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Depression, physical activity, and incident cardiovascular disease among American Indians: The strong heart family study

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Abstract

Background: Little is known about the relationship of depression with incident cardiovascular disease (CVD) among American Indians (AIs), a population with a high burden of depressive symptoms and CVD. In this study, we examined the association of depressive symptoms with CVD risk among AIs and assessed whether an objective marker of ambulatory activity influenced the relationship.

Methods: The study comprised participants from the Strong Heart Family Study, a longitudinal study of CVD risk among AIs free of CVD at baseline (2001–2003) and who participated in a follow-up examination (n = 2209). The Center for Epidemiologic Studies of Depression Scale (CES-D) was used to assess depressive symptoms and depressive affect. Ambulatory activity was measured using Accusplit AE120 pedometers. Incident CVD was defined as new myocardial infarction, coronary heart disease, or stroke (through 2017). Generalized estimating equations were used to examine the association of depressive symptoms with incident CVD.

Results: 27.5% of participants reported moderate or severe depressive symptoms at baseline and 262 participants developed CVD during follow-up. Compared to participants who reported no depressive symptoms, the odds ratios for developing CVD among those who reported mild, moderate, or severe symptoms were: 1.19 (95% CI: 0.76, 1.85), 1.61 (95% CI: 1.09, 2.37), and 1.71 (95% CI: 1.01, 2.91), respectively. Adjustment for activity did not alter findings.

Limitations: CES-D is a tool used to identify individuals with depressive symptoms and not a measure of clinical depression.

Conclusion: Higher levels of reported depressive symptoms were positively associated with CVD risk in a large cohort of AIs.

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Contributors

TES, MO and AMF designed research; AMF conducted statistical analyses; TES and AMF wrote paper; MO edited drafts of the paper.

Declaration of competing interest

None

Keywords

Cardiovascular disease; Depression; Physical activity; American Indians; Cohort study

1. Introduction

The prevalence of cardiovascular disease (CVD) and depressive symptoms are exceedingly high in American Indian (AI) communities, and CVD is a leading cause of morbidity and mortality among AIs in the United States (Howard et al., 1999). In 2018, AIs were 50% more likely to have CVD than non-Hispanic whites of similar age (Center for Disease Control and Prevention, 2018). Although there are no comprehensive studies of the prevalence of depressive symptoms in AIs, a report from the Department of Health and Human Services indicates that AIs were 2.5 times more likely to report serious psychological distress during the past month than the general US population (Indian Health Service et al., 2014). In non-AI populations, there is strong epidemiological evidence that supports the role of psychological health (e.g., depression/depressive symptoms) in the pathogenesis of CVD (Cohen et al., 2016; Kamphuis et al., 2007; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004; Whooley et al., 2008; Win et al., 2011; Ye et al., 2013). However, few studies have examined associations of psychological health with CVD in AIs (Sawchuk et al., 2005).

Previous studies that have examined the link between depression/depressive symptoms and incident CVD point to physical activity as a potential mechanism to explain the association. As physical inactivity is a major risk factor for development of CVD, a common hypothesis is that individuals with depression and/or depressive symptoms may be more likely to be physically inactive than individuals without depression and/or depressive symptoms (McConnell et al., 2005; Penninx, 2017). However, studies that have assessed the interplay of depression, physical activity, and CVD incidence show conflicting results—with some studies suggesting that physical activity impacts associations of depressive symptoms with incident CVD (Kamphuis et al., 2007; Whooley et al., 2008; Win et al., 2011; Ye et al., 2013), and others showing no association (Cohen et al., 2016; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004). To our knowledge, previous longitudinal studies that have examined the relationship of depressive symptoms, physical activity, and incident CVD utilized self-reported measures of physical activity (e.g., physical activity questionnaires) (Cohen et al., 2016; Kamphuis et al., 2007; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004; Whooley et al., 2008; Win et al., 2011; Ye et al., 2013). As self-reported activity is prone to recall-bias and social-desirability bias, studies that use objective measures of physical activity are needed. Additionally, activity levels differ across populations (e.g., rural versus urban; by race/ethnicity) (Chevli et al., 2022), and no previous studies have assessed the prospective association of depression/depressive symptoms with development of CVD in AIs despite the high burden of depression and/or CVD in many AI communities.

The purpose of this study was to assess the association of depressive symptoms with risk of CVD in a large cohort of AIs from across the United States. Secondarily, we explored whether an objective marker of ambulatory activity (steps per day) influenced the

relationship of depressive symptoms and CVD risk. We hypothesized that that participants who reported a greater number of depressive symptoms were more likely to develop CVD than participants who report fewer depressive symptoms. In addition, we hypothesized that adjustment for physical activity would attenuate associations of depressive symptoms with CVD.

2. Methods

2.1. Setting & study population

The Strong Heart Family Study (SHFS) is a family-based prospective study of risk factors for CVD in 12 AI communities in Arizona, North Dakota, South Dakota and Oklahoma. The SHFS included two examinations over an 8-year period: a baseline examination in 2001–2003 and a follow-up examination in 2007–2009. Study details have been previously described (Lee et al., 1990; North et al., 2003). There were 1127 men and 1684 women from 91 multi-generational families who participated in the baseline examination. Of these participants, 91% also participated in the follow-up examination. The Strong Heart Family Study protocol was approved by institutional review boards, participating tribal communities, and the respective area Indian Health Service IRBs, and all participants provided written informed consent. All study procedures were followed in accordance with tribal and institutional guidelines.

Of the 2811 SHFS participants who took part in the baseline exam, we excluded participants who did not complete the Center for Epidemiologic Studies of Depression Scale (CES-D) (n = 357), reported taking anti-depressive medications (n = 143), or who had prevalent CVD (n = 100) at baseline. Additionally, we excluded those who were currently pregnant (n = 2) since pregnancy may influence risk of depressive symptoms. In total, 2209 persons comprised the analytic cohort.

2.2. Data collection

Both baseline and follow-up examinations included a standardized personal interview, physical examination, medication review, laboratory testing, and one-week pedometer log. Information regarding medical history, education, smoking, alcohol consumption and dietary intake (from a 119-item Block food frequency questionnaire) during the past year was collected at the personal interview. Anthropometric measures were obtained with the participant wearing lightweight clothing and no shoes. Body weight was measured using a Tanita BWB-800 5 Adult Digital Scale, and height was measured using a vertical mounted ruler. Body mass index (BMI) was calculated as body weight divided by height-squared (kg/m^2) (Lee et al., 1990; North et al., 2003). Blood pressure was measured three times on the right arm using standard mercury sphygmomanometers after 5 min rest; the mean of the second and third systolic and diastolic measurements were used in this analysis. Blood samples were collected after a 12-h overnight fast and were stored at −70 °C. Plasma glucose, low density lipoprotein (LDL) and high-density lipoprotein (HDL) were measured using enzymatic methods (Lee et al., 1990; North et al., 2003).

2.3. Assessment of depressive symptoms

The 20-item CES-D was used to measure current depressive symptoms and depressive affect (Lewinsohn et al., 1997; Radloff, 1977). The CES-D is a widely-used self-administered questionnaire that has been shown to be both valid and reliable measure of depressive symptoms in several studies, including studies among AIs (Baron et al., 1990; Beals et al., 1991; Dick et al., 1994; Manson et al., 1990; Radloff, 1977; Somervell et al., 1993). The CES-D comprised 20 questions to assess the severity of depressive symptoms over the past week, including depressed mood, feelings of guilt and hopelessness, loss of appetite, sleep disturbance, and psychomotor impairment. For instance, example questions included: “in the past week, I felt that I could not just shake the blues even with help from my family and friends”, and “in the past week, I had trouble keeping my mind on what I was doing”. Each of the 20 questions was scored using a four-point Likert-scale; scores ranged from 0 (none of the time/rarely) to 3 (most of the time). Responses to individual questions were then summed (total possible score ranges between 0 and 60). A higher CES-D score indicated higher likelihood of depression/depressive symptoms. As in previous SHFS analyses, depressive symptoms were categorized as: none (CES-D<10), mild (CES-D 10–15), moderate (CES-D 162–4), and severe (CES-D 25þ) (Calhoun et al., 2010; Neff Warner et al., 2022; Zhao et al., 2016).

2.4. Assessment of physical activity

AccuSplit AE120 pedometers (Yamax Japan) were used to measure ambulatory physical activity. The pedometers have been shown to be both reliable and valid in laboratory and free-living conditions (Bassett et al., 2000; Le Masurier and Tudor-Locke, 2003; Schneider et al., 2004; Tudor-Locke et al., 2002). At the Phase 4 exam, participants were instructed to wear the Accusplit AE120 pedometer on the hip during waking hours for seven consecutive days (5-week days, 2 weekend days), except while bathing or swimming. Participants were issued a physical activity diary and instructed to record: (a) time pedometer was put on each morning (b) the number of steps taken per day (c) time the pedometer was removed each evening (d) whether the pedometer was taken off at any time during the day, and if so, (e) the length of time that the pedometer was off (minutes or hours). At the end of the seven-day period, participants returned the physical activity diary to the SHS investigators using a pre-addressed stamped envelope.

2.5. Assessment of CVD

Incident CVD was defined as new (non-fatal and fatal) myocardial infarction, coronary heart disease, or stroke. Subsequent to the follow-up examination in 2007–2009, CVD surveillance was performed using annual phone interviews and medical record reviews; all phone interviews and medical record reviews occurred between 2013 and 2017. During this time, CVD was identified by self-report (with study participant or next-of-kin in cases of a participant fatality) and confirmed by documentation in medical records.

2.6. Statistical analyses

Generalized estimating equations (GEE) with an independence working correlation structure and robust standard errors were used to examine the association of depressive symptoms

with the risk of CVD. Given the family-based sampling, GEE was used to address potential familial correlation within the data. All statistical analyses were conducted using STATA version 13.1 (Stata Corp, College Station, Texas).

Three levels of adjustment were used to examine the association of depressive symptoms with risk of CVD. Model 1 (crude model) adjusted for age, sex, and site. The second model (primary model) additionally adjusted for potential confounders selected *a priori* based on their potential association with depressive symptoms and CVD, including education, smoking status, alcohol consumption, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, prevalent type 2 diabetes, BMI, and diet quality (14). The effects of controlling for daily ambulatory activity were examined in Model 3 to better determine if physical activity might influence the relationship of depressive symptoms with risk of CVD.

As associations of depressive symptoms with risk of CVD may differ my sex, age, or geographic location of study participants, we examined the potential interaction of CES-D with sex, age, and study site on risk of CVD in sensitivity analyses by including a cross-product term of each factor and CES-D in the primary model. Wald tests were used to evaluate the statistical significance of each multiplicative interaction term.

Dr. Fretts had full access to all the data used in this analysis and takes responsibility for its integrity and the data analysis. The data that support the findings of this study are owned by the Tribal Nations that are part of the SHFS. Requests to access SHFS data for approved manuscripts/data analyses from qualified researchers trained in human subject confidentiality protocols may be submitted to the SHFS Coordinating Center: https://strongheartstudy.org/

3. Results

On average, participants were 38.8 years old (range 14.1–90.8 years) at baseline and 59.7% of the analytic cohort was female. In total, 51.4% of study participants reported no depressive symptoms, 21.1% reported mild symptoms, 15.5% reported moderate symptoms, and 12.0% reported severe symptoms. Baseline characteristics of the study participants according to CES-D category (i.e., no symptoms, mild symptoms, moderate symptoms, severe symptoms) are shown in Table 1. Participants who reported severe symptoms were younger, more likely to be female, and had fewer years of education compared to participants who reported no symptoms. Additionally, participants who reported severe symptoms were more likely to smoke, reported lower levels of ambulatory physical activity, and had higher BMI and waist circumference when compared to participants with no reported symptoms. Participants who reported severe symptoms had lower LDL cholesterol levels when compared to those with no reported symptoms.

Baseline characteristics of study participants according to those who developed and did not develop incident CVD during follow-up are described in Table 2. In general, participants who developed CVD were older, had larger waist circumference, and higher systolic blood pressure, LDL cholesterol, and triglycerides than participants who did not develop CVD. Participants who developed CVD also had lower HDL cholesterol, were more likely to have

prevalent diabetes, and took fewer steps per day than participants who did not develop CVD (Table 2).

During a median follow-up of 5 years, 262 participants developed CVD. Participants who reported more depressive symptoms were more likely to develop CVD during follow-up when compared to participants who reported fewer depressive symptoms. Compared to participants who reported no depressive symptoms, the odds of developing CVD among those who reported mild, moderate, or severe symptoms were: 1.19 (95% CI: 0.76, 1.85), 1.61 (95% CI: 1.09, 2.37), 1.71 (95% CI: 1.01, 2.91), (p-trend = 0.005) respectively, after adjustment for age, sex, site, education, smoking status, alcohol consumption, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, prevalent type 2 diabetes, BMI, and the diet quality (Table 3). Further adjustment for physical activity did not materially change the observed associations (Table 3). There was no statistically significant interaction of CES-D with age, sex, or study site on risk of CVD (smallest p = interaction = 0.26; data not shown).

4. Discussion

In this large cohort study of AIs, depressive symptoms were positively associated with CVD risk. Participants who reported moderate or severe depressive symptoms were 61%–71% more likely to develop CVD than participants who reported no depressive symptoms. Further, differences in levels of physical activity among those with and without depressive symptoms did not explain the relationship of depressive symptoms with CVD risk.

To date, there has been limited research on the impact of depression/depressive symptoms on risk of CVD in AIs. Unfortunately, the burden of depression in many AI communities is high—and is driven at least in part to historical trauma experienced by AI people with the forced migration onto reservations and systematic efforts to strip AIs of culture, beliefs/practices, and language (Burnette et al., 2020). In one cross-sectional study among AIs from the Northern Plains, individuals with depression were more than twice as likely to have CVD than participants without depression (Sawchuk et al., 2005). Although it was not possible to determine whether depression increased risk of CVD or CVD increased risk of depression in that cross-sectional study, our findings support and expand upon those findings to suggest that participants who report moderate or severe depression/depressive symptoms are 61%–71% more likely to develop CVD than participants who report no depressive symptoms.

Previous work in non-AI populations have consistently reported that depression is associated with a higher risk of CVD (Cohen et al., 2016; Kamphuis et al., 2007; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004; Whooley et al., 2008; Win et al., 2011; Ye et al., 2013). These studies use a wide variety of instruments to assess depression and/or depressive symptoms, including the Zung Self-Rating Depression Scale (Kamphuis et al., 2007), the 9-item Patient Health Questionnaire (PHQ) (Whooley et al., 2008), the University of Michigan Composite International Diagnosis Interview (Sawchuk et al., 2005), and the CES-D (Cohen et al., 2016; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004; Win et al., 2011; Ye et al., 2013). On the other hand, studies that have assessed the interplay of depression, physical

activity, and CVD risk show conflicting results. Some studies suggest that physical inactivity accounts for 20%–30% of the higher risk for cardiovascular events and cardiovascular-related deaths among individuals with depression (Whooley et al., 2008; Win et al., 2011; Ye et al., 2013). Other studies, including the results reported herein, suggest that physical activity does not impact the association of depressive symptoms with CVD risk (Cohen et al., 2016; Kamphuis et al., 2007; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004). Importantly, previous published studies have relied solely on self-reported activity (Cohen et al., 2016; Kamphuis et al., 2007; O'Brien et al., 2015; Wassertheil-Smoller et al., 2004; Whooley et al., 2008; Win et al., 2011; Ye et al., 2013); our findings build upon previous work by using an objective measure of activity.

Several biological mechanisms may explain the link between depressive symptoms and risk of CVD. In particular, the autonomic nervous system, platelet receptors & function, coagulation factors, pro-inflammatory cytokines, endothelial function, neurohormonal, and genetic factors may play a role in the pathogenesis of depression and CVD (Belvederi Murri et al., 2020; Falkai et al., 2021; Kramer, 2020; Raic, 2017). Additionally, individuals with depression or at high risk of depression have been shown to be more likely to engage in health behaviors that may promote risk of CVD, including smoking, consumption of a poor diet, physical inactivity, and poor medication adherence (Hare et al., 2014; McConnell et al., 2005; Penninx, 2017). Although physical activity did not appear to impact associations of depression/depressive symptoms with risk of CVD in the SHFS, it is possible that this is due to limited levels of activity in the cohort. In general, participants reported low levels of physical activity. On average, participants accumulated 5665 steps per day. Some guidelines recommend at least 8000–10,000 steps per day as part of a healthy lifestyle (Tudor-Locke et al., 2011). As such, it is possible that most SHFS participants did not accumulate enough steps per day to impact the relationship of depression/depressive symptoms with risk of CVD.

This study has many strengths. The SHFS is a large multi-site study of CVD risk factors in a large cohort of AIs, and to our knowledge, this is the first study to examine the association of depressive symptoms and CVD risk among AIs. The use of an objective measure of physical activity is also a strength of the study as pedometers are less prone to recall bias than physical activity questionnaires, and may more accurately capture walking and other unstructured ambulatory activities common in the population that are difficult to self-report on questionnaires. The SHFS also collected detailed data on many of the major demographic, behavioral, and health factors associated with depression/depressive symptoms and CVD risk using instruments known to be valid and reliable—which maximized our capacity to adjust for confounding.

This study is not without limitations. Although the CES-D is a tool used to identify individuals with depressive symptoms, it is not a measure of clinical depression. Although we adjusted for many factors that may be related to both depression/depressive symptoms and CVD risk, we cannot disregard the possibility of residual confounding due to unmeasured or poorly measured factors. Pedometers are designed to only capture ambulatory movement, such as walking and running. These are the most common activities reported in the SHFS, and the pedometer captures usual activity levels for most study

participants (Fretts et al., 2009, 2012). However, we cannot rule out the possibility that moderate-to-high intensity non-ambulatory activity (e.g., swimming, biking) influence the relationship of depressive symptoms with CVD risk. Finally, although the SHFS is the largest cohort study of CVD risk in 12 AI communities throughout the USA, most AIs in the SHFS reside in rural and/or reservation communities, and the generalizability of findings to AIs who live in urban or suburban areas is unclear.

In conclusion, higher levels of reported depression/depressive symptoms were positively associated with CVD risk in a large cohort of AI men and women over a wide age range. Physical activity did not appear to influence observed associations. As mental health is a potentially modifiable risk factor, these findings may be used to inform targeted interventions to lower risk of depression and CVD in this high-risk population.

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Abbreviations:

AI	American Indians
CES-D	Center for Epidemiologic Studies of Depression Scale
SHFS	Strong Heart Family Study

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Table 1

Characteristics of study participants according to baseline depressive symptoms.

	No Symptoms	Mild Symptoms	Moderate Symptoms	Severe Symptoms
N	1135	466	343	265
Age, years	40.0 (16.3)	38.5 (16.7)	39.1 (16.6)	34.2 (14.4)
Female, %	55.1	58.8	63.0	77.0
Education, years	12.7 (2.2)	12.0 (2.3)	11.6 (2.3)	11.4 (2.0)
Smokers, % current	35.2	35.3	38.1	48.3
BMI, kg/m^2	30.7 (7.0)	31.2 (7.3)	32.0 (8.9)	31.5 (8.0)
Waist circumference, cm	100.5 (17.4)	102.3 (17.7)	104.5 (21.3)	102.4 (19.0)
SBP, mm Hg	123.0 (16.7)	122.1 (15.7)	121.5 (15.5)	120.2 (17.9)
HDL cholesterol, mg/dL	51.8 (14.3)	52.0 (14.2)	50.4 (14.4)	50.7 (13.9)
LDL cholesterol, mg/ dL	101.6 (31.5)	100.3 (28.8)	96.9 (27.2)	94.3 (29.4)
Triglycerides, mg/dL	159.4 (175.9)	162.9 (125.0)	172.7 (121.6)	156.9 (161.2)
Prevalent diabetes, %	14.9	15.8	24.9	12.5
Ambulatory activity, steps/day	6524.3 (4257.8)	5685.7 (3332.9)	5201.6 (3563.9)	5246.9 (3296.0)
Diet quality, alternative healthy eating index	44.6 (9.2)	44.0 (9.0)	44.0 (8.4)	43.2 (8.7)

Table 2

Baseline characteristics of study participants who developed and did not develop cardiovascular diseases during follow-up.

	No Incident CVD	Incident CVD
N	1947	262
Age, years	36.8 (15.3)	54.0 (15.8)
Female, %	61.1	49.2
Education, years	12.2 (2.2)	12.2 (2.6)
Smokers, % current	37.0	39.3
BMI, kg/m2	31.0 (7.7)	31.8 (6.5)
Waist circumference, cm	101.0 (18.6)	106.8 (15.8)
SBP, mm Hg	120.8 (15.5)	132.3 (19.3)
HDL cholesterol, mg/dL	51.9 (14.3)	48.3 (13.4)
LDL cholesterol, mg/dL	98.3 (29.2)	110.1 (34.8)
Triglycerides, mg/dL	155.9 (128.6)	206.6 (287.1)
Prevalent Diabetes, %	12.8	49.2
Ambulatory activity, steps per day	6119.2 (3854.0)	5008.8 (4146.7)
Healthy Diet, Healthy Eating Index	44.0 (8.9)	46.2 (9.2)

Abbreviation: CVD, cardiovascular diseases.

Table 3

Hazard ratio for incident CVD according to reported depressive symptoms at baseline.

	CES-D Quartile				
	I	**II**	**III**	**IV**	**P-trend**
No. at Risk	1135	466	343	265	
No. of cases	131	54	54	23	
Model 1[a]	1.0 (ref)	1.23 (0.81, 1.87)	1.85 (1.28, 2.66)	1.74 (1.11, 2.72)	<0.001
Model 2[b]	1.0 (ref)	1.19 (0.76, 1.85)	1.61 (1.09, 2.37)	1.71 (1.01, 2.91)	0.005
Model 3‡	1.0 (ref)	1.19 (0.76, 1.85)	1.60 (1.09, 2.37)	1.70 (1.01, 2.88)	0.005

[a] Adjusts for age, sex, and study site.

[b] additionally adjusts for education (years), smoking (never, former, current), alcohol consumption (drinks per week), systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, diabetes, BMI, and diet quality (healthy eating index); additionally adjusts for ambulatory activity (steps per day).