Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study.

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Psychological and Somatic Symptoms of Anxiety and Risk of Coronary Heart Disease: The HeSSup Prospective Cohort Study

Running Title: Anxiety and Coronary Heart Disease

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ABSTRACT

Background: Despite evidence showing anxiety to be a negative emotion that can be accompanied by various psychological and somatic complaints, previous studies have rarely considered these two components of anxiety separately in relation to CHD events. This study aims to examine the extent to which the psychological and somatic components of anxiety are predictive of CHD.

Methods: This is a prospective population-based cohort study of 24128 participants (9830 men, 14298 women) aged 20-54 years. Psychological and somatic symptoms were assessed at study baseline in 1998. Fatal and non-fatal CHD events during the following 7 years were documented from data on hospitalisations from the National-Hospital-Discharge-Register and mortality records from the Statistics-Finland-Register.

Results: In men, unadjusted hazard ratios for CHD per one-unit increase in mean score were 1.50 (95% CI, 1.21-1.87) for somatic symptoms, and 1.04 (95% CI, 0.85-1.29) for psychological symptoms. After serial adjustment for sociodemographic characteristics, biobehavioural risk factors and clinically-significant symptoms of depression, these associations were completely attenuated. In women, the corresponding unadjusted hazard ratios were 2.25 (95% CI, 1.66-3.06), and 1.55 (95% CI, 1.12-2.13), respectively. The corresponding fully-adjusted hazard ratios were 1.47 (95% CI, 1.04-2.06) and 1.24 (0.91-1.70).

Conclusions: Somatic symptoms of anxiety were robustly associated with an increased risk of CHD in women. This finding lends support to the physiological pathway for the association between psychological factors, anxiety in particular, and CHD

INTRODUCTION

Several observational studies have shown anxiety, or specific features of anxiety such as worry and phobia, to be associated with an increased risk of coronary heart disease (CHD) in both initially healthy and patient populations (1-7); although this finding is not universal. In a systematic review (8) of 12 studies that evaluated clinical endpoints such as myocardial infarction (MI) and cardiac death, five studies reported significant associations, three studies reported marginally significant associations and four studies reported no association between indices of anxiety and cardiac events.

Anxiety is seen as a negative emotion, accompanied by distinct psychological and somatic attributes (9). However, previous studies have rarely considered these two components of anxiety separately in relation to CHD. The psychological symptoms of "prominent tension, worry and feelings of apprehension about everyday events and problems" are common features of anxiety (9). The specific somatic symptoms given prominence in the diagnosis of generalized anxiety disorder include symptoms of autonomic arousal (palpitation, sweating, trembling, dry mouth), chest and abdominal symptoms (difficulty breathing, feeling of choking, chest pain, nausea), and general symptoms (hot flushes or cold chills, numbness or tingling, muscle tension, restlessness and inability to relax, difficulty swallowing) (9).

In this report from the Health and Social Support (HeSSup) study, we used prospective data from a large sample of the Finnish population to examine the extent to which psychological and somatic symptoms of anxiety are predictive of CHD.

METHODS

Population

The Health and Social Support (HeSSup) study is a prospective cohort study on a population sample representative of the Finnish population of the following four age groups: 20-

24, 30-34, 40-44, and 50-54 years at baseline in 1998,(10) a total of 10,628 men and 15,267 women. The Turku University Central Hospital Ethics Committee approved the study.

Anxiety

We assessed both psychological and somatic symptoms of anxiety via a postal survey conducted in 1998 (i.e. at study baseline). This entailed sending a self-administrated questionnaire to all participants.

Psychological symptoms were assessed using the Reeder Stress Inventory (11, 12), a 4-item questionnaire instrument widely used earlier (11-14) that consists of the following statements: 1) "In general I am usually tense or nervous"; 2) "There is a great amount of nervous strain connected with my daily activities"; 3) "At the end of the day I am completely exhausted mentally and physically"; and 4) "My daily activities are extremely trying and stressful". A 5-point scale, with the response choices of "not at all" to "extremely," allowed participants to rate their level of tension or anxiety. Participants indicate the extent to which each statement applies to them using this 5-point Likert scale. The Cronbach's alpha for internal consistency was 0.77. Based of the follow-up questionnaire sent to all participants 5 years later (i.e. 2003) the estimate for the 5-year test-retest reliability was r = 0.53 (p<0.0001).

Somatic symptoms were measured by asking participants to complete a study-designed comprehensive symptom history scale. This 8-item scale measures symptoms that are included in the diagnostic criteria for anxiety disorders in the International Classification of Disease 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (15, 16) and consisting of the following 1) "Palpitation without exercise", 2) "Irregular heartbeat", 3) "Chest pain upon anger or emotion", 4) "Sweating without exercise", 5) "Flushing", 6) "Tremor of hands", 7) "Tremor of voice", 8) "Muscle twitching". The participant is asked whether these symptoms were experienced during the last month, responses are on a 4-point Likert scale from 3=daily or almost daily, 2=weekly, 1=less often, 0=never. The

Cronbach's alpha for internal consistency was 0.77. Based of the follow-up questionnaire sent to all participants 5 years later (i.e. 2003) the estimate for the 5-year test-retest reliability was r = 0.59 (p<0.0001).

The correlation between these sub-components of anxiety was 0.39 (p<0.001), suggesting that they are sufficiently distinct to be considered separately.

Follow-up of Coronary Heart Disease

Participants' personal identification numbers (a unique number assigned to each Finnish citizen) were used to collect data on hospitalisations from the national hospital discharge register as well as mortality data from the Statistics Finland register. These registers provide virtually complete population hospital discharge and mortality data and their diagnoses of fatal and non-fatal CHD events and have been shown to be a valid indicator for hard CHD events when compared with the population-based myocardial infarction register classifying the events according to the 2003 American Heart Association definition (17). For the follow-up, the date and cause of hospitalization and death for all participants who were treated in a hospital or died between January 1, 1999 and December 31, 2005 were obtained (17). CHD was determined by the International Classification of Disease (ICD)-10 codes I20-I25 as the main diagnosis of hospitalisation or death.

Baseline health status

Personal identification numbers were used to link the study participants to their medication records in the National Drug Reimbursement Register kept by the Social Insurance Institution of Finland. From the Drug Reimbursement Register, we identified hypertensive and diabetic participants as well as participants with coronary heart disease. The register contains information on persons entitled to special reimbursement and the date when the special

reimbursement was granted. In Finland, the national sickness insurance scheme covers the whole population and provides basic reimbursement of 50% for all filled prescriptions and special medication reimbursement of 75% or 100% for many chronic and severe diseases. Patients who apply for special reimbursement must attach a detailed medical statement prepared by the treating physician, who also provides data to confirm the diagnosis. The diagnostic criteria of qualification for special reimbursement for hypertension, for example, are a documentation of repeated blood pressure measurements $\geq$200 systolic or $\geq$105 diastolic, or lower figures $\geq$140 systolic or $\geq$95 diastolic with signs of complications or cardiovascular co-morbidities. Similarly, for type 2 diabetes they include disease-specific symptoms and repeated blood (plasma) glucose levels $\geq$7.0 mmol/l; and for coronary heart disease the presence of chronic angina or following myocardial infarction or coronary artery bypass. We identified all participants entitled to special reimbursements for medication for hypertension, diabetes and coronary heart disease in 1998 (ie. the survey year).

A proxy variable for clinically-significant symptoms of depression was assessed using data from the National-Drug-Prescription-Register data. The personal identification number of participants was used to collect data on the dates of purchase of antidepressants (ATC code N06A), bought on prescriptions that can only be written by physicians in Finland. The measures of prescription of medication for diabetes, hypertension and depression were used as covariates and the measure of special reimbursements for coronary heart disease in order to exclude these participants from the present analysis. We also excluded all participants hospitalized in 1998 for ischemic heart disease or cerebrovascular disease using the national hospital discharge register. Thus, the remaining sample consisted of initially healthy participants in relation to the outcome.

Background Variables

All background variables were measured at baseline. Sex, age, education (basic, secondary, lower tertiary, higher tertiary) and marital status (married or cohabiting, other) were

included in the analysis as demographic variables. We assessed four behaviour-related risk factors using standard questionnaire measurements in the baseline survey. Smoking status was measured with a dichotomous variable which describes current smoking (current /never- or ex-smoker). Participants reported the frequency and amount of beer, wine, and spirits they habitually consumed.(18) They were classified as having a high alcohol intake if their weekly consumption exceeded 16 drinks (200 g of alcohol). Body mass index (BMI), calculated from self-reported weight and height, was used to measure obesity (BMI $\geq$30 kg/m^2). Physical activity was calculated by the Metabolic Equivalent Task index to measure sedentary life style (<2 MET-hours per day).(19)

Statistical Analysis

The measures of psychological and somatic symptoms were used in all analyses as continuous variables. We assessed differences in the number of CHD events and differences in psychological and somatic symptoms scores as a function of sample characteristics using the chi-square test and one way analysis of variance with a linear trend fitted across the hierarchical variables, respectively. Pearson correlation coefficient was used to examine the association between psychological and somatic symptoms. This relationship was also modeled by regressing psychological symptoms scores on the presence (responses 1 to 3 on the Likert scale) or absence (response 0 on the Likert scale) of each somatic symptom in logistic models adjusted for sex, age and education.

We examined the association between anxiety symptoms and CHD using four serially adjusted Cox regression models and obtained estimates of the hazards ratios (HRs) and their 95% confidence intervals. The HR in survival analysis is the effect of an explanatory variable on the hazard or risk of an event taking into account the effect of the time to the event. It could be interpreted as relative risk (RR) which is a ratio of the probability of the event occurring in the exposed group versus a non-exposed group. The interaction term for anxiety symptoms and sex

in relation to CHD was significant (all $p<0.05$), leading us to perform analyses separately in men and women. In model 1, anxiety dimensions were the sole independent variables. In model 2, the hazard ratios (HRs) were adjusted for age and education. In model 3, these were then additionally adjusted for current smoking, high alcohol consumption, sedentary lifestyle, obesity, hypertension and diabetes. In model 4, the HRs were additionally adjusted for a proxy variable of clinically significant symptoms of depression as assessed by filled prescriptions for antidepressants. Follow-up period was calculated from January 1, 1999 (the year following the survey) to the date of the outcome of interest, death or, for those who remained disease-free and alive, to the end of the year 2005.

RESULTS

Of the 25 895 respondents to the baseline survey in 1998, 234 had moved abroad, and could not be included in the follow-up. Data on CHD were linked to survey responses from national health registers on the basis of a written consent from 24 128 (93%) participants, the numbers used in the analyses reported here. A total of 209 fatal and non-fatal incident CHD events (clinically verified definite angina pectoris, myocardial infarction, cardiac death) were documented during the follow-up

Table 1 presents differences in the number of CHD events and the sub-components of anxiety consisting of psychological and somatic symptoms as a function of sample characteristics at baseline. Men were more likely to have higher psychological symptoms ($p<0.001$) whereas women scored higher for somatic symptoms ($p<0.001$). Older participants, those with a lower education level, those who were not married or cohabiting, high alcohol consumers, those who were obese and have a sedentary life style, those with hypertension or diabetes, current smokers and those with clinically-significant symptoms of depression had higher levels of psychological and somatic symptoms ($p<0.001$).

Association between psychological and somatic symptoms

Figure 1 illustrates the relationship between a one-unit increase in the psychological symptoms scale and the presence of (either daily, weekly or less often) each somatic symptom. Participants with higher scores on psychological symptoms scale were more likely to report each of the eight somatic symptoms; odds ratio ranging from 1.63 to 2.35 (all $p<0.001$).

Somatic and psychological symptoms and incident CHD risk

Table 2 presents the association of somatic and psychological of of symptoms of anxiety with incident CHD events in analyses stratified by sex. In men, the crude hazard ratios (HR) for CHD per one-unit increase in somatic and psychological subscales were 1.50 (95% CI, 1.21-1.87), and 1.04 (95% CI, 0.85-1.29), respectively. In model 2, when adjustment was made for age and education, these HRs were reduced by up to 66% and were no longer significant at $p<0.05$. Further adjustments for biobehavioural risk factors (model 3) and for clinically-significant symptoms of depression (model 4) further attenuated these associations. The fully adjusted HRs were 1.15 (95% CI, 0.92-1.44) and 0.93 (95% CI, 0.75-1.14).

In women, the crude HRs for CHD per one-unit increase in the somatic and psychological subscales were 2.25 (95% CI, 1.66-3.06), and 1.55 (95% CI, 1.12-2.13), respectively. As in men, adjustment for age and education in model 2 reduced these associations considerably (by up to 43%), but all retained their significance. Further adjustments for biobehavioural risk factors (model 3) and for clinically-significant symptoms of depression (model 4) further attenuated these associations. However, the association with somatic symptoms persisted. The fully adjusted HRs for somatic and psychological symptoms were 1.47 (1.04-2.06) and 1.24 (0.91-1.70), respectively.

Figure 2 and 3 illustrate the association between the frequency of each somatic symptom of anxiety recoded into three categories [often (ie daily or almost daily); less often (weekly or less often); and never] and the risk of CHD in men and women. Only men who reported higher frequency of palpitation without exercise were statistically significant ($p<0.05$) at increased risk

of CHD. In women, those who reported more frequently the occurrence of palpitation without exercise, irregular heartbeat, sweating without exercise, flushing, and muscle twitching were statistically significant ($p<0.05$) at increased risk of CHD.

Sensitivity analyses

To test the robustness of our findings in women, we repeated the analyses excluding CHD events that occurred in the first two years of follow-up. These analyses resulted in a similar pattern of associations as those presented in Table 2. The number of events was reduced by 26% (n=43), but the unadjusted HR remained statistically significant, 2.25 ($p<0.001$) for somatic symptoms, and 1.61 ($p=0.01$) for psychological symptoms. A similar pattern of associations were obtained when the analyses were restricted to acute myocardial infarction (n=22). The corresponding unadjusted HR were 2.34 ($p=0.001$) for somatic symptoms, and 1.23 ($p=0.461$) for psychological symptoms.

DISCUSSION

In this large population sample representative of the Finnish population in four age groups with a 7-year follow-up, psychological and somatic components of anxiety were examined as predictors of CHD. In men, when no adjustment was made, only somatic symptoms were associated with an increased risk of CHD. However, successive adjustments for sociodemographic characteristics, biobehavioural risk factors and clinically-significant symptoms of depression completely attenuated these associations. In women, all markers of anxiety were strongly (HR $\geq$ 1.50) associated with an increased risk of CHD, particularly somatic symptoms. After the successive adjustments, only somatic symptoms of anxiety remained robustly associated with higher incidence of CHD.

There is a long tradition of psychiatric research on health and anxiety-related phenomena (20, 21). To the best of our knowledge, this is the first large-scale prospective population-based

study on the association between the symptom profile (somatic or psychological) of anxiety and the risk of CHD. In contrast to previous empirical studies, the present study includes a large number of men and women; allowing us to perform analysis separately in men and women. The CHD events were ascertained using records on hospitalizations from the Finnish national hospital discharge register and mortality data from the Statistics Finland register. Two validation studies (17, 22) have demonstrated that diagnoses of fatal and non-fatal CHD events and causes of death in these registers were in strong agreement with major coronary event defined by strict clinical criteria, justifying their use as endpoint measures in studies. Strengths of the present study also include the adjustment for a proxy measure of clinically-significant symptoms of depression assessed using pharmacy refill records of antidepressant medications. It should be noted that there was a 6-month lag period between the measurement of anxiety and the start of the follow-up for CHD. This lag period is likely to minimize the effect of overt disease of interest on the measurement of anxiety symptoms. In the same vein, we found a similar pattern of results as those presented in main analyses when analyses were restricted to CHD events that occurred two years after the measurement of anxiety symptoms. We also excluded from the study all participants entitled to special reimbursements for coronary heart disease or those hospitalized in 1998 due to ischemic heart disease or cerebrovascular disease using the national hospital discharge register. The analysis based on initially healthy participants (free of diagnosed CHD) in relation to the outcome suggests that the predictive value of somatic symptoms was not entirely attributable to increased somatic symptoms due to underlying cardiovascular disease at baseline, although an overlap of somatic symptoms between anxiety and CHD cannot be ruled out (23). In addition, we found (Appendix 1) that participants with clinically-significant depression symptoms (based on filled prescriptions for antidepressants drugs) were significantly more likely to report each specific somatic symptoms used in the present study, suggesting that the heightened somatic symptom reports provided by high-anxiety participants at least partly reflect greater responsiveness to psychological distress. We also found

(Appendix 1) corroborative evidence showing that the somatic symptoms correlate strongly and significantly with both somatic and psychological components of the Beck depression Inventory (24); one of the most widely used instruments for measuring the severity of depression. Furthermore, as showed in figure 2, presence of high frequency of specific somatic symptoms was more likely to be associated with an increase risk of incident CHD in women. Finally, we found that the 5-year test-retest reliability of these somatic symptoms score was 0.59. Thus, more enduring frequent somatic symptoms of anxiety are likely to influence the risk of CHD in women.

Evidence from observational studies suggests that anxiety (both anxiety symptoms and diagnosed anxiety disorder) is associated with an increased risk of CHD, even after controlling for traditional CHD risk factors (8, 25). In a relatively recent systematic review, it was concluded that (8) on the basis of the best prospective evidence available from samples without clinical disease at baseline, anxiety appears to be related to an increased risk of developing coronary heart disease. However, only 4 of the 12 studies included in this systematic review were based on anxiety symptoms recorded in an initially healthy population as opposed to diagnosed anxiety disorders in psychiatric outpatients and inpatients (1, 2, 26, 27). Of these four studies, three included only men (1, 26, 27) and the fourth only women (2) with the sample size varying between 749 and 6935 and the follow-up time between 12 and 32 years. Of these studies, three reported anxiety to be a risk factor (1, 2, 26, 27) and one reported mixed findings(26).

Our finding is consistent with at least three previous prospective studies conducted in women-only populations (2, 4, 28). In these studies, phobic anxiety (4), panic attacks (28), and symptoms of tension and anxiety (2) were found to be strongly associated with incident CHD and sudden cardiac death events. The robust association between somatic symptoms of anxiety and the risk of CHD in women compared to men could be related to a gender differences in the experience and impact of anxiety on health. Indeed, we found gender-related differences in

reports of anxiety symptoms, with men scoring higher on psychological symptoms scale and women scoring higher on the somatic symptoms of anxiety (Table 1). Generalized anxiety disorder and panic disorder have been found to be twice as common in women as in men (9, 29). It has also been shown that panic disorder in women tends to be more severe and associated with higher rates of significant co-morbidity such as somatization disorder (30). Moreover, recent data suggest that women reproductive hormones and related cycles, the menopause for example, may play an important role in these differences (31, 32). In order to examine this latter possibility, we tested for an interaction between somatic symptoms of anxiety and age in relation to CHD in women. The result revealed no evidence of significant interaction with age ($p=0.275$). Thus, the finding of a greater impact of somatic symptoms of anxiety on CHD in women needs further investigation in order to understand the sex-specific underlying mechanisms.

An important finding in the present study is that somatic symptoms, not assessed in previous studies, were much stronger and more consistent predictors of CHD relative to psychological symptoms of anxiety. The Normative Aging Study conducted among older men (3) also found the risk of incident myocardial infarction to be higher for the Manifest Anxiety scale assessing both the experience of tension and somatic symptoms of anxiety than for the other scales assessing solely the psychological symptoms of anxiety. This finding suggests that anxiety-related physiological hyperreactivity could be a major mechanistic pathway linking anxiety and CHD. Stressor hyperreactivity has been studied extensively with respect to hostility and anger (33) but less so with respect to anxiety; although somatic symptoms also characterize anxiety.(9) Supporting the potential role of stressor hyperreactivity in CHD, a study conducted in the Pittsburgh Healthy Heart Project (34) showed that the somatic-vegetative symptoms of depression, but not the cognitive-affective symptoms, were associated with a greater 3-year change in carotid intima-media thickness, a valid marker of preclinical atherosclerotic disease (35, 36). Moreover, a recent study (37) conducted among women with suspected myocardial

infarction, found that somatic but not cognitive/affective depressive symptoms were associated with an increased risk of cardiovascular-related mortality and events. The precise mechanism that could explain the current observations needs additional comprehensive studies, but several hypotheses seem plausible. There is some evidence that suggests episodes of anger, anxiety, or depressed mood trigger acute coronary ischemia(38, 39) via an increased platelet activation and altered homodynamic reactivity (40). Panic attacks for instance have been found to be associated with increased sympathetic outflow, a predisposing factor to disturbances in cardiac rhythm and coronary artery vasospasm (41) which might trigger ischemia. It has also been suggested that alterations in cardiac vagal tone may provide another pathophysiological link between anxiety and risk of cardiac morbidity and mortality. Several studies have shown a relationship between panic disorder and increased heart rate (42) that in itself has been found to be associated with an increased risk of acute cardiac events and ventricular arrthymias. Finally, hyperventilation, a common symptom of anxiety, can precipitate coronary artery spasm irrespective of the presence of atherosclerosis (43).

Our results should be interpreted in light of several study limitations. First, the use of self-report measure of psychological and somatic symptoms may have led to underreporting or overreporting of symptoms relative to objective measurement. However, the scales requested information on psychological symptoms of prominent tension; worry and feelings of apprehension about everyday events and problems; and anxiety-related physiological symptoms of autonomic arousal. All these symptoms are included in the diagnostic criteria for anxiety disorders in the ICD-10 and the DSM-IV (15, 16) indicating that these measures satisfy the criteria for good face validity. The items in these two scales also overlap with those in validated scales to measure anxiety by symptoms (44, 45) and both these symptoms and clinically assessed anxiety have been shown to be associated with increased risk of health problems including cardiovascular disease (1, 2, 12, 46). Thus we feel confident that our measure is indeed a valid instrument in detecting individuals liable to anxiety. In addition, we found

somatic symptoms of anxiety to be associated with higher likelihood (Odds Ratio= 2.95, $p<0.001$) of having clinically-significant symptoms of depression in cross-sectional analysis (based on filled prescriptions for antidepressants drugs) and as depression is known to co-vary with anxiety symptoms (47, 48) the validity of our measures is supported. Although antidepressants can be used as a proxy measure of depression, it should be noted that the antidepressants could also be used for the treatment of a range of neuropsychiatric disorders other than depression including anxiety and eating disorders. Moreover, our sensitivity analyses revealed that anxiety was associated with CHD even after the removal of events occurring in the first two years of follow-up.

Conclusions

In this study on working-age adults from a randomly selected population of Finnish men and women initially free from cardiovascular disease we found anxiety, particularly anxiety-related somatic symptoms such as palpitation without exercise, irregular heartbeat, sweating without exercise, flushing, and muscle twitching, to be associated with an increased risk of CHD in women. This finding suggests that individuals are able to assess their physiological responses to anxiety and lends support to the physiological pathway for the association between psychological factors, anxiety in particular, and CHD. This may have clinical significance, as self-perceptions of physiological responses are important part of information processing during diagnostic evaluation of somatic symptoms.

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Table 1- Number of incident Coronary Heart Disease (CHD) Cases and Psychological and Somatic symptoms means scores as a function of baseline characteristics of the participants

	Number of Participants	CHD Cases	Psychological symptoms	Somatic symptoms
Baseline Covariates	**N (%)**		**Means (SD)**	
All	24128 (100)	209 (0.87)	2.31 (0.75)	1.63 (0.60)
Sex				
Men	9830 (41)	151 (1.5)	2.36 (0.76)	1.60 (0.61)
Women	14298 (59)	58 (0.4)	2.28 (0.74)	1.65 (0.59)
Age-group (years)				
20-24	6563 (27)	1 (0.0)	2.23 (0.69)	1.59 (0.52)
30-34	5685 (24)	7 (0.1)	2.30 (0.74)	1.57 (0.55)
40-44	5722 (24)	45 (0.8)	2.35 (0.78)	1.63 (0.62)
50-54	6056 (25)	156 (2.6)	2.36 (0.80)	1.74 (0.67)
Education				
Basic	7568 (32)	94 (1.2)	2.34 (0.78)	1.71 (0.65)
Secondary	5419 (23)	38 (0.7)	2.36 (0.75)	1.64 (0.60)
Lower tertiary	7537 (32)	59 (0.8)	2.26 (0.72)	1.59 (0.55)
Higher tertiary	3224 (14)	18 (0.6)	2.29 (0.73)	1.52 (0.52)
Marital status				
Married/cohabiting	16 108 (67)	156 (1.0)	2.32 (0.76)	1.64 (0.60)
Other	8009 (33)	53 (0.7)	2.29 (0.80)	1.61 (0.58)
Current smoker				
No	16049 (67)	107 (0.7)	2.28 (0.74)	1.59 (0.56)
Yes	6086 (25)	88 (1.4)	2.39 (0.79)	1.73 (0.67)
Missing	1994 (8)	14 (0.7)	2.33 (0.75)	1.61 (0.57)
High alcohol intake ($\geq$200 g/week)				
No	21759 (90)	172 (0.8)	2.30 (0.74)	1.61 (0.58)
Yes	2326 (10)	37 (1.6)	2.46 (0.82)	1.83 (0.70)
Obesity (BMI$\geq$30)				
No	21671 (90)	170 (0.8)	2.30 (0.74)	1.63 (0.58)
Yes	2311 (10)	37 (1.6)	2.45 (0.81)	1.78 (0.68)
Sedentary life style (<2 MET hours/day)				
No	18352 (77)	135 (0.7)	2.28 (0.74)	1.61 (0.57)
Yes	5565 (23)	73 (1.3)	2.43 (0.79)	1.70 (0.66)
Hypertension or diabetes				
No	22997 (95)	162 (0.7)	2.30 (0.75)	1.62 (0.58)
Yes	1132 (5)	47 (4.2)	2.44 (0.83)	1.88 (0.74)
Clinically-significant symptoms of depression (filled antidepressants)				
No	23159 (96)	190 (0.8)	2.29 (0.74)	1.61 (0.57)
Yes	969 (4)	19 (2.0)	2.88 (0.89)	2.18 (0.87)

All associations are significant at $p \leq 0.01$

Table 2-Psychological and Somatic Symptoms and the Risk of Coronary Heart Disease (CHD) in Men and Women.

	Model 1		Model 2		Model 3		Model 4	
Anxiety and types of symptoms	N events/N participants	HR (95%CI)	N events/N participants	HR (95%CI)	N events/N participants	HR (95%CI)	N events/N participants	HR (95%CI)
				MEN				
Somatic Symptoms score								
1-Unit increase	150/9740	1.50 (1.21-1.87) ‡	150/9625	1.28 (1.04-1.58)*	147/9502	1.16 (0.93-1.44)	147/9514	1.15 (0.92-1.44)
Psychological Symptoms Score								
1-Unit increase	147/9761	1.04 (0.85-1.29)	147/9647	0.97 (0.79-1.19)	144/9524	0.94 (0.76-1.15)	144/9536	0.93 (0.75-1.14)
				WOMEN				
Somatic Symptoms score								
1-Unit increase	57/14208	2.25 (1.66-3.06) ‡	57/13967	1.71 (1.24-2.36) ‡	57/13763	1.59 (1.14-2.22) †	57/13776	1.47 (1.04-2.06)*
Psychological Symptoms Score								
1-Unit increase	57/14224	1.55 (1.12-2.13) †	57/13981	1.37 (1.01-1.87)*	57/13779	1.33 (0.98-1.81)	57/13792	1.24 (0.91-1.70)

* p<0.05, †<0.01, ‡ p<0.001
Model 1= crude model.
Model 2= model 1 adjusted for age and education and marital status
Model 3= model 2 additionally adjusted for current smoking, high alcohol intake, sedentary life style, obesity, hypertension or diabetes
Model 4= model 3 additionally adjusted for clinically-significant depressive symptoms (based on prescriptions of antidepressants

Figure 1: Association between one-unit increase in psychological symptoms score of anxiety and each somatic Symptom-Odd Ratio (OR) and Standard Error (SE).

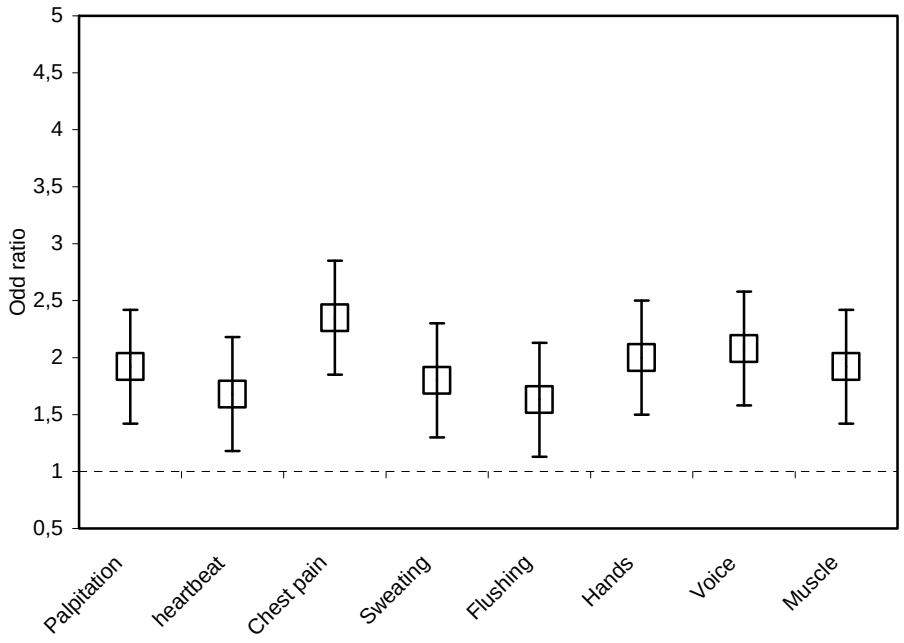


Figure 2: Specific Somatic Symptoms of Anxiety as predictors of Coronary Heart Disease Events in Men-Adjusted for age and education- Hazard Ratio (HR) and 95% Confidence Interval (CI).

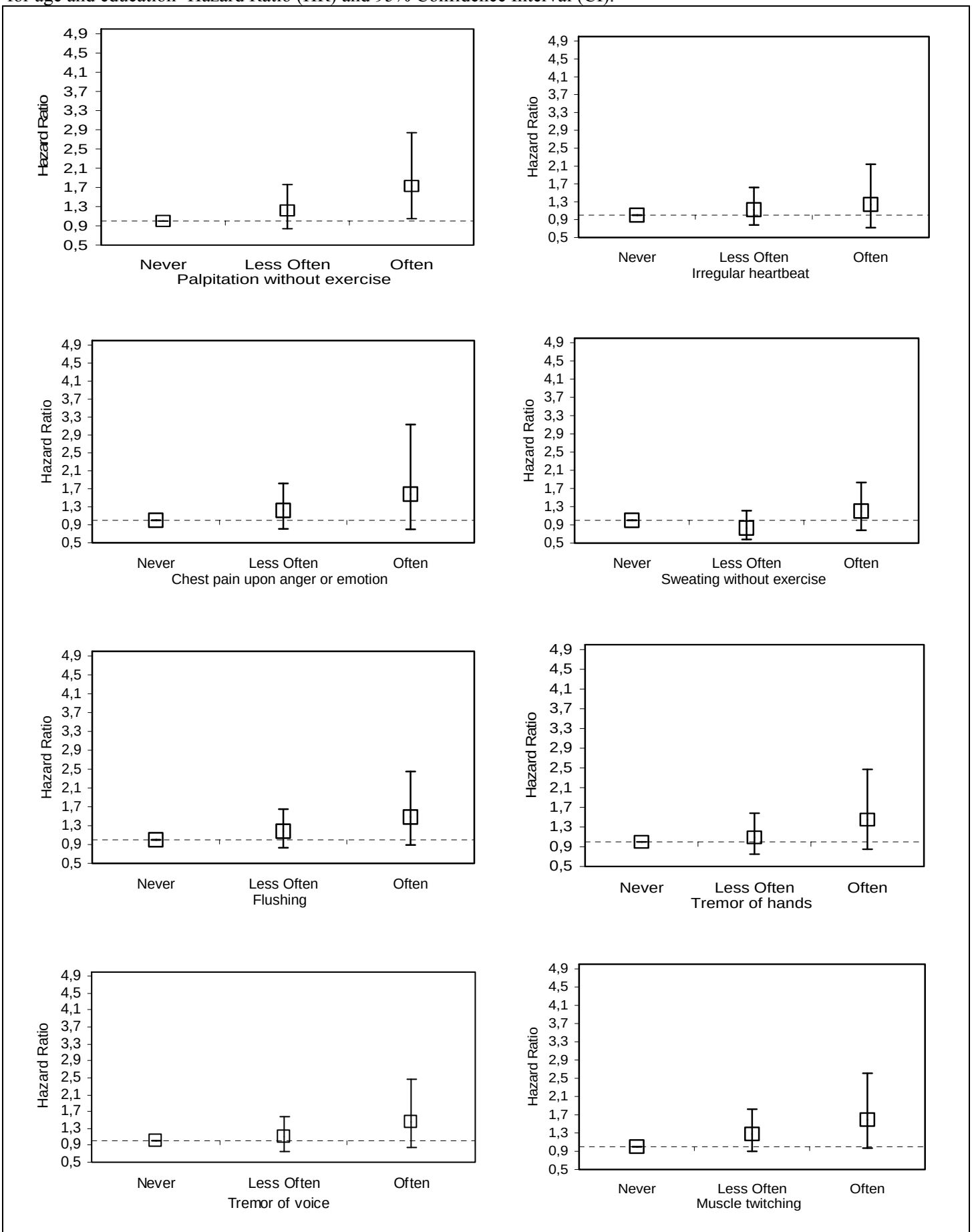
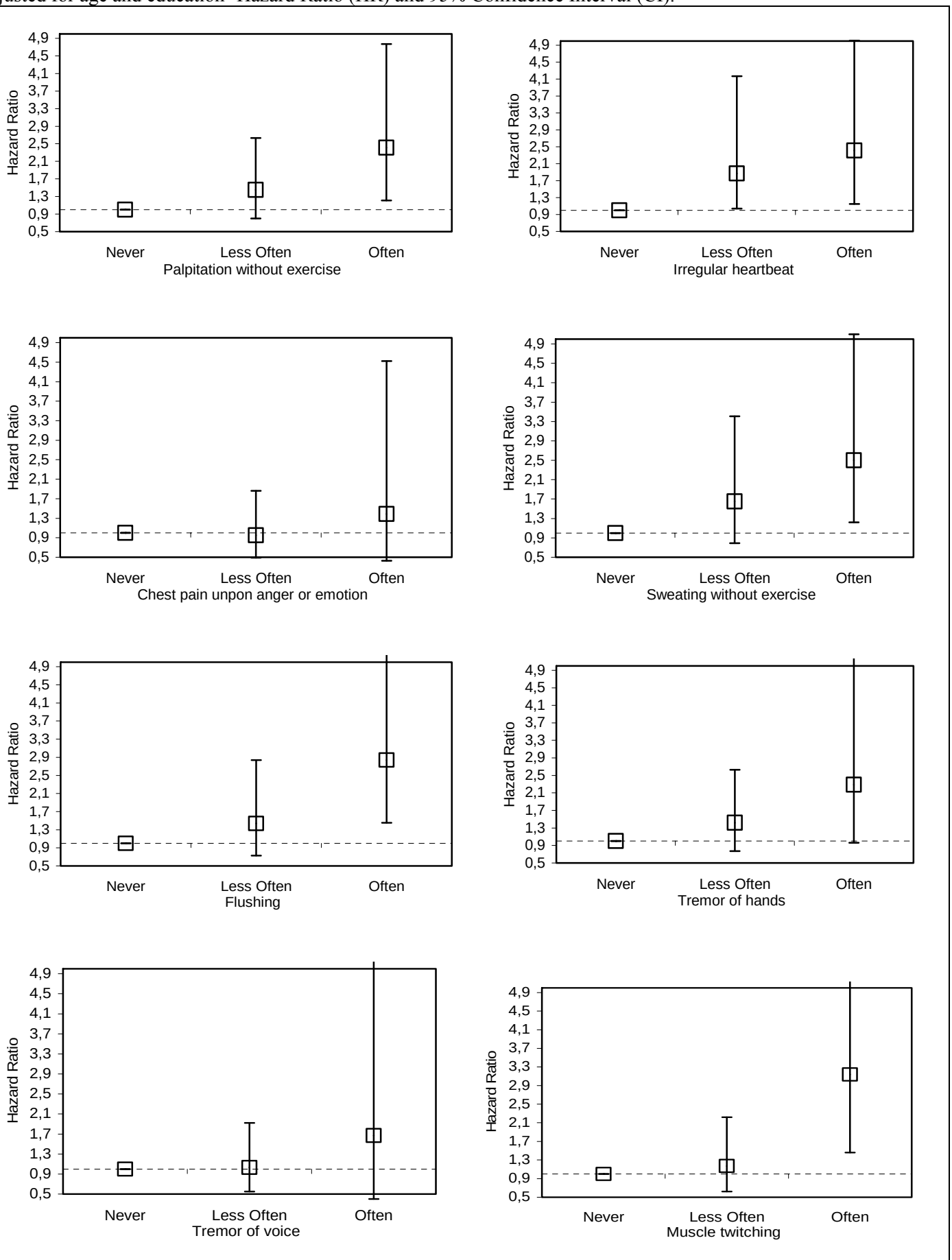


Figure 3: Specific Somatic Symptoms of Anxiety as predictors of Coronary Heart Disease Events in Women- Adjusted for age and education- Hazard Ratio (HR) and 95% Confidence Interval (CI).



Appendix 1: Correlations between Somatic symptoms used, validated self-reported and clinically-significant depression symptoms (filled antidepressant prescriptions).

Figure 4. Clinically-significant depression symptoms (filled antidepressant prescriptions) and odds for reporting each of the Somatic Symptoms at baseline -Odds Ratio (95% CI).

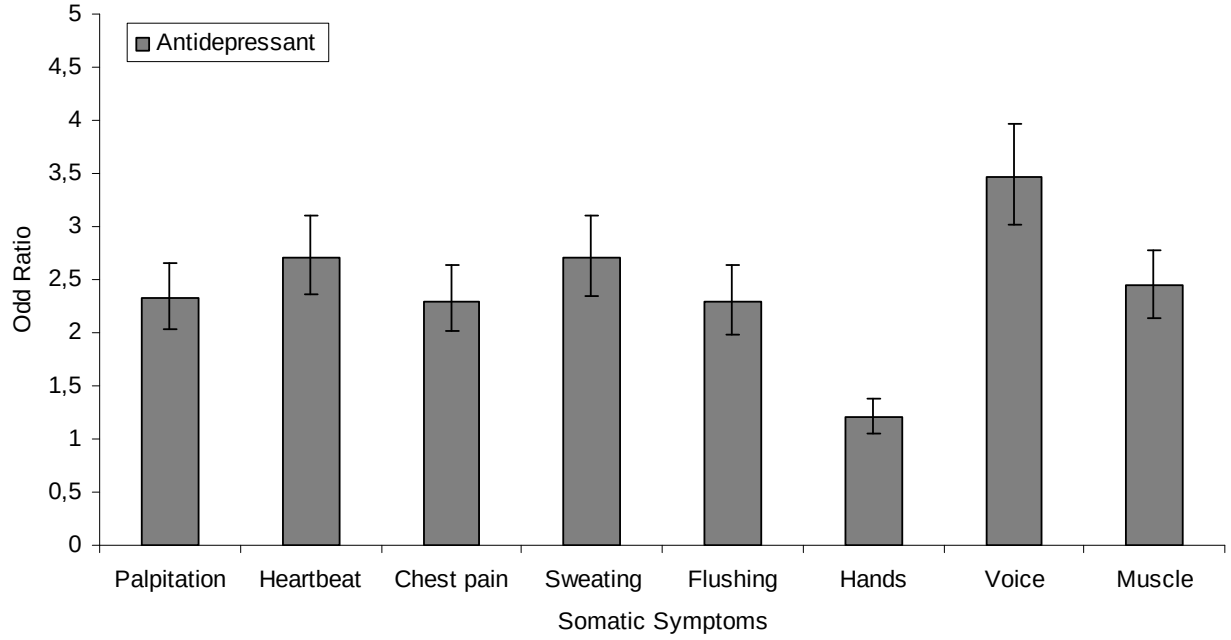
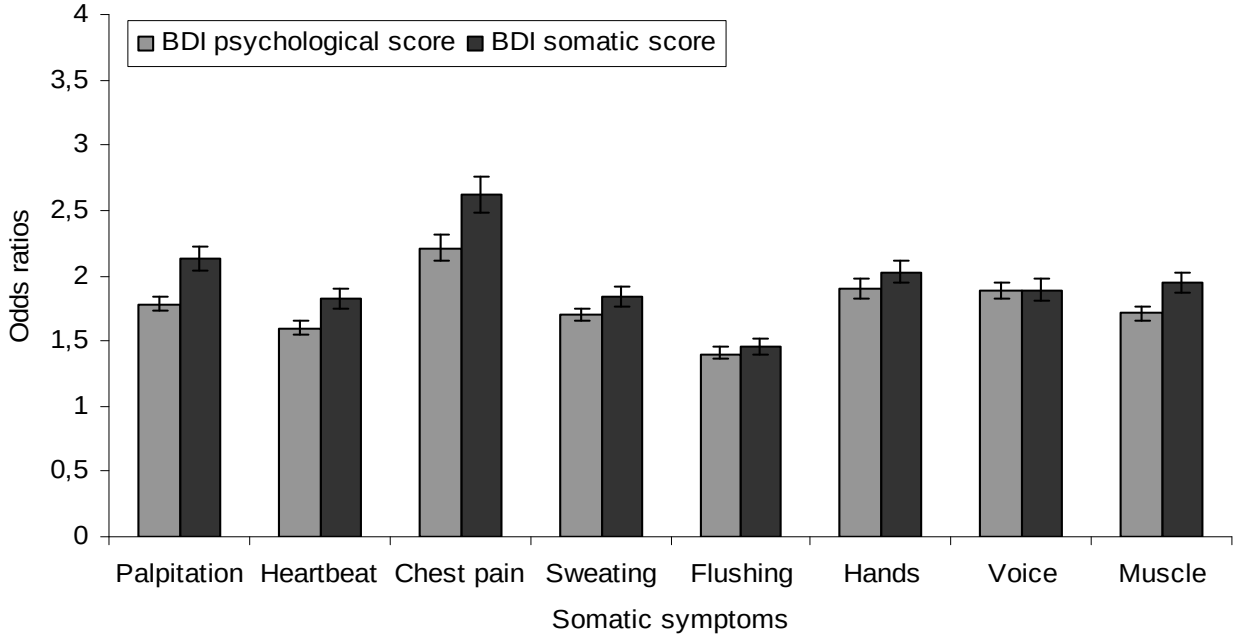


Figure 5. Psychological* and Somatic symptoms** scores of the Beck Depression Inventory (BDI) and odds for reporting each of the somatic symptoms at baseline-Odds Ratio (95% CI).



* Psychological symptoms: sadness, pessimism, sense of failure, dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal thoughts, crying, irritability, social withdrawal, indecisiveness, negative body image
** Somatic symptoms: work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, decreased libido