Positive and negative affect and risk of coronary heart disease: Whitehall II prospective cohort study.

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Abstract

Objectives: To examine the associations between positive and negative affect and subsequent coronary heart disease events independently of established risk factors.

Design: Prospective cohort study with follow up over 12 years.

Setting: 20 civil service departments originally located in London, Britain.

Participants: 10 308 civil servants aged 35-55 years at entry into the Whitehall II Study in 1985.

Main Outcome measures: Fatal coronary heart disease, clinically verified incident non-fatal myocardial infarction and definite angina (n=619, mean follow-up 12.5 years).

Results: In Cox regression analysis adjusted for age, sex, ethnicity and socioeconomic position, positive affect (hazard ratio=1.01, 95% confidence interval (0.82 to 1.24) and the balance between positive and negative affect, referred to as the affect balance score (hazard ratio=0.89, 95% confidence interval (0.73 to 1.09), were not associated with coronary heart disease. Further adjustment for behaviour-related risk factors (smoking, alcohol consumption, daily fruits and vegetables intake, exercise, body mass index), biological risk factors (hypertension, blood cholesterol, diabetes), and psychological stress at work did not change these results. However, participants in the highest tertile of negative affect had an increased incidence of coronary events (hazard ratio =1.32, 95% confidence interval 1.09 to 1.60) and this association remained unchanged after adjustment for multiple confounders.

Conclusions: Our findings suggest that positive affect and affect balance are not predictive of future coronary heart disease in men and women who are free of diagnosed coronary heart disease at recruitment to the study. A weak positive association between negative affect and coronary heart disease was found and requires confirmation in further studies.

What is already known on this subject?

Psychological factors are seen as important predictors of coronary heart disease. It has been suggested that negative affectivity may underlie these associations.

However, no large scale study has examined the association between negative affect and coronary heart disease.

It also remains unclear whether positive emotions might play a protective role in the development of coronary heart disease.

What this study adds?

Negative affect was a weak predictor of incident coronary heart disease in men and women who were free of diagnosed coronary heart disease at recruitment to the study. This association was not accounted for by established coronary risk factors.

No support was found for the associations of positive affect and affect balance with coronary heart disease.

INTRODUCTION

Smoking, hypertension, hypercholesterolemia and diabetes are established risk factors for coronary heart disease, a leading cause of morbidity and mortality in western industrialized countries [1 2]. However, psychological factors, such as emotions, may also have a role in the development of coronary heart disease [3 4]. A number of prospective studies have found anxiety, hostility/anger and depression to be associated with an increased risk of coronary heart disease in healthy participants [3 5]. As the relative importance of these three negative emotions on coronary heart disease risk remains largely undefined [6 7], it has been hypothesised that they are in fact the components of a single underlying factor, labelled negative affect. Negative affect refers to "a stable and pervasive individual differences in mood and self-concept characterised by a general disposition to experience a variety of aversive emotional states" [5 8], with high negative affect described as a general tendency to report "distress, discomfort, dissatisfaction, and feelings of hopelessness over time and regardless of the situation" and low negative affect characterised by "calmness and serenity" [8 9]. Supporting this conceptualisation, a considerable neurobiological and psychological overlap between anxiety, hostility/anger and depression has previously been shown [10 11].

As attempts to link psychological factors to heart disease have focused on negative emotions, mostly depression [7], it remains unclear whether positive emotions might also play a role in the development of coronary heart disease. Research suggests that positive affect and negative affect are two independent systems [12] and that positive affect is not simply the opposite of negative affect or an absence of negative affect [9]. High positive affect refers to be a general tendency to experience "state of high energy, full concentration, and pleasurable engagement", whereas low positive affect is characterised by "sadness and lethargy" [8 9]. It has been suggested that distinct neural networks exist in order to regulate positive and negative emotions, with dopamine metabolism associated with positive affect and serotonin associated

with negative affect [13 14] ; supporting therefore the assertion of the independence of the two types of affect.

To date, we are aware of no previous large-scale prospective studies on the independent effects of negative and positive affect on coronary heart disease. A 6-year follow-up [13] of 2478 older participants in North Carolina found positive affect to be associated with decreased risk of stroke, but it did not examine coronary heart disease as an outcome and the assessment of negative affect was limited to depressive symptoms. In this report from the Whitehall II study, we examine the independent associations of both negative affect and positive affect with subsequent coronary heart disease after taking account of established risk factors among individuals followed up over 12 years. In addition, we examine whether the balance between positive and negative affect is associated with subsequent coronary heart disease.

MATERIAL & METHODS

The Whitehall II study, established in 1985, is a longitudinal study to examine the socioeconomic gradient in health and disease among 10,308 civil servants (6,895 men and 3,413 women) [15]. All civil servants aged 35-55 years in 20 London based departments were invited to participate by letter, and 73% agreed. Baseline examination (phase 1) took place during 1985-1988, and involved a clinical examination and a self-administered questionnaire.

Measures

Positive affect and Negative affect were assessed at phases 1 (1985-1988) and 2 (1989-1990) using the Bradburn Affect Balance Scale [16], a widely used measure of psychological well-being. The Affect Balance Scale consists of 10 items, 5 of which are used to assess positive affect (Cronbach's α : 0.80) and the other five to assess negative affect

(Cronbach's α : 0.67). All items are formulated in general terms, as questions about the participant's feeling during the last few weeks. The items are phrased to elicit responses of the pleasurable or unpleasurable character of an experience instead of the context of the experience. Responses in this study are on a 4-point Likert scale from 0 (= not at all) to 3 (= a great deal). Scores for each subscale range from 0 to 15; with higher score indicating higher positive affect or higher negative affect. The affect balance score is computed by subtracting the negative affect score from the positive affect score and adding a constant of 15 to avoid negative values. Affect balance score ranges from 0 (lowest affect balance) to 30 (highest affect balance). Neither natural nor clinically-based thresholds are defined, so each scale was divided into low, middle and high exposure based on the tertile distribution in the total study population [positive affect scores, lowest (0 -4), middle (5-7), highest (8-15)]; negative affect scores, lowest (0 -1), middle (2-3), highest (4-15); and affect balance scores, lowest (0 -16), middle (17-20), highest (21-30)]. Only 75% of participants were asked to complete the Affect Balance Scale at phase 1 as this measure was introduced after the start of the baseline survey. Where phase 1 data were missing, positive and negative affect scores at phase 2 were used. The percentages of replacement were 15.0% and 14.3% for positive affect and negative affect, respectively. Correlations coefficients of scores at phase 1 (1985-1988) and phase 2 (1989-1990) suggests moderate degree of consistency of positive affect (r = 0.52, p<0.001), negative affect (r= 0.55 p<0.001) and affect balance (r = 0.54, p<0.001) across time.

Coronary heart disease incidence was assessed from phase 2 (1989-1990) to phase 7 (2003-04), a mean follow-up of 12.5 years (SD=3.8). Coronary heart disease included fatal coronary heart disease (defined by the International Classification of Diseases 9 codes 410–414 or I International Classification of Diseases 10 codes I20-25), first non-fatal myocardial infarction or first 'definite' angina. Fatal coronary heart disease was assessed by flagging participants at the National Health Service Central Registry, which provided information on

the date and cause of death. Potential non-fatal myocardial infarction was ascertained by questionnaire items on chest pain (the World Health Organisation Rose questionnaire [17]) and the physician's diagnosis of heart attack. Confirmation of myocardial infarction according to MONICA criteria (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) [18] was based on electrocardiograms, markers of myocardial necrosis, and chest pain history from the medical records. Angina was assessed based on participant's reports of symptoms with corroboration in medical records or abnormalities on a resting electrocardiogram, an exercise electrocardiogram, or a coronary angiogram.

Covariates

Sociodemographic measures included age, sex and socioeconomic position assessed by British civil service grade of employment taken from the phase 1 questionnaire.

Conventional risk factors assessed at phase 1 included smoking status (never, ex, and current), hypertension (systolic and diastolic blood pressure >140/90 mm/Hg, or treatment for hypertension), blood cholesterol (≥ 6.2 mmol/l), exercise (≥1.5 or <1.5 hours of moderate or vigorous exercise/week), daily fruits and vegetables intake (yes/no), alcohol consumption in units of alcohol consumed per week (low= <22 for men and <15 for women, moderate=22-51 for men and 15-35 for women, or high=>51 for men and >35 for women), body mass index (BMI) (<20, 20-24.9, 25-29.9, or ≥30 kg/m^2), and self-reported diabetes. For behavioural risk factors, missing values at phase 1 were replaced by information at phase 2.

Psychosocial stress at work (job-strain) measured at phase 1, using the self-administrated job strain model questionnaire [19] including scales of psychological job demands, decision latitude and social support at work [20 21]. Missing values at phase 1 were replaced by information at phase 2.

Statistical analyses

Differences in positive affect, negative affect, and affect balance scores as a function of sociodemographic characteristics and traditional coronary heart disease risk factors were assessed using one way-ANOVA, with a linear trend fitted across the hierarchical variables. The age- and sex-adjusted association between various covariates and coronary heart disease was assessed using Cox regression.

The associations of positive affect, negative affect and affect balance scores with incident coronary heart disease were modelled using six serially adjusted Cox regression models. Model 1 for the association between positive affect and incident coronary heart disease was adjusted for sex, age, ethnicity and employment grade (i.e., potential confounding factors) and the subsequent models included potential mediators for the association. Thus, in addition to potential confounders, model 2 was adjusted for behaviour-related risk factors. Model 3 is model 1 additionally adjusted for biological risk factors and model 4 is model 1 additionally adjusted for psychosocial stress at work. Model 5 was adjusted for all of the covariates outlined above and model 6 was additionally adjusted for negative affect. This whole exercise was repeated starting out with negative affect (using positive affect in model 6) and the affect balance score. Interactions between affect measures with sex in relation to coronary heart disease were also checked for on a multiplicative scale. The assumption of proportional hazards assessed by examining the time-dependent interaction term between each predictor and logarithm of the follow-up period (time variable) held (all $p>0.05$).

RESULTS

Of the 9745 participants with no history of clinically validated coronary heart disease at phase 2, 9568 (98.1%) and 9605 (98.1%) completed the positive affect and negative affect subscales, respectively, either at phase 1 or phase 2. Among the 8918 participants with

complete data on positive and negative affect and all covariates, 619 coronary events were documented between phases 2 and 7. The 827 participants who were not included in the analyses due to missing data on affect scales (n=614) or on covariates (n=213) were more likely to be women (11.5% vs. 7.0%), non-white (15.7% vs. 7.0%) and from the lowest employment grade (13.1% vs. 7.2%). There was no difference in age.

Table 1 shows the difference in mean positive, negative affect and affect balance scores as a function the sample characteristics.

Table 2 shows the age- and sex-adjusted associations between all of the covariates and coronary heart disease events. Examination of the interactions between sex and the affect variables in relation to coronary heart disease showed no evidence of sex differences. Thus, we combined men and women in the subsequent multivariate analyses.

Associations between positive affect, negative affect, affect balance score and coronary heart disease

Table 3 shows the six serially adjusted Cox regression models in order to estimate the associations of affect measures with coronary heart disease. There was no association between higher positive affect score and the incidence of coronary heart disease (hazard ratio=1.01, 95% confidence interval 0.82 to 1.24) in analysis adjusted for age sex, socioeconomic position and ethnicity (model 1) or after further adjustment for behaviour-related risk factors (model 2), biological risk factors (model 3), psychological stress at work (model 4), all covariates (model 5) and negative affect (model 6). However, participants with negative affect scores in the highest tertile had a slightly elevated risk (hazard ratio=1.32, 95% confidence interval 1.09 to 1.60) of coronary heart disease (model 1). Further serial adjustment (models 2 to 6) showed no substantial change in this association. Finally, participants with affect balance scores in the highest tertile had a lower, but statistically non-significant risk (hazard

ratio=0.89, 95% 0.73 to 1.09) of coronary heart disease which was little affected by adjustments (models 2 to 6).

Sensitivity analysis

To explore the effect of unmeasured co-morbidity at baseline, we examined the association between negative affect and incidence of coronary heart disease events after removing events that occurred within the first 5 years of the follow-up from the analysis. The number of events was reduced by 31.5% (n = 424) in this analysis, but there was no change in the magnitude of the association between higher negative affect and coronary heart disease (hazard ratio adjusted for age, sex, ethnicity and socioeconomic position = 1.32, 95% confidence interval 1.05 to 1.67, p=0.016), suggesting that this association is unlikely to be attributable to unmeasured co-morbidity at baseline. In the main analysis reported in the paper, we have replaced missing negative affect scores at phase 1 by scores at phase 2 if available. We performed sensitivity analysis using negative affect scores at each phase to test their association with coronary heart disease incidence without any replacement. In both cases, the pattern of associations was similar to that obtained using measures with replaced missing values.

DISCUSSION

Summary of findings

We examined the associations of positive and negative affect with incident coronary heart disease, followed-up over a 12-year period, in the Whitehall II cohort. There was no real association between positive affect, affect balance and incidence of coronary heart disease. Participants in the highest tertile of negative affect had a slightly increased risk of incident coronary heart disease and this association remained unchanged after taking into account the

effects of age, sex, employment grade, ethnicity, health-related behaviours, biological markers, job-strain and positive affect.

Findings in context of the literature and possible mechanisms

To our knowledge, this is the first prospective cohort study to examine the effects of both negative and positive affect on incident coronary heart disease, independently of known risk factors and of each other. The findings are based on a large well-characterized cohort with coronary heart disease ascertained by medical records and biological risk factors assessed by clinical examination.

The finding showing negative affect as an independent predictor of coronary heart disease incidence is consistent with some epidemiological investigations on negative emotions and coronary heart disease. A recent review of negative emotions, measured as anxiety, hostility/anger, and depression, supports their status as risk factors for coronary heart disease [3]. Anger in men has been found to be associated with a greater risk of coronary events incidence [22] and mortality [23]. Among men from the Northwick Park study [24] and among women from the Framingham Heart Study [25] greater anxiety predicted fatal coronary heart disease. According to a recent meta-analysis of 21 aetiological studies and 34 prognostic studies, depressive symptoms are associated with an 80% excess risk of developing coronary heart disease or dying from coronary heart disease [26].

The magnitude of the association between negative affect and coronary heart disease in the present study is small and requires replication in studies using measures of both positive and negative affect. In order to test the robustness of our findings, we repeated the analysis using continuous affect scores with assessments of the increase in risk of coronary events across the extremes of the distribution of the affect score. These results also supported the status of negative affect as a risk factor and provided no such support for other affect measures.

Further research is needed to examine the precise mechanisms through which negative affect might increase risk of coronary heart disease. As negative affect is thought to subsume high negative emotions such as anxiety and/or depression [8 27], it may be linked to coronary heart disease through physiological (cardiovascular and neuroendocrine) responses related to these emotions. Depression has been found to be associated with pathophysiological changes which may increase the risk of cardiac morbidity and mortality, including autonomic nervous system dysfunction (e.g., elevated heart rate, low heart rate variability, and exaggerated heart rate responses to physical stressors) [28], hypothalamic-pituitary-adrenal axis dysregulation (increased cortisol secretion) [29], enhanced inflammatory processes (higher levels of interleukin-6, C-reactive protein and fibrinogen) [30] and accelerated progression of atherosclerosis as indicated by change in carotid intima-media thickness [7 31]. Negative affect could also be linked to coronary heart disease via health-related behaviours [22]. In our study, negative affect was not associated with hypertension, higher body mass index, self-reported diabetes and was inversely associated with blood cholesterol, suggesting that these factors are not major mediators for the association observed. The association between negative affect and coronary heart disease was not attenuated after adjustment for behavioural factors; thus stable differences in these factors do not seem to be likely mediators. Further research should examine whether negative affect is related to risk factor trajectories over time or whether it increases episodic elevations in risk factors, such as blood pressure, which could act as a trigger for coronary events among employees with sub-clinical coronary heart disease.

Lack of robust association between positive affect and reduced risk of coronary heart disease in our study is in contrast to some previous reports. There has been a recent upsurge in interest in positive affect or happiness and its association with health [32 33]. In one study, low level of positive affect was associated with increased 10-year total mortality in older adults [34]. A major limitation of that study was the assessment of positive affect, done using the Center

for Epidemiologic Studies of Depression Scale. This scale, a measure of depression, may not provide reliable distinction between low positive affect and high negative affect. Another study, also conducted among older adults, found positive affect to have a protective association with stroke [13]. In that study, the analysis controlled for depressive symptoms, but not for the other components of negative affect and thus it remains unclear whether the observed association was independent of the effect of negative affect. Moreover, the measure of stroke was self-reported, without corroboration from medical reports. As positive and negative affect may be related to response styles, a subjective component in the outcome measure may introduce subjectivity bias that could artificially inflate associations.

Limitations

Interpretation of our findings should be considered within the context of the study limitations. Firstly, as coronary heart disease develops during a long time span, long-term rather than short-term higher levels of negative affect are assumed to influence coronary heart disease incidence. However, the relative temporal stability of negative affect scores between the two phases was found to be only moderate in the present study (test-retest reliability over 3 years 0.5). This suggests the presence of a certain amount of variability in negative affect levels over time and implies that we might have underestimated the cumulative impact of high negative affect on coronary heart disease incidence. On the other hand, the lack of stability and the relatively low internal consistency coefficient which was slightly below the conventional threshold of 0.7 for the negative affect scale call to question what precisely the scale measures. These factors are likely to have influenced our results and we cannot eliminate the possibility that negative affect might in part represent a marker of changing risk exposures rather than being solely a stable disposition to experience aversive emotional states. However, the proportional hazards assumption held in the Cox regression, suggesting relatively stable effects of negative affect over the follow-up period.

The second limitation involves modelling potential biological and behavioural confounders as time-independent covariates. Thus, the possible impact of changes in these factors on coronary heart disease event risk was not assessed. Thirdly, our cohort of civil servants did not include blue collar-workers and unemployed individuals and is thus not representative of the general population, which may limit the generalizability of our findings.

Unanswered questions and future research

In conclusion, data from a large occupational cohort provide no evidence for associations between positive affect, affect balance and coronary heart disease in men and women who were free of diagnosed coronary heart disease at recruitment to the study. However, we found negative affect to be weakly predictive of incident coronary heart disease events, independently of sociodemographic characteristics, conventional risk factors and job-strain. Further research is needed to examine whether our findings are generalizable to other populations as well as to disentangle the potential pathways that may link negative affect to coronary heart disease.

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Contributions

HN analysed and interpreted the data and wrote the first draft of the manuscript. MK and ASM contributed to the analysis and interpretation of data. MK, RDV, MGM & ASM made significant contributions to all subsequent revisions. HN will act as a guarantor.

Ethical approval

Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research, and written informed consent was obtained from each participant.

Statements

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Table 1. Sample characteristics as a function of positive and negative affect subscales and affect balance scale scores (n=8918)

Variables	N	Positive affect Means (SD)	*p* value or for trend	Negative affect Means (SD)	*p* value or for trend	Affect balance Means (SD)	*p* value or for trend
Sex			< 0.001		< 0.001		< 0.001
Male	6093	6.20 (2.91)		2.72 (2.27)		18.48 (4.01)	
Female	2825	5.81 (3.19)		2.94 (2.60)		17.87 (4.59)	
Age in years			0.002		< 0.001		< 0.001
39-45	2469	6.15 (2.96)		3.15 (2.42)		18.06 (4.23)	
45-50	2340	6.19 (2.98)		2.92 (2.41)		18.26 (4.24)	
50-55	1827	6.03 (3.07)		2.63 (2.32)		18.40 (4.19)	
55-64	2282	5.91 (3.02)		2.40 (2.29)		18.51 (4.16)	
Employment grade			< 0.001		0.005		< 0.001
High	2704	6.55 (2.80)		2.67 (2.19)		18.88 (3.87)	
Middle	4370	6.06 (2.99)		2.84 (2.36)		18.21 (4.18)	
Low	1844	5.44 (3.20)		2.85 (2.69)		17.58 (4.61)	
Ethnicity			< 0.001		0.553		< 0.001
White	8134	6.17 (2.95)		2.79 (2.36)		18.39 (4.16)	
Other	784	5.01 (3.39)		2.84 (2.64)		17.17 (4.58)	
Hypertension			0.147		< 0.001		0.113
No	7273	6.10 (3.00)		2.85 (2.39)		18.25 (4.22)	
Yes	1645	5.98 (3.04)		2.55 (2.34)		18.44 (4.15)	
Smoking status			0.992		< 0.001		0.018
Never smoker	4461	6.02 (2.99)		2.71 (2.31)		18.31 (4.12)	
Ex smoker	2893	6.25 (3.02)		2.80 (2.33)		18.45 (4.20)	
Current smoker	1564	5.92 (3.01)		3.01 (2.67)		17.90 (4.43)	
Alcohol			0.028		< 0.001		0.527
Low	7515	6.04 (3.00)		2.76 (2.37)		18.29 (4.20)	
Moderate	1198	6.30 (3.00)		2.92 (2.38)		18.38 (4.21)	
High	205	6.10 (3.09)		3.36 (2.64)		17.75 (4.51)	
Exercise			< 0.001		< 0.001		< 0.001
≥ 1.5 h/ week	1659	6.83 (2.98)		2.59 (2.20)		19.24 (4.00)	
< 1.5 h /week	7259	5.90 (2.98)		2.84 (2.42)		18.07 (4.22)	
Daily fruits and vegetables			< 0.001		< 0.001		< 0.001
Yes	5260	6.26 (3.03)		2.72 (2.36)		18.54 (4.22)	
No	3658	5.82 (2.95)		2.90 (2.41)		17.92 (4.16)	
Body mass index			0.234		0.001		0.005
< 20	539	5.63 (3.06)		3.19 (2.49)		17.43 (4.42)	
20-24.9	4960	6.11 (2.96)		2.81 (2.37)		18.30 (4.13)	
25-29.9	2850	6.14 (3.02)		2.68 (2.34)		18.45 (4.23)	
≥ 30	569	5.92 (3.23)		2.78 (2.54)		18.14 (4.56)	
Diabetes			0.048		0.055		0.013
No	8837	6.08 (3.00)		2.79 (2.39)		18.30 (4.20)	
Yes	81	5.42 (3.26)		3.30 (2.33)		17.12 (4.59)	
Job-strain			< 0.001		< 0.001		< 0.001
No	7859	6.22 (2.99)		2.67 (2.31)		18.55 (4.12)	
Yes	1059	5.03 (2.87)		3.66 (2.68)		16.37 (4.33)	
Blood Cholesterol			0.179		< 0.001		0.107
< 6.2	5424	6.11 (3.01)		2.88 (2.41)		18.23 (4.26)	
≥ 6.2	3494	6.02 (2.99)		2.65 (2.33)		18.38 (4.13)	

Table 2. Age- and sex-adjusted associations between the covariates and coronary heart disease among 8918 participants (619 events)

	Risk of coronary heart disease		
Variables	N events/ N participants	HR*	95% CI
Employment grade			
High	208/2704	1	
Middle	283/4370	1.05	(0.88 to 1.26)
Low	128/1844	1.29	(1.00 to 1.66)
Ethnicity			
White	531/8134	1	
Other	88/784	1.88	(1.50 to 2.36)
Hypertension			
No	425/7273	1	
Yes	194/1645	1.85	(1.55 to 2.19)
Smoking status			
Never smoker	286/4461	1	
Ex smoker	206/2893	1.02	(0.85 to 1.22)
Current smoker	127/1564	1.42	(1.15 to 1.75)
Alcohol			
Low	519/7515	1	
Moderate	87/1198	1.09	(0.87 to 1.37)
High	13/205	1.07	(0.62 to 1.86)
Exercise			
≥ 1.5 h/ week	105/1659	1	
< 1.5 h /week	514/7259	1.14	(0.92 to 1.41)
Daily fruits and vegetables			
Yes	354/5260	1	
No	265/3658	1.13	(0.96 to 1.32)
Body mass index			
< 20	14/539	1	
20-24.9	291/4960	1.87	(1.09 to 3.20)
25-29.9	250/2850	2.60	(1.51 to 4.45)
≥ 30	64/569	3.81	(2.13 to 6.80)
Diabetes			
No	610/8837	1	
Yes	9/81	1.54	(0.79 to 2.98)
Job-strain			
No	537/7859	1	
Yes	82/1059	1.23	(0.98 to 1.56)
Blood Cholesterol (mmol/l)			
< 6.2	288/5424	1	
≥ 6.2	331/3494	1.55	(1.32 to 1.82)

* HR, hazard ratios.

Table 3 Associations between positive affect, negative affect and affect balance scores in tertiles and coronary heart disease (number of events/Number of participants ††: 619/8918).

Scores in tertiles	Positive Affect		Negative Affect		Affect balance	
	HR*	95% CI	HR*	95% CI	HR*	95% CI
Model 1**						
Lowest	1		1		1	
Middle	1.19	(0.98 to 1.44)	1.12	(0.92 to 1.36)	0.97	(0.80 to 1.17)
Highest	1.01	(0.82 to 1.24)	1.32	(1.09 to 1.60)	0.89	(0.73 to 1.09)
Model 2**						
Lowest	1		1		1	
Middle	1.18	(0.97 to 1.43)	1.13	(0.93 to 1.37)	0.97	(0.80 to 1.18)
Highest	1.01	(0.82 to 1.25)	1.33	(1.10 to 1.61)	0.89	(0.72 to 1.09)
Model 3 †						
Lowest	1		1		1	
Middle	1.22	(1.01 to 1.48)	1.15	(0.94 to 1.39)	0.98	(0.81 to 1.19)
Highest	1.02	(0.83 to 1.26)	1.37	(1.13 to 1.66)	0.89	(0.73 to 1.09)
Model 4‡						
Lowest	1		1		1	
Middle	1.20	(0.99 to 1.46)	1.11	(0.92 to 1.35)	0.98	(0.81 to 1.19)
Highest	1.03	(0.83 to 1.27)	1.30	(1.07 to 1.50)	0.91	(0.74 to 1.11)
Model 5 §						
Lowest	1		1		1	
Middle	1.22	(1.01 to 1.48)	1.15	(0.94 to 1.40)	1.00	(0.82 to 1.21)
Highest	1.04	(0.85 to 1.29)	1.36	(1.12 to 1.65)	0.91	(0.74 to 1.12)
Model 6 ¶						
Lowest	1		1		-	
Middle	1.26	(1.04 to 1.53)	1.16	(0.95 to 1.41)	-	
Highest	1.10	(0.89 to 1.36)	1.39	(1.14 to 1.69)	-	

* HR, hazard ratios.
** Model 1: HR adjusted for age, sex, socioeconomic position and ethnicity
***Model 2: model 1 additionally adjusted for health-related behaviours (body mass index, smoking status, exercise, daily fruit and vegetable intake, alcohol consumption)
† Model 3: model 1 additionally adjusted for biological risk factors (blood cholesterol, diabetes , hypertension)
‡ Model 4: model 1 additionally adjusted for psychosocial stress at work
§ Model 5: model 1 + model 2 + model 3 + model 4
¶ Model 6: model 5 additionally adjusted for positive or negative affect
†† Number of events/Number (percentage) participants for lowest, middle and highest scores tertiles were: 183/2746(30.8), 257/3403 (38.2), and 179/2769 (31), respectively, for positive affect; 208/3135 (35.2), 197/2856 (32), and 214/2927 (32.8), respectively, for negative affect; and 200/2817 (31.6), 236/3357 (37.6), and 183/2744 (30.8), respectively, for affect balance.