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Original Article

Sedentary Time as a Mediator Linking Cardiovascular Disease to Depression: NHANES Evidence for Public Health Intervention

Hong Lu[1#], Zhen Tan[1#], Wei Liu[2], Ting Zhang[3*], Mei Ling Li[4*]

[1]Department of Medical Service Training Center, the General Hospital of Western Theater Command PLA, China

[1]Department of General Surgery, the General Hospital of Western Theater Command PLA, China

[2]The Fifth Outpatient Department, the General Hospital of Western Theater Command PLA, China

[3]The Fifth Outpatient Department, the General Hospital of Western Theater Command PLA, China

[4]Department of Cardiovascular Internal Medicine, the General Hospital of Western Theater Command PLA, China

Hong Lu[#] and Zhen Tan[#] are Co-First Authors

[*]Corresponding Author: Ting Zhang, Mei Ling Li

Abstract:
Both cardiovascular disease (CVD) and depression are linked to sitting time (ST). However, there is still no research on association among them. We aimed to use a large sample (n=11,667) from the National Health and Nutrition Examination Survey (NHANES) to disentangle the relationship. We found participants experienced depression with CVD had more sitting time compared to those with single depression or CVD. Depression was positively associated with CVD, ST (OR:4.56, 95% CI:1.47-2.02, P＜0.001; OR:1.05, 95% CI:1.04-1.07, P＜0.001). Besides, ST was associated with CVD (OR:38.49, 95% CI:25.65-51.33, P＜0.001). ST was non-linearly associated with depression/CVD, and it was positively associated with depressive symptoms after reaching the inflection point (360 minutes). Our result showed that ST mediated 1.6% association between CVD and depression.

1. Introduction

Depression is a psychiatric disorder characterized by alterations of mood, behavior and affection(1). Depression affects more than 350 million people globally, accounting for about 4.4% of the world's population, and causes a heavy burden on public health and the economies of countries(2). The high prevalence and disability of depression make it a major public health problem worldwide. The World Health Organization (WHO) predicts that depression will be the leading cause of chronic disease in high-income countries in the future (3). Study has reported that a significant proportion of depressed individuals suffer from other chronic diseases, it can also trigger or aggravate chronic diseases and affect the prognosis (4).

Cardiovascular disease (CVD) is the leading cause of mortality in the worldwide with 19.05 million annual deaths globally(5). Depression, in particular, induces a remarkable risk for the evolution of CVD and intimately relates to adverse cardiovascular outcomes and mortality(6). In the clinic setting, it is usually observed that cardiovascular disease and depression co-occur(7). Some studies have shown that there may

be a strong association between cardiovascular disease and depression, with a higher risk of cardiovascular disease in patients with depression, and that the longer duration of cardiovascular disease, the need for long-term medication, the increased dependence on others, the decline in physical function, and the emergence of comorbidities increase the risk of depression in CVD patients(8, 9). At the same time, a study found that the onset of depression was independently associated with an increased risk of cardiovascular disease(10). It suggests that depression could be a significant predictor of incident CVD (11). A study by Daskalopoulou et al. (12) confirmed that depression can increase the risk of heart failure by 18% (OR, 1.18; 95% CI, 1.13-1.24). In the heart failure population, the prevalence of depression was approximately 21.5%, and interestingly, the prevalence of depression increased as the cardiac function class of heart failure patients increased(13). Based on the above views, we suggest that this relationship may be bidirectional(7).

Prolonged sitting time (ST), also known as sedentary behavior, means that "any position that involves sitting, leaning or lying down and which does not use more than 1.5 (Metabolic Equivalent, METs) of energy while you are awake"(14). In everyday life, this mainly refers to behaviors such as watching television, reading, writing or using electronic entertainment products such as computers and mobile phones. It is emerging as a modifiable risk factor for several chronic diseases, prolonged sitting is associated with harmful health outcomes, including cancer, metabolic and CVD(15-17). In recent years, a large number of studies have shown that prolonged sitting is associated with an increased risk of cardiovascular disease(18, 19). A longer sitting time has a negative impact on markers of vascular health, causing changes in risk factors including vascular structure and function, blood pressure, blood lipids, oxidative stress, inflammation, and metabolic damage(20). The mechanisms by which sedentary behavior contributes to CVD and death are unclear, but have been shown to be strongly associated with defects in lipoprotein metabolism, early atherosclerosis, insulin resistance and the development of metabolic syndrome(21).

On the other hand, several studies have found that prolonged sitting is highly associated with negative emotion, including stress, anxiety and depression, and that the longer the average time spent sedentary, the higher risk of depression(22, 23). One researcher concluded that for each 1 h/day increase in television watching, risk of depression was increased by 5 % (24). As such, experts suggest that shortening and interrupting accumulated periods of sitting time may be an effective strategy to preserve mental health in self-care(25).

Based on the current findings mentioned above, we found both CVD and depression are linked to ST. After reviewing the related studies, in the majority of studies, the sample sizes are limited, and to date, there has been no exploration of the relationship between CVD, ST and depression.

Thus, this study is the first attempt to investigate the relationship between CVD, ST and depression, explore whether ST can mediate the association between CVD and depression. Prior to this research, we suspected that: (1) there is an association between CVD, ST and depression, (2) ST can partially mediate the effect of CVD on depression.

1. Materials and Methods

2.1 Data source and study population

A cross-sectional study was designed using data from the National Health and Nutrition Examination Survey (NHANES) 2011-2020. The present study population was from four cycles of "continuous NHANES". The National Center for Health Statistics (NCHS) Ethics Review Board approved the NHANES study protocol, and all participants provided written informed consent.

The study procedure is illustrated in Fig.1.We excluded participants according to the following: (1) age < 18 years; (2) lack of information on general characteristics, PHQ-9, CVD diagnosis and sitting time. Finally, we included 11,667 participants in this study (Figure 1).

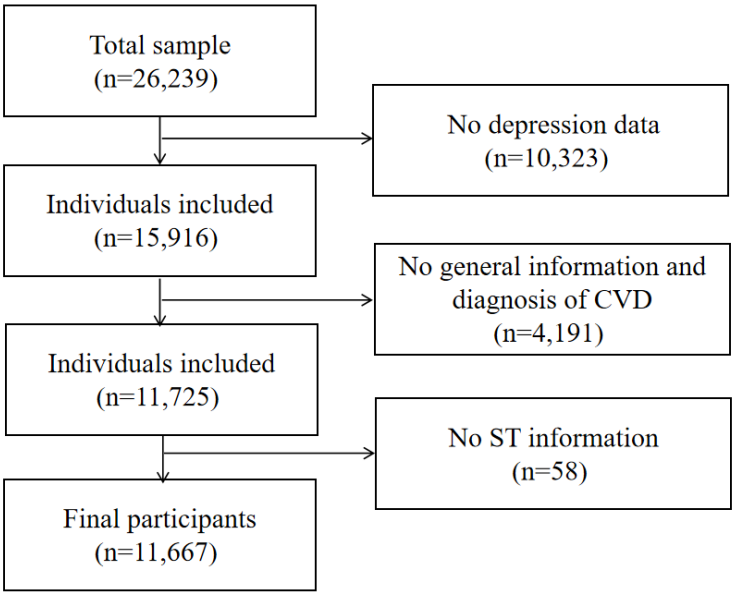

Figure.1. Flowchart of the study design and participants excluded from the study.

2.2 Data Collection

This study collected information on demographics, comorbidities, and physical measurements. Demographic and comorbidity data were recorded in household interviews via a questionnaire. Standardized body measurements (e.g., BMI) were provided by trained health technicians for all examinees at the mobile examination center.

2.3 Primary Measures

The depression symptom was assessed by PHQ-9, with total score of ≥10 was defined as depression. With score of ＜10 was defined as non-depression .

Participants who answered "yes" to the question "Has a doctor or other health professional ever told you that you have coronary heart disease/stroke/angina/heart disease/heart failure?" in the medical status section of the household questionnaire of the household interviews were considered to experience cardiovascular disease （CVD）.

Sitting time was assessed by minutes sedentary activity questionnaire: "The following question is about sitting at school, at home, getting to and from places, or with friends including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer. Do not include time spent sleeping. How much time do you usually spend sitting on a typical day?".

2.4 Covariates

In this research, general information included age, gender, race, smoking status, alcohol status, educational background, marital status, income-poverty ratio (PIR) and body mass index (BMI) was adjusted.

The following variables were further categorized to facilitate data integration:

1. Race: Mexican-America, Non-Hispanic Black, Non-Hispanic White and others.
2. Age: 18-40, 41-60, 61-80.
3. Alcohol status: Excessive consumption (4-5 drinks/day), Non excessive consumption.
4. Smoking status: Yes, No, Quit. Yes (smoked at least 100 cigarettes in their lifetime and have smoked in the last 5 days). No (smoked 100 cigarettes in his/her lifetime). Quit (smoked at least 100 cigarettes in his or her lifetime but has smoked in the last 5 days). In the original NHANES survey, responses coded "missing," "refused," or "don't know" were considered missing.
5. Educational background:＜9th grade, 9-11th grade, High school, College or above.
6. PIR category: there were four distinct categories of Poverty Income Ratio(PIR): poor (<1.0), nearly poor (1.0-1.9), middle income

(2.0-3.9), high income (≥4.0).

7. BMI: According to the CDC, the classification of adults aged 20 years and over: Low(＜18.5kg/m2), Normal(≥18.5, ＜25kg/m2), Overweight（≥25kg/m2）.

2.5 Statistical Analysis

Statistical software (R version 4.4.0 and STATA) was used for statistical analysis. A double tailed p-value of <0.05 was considered to indicate statistical significance in all analyses. In descriptive statistics, continuous variables are expressed as mean and standard deviation or median and interquartile range, and categorical variables are expressed as proportion and percentage. One-way ANOVA was used to compare differences in levels of variables among multiple groups. Single-factor and multifactor logistic regression analyses were performed to assess the relationship between CVD, ST and depression.

Covariates were incorporated as gender, age, race, smoking, excessive alcohol consumption, marital status, educational status, PIR, and BMI. To explore the mediating effects of subgroups, we calculated the strength of the association between both depressive symptoms, cardiovascular disease, and ST in the subgroups. To better characterize the associations between ST separately and between depressive symptoms and CVD, we performed nonlinear fitting analyses. Multi-model logistic regression based on cut points was then performed to analyze the association between ST, depression and CVD.

3. Result

3.1 Demographic and Clinical Characteristics of Participants

Characteristics of participants were presented in table 1. In total, 11,667 participants were enrolled in this study. 1,808 of them were diagnosed with depression symptoms (PHQ-9≥10), 9,859 were identified as non-depression. Notably, individuals with depression were more likely to be older, female, poorer, higher level of BMI and high prevalence of CVD. Meanwhile, results showed that depressed individuals usually spent more time in sitting (400±221 minutes).

Table 1 Characteristics of participants by the presence of depression and non-depression.

Variables	Total	Depression	Non-depression	P-Value
	N=11,667	N=1,808	N=9,859	
Age, n (%)				<0.001
18-40	4147 (35.5)	576 (31.9)	3571 (36.2)	
41-60	3903 (33.5)	692 (38.3)	3211 (32.6)	
61-80	3617 (31.0)	540 (29.8)	3077(31.2)	
Gender, n (%)				<0.001
Female	6158 (52.8)	1100 (60.8)	5058 (51.3)	
Male	5509 (47.2)	708 (39.2)	4801 (48.7)	
Race, n (%)				0.165
Mexican-American	1370 (11.7)	189 (10.5)	1181 (12.0)	
Non-Hispanic Black	2653 (22.7)	418 (23.1)	2235 (22.7)	
Non-Hispanic White	5000 (42.9)	805 (44.5)	4195 (42.5)	
Other Race	2644 (22.7)	396 (21.9)	2248 (22.8)	
CVD, n (%)				<0.001
No	10291 (88.2)	1472 (81.4)	8819 (89.5)	
Yes	1376 (11.8)	336 (18.6)	1040 (10.5)	
BMI, kg/m^2	30.1 (7.75)	31.7 (8.69)	29.8 (7.53)	<0.001
Alcohol status, n (%)				<0.001
Excessive consumption	2154 (18.5)	534 (29.5)	1620 (16.4)	
Non excessive consumption	9513 (81.5)	1274 (70.5)	8239 (83.6)	
Smoke status, n (%)				<0.001
No	5548 (47.6)	638 (35.3)	4910 (49.8)	

Quit	2876 (24.7)	407 (22.5)	2469 (25.0)	
Yes	3243 (27.8)	763 (42.2)	2480 (25.2)	
Educational background, n (%)				<0.001
＜9th grade	668 (5.7)	152 (8.4)	516 (5.2)	
9-11th grade	1398 (12.0)	318 (17.6)	1080 (11.0)	
High school	2726 (23.4)	464 (25.7)	2262 (22.9)	
College or above	6875 (58.9)	874 (48.5)	6001 (60.9)	
Marital status, n (%)				<0.001
Married/living with partner	6505 (55.8)	804(44.5)	5701 (57.8)	
Single/divorced/widowed	5162 (44.2)	1004 (55.5)	4158 (42.2)	
PIR	2.48 (1.62)	1.79 (1.41)	2.61 (1.63)	<0.001
PIR category, n (%)				<0.001
High income	3006 (25.8)	220 (12.2)	2786 (28.3)	
Middle income	3219 (27.6)	391 (21.6)	2828 (28.7)	
Nearly poor	2929 (25.1)	559 (30.9)	2370 (24.0)	
Poor	2513 (21.5)	638 (35.3)	1875 (19.0)	
BMI, n (%)				<0.001
Low, ＜18.5kg/m2	179 (1.53)	33 (1.83)	146 (1.48)	
Normal, 18.5-24kg/m2	2957 (25.3)	373 (20.6)	2584 (26.2)	
Overweight，≥24kg/m2	8531 (73.1)	1402 (77.5)	7129 (72.3)	
Sitting time per day, minutes	383 (205)	400 (221)	379 (202)	<0.001
PHQ-9 Score	5.17 (4.87)	14.5 (4.40)	3.45 (2.32)	<0.001

3.2 Sitting Time in Different Groups

As shown in table 2, participants with a mean sitting time of 382.65(±205.26) minutes. Based on diagnosis of depression and CVD, we categorized participants into four groups: “CVD without depression” group, “Depression with CVD” group, “Depression without CVD” group, and “Without depression and CVD” group. Result showed participants with depression and CVD had more sitting time compared to those without depression or CVD. And it showed a statistically significant difference among four groups (F = 13.24, P<0.001).

Table 2 Sitting time(minutes) in different groups

Variable	n (%)	Mean ± SD	Statistics	P
Total, n (%)	11667 (100)	382.65 ± 205.26		
CVD without depression	1040 (8.9)	396.27 ± 199.18	F = 13.24	<0.001
Depression with CVD	336 (2.9)	440.54 ± 240.59		
Depression without CVD	1472 (12.6)	391.20 ± 215.59		
Without depression and CVD	8819 (75.6)	377.41 ± 202.30		

SD: standard deviation
CVD: cardiovascular disease
F: ANOVA

3.3 Associations between ST, CVD and Depression

In the regression analysis, depression as a dependent binary outcome, using cardiovascular disease (dichotomized) and sitting time (continuous variable measured in hours) as exposure factor. Significant positive correlation was found between CVD and depression(OR:4.56, 95% CI: 1.47-2.02, P＜0.001) after adjusting potential confounders (sex, age, race, smoking status, alcohol status, marital status, educational background, PIR and BMI). ST was associated with depression(OR:1.05, 95% CI:

1.04-1.07, P＜0.001). Besides, ST was associated with CVD(OR:38.49, 95% CI: 25.65-51.33, P＜0.001). Gender and alcohol status moderated the relationship between CVD and depression (P for interaction:0.026, 0.034). BMI and excessive alcohol consumption moderated the relationship between ST and depression (P for interaction:0.025, 0.030). Income level moderated the relationship between ST and CVD (P for interaction:＜0.001). After adjusting all confounders, ST was associated with CVD in poor individuals(P＜0.05), but not in high-income individuals (Table 3).

Table 3 Associations between ST, CVD and depression.

		Crude Model			Adjusted Model		
Variables	**n (%)**	**OR (95%CI)**	**P**	**P for interaction**	**OR (95%CI)**	**P**	**P for interaction**
Associations between CVD and depression							
Total, n (%)	11667 (100.0)	1.94 (1.69-2.21)	<0.001		1.72 (1.47-2.02)	<0.001	
Gender, n (%)				0.025			0.026
Female	6158 (52.8)	2.35 (1.95-2.82)	<0.001		2.01 (1.62-2.50)	<0.001	
Male	5509 (47.2)	1.72 (1.40-2.10)	<0.001		1.42 (1.11-1.81)	0.005	
Alcohol status, n (%)				0.004			0.034
Yes	2154 (18.5)	1.34 (1.05-1.72)	0.019		1.39 (1.04-1.85)	0.024	
No	9513 (81.5)	2.06 (1.75-2.42)	<0.001		1.91 (1.58-2.31)	<0.001	
Associations between ST and depression							
Total, n (%)	11667 (100.0)	1.03 (1.02-1.04)	<0.001		1.05 (1.04-1.07)	<0.001	
BMI, n (%)				0.014			0.025
Low	179 (1.5)	1.20 (1.06-1.37)	0.004		1.17 (1.01-1.37)	0.043	
Normal	2957 (25.3)	1.00 (0.97-1.04)	0.845		1.03 (1.00-1.07)	0.077	
Overweight	8531 (73.2)	1.03 (1.02-1.05)	<0.001		1.06 (1.04-1.08)	<0.001	
Excessive alcohol consumption, n (%)				0.003			0.030
Yes	2154 (18.5)	1.07 (1.04-1.10)	<0.001		1.08 (1.05-1.11)	<0.001	
No	9513 (81.5)	1.02 (1.00-1.03)	0.072		1.04 (1.02-1.06)	<0.001	
Associations between ST and CVD							
Total, n (%)	11667 (100.0)	27.70 (16.16-39.23)	<0.001		38.49 (25.65-51.33)	<0.001	

Variables	n (%)	Crude Model OR (95%CI)	P	P for interaction	Adjusted Model OR (95%CI)	P	P for interaction
PIR, n (%)				<.001			<0.001
High Income	3006 (25.8)	7.12 (-21.08-35.31)	0.621		12.81 (-19.61-45.24)	0.439	
Middle Income	3219 (27.6)	19.11 (-3.01-41.23)	0.091		24.89 (-0.42 ~ 50.21)	0.054	
Nearly Poor	2929 (25.1)	70.89 (50.92-90.86)	<0.001		62.41 (39.79-85.03)	<0.001	
Poor	2513 (21.5)	36.83 (13.75-59.91)	0.002		30.59 (5.45-55.74)	0.017	

3.4 Nonlinear Association between ST and Depressive Symptoms /CVD

Logistic regression analysis was performed to evaluate the association between ST and depressive symptoms/CVD. Besides, curve fitting and threshold effect analyses were also performed to characterize the association. Result showed that the associations were non-liner (Figure 2). The reference value of the curve fitting was 360 minutes for PAD680 (sitting time). According to the cut point, we categorized ST into two groups: <360, ≥360. Result showed that in groups who had sitting time over than 360 minutes per day, they were easier to experience depression (OR:1.18, 95%CI:1.06-1.30). After further adjustment of gender, race, age, BMI, alcohol status, PIR, Smoke status, Education background and marital status (Model 3), the trends remained the same (Table 4). Moreover, we further investigated the associations between different ST and CVD. After adjusting all covariates, result revealed that for shorter ST (less than 360 minutes per day), those participants who had longer ST were more likely to experience CVD (OR:1.40, 95%CI:1.23-1.61, P < 0.001) (Supplementary Table 1).

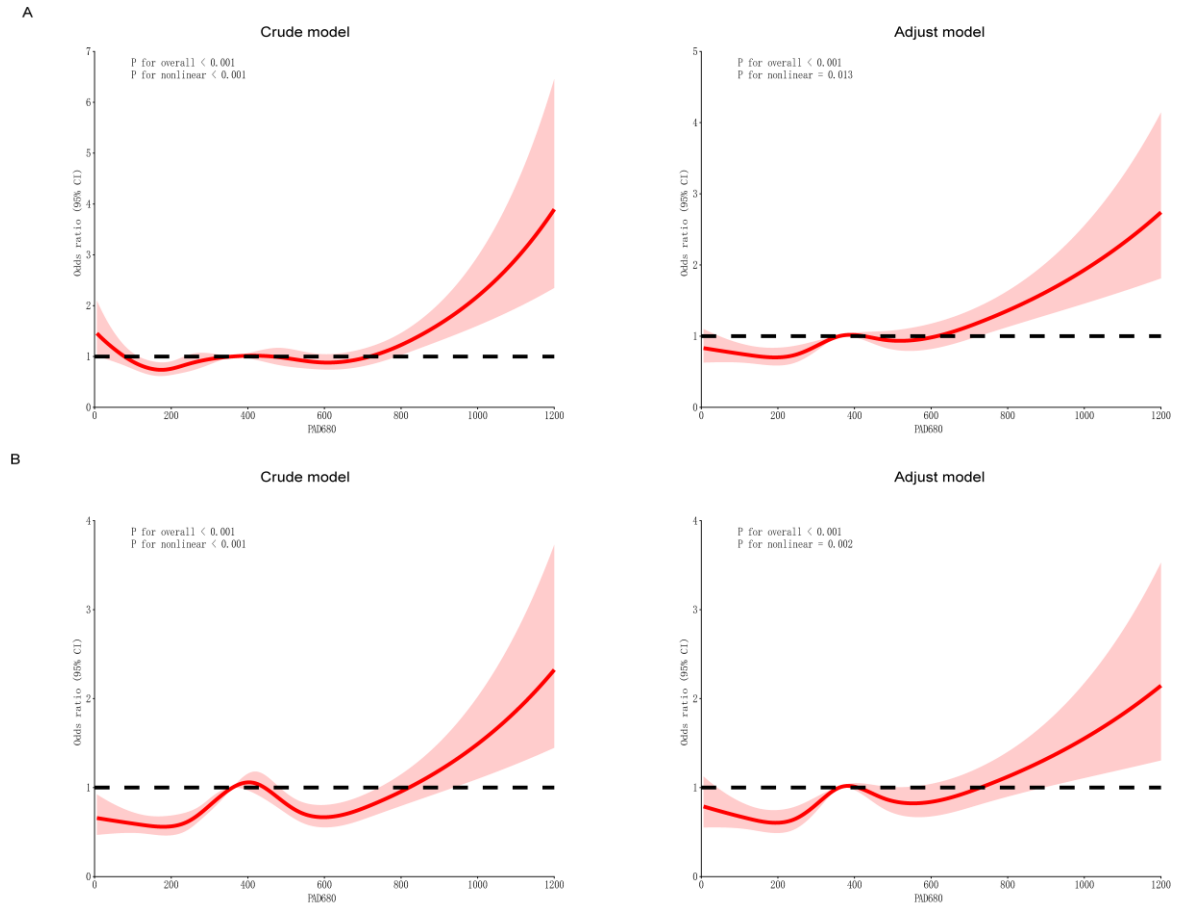

Figure.2. Curve fitting analysis of ST with depressive symptoms, CVD.
A. The relationship between PAD680 (Sitting time, ST) and depression.
B. The relationship between PAD680 (Sitting time, ST) and CVD.
Crude model: unadjusted
Adjust model: gender, race, age, BMI, alcohol status, PIR, Smoke status, Education background, marital status

Table 4 Regression analysis of ST and depression according to cut points.

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Cut points						
<360	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥360	1.18 (1.06-1.30)	0.002	1.17 (1.06-1.30)	0.003	1.36 (1.22-1.52)	<0.001

OR: Odds Ratio, CI: Confidence Interval
Model 1: Crude: unadjusted
Model 2: Adjust: gender, race, age
Model 3: Adjust: gender, race, age, BMI, alcohol status, PIR, Smoke status, Education background, marital status

3.5 Result of Mediation Analysis

In mediation analysis, depression was dependent variable, CVD as the independent variable, and PAD680 (sitting time, ST) as the mediating variable. The result of the mediation analysis signaled that ST mediated the association between CVD and depression (Prop. Mediated:0.0160, ACME: 0.0016 (95%CI : 0.0006-0.0020), Table 5 and Figure 3).

Table 5 Results of mediation effect model on ST, CVD and depression

	Estimate	Lower 95% CI	Upper 95% CI	p-value
ACME	0.0016	0.0006	0.0020	0.002
ADE	0.0995	0.0767	0.1200	<0.001
Total Effect	0.1011	0.0786	0.1200	<0.001
Prop. Mediated	0.0160	0.0059	0.0300	0.002

ACME (Averaged Causal Mediation Effects); ADE (Average Direct Effect); Prop. Mediated (Proportion Mediated, PM)

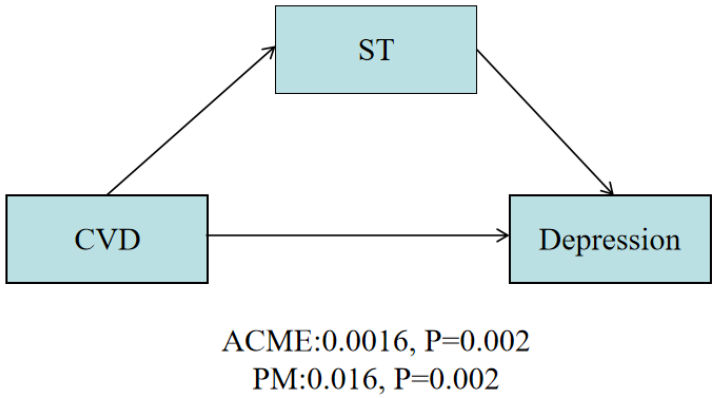

Figure 3 Mediational models

Discussion

The aim of this study was to explore the relationship between CVD and depression in adults and to determine whether this association is mediated by sitting time.

Firstly, in the population-based cross-sectional study, we found that CVD is associated with depression closely, especially in females. Our findings of this study indicate that patients suffering from CVD exhibit an approximate twice elevated probability of developing depression in comparison with those not afflicted with CVD. Wang et al.,(26) also found patients with CVD (28.7%) had depression symptoms, and even 19.3% of them experienced both anxiety and depression symptoms. As is known, depression and cardiovascular health are interconnected(27). A mendelian randomization study found causality was inferred between depression and CVD(28) and it has been confirmed through many years of research. But the mechanism is under-explored. Experts thought inflammation involving specific cytokines, for example, C-reactive protein (CRP), is proposed to play an important role in bridging the link between depression and CVD. This is need to validate in further research.

Secondly, it is important to note that mentally active sedentary behaviors has been found to be associated with positive emotional responses and mental health. The prevalence of mentally active sedentary behaviors in the workplace has the potential to act as a protective factor against depressive episodes(29). In this study, we want to focus on passive sedentary behaviors. The result showed that prolonged sitting is associated with depression. And it has been demonstrated that an increase of one hour of sitting time per day, resulting in increasement of the depression prevalence. Compared with individuals with normal BMI, we found that individuals of both higher and lower BMI are at greater risk of depression as the amount of time spent sedentary increases. One plausible explanation for its mechanism of action is the time substitution hypothesis(30). The hypothesis suggests that individuals have a limited amount of time to be active during the day, and that as the amount of time they spend using mobile phones or other sedentary activities increases, the amount of time they spend in other social activities decreases, leading to decreased social engagement and low mood, which can lead to depression or other psychological problems. In addition, some studies have found that increased levels of pro-

inflammatory factors and reduced anti-inflammatory effects triggered by sedentary behaviors are associated with depressive symptoms(31).

In our study, participants with depression and CVD usually had more sitting time compared to those without depression or CVD. After adjusting all covariates, compared with ST less than 6 hours/day, strong relationship existed between ST and depression among individuals with longer ST. A large prospective cohort study identified that compared with ST<5 hours/day, the risk of cardiovascular disease increased by 7%, 27%, and 51% for ST 5-8, 8-10, and ≥10 hours/day respectively, and the risk of cardiovascular disease was highest in those who were sedentary for ≥10 hours/day and who were moderately or severely physically active for <150 minutes/week(32). The mechanisms why sedentary behaviors leading to CVD is not well-understand. It is hypothesized by researchers that there is a strong association with defective lipoprotein metabolism, early atherosclerosis, insulin resistance and the development of metabolic syndrome(33). Interestingly, we found the association between ST and CVD was stronger in poor groups. A cohort study including 105 677 participants from 21 countries found that higher ST was associated with an increased risk of CVD, and the association was more pronounced in low-income and lower-middle–income countries(34). In a low poverty-income ratio family, viewing television is more common. By contrast, high-income family will spend more time in occupational sitting and they prefer to choose a healthier lifestyle(35). Meanwhile, having a low family-poverty-income ratio correlate with negative emotion(36). Emotions are an important expression of the inner state of human beings, directly affecting an individual's mental health and quality of life(37). Sedentary behaviors is directly manifested in a significant lack of social engagement in individual behaviors, increased levels of psychological repression, finally increased the risk of depression(38). Then depression has a negative impact on risk of CVD.

Lastly, our finding suggests that ST mediates the association between CVD and depression (PM:1.6%). According to the existing studies(39), it is believed that prolonged ST can cause physical and mental health problems. A study reported that (neutrophil-to-lymphocyte ratio, NLR) partially mediates a modest yet statistically significant portion (1.920 %, p = 0.014) of the association between sedentary behavior and depression(40). It indicates that a reduction in sedentary time may be a factor in the control of systemic inflammation, and that this, in turn, may ultimately prevent from depression.

This study is our first attempt to identify the mediation effect of ST for CVD on depression. We adjusted for confounding factors including gender, race, age, BMI, alcohol status, PIR, smoke status, educational background and marital status, it produced reliable results. Besides, a curve fitting analysis was done to reveal the non-liner association between CVD, depression and ST.

However, this study has some limitations. First of all, it cannot explain cause and effect because it is a cross-sectional study. Additionally, further blood test results, such as CRP, were not obtained. And a diagnosis of CVD is based on a response to the question “Has a doctor or other health professional ever told you that you have coronary heart disease/stroke/angina/heart attack/heart failure?”, it is with little credibility.

Conclusion

In conclusion, the study found that CVD, sitting time and depression are correlated. And sitting time marginally mediated the association between CVD and depression. It suggests that effective management of sitting time may be a viable strategy for mitigating the impact of cardiovascular disease (CVD) on depression. Future prospective and experimental studies are required to validate the association and underlying mechanisms, as it may help to explore specific interventions targeting at depression through reducing sitting time.

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