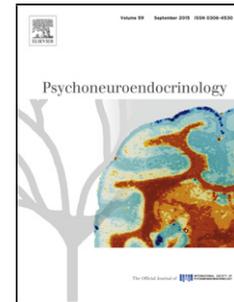


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Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study

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Running title: Association of Depression and Anxiety disorders with Inflammation

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Highlights:

- Depression and anxiety disorders are associated with elevated levels of hs-CRP, especially among men.
- Depression and anxiety disorders also have a significant positive association with inflammation linked conditions such as smoking in both sexes.
- Depression and anxiety disorders also have a significant positive association with inflammation linked conditions such as obesity; however, this association was only present in women.

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 psychological 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 perform a gender-stratified examination of 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) aged 35-65 years, enrolled in a population-based cohort (MASHAD) study in north-eastern Iran. 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. Also, there is 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 is only present in women.

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

1. Introduction

Depression and anxiety are two important psychological 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 perform a gender-stratified examination of 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 MASHAD study is a 10-year cohort study that aims to evaluate the impact of various genetic, nutritional, environmental, and psychosocial risk factors on the incidence of cardiovascular events among a general urban population aged 35-65 years in northeastern Iran (Ghayour-Mobarhan et al., 2015). The mean age of men and women were 48.86 y and 47.54 y, respectively. Moreover, the mean age for premenopausal women was 42.6 ± 5.2 years and that for postmenopausal women was 55.1 ± 5.7 years (unshown data). The overall inclusion and exclusion criteria of MASHAD study 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.

Menopausal status was determined by asking women whether they had passed the menopause and, if so, whether their menopause was natural or surgically induced. Women who reported menses were considered as premenopausal (n=3352) and who reported passing the menopause (not due to pregnancy, medication, or severe weight loss) were defined as postmenopausal (n=1834). Women who had undergone a hysterectomy and/or bilateral oophorectomy were defined as surgically menopausal (n=486). All hormone replacement therapy (HRT) users were determined as hormone users (n=87).

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 \pm standard deviation (SD) for variables with normally distribution or median \pm 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. Multivariate analyses were used to estimate the risk, as approximated by the odds ratio (OR). The odds ratios, with 95% confidence intervals (CI), were obtained using multivariate logistic regression,

in order to determine the influence of potential confounding factors, e.g. age, total cholesterol, BMI, current smoking, and MetS.

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, $p < 0.01$). 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, adjusted for potential confounders, 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. There were also 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). Since 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. Thus, the nonsignificant association between depression and hs-CRP levels among postmenopausal women (shown in the present study) may partly explain the weak association observed between depression and hs-CRP levels among women compared to men.

Some authors found no (Annie 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 (TNF α -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 differ 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). Dixon et al. observed higher scores of BDI in younger subjects, women, and those with poorer body image. Moreover, the authors reported that weight loss was associated with a significant and sustained fall in depression scores especially among those with greater excess weight loss (Dixon et al., 2003). In their review of the literature, Stunkard and colleagues found a relationship between obesity and major depression among women, which was stronger in those of high socioeconomic status. While among men, the authors observed an inverse relationship between depression and obesity, and there was no relationship with socioeconomic status (Stunkard et al., 2003). In a study by Jorm et al., obesity was significantly associated with depression among men; however, this association was weak and inconsistent. While for women, obesity was found to be associated with significantly higher levels of anxiety and depression symptoms (Jorm et al., 2003). In a systematic review investigating the association between obesity and anxiety disorders, Garipey et al. concluded that there is a positive association in both men and women (Garipey et al., 2010). Palinkas et al. examined the association between body weight and depressive symptoms in 2,245 noninstitutionalized men and women aged 50 to 89 and found an inverse association between BDI scores and body weight in men. Similar to other studies, the authors also found overweight and obese women more depressed than healthy-weight women. It was suggested that more stigma is attached to excessive weight in women than men which may result in positive association between body weight and depression in women (Palinkas et al., 1996).

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 controlling 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). Brown et al. suggested an important relationship between cigarette smoking and psychiatric disorders among adolescents, particularly with regard to major depressive disorder, drug abuse, and disruptive behavior disorders (Brown et al., 1996). Evidence concerning the comorbidity between smoking and depression is generally stronger and more consistent than the evidence concerning the comorbidity between smoking and anxiety. Collins et al. 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). In their review of the literature, Morrell and colleagues confirmed that cigarette smoking is highly comorbid with clinical depression and anxiety disorders (Morrell and Cohen, 2006). However, research findings have not yet been able to clarify whether depression/anxiety lead to smoking or whether the reverse is true. Some studies suggested depression/anxiety as a predictor of smoking (Escobedo et al., 1998; Mitchell and Dahlgren, 1986), some of them found current smoking habit as a predictor of depression/anxiety (Boden et al., 2010; Choi et al., 1997; Johnson et al., 2000), and others observed highly significant relationships in both directions (Breslau et al., 1998; Brown et al., 1996).

The strengths of our study include a large sample size, a population-based study, and standardized tools for assessment 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 anxiety 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 aggravation 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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References

- Abu-Taha, M., Rius, C., Hermenegildo, C., Noguera, I., Cerda-Nicolas, J.M., Issekutz, A.C., Jose, P.J., Cortijo, J., Morcillo, E.J., Sanz, M.J., 2009. Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan. *Journal of immunology (Baltimore, Md. : 1950)* 183, 1393-1402.
- Anda, R., Williamson, D., Jones, D., Macera, C., Eaker, E., Glassman, A., Marks, J., 1993. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. *Epidemiology* 4, 285-294.
- Anda, R.F., Williamson, D.F., Escobedo, L.G., Mast, E.E., Giovino, G.A., Remington, P.L., 1990. Depression and the dynamics of smoking: a national perspective. *Jama* 264, 1541-1545.
- Annique, S., Dorien, T., Richel, L., Gunter, K., Joris, D., Harry, J.C., Gert, G., Frank, S., Michael, M., Adriaan, H., 2005. Inflammatory markers in depressed post-myocardial infarction patients. *Journal of psychiatric research* 39, 137-144.
- Bankier, B., Barajas, J., Martinez-Rumayor, A., Januzzi, J.L., 2008. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. *European heart journal* 29, 2212-2217.
- Baune, B., Smith, E., Reppermund, S., Air, T., Samaras, K., Lux, O., Brodaty, H., Sachdev, P., Trollor, J., 2012. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology* 37, 1521-1530.
- Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology* 56, 893.
- Boden, J.M., Fergusson, D.M., Horwood, L.J., 2010. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *The British journal of psychiatry : the journal of mental science* 196, 440-446.

- Bremmer, M., Beekman, A., Deeg, D., Penninx, B., Dik, M., Hack, C., Hoogendijk, W., 2008. Inflammatory markers in late-life depression: results from a population-based study. *Journal of affective disorders* 106, 249-255.
- Breslau, N., Peterson, E.L., Schultz, L.R., Chilcoat, H.D., Andreski, P., 1998. Major depression and stages of smoking. A longitudinal investigation. *Archives of general psychiatry* 55, 161-166.
- Brown, C., Madden, P.A., Palenchar, D.R., Cooper-Patrick, L., 2000. The association between depressive symptoms and cigarette smoking in an urban primary care sample. *International journal of psychiatry in medicine* 30, 15-26.
- Brown, R.A., Lewinsohn, P.M., Seeley, J.R., Wagner, E.F., 1996. Cigarette smoking, major depression, and other psychiatric disorders among adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 35, 1602-1610.
- Camacho, Á., Larsen, B., McClelland, R.L., Morgan, C., Criqui, M.H., Cushman, M., Allison, M.A., 2014. Association of subsyndromal and depressive symptoms with inflammatory markers among different ethnic groups: The multi-ethnic study of atherosclerosis (MESA). *Journal of affective disorders* 164, 165-170.
- Chocano-Bedoya, P.O., Mirzaei, F., O'Reilly, E.J., Lucas, M., Okereke, O.I., Hu, F.B., Rimm, E.B., Ascherio, A., 2014. C-reactive protein, interleukin-6, soluble tumor necrosis factor α receptor 2 and incident clinical depression. *Journal of affective disorders* 163, 25-32.
- Choi, W.S., Patten, C.A., Gillin, J.C., Kaplan, R.M., Pierce, J.P., 1997. Cigarette smoking predicts development of depressive symptoms among U.S. adolescents. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 19, 42-50.
- Collins, B.N., Lepore, S.J., 2009. Association between anxiety and smoking in a sample of urban black men. *Journal of Immigrant and Minority Health* 11, 29-34.
- Danner, M., Kasl, S.V., Abramson, J.L., Vaccarino, V., 2003. Association between depression and elevated C-reactive protein. *Psychosomatic medicine* 65, 347-356.
- Davidson, K.W., Schwartz, J.E., Kirkland, S.A., Mostofsky, E., Fink, D., Guernsey, D., Shimbo, D., 2009. Relation of inflammation to depression and incident coronary heart disease (from the Canadian Nova Scotia Health Survey [NSHS95] Prospective Population Study). *The American journal of cardiology* 103, 755-761.
- de Wit, L., Luppino, F., van Straten, A., Penninx, B., Zitman, F., Cuijpers, P., 2010. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry research* 178, 230-235.
- Dixon, J.B., Dixon, M.E., O'Brien, P.E., 2003. Depression in association with severe obesity: changes with weight loss. *Archives of internal medicine* 163, 2058-2065.

- Dozois, D.J., Dobson, K.S., Ahnberg, J.L., 1998. A psychometric evaluation of the Beck Depression Inventory—II. *Psychological assessment* 10, 83.
- Duivis, H.E., Vogelzangs, N., Kupper, N., de Jonge, P., Penninx, B.W., 2013. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology* 38, 1573-1585.
- Elovainio, M., Aalto, A.-M., Kivimäki, M., Pirkola, S., Sundvall, J., Lönnqvist, J., Reunanen, A., 2009. Depression and C-reactive protein: population-based Health 2000 Study. *Psychosomatic medicine* 71, 423-430.
- Elovainio, M., Keltikangas-Järvinen, L., Pulkki-Råback, L., Kivimäki, M., Puttonen, S., Viikari, L., Räsänen, L., Mansikkaniemi, K., Viikari, J., T RAITAKARI, O., 2006. Depressive symptoms and C-reactive protein: the Cardiovascular Risk in Young Finns Study. *Psychological medicine* 36, 797-805.
- Emamian, M., Hasanian, S.M., Tayefi, M., Bijari, M., Movahedian Far, F., Shafiee, M., Avan, A., Heidari-Bakavoli, A., Moohebaty, M., Ebrahimi, M., Darroudi, S., Zamani, P., Azarpazhooh, M.R., Nematy, M., Safarian, M., Ferns, G.A., Esmaeili, H., Parizadeh, M.R., Ghayour-Mobarhan, M., 2017. Association of hematocrit with blood pressure and hypertension. *J Clin Lab Anal.*
- Escobedo, L.G., Reddy, M., Giovino, G.A., 1998. The relationship between and cigarette smoking in depressive symptoms US adolescents. *Addiction* 93, 433-440.
- Fergusson, D.M., Goodwin, R.D., Horwood, L.J., 2003. Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychological medicine* 33, 1357-1367.
- Ferketich, A.K., Schwartzbaum, J.A., Frid, D.J., Moeschberger, M.L., 2000. Depression as an antecedent to heart disease among women and men in the NHANES I study. *Archives of Internal Medicine* 160, 1261-1268.
- Ford, D.E., Erlinger, T.P., 2004. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Archives of internal medicine* 164, 1010-1014.
- Ford, D.E., Mead, L.A., Chang, P.P., Cooper-Patrick, L., Wang, N.Y., Klag, M.J., 1998. Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch Intern Med* 158, 1422-1426.
- Garipey, G., Nitka, D., Schmitz, N., 2010. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *International journal of obesity (2005)* 34, 407-419.
- Ghassemzadeh, H., Mojtabai, R., Karamghadiri, N., Ebrahimkhani, N., 2005. Psychometric properties of a Persian-language version of the Beck Depression Inventory-Second edition: BDI-II-PERSIAN. *Depression and anxiety* 21, 185-192.

- Ghayour-Mobarhan, M., Moohebati, M., Esmaily, H., Ebrahimi, M., Parizadeh, S.M.R., Heidari-Bakavoli, A.R., Safarian, M., Mokhber, N., Nematy, M., Saber, H., 2015. Mashhad stroke and heart atherosclerotic disorder (MASHAD) study: design, baseline characteristics and 10-year cardiovascular risk estimation. *International journal of public health* 60, 561-572.
- Gimeno, D., Kivimäki, M., Brunner, E.J., Elovainio, M., De Vogli, R., Steptoe, A., Kumari, M., Lowe, G.D., Rumley, A., Marmot, M.G., 2009. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological medicine* 39, 413-423.
- Halder, I., Marsland, A.L., Cheong, J., Muldoon, M.F., Ferrell, R.E., Manuck, S.B., 2010. Polymorphisms in the CRP gene moderate an association between depressive symptoms and circulating levels of C-reactive protein. *Brain, behavior, and immunity* 24, 160-167.
- Johnson, J.G., Cohen, P., Pine, D.S., Klein, D.F., Kasen, S., Brook, J.S., 2000. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Jama* 284, 2348-2351.
- Jorm, A.F., Korten, A.E., Christensen, H., Jacomb, P.A., Rodgers, B., Parslow, R.A., 2003. Association of obesity with anxiety, depression and emotional well-being: a community survey. *Australian and New Zealand journal of public health* 27, 434-440.
- Kamphuis, M.H., Kalmijn, S., Tjhuis, M.A., Geerlings, M.I., Giampaoli, S., Nissinen, A., Grobbee, D.E., Kromhout, D., 2006. Depressive symptoms as risk factor of cardiovascular mortality in older European men: the Finland, Italy and Netherlands Elderly (FINE) study. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 13, 199-206.
- Kaviani, H., Mousavi, A., 2008. Psychometric properties of the Persian version of Beck Anxiety Inventory (BAI). *Tehran University Medical Journal (TUMJ)* 66, 136-140.
- Kazemi-Bajestani, S.M., Tayefi, M., Ebrahimi, M., Heidari-Bakavoli, A.R., Moohebati, M., Parizadeh, S.M., Esmaeili, H., Ferns, G.A., Ghayour-Mobarhan, M., 2017. The prevalence of metabolic syndrome increases with serum high sensitivity C-reactive protein concentration in individuals without a history of cardiovascular disease: a report from a large Persian cohort. *Ann Clin Biochem*, 4563216676842.
- Kazemi-Bajestani, S.M.R., Ghayour-Mobarhan, M., Ebrahimi, M., Ebrahimi, M., Moohebati, M., Esmaeili, H., Ferns, G., 2007. C-reactive protein associated with coronary artery disease in Iranian patients with angiographically defined coronary artery disease. *Clinical laboratory* 53, 49.

- Keddie, A.M., 2011. Associations between severe obesity and depression: results from the National Health and Nutrition Examination Survey, 2005-2006. *Prev Chronic Dis* 8, A57.
- Kendler, K.S., Neale, M.C., MacLean, C.J., Heath, A.C., Eaves, L.J., Kessler, R.C., 1993. Smoking and major depression: a causal analysis. *Archives of general psychiatry* 50, 36-43.
- Koenig, W., Sund, M., Fröhlich, M., Fischer, H.-G., Löwel, H., Döring, A., Hutchinson, W.L., Pepys, M.B., 1999. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 99, 237-242.
- Kuller, L.H., Tracy, R.P., Shaten, J., Meilahn, E.N., Group, M.R., 1996. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *American Journal of Epidemiology* 144, 537-547.
- Liukkonen, T., Räsänen, P., Jokelainen, J., Leinonen, M., Järvelin, M.-R., Meyer-Rochow, V., Timonen, M., 2011. The association between anxiety and C-reactive protein (CRP) levels: results from the Northern Finland 1966 birth cohort study. *European Psychiatry* 26, 363-369.
- Ma, J., Xiao, L., 2010. Obesity and depression in US women: results from the 2005-2006 National Health and Nutritional Examination Survey. *Obesity (Silver Spring, Md.)* 18, 347-353.
- Ma, Y., Chiriboga, D.E., Pagoto, S.L., Rosal, M.C., Li, W., Merriam, P.A., Hébert, J.R., Whited, M.C., Ockene, I.S., 2010. Association between depression and C-reactive protein. *Cardiology research and practice* 2011.
- Mirhafez, S.R., Mohebati, M., Feiz Disfani, M., Saberi Karimian, M., Ebrahimi, M., Avan, A., Eslami, S., Pashar, A., Rooki, H., Esmaeili, H., Ferns, G.A., Ghayour-Mobarhan, M., 2014. An imbalance in serum concentrations of inflammatory and anti-inflammatory cytokines in hypertension. *Journal of the American Society of Hypertension : JASH* 8, 614-623.
- Mitchell, J.E., Dahlgren, L.A., 1986. Prevalence of smoking among psychiatric outpatients. *The American journal of psychiatry* 143, 993-997.
- Morrell, H.E., Cohen, L.M., 2006. Cigarette smoking, anxiety, and depression. *Journal of Psychopathology and Behavioral Assessment* 28, 281-295.
- Morris, A., Zhao, L., Ahmed, Y., Stoyanova, N., Hooper, W.C., Gibbons, G., Din-Dzietham, R., Quyyumi, A., Vaccarino, V., 2011. Association between depression and inflammation—differences by race and sex: the META-Health study. *Psychosomatic medicine* 73, 462.
- Muntingh, A.D., van der Feltz-Cornelis, C.M., van Marwijk, H.W., Spinhoven, P., Penninx, B.W., van Balkom, A.J., 2011. Is the beck anxiety inventory a good tool to assess the severity of anxiety? A

primary care study in The Netherlands study of depression and anxiety (NESDA). *BMC family practice* 12, 66.

Palinkas, L.A., Wingard, D.L., Barrett-Connor, E., 1996. Depressive symptoms in overweight and obese older adults: a test of the "jolly fat" hypothesis. *J Psychosom Res* 40, 59-66.

Ridker, P.M., Hennekens, C.H., Buring, J.E., Rifai, N., 2000. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England Journal of Medicine* 342, 836-843.

Scogin, F., Beutler, L., Corbishley, A., Hamblin, D., 1988. Reliability and validity of the short form Beck Depression Inventory with older adults. *Journal of clinical psychology* 44, 853-857.

Stone, N.J., Bilek, S., Rosenbaum, S., 2005. Recent National Cholesterol Education Program Adult Treatment Panel III update: adjustments and options. *The American journal of cardiology* 96, 53e-59e.

Stunkard, A.J., Faith, M.S., Allison, K.C., 2003. Depression and obesity. *Biological psychiatry* 54, 330-337.

Surtees, P.G., Wainwright, N.W., Luben, R.N., Wareham, N.J., Bingham, S.A., Khaw, K.-T., 2008. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. *American Journal of Psychiatry* 165, 515-523.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A., 2007. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International journal of geriatric psychiatry* 22, 613-626.

Vetter, M.L., Wadden, T.A., Vinnard, C., Moore, R.H., Khan, Z., Volger, S., Sarwer, D.B., Faulconbridge, L.F., 2013. Gender differences in the relationship between symptoms of depression and high-sensitivity CRP. *International Journal of Obesity* 37, S38-S43.

Vogelzangs, N., Beekman, A., De Jonge, P., Penninx, B., 2013. Anxiety disorders and inflammation in a large adult cohort. *Translational psychiatry* 3, e249.

Whooley, M.A., Caska, C.M., Hendrickson, B.E., Rourke, M.A., Ho, J., Ali, S., 2007. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. *Biological psychiatry* 62, 314-320.

Table Legends

Table 1. Values are expressed as mean \pm SD for variables with normal distribution, and median and interquartile range for hs-CRP as a non-normally distributed variable. 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 adjusted for potential confounders. 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 potential confounders in addition to 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/m²)	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 (1.21-4.40)	2.12 (1.14-4.18)	2.00 (1.23-5.21)	2.35 (1.23-4.83)	1.93 (1.16-3.74)	2.27 (1.21-4.88)	2.15 (1.28-4.97)	2.28 (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)***