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The relationship between depression, anxiety and cardiovascular disease: findings from the Hertfordshire Cohort Study

Richard IG Holt¹, David IW Phillips^{1,2}, Karen A Jameson^{1,2}, Cyrus Cooper^{1,2}, Elaine M Dennison^{1,2}, Robert C Peveler³, and The Hertfordshire Cohort Study Group

¹Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

²MRC Lifecourse Epidemiology Unit, Faculty of Medicine, University of Southampton, Southampton, UK

³Clinical and Experimental Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

Abstract

Background—Previous studies suggest a link between depression, anxiety and cardiovascular disease (CVD). The aim of the study was to determine the relationship between depressive and anxiety symptoms and CVD in a population based cohort.

Methods—1,578 men and 1,417 women from the Hertfordshire Cohort Study were assessed for CVD at baseline and after 5.9±1.4 years. Depressive and anxiety symptoms were measured using the HADS Scale.

Results—Baseline HAD-D score, but not HAD-A, was significantly associated with baseline plasma triglycerides, glucose and insulin resistance (men only) and HDL cholesterol (women only).

After adjustment for CVD risk factors, higher baseline HAD-D scores were associated with increased odds ratios for CVD (men: 1.162 [95% CI 1.096 - 1.231]; women: 1.107 [1.038 - 1.181]). Higher HAD-A scores associated with increased CVD in men only.

High HAD-D scores predicted incident CVD (adjusted OR 1.130 [1.034 - 1.235]), all-cause mortality (adjusted HR 1.081, [1.012 - 1.154]) and cardiovascular mortality (adjusted HR 1.109 [1.002 - 1.229]) in men but not in women.

Limitations—The use of a self-report measure of depressive and anxiety symptoms, ‘healthy’ responder bias and the low number of cardiovascular events are all limitations.

Address for Correspondence: Professor RIG Holt, The Institute of Developmental Sciences (IDS Building), MP887, University of Southampton, Southampton General Hospital, Tremona Road, Southampton SO16 6YD UK Tel: +44 23 8079 4665, Fax: +44 23 8079 5255 R.I.G.Holt@soton.ac.uk.

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Declaration of Interest There are no conflicts of interest for this paper.

Conclusions—Depressive and anxiety symptoms are commoner in people with CVD. These symptoms are independent predictors of CVD in men. Although HAD-D score was significantly associated with several cardiovascular risk factors, this did not fully explain the association between HAD-D and CVD.

Keywords

Depression; anxiety; cardiovascular disease; epidemiology; population studies

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide; in 2008, an estimated 17.3 million people died from CVD representing approximately 30% of all deaths. By 2030, it is estimated that this number will increase to 23.6 million largely through increases in low- and middle-income countries. Mental illness is also common, affecting 1 in 10 people at any one time. The World Health Organisation predicts that by 2030, depression alone will be the second leading cause of disability worldwide after CVD. Given the high prevalence of both CVD and depression, a degree of co-morbidity is to be expected but it is clear that depression occurs more commonly among people with CVD than expected, and vice versa (Katon 2011).

The relationship between CVD and depression appears to be bi-directional, as depression may be both a cause and consequence of CVD. The prevalence of depression is increased in people with CVD; up to 40% of people have either major or minor depression following a myocardial infarction (Carney and Freedland 2003). Furthermore depression increases the risk of CVD by 1.5-2.0 fold in both men and women, independent of other risk factors (Rudisch and Nemeroff 2003; Rugulies 2002). Depression may also worsen the severity of CVD as mortality is increased 2.0-2.5 fold in people with co-morbid depression following a myocardial infarction (Sorensen et al. 2005; van Melle et al. 2004), with the highest relative risk being in those with new-onset depression (de Jonge et al. 2006).

Gender may affect the relationship between CVD and depression, with a higher prevalence of co-morbidity in women; however, there are very few studies examining depression as a risk factor for the development of CVD in populations with similar numbers of men and women and these studies have given inconsistent results (Moller-Leimkuhler 2010).

Anxiety also appears to be an independent risk factor for incident coronary heart disease and cardiac mortality. A meta-analysis of 20 studies involving nearly a quarter of a million patients found that the risk of coronary heart disease and cardiac death was increased by 26% and 48% respectively in anxious people (Roest et al. 2010a).

The aim of the current study was to examine the relationship between depression and anxiety symptom scores as assessed by the Hospital Anxiety and Depression Scale and CVD in a well-characterised population study of both men and women. The relationship between depressive and anxiety scores and CVD and its risk factors (both traditional and non-traditional) was first examined at baseline in a cross-sectional manner. Long term follow-up of the subjects then assessed the prognostic value of depressive and anxiety symptoms for CVD and cardiovascular mortality in those without CVD at baseline.

Methods and Materials

Cohort

The Hertfordshire Cohort Study was established as an internationally unique study of 1,579 men and 1,418 women born in Hertfordshire during 1931-39 and still resident in the county in the late 1990's (Syddall et al. 2005). The participants were generally comparable with those in the nationally representative Health Survey for England although some differences were identified (Syddall et al. 2005); there was some evidence that a 'healthy', or 'health-aware' responder bias was apparent as participants were less likely to be in the extremes of the socioeconomic distribution, were taller, had better self-reported general health (SF-36), and the study women were less likely to be current smokers or heavy drinkers.

In 2004-5, a follow-up study was performed in East Hertfordshire with permission of the participants' family doctors. Of 498 men and 468 women from the original cohort based in this area of the county, 82 had either died, moved away, were no longer on family doctor lists, were unavailable or the family doctor declined permission to approach them. Hence, 437 men and 447 women were invited to participate in the follow-up study. 322 men (74%) and 320 women (72%) agreed to attend a follow-up clinic. In 2007, a postal questionnaire recording details of various clinical outcomes was completed by 2,299 (1,168 men and 1,131 women) of the original participants in the whole Hertfordshire Cohort Study. The cohort is flagged on the NHS Central Register for notification of death.

Ethical approval was obtained from the Hertfordshire and Bedfordshire Local Research Ethics Committees and all subjects gave written informed consent. All studies were conducted according to the principles expressed in the Declaration of Helsinki.

Methods

Baseline data—A detailed medical and social history was obtained during a home visit between December 1998 and July 2004. Social class was identified on the basis of current or most recent full-time occupation for men and never-married women, and on the basis of the husband's occupation for ever-married women.

Height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors, London, UK) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors). Body mass index (BMI) was calculated as weight divided by height² (kg/m²).

Subjects without a self-reported previous diagnosis of diabetes completed a standard 75-g oral glucose tolerance test; the WHO criteria were used to classify diabetes. Resting blood pressure was recorded as the mean of three measurements on a Dinamap Model 8101 (GE Medical Systems, Slough, UK). An electrocardiogram (ECG) was performed and graded according to the Minnesota protocol. Ischaemic heart disease (IHD) was defined by the presence of major-Q waves on the ECG or Rose questionnaire typical angina or history of coronary artery bypass graft or angioplasty. CVD was defined as ischaemic disease or a history of stroke.

Fasting venous blood samples were taken for measurements of plasma glucose, insulin, lipid profile, cortisol, IL-6 and C-reactive protein using multiplex technology.

Depressive and anxiety symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) during the initial medical history (Zigmond and Snaith 1983). The overwhelming majority (over 99%) of people answered all questions for HAD-A and HAD-D. In the small minority of cases where there were missing data (ie when a question was not answered), missing values were imputed using the mean of other items within the

appropriate subscale. A possible case of any depressive or anxiety disorder was defined as a HAD-D or HAD-A score respectively between 8 and 10 and a probable case as a score 11 (Zigmond & Snaith 1983).

Follow-up data—During the follow-up study, data were collected on self-reported cardiovascular conditions and depression. Incident CVD was defined as a report of heart attack, angina, serious cardiovascular illness or hospital admission, angioplasty or coronary artery bypass graft in those not identified as having CVD at baseline. Data were collected on the date and cause of death of any of the original clinic subjects who had died up to the end of 2007. Deaths with ICD10 codes I00 – I99 were classed as cardiovascular deaths.

Statistical methods

Men and women were analysed separately. Body mass index, triglycerides, HDL cholesterol, plasma glucose and insulin concentrations had skewed distributions and were therefore transformed to Normality before analysis; the means and SDs presented are therefore geometric. Assessment of insulin secretion and insulin resistance was by homeostasis model assessment (HOMA). The relationships between the HAD scores (both as a categorical variable and continuously as a trend) and baseline and incident CVD were assessed using logistic regression. Cox's proportional hazards regression was used to assess the relationship between HAD scores and cardiovascular death. Linear regression was used to assess the relationship between the HAD scores and the cardiovascular risk factors; P values refer to analyses using the full range of continuously distributed variables. Chi-square tests were carried out to determine if there was a difference in the prevalence of CVD and of possible or probable depression between men and women.

All analyses were carried out using STATA, release 11. A P value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Hospital Anxiety and Depression scale data were not available for one man and one woman and these two were therefore excluded from this study. The basic characteristics of the remaining 1,578 men and 1,417 women are shown in table 1.

59 (3.7%) men and 65 (4.6%) women had HAD-D scores indicating possible depression. Probable depression was noted in 17 (1.1%) men and 20 (1.4%) women, with no difference in overall prevalence between men and women ($p=0.35$). Prevalence of anxiety was significantly higher in women ($p<0.001$) with 154 (9.8%) men and 209 (14.8%) women having HAD-A scores indicating possible anxiety and 78 (4.9%) men and 146 (10.3%) women having scores indicating probable anxiety.

Data on baseline cardiovascular heart disease were available for 1,532 men and 1,376 women. Prevalence of cardiovascular heart disease was significantly higher in men (281 [18.3%]) than in women (158 [11.5%], $p<0.001$).

Relationship between HAD scores and cardiovascular risk factors

In men, baseline HAD-D score was significantly associated with baseline plasma triglycerides, fasting and 2-hour glucose, fasting insulin and insulin resistance as measured by the HOMA (table 2). With the exception of plasma triglycerides and fasting glucose, these associations remained significant after adjustment for age, BMI, smoking, social class,

and alcohol consumption. By contrast, HAD-A was not associated with any of these variables (data not shown).

In women, baseline HAD-D score was significantly associated with baseline plasma triglycerides, HDL cholesterol and 2-hour glucose (table 2). After adjustment for age, BMI, smoking, social class, and alcohol consumption, baseline HAD-D score was significantly associated with systolic blood pressure and 2-hour glucose. Baseline HAD-A was associated with diastolic blood pressure and 2-hour insulin but only diastolic blood pressure remained significant after adjustment (regression coefficient -0.17 [$-0.31, -0.02$], $p=0.042$).

Neither baseline HAD-D nor HAD-A score was associated with IL-6, CRP or cortisol in men; however, baseline CRP was associated with HAD-A (regression co-efficient 1.033 [$1.001, 1.067$], $p=0.042$, where the regression coefficient represents a multiplicative change) in women after adjustment for age, BMI, smoking, social class and alcohol consumption.

Baseline association between HAD scores and cardiovascular disease

In both men and women, higher HAD-D scores were associated with a higher prevalence of CVD (p value for trend <0.001 for both men and women, table 3). However, higher HAD-A scores were only associated with a higher prevalence of CVD in men (p value for trend <0.001 for men and 0.099 for women). After adjustment for age, BMI, social class, smoker status, alcohol consumption, triglycerides, total, HDL and LDL cholesterol, pack years smoked and diabetes, high HAD-D scores were associated with an odds ratio for CVD of 1.162 (95% CI $1.096 - 1.231$, $p<0.001$) in men and 1.107 (95% CI $1.038 - 1.181$, $p = 0.002$) in women. High HAD-A scores were associated with an odds ratio for CVD of 1.101 (95% CI $1.053 - 1.150$, $p<0.001$) in men but not in women (1.037 ; 95% CI $0.990 - 1.087$, $p = 0.124$).

HAD score and incident cardiovascular disease

Follow-up data were available for 1,162 men and 1,129 women (after mean 5.5 [SD 1.4] years). 111 (9.6%) men and 56 (5.0%) women developed CVD during the period of follow-up. Higher baseline HAD-D scores were associated with a higher incidence of CVD in men (p value for trend 0.003). This association remained after adjustment for age, BMI, social class, smoker status, alcohol consumption, triglycerides, total, HDL and LDL cholesterol, pack years smoked and diabetes (OR 1.130 , 95% CI $1.034 - 1.235$, $p=0.007$). No significant association was found in women ($p=0.154$) (table 4). HAD-A scores were not associated with incident CVD in either men or women.

HAD score and all-cause mortality

By the end of 2007 (a mean 6.1 (SD 1.4) years after the baseline clinic), 137 men and 46 women had died. In men, high HAD-D scores were associated with a hazards ratio for death of 1.122 (95% CI $1.061 - 1.185$, $p<0.001$). This association remained after adjustment for age, BMI, social class, smoker status, alcohol consumption, triglycerides, total, HDL and LDL cholesterol, pack years smoked and diabetes (HR 1.081 , 95% CI $1.012 - 1.154$, $p = 0.020$). No association was seen in women ($p=0.143$) nor was there an association between HAD-A scores and subsequent death in either men or women.

HAD score and cardiovascular mortality

Cardiovascular death accounted for 42 (30.7%) deaths in men and 7 deaths in women (15.2%). In men, high HAD-D scores were associated with a hazards ratio for dying from CVD of 1.109 (95% CI $1.002 - 1.228$, $p = 0.046$) (table 5). This association did not remain significant after adjustment. Again, no association was seen in women nor was there an association between HAD-A scores and cardiovascular death in either men or women.

Gender Differences

There were no significant interactions between gender and HAD-D on risk factors, baseline CVD, incident CVD or CVD deaths. Similarly there were no significant interactions between gender and HAD-A, with one exception; there was a significant interaction with cortisol ($p = 0.033$).

Discussion

This study of a well characterised cohort, which is largely representative of the UK general population, showed that depressive and anxiety symptoms were commoner in men and women with CVD. Furthermore, depressive symptoms were an independent predictor of incident CVD, all-cause mortality and cardiovascular mortality in men. Although HAD-D score was significantly associated with a number of traditional cardiovascular risk factors, the association between HAD-D and CVD was still apparent after adjustment for these suggesting that the relationship between depressive symptoms and CVD is not wholly explained by an increase in traditional risk factors.

Association between depressive and anxiety symptoms and cardiovascular disease

The current study adds to the evidence of a relationship between depressive symptoms and CVD. A previous meta-analysis of 21 studies, including 124,509 participants free of CVD at baseline and 4,016 events, found an 81% increased risk of incident coronary heart disease events in people with depression at baseline during the mean follow-up of 10.8 years, although there was considerable heterogeneity between studies (Nicholson et al. 2006). This result is consistent with our findings where the risk of incidence CVD was almost doubled in those with possible or probable depression. A further meta-analysis of 28 studies found that depressed mood increased the risk for myocardial infarction, coronary heart disease, cerebrovascular diseases and other cardiovascular diseases by 43% – 63% (Van der Kooy et al. 2007). Considerable heterogeneity between studies was reported with the 60% increased risk of myocardial infarction in those with depression being most consistent. Not only does depression appear to contribute the onset of CVD but it also worsens its severity, with depressive symptoms increasing the risk of mortality following a myocardial infarction (Sorensen et al. 2005; van Melle et al. 2004). In the current study, depressive symptoms were associated with increase cardiovascular mortality in men.

The cross sectional relationship between prevalent CVD and anxiety in our study is consistent with previous studies that have shown that the prevalence of anxiety is approximately 30% of people with acute myocardial infarction (Roest et al. 2010b). In contrast to previous studies, however, anxiety symptoms in our study did not predict the development of incident CVD or mortality. A recent meta-analysis showed that symptoms of anxiety were associated with a 26% increased risk of incident coronary heart disease (Roest et al. 2010a). Anxiety disorders have also been associated with all-cause mortality in some (Phillips et al. 2009; van Hout et al. 2004) but not all studies (Holwerda et al. 2007).

Mechanisms

The mechanisms by which depression may lead to CVD are uncertain. We have examined whether the association is explained by an increased prevalence of traditional and non-traditional cardiovascular risk factors. This was important in light of previous criticisms that studies have failed to adjust for conventional risk factors in a complete and unbiased manner (Nicholson et al. 2006). Only 11 of the 54 studies included in the meta-analysis reported adjustment for conventional cardiovascular risk factors and where these were reported, the effect estimate was reduced by 12% (Nicholson et al. 2006). Similarly in the baseline cross-sectional analysis of our study, the relationship between depressive scores and prevalent

CVD remained after adjustment for conventional cardiovascular risk factors but the effect of HAD-D was reduced by 11% when the data were combined for men and women and adjusted for gender.

This finding would suggest that the effect of depression on CVD is not acting primarily through traditional risk factors. Furthermore, contrary to expectation, a meta-analysis of 30 studies examining the relationship between lipid profile and depression found that higher total cholesterol and lower HDL-cholesterol was associated with lower levels of depression (Shin et al. 2008).

This study explored whether chronic inflammation may also underlie the association as cytokines and other inflammatory markers, such as increased C-reactive protein, TNF- α and proinflammatory cytokines, are increased in CVD and are implicated in causing sickness behaviour and depression (Dantzer et al. 2008). This did not appear to be the case in our study because, with the exception of a relationship between C-reactive protein and depressive and anxiety scores in women, no relationship was found. Furthermore 0900 cortisol, which is a crude measure of hypothalamic-pituitary-adrenal axis function, was not associated with depressive and anxiety scores. These findings contradict previous studies that have shown an association between depression and CRP, IL-1, and IL-6 in both clinical and community samples (Howren et al. 2009). When studies adjusted for body mass index, weaker associations were found suggesting that body fat may be a mediating or moderating factor.

Gender Differences

Previous studies have suggested that gender may affect the relationship between CVD and depression, in the light of the differing epidemiology of depression and CVD between genders (Moller-Leimkuhler 2010). Although CVD has a lower prevalence in younger premenopausal women than men, it remains the leading cause of death in both men and women. Furthermore while the prevalence of CVD is decreasing in men, the same is not true for women (Moller-Leimkuhler 2010). Contrary to the findings in this study, most studies report that depression is commoner in women than men and co-morbid depression in women with CVD is higher than in men (Moller-Leimkuhler 2010). Although some of the relationships between depressive symptoms and CVD were only found in men, formal statistical analysis failed to find any interaction between gender and HAD-D on risk factors, baseline CVD, incident CVD or CVD deaths. The lack of a finding of relationships between depressive symptoms and CVD in women may therefore reflect the comparatively lower number of events in women. Overall this low number of CVD events will have reduced the power to detect an association.

Clinical implications

The relevance of these findings is not immediately apparent as previous studies have shown that treatment of depression alone, while improving depressive symptoms, does not substantially alter the subsequent cardiovascular event rate. The Sertraline Anti-Depressant Heart Attack Trial (SADHEART) was the first trial to investigate the safety and efficacy of sertraline treatment in depressed patients with CVD. The use of Sertraline (50-200 mg daily) for 6 months led to a modest improvement in depressive symptoms but no significant reduction in severe cardiac events (14.5% vs. 22.4%, RR 0.77, 95% CI 0.51–1.16) (Glassman et al. 2002).

The Myocardial INfarction and Depression-Intervention Trial randomised 331 patients with depression post-myocardial infarction to usual care or a depression intervention incorporating either an antidepressant or psychotherapy (van Melle et al. 2007). After 18

months there was no difference between groups in either depression or cardiac event rate but survival was predicted by response rate. The cardiac event rate was 25.6% among non-responders compared to 11.2% among untreated control subjects, and 7.4% among responders (de Jonge et al. 2007).

The ENhancing Recovery In Coronary Heart Disease (ENRICHD) study evaluated the effect of a cognitive behaviour therapy based intervention, initiated 2 to 3 weeks after myocardial infarction and continued for a median of 11 sessions over 6 months (Berkman et al. 2003). The results were mixed with improvements in psychological well-being after 6 months but not after 30 months. Although depression predicted the risk of death after myocardial infarction, there was no difference in cardiac events between groups.

These studies suggest that treatment of depression alone is not enough and clinicians will need to consider the aggressive management of other traditional risk factors, such as cholesterol and blood pressure, if the cardiovascular outcomes are to be improved.

Limitations

The current study has a number of limitations. The first is the use of a self-report measure of depressive and anxiety symptoms at a single time point. Depressive and anxiety symptoms vary with time and a single measure may underestimate these over a prolonged period of time. Overall the number of people with high depressive or anxiety symptom was lower in than expected, and this may reflect a 'healthy', or 'health-aware' responder bias that is apparent in the cohort. Such response bias could be a concern if the relationships between risk factors and disease outcomes differed systematically in men and women who participated in the study and those who did not. Alternatively it may also reflect the secular trend towards lower depression scores in older cohorts. Effective treatment does not explain the low numbers of people reporting high depressive symptoms as only 49 (3.1%) men and 115 (8.1%) women reported the use of antidepressants. It is likely that any effect of depression on cardiovascular risk will be cumulative over a period of time and a reduced sensitivity to detect depression would likely weaken any association between CVD and depression. The low number of cardiovascular events, particularly in women, will have reduced our power to detect a significant association between depressive and anxiety symptoms and events. A further limitation relates to the different definitions of CVD used at baseline and follow-up, including the use of self-reported cardiovascular events in the follow-up. This latter method has been used in the past, for example in the Whitehall study (Bulpitt et al. 1990), and was necessary because of the available funding and ethical approval for the follow-up study but prevents a direct comparison of the cross-sectional and longitudinal studies.

Conclusions

This study indicates there is a relationship between depressive symptoms and CVD in both the cross-sectional and longitudinal studies. Further studies are needed to understand the relationship between depression and CVD to inform intervention trials to reduce the excess CVD burden in people with depression.

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Table 1

Characteristics of the men and women in the Hertfordshire Cohort

	N	Mean	SD	N	Mean	SD
Age (yrs)	1578	65.7	2.9	1417	66.6	2.7
BMI (kg/m²) *	1570	26.9	1.1	1415	27.2	1.2
Triglycerides (mmol/l) *	1458	1.45	1.6	1328	1.47	1.6
Total Cholesterol (mmol/l)	1458	5.93	1.0	1328	6.54	1.2
HDL Cholesterol (mmol/l) *	1458	1.32	1.3	1328	1.66	1.3
LDL Cholesterol (mmol/l)	1434	3.82	0.9	1312	4.08	1.1
Fasting glucose (mmol/l) *	1456	5.99	1.2	1323	5.78	1.1
Fasting insulin (pmol/l) *	1451	72.2	2.0	1270	69.3	1.8
	Overall N	N	%	Overall N	N	%
Diabetes	1561	232	14.9	1390	199	14.3
Social class **						
I-IIIINM		623	40.7		590	41.7
IIIM-V	1530	907	59.3	1416	826	58.3
Smoker status						
Never		520	33.0		865	61.1
Ex	1578	820	52.0	1415	411	29.0
Current		238	15.1		139	9.8
Alcohol consumption						
Non-drinker		89	5.6		283	20.0
recommended units [†]	1577	1148	72.8	1417	1067	75.3
> recommended units		340	21.6		67	4.7
	N	Median	IQR	N	Median	IQR
Pack years smoked (amongst ex and current smokers)	1049	23	11 - 40	549	15	5 - 29

* Geometric mean (SD)

** Social class I-IIIINM denotes classes one to three (non-manual) of the 1990 OPCS Standard Occupational Classification scheme for occupation and social class; while IIIM-V denotes classes three (manual) to five.

[†] 21 units per week for men; 14 units per week for women

Table 2

Association between the HAD-D scores and measurements of blood pressure, plasma lipids and glucose tolerance.

	N	Regression coefficient	95% CI	p-value	p-value*
Men					
Systolic BP (mmHg)	1573	0.075	(−0.304, 0.454)	0.698	0.830
Diastolic BP (mmHg)	1573	−0.041	(−0.251, 0.169)	0.702	0.806
Triglycerides (mmol/l) [‡]	1458	0.015	(0.004, 0.025)	0.006	0.062
HDL cholesterol (mmol/l) [‡]	1458	−0.002	(−0.008, 0.003)	0.344	0.799
LDL cholesterol (mmol/l)	1434	−0.008	(−0.028, 0.012)	0.437	0.482
Total cholesterol (mmol/l)	1458	0.002	(−0.020, 0.024)	0.872	0.930
Fasting glucose (mmol/l) [‡]	1456	0.004	(0.001, 0.007)	0.008	0.075
2 hr glucose (mmol/l) [‡]	1453	0.012	(0.005, 0.020)	0.002	0.020
Glucose AUC (min.mmol) [‡]	1226	0.009	(0.004, 0.014)	<0.001	0.013
Fasting insulin (pmol/l) [‡]	1451	0.021	(0.007, 0.036)	0.004	0.029
2hr insulin (pmol/l) [‡]	988	0.023	(−0.002, 0.049)	0.071	0.112
Insulin resistance (HOMA) [‡]	986	0.023	(0.005, 0.041)	0.012	0.024
Insulin secretion (HOMA) [‡]	984	0.013	(−0.002, 0.028)	0.094	0.120
Women					
Systolic BP (mmHg)	1411	−0.387	(−0.797, 0.023)	0.064	0.011
Diastolic BP (mmHg)	1411	−0.168	(−0.384, 0.047)	0.126	0.145
Triglycerides (mmol/l) [‡]	1328	0.014	(0.005, 0.024)	0.003	0.100
HDL cholesterol (mmol/l) [‡]	1328	−0.009	(−0.014, −0.004)	0.001	0.113
LDL cholesterol (mmol/l)	1312	−0.019	(−0.041, 0.004)	0.109	0.053
Total cholesterol (mmol/l)	1328	−0.016	(−0.041, 0.010)	0.221	0.210
Fasting glucose (mmol/l) [‡]	1323	0.001	(−0.002, 0.003)	0.466	0.965
2 hr glucose (mmol/l) [‡]	1316	0.01	(0.003, 0.016)	0.004	0.034
Glucose AUC (min.mmol) [‡]	870	0.005	(−0.000, 0.010)	0.054	0.082
Fasting insulin (pmol/l) [‡]	1270	0.005	(−0.008, 0.018)	0.440	0.313
2hr insulin (pmol/l) [‡]	631	0.004	(−0.018, 0.025)	0.733	0.933
Insulin resistance (HOMA) [‡]	625	0.017	(−0.002, 0.036)	0.082	0.362
Insulin secretion (HOMA) [‡]	625	0.015	(−0.001, 0.031)	0.060	0.302

* p-value adjusted for age, BMI, smoking, social class, alcohol consumption

[‡]Regression coefficients represent a multiplicative change in outcome per unit increase in HAD score

Table 3

Prevalence of cardiovascular disease (CVD) by HAD score in men and women in the Hertfordshire Cohort study at baseline.

Men				
	No CVD		CVD	
	N	%	N	%
HAD-D score				
0-7 non-case	1204	82.5	256	17.5
8-10 possible case	37	66.1	19	33.9
11+ probable case	10	62.5	6	37.5
<i>P- value for trend <0.001</i>				
HAD-A score				
0-7 non-case	1095	83.5	216	16.5
8-10 possible case	104	70.8	43	29.3
11+ probable case	52	70.3	22	29.7
<i>P- value for trend <0.001</i>				
Women				
	No CVD		CVD	
	N	%	N	%
HAD-D score				
0-7 non-case	1154	89.2	140	10.8
8-10 possible case	53	84.1	10	15.9
11+ probable case	11	57.9	8	42.1
<i>P- value for trend <0.001</i>				
HAD-A score				
0-7 non-case	918	89.1	112	10.9
8-10 possible case	182	87.9	25	12.1
11+ probable case	118	84.9	21	15.1
<i>P- value for trend =0.099</i>				

Table 4

Prediction of incident cardiovascular disease in men and women according to depressive and anxiety symptoms scores at the initial visit.

	Men		Women	
	Total	CVD (%)	Total	CVD (%)
HAD-D				
0-7	1122	103 (9.2)	1068	52 (4.9)
8-10	32	5 (15.6)	48	2 (4.2)
11+	8	3 (37.5)	13	2 (15.4)
<i>P- value for trend</i>		0.003		0.154
HAD-A				
0-7	1006	88 (8.8)	853	45 (5.3)
8-10	101	14 (13.9)	165	7 (4.2)
11+	55	9 (16.4)	111	4 (3.6)
<i>P- value for trend</i>		0.324		0.344

P for trend obtained using continuous HAD scores. Incident cardiovascular disease was defined as a report of heart attack, angina, serious cardiovascular illness or hospital admission, angioplasty or coronary artery bypass graft in those not having cardiovascular disease at baseline.

Table 5

Prediction of cardiovascular death in men and women according to the depressive and anxiety symptom score at the initial visit.

	Men		Women	
	Total	Deaths (%)	Total	Deaths (%)
HAD-D				
0-7	1502	37 (2.5)	1332	6 (0.5)
8-10	59	4 (6.8)	65	1 (1.5)
11+	17	1 (5.9)	20	0 (0)
<i>P- value for trend</i>		0.046		0.194
HAD-A				
0-7	1346	36 (2.7)	1062	5 (0.5)
8-10	154	5 (3.3)	209	0 (0)
11+	78	1 (1.3)	146	2 (1.8)
<i>P- value for trend</i>		0.429		0.284

P for trend obtained using continuous HAD scores. Notification and cause of death was obtained from the NHS Central Register.