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

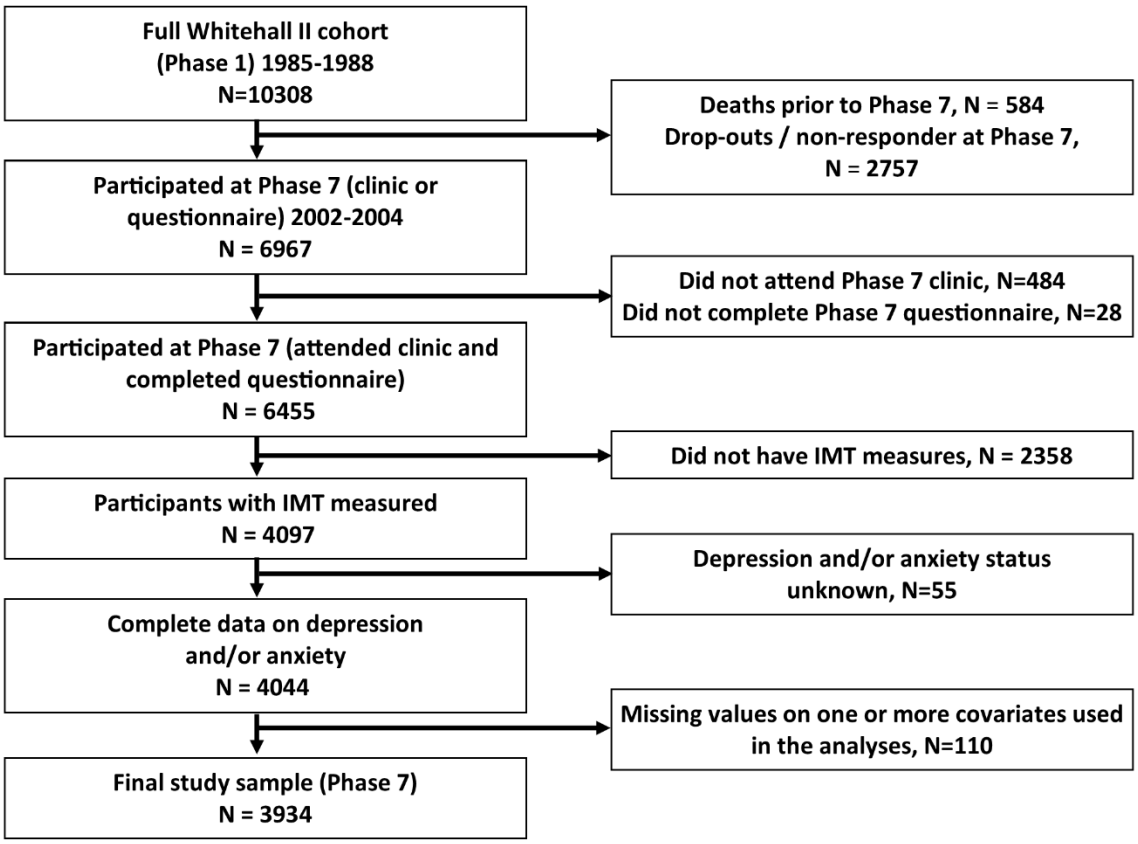
[a] Sensitivity analysis uses cut off of ≥6 for anxiety score, so prevalence of anxiety = 16%.
[b] All analyses are also adjusted for age, dyslipidaemia, systolic blood pressure, waist circumference, body mass index, fasting glucose, c-reactive protein, interleukin-6, smoking status and socio-economic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



Supplementary References

1. Goldberg DP. *The Detection of Psychiatric Illness by Questionnaire*. Great Britain: Oxford University Press, 1972.
2. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement* 1977; 1: 385-401.
3. Stansfeld SA, Head J, Fuhrer R, et al. Social inequalities in depressive symptoms and physical functioning in the Whitehall II study: exploring a common cause explanation. *Journal Of Epidemiology And Community Health* 2003; 57: 361-367.
4. Hemingway H, Shipley M, Mullen MJ, et al. Social and psychosocial influences on inflammatory markers and vascular function in civil servants (the Whitehall II study). *The American Journal of Cardiology* 2003; 92: 984-987.