ASSESSING THE ASSOCIATION OF TEN-YEAR CARDIOVASCULAR DISEASE RISK WITH DEPRESSION IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS

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ABSTRACT

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Major depressive disorder and cardiovascular diseases (CVD) are two of the leading causes of disability worldwide and CVD is the leading cause of death in the US. There is strong evidence that depression is associated with increased risk of initial CVD events and thus it is important to quantify CVD risk by depression status in persons free of clinical CVD. Extant literature characterizing this association is limited by heterogeneous and suboptimal assessments of both depression and CVD risk, hindering prevention and treatment. In particular, almost no studies to date have examined the depression/CVD risk association using contemporary, ecologically valid depression and CVD risk assessments. The objective of this study was to evaluate the association between depression, measured by the Patient Health Questionnaire-9 (PHQ-9), with CVD risk, as measured by the pooled cohort equations, in a national sample of U.S. adults. In sex-specific analyses, depression was consistently associated with higher 10-year ASCVD risk for women, with observed ten-year risk 1-3% higher for depressed women. However, depression was associated with higher ASCVD risk for men 40-49 years of age but not associated with ASCVD risk in older groups. These findings may be useful for identifying comorbid CVD risk when screening for depression and determining appropriate risk reduction strategies for depressed persons, particularly women, who are at elevated medium-term risk for clinical CVD.

Keywords: depression, ASCVD risk, PHQ-9, risk factors, cardiovascular disease, assessment

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Assessing the Association of Ten-Year Cardiovascular Disease Risk with Depression in the National Health and Nutrition Examination Surveys

It is estimated that over 16 million adults in the U.S. suffer from major depressive disorder (also known as clinical depression or unipolar depression; hereafter, depression). Depression is associated with substantial morbidity as well as considerable economic cost due to treatment and lost productivity (Kessler, 2012; McLaughlin, 2011). In addition, depression is linked to other adverse health outcomes, such as increased cardiovascular disease risk. Cardiovascular disease (CVD) is the leading cause of death in the United States (Benjamin et al., 2019; Center for Disease Control [CDC], 2020). Specifically, depressed persons are at greater risk of recurrent events, i.e., new heart attacks or strokes among persons with existing CVD (Barth et al., 2003; Bradley & Rumsfeld, 2015; Glassman, 2007; Meijer et al., 2011; Stewart et al., 2003; van Melle et al., 2004). Evidence also links depression with an increased risk of initial coronary heart disease (CHD) and stroke events. For example, two meta-analytic reviews encompassing 26 studies and over 3,000 events found that depression (diagnosed with interviews or self-report measures) was prospectively associated with increased risk of CHD, with relative risks (RR) of 1.60 (95% confidence interval (CI) [1.34, 1.92]) and 1.64 (95% CI [1.41, 1.90]), respectively (Van der Kooy et al., 2007; Wilson & Singal, 2003). These findings are echoed by three large meta-analyses showing a prospective association between depression and incident stroke, with excess risk between 34% and 45% (RR = 1.34, 95% CI [1.17, 1.54]; RR = 1.45, 95% CI [1.29, 1.63]; RR = 1.43, 95% CI [1.17, 1.75], respectively) (Dong et al., 2011; Pan et al., 2011; Van der Kooy et al., 2007). This evidence establishes an association between depression and CVD risk, and in turn, points to the need to characterize this association before the occurrence of a cardiovascular event, i.e., in a primary prevention context, where prevention is

possible. The purpose of the current study was to estimate the association between ten-year cardiovascular disease risk and depression among persons free of clinical cardiovascular disease.

Ideally, efforts to characterize this association would use structured clinical interviews to assess depression, but this gold standard assessment is not feasible in primary care settings or in population-based health surveys. Therefore, brief screening instruments have been developed to identify depression in these settings. The Patient Health Questionnaire (PHQ), a nine-item self-administered depression assessment, is considered the best available tool for depression screening outside the structured interview. It is brief and has excellent sensitivity (88%) and specificity (85%) compared to depression classification using structured clinical interviews (Levis et al., 2019). In addition, the PHQ-9 was developed to screen depression in primary care and other medical settings (Gilbody et al., 2007; Kroenke et al., 2001; Kroenke et al., 2002; Spitzer et al., 1999). Because of these strengths, the PHQ has been identified as the depression assessment of choice to harmonize otherwise heterogeneous depression assessments in patient registries, quality improvement initiatives, and in clinical practice (Gliklich et al., 2020). This harmonization is part of a broader effort, initiated in part by the U.S. Agency for Healthcare Research and Quality (Gliklich et al., 2014), to classify outcomes in a way that is "…relevant to patients and providers across most conditions" (Gliklich et al., 2020, p. 1). In the spirit of this harmonization goal, the current study examined depression and cardiovascular disease risk using the PHQ depression assessment in conjunction with another U.S. standard for CVD risk assessment, the pooled cohort equations.

The pooled cohort equations estimate the ten-year absolute risk of a primary atherosclerotic CVD (ASCVD) event, which includes nonfatal myocardial infarction (MI), CHD death, or fatal or nonfatal stroke. These risk algorithms (interchangeably referred to as "ASCVD

risk" or "pooled cohort equations") were developed using multiple contemporary U.S. cohorts and provide race- and sex-specific estimates of ASCVD risk. These scores use state of the art quantitative methods to derive and validate risk estimates and are the only estimates that included a substantial number of African-American participants in model development (Goff et al., 2014). These rigorous risk estimates have been endorsed by the American College of Cardiology and the American Heart Association in their clinical guidelines for the management of cardiovascular diseases (Goff et al., 2014). Echoing the PHQ harmonization goal, the approach that produced the pooled cohort equations was grounded in using information easily and routinely collected by primary care providers in clinical practice (Goff et al., 2014). This risk assessment permits "…matching the intensity of preventive efforts with the individual's absolute risk" (Goff et al., 2014, p. S53). The ASCVD risk score thus represents a critical element of managing CVD risk in US primary prevention settings. Given the dual burdens of depression and CVD, as well as the need to utilize state of the art, harmonized assessments of these constructs, the current study characterized the association between depression CVD risk using both core assessment instruments, the PHQ and the pooled cohort equations.

Although other studies have examined the association between depression and CVD risk (Daskalopoulou et al., 2016; Koponen et al., 2010; Jee et al., 2019; O'Neil et al., 2016; Sun et al., 2019), no U.S. studies to date have characterized this association using the depression and CVD risk metrics optimized for both clinical and public health application. Characterizing differences in ten-year ASCVD risk as a function of PHQ depression will permit a readily interpretable snapshot of the ASCVD risk burden among depressed persons, with application to medical care providers, mental health providers, and to psychiatric and CVD epidemiology more generally.

This approach also aligns with harmonization goals for depression assessment and for CVD risk assessment.

Well-established sex differences in both depression and ASCVD risk are important considerations for this research (Appelman et al., 2015; Bots et al., 2017; Mosca et al., 2011; Nolen-Hoeksema, 1987; Piccinelli & Wilkinson, 2000; Salk et al., 2017). For example, ASCVD risk is higher for men, whereas depression is more prevalent for women (Morris et al., 2018; Weissman et al., 1993). Therefore, we examined the depression/ASCVD risk association among men and women separately. Additionally, ASCVD risk scores are strongly age-sensitive, so to minimize the influence of this nonmodifiable risk factor, we examined the sex-specific depression/ASCVD risk association within ten-year age bands.

To illustrate the age sensitivity of ASCVD risk calculations, a never smoker 50-year-old White man free of diabetes with unmedicated blood pressure (with systolic values of 130 mmHg), total cholesterol of 203 mg/dL and HDL cholesterol of 45 mg/dL has a 4.1% risk of an ASCVD event over the next ten-years. The same risk factor profile at age 59 has more than double the absolute risk at age 50 (8.9%), and this risk increases to 14% for the same risk factor levels at 65 years of age. Stratifying by age groups is thus an important methodological approach to help partition age-related CVD risk from CVD risk associated uniquely with depression. This age-related risk difference observable *within* ten-year age bands also supports our choice to include age as a covariate within age bands.

To estimate the association between ASCVD risk and depression, the current study used data from the National Health and Nutrition Examination Surveys (NHANES), a probability sample of the civilian, noninstitutionalized U.S. population. NHANES is designed to assess the health and nutritional status of the U.S. population through interviews, medical/physical

examinations, and laboratory tests (Zipf, 2013). NHANES uses the PHQ-9 to assess depression and also includes all the variables (i.e., demographic, examination, and laboratory assessments) needed to calculate ten-year ASCVD risk. Combining multiple NHANES cycles (NHANES are released in 2-year increments) permits accrual of a substantial number of participants which in turn allows stable estimation of the depression/ASCVD association within sex and age groups.

To summarize, the current study estimated the association of depression and ASCVD risk using metrics common to clinical practice, patient registries and population health surveillance. We examined this association in a large cohort by combining six NHANES cycles comprising 12 years of data with a substantial number of participants eligible for ASCVD risk calculation (N = 14,407).

Methods

Data Overview

We combined the 2005–2016 NHANES cycles for analysis. NHANES participants were interviewed at home with a computer assisted personal interview (CAPI) system and subsequently completed a physical examination in a mobile examination center (MEC). The current ten-year ASCVD risk assessment formulae are relevant to adults aged 40 to 79 years who are free of clinical CVD; thus, analyses were limited to this subgroup. All participants provided informed consent, and the study was approved by the National Center for Health Statistics (NCHS) Ethical Review Board and because it was secondary data analysis it was deemed not human subjects research by the Northern Arizona University (NAU) Institutional Review Board (IRB).

Approximately two weeks after a participant completes the interview, most are subsequently examined at the MEC. Examinations include biochemical and anthropometric

measures. The details for NHANES data collection have been previously described (Zipf et al., 2013). Data collection is conducted by qualified professionals and staff. The biochemical/laboratory data, depending on the NHANES cycle years, were shipped either to Johns Hopkins University Lipoprotein Analytical Laboratory (2005-2006) or the University of Minnesota (2007-2016 years) for analysis (Zipf et al., 2013).

The unweighted response rates for adults in the interview portion of NHANES 2005-2016 averaged between 56.3% and 73.0% and averaged between 53.8% and 70.9% for the MEC portion (NCHS, 2020).

Depression Assessment

Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9), a 9-item, self-reported screening instrument widely used in primary health care (Spitzer et al., 1999). The PHQ-9 encompasses each of the nine diagnostic criteria for major depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (5^{th} ed.; DSM 5; American Psychiatric Association [APA], 2013). It assesses the frequency of depressive symptoms during the past two weeks based on summary scores derived from the frequency of symptom experience: not at all = 0, several days =1, more than half the days = 2, and nearly every day = 3. The total score ranges from 0 to 27, and a score ≥ 10 has been recommended as the cut-off score for detecting major depressive disorder (Levis et al., 2019; Manea et al., 2012). This cut score had a sensitivity of 88% and a specificity of 85% for major depression classified using structured clinical interviews (Levis et al., 2019). The PHQ-9 also has good internal consistency (Cronbach's α = 0.89) and test-retest reliability (r = 0.94) (Kroenke et al., 2001; Zuithoff et al., 2010). We therefore classified persons as nondepressed with PHQ-9 scores ≤ 9 and as depressed with scores ≥10.

Atherosclerotic Cardiovascular Disease Risk Assessment

Cardiovascular disease risk was estimated using the ten-year ASCVD risk score. The ten-year ASCVD risk score is calculated using the race/ethnic and sex-specific multivariable risk factor equations constructed by the American College of Cardiology (ACC), American Heart Association (AHA), and National Heart Lung and Blood Institute (NHLBI) (Goff et al., 2014). This equation estimates absolute ten-year risk based on the following variables: sex, age, race/ethnicity, treated or untreated systolic blood pressure (SBP), total cholesterol (TC), high density cholesterol (HDL-C), current smoking status (yes/no), and diabetes mellitus (yes/no).

Blood pressure (BP; both systolic and diastolic) was measured during the NHANES physical examination in the MEC. Up to four BP measurements were taken by a trained physician examiner after a 5-minute rest following the NHANES standard protocol, and the average of the systolic BP measurements was used for analysis (only systolic BP is used in the risk score). Total cholesterol (TC) was measured using enzymatic reactions, and high-density lipoprotein cholesterol (HDL-C) was measured by the direct immunoassay method. Current smoking status, assessed during the interview portion of NHANES, was defined as either yes (current smoker) or no (not a current smoker). Diabetes mellitus was defined as self-reported history of diabetes mellitus, current use of oral glucose-lowering medication or insulin, or a Hemoglobin A1c (HbA1c) value $\geq 6.5\%$ (American Diabetes Association [ADA], 2013). This method of defining of diabetes mellitus has been used in other NHANES analysis (Rethy et al., 2020).

Statistical code was created for this study to calculate ten-year ASCVD risk scores. These calculations were compared to estimates from the American College of Cardiology (ACC) online ASCVD Risk Estimator Plus (http://tools.acc.org/ASCVD-Risk-Estimator-

Plus/#!/calculate/estimate/). Study-computed estimates closely mirrored the online calculator estimates (see Appendix A).

Sensitivity Analyses

Current use of antidepressant medication can influence depression status and possibly ASCVD risk (Sherwood et al., 2016). We therefore conducted sensitivity analyses controlling for 30-day antidepressant use. All NHANES participants were asked if they used medication which required a prescription over the last 30 days. Those who said yes were asked to show their medication(s) to the NHANES staff. NHANES staff entered the medications into a computer where they were matched to a prescription drug database (NCHS, 2012). From the list of prescription medications, antidepressant medications were identified using generic names from the drug database (Rhee & Rosenheck, 2019). A binary (yes/no) variable reflecting current (30-day) antidepressant use was added to each of the sex and age specific regression models to evaluate whether models were sensitive to antidepressant use.

Statistical Analysis

Ten-year ASCVD risk was regressed on a binary depression score with age as a covariate. Depression and ASCVD risk are both related to age and sex so analyses were conducted for men and women separately for the full sample and repeated within ten-year age bands. Age was included in each model to more clearly partition the unique association of depression with ASCVD risk. We examined model specification by using the *linktest* command in Stata. This evaluates model specification by creating squared predicted scores from the fitted model and entering these back into the previously fitted model. If this term is statistically significant it provides evidence of a potentially misspecified model, e.g., a model specified as linear may have both a linear and quadratic form and thus require both first-order and second

order (squared) terms for adequate specification. Sex-specific analyses within ten-year age bands were adequately specified with age and depression as predictors. However, in sex-specific analysis examining the full eligible age range (40-79 years) both second and third-order age terms (i.e., squared and cubed age, centered at the mean) were required to achieve adequately specified models for women. Second order terms were required to achieve adequately specified models for men.

None of the cell sizes for the predictor variable (i.e., categories of depressed and nondepressed) were smaller than 30, the smallest being $N = 39$ for depressed males 70-79 years of age. Therefore, mean ASCVD risk should be estimated with reasonable precision and we did not suppress any of our estimates.

As per analytic guidelines (Johnston et al., 2013), we examined temporal patterns of depression and ten-year ASCVD risk across the survey cycles. This was done by creating an interaction term between our binary depression predictor and the continuous cycle year variable. There were no significant interactions of the depression variable with the survey cycle year (women; b = 0.14, 95% CI [-0.11, 0.39], $p = 0.26$; men; b = -0.03, 95% CI [-0.58, 0.51], $p = 0.91$). It was therefore appropriate to pool the survey cycles for analysis.

We used StataMP software (version 16.1; Stata Corp LP, College Station, TX) for all analyses. Analyses incorporated the strata, clustering, and survey weights to represent the civilian, non-institutionalized population of the U.S. We used the MEC weights because a number of key variables (i.e., blood pressure, lipids, and the PHQ-9 scores, etc.) were only measured in the MEC and that is the appropriate weight to use when analyzing those data. These weights were adjusted for the pooling of survey years by multiplying the 2-year MEC weights by 1/6 (Johnston et al., 2013). Statistical significance was defined as a two-tailed $p \geq 0.05$.

Results

Characteristics of the Study Population

Of the 58,660 participants who participated in both the interview and MEC portion of NHANES, 46,529 were excluded from the analysis due to exclusion criteria or missing data, leaving a total of 14,407 participants (7,489 women and 6,918 males; 13,194 not depressed and 1,213 depressed) with a mean age of 55.1 years old. Details on the exclusions are in Figure 1. Table 1 presents the baseline characteristics of the study for the entire sample and by depression status.

Frequency of depression status by sex and age bands is presented in Table 2. Women aged 50-59 had the highest depression prevalence followed by women 40-49. Although men had lower prevalent depression relative to women, men aged 50-59 had the highest depression prevalence followed by men who were 40-49.

Depression and Ten-Year ASCVD Risk

Before running the focal analyses, we present naïve, i.e., unadjusted models, to illustrate the importance of addressing age and sex differences in the association of depression and ten-year ASCVD risk. In a model including 40-79 year old men and women, and without any additional covariates, the association of depression and ten-year ASCVD risk was inverse, b = -0.17, 95% CI [-0.78, 0.45]; $p = 0.59$. That is, being depressed was associated with lower (but not significantly so) ASCVD risk. The association reversed when adding age into the model, showing a significantly positive association of depression with ASCVD risk, b = 0.69, 95% CI [0.22, 1.2]; $p = 0.005$). The association with depression became larger when further adding sex into the model containing age, b = 1.30, 95% CI [0.89, 1.80]; $p < 0.005$. Thus, an accurate depiction of the depression/ASCVD risk association requires careful adjustment for these

important confounders. In addition, we examined if sex moderated the association between depression and ten-year ASCVD risk by creating an interaction term between our sex variable and our binary depression predictor variable for the whole eligible sample 40-79 years old. There was no significant interaction between sex and depression (b = -0.64, 95% CI [-1.57, 0.29], p = 0.17). However, when examining this interaction within ten-year age-bands sex did moderate the association among those 60-69 years old (b = -3.18, 95% CI [-4.97, -1.39], p = 0.001). Therefore, sex did not moderate the association between depression and ten-year ASCVD risk for 40-79 years old but did for 60-69 years old. Thus, that association was higher for women than men in that age band.

The focal regression analyses for the association of ten-year ASCVD risk and depression stratified by age and sex are in Table 3. Depression was consistently associated with elevated risk for women (Table 3). Absolute age-adjusted mean ten-year ASCVD risk for depressed women between the ages of 40-79 was 7.7% (95% CI 7.2, 8.1) compared to 6.1% (95% CI 5.9, 6.3) for nondepressed women (Table 4). This 1.6% (95% CI 1.2, 2.0) difference persisted when adjusting for antidepressants (1.6%, 95% CI 1.2, 2.0). This general pattern of elevated ASCVD risk among depressed persons persisted within each age-band for women. The absolute differences in ASCVD risk by depression within ten-year age-bands ranged from 1.0% to 3.1%. These differences were robust to adjustment for antidepressants (Table 3). Age-adjusted mean ten-year ASCVD risk by depression status can be found in Table 4.

The association of depression and elevated ten-year ASCVD risk was less consistent for men than it was for women. Absolute age-adjusted ASCVD risk for depressed men aged 40-49 was 8.9% (95% CI 7.1, 10.7) and 7.0% (95% CI 6.7, 7.4). However, only men aged 40-49 who were depressed had statistically elevated risk (difference = 1.9%; 95 CI 0.1, 3.7). This difference

persisted when adjusting for antidepressants (1.9%; 95% CI 0.0, 3.8). Absolute age-adjusted ASCVD risk for depressed men aged 40-49 was 8.9% (95% CI 7.1, 10.7) and 7.0% (95% CI 6.7, 7.4) for nondepressed men. Thus, depression was unrelated to ASCVD risk for men in the older (above 50) age-bands.

Discussion

We estimated the association of depression and ten-year ASCVD risk in a probability sample of U.S. adults of 40-79 years of age. The results showed that depression was consistently associated with higher ten-year ASCVD risk for women; however, depression was inconsistently associated with ASCVD risk for men. Despite the apparently stronger association among women, sex did not moderate the association between depression and ten-year ASCVD risk, except for those between the ages of 60-69 years old.

For depressed women mean ASCVD risk was 1-3% higher compared to their nondepressed counterparts. Risk was approximately 2% higher among depressed men aged 40-49 years of age, but no depression-related ASCVD risk differences were observed for men in other age groups. From an individual perspective, a 1-3% (if you are a woman) or a 2% (if you are man between the ages of 40-49 years old) higher risk for a depressed person is modest. However, from a population perspective this modestly higher risk would be meaningful given that 17.3 million adults in the U.S. had at least one major depressive episode in 2017 (National Institute of Mental Health [NIMH], 2019). Thus, if persons with depression were at an average of 10% risk this would mean an excess of 346,000 ASCVD events over ten-years relative to if they were at 2% lower risk, i.e., at 8%. This overestimates the excess ASCVD cases given that the depression prevalence reflects all adults and ASCVD risk is restricted to persons 40-79 years

old free of CVD. However, in absolute terms this modest excess risk at the individual level translates into substantial population burden.

The 7% absolute ASCVD risk for nondepressed men 40-49 is considered low risk (Goff et al., 2014) whereas risk for depressed men in that age group (8.9%) indicates intermediate/elevated risk (Goff et al., 2014). Thus, depression bisects clinical risk categories among men 40-49 and this risk difference would indicate more aggressive risk management for depressed men. This is the most clinically relevant distinction observed between depressed and nondepressed persons in this sample. However, the relatively modest risk elevation observed among depressed women would translate into substantial ASCVD burden in the population. From a practical standpoint, the risk difference we observed for 40-49 year old men warrants screening for both depression and ASCVD risk jointly for men in this age group.

The observed ASCVD risk differences by depression status were robust to statistical control of antidepressant medication use. That is, 30-day antidepressant use did not modify the association of depression with ten-year ASCVD risk in the current study. However, a small, randomized study (n = 202) showed that antidepressant medication was associated with lower ten-year ASCVD risk scores after four months (mean ASCVD risk decrease 0.61%; 95% CI [0.01, 1.2]) (Sherwood et al., 2016). Therefore, antidepressants represent a promising avenue for prevention of both depression and CVD risk, and that trial underscores the importance of examining antidepressant use in studies using ASCVD risk scores as an outcome.

Many prospective studies have investigated the association of depression and incident CVD (Abramson et al., 2001; Ahto et al., 2007; Ariyo et al., 2000; Everson et al., 1998; Gump et al., 2004; Harshfield et al., 2020; Jee et al., 2019; Wassertheil-Smoller et al., 1996; Whooley & Browner, 1998; Williams et al., 2002). Although relatively few of those studies examined

combined CVD events, the association of depression and incident CVD appears to be similar for women and men. Thus, the weaker association between depression and ASCVD risk we observed is not expected given the prospective epidemiological evidence using clinical endpoints. However, the absence of moderation by sex indicates that this apparent difference does not exceed what would be expected by chance. Modest sex differences have been observed in fatal vs. nonfatal incident CHD events (Ferketich et al., 2000) but the ASCVD risk validation outcome does not distinguish between fatal and nonfatal events.

It is possible that different risk periods may explain the apparent discrepancy between clinical CVD risk for depressed men versus ten-year risk scores for depressed men. It has been noted that that the majority of adults in the US who are considered to be at low ten-year CVD risk are at high lifetime risk (Marma et al., 2010). This indicates that the association of depression with CVD risk may vary with the CVD risk event horizon and therefore future research should examine whether depression is more consistently linked to lifetime CVD risk for men. The time frame for depression assessment (past 2 weeks; past year; lifetime) may also contribute to this apparent discrepancy (Leung et al., 2012).

In contrast to the clinical CVD event literature, these data are consistent with studies examining depression and risk *scores*, the latter of which are benchmarked to the same intermediate risk period used here (ten-years). A recent study in China examined a different ten-year ASCVD risk score and found that depressive symptoms (measured by the PHQ-9) were more common in participants with higher ten-year ASCVD risk, with this association being more apparent in women than in men (Sun et al., 2019). Another study examined the association between depression (measured by the Beck Depression Inventory) and change in CHD risk status measured by the ten-year Framingham Risk Scores (FRS) (Jang et al., 2018). After an eight-year

follow-up women with depression showed significantly higher rates of changing to intermediate or high CHD risk based on FRS (≥10%) compared to nondepressed women (adjusted OR 1.54; 95% CI [1.08, 2.03]) (Jang et al., 2018). However, depression was not associated with intermediate or high FRS in men. Thus, as in the present study, there is some evidence that medium term risk scores appear to be more sensitive to depression in women versus men.

Depression is linked to unhealthy behaviors, many of which are on the causal pathway for CVD. These include smoking (Mykletun et al., 2008), excessive drinking (Levola et al., 2011), physical inactivity (Bélair et al., 2018; Patten et al., 2009; Win et al., 2011), and overeating (Murphy et al., 2009). Depression is associated with an increased risk of becoming a smoker, with an increased rate of smoking, and with a lower probability of quitting smoking (Anda et al., 1990; Breslau et al., 1998; Fergusson et al., 2003; Hall et al., 1993). Depression is also associated with overweight and obesity (de Wit et al., 2010; Luppino et al., 2010; Murphy et al., 2009), and with an approximately 40% higher risk of developing type 2 diabetes (Golden et al., 2004; Arroyo et al., 2004). In sum there is a strong co-occurrence of depression with the behavioral factors that contribute to CVD risk.

Beyond its association with CVD risk, depression is intrinsically important due to the associated burdens of impaired quality of life (QOL), poorer functioning, and comorbidity with other chronic diseases (Greden, 2001; Greenberg & Birnbaum, 2005; Gold et al., 2020; Lépine & Briley, 2011). These data show a high point prevalence of depression in the population, consistent with NIMH estimates of 17.3 million (6.7%) adults in the US with at least one major depressive episode in 2017 (NIMH, 2019). The current data also underscore the sex disparity in depression where from 2013 to 2016 women (10.4%) were almost twice as likely as men (5.5%)

to have had major depression (Brody et al., 2018). Depression is a highly recurrent disorder which further increases this burden (Lépine & Briley, 2011; APA, 2013).

This study has a number of strengths, including using a harmonized depression assessment that is widely available, self-administered, and clinically relevant. The study therefore fulfills recommendations to adopt harmonized outcome measures that are "…relevant to patients and providers across most conditions" (Gliklich et al., 2020, p. 1). Our risk score, based upon the pooled cohort equations, is calculated using widely available laboratory assessments (i.e., cholesterol) and generates clinically meaningful absolute risk estimates for hard health outcomes, i.e., ASCVD. In turn, ASCVD comprises the majority of the components of the leading cause of death in the U.S., CVD. Lastly, the present study utilizes a probability sample of over 14,000 persons which was not selected for either depression risk or CVD risk. Thus, the observed depression/ASCVD associations are generalizable to the U.S. adult population.

This study also has several limitations. First, this was a cross-sectional study; therefore, we cannot determine whether the association between depression and ten-year ASCVD risk scores is causal, nor can we evaluate the directionality of the association. Second, we did not examine subclinical depression. Evaluating levels of depression, including subclinical depression, may reveal a dose-response association with ten-year risk. Consistent with this possibility, a meta-analytic review showed that depressive mood was also predictive of incident CHD (RR = 1.49, 95% CI [1.16, 1.92], $p = 0.02$) although clinical depression had a stronger association (RR = 2.69, 95% CI [1.63, 4.43], $p < 0.001$) (Rugulies, 2002). Similarly, a pooled analysis of over 500,000 individual participant-level data from the Emerging Risk Factors Collaborations and the UK Biobank Study found that subclinical depressive symptoms were

indeed associated with CVD incidence (Harshfield et al., 2020). These findings underscore the importance of examining subclinical depression in future studies.

In conclusion, this study found that depression was consistently associated with statistically higher ten-year ASCVD for women; however, depression was only associated with higher ASCVD risk for men between the ages of 40 and 49. These findings may be useful for determining appropriate risk management strategies or therapeutic lifestyle changes for depressed persons who are at elevated short-term risk for CVD. In addition, this study is the first in the United States to characterize differences in ten-year ASCVD risk as a function of PHQ-9 depression. These standardized, widely available metrics will permit a readily interpretable picture of the ASCVD risk burden among depressed persons. These estimates should be applicable for medical and mental health care providers in particular and to the scientific disciplines of cardiovascular and psychiatric epidemiology more generally.

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Table 1

Baseline Characteristics of 2005-2016 NHANES Participants by Depression Status

	Not Depressed *n* = 13,194 *%* or $\bar{x} \pm SD$	Depressed *n* = 1,213 *%* or $\bar{x} \pm SD$	Total Sample *n* = 14,407 *%* or $\bar{x} \pm SD$
Sex, *%* (*n*)			
Female	51.7 (6,690)	65.5 (799)	52.0 (7,489)
Male	48.3 (6,504)	34.5 (414)	48.0 (6,918)
Age, years	53.8 ± 9.5	55.2 ± 9.7	55.1 ± 9.7
Race/Ethnicity, *%* (*n*)			
Non-Hispanic White	74.1 (5,755)	66.9 (506)	73.6 (6,261)
Non-Hispanic Black	9.5 (2,786)	11.4 (242)	9.7 (3,028)
Hispanic	10.6 (3,497)	15.5 (393)	11 (3,890)
Other	5.7 (1,156)	6.1 (72)	5.8 (1,228)
Education, *%* (*n*)			
< High School	14.4 (3,269)	26.8 (468)	15.2 (3,737)
= High School	22.5 (2,987)	26.5 (275)	22.8 (3,262)
≥ High School	63.1 (6,930)	46.7 (470)	62.0 (7,400)
Missing	3.5 (8.0)	0.0 (0.0)	3.3 (8.0)
SBP, mmHg	123.8 ± 19.2	124.7 ± 16.1	124.7 ± 16.4
HbA1c, *%*	5.9 ± 1.3	5.7 ± 0.9	5.7 ± 0.9
Cholesterol, mg/dL	204.5 ± 47.2	203.8 ± 39.3	203.8 ± 39.8
HDL-C, mg/dL	52.6 ± 17.0	55.0 ± 16.7	54.8 ± 16.8

Diabetic, *% (n)*	13.4 (2,431)	19.3 (316)	13.9 (2,747)
Smoking Status, *% (n)*			
Never/former smoker	82.7 (10,801)	62.3 (780)	81.2 (11,581)
Current smoker	17.3 (2,393)	37.7 (433)	18.7 (2,826)
Antidepressant, *% (n)*			
No	86.7 (11,906)	60.8 (809)	84.9 (12,715)
Yes	13.3 (1,288)	39.2 (404)	15.1 (1,692)
Ten-Year ASCVD Risk, *%*	8.7 ± 9.0	8.4 ± 9.5	8.7 ± 9.0

Note. Results are percentage and N for categorical variables and mean ($\bar{x}$) ± standard deviation (SD) for continuous variables. Results are weighted to represent the 40-79 year old population free of cardiovascular disease. Depression was classified as Patient Health Questionnaire-9 scores ≥ 10.

ASCVD, atherosclerotic cardiovascular disease; HbA1c, hemoglobin A1C; HDL-C, high density cholesterol; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; Cholesterol, total cholesterol.

Table 2

Percent and Cell Sizes for Depressed and Nondepressed Persons, Stratified by Age and Sex, 2005-2016 NHANES

	Not Depressed *n* = 13,194	Depressed *n* = 1,213
Sex, % (n)		
Female		
40-49	88.4 (2,058)	11.6 (269)
50-59	86.4 (1,732)	13.6 (272)
60-69	90.8 (1,850)	9.2 (188)
70-79	93.8 (1,050)	6.3 (70)
40-79	91.1 (6,690)	8.8 (799)
Male		
40-49	94.5 (2,008)	5.5 (116)
50-59	92.1 (1,812)	7.9 (156)
60-69	94.3 (1,715)	5.7 (103)
70-79	96.1 (969)	3.9 (39)
40-79	94.8 (6,504)	5.2 (414)

Note. NHANES, National Health and Nutrition Examination Survey

Table 3

Coefficients Regressing Ten-Year Absolute ASCVD Risk on Binary Depression, Stratified by Age and Sex, and Unadjusted and Adjusted for Antidepressant Use, NHANES 2005-2016

	Women *n* = 7,489				Men *n* = 6,918			
	Unadjusted for Antidepressants		Adjusted for Antidepressants		Unadjusted for Antidepressants		Adjusted for Antidepressants	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
All ages (40-79)								
Not Depressed	ref		ref		ref		ref	
Depressed	1.6 (1.2, 2.0)	<0.001	1.6 (1.2, 2.0)	<0.001	0.6 (-0.9, 2.1)	0.4	0.9 (-0.5, 2.4)	0.2
40-49								
Not Depressed	ref		ref		ref		ref	
Depressed	1.0 (0.5, 1.5)	<0.001	1.0 (0.4, 1.5)	<0.001	1.9* (0.1, 3.7)	<0.001	1.9 (0.0, 3.8)	<0.001
50-59								
Not Depressed	ref		ref		ref		ref	
Depressed	1.5 (0.9, 2.0)	<0.001	1.5 (1.0, 2.0)	<0.001	-0.9* (-3.0, 1.3)	0.4	0.0 (-2.1, 2.2)	1.0
60-69								
Not Depressed	ref		ref		ref		ref	

Depressed	2.4 (1.3, 3.4)	<0.001	2.5 (1.4, 3.7)	<0.001	0.9* (-3.4, 5.2)	0.7	1.1 (-3.3, 5.5)	0.6
70-79								
Not Depressed	ref		ref		ref		ref	
Depressed	3.1 (1.3, 4.9)	0.001	3.1 (1.3, 5.0)	0.001	4.0* (-0.8, 8.8)	0.1	3.6 (-1.2, 8.5)	0.1

Note. Risk is expressed as percentages. Depression is measured by the PHQ-9. Scores ≥ 10 are depressed, scores 0-9 are not depressed.

NHANES; National Health and Nutrition Examination Survey

*Relative standard error >30%

Table 4

Age-Adjusted Mean Ten-Year ASCVD Risk (%) by Depression, Stratified by Age and Sex, NHANES 2005-2016

	Women *n* = 7,489	Men *n* = 6,918
	Coefficient (95% CI)	Coefficient (95% CI)
All ages (40-79)		
Not Depressed	**6.1 (5.9, 6.3)**	11.4 (11.0, 11.8)
Depressed	**7.7 (7.2, 8.1)**	12.0 (10.6, 13.4)
40-49		
Not Depressed	**1.8 (1.7, 1.9)**	**7.0 (6.7, 7.4)**
Depressed	**2.8 (2.3, 3.3)**	**8.9 (7.1, 10.7)**
50-59		
Not Depressed	**3.4 (3.2, 3.6)**	12.3 (11.7, 13)
Depressed	**4.9 (4.4, 5.4)**	11.5 (9.4, 13.6)
60-69		
Not Depressed	**8.4 (8.1, 8.7)**	15.7 (14.8, 16.7)
Depressed	**10.8 (9.8, 11.8)**	16.6 (12.5, 20.7)
70-79		
Not Depressed	**20.2 (19.6, 20.8)**	15.5 (14.2, 16.7)
Depressed	**23.3 (21.6, 25.0)**	19.5 (14.9, 24.1)

Note. Within sex, means different at $p \leq 0.05$ are in **bold** for reference. Exact *p*-values for the comparison are in Table 3.

NHANES; National Health and Nutrition Examination Survey

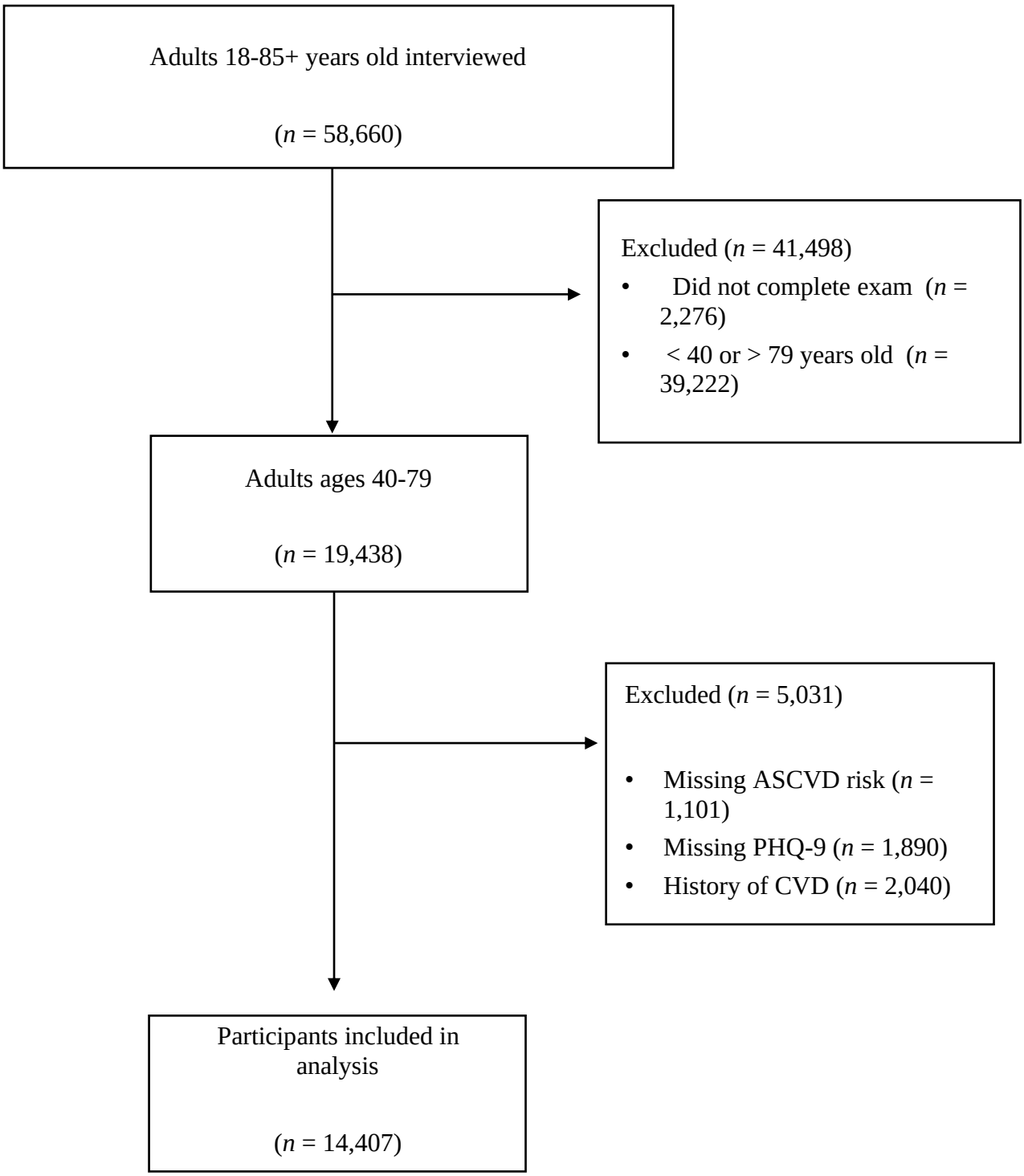
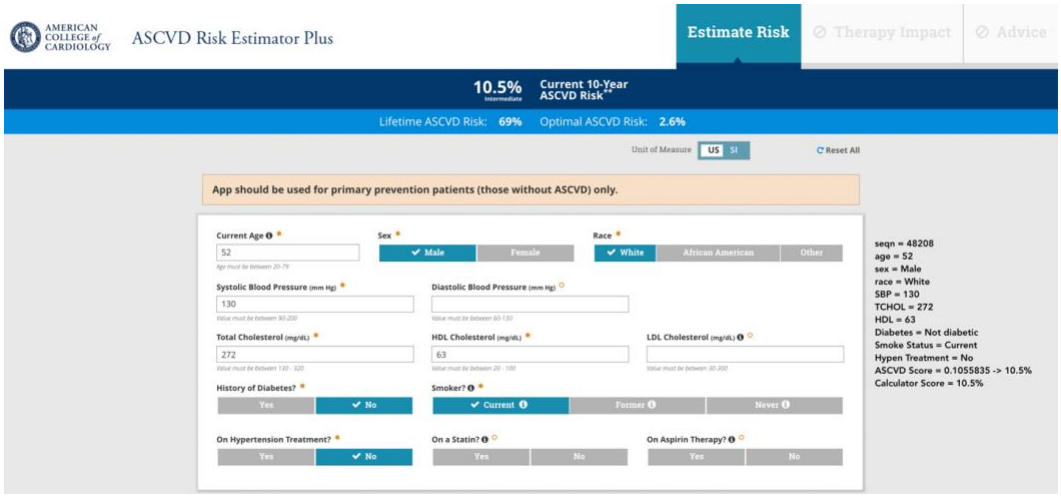
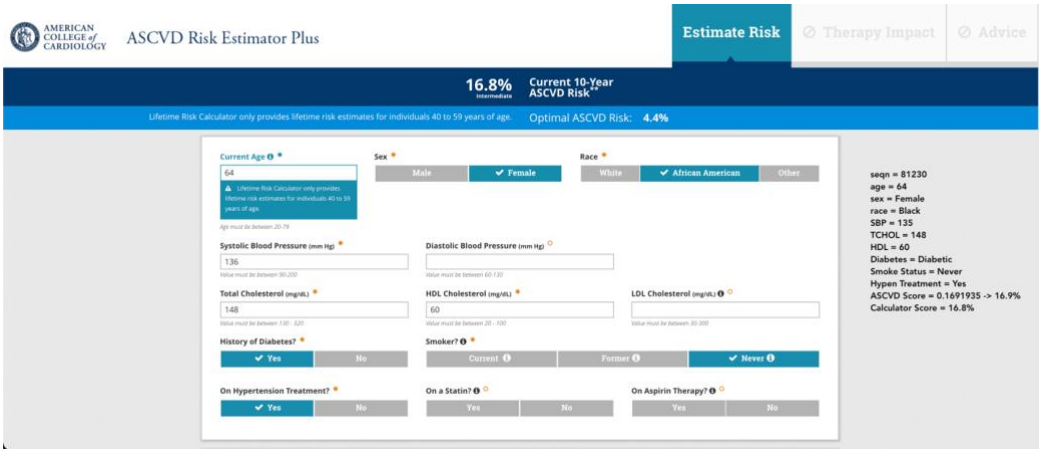


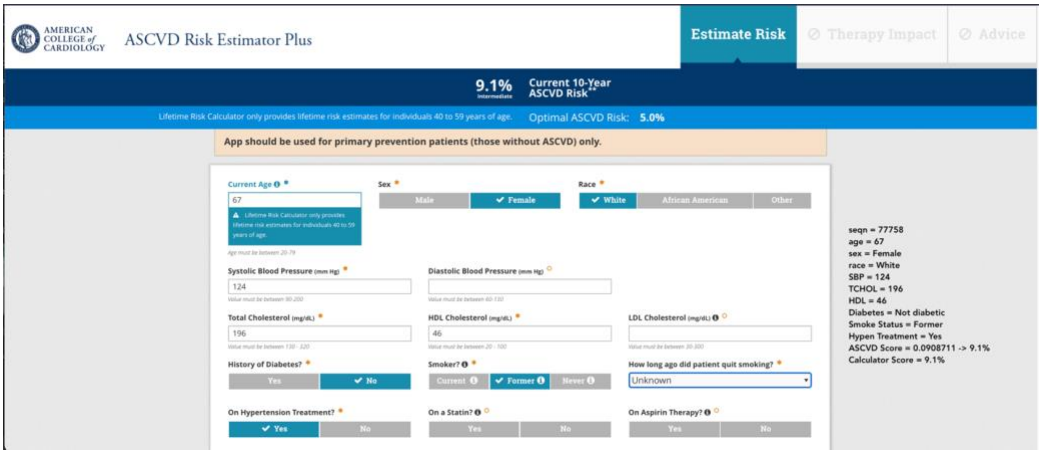
Figure 1. Participants selection flow diagram, 2005-2015 National Health and Nutrition Examination Surveys. ASCVD indicates atherosclerotic cardiovascular disease. PHQ-9 indicated Patient Health Questionnaire-9.

Appendix A

Ten-Year ASCVD Risk Verification







DEPRESSION & ASCVD RISK