Associations of depression-anxiety and dyslipidaemia with subclinical carotid arterial disease: Findings from the Whitehall II Study

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Abstract

Aims: There is mixed evidence for an association between depression and/or anxiety (DA) and carotid intima-media thickness (IMT), and limited information on the related role of dyslipidaemia. Here we report associations between DA and IMT in the Whitehall II cohort, considering the moderating effects of sex and dyslipidaemia.

Methods: 2,822 males and 1,112 females (61±6 years) were studied during phase 7 (2002-4) of the Whitehall II study. IMT and lipid levels were assessed, and questionnaires (General Health Questionnaire [GHQ] and Centre for Epidemiologic Studies Depression Scale [CES-D]) completed. Linear regression was used to explore relationships between DA and IMT and the moderating effects of sex and dyslipidaemia.

Results: 1,461 participants were categorised with DA. The association between DA and IMT differed between men and women so analyses were undertaken separately by sex. In men, IMT was significantly associated with dyslipidaemia (p=0.002) but not DA (p=0.29). In women, both dyslipidaemia and DA were independently associated with IMT (p=0.028 & p=0.031). The greatest IMT was in women with both DA and dyslipidaemia. These results were replicated when GHQ score was substituted for DA and non-HDL cholesterol for dyslipidaemia.

Conclusions: DA is associated with increased IMT in women but not in men. Dyslipidaemia is associated with IMT in both men and women. Women with both DA and dyslipidaemia are potentially at the greatest risk of CVD.

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Keywords: Depression; Anxiety; Intima-media thickness; lipids

Introduction

Depression and anxiety, which have a high level of comorbidity, are associated with increased risk of cardiovascular disease within the general population and risk of recurrent coronary events.[1-4] However, whether these chronic stressors trigger cardiovascular events in those with underlying disease and/or contribute to the development of atherosclerotic disease is unclear.[1-3, 5]

Depression and/or anxiety (DA) disorders are more prevalent in women, whereas cardiovascular disease (CVD) is traditionally more prevalent in men,[6, 7] with conflicting associations between depression and CVD in men and women.[8-11]

Increased intima-media thickness (IMT) reflects sub-clinical arterial disease and predicts clinical cardiovascular events.[12] Both depression and anxiety have been associated with increased IMT in some studies but others found no association, or differing results by sex.[13-18]

Dyslipidaemia is a key determinant of atherosclerosis and is associated with increased IMT.[19] However, the relationship between DA and dyslipidaemia is less clear.[20, 21] Regardless of how DA influences CVD risk factors, the effects of DA on atherogenesis may be greater in those with risk factors (e.g. dyslipidaemia), but have not been investigated specifically.

To investigate this issue, we hypothesised that DA would be associated with carotid IMT, that this relationship differed by sex and would be stronger among participants with dyslipidaemia.

Patients and methods

Participants

The Whitehall II cohort comprised 10,308 civil servants recruited between 1985 and 1988, undergoing regular follow-up. In 2002-4 (Phase 7), 4,097 participants completed questionnaires including questions regarding depression and anxiety symptoms and underwent assessment of

cardiovascular disease risk factors, disease status, body habitus and carotid artery IMT (Supplementary Figure 1). The University College London Medical School committee on the ethics of human research provided ethical approval.

Carotid intima-media thickness

The IMT of the far wall of both common carotid arteries was measured. The mean of the two arteries was taken (supplement).

Depression and/or anxiety

Participants completed the General Health Questionnaire (GHQ) and the Centre for Epidemiologic Studies Depression Scale (CES-D) (supplement) and were categorised thereby into two groups as having DA or neither. Depression was defined if meeting ≥1 of the following criteria: score ≥4 on GHQ depression subscale; score ≥16 on the CES-D scale; prior diagnosis of depression; prescribed antidepressant medications. Anxiety was defined if meeting ≥1 of the following criteria: score ≥5 on GHQ anxiety subscale and/or use of anxiolytic medication.

Dyslipidaemia

Fasting blood was collected for total cholesterol (TC), high density lipoprotein (HDL-C) and triglycerides (Trigs); low density lipoprotein (LDL-C) was calculated using the Friedewald formula; non-HDL-C was calculated from TC and HDL-C[22]. Participants were categorized with dyslipidaemia if meeting ≥1 of the following: TC >6.0, Trigs>1.7, HDL-C<1.0 and LDL-C>4.0mmol/L or receiving lipid lowering therapy. Glucose, C-reactive protein (CRP) and interleukin-6 (IL-6) were also measured (supplement).

Other covariates

Anthropometric measures including height, weight, hip and waist measurements were taken and body mass index (BMI) was calculated. Seated brachial blood pressure was assessed using an automated Omron 907 device.

Statistical analysis

In brief, right-skewed distributions were log transformed and cardiovascular risk factors compared between those included and excluded from the analytical sample using standard tests. The relationship between DA and IMT was explored using multiple regression and adjusted for cardiovascular risk factors. Interaction terms between DA and sex showed that the effects of DA on IMT differed between men and women. Subsequent analyses, therefore, were conducted separately in men and women. (Full details in supplement).

Results

The cohort consisted of 3,934 participants with complete data on IMT, GHQ score and all covariates (supplementary Figure 1). These participants did not differ in age from the 2,521 who were not included in this sample, but had a more favourable cardiovascular risk profile (Supplementary Table 1). Study population characteristics are shown by sex in Table 1 (combined in Supplementary Table 1).

Relationship between depression and/or anxiety and IMT

1,461(37%) participants (937 [33%] men and 524 [47%] women) were categorised with DA.
IMT was correlated with all risk factors, whereas DA was negatively correlated with age, systolic blood pressure and IMT (Supplementary Table 2).

In men and women combined, unadjusted analysis showed IMT was negatively associated with DA (Cohen's D=-0.09, p=0.006). However, adjustment for cardiovascular risk factors removed this association (p=0.96). Inclusion of the interaction variable "DA by sex" demonstrated that the association of DA with IMT differed between men and women (sex*DA interaction, p=0.016). Therefore, further analyses were conducted separately for men and women. Adjustment for the presence of dyslipidaemia confirmed the sex differences in the relationship between DA and IMT (Table 2).

In men, there was an association between dyslipidaemia and IMT (Cohen's D=0.12, p=0.002), but no association between DA and IMT (p=0.27) plus no interaction between dyslipidaemia and DA on IMT (p=0.50).

However, in women there were independent associations between IMT and both dyslipidaemia (Cohen's D=0.14, p=0.028) and DA (Cohen's D=0.13, p=0.031), but no evidence of an interaction between dyslipidaemia and DA on IMT (p=0.15). Thus, women with both DA and dyslipidaemia have greater IMT than those in other categories (Figure 1). Further adjustment for use of antihypertensive medication did not affect these findings (data not shown). The associations between DA and IMT were unaffected following sensitivity analysis using a more extreme cut-off for anxiety (Supplementary Table 5). When the DA group was separated into D only, A only and D+A, there was no overall difference in IMT for either men or women (supplementary Table 3). However, women with D+A had greater IMT than those with neither (Cohen's D=0.17 p=0.047). This was replicated in the sensitivity analysis using a greater threshold for anxiety and resulted in greater separation in IMT between those with D+A versus neither (Cohen's D=0.22 p=0.025) (Supplementary Table 5).

We also explored the relationship between non-HDL-C, DA and sex (excluding those on lipid lowering therapy). The association between DA and IMT still differed by sex (DA by sex interaction, Cohen's D=0.19, p=0.013), therefore, the association between DA and non-HDL-C was examined separately in men and women.

Furthermore, consideration of non-HDL-C confirmed the differences in the effect of DA on IMT between the sexes (Table 2). In men, there was a strong positive association between non-HDL-C and IMT (Cohen's D=0.22, p<0.001), but no association between DA and IMT (p=0.32). There was no evidence for an interaction effect between non-HDL-C and DA on IMT (p=0.93). In women, both non-HDL-C (Cohen's D=0.20, p=0.016) and DA (Cohen's D=0.14, p=0.025) were independently

associated with IMT with no interaction (p=0.70). Thus, women with both DA and high non-HDL-C have greater IMT than those in other categories (as for women with DA and dyslipidaemia).

Relationship between GHQ score and IMT

GHQ score was higher in women than men (Cohen's D=0.17, p<0.001), positively correlated with BMI, and negatively correlated with age, systolic and diastolic blood pressure and IMT (Supplementary Table 4). However, following adjustment for major cardiovascular risk factors, this association between GHQ score and IMT disappeared (p=0.33). The addition of an interaction term between sex and GHQ score again showed that the association of GHQ score with IMT differed between men and women (Cohen's D=0.07, p=0.05). The results mirrored those with DA such that, in women, both dyslipidaemia (Cohen's D=0.14, p=0.024) and GHQ score (Cohen's D=0.08, p=0.010) were independently associated with IMT, but without interaction (p=0.82). In men, dyslipidaemia (Cohen's D=0.13, p=0.002), but not GHQ score (p=0.93), was associated with IMT and there was no interaction (p=0.31).

Discussion

Our principal findings are finding that women with both DA and dyslipidaemia have greater IMT than women within the other categories. Sex had a moderating effect on the relationship between DA and IMT: women with DA were more likely to have greater IMT than those without DA, but no such relationship is seen in men.

Sex differences in the associations of depression and/or anxiety with IMT

Our finding of a moderating effect of sex on the association between DA and IMT with higher IMT in women with DA agrees with previous work.[17, 23] However, studies tended to consider depression or anxiety individually, despite co-morbidity between the two conditions. In a middle-aged Korean cohort, females with depressive symptoms had greater IMT, but there was no such difference in males.[17] In contrast, in a Hispanic cohort, a moderating effect of sex on IMT in depression was only found in males.[16] The reasons for these differences are unclear, but neurological influences may

contribute. Women appear to have greater amygdala activity in response to negative emotion, linked to greater prevalence of depression.[24] A small study found that greater amygdala activity, in response to behaviourally relevant stimuli, is associated with increased IMT.[25] Loss of the protective effect of oestrogen in postmenopausal women may also contribute as IMT progression accelerates beyond the age of 50,[26] as may methodological differences in the assessment of cIMT and DA symptoms.[16, 17] Furthermore, depression develops earlier in women, potentially extending exposure promoting subclinical atherogenesis.[27]

Dyslipidaemia, depression and/or anxiety

The observation that women with DA who also have dyslipidaemia had greater IMT is particularly interesting. Although differences between the groups were small, the adjusted effect of DA on IMT in women is similar in magnitude to that of dyslipidaemia in both sexes (according to both absolute and Cohen's D values). Thus, the cumulative combined effect on the arteries could have a clinically significant impact over time, as seen in both the healthy population and those with pre-existing coronary disease.[1, 2, 20, 21] Our findings identify a group of older women with high lipid levels and DA symptoms, that are potentially at greater risk of future cardiovascular events. Analyses categorising the participants into the separate depression, anxiety or depression and anxiety indicated that both groups with depression had greater IMT, but it was only the combined group where this difference was significant when compared with those without either depression or anxiety. However, diminishing numbers in these subgroups limits analysis power.

Our study explored a prespecified hypothesis that the presence of dyslipidaemia, itself associated with subclinical vascular pathophysiology and worse cardiovascular outcome,[19, 28, 29] would be associated with DA and arterial disease. Patients with depression or anxiety have been shown to have increased lipid levels and increased risk of cardiovascular disease[1, 2, 21] and patients with more severe symptoms of DA are more prone to dyslipidaemia alongside obesity.[20] Notably, we found the relationship between dyslipidaemia and IMT remained after adjustment for obesity measures. The combination of depression and dyslipidaemia resulting in the greatest IMT in these women may be

due to a mixture of lifestyle factors, and biological mechanisms such as inflammation (although we found no evidence of a further interaction between DA and CRP or IL6 [data not shown]), as well as other possible psychophysiological influences on lipid metabolism.

Little previous work has explored the impact of specific cardiovascular risk factors on the relationship between DA and subclinical vascular pathophysiology. Violanti et al found an association between depressive symptoms and IMT but only in those without hypertension.[30] Wagner et al found that type 2 diabetes had no impact on the association between lifetime history of depression and impaired endothelial function.[31] Therefore, the finding that women with DA and dyslipidaemia have greater IMT, may have important clinical implications, suggesting that there may be a particular benefit in treating dyslipidaemia in women with DA. Our findings confirm the importance of dyslipidaemia in men but suggest no incremental impact of DA on atherogenesis. We hypothesised that dyslipidaemia would be associated with subclinical arterial disease (cIMT) in DA in our prespecified analysis plan, rather than undertaking a "hypothesis-generating" exploratory analysis of multiple primary risk factors of interest (e.g. smoking, hypertension, diabetes, inflammation), but fully adjusted for these parameters in our multivariable analyses.

Potential mechanisms

A number of potential mechanisms may mediate the risk of cardiovascular disease in depression/anxiety, including increased hypothalamic-pituitary-adrenal axis activity (HPA) and inflammation, which promote cardiovascular and platelet dysfunction.[32-34]

Lifestyle behaviours including cigarette smoking, lower physical activity and poor diet are all associated with common mental disorders and increased cardiovascular risk[3, 35] through creation of an atherogenic vascular milieu. Although we adjusted for socioeconomic status, smoking and obesity, other less well-characterised "lifestyle"-related factors may have contributed.

Limitations

IMT was only assessed during Phase 7 of the WHII study. Therefore, we were only able to explore cross-sectional but not prospective relationships between DA and IMT. The depression group is a composite of participants, including those with symptoms meeting depression 'cut-offs', those previously diagnosed as depressed and those taking anti-depressant medication. Thus, a wide range of symptom severity from mild- to severe clinical- depression, may have differing relationships with the vascular measures. Not all participants would have currently been undergoing a depressive episode, as participants previously diagnosed with depression were included in the depression group. Equally, both the GHQ and CES-D questionnaires only concern recent symptoms and so may miss those participants who have previously had a biologically relevant period of DA. This study also could not discriminate single or recurrent episodes of DA. These limitations also apply to some extent to those with anxiety.

DA was examined as a combined variable due to the considerable overlap in conditions. However, we did consider depression and anxiety conditions separately and combined but found no overall differences in IMT between the four symptom groups. Whether these tools for identifying DA symptoms are sensitive enough to fully disentangle A from D is uncertain. Furthermore, splitting the analysis by gender and DA category reduces the group size considerably and we cannot be sure that the study was sufficiently powered to assess the separate effect of D and A. A larger prospective cohort would be required. Despite this, most of the associations described in women have small effect sizes, below or close to 0.2 as indicated by Cohen's D measure of the standardised effect (albeit similar in magnitude to the relationship between dsylipidaemia and IMT in men). Confirmatory findings from other studies are needed before these results could be generalised.

Only a small proportion of those classified with DA were taking psychotropic medication, similar to prior observations in EUROASPIRE cardiac patients.[36] This may partly be due to our only assessing current, but not prior, symptoms and use of psychotropic medication; plus a large proportion of those with DA were likely to subclinical or mild symptomology. There may also have been a reluctance to declare psychotropic medication use due to perceived stigma.

As this was a relatively healthy population, the dyslipidaemia definition was quite broad, therefore participants meeting the criteria did not necessarily have severe dyslipidaemia. The lipid cut-offs were based on European Guidelines and associated with increased cardiovascular risk.[37] Using more stringent lipid levels would reduce sample size, with consequent loss of power. However, similar relationships were observed when restricting the analysis to non-HDL-C.

Conclusion

In conclusion, we found that women with DA and dyslipidaemia have increased IMT. Regardless of the presence or absence of dyslipidaemia, DA did not have a significant effect on IMT in men.

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Conflict of interest: none declared

Author contributions

JH and EE contributed to the conception of the work. EE, MS and JH contributed to the analysis and interpretation of data for the work. EE drafted the manuscript. MS, EB, AR, AK, JD And JH critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1: Participant characteristics of the whole population and divided by sex.

	Mean ± Standard deviation / Percentage (N)	
	Men (n=2822)	**Women (n=1112)**
Age (yrs)	61.1 ± 5.8	60.9 ± 5.9
Waist circumference (cm)	93.7 ± 10.4	82.8 ± 12.4
Body mass index (kg/m^2)	26.4 ± 3.7	26.7 ± 5.1
Low employment grade	3.5% (99)	26.5% (295)
Current smokers	6.2% (174)	8.4% (92)
Antidepressants	2.5% (69)	4.4% (49)
Anxiolytics	0.3% (8)	0.4% (4)
Lipid lowering therapy	12.0% (337)	9.1% (101)
Antihypertensive therapy	22.6% (637)	23.7% (263)
Systolic blood pressure (mmHg)	127.4 ± 15.4	125.2 ± 173
Diastolic blood pressure (mmHg)	74.2 ± 10.2	72.5 ± 10.4
Heart rate (bpm)	66.6 ± 11.6	67.8 ± 9.7
Fasting glucose[a] (mmol/L)	5.43 ± 0.16	5.20 ± 0.15
Total cholesterol (mmol/L)	5.63 ± 0.99	5.92 ± 1.01
HDL-cholesterol (mmol/L)	1.48 ± 0.39	1.82 ± 0.49
Triglycerides (mmol/L)	1.41 ± 0.90	1.21 ± 0.68
LDL-cholesterol (mmol/L)	3.51 ± 0.91	3.54 ± 0.96
NonHDL-cholesterol (mmol/L)	4.15 ± 1.01	4.09 ± 1.06
Dyslipidaemia	60% (1692)	58% (647)
C-reactive protein[a] (mg/L)	1.21 ± 1.06	1.43 ± 1.13
Interleukin 6[a] (pg/ml)	1.88 ± 0.57	1.75 ± 0.56
Depression and/or anxiety	33% (937)	47% (524)
General health questionnaire score[b]	2.59 ± 5.13	3.34 ± 5.80
Intima-media thickness (mm)	0.80 ± 0.16	0.77 ± 0.14

HDL = high density lipoprotein, LDL = low density lipoprotein

[a] Estimates shown for fasting glucose, C-reactive protein and interleukin 6 are the geometric mean ± standard deviation of the logged values.

[b] Estimates shown are for untransformed GHQ. Log(GHQ+1.0) transformation used in all other analyses.

Table 2. Association between IMT and, (A) depression and/or anxiety and dyslipidaemia, and (B) depression and/or anxiety and non-HDL, separately in men and women

	Men		Women	
	N	**Mean IMT[a] (95%CI)**	**N**	**Mean IMT[a] (95%CI)**
Analysis A				
Depression and/or anxiety				
No	1885	0.798 (0.790, 0.805)	588	0.766 (0.755, 0.776)
Yes	937	0.791 (0.781, 0.801)	524	0.782 (0.771, 0.793)
p-value		0.27		0.031
Dyslipidaemia				
No	1130	0.785 (0.775, 0.794)	465	0.765 (0.753, 0.777)
Yes	1692	0.803 (0.796, 0.811)	647	0.783 (0.773, 0.793)
p-value		0.002		0.028
Analysis B				
Depression and/or anxiety				
No	1671	0.794 (0.786, 0.801)	536	0.764 (0.753, 0.775)
Yes	814	0.787 (0.777, 0.797)	475	0.782 (0.771, 0.794)
p-value		0.32		0.025
Non-HDL				
Lowest third (≤ 3.6)	642	0.776 (0.764, 0.788)	340	0.761 (0.748, 0.775)
Middle third (3.7 – 4.5)	945	0.788 (0.778, 0.797)	337	0.771 (0.757, 0.785)
Highest third (> 4.5)	898	0.808 (0.798, 0.818)	334	0.786 (0.772, 0.801)
p-value (trend)		<0.001		0.016

[a] Associations of depression and/or anxiety and dyslipidaemia (Analysis A) and of depression and/or anxiety and non-HDL (Analysis B), are mutually adjusted. All analyses are also adjusted for age, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic status.

Figure 1: IMT in women with and without DA and dyslipidaemia. IMT is adjusted for age, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic status (Bars show standard errors of the means).

Supplementary information:

Supplementary methods

Participants completed the 30-item General Health Questionnaire (GHQ) and the Centre for Epidemiologic Studies Depression Scale (CES-D)[1, 2]. The GHQ focuses on self-reported symptoms of anxiety, depression and associated psychosocial dysfunction. Within each question, the participant confirms whether or not a specific symptom is present. The scores were then summed, with a higher score reflecting more severe symptoms of common mental disorders. In addition, subscales were identified for depression and anxiety using factor analysis. Based on previous studies, depression was defined as having a score of ≥4 on the depression subscale, and anxiety was identified as having a score of ≥5 of the anxiety subscale[3, 4]. The depression subscale has a Cronbach α of =0.88 and a retest correlation of r=0.78 and the anxiety subscale has a Cronbach α of =0.86. Using the CES-D scale, clinically significant depression symptoms were defined by a score of ≥16. Participants had also been questioned about prior clinical diagnoses of depression and use of anti-depressant and anxiolytic medications.

Carotid intima-media thickness.

Participants rested in a supine position, the right and left common carotid arteries were imaged using an ALOKA Prosound 5500 ultrasound machine. Longitudinal images of the common carotid artery approximately 1 cm proximal to the bifurcation, with a clearly defined far wall intima-media complex, were zoomed and triggered to the R-wave of the ECG and recorded for later analysis.

IMT was measured as the distance between the leading edge of the intima and the media-adventitia border using callipers integral to the ultrasound machine. Three measurements, each from a separate frame, were taken from the left and right arteries; mean IMT was calculated from the combined results.

Measurement of inflammatory markers.

Interleukin-6 (IL-6) and c-reactive protein (CRP) were measured in the serum stored at -70^{O}C until analysis. CRP was assessed using a high sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). Values lower than the detection limit (0.154 mg/l) were assigned a value equal to half the detection limit. For assessment of short term biological variation and laboratory error a repeated sample was taken from 533 participants. Intra- and inter-assay coefficients of variation were 4.7% and 8.3%. Reliability between samples was assessed with Pearson's r correlation coefficients: r =0.72

IL-6 was assessed using a high-sensitivity enzyme linked immunosorbent assay (ELISA) (R&D systems, Oxford, UK). Values lower than the detection limit (0.08pg/ml) were assigned a values equal to half the detection limit. For assessment of biological variation and laboratory error, a repeated sample was taken from 329 participants at phase. Intra and inter-assay coefficients of variation were 7.5% and 8.9%. Reliability between samples was assessed with Pearson's r coefficients: r = 0.63.

Statistical analysis

The distributions of fasting glucose, CRP and IL-6 were right-skewed and log transformed for analysis. Similarly, GHQ score, range 0 to 30, was log transformed after the addition of one to produce a more normally distributed variable. Cardiovascular risk factors were compared between those included and not included in the final analytic sample using independent t-tests, independent Mann Whitney U tests or Chi square tests, where appropriate. Pearson and Spearman correlations were used to compare associations between cardiovascular risk factors and IMT, DA classification and GHQ score.

Linear regression was used to explore the relationship between DA and IMT and Cohen's D used to show the standardised effect. The initial regression model was unadjusted while the second model included the following cardiovascular risk factors: age, systolic blood pressure (SBP), TC, fasting

glucose, waist, BMI, CRP, IL-6, smoking and socio-economic status (defined as last known employment grade). To investigate the moderating effects of sex on the relationship between IMT and DA, a sex by DA interaction term was added to this model. Since this indicated that the relationship between DA and IMT differed in men and women, further models examining the confounding and moderating effects of dyslipidaemia and non-HDL were fitted in men and women separately. Associations between IMT and non-HDL were assessed using tests for trend across the non-HDL categories and the magnitude of these associations was described using Cohen's D comparing the highest versus lowest third of non-HDL.

Analyses were repeated, replacing DA with the GHQ score, as a continuous variable as an indicator of DA.

Supplementary Table 1: Characteristics of 6455 participants who completed the Phase 7 questionnaire and screening in 2002-04 according to whether they are in the analytic sample

	Study sample		p-value
	Not in sample	In sample	
	Mean ± SD or % (n)	Mean ± SD or % (n)	
Number	2521	3934	
Age (yrs)	61.2 ± 6.1	61.1 ± 5.9	0.52
Female, %	30.6% (771)	28.3% (1112)	0.049
Waist circumference (cm)	92.5 ± 12.8	90.6 ± 12.0	<0.001
Body mass index (kg/m^2)	27.2 ± 4.7	26.5 ± 4.2	<0.001
Low employment grade	12.0% (299)	10.0% (394)	0.014
Current smokers	10.2% (255)	6.8% (266)	<0.001
Antidepressants	4.6% (115)	3.0% (118)	0.001
Anxiolytics	0.7% (18)	0.3% (12)	0.030
Lipid lowering therapy	12.4% (313)	11.1% (438)	0.12
Antihypertensive therapy	27.2% (683)	22.9% (900)	<0.001
Systolic blood pressure (mmHg)	130.6 ± 18.0	126.8 ± 16.0	<0.001
Diastolic blood pressure (mmHg)	75.7 ± 10.7	73.7 ± 10.3	<0.001
Heart rate (bpm)	69.1 ± 11.7	67.0 ± 11.1	<0.001
Fasting glucose[a] (mmol/L)	5.41 ± 0.19	5.36 ± 0.16	0.04
Total cholesterol (mmol/L)	5.75 ± 1.07	5.71 ± 1.01	0.10
HDL-cholesterol (mmol/L)	1.58 ± 0.46	1.58 ± 0.44	0.95
Triglycerides (mmol/L)	1.47 ± 1.05	1.35 ± 0.85	<0.001
LDL-cholesterol (mmol/L)	3.52 ± 0.96	3.52 ± 0.92	0.96
Non-HDL-cholesterol (mmol/L)	4.17 ± 1.07	4.13 ± 1.03	0.11
Dyslipidaemia	62% (1551)	59% (2339)	0.094
C-reactive protein[a] (mg/L)	1.45 ± 1.13	1.27 ± 1.09	<0.001
Interleukin 6[a] (pg/ml)	2.10 ± 0.67	1.84 ± 0.58	<0.001
Depression and/or anxiety	42% (1066)	37% (1461)	<0.001
General health questionnaire score[b]	3.30 ± 5.77	2.80 ± 5.34	<0.001

HDL = high density lipoprotein, LDL = low density lipoprotein

[a] Estimates shown for fasting glucose, C-reactive protein and interleukin 6 are the geometric mean ± standard deviation of the logged values.

[b] Estimates shown are for untransformed GHQ. Log(GHQ+1.0) transformation used in all other analyses.

Supplementary Table 2: Pearson correlations of cardiovascular risk factors with intima-media thickness and depression and/or anxiety grouping.

	Intima-media thickness (N=3934)		Depression and/or anxiety (N=3934)	
	Correlation	**p-value**	**Correlation**	**p-value**
Age (yrs)	0.307	<0.001	-0.124	<0.001
Waist circumference (cm)	0.132	<0.001	-0.035	0.027
Body mass index (kg/m^2)	0.090	<0.001	0.026	0.10
Systolic blood pressure (mmHg)	0.225	<0.001	-0.056	<0.001
Diastolic blood pressure (mmHg)	0.067	<0.001	-0.033	0.039
Heart rate (bpm)	-0.062	0.001	0.025	0.19
Fasting glucose[a] (mmol/L)	0.089	<0.001	-0.015	0.35
Total cholesterol (mmol/L)	0.047	0.003	-0.009	0.58
HDL-cholesterol (mmol/L)	-0.069	<0.001	0.001	0.93
Triglycerides (mmol/L)	0.026	0.010	0.026	0.11
LDL-cholesterol (mmol/L)	0.071	<0.001	-0.015	0.35
NonHDL-cholesterol (mmol/L)	0.076	<0.001	-0.009	0.56
C-reactive protein[a] (mg/L)	0.091	<0.001	0.013	0.43
Interleukin 6[a] (pg/ml)	0.107	<0.001	-0.003	0.84
Intima-media thickness (mm)	-		-0.044	0.006

HDL = high density lipoprotein, LDL = low density lipoprotein

[a] Logged values for fasting glucose, C-reactive protein and interleukin 6 are used in the analyses.

Supplementary Table 3: Association between IMT and depression and/or anxiety and dyslipidaemia, separately in men and women

	Men		Women	
	N	Mean IMT[a] (95%CI)	N	Mean IMT[a] (95%CI)
Depression and/or anxiety				
Neither	1885	0.798 (0.790, 0.805)	588	0.766 (0.755, 0.776)
Anxiety only	431	0.793 (0.779, 0.808)	212	0.776 (0.759, 0.793)
Depression only	220	0.798 (0.777, 0.818)	120	0.786 (0.764, 0.809)
Depression and anxiety	286	0.781 (0.763, 0.799)	192	0.787 (0.769, 0.805)
p-value		0.40		0.13
Dyslipidaemia				
No	1130	0.783 (0.772, 0.793)	465	0.770 (0.757, 0.783)
Yes	1692	0.802 (0.793, 0.811)	647	0.787 (0.777, 0.798)
p-value		0.002		0.027

[a] Associations of depression and/or anxiety and dyslipidaemia are mutually adjusted. All analyses are also adjusted for age, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic status.

Supplementary Table 4: Spearman correlation coefficients between cardiovascular risk factors and GHQ score.

	GHQ score	
	Correlation	**p-value**
Age (yrs)	-0.152	<0.001
Waist circumference (cm)	0.017	0.30
Body mass index (kg/m^2)	0.058	<0.001
Systolic blood pressure (mmHg)	-0.065	<0.001
Diastolic blood pressure (mmHg)	-0.022	0.18
Heart rate (bpm)	0.032	0.087
Fasting glucose (mmol/L)	-0.018	0.26
Total cholesterol (mmol/L)	-0.018	0.27
HDL-cholesterol (mmol/L)	-0.027	0.089
Triglycerides (mmol/L)	0.030	0.056
LDL-cholesterol (mmol/L)	-0.007	0.66
Non-HDL-cholesterol (mmol/L)	0.000	0.99
C-reactive protein (mg/L)	0.031	0.052
Interleukin 6 (pg/ml)	0.033	0.004
Intima-media thickness (mm)	-0.035	0.030

HDL = high density lipoprotein, LDL = low density lipoprotein

Supplementary Table 5: Sensitivity analysis of the association between IMT and depression and/or anxiety using a more extreme cut off for anxiety[a], separately in men and women

	Men		Women	
	N	Mean IMT[b] (95%CI)	N	Mean IMT[b] (95%CI)
Depression and/or anxiety				
Neither	2108	0.797 (0.790, 0.803)	696	0.766 (0.756, 0.775)
Depression and/or anxiety	714	0.791 (0.779, 0.802)	416	0.786 (0.774, 0.798)
p-value		0.37		0.027
Depression and/or anxiety				
Neither	2108	0.797 (0.790, 0.803)	696	0.766 (0.756, 0.775)
Anxiety only	208	0.796 (0.775, 0.817)	104	0.785 (0.760, 0.809)
Depression only	314	0.794 (0.777, 0.811)	180	0.781 (0.763, 0.801)
Depression and anxiety	192	0.780 (0.758, 0.802)	132	0.793 (0.771, 0.815)
p-value		0.53		0.067

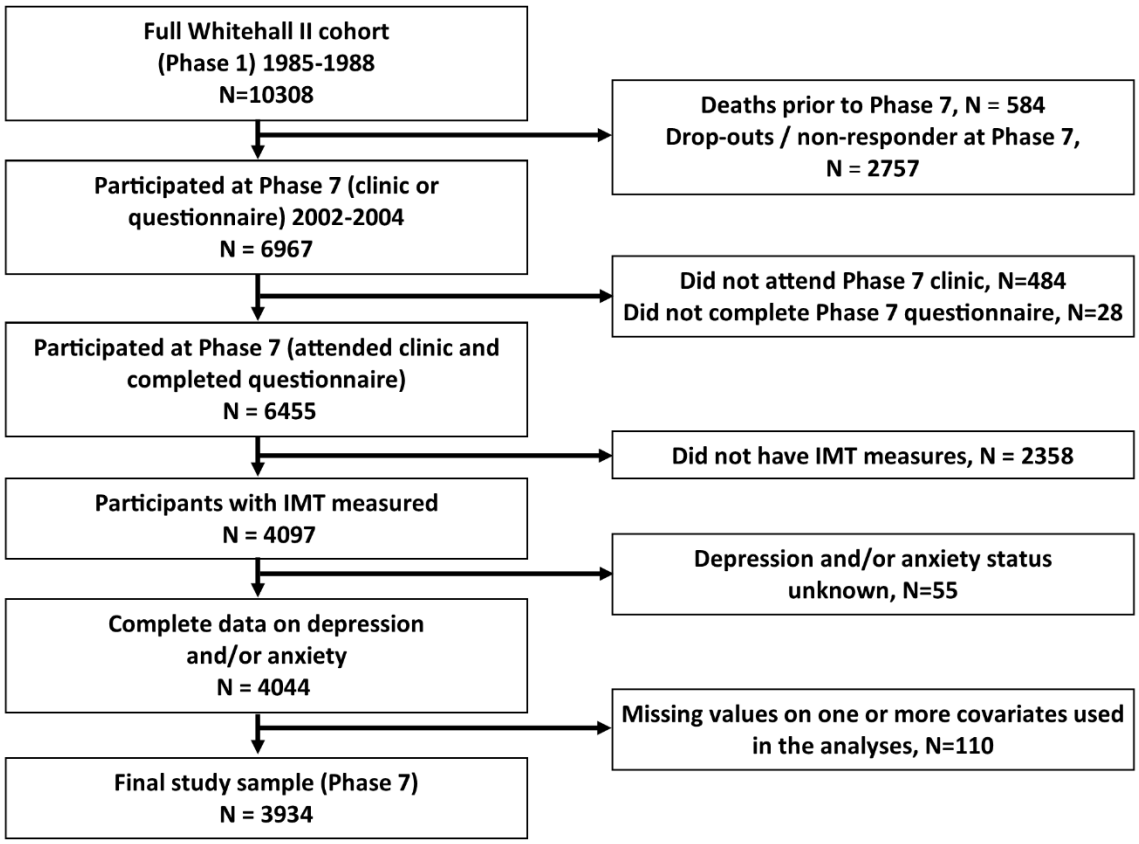
[a] Sensitivity analysis uses cut off of ≥6 for anxiety score, so prevalence of anxiety = 16%.
[b] All analyses are also adjusted for age, dyslipidaemia, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic status.

Supplementary Table 6: Association between IMT and depression and/or anxiety and non-HDL, separately in men and women

	Men		Women	
	N	Mean IMT[a] (95%CI)	N	Mean IMT[a] (95%CI)
Depression and/or anxiety				
Neither	1671	0.794 (0.786, 0.801)	536	0.763 (0.753, 0.774)
Anxiety only	383	0.790 (0.774, 0.805)	189	0.774 (0.756, 0.793)
Depression only	191	0.789 (0.768, 0.810)	113	0.784 (0.761, 0.808)
Depression and anxiety	240	0.781 (0.762, 0.800)	173	0.789 (0.770, 0.808)
p-value		0.67		0.11
Non-HDL				
Lowest third (≤ 3.6)	642	0.774 (0.761, 0.787)	340	0.767 (0.752, 0.781)
Middle third (3.7 – 4.5)	945	0.785 (0.774, 0.797)	337	0.776 (0.761, 0.790)
Highest third (> 4.5)	898	0.806 (0.794, 0.817)	334	0.791 (0.776, 0.806)
p-value (trend)		<0.001		0.018

[a] Associations of depression and/or anxiety and dyslipidaemia are mutually adjusted. All analyses are also adjusted for age, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic status.

Supplementary Figure 1: Cohort flowchart



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