Depression and anxiety both associate with serum level of hs-CRP: a gender- stratified analysis in a population-based study

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Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study

Maryam Tayefi[1*], Mojtaba Shafiee[2*], Seyyed Mohammad Reza Kazemi-Bajestani[1,3,4*], Habibolah Esmaeili[5*], Susan Darroudi[6], Samaneh Khakpouri[2], Maryam Mohammadi[6], Zahra Ghaneifar[1], Mahmoud Reza Azarpajouh[3], Mohsen Moohebati[3], Alireza Heidari-Bakavoli[3], Mohammad Reza Parizadeh[1], Mohsen Nematy[2], Mohammad Safarian[2], Mahmoud Ebrahimi[3], Gordon A. Ferns[7], Naghmeh Mokhber[1,3#], Majid Ghayour-Mobarhan[1,6#]

Affiliations:

1) Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2) Department of Nutrition, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
3) Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
4) Department of Oncology, Faculty of Medicine, University of Alberta, Edmonton, Canada.
5) Department of Biostatistics & Epidemiology, School of Health, Management & Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
6) Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
7) Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK

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[#]**Corresponding Authors:**

Majid Ghayour-Mobarhan MD, PhD, Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, 99199-91766, Mashhad, Iran; Tel:+985138002288, Fax: +985138002287; Email: ghayourm@mums.ac.ir
Naghmeh Mokhber, MD, Biochemistry of Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, 99199-91766, Mashhad, Iran, Tel: +985138002288, Fax: +985138002287; Email: Mokhbern@mums.ac.ir

* Equally contributed as first author

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Abstract

Background: Depression and anxiety are two important mood disorders that are frequently associated with chronic diseases such as cardiovascular diseases (CVDs). Hyper-inflammation is related to both CVDs and psychiatric conditions such as depression and anxiety. Therefore, inflammation may partially explain the relationship between depression and cardiovascular disease.

Objective: The objective of this study was to investigate the association between symptoms of depression/anxiety disorders and serum hs-CRP and inflammation linked conditions in a large Iranian population.

Methods: Symptoms of depression and anxiety disorders and serum hs-CRP levels were measured in 9,759 participants (40% males and 60% females) enrolled in MASHAD study. Symptoms of depression and anxiety were evaluated with Beck Depression and Anxiety Inventories. According to the scores of depression and anxiety, individuals were categorized into four groups of no or minimal, low, moderate and severe categories.

Results: The median serum hs-CRP concentration increased with increasing severity of depression and anxiety disorders. Male participants with severe depression had significantly higher levels of hs-CRP ($p < 0.001$); however, this relationship was less marked among women ($p = 0.04$). Subjects with severe anxiety also had significantly higher levels of hs-CRP ($p < 0.001$). Moreover, women with severe depression and anxiety had higher BMI. There was also a positive association between current smoking habit and depression/anxiety disorders.

Conclusion: Depression and anxiety disorders are associated with elevated levels of hs-CRP, particularly among men. There were also a significant positive association between depression/anxiety disorders and inflammation linked conditions such as smoking and obesity; however, in the case of obesity this association was only present in women.

Keywords: High-sensitivity C-reactive protein; Inflammation; Obesity; Smoking; Depression; Anxiety

1. Introduction

Depression and anxiety are two important psychiatric conditions substantially associated with a variety of chronic conditions including cardiovascular diseases (CVDs) (Anda et al., 1993; Ferketich et al., 2000; Van der Kooy et al., 2007). A heightened inflammatory state relates to an enhanced CV risk (Kazemi-Bajestani et al., 2007; Koenig et al., 1999; Kuller et al., 1996; Ridker et al., 2000). Furthermore, an increased level of serum inflammatory markers associates with both anxiety and depression (Bankier et al., 2008; Danner et al., 2003; Duivis et al., 2013; Elovainio et al., 2009). The exploration of connections between level of inflammation, anxiety/depression and aggravated CV risk factors may elucidate some critical pathophysiologic connections.

C-reactive protein (CRP) is a marker of systemic inflammation that is produced in the liver in response to interleukin-6 (IL-6). Low levels of systemic inflammation may potentiate CV risk, and this may be assessed using high-sensitivity CRP (hs-CRP) assays. Several studies have found that depression is associated with higher levels of pro-inflammatory cytokines and acute phase proteins such as CRP and IL-6 (Baune et al., 2012; Danner et al., 2003; Elovainio et al., 2006; Gimeno et al., 2009). However, there have been some inconsistent reports on the relationship between depression and inflammation, and the role of gender. Although, some studies have shown that gender may influence this relationship and have reported a stronger association between depression and elevated CRP concentrations in men than in women (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Vetter et al., 2013), others have observed similar results for men and women (Davidson et al., 2009; Elovainio et al., 2006). In contrast to these reports, other studies observed no association between depression and CRP concentrations (Annique et al., 2005; Bremmer et al., 2008; Chocano-Bedoya et al., 2014) or have observed an inverse relationship (Camacho et al., 2014; Whooley et al., 2007). Some of these inconsistent findings can be explained by differences in sample size, population samples being investigated (e.g.: clinical samples, cardiac patients and population-based samples), measures to assess depression (clinical diagnosis or questionnaires) and variations in methodology or analysis used. In comparison to depression, fewer studies have been conducted on the association between anxiety and inflammation. However, there are some reports of positive

association between anxiety and inflammation (Bankier et al., 2008; Duivis et al., 2013). Liukkonen et al. (2011) showed that symptoms of anxiety may be associated with an increased levels of serum biomarkers of low-grade inflammation in males, but not in females (Liukkonen et al., 2011).

There are also reports regarding the positive association between depression/anxiety disorders and conditions linked to inflammation such as obesity and smoking (Brown et al., 2000; Collins and Lepore, 2009; de Wit et al., 2010; Gariepy et al., 2010). For instance, de Wit et al. conducted a meta-analysis of cross-sectional studies and observed a significant positive association between depression and obesity in the general population, which appeared to be more marked among women (de Wit et al., 2010). In another systematic review and meta-analysis by Gariepy and colleagues, found a positive association between obesity and anxiety disorders among both sexes (Gariepy et al., 2010). Brown et al. conducted a study on 526 patients aged 18 to 64 and reported an association between smoking behavior and depressive symptoms (Brown et al., 2000). Collins et al., observed a significant association between anxiety and smoking status on a sample of middle-aged black men (Collins and Lepore, 2009). To clarify the association between depression/anxiety disorders and levels of hs-CRP and also inflammation-linked conditions, studies based on wider population samples appear to be necessary.

The primary objective of the present study was to investigate the association between depression/anxiety severity and the presence of a low-grade systemic inflammation as measured by serum hs-CRP levels and other inflammation linked conditions such as obesity and smoking and metabolic syndrome (i.e., cluster of CV risk factors) in a sample of 9759 subjects without a history of cardiovascular diseases who took part in the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study.

2. Materials and Methods

2.1 Study population

A total sample of 9,759 subjects [3903 (40%) males and 5856 (60%) females], were recruited from Mashhad, northeastern Iran, using a stratified-cluster method and derived from the MASHAD

study (Ghayour-Mobarhan et al., 2015). The mean age of men and women were 48.86 y and 47.54 y, respectively. The overall inclusion and exclusion criteria of MASHAD study, the overall study goals and the general characteristics of the sample population such as marriage status, job status, education level, medication use, comorbid conditions, biochemical and anthropometric measurements have been reported earlier (Ghayour-Mobarhan et al., 2015). Of the original, 9908 individuals recruited, 149 participants were excluded (19 with missing data of depression and anxiety, 74 with missing data of hs-CRP, and 56 taking medication for anxiety/depression). All participants gave informed, written consent to contribute in the survey, which was approved by the Ethics Committee of Mashhad University of Medical Sciences.

2.2 Demographic, anthropometric and metabolic data

For all subjects that participated in the study, height (in cm), weight (in kg), body mass index (in kg/m^2) and waist circumference were measured. Body weight was measured to the nearest 0.1 kg with electronic scales, and height and waist circumference were measured to the nearest millimeter with a tape measure. The largest circumference of the buttocks was used for measuring hip circumference, with a flexible tape.

Fasting blood samples were collected after a 12-hour overnight fast to determine fasting blood glucose (FBG) and a full fasted lipid profile, consist of high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol, and triglyceride (TG), as described previously (Emamian et al., 2017; Kazemi-Bajestani et al., 2007; Mirhafez et al., 2014). Serum hs-CRP concentration was estimated using a immunoturbidimetry method, with detection limit of 0.06 mg/L (Pars Azmun, Karaj, Iran) (Kazemi-Bajestani et al., 2017). The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Stone et al., 2005) criteria for metabolic syndrome (MetS) were used in our analysis. According to the ATP II definition, MetS was determined with the presence of 3 or more of the following metabolic abnormalities: (1) waist circumference > 102 cm (40 inches) in men and 88 cm (35 inches) in women, (2) fasting glucose >100 mg/dL, (3) blood pressure (BP) >130/85 mmHg, (4) triglycerides (TG) >150 mg/dL and (5) high-density lipoprotein cholesterol (HDL-C) < 40 in men and <50 mg/dL in women.

2.3 Measurement of depression

The Beck Depression Inventory (BDI) was used in this study (Dozois et al., 1998). This questionnaire contains 21 items and each question is a 4-point scale that provides a score between 0 to 63. Each item represents a single symptom associated with depression, including crying, feelings of hopelessness, fear and loss of appetite, sadness, feelings of guilt, and sleep disturbance over the past 2 weeks (Scogin et al., 1988). The interpretations of scores are as follow: 0-13: no, or minimal depression, 14-19: mild depression, 20-28: moderate depression, and 29-63: severe depression (Scogin et al., 1988). Ghassemzadeh et al. (2005) have validated this questionnaire in its Persian (Farsi) translation, with an acceptable internal consistency (Cronbach's alpha = 0.87) and test-retest reliability (r = 0.74) (Ghassemzadeh et al., 2005).

2.4 Measurement of anxiety

The Beck Anxiety Inventory (BAI) was used for assessing the symptoms of anxiety in this study (Beck et al., 1988). This questionnaire reviews the frequency of symptoms of anxiety in the last week but it can also be used to measure the severity of anxiety (Muntingh et al., 2011). The BDI questionnaire contains 21 items and each item achieves a score between 0 and 3 based on a 4-point Likert scale. Accordingly, the final score can be between 0 (minimum) and 63 (maximum). Cut off scores of this questionnaire are as follows: 0-7= minimal or no anxiety, 8-15= mild anxiety, 16-25= moderate anxiety and 26-63= severe anxiety (Beck et al., 1988). According to a study by Kaviani and Mousavi (2008), the Persian version of BAI has good reliability ($r = 0.83$, $P < 0.001$), validity ($r = 0.72$, $P < 0.001$), and an appropriate internal consistency (Alpha = 0.92) (Kaviani and Mousavi, 2008).

2.5 Statistical analysis

Data analysis was carried out using SPSS-18 software (SPSS Inc., IL, USA). The normality of data was evaluated using Kolmogorov–Smirnov test. Descriptive statistics including mean, frequency, and standard deviation (SD) were determined for all variables and expressed as Mean±standard deviation (SD) for variables with normally distribution or median±IQR for non-

normally distributed variables. For normally distributed variables, analysis of variance (ANOVA) was performed. The Mann-Whitney U test was used for serum hs-CRP since it was a continuous non-normal variable even after logarithmically transformed. All the analyses were two-sided and p-value <0.05 was considered as significant. Chi-square tests were used to compare the qualitative variables. Depression and anxiety scores were divided into categories according to their severity and participants in the first group (no or minimal depression or anxiety) were considered as a reference group. Odds ratios (ORs) with 95% confidence intervals were obtained using regression analysis.

3. Results

Among the 9,759 adults, the average age was 48.0± 8.2 y, with 40% being male. Participants were stratified into depression and anxiety status according to depression and anxiety scores. Clinical and biochemical characteristics of the study population are presented in Table 1. With respect to anxiety, male participants in the group with severe anxiety were significantly younger than those with a normal score (47.5±8.2 y vs. 49.1±8.3 y, p = 0.0xxx). There was no significant difference in total cholesterol between different categories of depression and anxiety among men and women. The severity of depression and anxiety disorders increased with increasing BMI among women. Among both sexes, the percentage of current smokers also increased with increasing severity of depression and anxiety (Table 1). There was a positive association between the levels of serum hs-CRP and the severity of both depression and anxiety disorders; however, with regards to depression this association was much stronger among men. After further stratifying for menopausal status, it was clarified that there was no significant difference in levels of hs-CRP between different categories of depression among postmenopausal women (Table 1).

In all our multivariate analyses, the group who had normal scores for depression, or anxiety, served as a reference group. Multivariate analysis showed that in the mild, moderate and severely affected groups compared with the reference group, a positive current smoking habit, BMI and the levels of hs-CRP were the strongest determinants for the severity of depression and anxiety disorders

(Table 2). Even after adjusting for gender, variables such as BMI, smoking habit, and levels of serum hs-CRP had a significant impact on severity of depression and anxiety disorders (Table 3).

4. Discussion

Our results suggest that higher depression and anxiety scores are associated with an enhanced inflammatory state, as assessed by higher serum hs-CRP levels. In the case of depression, this association was much stronger among men than women. The findings also showed that male participants in the severe anxiety group were significantly younger than other groups. There were a significant positive association between inflammation linked conditions such as smoking and obesity with depression/anxiety disorders; however, in the case of obesity the association was only present in women.

Some previous studies have similarly shown a strong association between depression and elevated serum CRP concentrations, especially among men (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Vetter et al., 2013). Danner et al. (2003) conducted a study in a large representative US sample aged 17 to 39 years who were free of CVD and chronic inflammatory conditions and found a strong association between history of major depressive episode and elevated CRP in men (Danner et al., 2003). Vetter et al. (2013), have reported a significant association between symptoms of major depression and hs-CRP in men only, even after adjusting for confounders such as obesity class, metabolic variables, age, and medication known to affect inflammation (Vetter et al., 2013). Ford et al. (2004), in a large population-based study, also reported a strong association between major depression assessed by Diagnostic Interview Schedule depression questionnaire and levels of CRP among men (Ford and Erlinger, 2004). Elovainio et al. (2009) observed that higher scores on the BDI-21 are related to higher serum CRP levels in both men and women, but this relationship persisted only in men after adjustment for a number of other known risk factors (Elovainio et al., 2009). In contrast to our findings and other previous reports, Ma et al. (2010) conducted a study on 508 healthy adults residing in central Massachusetts and found an independent association between depression scores and hs-CRP among women, but not among men (Ma et al., 2010). However, caution must be

used in interpreting and generalizing these findings since the study sample had a limited range of depression scores and they were predominantly well-educated and employed. These results support the hypothesis that inflammatory biomarkers may partially explain the association between depression and coronary artery disease (CAD) incidence (Surtees et al., 2008) and also perhaps why men are more susceptible to cardiovascular disease associated with depression (Ford et al., 1998; Kamphuis et al., 2006). The menopause and ovariectomy are associated with a low grade systemic inflammation (Abu-Taha et al., 2009), postmenopausal women have significantly higher levels of hs-CRP than premenopausal women which can confound the relationship between depression and hs-CRP among women.

Some authors found no (Annique et al., 2005; Bremmer et al., 2008; Chocano-Bedoya et al., 2014) or even inverse (Camacho et al., 2014; Whooley et al., 2007) association between depression and levels of hs-CRP. Chocano-Bedoya et al. (2014) failed to observe a significant association between markers of inflammation such as CRP, IL-6, and tumour necrosis factor α receptor 2 (TNFα-R2) and incident depression, during a follow-up of 6-18 years (Chocano-Bedoya et al., 2014). However, the lag time between blood sampling, and the assessment of depression in this study may have a considerable impact on the results. Another study that observed no significant association was conducted on participants aged 65 and over who were significantly older than ours (Bremmer et al., 2008). In contrast to our findings, Whooley et al. (2007) found that depression was associated with lower levels of inflammatory markers such as CRP, fibrinogen, and IL-6 (Whooley et al., 2007). The generalizability of the study results is limited by the characteristic of the sample, which consisted of mostly old men with stable CAD. Camacho et al. (2014) also observed an inverse association between depressive symptoms and inflammation (CRP) (Camacho et al., 2014). However, it is possible that the association between depression and inflammation may differs by race (Morris et al., 2011), sex (Vetter et al., 2013), and CRP-related genetic variation (Halder et al., 2010).

There are also several reports of positive associations between anxiety and hs-CRP levels (Bankier et al., 2008; Duivis et al., 2013; Liukkonen et al., 2011; Vogelzangs et al., 2013). Vogelzangs et al. (2013), in a large adult cohort, observed elevated levels of CRP in men, but not in women, with a current anxiety disorder compared with controls after adjustment for socio-

demographic, lifestyle and disease-related covariates (Vogelzangs et al., 2013). Another study showed that anxiety symptoms caused over two-fold increase in the probability for elevated hs-CRP levels in males at population level, after adjusting for confounders such as body mass index, smoking, alcohol intake, systolic blood pressure, physical inactivity, and social class (Liukkonen et al., 2011). Duivis et al. (2013) also reported that somatic symptoms of anxiety are associated with higher levels of CRP, IL-6 and TNF-α, whereas cognitive symptoms of anxiety are associated with CRP in men only (Duivis et al., 2013).

In agreement with our results regarding the positive association between depression and anxiety disorders and BMI among women, Keddie et al. conducted a study on 3,599 non-pregnant women aged 20 years or older and found an association between depression and obesity only in women who were severely obese (Keddie, 2011). In a population-based sample of US women, Ma and colleagues observed increasing risk of depression among women with BMI more than 30 (Ma and Xiao, 2010). Also, in a meta-analysis of cross-sectional studies in the general population the authors found a significant positive association between depression and obesity which appeared to be more marked among women (de Wit et al., 2010). In another systematic review investigating the association between obesity and anxiety disorders, Gariepy et al. concluded that there is a positive association in both men and women (Gariepy et al., 2010).

There are also several studies indicating an increased prevalence of smoking among individuals with mood disorders such as depression and anxiety (Anda et al., 1990; Brown et al., 2000; Collins and Lepore, 2009; Fergusson et al., 2003; Kendler et al., 1993), which are consistent with our findings. Results from a 21-year longitudinal study also revealed that even after control for confounding factors there is yet a possible causal linkage between smoking and depression (Fergusson et al., 2003). Joseph and colleagues conducted a birth cohort of over 1000 individuals and suggested a cause and effect relationship between smoking and depression in which cigarette smoking increases the risk of symptoms of depression (Boden et al., 2010). Collins et al. also conducted a study on a sample of middle-aged black men and observed a significant association between Hospital Anxiety and Depression Scale (HADS) anxiety category and smoking status (Collins and Lepore, 2009).

The strengths of our study include a large sample size, a population-based study, and standardized tools for assesment of depression and anxiety disorders. We acknowledge the limitations in our study, including: (a) the greater percent of study sample was women (60%), (b) some misclassification of depression and anxiety may have occurred due to the use of self-administered tools instead of more accurate face-to-face interviews, and (c) the fact that we had measured both depression and anixety symptoms and inflammation at baseline and we cannot say whether the inflammation preceded the depression or vice-versa. The MASHAD study is a longitudinal cohort and will be continued for at least a decade. We intend to analyze the relationship between aggrevation of depression/anxiety and baseline hs-CRP.

5. Conclusion

In summary, we found that depression and anxiety disorders are associated with elevated levels of serum hs-CRP. We observed a stronger association between depression and inflammation in men. There were also a significant positive association between depression/anxiety disorders and inflammation linked conditions such as smoking and obesity; however, in the case of obesity this association was only present in women.

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Table Legends

Table 1. Values are expressed as mean±SD for variables with normal distribution, and median and interquartile range for non-normally distributed data. BMI: body mass index; hs-CRP: high sensitivity C-reactive protein. *P<0.05; **P<0.01; ***P<0.001.

Table 2. Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests among men and women. BMI: body mass index; hs-CRP: high sensitivity C-reactive protein; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TC: total cholesterol; MetS: metabolic syndrome. *P<0.05; **P<0.01; ***P<0.001.

Table 3. Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests adjusted for sex. BMI: body mass index; hs-CRP: high sensitivity C-reactive protein; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TC: total cholesterol; MetS: metabolic syndrome. *P<0.05; **P<0.01; ***P<0.001.

Table 1. Demographic and biochemical characteristics of individuals in groups of Depression and Anxiety.

			Depression severity				Anxiety severity			
			No or minimal N=6362 (M:45%; F:55%)	Low N=1574 (M:35%; F:65%)	Moderate N=1204 (M:30%; F:70%)	Severe N=619 (M:24%; F:76%)	No or minimal N=5082 (M:48%; F:52%)	Low N=2449 (M:35%; F:65%)	Moderate N=1364 (M:28%; F:72%)	Severe N=864 (M:25%; F:75%)
Age (y)		Male	48.8±8.4	49.2±8.6	48.5±8.6	48.6±7.7	49.1±8.3	48.3±8.7	49.0±8.6	47.5±8.2**
		Female	47.4±8.0	47.9±7.8	47.3±8.5	48.2±8.1	47.3±8.0	47.7±8.0	47.9±8.2	47.5±8.3
Total serum cholesterol (mg/dL)		Male	187.0±37.8	187.9±38.4	182.0±35.6	188.7±41.0	187.0±37.5	185.6±37.0	188.4±40.5	184.5±39.0
		Female	194.5±40.2	194.3±37.6	193.6±39.0	194.3±41.2	193.9±39.6	195.0±39.3	195.0±40.6	193.2±39.2
BMI (kg/m^2)		Male	26.3±4.0	26.7±4.2	25.9±4.5	26.2±4.6*	26.3±4.0	26.3±4.2	26.6±4.4	26.0±4.5
		Female	28.6±4.7	29.1±4.8	29.2±5.0	29.5±5.2***	28.5±4.7	28.9±4.7	29.4±5.1	29.6±4.9***
Current smoking n(%)		Male	682 (23.9)	174 (31.8)	138 (38.2)	68 (46.6)***	600 (24.5)	254 (29.6)	123 (32.2)	85 (39.3)***
		Female	533 (15.2)	183 (17.8)	185 (21.9)	132 (27.9)***	367 (13.9)	297 (18.6)	211 (21.5)	158 (24.4)***
Metabolic syndrome n(%)		Male	686 (24.4)	145 (26.6)	69 (19.1)	30 (20.5)*	579 (24.0)	217 (25.3)	95 (25.1)	39 (18.1)
		Female	1410 (40.5)	429 (42.2)	350 (42.0)	193 (41.2)	1050 (40.3)	645 (41.0)	394 (40.4)	293 (45.5)
Serum hs-CRP (mg/L)		Male	1.35 (0.89-2.61)	1.62 (0.89-3.78)	1.62 (0.92-3.84)	2.09 (1.08-6.22)***	1.37 (0.88-2.64)	1.43 (0.90-2.87)	1.7 (0.95-4.01)	1.68 (1.01-4.27)***
	Female	Total	1.76 (1.04-3.72)	1.95 (1.09-3.96)	1.84 (1.10-4.46)	1.92 (1.06-4.41)*	1.66 (1.02-3.49)	2.01 (1.10-4.36)	1.77 (1.06-3.86)	2.06 (1.19-5.00)***
		Premenopausal (n=3352)	1.57 (0.96-3.29)	1.75 (1.05-3.80)	1.84 (1.05-4.18)	1.70 (0.93-3.82)*	1.51 (0.97-3.20)	1.83 (0.99-3.88)	1.61 (1.00-3.29)	1.90 (0.95-4.75)**
		Postmenopausal (n=1834)	2.07	2.12	2.00	2.35	1.93	2.27	2.15	2.28

			(1.21-4.40)	(1.14-4.18)	(1.23-5.21)	(1.23-4.83)	(1.16-3.74)	(1.21-4.88)	(1.28-4.97)	(1.31-5.85)**

Table 2. The odds ratio of having mild, moderate or severe Depression or Anxiety associated with risk factors and metabolic syndrome among men and women.

		Depression severity			**Anxiety severity**		
		Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group	Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group
Age (y)	Males	1.007 (0.99-1.01)	1.001 (0.98-1.01)	1.002 (0.98-1.02)	0.98 (0.97-0.99)*	0.99 (0.98-1.01)	0.98 (0.96-0.99)*
	Females	1.008 (0.99-1.01)	0.99 (0.98-1.00)	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.01 (1.00-1.02)*	1.00 (0.99-1.01)
Total cholesterol (mg/dL)	Males	1.00 (0.99-1.00)	0.99 (0.99-1.00)*	1.00 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
	Females	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
BMI (kg/m2)	Males	1.02 (0.99-1.04)	0.99 (0.96-1.02)	1.01 (0.96-1.05)	0.99 (0.97-1.02)	1.01 (0.98-1.04)	1.00 (0.96-1.03)
	Females	1.02 (1.00-1.03)**	1.02 (1.00-1.03)*	1.04 (1.01-1.05)**	1.01 (0.99-1.02)	1.03 (1.01-1.05)***	1.04 (1.01-1.05)***
Current smoking n(%)	Males	1.53 (1.25-1.88)***	1.88 (1.49-2.37)***	2.73 (1.93-3.85)***	1.26 (1.06-1.51)**	1.48 (1.16-1.87)**	1.86 (1.39-2.5)***
	Females	1.47 (1.00-1.45)*	1.54 (1.27-1.86)***	2.14 (1.71-2.67)***	1.41 (1.19-1.67)***	1.68 (1.39-2.03)***	1.97 (1.59-2.44)***
Metabolic syndrome n(%)	Males	0.97 (0.77-1.23)	1.26 (0.93-1.70)	1.24 (0.79-1.96)	0.89 (0.72-1.08)	0.97 (0.73-1.28)	1.31 (0.88-1.95)
	Females	1.04 (0.88-1.21)	1.03 (0.86-1.22)	1.21 (0.97-1.51)	1.08 (0.93-1.24)	1.21 (1.02-1.43)*	0.94 (0.77-1.14)
hs-CRP(mg/L)	Males	1.018 (1.00-1.02)**	1.015 (1.00-1.02)*	1.038 (1.02-1.05)***	1.00 (0.99-1.01)	1.017 (1.007-1.028)**	1.024 (1.01-1.03)***
	Females	1.004 (0.99-1.01)	1.014 (1.00-1.02)***	1.007 (0.99-1.01)	1.01 (1.006-1.02)***	1.01 (1.005-1.02)***	1.02 (1.01-1.03)***

Table 3. The odds ratio of being within the mild, moderate and severely affected groups for Depression or Anxiety associated with risk factors and metabolic syndrome adjusted for sex.

	Depression severity			**Anxiety severity**		
	Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group	Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group
Sex	0.66 (0.58-0.75)***	0.51 (0.44-0.58)* **	0.35 (0.29-0.43)* **	0.58 (0.52-0.65)***	0.41 (0.36-0.48)***	0.36 (0.30-0.43)***
Age (y)	1.007 (1.00-1.01)*	1.000 (0.99-1.01)	1.011 (1.00-1.02)*	0.99 (0.99-1.00)	1.00 (0.99-1.01)	0.99 (0.98-1.00)
Total cholesterol (mg/dL)	0.99 (0.99-1.00)	0.99 (0.99-1.00)*	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
BMI (kg/m2)	1.02 (1.00-1.03)**	1.01 (0.99-1.02)	1.03 (1.01-1.05)**	1.01 (0.99-1.02)	1.03 (1.01-1.04)***	1.03 (1.01-1.04)**
Current smoking n(%)	1.35 (1.18-1.55)***	1.70 (1.47-1.97)***	2.39 (1.99-2.87)***	1.35 (1.19-1.52)***	1.61 (1.39-1.86)***	1.97 (1.66-2.33)***
Metabolic syndrome n(%)	1.02 (0.89-1.16)	1.07 (0.92-1.23)	1.21 (1.00-1.47)*	0.99 (0.89-1.12)	1.13 (0.98-1.30)	0.98 (0.82-1.16)
hs-CRP(mg/L)	1.00 (1.00-1.02)**	1.01 (1.00-1.02)***	1.02 (1.02-1.05)***	1.010 (1.004-1.015)**	1.015 (1.01-1.02)***	1.020 (1.01-1.03)***