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Associations Between Depression and Cardiometabolic Health: A 27-Year Longitudinal Study

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Abstract

Background: Clarifying the relationship between depression symptoms and cardiometabolic and related health could clarify risk factors and treatment targets. The objective of this study was to assess whether depression symptoms in midlife are associated with the subsequent onset of cardiometabolic health problems.

Methods: The study sample comprised 787 male twin veterans with polygenic risk score data who participated in the Harvard Twin Study of Substance Abuse ("baseline") and the longitudinal Vietnam Era Twin Study of Aging ("follow-up"). Depression symptoms were assessed at baseline (mean age 41.42 years (SD=2.34)) using the Diagnostic Interview Schedule, Version III, Revised. The onset of eight cardiometabolic conditions (atrial fibrillation, diabetes, erectile dysfunction, hypercholesterolemia, hypertension, myocardial infarction, sleep apnea, and stroke) were assessed via self-reported doctor diagnosis at follow-up (mean age 67.59 years (SD=2.41)).

Results: Total depression symptoms were longitudinally associated with incident diabetes (OR=1.29, 95% CI 1.07–1.57), erectile dysfunction (OR=1.32, 95% CI 1.10–1.59), hypercholesterolemia (OR=1.26, 95% CI 1.04–1.53), and sleep apnea (OR=1.40, 95% CI 1.13–1.74) over 27 years after controlling for age, alcohol consumption, smoking, body mass index, C-reactive protein, and polygenic risk for specific health conditions. In sensitivity analyses that excluded somatic depression symptoms, only the association with sleep apnea remained significant (OR=1.32, 95% CI 1.09–1.60).

Conclusions: A history of depression symptoms by early midlife is associated with elevated risk for subsequent development of several self-reported health conditions. When isolated, non-somatic depression symptoms are associated with incident self-reported sleep apnea. Depression symptom history may be a predictor or marker of cardiometabolic risk over decades.

Introduction

Physical and mental health interact across the lifespan. Psychiatry has moved away from a Cartesian perspective that separates mind from body and toward an integrated biopsychosocial model of "empirically based pluralism" (Kendler, 2012). Many risk factors affect both physical and mental wellness (Cohen et al., 2015; Freitas et al., 2016; Ho et al., 2014; Keyes, 2004; Richard et al., 2017). Although an extensive literature exists on the

comorbidity of mental and physical health problems and having a diagnosed mental disorder is associated with increased risk of a subsequent medical condition (Momen et al., 2020), the role of psychopathology in the development of physical illness has not yet been as clearly elucidated. Understanding whether psychopathology symptoms confer risk for the onset of physical illness could have important implications for reducing global disease burden.

Depression has been associated with a range of cardiovascular, metabolic, and related conditions, including acute coronary syndrome and coronary artery disease (Carney & Freedland, 2017; Lichtman et al., 2014), cardiovascular disease (Cohen et al., 2015; Rajan et al., 2020), diabetes (Kan et al., 2016; Semenkovich et al., 2015), erectile dysfunction (Liu et al., 2018), hypertension (Meng et al., 2012), ischemic heart disease (Xian et al., 2010), sleep apnea (BaHammam et al., 2016; Harris et al., 2009), and stroke (Pan et al., 2011). Depressed mood has been identified as an independent risk factor for cardiovascular problems, including myocardial infarction, coronary artery disease (CAD), cerebrovascular diseases, and cardiovascular disease (Van der Kooy et al., 2007; van Marwijk et al., 2015). Additionally, current clinical recommendations acknowledge that depression may confer risk for poor prognosis among patients with acute coronary syndrome (Lichtman et al., 2014). The interaction of depression symptoms with cardiometabolic abnormalities has been found to increase the risk of type 2 diabetes in patients over age 50 (Freitas et al., 2016). These findings suggest that depression symptoms may play a role in the onset, course, and/or outcome of cardiovascular and metabolic pathophysiology. A recent large-scale study found an association between depression symptoms and incident cardiovascular disease independent of traditional risk factors for non-communicable diseases (Rajan et al., 2020). However, the relationship between depression symptoms and cardiometabolic health may not be causal; instead, depression symptoms, particularly somatic symptoms such as sleep problems, may covary with cardiometabolic health without playing a causal role (Meijer et al., 2013). It is important to consider the possibility that non-causal mechanisms may underlie associations between depression and cardiometabolic conditions.

Previous research has suggested that somatic (e.g., fatigue, insomnia, and appetite disturbance) and non-somatic depression symptoms may be differentially associated with cardiometabolic outcomes. A 2014 meta-analysis reported that, among patients with heart disease, somatic/affective symptom, but not cognitive/affective symptoms, were associated with adverse cardiovascular outcomes (de Miranda Azevedo et al., 2014) However, both somatic and cognitive dimensions of depression symptoms were independently associated with risk for new cardiac events in a recent study of heart disease patients (Norton et al., 2020). Somatic depression symptoms, both before and after incidence of cardiovascular disease, have been associated with increased mortality (Freak-Poli et al., 2018). Somatic and non-somatic depression symptoms may therefore play differential roles in relation to cardiometabolic health.

Little research has examined genetic influences on the relationship between depression symptoms and cardiometabolic health. However, there is significant genetic overlap between depression and type 2 diabetes (Kan et al., 2016), and recent genetic evidence from Mendelian randomization suggests that MDD causally influences CAD but not vice versa (Coleman et al., 2020). It is likely that given pleiotropy (Gale et al., 2016) and correlated

genetic risks (Palmer, n.d.) that may predispose one to psychopathology, cardiovascular and metabolic health problems, and unhealthy lifestyle factors, there are non-causal mechanisms affecting associations between mental and cardiometabolic health across multiple physical and mental health phenotypes.

Studying mental health as a contributor to cardiometabolic conditions could enable a better understanding of biological and psychosocial mechanisms that impact cardiovascular and metabolic health. Most existing longitudinal studies have examined associations between depression symptoms and physical illness over comparatively short follow-up periods (e.g., a 2012 meta-analysis of literature on depression and hypertension found a mean follow-up period of 9.6 years) (Meng et al., 2012; Semenkovich et al., 2015). Additionally, studying the longitudinal relationships between depression and cardiometabolic health enables the identification of targetable risk factors for chronic physical conditions that account for a large proportion of the global disease burden.

In the current analyses, we examined longitudinal associations between total and non-somatic depression symptoms at midlife and the subsequent onset of cardiometabolic and related health outcomes (atrial fibrillation, diabetes, erectile dysfunction, hypercholesterolemia, hypertension, myocardial infarction, sleep apnea, and stroke) in later life, excluding individuals with disease onset before baseline, to establish whether depression may increase the risk of developing cardiometabolic problems. These analyses are novel given the extended period (approximately 27 years) between baseline and follow-up, as well as the inclusion of polygenic risk scores (PRSs) for each of the eight cardiometabolic conditions as covariates to further isolate the effect of depression on long-term health outcomes. Including PRSs as covariates enabled these analyses to partially control for the influence of polygenic risk on the development of each health condition, enabling us to clarify how the experience of depression symptoms may be associated with these health outcomes over and above the influence of common genetic variation. Clarifying the physiological risk that may be conferred by depression symptoms provides insight into the long-term course of health and bolsters the rationale for screening and interventions to address depression earlier in the life course.

Methods

Description of the Sample

This study includes data from the longitudinal Vietnam Era Twin Study of Aging (VETSA). VETSA is a longitudinal study of cognitive and brain aging in men, comprising a subset of twins from the Vietnam Era Twin Registry (VETR) (Kremen et al., 2006, 2013). All twin pairs in the VETR served in the United States military sometime between 1965 and 1975, although the majority of VETSA participants did not serve in combat or in Vietnam (Tsuang et al., 2001). VETSA participants are comparable to the US male population with respect to demographic and health characteristics (Kremen et al., 2013). All VETSA participants were randomly selected from the Harvard Twin Study of Substance Abuse (HTS/baseline) (Tsuang et al., 2001; Tsuang et al., 1996). Importantly, the HTS did not select on the basis of any diagnostic or other characteristic. The only inclusion criteria for VETSA participants were being between 51 and 59 at the time of initial recruitment and both twins in a pair

agreeing to participate at baseline, although individuals were allowed to participate without their co-twin in subsequent waves of the study. For the present study, the sample was restricted to the 787 individual participants with genetically determined white, non-Hispanic European ancestry who participated both during the HTS and the most recent (third) wave of VETSA and who were healthy enough to participate in data collection (see Figure 1). The sample was limited to subjects with genetically determined European ancestry to enable the inclusion of PRSs as covariates; sample sizes of GWAS studies of non-European cohorts are unfortunately limited for most traits, and PRSs are generally poorer predictors of risk when calculated from a GWAS of one ancestral group and applied to another (Martin et al., 2019).

The mean age of participants during the HTS ("baseline") was 41.42 (SD=2.34) years, and the mean age at participation in the third wave of VETSA ("follow-up") was 67.59 (SD=2.41) years. Table 1 shows the socio-demographic and clinical characteristics of the sample.

Measures of Mental and Physical Health

At baseline, participants completed the National Institute of Mental Health Diagnostic Interview Schedule, Version III, Revised (DIS-III-R), a structured psychiatric interview for use in epidemiologic research (Robins et al., 1989). The DIS-III-R assesses lifetime psychopathology symptoms using criteria from the *DSM-III-R* (American Psychiatric Association, 1987). The DIS-III-R assesses nine depression symptoms: depressed mood, anhedonia, appetite or weight changes, sleep disturbance, psychomotor disturbance, fatigue, feelings of guilt or worthlessness, difficulty concentrating or making decisions, and thoughts of death, suicidal ideation, or suicide attempt (Robins et al., 1989). We used only DIS-III-R symptom counts, not diagnoses, in these analyses. In sensitivity analyses, we excluded symptoms assessing appetite, weight, and sleep disturbance.

At follow-up, participants reported whether a doctor had ever told them that they had any of 65 specific mental or physical health problems. For these analyses, eight cardiovascular and metabolic disorders—atrial fibrillation, diabetes, erectile dysfunction, hypercholesterolemia, hypertension, myocardial infarction, sleep apnea, and stroke—were selected based on their prevalence in the sample as well as on putative relationships with depression based on existing literature (BaHammam et al., 2016; Carney & Freedland, 2017; Harris et al., 2009; Kan et al., 2016; Liu et al., 2018; Meng et al., 2012; Pan et al., 2011; Semenkovich et al., 2015). Other cardiometabolic conditions (such as angina and heart murmur) were assessed in VETSA, but were not included in these analyses due to their low incidence in the sample, which could result in effects of depression on these conditions being undetected due to low power, and/or the unavailability of polygenic risk scores for these conditions. Self-reported year of diagnosis was used to determine onset of each health problem. Cases with onset of a condition prior to participation in the baseline assessment were excluded from analyses of that condition. Table 2 shows the incidence of physical health outcomes between baseline and follow-up.

Covariates

Covariates in all analyses included age at follow-up, alcohol consumption, smoking, body mass index (BMI), C-reactive protein (CRP), and polygenic risk for specific health outcomes to account for known risk factors from the literature on depression and physical health (Capuron et al., 2008; Freitas et al., 2016; Janszky et al., 2007; Pan et al., 2011). Smoking behavior was measured at baseline as the number of cigarettes participants reported smoking daily during the period of their life when they smoked most, and alcohol consumption was measured at baseline as the average number of drinks per day participants reported consuming over the past year. Analyses used baseline substance use covariates to examine how substance use at baseline was related to the subsequent onset of cardiovascular conditions; BMI and CRP were not available at baseline. BMI was computed using participants' measured height and weight at follow-up, and was consistent with nationally representative data for men over age 60 (Fryar et al., 2018). High-sensitivity CRP (mg/L) was measured from fasting blood samples at follow-up and used as a marker of inflammation.

Genotyping Methods and SNP Imputation

Each set of health outcome analyses controlled for polygenic risk for the cardiometabolic outcome under study. These scores were included in order to control for underlying biological risk for physical health conditions and partly isolate the potential effects of depression symptoms on physical health outcomes. PRSs were calculated using summary statistics from genome-wide association studies (GWAS) for: atrial fibrillation (Cardiovascular Disease Knowledge Portal, n.d.; Roselli et al., 2018); type 2 diabetes (Morris et al., 2012); erectile dysfunction (Bovijn et al., 2019); total cholesterol (Willer et al., 2013); systolic blood pressure (Evangelou et al., 2018); CAD (a phenotype including myocardial infarction; PRSs computed from this GWAS were used in myocardial infarction analyses) (Nelson et al., 2017); sleep apnea (UK Biobank, n.d.); and stroke (Malik et al., 2018). Individual SNP effect estimates and *P*-values were extracted from summary statistics. PRSs were computed by PLINK v1.9 using nine different *P*-value thresholds: $P<0.00000001$, 0.00001, 0.01, 0.05, 0.10, 0.20, 0.30, 0.40, and 0.50. The PRS used in each of the health condition analyses was chosen based on how highly it correlated with the condition (see eTable 1). Analyses additionally controlled for the first three principal components calculated from genome-wide genotype data of the European-descent subsample in order to account for any cryptic population substructure.

A detailed description of VETSA genotyping procedures is available in Logue et al (2019). Whole-genome genetic variation was assessed at deCODE Genetics (Reykjavík, Iceland) using Illumina HumanOmniExpress-24 v1.0A BeadChips (Illumina, San Diego, CA). Before PRS calculations, we cleaned and conducted quality control of genotype data using PLINK v1.9 (Chang et al., 2015). Single nucleotide polymorphism weights (SNPweights) and principal components computed using PLINK v1.9 in conjunction with 1000 Genomes Phase 3 reference data were used to identify a European ancestry subset of the data (1000 Genomes Project Consortium, 2015; Chen et al., 2013). Principal components were computed based on a linkage-disequilibrium pruned set of 100,000 common (minor allele frequency >0.05) genotyped SNPs. Within the subset of participants with genetically

determined European ancestry, principal components were recomputed for use as covariates for population substructure in the analyses. Imputation was performed using MiniMac (Fuchsberger et al., 2015; Howie et al., 2012) computed at the Michigan Imputation Server (https://imputationserver.sph.umich.edu). The 1000 Genomes Phase 3 EUR data were used as a haplotype reference panel.

Statistical Analyses

Analyses were performed in SPSS Statistics Version 26 (2018). Generalized estimating equations (GEEs) were used to account for the non-independence of observations within twin pairs. Separate multivariable models were run using each of the eight health conditions. Analyses were performed using the logit link function to obtain log odds ratios. All models assumed an exchangeable correlation structure, and robust variance estimators were used. All covariates were standardized using z-scores. Analyses were run on complete cases; for a comparison between participants with complete and incomplete data, see eTable 2.

Analyses examined associations between total depression symptoms at baseline and the subsequent onset of health conditions by follow-up, controlling for age, alcohol consumption and smoking at baseline, BMI and CRP at follow-up, and PRS for the health outcome under study. The significance threshold was $P<.05$ after correcting for multiple comparisons across eight sets of analyses, using the false discovery rate proposed by Benjamini and Hochberg (1995; Radua & Albajes-Eizagirre, n.d.).

Sensitivity analyses were conducted using a measure of depression symptoms that removed somatic items (those assessing weight, appetite, and sleep disturbances) to determine whether the results were sensitive to the exclusion of somatic depression symptoms.

Supplementary analyses were conducted to examine crude associations between total depression symptoms reported at baseline and incident health outcomes twenty-seven years later (see eTable 3). Additional supplementary analyses were conducted without the inclusion of PRSs as covariates, which allowed the inclusion of an additional 408 participants (total N=1195) for whom genetic data were not available and/or who were not of genetically-determined white, non-Hispanic European ancestry (see eTables 4–5 and Figure 1).

Results

Table 3 displays standardized results from longitudinal analyses that examined associations between total depression symptoms reported at baseline and incident health outcomes twenty-seven years later, controlling for age, alcohol consumption, smoking, BMI, CRP, and polygenic risk. After correcting for multiple comparisons, total depression symptoms at baseline were significantly longitudinally associated at follow-up with incident diabetes (OR=1.29, CI 1.07–1.57), erectile dysfunction (OR=1.32, CI 1.10–1.59), hypercholesterolemia (OR=1.26, CI 1.04–1.53), and sleep apnea (OR=1.40, CI 1.13–1.74). BMI was significantly associated with atrial fibrillation (OR=1.38, CI 1.03–1.85), diabetes (OR=1.64, CI 1.36–1.99), hypercholesterolemia (OR=1.30, CI 1.06–1.61), hypertension (OR=1.77, CI 1.39–2.25), and sleep apnea (OR=2.23, CI 1.75–2.83). In multivariate models,

PRSs for atrial fibrillation (OR=1.90, CI 1.30–2.78), diabetes (OR=1.55, CI 1.26–1.91), CAD (OR=1.58, CI 1.21–2.07, in myocardial infarction analyses), cholesterol (OR=1.75, CI 1.41–2.17), systolic blood pressure (OR=1.53, CI 1.25–1.86, in hypertension analyses), and stroke (OR=1.52, CI 1.15–2.02) all were significantly associated with their respective health variable.

Table 4 displays results of sensitivity analyses that used a measure of depressive symptoms without somatic items (appetite, weight, and sleep disturbances). After correcting for multiple comparisons, non-somatic depressive symptoms at baseline were significantly longitudinally associated with sleep apnea (OR=1.32, CI 1.09–1.60) at follow-up. Non-somatic symptoms were not significantly associated with incident diabetes, erectile dysfunction, or hypercholesterolemia.

Discussion

Total depression symptoms were longitudinally associated, over a 27-year follow-up period, with the incidence of several chronic cardiometabolic health conditions, after controlling for available physiological and behavioral risk factors such as alcohol consumption, smoking, BMI, CRP, and polygenic risk. A lifetime history of depression symptoms, assessed at midlife, was associated with significantly increased odds of subsequently developing diabetes, erectile dysfunction, hypercholesterolemia, and sleep apnea in later life. Thus, having depression symptoms earlier in life may increase risk for the later onset of chronic health conditions above and beyond the contributions of alcohol consumption history, smoking history, BMI, inflammation (CRP), and polygenic risk. The length of follow-up is particularly noteworthy. Lifetime total depression symptoms were assessed at average age 41 and they predicted risk for these chronic health conditions over two decades later. Our results suggest that the effects of depression symptoms on cardiometabolic health could be very long-lasting, and that, consistent with prior research, these associations are robust to the inclusion of traditional risk factors for noncommunicable diseases such as smoking and alcohol use (Rajan et al., 2020). However, it is also possible that causal factors not assessed in this study could be increasing risk for both depression and later cardiometabolic health, or that non-causal mechanisms explain these relationships. For example, individuals with a history of depressive symptoms may be more likely to access health care generally, therefore enhancing the rate of detection of cardiometabolic conditions compared to individuals without a history of depressive symptoms.

Our finding that total depression symptoms were significantly associated with incident diabetes is consistent with previous research demonstrating that depression increases the risk for type 2 diabetes; this research also indicates that this relationship is bidirectional (Semenkovich et al., 2015). We also found that depression was longitudinally related to erectile dysfunction, hypercholesterolemia, and sleep apnea; these findings extend previous work that has identified relationships between depression and cardiometabolic health cross-sectionally or over a shorter timeframe (BaHammam et al., 2016; Harris et al., 2009; Liu et al., 2018; Montazer & Wheaton, 2011).

Sensitivity analyses revealed that, when somatic depression symptoms (i.e., weight, appetite, and sleep disturbances) were excluded, the remaining non-somatic symptoms were significantly associated with incident sleep apnea. The associations between non-somatic depression symptoms and erectile dysfunction and hypercholesterolemia were not significant, and the association between these non-somatic symptoms and diabetes did not survive correction for multiple comparisons. This is consistent with previous literature finding that somatic depression symptoms are associated with poor cardiometabolic outcomes (de Miranda Azevedo et al., 2014)., Depression-related changes in appetite, weight, and/or sleep may either lead to or indicate physiological changes that impact cardiometabolic health over time. A large-scale study of dimensions of depression symptoms found that somatic symptoms, measured both before and after cardiovascular disease onset, are associated with mortality (Freak-Poli et al., 2018). Future research could investigate whether particular symptom clusters, or even individual symptoms, are uniquely associated with risk for specific cardiometabolic outcomes, particularly in populations with higher overall depression symptom burden than our study.

Of the cardiometabolic outcomes with which total depression symptoms were not significantly associated in full models, myocardial infarction and stroke are likely to be the most reliably reported by participants, given that these health outcomes are discrete events which often require emergency medical care, and thus potentially less likely to be underreported than other health outcomes. One possible explanation for the lack of observed association with myocardial infarction is the relatively low base rate of this outcome in our sample (8.3%). These analyses may have been underpowered, especially as the odds ratio for myocardial infarction (1.25) was of a similar magnitude to other health outcomes that were significantly associated with depression symptoms. Future studies should examine whether myocardial infarction is associated with a history of depressive symptoms in other samples, including samples with a higher base rate of this outcome.

PRSs were significantly associated with their respective cardiometabolic conditions in most models. Although PRSs represent only genetic risk due to common variation, these findings demonstrate the importance of more in-depth screening for both depression and genetic risk factors for cardiometabolic health. These results could also reflect the influence of genes relevant to depression on cardiometabolic outcomes.

Several putative mechanisms responsible for the longitudinal relationships between psychopathology and cardiometabolic health have been suggested. These mechanisms fall into two major categories: behavioral and biological processes. Hypothesized behavioral mechanisms linking depression to cardiovascular and metabolic health problems include lifestyle and compliance factors associated with depression, such as smoking, poor diet, lack of exercise, weight gain, and reduced medication compliance (Chaddha et al., 2016; Colotto et al., 2010; Semenkovich et al., 2015; Serrano et al., 2011). In our analyses, BMI at age 68 was associated with cardiometabolic conditions when controlling for other covariates. Of note, BMI could be considered both a biological and a behavioral process, as it is a complex phenotype associated with a multitude of biological factors (e.g., genetics) as well as non-biological factors (e.g., walkability of one’s environment) (Locke et al., 2015; Tarlov et al., 2020). BMI and major psychiatric disorders, including major depression, have extensive

polygenic overlap (Bahrami et al., 2020), and higher BMI is likely causally associated with the incidence of depression (Tyrrell et al., 2019). Although our study did not examine BMI longitudinally, it is possible that BMI influenced both the development of depression symptoms and of cardiometabolic health outcomes in our sample. It is noteworthy that BMI was significantly associated with five of the eight cardiometabolic conditions examined.

Other hypothesized biological mechanisms linking depression to cardiovascular and metabolic health problems include abnormal cardiac function (e.g., heart rate variability, left ventricular impairment), hyperinflammation, serotonin transport gene polymorphisms, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, endothelial dysfunction, endocrine changes, and greater platelet activation and aggregation (Chaddha et al., 2016; Monami & Marchionni, 2007; Pozuelo et al., 2009; Schoevers et al., 2004; Semenkovich et al., 2015; Serrano et al., 2011). In our analyses, CRP was not significantly associated with cardiometabolic conditions when controlling for other covariates. Notably, several antidepressant medications affect these physiological processes, which suggests the possibility that antidepressant treatment could reduce the heightened cardiovascular and metabolic risk burden conferred by depression (Monami & Marchionni, 2007). Future work could examine these hypothesized mechanisms directly through mediation analyses. Another possible non-causal mechanism could be correlated genetic risk for both depression and cardiometabolic health problems; genetic correlations between other complex traits and health outcomes have been found in GWAS data (Bulik-Sullivan et al., 2015).

This study has several limitations that should be considered. The sample includes only men, and we limited our main analyses to participants of genetically determined European ancestry to permit the inclusion of PRSs as covariates. These factors limit the generalizability of these findings; however, supplementary analyses in the full sample (N=1195; see eTables 4–5) follow the same general pattern of results as the main analyses. This may be due to the relatively low proportion of variance that is generally explained by polygenic risk scores, which index common genetic variation and may not reflect all genetic influences on risk of outcomes. Also, cardiometabolic health was assessed using self-report binary (yes/no) measures of doctor diagnosis, which does not account for disease severity and means that the identification of cases depended on access to healthcare. Although more objective measures exist for some conditions examined (e.g., blood pressure or use of antihypertensive medications), objective measures were not available for all health conditions, and reliance on them could also result in missed cases. As several of the conditions we assessed are often undiagnosed—such as sleep apnea (Finkel et al., 2009)—the true prevalence of these conditions in our sample may well be underestimated. This may mean that the estimates presented in these analyses are conservative: if the true prevalence of these conditions is higher, then the strength or magnitude of their associations with a history of depressive symptoms may be masked or biased towards the null. 103 participants died before the third wave of VETSA; their exclusion from these analyses may indicate that our sample is biased towards healthier participants. This potential selection bias may have resulted in more conservative estimates of the associations between depression and cardiometabolic outcomes. Future work should include medical record information and other objective measures of disease burden when possible. Additionally, the initial requirement in the first wave of VETSA that both twins must participate in the study may

have introduced volunteer bias (Neale & Eaves, 1993). Finally, the odds ratio values in our findings should not be compared directly to each other because the base rates for the health conditions vary.

Although this study was observational and the associations between depression and cardiometabolic health conditions cannot be interpreted causally, the longitudinal design as well as the exclusion of cases of cardiometabolic health problems that were diagnosed before baseline strengthen the conclusions that can be drawn about how total depression symptoms in midlife impact the subsequent development of health problems in later life. These stable, longitudinal patterns of association could also be explained by non-causal correlated genetic risk factors not tested here. Our next step is to fit biometrical genetic twin models to the data to model both cross-temporal causality and correlated genetic risk factors, which may provide alternative, mechanistic explanations. Whether causal or not, depression symptoms were still predictive of cardiometabolic health problems over two decades later. Future research should strive to further elucidate causal relationships and paths between depression and cardiometabolic health over time, and to identify any common causes they may share. Finally, the results suggest that clinicians treating depression should pay careful attention to cardiometabolic risk factors in addition to depression symptoms themselves.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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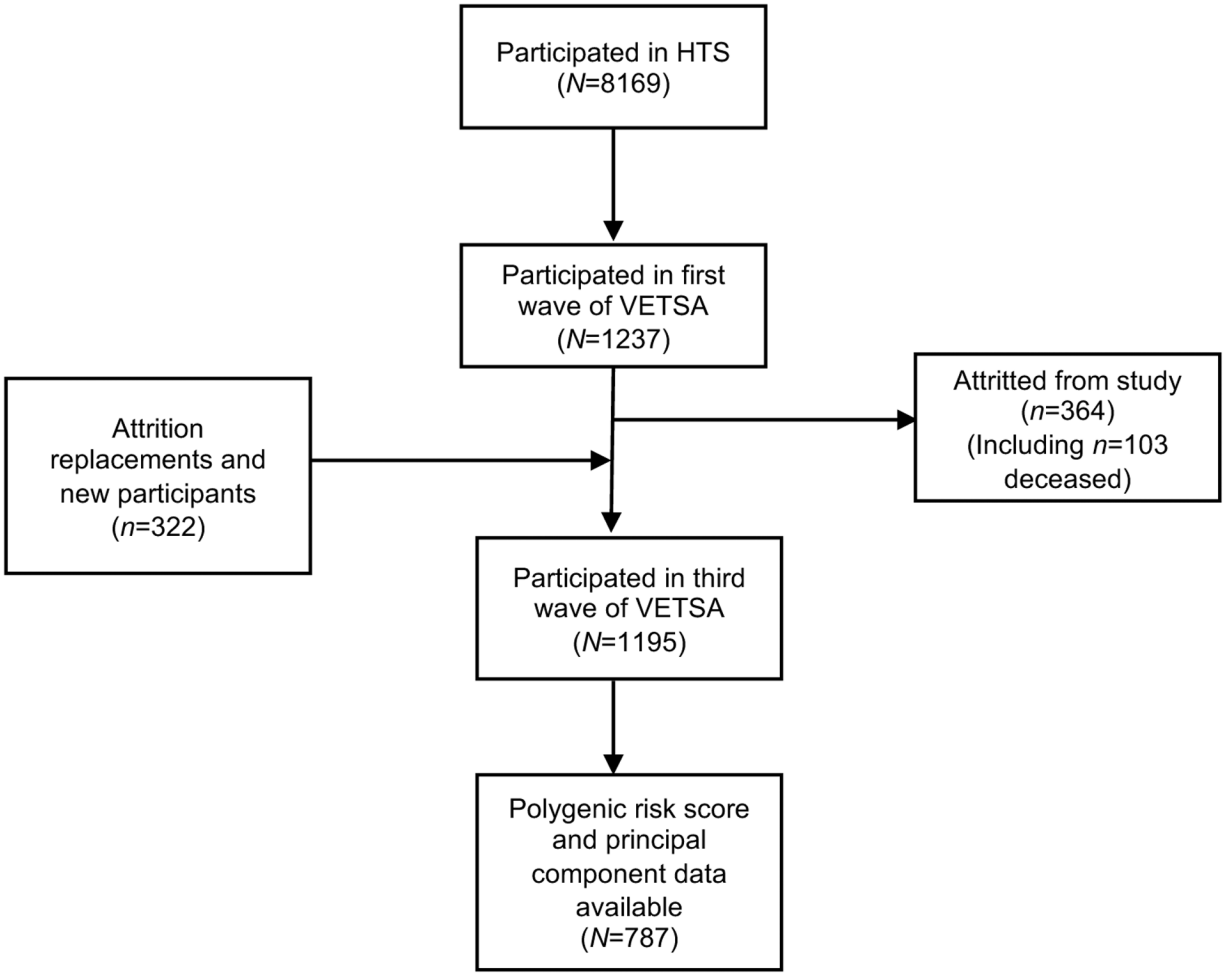

Figure 1.
Flowchart of study population and sample size.

Table 1.

Sample characteristics (N=787)

	Mean (SD)
Age at baseline (years)	41.42 (2.34)
Age at follow-up (years)	67.59 (2.41)
# drinks/day at baseline	2.17 (2.06)
# cigarettes/day at baseline	19.11 (19.13)
BMI at follow-up	29.89 (5.47)
CRP (mg/L) at follow-up	3.49 (7.01)
# depression symptoms at baseline	2.00 (2.30)

BMI = body mass index; CRP = C-reactive protein

Table 2.

Incidence of cardiometabolic conditions

	Atrial Fibrillation	Diabetes	Erectile Dysfunction	Hyperchol-esterolemia	Hypertension	Myocardial Infarction	Sleep Apnea	Stroke
Frequency of incident cases [a]	62 (8.0%) (N=778)	174 (22.5%) (N=774)	176 (22.9%) (N=770)	408 (57.1%) (N=715)	370 (53.6%) (N=690)	65 (8.3%) (N=781)	159 (20.5%) (N=774)	43 (5.5%) (N=785)
Frequency of early-onset cases (N=787) [b]	4 (0.5%)	12 (1.5%)	5 (0.6%)	65 (8.3%)	89 (11.4%)	6 (0.8%)	8 (1.0%)	0 (0.0%)

[a] Ns vary due to condition-specific exclusion of early-onset cases or missing data

[b] Cases with onset prior to baseline were excluded from analyses

Table 3.

Longitudinal associations between depression symptoms at baseline and health conditions at follow-up

	Exponentiated Odds Ratio [95% CI]							
	Atrial Fibrillation	**Diabetes**	**Erectile Dysfunction**	**Hyperchol-esterolemia**	**Hypertension**	**Myocardial Infarction**	**Sleep Apnea**	**Stroke**
Baseline depression symptoms	1.09 [0.77, 1.53] (*p*=.633)	1.29^ [1.07, 1.57] (*p*=.009)	1.32^ [1.10, 1.59] (*p*=.003)	1.26^ [1.04, 1.53] (*p*=.017)	1.22 [1.02, 1.47] (*p*=.033)	1.25 [0.96, 1.62] (*p*=.095)	1.40^ [1.13, 1.74] (*p*=.003)	1.07 [0.71, 1.61] (*p*=.744)
Age at follow-up	1.67^ [1.17, 2.39] (*p*=.005)	1.12 [0.89, 1.41] (*p*=.338)	1.21 [0.96, 1.54] (*p*=.112)	1.07 [0.87, 1.30] (*p*=.542)	1.34^ [1.09, 1.64] (*p*=.005)	1.07 [0.75, 1.53] (*p*=.697)	1.14 [0.89, 1.45] (*p*=.303)	1.29 [0.80, 2.10] (*p*=.298)
Drinks per day at baseline	0.89 [0.58, 1.36] (*p*=.594)	1.08 [0.85, 1.37] (*p*=.535)	1.06 [0.85, 1.34] (*p*=.591)	0.91 [0.73, 1.13] (*p*=.390)	1.21 [0.95, 1.55] (*p*=.123)	0.74 [0.45, 1.22] (*p*=.238)	0.70 [0.51, 0.96] (*p*=.028)	0.97 [0.58, 1.61] (*p*=.899)
Cigarettes per day at baseline	1.03 [0.77, 1.38] (*p*=.822)	0.92 [0.77, 1.10] (*p*=.344)	0.96 [0.79, 1.16] (*p*=.660)	1.23 [1.02, 1.48] (*p*=.031)	1.08 [0.89, 1.30] (*p*=.449)	1.33 [1.04, 1.71] (*p*=.024)	1.10 [0.90, 1.35] (*p*=.370)	1.56 [1.13, 2.16] (*p*=.007)
BMI at follow-up	1.38^ [1.03, 1.85] (*p*=.030)	1.64^ [1.36, 1.99] (*p*<.001)	1.09 [0.91, 1.31] (*p*=.360)	1.30^ [1.06, 1.61] (*p*=.012)	1.77^ [1.39, 2.25] (*p*<.001)	1.03 [0.76, 1.39] (*p*=.851)	2.23^ [1.75, 2.83] (*p*<.001)	1.09 [0.77, 1.54] (*p*=.614)
CRP at follow-up	1.08 [0.87, 1.34] (*p*=.497)	1.09 [0.89, 1.34] (*p*=.413)	0.95 [0.74, 1.21] (*p*=.674)	0.81 [0.68, 0.96] (*p*=.015)	1.27 [1.02, 1.57] (*p*=.030)	1.24 [1.01, 1.51] (*p*=.036)	1.18 [0.97, 1.44] (*p*=.093)	1.28 [1.02, 1.60] (*p*=.030)
PRS for health condition	1.90^ [1.30, 2.78] (*p*=.001)	1.55^ [1.26, 1.91] (*p*<.001)	1.09 [0.90, 1.33] (*p*=.365)	1.75^ [1.41, 2.17] (*p*<.001)	1.53^ [1.25, 1.86] (*p*<.001)	1.63^ [1.17, 2.29] (*p*=.004)	0.87 [0.70, 1.08] (*p*=.212)	1.52^ [1.15, 2.02] (*p*=.004)

CI = confidence interval; BMI = body mass index; CRP = C-reactive protein; PRS = polygenic risk score

^ = Association remained significant after correcting for multiple comparisons.

[a] Polygenic risk scores (PRSs) for health conditions: atrial fibrillation, diabetes, erectile dysfunction, coronary artery disease (for myocardial infarction), cholesterol, systolic blood pressure (for hypertension), sleep apnea, and stroke. All analyses also controlled for first three principal components (not shown)

Table 4.

Sensitivity analyses: Longitudinal associations between depression symptoms (excluding somatic items) at baseline and health conditions at follow-up

	Exponentiated Odds Ratio [95% CI]							
	Atrial Fibrillation	**Diabetes**	**Erectile Dysfunction**	**Hyperchol-esterolemia**	**Hypertension**	**Myocardial Infarction**	**Sleep Apnea**	**Stroke**
Baseline non-somatic depression symptoms	1.20 [0.89, 1.62] (*p*=.226)	1.24 [1.03, 1.49] (*p*=.023)	1.18 [0.99, 1.41] (*p*=.073)	1.16 [0.96, 1.40] (*p*=.115)	1.10 [0.93, 1.30] (*p*=.268)	1.19 [0.92, 1.53] (*p*=.191)	1.32^ [1.09, 1.60] (*p*=.005)	1.31 [1.00, 1.72] (*p*=.050)
Age at follow-up	1.70^ [1.18, 2.44] (*p*=.004)	1.11 [0.88, 1.39] (*p*=.388)	1.19 [0.94, 1.50] (*p*=.151)	1.05 [0.86, 1.29] (*p*=.608)	1.32^ [1.08, 1.61] (*p*=.007)	1.06 [0.74, 1.52] (*p*=.747)	1.12 [0.88, 1.43] (*p*=.369)	1.33 [0.81, 2.18] (*p*=.255)
Drinks per day at baseline	0.90 [0.59, 1.37] (*p*=.615)	1.08 [0.85, 1.37] (*p*=.523)	1.07 [0.85, 1.35] (*p*=.576)	0.92 [0.74, 1.14] (*p*=.442)	1.22 [0.96, 1.55] (*p*=.108)	0.74 [0.45, 1.23] (*p*=.242)	0.70 [0.51, 0.96] (*p*=.027)	0.99 [0.59, 1.65] (*p*=.953)
Cigarettes per day at baseline	1.03 [0.77, 1.37] (*p*=.845)	0.93 [0.77, 1.12] (*p*=.432)	0.98 [0.81, 1.18] (*p*=.815)	1.25 [1.04, 1.50] (*p*=.020)	1.09 [0.91, 1.32] (*p*=.349)	1.36 [1.05, 1.75] (*p*=.019)	1.12 [0.91, 1.38] (*p*=.273)	1.54 [1.12, 2.11] (*p*=.008)
BMI at follow-up	1.40^ [1.04, 1.87] (*p*=.026)	1.64^ [1.36, 1.98] (*p*<.001)	1.09 [0.91, 1.30] (*p*=.355)	1.30^ [1.05, 1.60] (*p*=.014)	1.76^ [1.38, 2.23] (*p*<.001)	1.03 [0.77, 1.39] (*p*=.828)	2.21^ [1.75, 2.80] (*p*<.001)	1.11 [0.79, 1.57] (*p*=.542)
CRP at follow-up	1.07 [0.85, 1.34] (*p*=.565)	1.08 [0.88, 1.34] (*p*=.451)	0.95 [0.75, 1.19] (*p*=.648)	0.81 [0.68, 0.96] (*p*=.013)	1.27 [1.02, 1.57] (*p*=.030)	1.23 [1.00, 1.50] (*p*=.046)	1.17 [0.96, 1.43] (*p*=.112)	1.28 [1.02, 1.60] (*p*=.032)
PRS for health condition	1.92^ [1.31, 2.80] (*p*=.001)	1.55^ [1.26, 1.90] (*p*<.001)	1.10 [0.91, 1.33] (*p*=.339)	1.76^ [1.42, 2.17] (*p*<.001)	1.50^ [1.23, 1.84] (*p*<.001)	1.65^ [1.18, 2.30] (*p*=.004)	0.89 [0.71, 1.10] (*p*=.279)	1.55^ [1.16, 2.08] (*p*=.003)

CI = confidence interval; BMI = body mass index; CRP = C-reactive protein; PRS = polygenic risk score

^ = Association remained significant after correcting for multiple comparisons.

[a] Polygenic risk scores (PRSs) for health conditions: atrial fibrillation, diabetes, erectile dysfunction, coronary artery disease (for myocardial infarction), cholesterol, systolic blood pressure (for hypertension), sleep apnea, and stroke. All analyses also controlled for first three principal components (not shown)