General Psychiatry

Effect of gender on the association between cumulative cardiovascular risk factors and depression: results from the US National Health and Nutrition Examination Survey

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To cite: Li S, Jia Z, Zhang Z, *et al*. Effect of gender on the association between cumulative cardiovascular risk factors and depression: results from the US National Health and Nutrition Examination Survey. *General Psychiatry* 2023;**36**:e101063. doi:10.1136/gpsych-2023-101063

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101063).

Received 21 March 2023
Accepted 20 July 2023

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ABSTRACT

Background The comorbidity of cardiovascular disease (CVD) and depression has been well established, as depression usually presents simultaneously with CVD risk factors. However, the potential association between cumulative exposure to CVD risk and depression remains unclear, so we conducted the current investigation. To our knowledge, this is the first study that employs the cumulative risk model to examine the effect of CVD risk factors on depression using nationally representative population and gender, age and CVD status-stratified subpopulations.

Aims To systematically study the possible individual and cumulative effect of 18 CVD risk factors on depression.

Methods A cross-sectional, secondary analysis investigated associations between 18 CVD risk factors and depression. The interaction effect between CVD risk factors and age, gender and CVD status was also examined. Enrolment included 20 816 participants from the US National Health and Nutrition Examination Survey 2005–2016. Participants with Patient Health Questionnaire-9 scores over 15 or who were using an antidepressant were considered depressive; 18 known cardiovascular risk factors were incorporated in the present study.

Results At the individual risk factor level, smoking, drinking, living alone, sleep quality, body mass index, waist circumference and diabetes status had differential associations with depression risk according to the gender, age or CVD status of the participants. Most importantly, gender-stratified cumulative risk analysis indicated that similar depression risk was found in both genders with a small number of CVD risk factors (odds ratio $(OR)_{adjusted}$=1.32; 95% confidence interval (CI): 0.87 to 1.99), but females had a significantly higher depression risk compared with males under high cumulative risk exposure ($OR_{adjusted}$=2.86; 95% CI: 1.79 to 4.59).

Conclusions Clarifying the association of numerous CVD risk factors with depression according to gender, age and overall CVD status may be beneficial for risk stratification and the prevention of depression in clinical practice. Moreover, the observed novel evidence of high cumulative risk exposure-mediated gender disparities in depression risk may shed light on the underlying mechanism of females' greater vulnerability to depression.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depression usually co-occurs with cardiovascular disease (CVD) risk factors. However, risk factors for CVD rarely occur singly in individuals, and the potential association between cumulative CVD risk exposure and depression remains to be elucidated.

WHAT THIS STUDY ADDS

⇒ A higher prevalence of depression was found in participants with greater cumulative risk exposure, and females had a significantly higher depression risk than males with high cumulative risk exposure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The observed high stress-mediated gender disparities in depression risk highlight the importance of depression prevention in females with high cumulative risk exposure.

INTRODUCTION

Cardiovascular disease (CVD) and depression are both major public health issues and represent the leading cause of global death and disability. CVD and depression often occur comorbidly. For instance, 30%–45% of individuals with coronary artery disease manifest symptoms of clinical depression.[1] Moreover, it has been known for decades that 40% of patients with acute myocardial infarction will experience depression.[2] Depressive symptoms can also predict coronary heart disease (CHD) incidence. Moreover, a study of the 2010 Global Burden of Disease estimates suggested that depression be formally listed as a novel risk factor for CHD.[3]

CVD risk factors linked to depression onset in individuals over 65 years include hypertension, hyperlipidaemia and diabetes.[4] An English cohort study found that the inflammatory markers C reactive protein and serum interleukin 6 identified during childhood increased the risk of depression during young adulthood.[5] Depression is also correlated with specific lifestyle behaviours related to CVD, such as smoking, alcohol use, sedentary status, living status, self-rated health and sleep disorder.[6]

Given the close ties between CVD and depression, a comprehensive assessment of the relationship between CVD risk factors and depression is particularly relevant. Significantly, risk factors rarely occur singly in individuals. In approximately 70% of individuals at risk of the illness, a combination of risk factors increases the total risk of CVD.[7] Additionally, metabolic syndrome—a combination of multiple CVD risk factors—highly increases the risk of developing CVD.[8] Published studies mainly focus on the role of single CVD risk factors, so the potential association between cumulative CVD risk exposure and depression remains unelucidated. Thus, we conducted the current investigation to systematically study possible associations between 18 CVD risk factors and depression at both individual and cumulative levels. Our aim is to aid the assessment of depression risk for clinical prevention and provide insights into the underlying pathophysiological mechanisms of depression.

METHODS

Study population

In the 1960s, the US National Health and Nutrition Examination Survey (NHANES) Project began to evaluate the nutritional and health status of adults and children.[9] Interviews (questionnaires on demographic, socioeconomic, nutritional and health-related factors) and laboratory testing (medical, dental and physiological measurements) comprised most of the NHANES data. The study population employed in this cross-sectional study was derived from continuous NHANES 2005–2016 evaluations (n=58 660). In this secondary analysis, we excluded individuals with missing data regarding their depression and demographic status and other related variables such as living status, self-rated health and sleep duration; the result was a study population of 20 816 participants (figure 1). Due to insufficient information on low-density lipoprotein (LDL) cholesterol and triglyceride (TG) levels in much of the collected data, we further reduced the number of participants to 9906 for the LDL and TG analysis (figure 1).

Depression status

The definition of depression for the study was based on the responses to nine questions in the Patient Health Questionnaire-9 (PHQ-9); a participant with a final score over 15 was considered depressive, as reported in a previous study.[10] Moreover, participants in the sample who reported taking antidepressants were also defined as depressive.

CVD risk factors and cumulative risk exposure

The current study included 18 reported CVD risk factors divided into three categories: lifestyle behaviours, biomarkers and chronic disease status. The lifestyle behaviour risk factors included sedentary status, smoking, alcohol use, living status, self-rated health, sleep quality

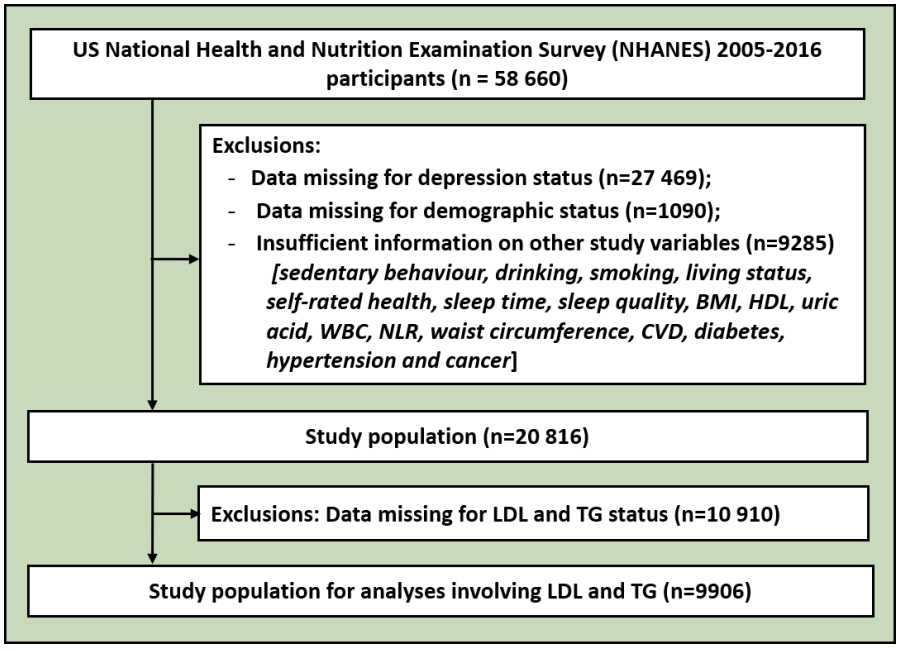

Figure 1 Participant enrolment flow chart for NHANES 2005–2016. BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; NLR, neutrophil–lymphocyte ratio; TG, triglyceride; WBC, white blood cell.

and sleep duration. The biomarker category included levels for high-density lipoprotein (HDL), cholesterol, LDL, TG, uric acid, inflammatory markers (white blood cell (WBC) count and the neutrophil–lymphocyte ratio (NLR)) and adiposity indicators (body mass index (BMI) and waist circumference (WC)). The clinical thresholds for coding biomarkers from continuous to categorical variables were according to the Adult Treatment Panel III guidelines,[11] National Institutes of Health guidelines[12] and other studies[13–15] (online supplemental table 1). The chronic disease status category included CVD, diabetes, hypertension and cancer. For depression prediction by the cumulative risk model, 18 CVD risk factors were dichotomised (ie, 1=high risk, 0=no or low risk) and summed to derive a cumulative risk index; higher scores represented higher levels of cumulative risk exposure of multiple risk factors.

Confounding variables

The potential confounders used for adjustment while investigating the association between CVD risk factors and depression were similar to those used in our previous publication[16]: gender, age, race, education and poverty–income ratio. The latter, the official US Census measure of poverty, evaluates the socioeconomic status of individuals and households within the poverty threshold.

Statistical analysis

Statistical differences in categorical variables between participants were examined by the Rao-Scott χ^2 test. The association between CVD risk factors and depression status was investigated by logistic regression. Because the effects of CVD risk factors on depression differ in specific populations, the possible interaction effect between the CVD risk factors and age, gender or existing CVD status was also examined by adding a multiplicative interaction term to the regression model. For the continuous variables in the CVD risk factors, the dose–response relationship between the variable and depression status was investigated by the three-knot restricted cubic splines.[17] To examine whether the relationship between the cumulative risk index and the PHQ-9 mean score was nonlinear, a quadratic term (squared cumulative risk index) was added in a one-way analysis of variance (ANOVA) that examined the statistical differences of the PHQ-9 mean scores among the groups with a specific number of risk factors. SAS V.9.4 (SAS Institute) was applied for the analyses. Two-tailed tests were used to evaluate statistical significance.

RESULTS

From the NHANES 2005–2016 dataset (n=58 660), a total of 20 816 participants were included in the study population, with 9906 participants specifically considered for LDL and TG analysis. Characteristics of the study samples are shown in table 1. Participants with depression exhibited a range of characteristics. They tended to be female, aged between 40 and 59 years, smokers, living alone, physically inactive, of non-white ethnicity, with lower education levels, income below the median, poor self-rated health, poor sleep quality and shorter sleep duration. Additionally, they had elevated levels of LDL, TG, WBC, BMI, WC, lower levels of HDL, and a history of CVD, diabetes and hypertension.

The association between CVD and depression was identified (odds ratio (OR)=1.36, 95% confidence interval (CI): 1.05 to 1.76, p=0.020) by multivariable-adjusted logistic regression (online supplemental table 2). We then examined the possible associations between numerous CVD risk factors and depression at the individual risk factor level. We found that smoking (OR=1.48, 95% CI: 1.20 to 1.81), living alone (OR=1.55, 95% CI: 1.26 to 1.91), poor self-rated health (OR=4.91, 95% CI: 3.82 to 6.32), poor sleep quality (OR=4.04, 95% CI: 3.18 to 5.13), short sleep time (OR=2.75, 95% CI: 2.14 to 3.52), high WBC level (OR=1.74, 95% CI: 1.28 to 2.36), higher BMI (OR=1.31, 95% CI: 1.00 to 1.72), sedentary behaviour (OR=1.65, 95% CI: 1.29 to 2.12), hypertension (OR=1.92, 95% CI: 1.47 to 2.51) and cancer (OR=1.51, 95% CI: 1.06 to 2.15) were associated with increased risk of depression after confounder adjustment (online supplemental table 2). For BMI and WBC as continuous variables, we also studied the dose–response relationship between these variables and depression by cubic regression spline, which indicated that the ORs of depression increased with the increase in BMI or WBC (online supplemental figure 1). We then investigated the possible interaction effect between each risk factor and gender, age or CVD status by adding a multiplicative interaction term to the main model (online supplemental table 3). Next, gender, age or CVD status-stratified subpopulations were employed to illustrate the differential associations of CVD risk factors with depression. The results indicated that the association between drinking and depression was positive in females but negative in males. Living alone was associated with depression in participants aged 20–59 years, and diabetes was only associated with depression in older adults. Interestingly, BMI had significant interaction effects with gender and age on depression. The stratified analysis showed a negative relationship between BMI and depression in men aged 40–59 years old, while females generally had a positive association between BMI and depression in all age ranges. Moreover, WC was positively associated with depression in individuals with CVD, and no association between smoking and depression was found in this subpopulation (table 2).

We then investigated the possible cumulative effect of these risk factors on depression and found that participants who had multiple risk factors (ie, a higher cumulative risk index) were at higher risk of depression (p_{trend}<0.001, t value=11.35) (online supplemental table 4 and online supplemental figure 2). Similar results were obtained if all risk factors were divided into the lifestyle behaviour, biomarker and chronic disease status categories (all three p_{trend}<0.001, t value=10.56, 12.53 and 10.73,

Table 1 Baseline characteristics of the study population according to depression status

Variables	Overall		Depression		No depression		P value	χ^2
	%	SE	%	SE	%	SE		
Gender								
Male	49.17	0.33	34.57	2.49	49.57	0.33	<0.001	31.76
Female	50.83	0.33	65.43	2.49	50.43	0.33		
Age								
20–39 years	36.84	0.75	34.93	2.52	36.89	0.77	<0.001	35.46
40–59 years	38.84	0.55	48.83	2.40	38.56	0.55		
60–79 years	20.61	0.52	14.69	1.15	20.77	0.53		
≥80 years	3.72	0.19	1.54	0.40	3.78	0.19		
Race								
White	70.89	1.45	64.59	2.80	71.06	1.45	0.009	9.77
Black	10.21	0.74	13.43	1.61	10.12	0.74		
Others	18.90	1.09	21.98	2.27	18.82	1.08		
Education								
<High school	16.32	0.67	27.63	2.39	16.01	0.68	<0.001	34.22
=High school	22.71	0.58	27.54	2.44	22.58	0.58		
>High school	60.97	1.02	44.83	2.98	61.41	1.02		
PIR								
<1	13.59	0.59	32.23	2.18	13.08	0.57	<0.001	142.22
1<PIR≤median	30.42	0.68	40.26	2.16	30.15	0.68		
>Median	55.99	1.02	27.52	2.52	56.77	1.01		
Smoking	46.05	0.71	59.78	2.58	45.68	0.70	<0.001	28.64
Alcohol use	77.71	0.75	76.20	1.93	77.75	0.76	0.419	0.66
Sedentary	35.19	0.82	43.29	3.02	34.97	0.84	0.009	7.18
Living alone	35.43	0.74	50.83	2.28	35.01	0.75	<0.001	44.03
Poor self-rated health	16.00	0.46	55.80	2.80	14.92	0.44	<0.001	160.75
Poor sleep quality	8.54	0.26	30.58	1.94	7.94	0.26	<0.001	95.31
Short sleep duration	12.96	0.33	34.42	2.47	12.38	0.34	<0.001	65.98
HDL (≤40 mg/dL)	19.26	0.47	23.10	1.95	19.16	0.47	0.040	4.34
LDL (≥160 mg/dL)*	10.30	0.38	14.41	1.97	10.21	0.40	0.041	4.18
TG (≥200 mg/dL)*	12.13	0.47	19.25	3.02	11.97	0.44	0.016	6.06
Uric acid								
≥6.0 mg/dL (female)	19.08	0.44	23.13	2.20	18.97	0.45	0.060	3.64
≥7.0 mg/dL (male)								
WBC (≥11×10^9/L)	5.20	0.21	12.07	1.61	5.02	0.20	<0.001	18.31
NLR (≥3.5)	9.59	0.30	12.02	1.65	9.52	0.30	0.138	2.24
WC								
≥88 cm (female)	55.32	0.69	68.54	2.85	54.96	0.71	<0.001	19.63
≥102 cm (male)								
BMI (>25 kg/m^2)	69.34	0.62	77.20	2.39	69.13	0.64	0.002	9.75
CVD	6.44	0.23	10.63	1.07	6.32	0.23	<0.001	15.64
Diabetes	8.42	0.25	13.26	1.18	8.29	0.25	<0.001	18.28
Hypertension	31.14	0.58	46.13	2.94	30.73	0.58	<0.001	23.69
Cancer	9.41	0.28	11.93	1.66	9.34	0.28	0.127	2.38

*A sample of 9906 participants was employed for analyses involving LDL and TG.
%, weighted per cent; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NLR, neutrophil–lymphocyte ratio; PIR, poverty–income ratio; SE, standard error; TG, triglyceride; WBC, white blood cell; WC, waist circumference.

Table 2 OR for depression by status of CVD risk factors in gender/age/CVD status-stratified populations

		Depression			
		Model 1	Model 2	Model 3	Model 4
Variables	N	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender/drinking status					
Male, no drinking	1681	1	1	1	1
Male, drinking	8632	0.59 (0.41 to 0.85)	0.62 (0.43 to 0.90)	0.57 (0.38 to 0.84)	0.57 (0.38 to 0.84)
Female, no drinking	4024	1	1	1	1
Female, drinking	6479	1.32 (1.02 to 1.71)	1.59 (1.21 to 2.10)	1.48 (1.13 to 1.93)	1.52 (1.16 to 1.99)
Age group/living status					
20–39 years, not living alone	4108	1	1	1	1
20–39 years, living alone	3153	1.58 (1.12 to 2.25)	1.45 (0.99 to 2.14)	1.53 (1.03 to 2.26)	1.59 (1.07 to 2.35)
40–59 years, not living alone	4556	1	1	1	1
40–59 years, living alone	2319	2.69 (1.96 to 3.70)	1.88 (1.30 to 2.71)	1.86 (1.28 to 2.70)	1.84 (1.25 to 2.69)
≥60 years, not living alone	3972	1	1	1	1
≥60 years, living alone	2708	1.38 (0.97 to 1.97)	0.92 (0.59 to 1.45)	0.89 (0.57 to 1.42)	0.91 (0.57 to 1.43)
Age group/diabetes					
20–39 years, no diabetes	7105	1	1	1	1
20–39 years, has diabetes	156	2.71 (1.15 to 6.41)	2.56 (1.07 to 6.14)	0.44 (0.19 to 1.03)	1.86 (0.76 to 4.59)
40–59 years, no diabetes	6103	1	1	1	1
40–59 years, has diabetes	772	1.41 (1.02 to 1.94)	1.10 (0.81 to 1.49)	0.99 (0.71 to 1.38)	0.76 (0.51 to 1.12)
≥60 years, no diabetes	5247	1	1	1	1
≥60 years, has diabetes	1433	2.67 (1.88 to 3.79)	2.27 (1.64 to 3.15)	0.49 (0.34 to 0.70)	1.87 (1.31 to 2.67)
Gender/age group/BMI					
Male, 20–39 years, BMI <25 kg/m^2	1248	1	1	1	1
Male, 20–39 years, BMI >25 kg/m^2	2291	0.75 (0.41 to 1.39)	0.80 (0.43 to 1.50)	0.80 (0.43 to 1.50)	0.75 (0.39 to 1.42)
Male, 40–59 years, BMI <25 kg/m^2	751	1	1	1	1
Male, 40–59 years, BMI >25 kg/m^2	2660	0.58 (0.29 to 1.16)	0.65 (0.33 to 1.29)	0.66 (0.34 to 1.28)	0.47 (0.24 to 0.91)
Male, ≥60 years, BMI <25 kg/m^2	836	1	1	1	1
Male, ≥60 years, BMI >25 kg/m^2	2527	1.94 (0.79 to 4.80)	2.13 (0.89 to 5.08)	2.12 (0.87 to 5.16)	2.14 (0.86 to 5.32)
Female, 20–39 years, BMI <25 kg/m^2	1413	1	1	1	1
Female, 20–39 years, BMI >25 kg/m^2	2309	2.39 (1.45 to 3.94)	2.08 (1.26 to 3.43)	2.06 (1.24 to 3.41)	1.81 (1.07 to 3.05)
Female, 40–59 years, BMI <25 kg/m^2	959	1	1	1	1
Female, 40–59 years, BMI >25 kg/m^2	2505	2.24 (1.31 to 3.84)	1.78 (1.05 to 3.03)	1.80 (1.06 to 3.06)	1.66 (0.95 to 2.89)
Female, ≥60 years, BMI <25 kg/m^2	896	1	1	1	1
Female, ≥60 years, BMI >25 kg/m^2	2421	4.63 (2.10 to 10.21)	4.23 (1.93 to 9.28)	4.31 (1.96 to 9.46)	3.64 (1.63 to 8.13)
CVD/smoking status					
CVD, no smoking	640	1	1	1	1
CVD, smoking	1041	1.09 (0.69 to 1.72)	0.92 (0.55 to 1.53)	0.96 (0.58 to 1.61)	1.00 (0.59 to 1.68)
No CVD, no smoking	10565	1	1	1	1
No CVD, smoking	8570	1.80 (1.46 to 2.23)	1.65 (1.33 to 2.05)	1.60 (1.29 to 1.99)	1.54 (1.24 to 1.91)
CVD/sleep status					
CVD, no poor sleep quality	1366	1	1	1	1
CVD, poor sleep quality	315	2.39 (1.40 to 4.07)	2.18 (1.29 to 3.69)	1.95 (1.13 to 3.36)	1.90 (1.09 to 3.31)
No CVD, no poor sleep quality	17716	1	1	1	1
No CVD, poor sleep quality	1419	5.52 (4.47 to 6.83)	5.44 (4.31 to 6.87)	4.97 (3.87 to 6.40)	4.54 (3.49 to 5.91)
CVD/WC					
CVD, WC: <88 cm (female); <102 cm (male)	498	1	1	1	1
CVD, WC: ≥88 cm (female); ≥102 cm (male)	1183	2.94 (1.73 to 4.99)	2.89 (1.68 to 4.97)	2.46 (1.18 to 5.11)	2.34 (1.09 to 5.02)

Continued

Table 2 Continued

Variables	N	Depression			
		Model 1	Model 2	Model 3	Model 4
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No CVD, WC: <88 cm (female); <102 cm (male)	8520	1	1	1	1
No CVD, WC: ≥88 cm (female); ≥102 cm (male)	10615	1.68 (1.25 to 2.26)	1.45 (1.08 to 1.94)	1.23 (0.88 to 1.72)	1.11 (0.80 to 1.55)

Model 1: unadjusted.
Model 2: model 1 adjusted for age, sex, race/ethnicity, education and PIR.
Model 3: model 2 adjusted for smoking, alcohol use, activity and BMI.
Model 4: model 3 adjusted for CVD, diabetes, hypertension and cancer.
The p-value is less than 0.05 if the 95% CI excludes the null value.
BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; N, number; OR, odds ratio; PIR, poverty–income ratio; WC, waist circumference.

respectively). Most importantly, the interaction effect between the cumulative risk exposure level and gender on depression was significant ($p_{interaction}$=0.031, χ^2=6.94). The interaction effects between the cumulative risk exposure level and age ($p_{interaction}$=0.943, χ^2=0.76) or CVD ($p_{interaction}$=0.521, χ^2=1.31) on depression were not significant. This indicated that the association between the cumulative risk exposure level and depression varied across gender. Indeed, similar depression prevalence was found in males and females with a small number of CVD risk factors, but with high cumulative risk exposure, females had a significantly higher depression risk than males (figure 2 and table 3). Similarly, the PHQ-9 mean score difference between males and females was greater with high cumulative risk levels (online supplemental figure 3). One-way ANOVA analysis with a quadratic term indicated that the relationship between the cumulative index and the PHQ-9 mean score was non-linear in males and females (online supplemental table 5). The PHQ-9 score increased slowly when the cumulative exposure was low but increased rapidly under high cumulative exposure. Thus, exposure to an increasing number of CVD risk factors, regardless of their exact nature, disproportionately influenced depression in both genders.

DISCUSSION

Main findings

The incidence and costs of depression continue to increase globally, highlighting the need to understand the involved risk factors better. CVD and depression are highly comorbid, suggesting that CVD risk factors may independently predict depression. Indeed, the vascular depression hypothesis indicates that late-life depression is caused by abnormalities in cerebral vessels that are partly attributed to CVD risk factors.[18] Despite the interrelationship between these two diseases and the potential role of CVD risk factors in the pathogenesis of depression, no study has systematically and comprehensively investigated the individual and cumulative effect of CVD risk factors on depression. Thus, the current work investigated the possible association between each/cumulative index of 18 CVD risk factors and depression in a nationally representative population.

We found that various CVD risk factors were independently associated with depression after a multivariable adjustment. For example, smoking, living alone, poor self-rated health, poor sleep quality, short sleep time, high WBC level, higher BMI, having sedentary behaviour, hypertension and cancer were associated with increased risk of depression after confounder adjustment. The association between several lifestyle behaviours and depression has been identified. For example, adherence to aerobic exercise consistent with public health recommendations is an effective method for treating mild to moderate depression[19]; likewise, our results indicated that sedentary behaviour was significantly associated with depression. Smoking has been reported as a risk factor most closely related to depression, and we consistently observed that smoking was positively associated with depression. Although depression is considered a potential predictor for smoking, a systematic review has also reported a bidirectional relationship between tobacco use and depression.[20] Therefore, further studies are needed to confirm the direction of this relationship. For living status, our results showed that participants living alone had an elevated risk of depression, presumably because living with others can enhance social connections and thus help prevent or alleviate the symptoms of depression.[21] Similarly, participants with poor self-rated health had a significantly higher risk of depression, agreeing with a previous study reporting self-perceived health as an important risk factor for predicting depressive symptoms among American Indians and Alaskan Natives.[21] For sleep-related variables, a previous meta-analysis indicated that sleep disorder is a statistically significant risk factor for depression among older adults in the community.[22] Our data also revealed a significant association between depression and poor sleep quality or short sleep duration in a nationally representative population. Lifestyle behaviours aside, several studies have investigated the association between biomarkers and depression. For instance, a systematic review of observational studies has shown mixed evidence about the association between

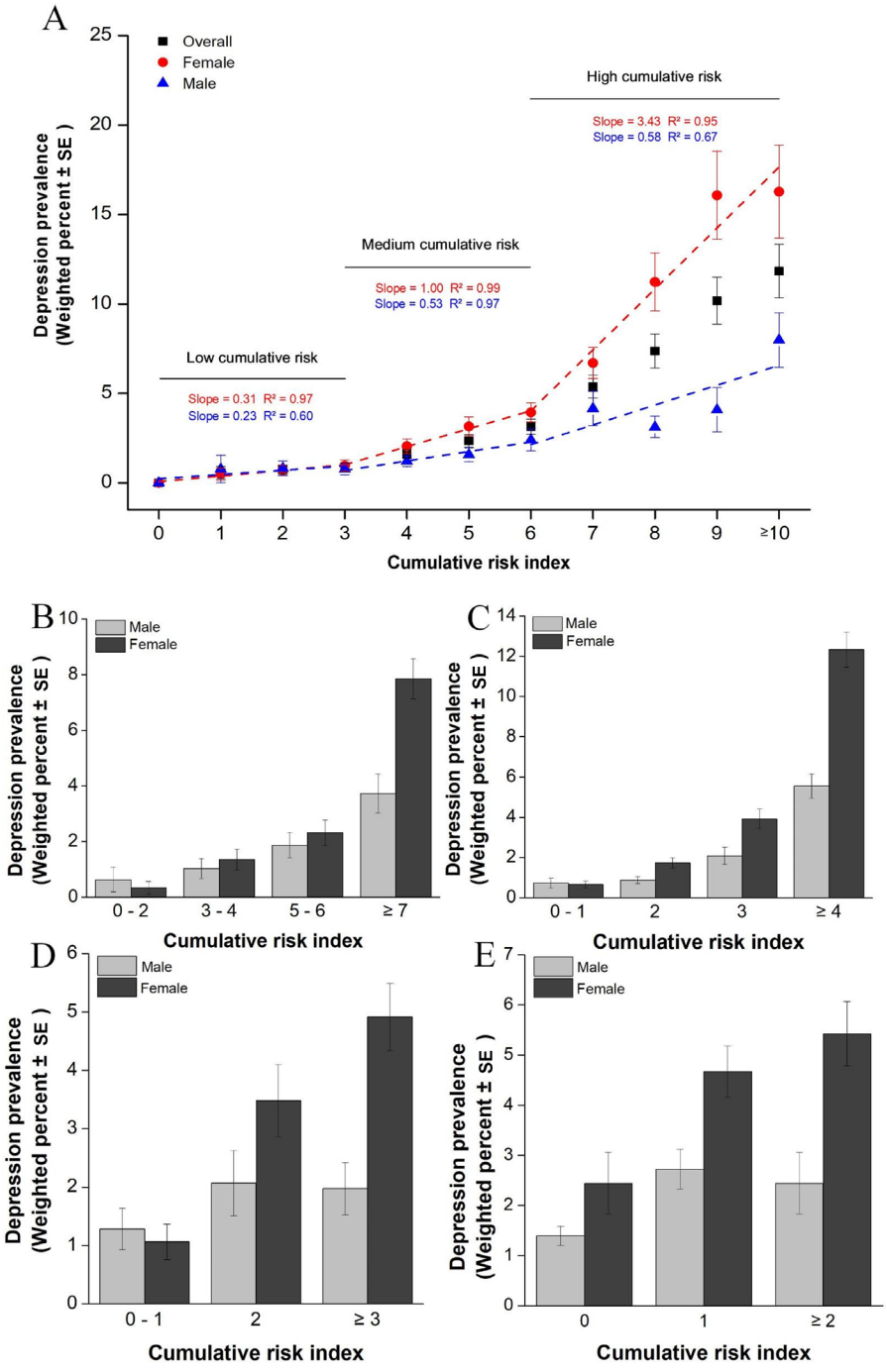

Figure 2 (A) Weighted prevalence of depression according to the cumulative risk index (the number of CVD risk factors) in males and females. The dash lines were linear regression curves generated by separately fitting data points of low, medium and high cumulative risk index in males and females. The slope and R^2 of the fitted curves were given. (B–E) Weighted depression prevalence in males and females with different numbers of all 16 CVD risk factors (N=20 816) (B) and risk factors related to lifestyle behaviours (N=20 816) (C), biomarkers (N=20 816) (D) or status of chronic diseases (N=20 816) (E). CVD, cardiovascular disease. SE, standard error.

LDL cholesterol and depression.[23] In addition, higher TG levels were found in people with depression.[24] In our study population, we found TG, LDL, HDL and uric acid were all associated with depression in crude logistic regression, but no association could be identified after confounder adjustments. In addition, inflammation, a common risk factor for both CVD and depression, has been observed in individuals with depressive symptoms as indicated by elevated levels of circulatory proinflammatory cytokines.[25] Moreover, longitudinal studies have shown that the inflammatory markers of higher C reactive protein or interleukin 6 concentrations in children or adults are related to the elevated risk of depression during subsequent follow-up.[5] Inflammation leads to changes in mood state and autonomic cardiovascular regulation, and the underlying mechanisms may involve increased serotonin

Table 3 OR for depression by gender in CVD risk factor number-stratified populations

	Depression				
		Model 1		Model 2	
	N	OR (95% CI)	P value	OR (95% CI)	P value
Number of risk factors present*	20816				
Male, 0–4 risk factors	4859	1		1	
Female, 0–4 risk factors	5263	1.25 (0.83 to 1.88)	0.28	1.32 (0.87 to 1.99)	0.18
Male, 5–6 risk factors	3209	1		1	
Female, 5–6 risk factors	3065	1.83 (1.23 to 2.73)	<0.01	1.84 (1.22 to 2.77)	<0.01
Male, 7–8 risk factors	1625	1		1	
Female, 7–8 risk factors	1620	2.33 (1.54 to 3.53)	<0.01	2.28 (1.55 to 3.35)	<0.01
Male, ≥9 risk factors	620	1		1	
Female, ≥9 risk factors	555	3.19 (2.05 to 4.98)	<0.01	2.86 (1.79 to 4.59)	<0.01
Number of lifestyle factors present	20816				
Male, 0–2 lifestyle factors	5571	1		1	
Female, 0–2 lifestyle factors	6345	1.49 (1.00 to 2.21)	0.05	1.53 (1.02 to 2.28)	0.04
Male, 3 lifestyle factors	2743	1		1	
Female, 3 lifestyle factors	2355	1.92 (1.21 to 3.04)	<0.01	1.88 (1.19 to 2.96)	<0.01
Male, ≥4 lifestyle factors	1999	1		1	
Female, ≥4 lifestyle factors	1803	2.39 (1.78 to 3.22)	<0.01	2.32 (1.72 to 3.13)	<0.01
Number of biomarkers present†	20816				
Male, 0–1 biomarker	4211	1		1	
Female, 0–1 biomarker	3502	0.97 (0.62 to 1.53)	0.91	1.07 (0.67 to 1.72)	0.76
Male, 2 biomarkers	2887	1		1	
Female, 2 biomarkers	4111	2.09 (1.34 to 3.27)	<0.01	1.99 (1.28 to 3.10)	<0.01
Male, ≥3 biomarkers	3215	1		1	
Female, ≥3 biomarkers	2890	2.77 (2.11 to 3.64)	<0.01	2.56 (1.93 to 3.39)	<0.01
Number of chronic diseases	20816				
Male, 0 chronic disease	6031	1		1	
Female, 0 chronic disease	6068	1.79 (1.31 to 2.45)	<0.01	1.88 (1.37 to 2.59)	<0.01
Male, 1 chronic disease	3031	1		1	
Female, 1 chronic disease	3142	1.75 (1.23 to 2.49)	<0.01	1.67 (1.17 to 2.38)	<0.01
Male, ≥2 chronic diseases	1251	1		1	
Female, ≥2 chronic diseases	1293	2.29 (1.29 to 4.08)	<0.01	2.00(1.12 to 3.58)	0.02

Model 1: unadjusted; model 2: model 1 adjusted for age, sex, race/ethnicity, education and PIR.
*Sixteen factors were included.
†LDL and TG were excluded in the analysis in order to increase sample size.
CI, confidence interval; CVD, cardiovascular disease; LDL, low-density lipoprotein; N, number; OR, odds ratio; PIR, poverty–income ratio; TG, triglyceride.

turnover, oxidative stress and hypothalamic–pituitary–adrenal axis activation.[26] In our analysis, logistic regression revealed that clinically higher levels of WBC, but not NLR, were associated with depression. The association between adiposity and depression is still controversial. Results from a meta-analysis suggest that depression is positively correlated with obesity.[27] However, other studies only weakly support the association between obesity and depression. For instance, one Mendelian randomisation study provided no evidence of causality in obesity as a risk factor for depression.[28] The results of the adiposity indicators in our overall study population supported a significantly positive association between depression and higher BMI but not WC. Moreover, the association between physical health status and depression is inconsistent in the literature. We investigated the possible association between a history of specific chronic diseases and depression; the results showed that, as expected, CVD was associated with depression. Moreover, an increased risk of depression was observed in patients with cancer, possibly

because a cancer diagnosis can induce feelings of anxiety and depression.[29]

Extensive evidence confirms that cumulative risk predicts outcomes more accurately than any single risk factor alone.[30] Therefore, the present study adopted the method of combining multiple risk factors as a cumulative risk index, constructed a cumulative risk index and tested the hypothesis that the incidence of depression increased with the cumulative risk exposure levels. For all the risk factors associated with CVD and those in the three domains, significantly higher depression risk was observed in participants with greater cumulative risk exposure.

Gender difference in disease onset is one of psychiatric research's most widely supported observations.[31] According to a recent meta-analysis of nationally representative samples, the risk of depression in women is about twice that of men,[32] which is consistent with our result that females had an increased prevalence of depression compared with males. Moreover, we found that the association between CVD risk factors and depression varied with gender, based on the interaction effect of CVD risk factors and gender. Our analyses revealed that higher BMI was associated with depression in females but not males, which agreed with the findings of a stronger association between depression and obesity in women than men.[33] Interestingly, the association between drinking and depression was positive in women, but negative in men, leading to its null association in the overall study population. A common limitation of studies investigating risk factors of depression is that these variables usually are studied in isolation. However, risk factors do not exist independently but usually aggregate in one person. Based on the significant interaction effect between gender and the number of CVD risk factors on depression ($p_{interaction}<0.05$), we performed cumulative risk assessment in sex-stratified subpopulations, and the results indicated that females had a similar depression risk compared with males at a low level of cumulative risk exposure ($OR_{adjusted}=1.32$; 95% CI: 0.87 to 1.99). However, a significantly higher depression risk was found for females at a high level of cumulative risk index ($OR_{adjusted}=2.86$; 95% CI: 1.79 to 4.59). Consistent results of the cumulative risk analysis were obtained if only including 10 of the CVD risk factors (sedentary status, smoking, living alone, poor self-rated health, poor sleep quality, sleep duration, WBC, BMI, hypertension and cancer) associated with depression (online supplemental table 6). It is noted that the prevalence of CVD risk factors may vary between males and females (online supplemental figure 4), and they may be prone to have different risk factors at all levels of cumulative risk exposure. However, the number of risk factors has been known to be more indicative of depression risk than the type or nature of risk factors in cumulative risk analysis.[34] Differential coping styles between males and females may serve as an explanation of high cumulative risk-mediated gender disparities in depression prevalence.[35]

Individuals are exposed to different risk factors over their lifespan. We found significant interaction effects between age and living status, BMI or diabetes status, suggesting the associations of these factors with depression were dependent on age. Interestingly, BMI had an interaction effect with both gender and age, which may explain the inconsistency mentioned above about the association between BMI and depression in different study populations in the literature. Our analysis of gender and age-stratified population showed that BMI was generally associated with depression in women of any age range but only in men who were 40–59 years old. It has been known that people with cardiac metabolic diseases are more likely to develop depression compared with healthy individuals.[36] Our data indicated that smoking and poor sleep quality had a stronger association with depression in the population without CVD. In contrast, a positive association between WC and depression could only be identified in participants with CVD. In cumulative risk analyses, there was no interaction effect between the number of CVD risk factors and age/CVD status on depression, suggesting the association between cumulative risk exposure and depression was not dependent on age or CVD status.

Limitations

The current study has several limitations. First, causality or the direction of the association between CVD risk factors and depression could not be determined because of the study's cross-sectional design. As a result, the reverse causality of the observed associations could not be excluded. For example, depression may hinder individuals from living with others, leading to the association between living status and depression. Second, information about the chronic disease status of participants was self-reported. Third, while we have included several important confounding variables in our study, residual confounding factors may remain. Fourth, this study lacked a formal depression diagnosis.

Implications

This is the first study to investigate the individual and cumulative effects of as many as 18 CVD risk factors on depression in a nationally representative population. It illustrated gender differences in the association of cumulative risk exposure with depressive symptoms.

CONCLUSIONS

Depression is a complex multifactorial disease. The current study identified numerous modifiable CVD risk factors that had differential associations with depression according to gender, age or the CVD status of participants. These findings may benefit clinical practice for risk stratification towards depression prevention. Most importantly, our study provided novel evidence of high stress-mediated gender disparities in depression risk by employing the cumulative risk model,

which may help to understand the underlying mechanism of depression vulnerability in females.

Contributors SL and SG designed the study. ZJ carried out the statistical analysis. SL, ZZ and ZJ drafted the manuscript. ZQ, YL, YD and SG critically reviewed the manuscript. SL acts as the guarantor of this study. All authors read and approved the final manuscript.

Funding This study was supported by the National Natural Science Foundation of China (grant no. 81973698 and 81703942), the Young Elite Scientists Sponsorship Program by CACM (grant no. 2019-QNRC2-B08), the BUCM Precision Cultivation Program (grant no. JZPY-202205), the Science Fund for Distinguished Young Scholars in BUCM (grant no. BUCM-2019-JCRC004) and the BUCM Research Development Fund (grant no. 2021-ZXFZJJ-052).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and data analysed in the current study were from NHANES. Protocols involved were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB), and consent from all participants was documented.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data analysed in this study are from NHANES (1999–2016). Data are publicly available and can be downloaded from NHANES website: http://www.cdc.gov/nchs/nhanes.htm.

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