressors, health concerns-self, health concerns-others, financial stressors, and criminal/legal stressors.

Statistical Analyses Plan

For the primary analyses, logistic regression analyses were conducted for the binary outcomes of CVD, CVD risk, and diabetes. For each cross-sectional logistic regression equation, eight variables were initially entered in a first step of the equation, and then the hypothesis-driven variables of single-episode or recurrent MDD were entered as a second step. The initial eight variables were selected to control for possible covariates that may confound the interpretation of the depression–outcome relationships (i.e., they could provide alternative explanations for the findings). Two dummy variables were created for the depressive disorder variables—one was coded “1” for MDD single episode and otherwise “0”; the second variable was coded “1” for MDD recurrent episodes and otherwise “0”. The dummy variable coding incorporated the “control” group (i.e., the non-depressive disorder group) in the “0” category for both variables. Similar to the cross-sectional analyses, eight covariates were included in the longitudinal (prospective) logistic regression models to predict Wave 7 outcomes, plus Wave 6 scores of the respective dependent variables were

entered as control variables (e.g., Wave 6 CVD was controlled in the prediction of Wave 7 CVD). These longitudinal models provided robust tests of the longitudinal associations between depression and medical outcomes because control was provided for Wave 6 conditions; hence, the predictors were required to significantly predict *change* across time in CVD, CVD risk, and diabetes. Note that change in these models reflects the occurrence of new cases between Wave 6 and Wave 7. The findings for the cross-sectional and longitudinal models were reported as adjusted odds ratios (AORs) to facilitate interpretation of individual effect sizes while controlling for all other variables in the regression model.

RESULTS

As shown in Table 1, approximately 19% of the sample reported a single episode of MDD and 20.3% reported recurrent MDD. The prevalence of chronic medical conditions at Waves 6 and 7 are provided in Table 2 and indicated a moderate increase in conditions across the approximately five-year interval. The retention rate from Wave 6 (*n=557*) to Wave 7 (*n=506*) was 90.8%. Attrition analyses were conducted by comparing those who participated at both waves of assessment with those who participated only at Wave 6. These comparisons on Wave 6 variables indicated no statistically significant differences in the prevalence of any of the medical conditions, on lifetime anxiety or major depressive disorders (whether single or recurrent MDD), on age, education level, BMI, or level of alcohol use. Those who did not participate at Wave 7 reported a somewhat lower family income and smoked more cigarettes per day than the participant group. Collectively, there was scant evidence of selective drop-out that may have biased parameter estimates in the longitudinal analyses.

Cross-sectional analyses

Table 3 summarizes the findings for the full model equations (i.e., the step 2 model). Pertinent specifically to the proposed hypotheses, single episode MDD was not significantly related to any of the three health outcomes while controlling for the eight covariates. By contrast, recurrent MDD was significantly related both to CVD risk and diabetes, but not to CVD. The AOR for recurrent MDD indicated that while controlling for the influences of the other eight covariates, CVD risk was increased approximately one-and-one-half times (AOR=1.63) and diabetes was increased approximately two-and-one-half times (AOR=2.66) by recurrent MDD. Other prominent risk factors for these health outcomes were also statistically significant (e.g., BMI), but the largest AOR for CVD risk and diabetes was for recurrent MDD.

Longitudinal analyses

Table 4 summarizes the prospective, five year interval findings and indicated that while controlling for Wave 6 conditions and the eight covariates, single episode MDD did not significantly predict any of the three outcomes. However, recurrent MDD significantly predicted increases in CVD and diabetes. The AOR for recurrent MDD indicated that while controlling for the influences of the other eight covariates, CVD was increased approximately three-and-one-half times (AOR=3.59) and diabetes was increased approximately three times (AOR=3.20) by recurrent MDD. Note that the largest AORs (and confidence intervals) in the prospective analyses were for the Wave 6 health control variable (e.g., Wave 6 CVD) and this is not surprising given that the Wave 7 health outcomes included all of the Wave 6 cases plus new cases that occurred between Wave 6 and Wave 7. This is analogous to a very high correlation between continuous variables at two occasions of measurement. The inclusion of the Wave 6 control variables for each health outcome was to provide a stringent test for the substantive hypotheses investigated in this study.

Ancillary sensitivity analyses

Because the proposed CVD risk factors (hypertension, high cholesterol) and diabetes are often viewed as risk factors for CVD, we conducted an additional analysis that included these two Wave 6 variables as predictors in the prospective logistic regression model of CVD at Wave 7. This analysis was completed to determine if the AOR for recurrent MDD remained statistically significant and of a similar magnitude following the inclusion of these additional predictors (i.e., was the AOR sensitive to the exclusion of these two risk factors for CVD). Hence, this model included the eight covariates reported in Table 4, and Wave 6 CVD, CVD Risk, and Diabetes. Similar to the findings reported in Table 4, recurrent MDD remained statistically significant and the magnitude of the AOR was unchanged (*AOR=3.58, CI=1.36–9.45*).

DISCUSSION

Our findings with a community sample of women were supportive of the hypothesized relationships between single versus recurrent MDD on CVD, CVD risk, and diabetes. The cross-sectional findings indicated that, consistent with prior research, older age, lower education level, and BMI were related to the medical conditions assessed. However, after controlling for these, and other covariates, recurrent MDD still significantly predicted CVD Risk (hypertension and high cholesterol) and diabetes. Single episode MDD was not a significant predictor of any of the three medical outcomes once other predictors were included in the regression equations. Similarly, in the prospective analyses with a five-year interval between waves of measurement, recurrent MDD significantly predicted CVD and diabetes, but single episode MDD did not significantly predict any of the three medical outcomes. These findings are bolstered by having controlled for a number of major potential third variable causes (e.g., BMI, tobacco use, alcohol use), and in the longitudinal analyses controlling for prior health outcomes (e.g., controlling for previous CVD). Thus, recurrent depression was a significant predictor of increases in the occurrence of CVD and diabetes across this five-year window. These findings regarding the importance of recurrent depression are consistent with prior research that has indicated that recurrence or persistence of depression is more strongly associated with CVD and diabetes than single episode or less persistent depression (Jones et al., 2003; Wagner et al., 2009). The findings also advance the literature both with regard to including comparisons among important sub-groups (single episode versus recurrent MDD) (Monroe and Harkness, 2011), and with using a prospective versus cross-sectional research design (Holzel et al., 2011).

Because of the constraints of our data, we were unable to address the issue of directionality in the depression—CVD and depression—diabetes relationships. However, illuminating to this issue, three recent studies investigated the directionality between depression and coronary heart disease indicators and risk factors employing longitudinal methodologies (Duivis et al., 2011; Rowan et al., 2005; Wassertheil-Smoller et al., 2004). Using data from the Women's Health Initiative, Wassertheil-Smoller et al. investigated the ability of baseline depressive symptoms to predict CVD events across a four year period. Their results indicated that, among women with no history of CVD, depressive symptoms independently predicted CVD death and all-cause mortality after adjusting for a range of CVD risk factors. Likewise, Rowan et al. found that, among a sample of adults with no overt CHD at baseline, baseline depressive symptoms were significant predictors of MI-related hospitalizations and CHD-related deaths four years later after controlling for a range of CVD risk factors. They also reported a gradient effect of depressive symptoms such that the higher the symptoms the greater the risk for a CHD event. A recent longitudinal study of outpatients with coronary heart disease by Duivis et al. (2011) indicated that depressive symptoms were significant prospective predictors of inflammation markers, specifically IL6 and hsCRP levels, but that initial higher inflammation levels were not significant prospective predictors

of depression. Finally, Mezuk et al. (2008) conducted a meta-analysis and concluded that depression represented a robust risk factor for the development of Type 2 diabetes, but that the relationship of Type 2 diabetes to depression was much less strong. Our findings are congruent with those described above in that a lifetime diagnosis of recurrent MDD was a prospective predictor of increased risk for CVD and diabetes.

Our finding that recurrent MDD, but not single-episode MDD, was significantly associated with CVD risk factors and diabetes cross-sectionally and CVD and diabetes longitudinally is potentially quite important given that the chronic nature of recurrent MDD, and the subclinical depressive symptoms that sometimes continue during periods of remission, provide a plausible explanation for MDD's long-term impact on biological (e.g., levels of inflammation, plaque build-up, platelet levels), psychological (sadness, hopelessness), behavioral (smoking, poor dietary habits, sedentary life style, alcohol and substance abuse), and social (isolation, poor interpersonal relationships) domains that are associated with higher rates of CVD and diabetes (Rozanski et al., 1999). With regard to the chronic and progressive nature of recurrent MDD, Solomon et al. (2000) found that the risk of MDD recurrence increased by 16% with each recurring episode. Kennedy and Paykel (2004) followed-up a group of severe recurrent depressives 8–10 years after they had remitted from an index episode. They found that patients who had remitted from the depressive episode with residual sub-clinical symptoms continued to manifest depressive symptoms across the years and to report greater social impairment.

Population estimates of the number of acute, single-episode forms of depression are about 60% and the remaining 40% are recurrent cases (Moffitt et al., 2010). Studies focused on distinguishing single episode versus recurrent MDD have indicated that the latter are characterized by a younger age of onset, longer duration of depressive episode, family history of mood disorders, psychiatric co-morbidity, and more negative social interactions (Burcusa and Iacono, 2007; Holzel et al., 2011; Monroe and Harkness, 2011). Burcusa and Iacono (2007) also reviewed findings on risk recurrence and concluded that genetic and biological factors may be more prominent among recurrent cases via increased vulnerability to stressors. Jindal et al. (2002) compared the electroencephalographic sleep profiles of remitted patients who had been diagnosed with a single MDD episode versus patients with recurrent MDD. They found that patients with recurrent MDD continued to manifest greater sleep disturbances during early remission relative to the single-episode patients. They concluded that their findings were supportive of a more severe neurophysiological substrate of MDD among recurrent patients than among single-episode patients. Kendler et al. (1999) suggested that the clinical features of MDD recurrence, long duration of episodes, high levels of impairment, and recurrent thoughts of death or suicide likely reflected a high genetic liability to depressive illness.

Investigation of the mechanisms by which depression may facilitate the development of CVD and diabetes has focused on the role of immune system functioning and how persistent or chronic depression suppresses immune system responses which, in turn, yield the body and associated organ systems (e.g., the heart) more vulnerable to disruption and disease. For example, Howren et al. (2009) have suggested that inflammatory markers, including C-reactive protein, interleukin (IL)-1 and IL6 are associated with depression that may, in turn, be associated with greater cardiac risk. Others have proposed additional neurotransmitter, neuroendocrine, and autonomic nervous system factors that may serve as mechanisms to account for the relationships between depression and CVD and diabetes (Gehi et al., 2005; Nakatani et al., 2005). The role of the hypothalamic-adrenal-cortical system as a central mechanism whereby stress and depression may overload stress-response circuits and yield the body more susceptible to disease, including CVD, has also been proposed (Kent and Shapiro, 2009; Danese et al., 2008). Recurrent depression versus single episode depression

may reflect both initial greater genetic and biological vulnerability to stressful events and precipitants of depression, as well as neuroadaptations and bio-regulatory processes that are non-salubrious with regard to CVD and diabetes. That is, ongoing stress-generation processes and cognitive, affective, social, and behavioral dysregulation may be more common among those with recurrent MDD than among those with a time-limited, discrete episode. Such dysregulated systems may elicit ongoing demands on cellular and organ systems and not be adaptive with regard to new stress.

Because large epidemiologic studies have indicated an association between depression and anxiety disorders and cardiovascular disease (Goodwin et al., 2009; Ormel et al., 2007), because of the high comorbidity between MDD and anxiety disorders, and because anxiety disorders are more prevalent among women than men, we included a binary (absent/present) indicator of anxiety disorders in our regression analyses. Within the context of our multi-variable models, both our cross-sectional and longitudinal analyses indicated no significant relationships between anxiety disorders and CVD, CVD risk factors, and diabetes. This finding is similar to that of Jones et al. (2003). In their review of the literature, Rozanski et al. (1999) found that anxiety disorders were indeed linked to the incidence of acute, cardiac events (e.g., sudden cardiac death) but not to myocardial infarction. They suggested that ventricular arrhythmias may be the mechanism by which sudden cardic death (but not MI) occurs among individuals with anxiety disorders. Because sudden cardiac death was not an outcome in this study, we were unable to test this hypothesized relationship. Furthermore, the limited prevalence of some of the specific anxiety disorders precluded the disaggregation of these disorders.

Recurrent MDD is characterized by an earlier age of onset, longer and more severe episodes, and a family history of depression (Burcusa and Iacono, 2007; Holzel et al., 2011; Kendler et al., 1999; Monroe and Harkness, 2011); as such, identification of individuals at-risk for recurrent MDD earlier in their lifespan and successful treatment of MDD may ameliorate or prevent the development of cardiovascular disease and diabetes. As we suggested earlier, individuals with recurrent MDD may get “caught-up” in cycles of non-adaptive functioning, such as higher levels of stress (e.g., interpersonal, financial), feelings of hopelessness, tobacco, alcohol, and drug use, poor dietary habits, and low physical activity. Psychotherapeutic, pharmacological, and behavioral interventions that disrupt these dysfunctional behaviors and redirect them toward pro-health trajectories would promote more positive cardiovascular and endocrine functioning.

This study has limitations that need to be considered in interpreting the findings. First, the sample was primarily non-Hispanic white and female; therefore, findings may not generalize to other ethnic groups or to men. Second, the medical conditions were self-reported without verification from other sources (e.g., medical records or physical exam)—faulty memory or intentional misrepresentation (e.g., social desirability) could have impacted the validity of these self-reports of medical conditions, though other data suggest the general reliability and validity of self-report measures of medical conditions (Yoon et al., 2012). Third, while the longitudinal findings help support that recurrent MDD was a prospective predictor of CVD and diabetes, the data did not enable the evaluation of bidirectional influences; furthermore, potential biomarkers and mechanisms that may account for this relationship were not examined in this study.

Despite these limitations, the study advances knowledge in this area of investigation in three ways. First, it used both cross-sectional and longitudinal data to examine the associations between depression and CVD and diabetes while controlling for important covariates. Second, it specifically compared single versus recurrent MDD while controlling for anxiety disorders—this facilitated the testing of the specificity of recurrent depression that could not

be explained by co-occurring anxiety disorders (or other covariates). Third, the study included middle-aged and older adult women, an age group at increasingly high risk for cardiac events and diabetes, and the findings support the potential value of supporting research and targeted interventions that address the relationships between recurrent depression and CVD and diabetes. Future research would benefit from a focus on the specific genetic, biological, and psychosocial mechanisms that account for the relationship between recurrent MDD and CVD and diabetes, and the evaluation of interventions designed to reduce recurrent MDD and its impact on CVD and diabetes.

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Table 1

Wave 6 Sample Characteristics (N=557)

Variables	
Ethnicity	
Non-Hispanic White	99.5%
Other	0.5%
Age	Wave 6: 55.66 *(SD=4.71)*
	Wave 7: 59.98 *(SD=4.60)*
Current Marital Status	
Married	458 (78.6%)
Cohabitation	15 (2.6%)
Divorced	77 (13.2%)
Widowed	32 (5.5%)
Never married	1 (0.2%)
Average Number Years of Education	13.84 *(SD=2.33)*
Employment Status	
Employed full-time	47.7%
Employed part-time	16.8%
Full-time homemaker	10.1%
Unemployed looking for work	2.0%
Unemployed not looking for work	6.1%
Retired	17.2%
Median Family Income (past year)	$40,000–$54,999
Lifetime DSM-IV Disorders (%)	
Anxiety Disorder	42.8%
MDD-Single Episode	19.1%
MDD-Recurrent Episodes	20.3%

Table 2

Percentage of Chronic Medical Conditions at Wave 6 (N=557) and Wave 7 (N=506) for Adult Women

Medical Condition	Wave 6 (%)	Wave 7 (%)
Heart attack	4.3	4.7
Angina	3.9	6.3
Stroke	1.8	2.4
Hypertension	32.4	41.5
High Cholesterol	39.7	49.2
Diabetes	7.2	11.3

Table 3

Cross-Sectional Logistic Regression Analyses Predicting CVD, CVD Risk, and Diabetes

	Single Episode MDD			Recurrent MDD		
Predictors	**Model 1: CVD**	**Model 2: CVD Risk**	**Model 3: Diabetes**	**Model 1: CVD**	**Model 2: CVD Risk**	**Model 3: Diabetes**
Age	1.08[a] (1.00–1.17)	1.09[c] (1.04–1.13)	1.08[a] (1.00–1.16)	1.08[a] (1.00–1.17)	1.09[c] (1.04–1.14)	1.08[a] (1.00–1.16)
Education	0.79[a] (.65–.96)	0.91[a] (.85–.99)	1.03 (.89–1.19)	0.80[a] (.65–.97)	0.91[a] (.84–.99)	1.03 (.89–1.20)
BMI	1.05 (1.00–1.11)	1.08[c] (1.04–1.11)	1.12[c] (1.06–1.17)	1.05 (1.00–1.11)	1.08[c] (1.04–1.11)	1.12[c] (1.07–1.18)
Alcohol use	0.63 (.22–1.81)	1.38 (.89–2.15)	0.34 (.09–1.22)	0.62 (.21–1.80)	1.42 (.91–2.22)	0.34 (.09–1.25)
Cigarette use	1.01 (.96–1.06)	0.99 (.96–1.01)	0.98 (.92–1.05)	1.01 (.96–1.06)	0.99 (.96–1.01)	0.99 (.93–1.05)
Lifetime Anxiety	1.34 (.62–2.85)	1.24 (.85–1.81)	1.12 (.54–2.32)	1.56 (.73–3.34)	1.16 (.79–1.70)	0.87 (.41–1.84)
Disorder Stressful events (past 12 months)	1.19[a] (1.03–1.38)	1.03 (.95–1.12)	1.06 (.91–1.24)	1.23[b] (1.05–1.43)	1.02 (.94–1.11)	1.01 (.86–1.18)
Stressful events (3 years prior to past 12 months)	0.96 (.81–1.14)	0.98 (.90–1.06)	1.00 (.86–1.17)	0.99 (.83–1.17)	0.96 (.89–1.05)	0.96 (.83–1.13)
Lifetime Single Episode MDD	1.70 (.75–3.84)	1.15 (.72–1.84)	0.37 (.12–1.12)	---	---	---
Lifetime Recurrent MDD	---	---	---	0.44 (.15–1.29)	1.63[a] (1.00–2.66)	2.66[a] (1.17–6.06)
χ^2-statistic	23.44[b]	48.15[c]	35.36[c]	24.44[b]	51.74[c]	36.75[c]
Df	9	9	9	9	9	9
Nagelkerke R^2	.12	.12	.16	.12	.13	.17

[a] p<.05;

[b] p<.01;

[c] p<.001

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Table 4

Longitudinal Logistic Regression Analyses Predicting CVD, CVD Risk, and Diabetes

Predictors	Single Episode MDD			Recurrent MDD		
	Model 1: CVD	Model 2: CVD Risk	Model 3: Diabetes	Model 1: CVD	Model 2: CVD Risk	Model 3: Diabetes
CVD (Wave 6)	62.06$_c$ (20.59–187.07)	---	---	83.17$_c$ (25.62–269.98)	---	---
CVD Risk (Wave 6)	---	31.90$_a$ (17.80–57.16)	---	---	32.16$_c$ (17.90–57.76)	---
Diabetes (Wave 6)	---	---	1425.44$_c$ (106.31–19,112.47)	---	---	1361.09$_c$ (110.33–16,791.26)
Age	1.13$_b$ (1.04–1.22)	1.01 (.95–1.08)	1.04 (.94–1.15)	1.13$_b$ (1.04–1.23)	1.01 (.95–1.08)	1.03 (.93–1.15)
Education	0.88 (.74–1.06)	0.99 (.89–1.11)	0.90 (.72–1.13)	0.89 (.74–1.07)	1.00 (.89–1.12)	0.89 (.70–1.12)
BMI	1.06 (.99–1.13)	1.04 (.99–1.09)	1.08$_a$ (1.01–1.16)	1.07 (1.00–1.15)	1.04 (.99–1.09)	1.09$_a$ (1.01–1.16)
Alcohol use	0.77 (.26–2.29)	1.74 (.89–3.41)	0.06$_b$ (.01-.51)	0.77 (.25–2.43)	1.75 (.89–3.43)	0.05$_b$ (.01-.46)
Cigarette use	1.01 (.95–1.07)	1.00 (.97–1.04)	0.94 (.84–1.06)	1.01 (.95–1.07)	1.00 (.97–1.04)	0.94 (.83–1.06)
Lifetime Anxiety Disorder	0.65 (.27–1.57)	0.63 (.36–1.09)	0.77 (.28–2.14)	0.51 (.21–1.26)	0.65 (.37–1.16)	0.57 (.20–1.64)
Stressful events (past 12 months)	.99 (.82–1.20)	1.02 (.90–1.15)	1.38$_b$ (1.12–1.70)	0.95 (.78–1.16)	1.02 (.90–1.16)	1.33$_b$ (1.08–1.65)
Stressful events (3 years prior to past 12 months)	1.06 (.88–1.28)	0.94 (.83–1.05)	0.95 (.76–1.20)	1.02 (.85–1.22)	0.94 (.84–1.06)	0.92 (.73–1.16)
Lifetime Single Episode MDD	0.74 (.25–2.16)	1.41 (.72–2.76)	0.50 (.13–1.88)	---	---	---
Lifetime Recurrent MDD	---	---	---	3.59$_b$ (1.39–9.26)	0.91 (.44–1.88)	3.20$_a$ (1.10–9.33)
χ^2-statistic	92.42$_c$	238.38$_c$	180.37$_c$	98.73$_c$	237.44$_c$	183.46$_c$
Df	10	10	10	10	10	10
Nagelkerke R^2	.40	.55	.65	.42	.55	.66

^{a}p<.05;

^{b}p<.01;

^{c}p<.001