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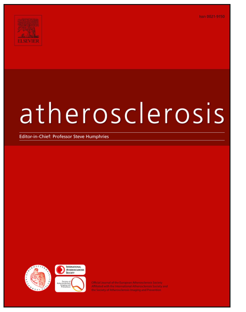


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*Short Communication: Atherosclerosis*

# Psychological Distress and Risk of Peripheral Vascular Disease, Abdominal Aortic Aneurysm, and Heart Failure: Pooling of Sixteen Cohort Studies

*Distress and Cardiovascular Disease Presentation*

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*Key words: epidemiology, mental health, cardiovascular disease, psychological distress, peripheral vascular disease, abdominal aortic aneurysm, heart failure.*

**Abstract**

*Objectives:* Examine the little-tested relation of psychological distress with peripheral vascular disease, abdominal aortic aneurysm, and heart failure.

*Methods:* Pooling of raw data from 166,631 male and female participants in 16 UK-based cohort studies. Psychological distress was measured using the 12-item General Health Questionnaire. Peripheral vascular disease, abdominal aortic aneurysm, and heart failure events were based on death register linkage.

*Results:* During a mean follow up 9.5 years there were 17,368 deaths of which 5922 were cardiovascular disease-related. Relative to the asymptomatic group (0 score), the highly distressed group (score 7-12) experienced an elevated risk of peripheral vascular disease (adjusted hazard ratio; 95% confidence interval: 3.39; 1.97, 5.82) and heart failure (1.76; 1.37, 2.26). Psychological distress was weakly related to the risk of death from abdominal aortic aneurysm. As anticipated, distress was associated with cardiovascular disease, coronary heart disease, and all strokes combined.

*Conclusions:* We provide new evidence of mental health-related cardiovascular disease presentations relevant to primary care physicians.

## Introduction

Meta-analyses of a series of population-based studies demonstrate that psychological distress (depression and anxiety) is related to both coronary heart disease[1] and stroke,[2] such that the presence of distress apparently confers as much as twice the risk of these conditions. These associations do not appear to be substantially confounded by conventional risk factors such as socioeconomic deprivation, cigarette smoking, and raised blood pressure. While this evidence base is expanding, little is understood about the link, if any, between psychological distress and other cardiovascular disease presentations. While there has been one study examining the link between depression and heart failure in the general population,[3] we are unaware of any investigations linking psychological distress or depression with peripheral vascular disease or abdominal aortic aneurysm. The findings of patient-based cohorts,[4;5] although providing important prognostic observations, are not necessarily transportable to people who are disease-free at study induction.

Accordingly, in a large scale pooling of data across 16 cohort studies, we tested the link between psychological distress and a range of cardiovascular disease phenotypes. For the purposes of comparing the magnitude of effects across other cardiovascular disease phenotypes, we also include total cardiovascular disease, coronary heart disease, and stroke as endpoints of interest.

## Material and Methods

Participants were taken from the Health Survey for England[6] and Scottish Health Survey,[7] a series of geographically-representative health examinations of people living in private households. Between 1994 and 2008, 16 independent, cross-sectional studies with identical methodologies were conducted either on an annual (Health Survey for England; N=13) or intermittent (Scottish Health Surveys; N=3) basis. Ethical approval was obtained from the London Research Ethics Council.

*Measurement of psychological distress*

During a household visit, nurse interviewers collected information using computer-assisted personal interviewing modules. Psychological distress was measured using the 12-item version of the General Health Questionnaire (GHQ-12),[8] a widely utilised inventory in population-based studies. Validated against standardised psychiatric interviews,[9;10] this unidimensional scale of distress consists of items capturing symptoms of depression, anxiety, social dysfunction, and loss of confidence. We applied existing thresholds to the GHQ-12 data to create categories of clinical relevance: asymptomatic (score 0), subclinically symptomatic (1-3), symptomatic (4-6), and highly symptomatic (7-12).[11]

*Measurement of collateral data*

A range of covariate data were collected using standard protocols:[6;7] current occupational social class (professional, managerial or technical, skilled non-manual, skilled manual, partly skilled, and unskilled), age upon leaving full-time education, body mass index (based on directly ascertained height[m] and weight[kg]), smoking status (not a current smoker; or <5, 5-10, 10-15, 15-20, and >20 cigarettes per day), alcohol consumption (frequency of drinking), and the presence of a long-standing illness (yes/no). Diabetes was denoted by one or more of the following: self-report of doctor-diagnosed diabetes, self-report of diabetes as a long standing illness, hospitalisation for diabetes, or HbA1c>=6.5. Hypertension was denoted by one or more of the following: self-report of doctor-diagnosed hypertension, self-report of hypertension as a long standing illness, and measured systolic blood pressure of >=140 mmHg or a diastolic blood pressure of 90 mmHg.

*Mortality ascertainment*

Consenting study members (166,631 [88.2%]) were linked to UK National Health Service mortality records which provided data on the principal and contributing causes of death. In preliminary survival analyses, the use of a narrow, mutually exclusive case definition (i.e., underlying cause of death only) or a broad, non-mutually exclusive (i.e., any mention of the condition on the death certificate) resulted in the same conclusions about the relation of distress with each of the six outcomes under study. We therefore used the latter as this provided the highest number of events and therefore the greatest statistical power. Cardiovascular disease was denoted by any mention of the following codes on death certificates: 390-459 (ICD-9) or I00-I99 (ICD-10). The corresponding codes were 410-414 or I20-I25 for ischaemic heart disease; 430-438 or I60-I69 for stroke; 443 or I73 for peripheral vascular disease; 428 or I50 for heart failure; and 441.3/441.4 or I71.3/ I71.4 for abdominal aortic aneurysm.

*Statistical analyses*

We used raw data from people aged 16 years and over from all study years, the only exceptions being the surveys years 1996 and 2007 when psychological distress was not measured. In preliminary analyses, we determine that the proportional hazards assumption had not been violated by inspecting the survival curves according to distress categories. Accordingly, we used Cox proportional hazards models[12] to compute study-specific hazard ratios with accompanying 95% confidence intervals for the association of distress score with each cardiovascular disease outcome. We used calendar time (months) as the time scale with study members censored at the date of death or the end of follow-up (15 February 2011) – whichever came first. Hazard ratios were adjusted minimally (age and sex) then maximally (age, sex, occupational social class, educational attainment, smoking status, frequency of alcohol consumption, BMI, diabetes, hypertension, and self-reported longstanding illness). The $I^2$ statistic, which quantifies the proportion of the total variation in effect estimates due to between-studies variation, ranged between 0% and 66.8% depending on the mortality outcome used in the analysis. Owing to this heterogeneity, we pooled the study-specific effect estimates and their standard errors in random effects meta-analyses.

**Results**

From an initial sample of 199,504 participants, 32,873 did not consent to record linkage, and/or were missing data on consent, and/or were missing a distress score, giving a maximum analytic sample of 166,631 (55% female, mean age 46.6 years, SD=18.4, range=16-102). The characteristics of study members excluded from analyses were similar to those in the included group.

A total of 1.58 million person-years at risk (mean (SD) follow up of 9.5 (4.3) years) gave rise to 17,368 deaths, 5922 of which were cardiovascular disease-related. The latter comprised the occasionally overlapping causes of ischaemic heart disease (N=4519), stroke (2225), heart failure (1948), peripheral vascular disease (247), and abdominal aortic aneurysm (220). Relative to the group without any such symptoms, the most distressed study members experienced around twice the rate of death due to heart failure (table 1, figure 1). There was almost a four-fold increase in the risk of peripheral vascular disease when the same categories were compared. Notably, both these relationships appeared to occur in a stepwise manner ($p<0.001$), such that the greater the degree of reported distress, the higher the risk of death ascribed to these cardiovascular disease endpoints. The magnitude of the relationships was only partially diminished by statistical control for potential confounding factors. There was a suggestion that abdominal aortic aneurysm was also positively related to psychological distress score, however, the magnitude of this relationship was lower and statistical significance at conventional levels was not apparent. As anticipated, high psychological distress was positively related to mortality ascribed to all cardiovascular disease, coronary heart disease, and stroke, such that around a doubling of death rate was evident in the most distressed individuals relative to those who were symptom-free. Figure 2, which depicts the association between one standard deviation increase (disadvantage) in psychological distress and mortality from a range of cardiovascular disease phenotypes, provides an at-a-glance summary of our results.

In order to take into account reverse causality – the notion the baseline somatic illness, whether measured or hidden, might be generating the positive relation between distress and the various CVD phenotypes in the present analyses – we carried out some sensitivity analyses. First, we additionally adjusted for self-reported doctor-diagnosed cardiovascular disease (recorded in 11 cohort studies: N=82,977, 2501 CVD deaths). Second, we dropped deaths arising in the first 2 years of follow-up (left censoring: N=109,070, 3182 CVD deaths), reasoning that these would largely be due to baseline illness. In each of these sets of analyses the resulting effects estimates were essentially unchanged.

**Discussion**

This individual participant meta-analysis shows that higher levels of psychological distress are associated with a raised risk of death from heart failure and peripheral vascular disease. In contrast, links with abdominal aortic aneurysm were generally weak. To the best of our knowledge, this is the first examination of the association of distress with peripheral vascular disease and abdominal aortic aneurysm. Positive relationships for distress with cardiovascular disease, coronary heart disease, and all strokes combined, apparent in an earlier follow-up of these study members,[11] were also seen in these analyses.

That psychological distress was not strongly related to abdominal aortic aneurysm in our analyses suggests a specificity of association. The alternative, a general susceptibility to all forms of cardiovascular disease among people with mental health problems, would imply that the associations are less likely to be causative.[13] We took into account a wide range of confounding variables to address the well-established observation of an unfavourable risk factor profile in people experiencing psychological distress and our hazard ratios were only marginally diminished. Furthermore, that an increased cardiovascular disease risk was evident even at low to moderate levels of psychological distress, rather than just at the most severe end of the continuum, suggests that reverse causation is an unlikely explanation for our findings. Provided our observational results are replicated, further mechanistically-orientated research is therefore justified on pathways that potentially may include neuroendocrine (e.g., heightened platelet aggregation), immunology, and inflammation.[14;15]

In conclusion, in showing psychological distress is associated with an increased risk of peripheral vascular disease and heart failure, we provide new evidence of mental health-related cardiovascular disease presentations relevant to primary care physicians.

**Competing interests**: The authors declare that they have no competing interests.

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## References


(1) Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006; 27(23):2763-2774.

(2) Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 2011; 306(11):1241-1249.

(3) Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosom Med* 2002; 64(1):6-12.

(4) Abramson J, Berger A, Krumholz HM, Vaccarino V. Depression and risk of heart failure among older persons with isolated systolic hypertension. *Arch Intern Med* 2001; 161(14):1725-1730.

(5) Grenon SM, Hiramoto J, Smolderen KG, Vittinghoff E, Whooley MA, Cohen BE. Association between depression and peripheral artery disease: insights from the heart and soul study. *J Am Heart Assoc* 2012; 1(4):e002667.

(6) Mindell J, Biddulph JP, Hirani V, Stamatakis E, Craig R, Nunn S et al. Cohort profile: the health survey for England. *Int J Epidemiol* 2012; 41(6):1585-1593.

(7) Gray L, Batty GD, Craig P, Stewart C, Whyte B, Finlayson A et al. Cohort profile: the Scottish health surveys cohort: linkage of study participants to routinely collected records for mortality, hospital discharge, cancer and offspring birth characteristics in three nationwide studies. *Int J Epidemiol* 2010; 39(2):345-350.

(8) Goldberg D. Manual of the General Health Questionnaire. Windsor, England: NFER; 1978.

(9) Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997; 27(1):191-197.

(10) Stansfeld SA, Sharp DS, Gallacher JE, Yarnell JW. A population survey of ischaemic heart disease and minor psychiatric disorder in men. *Psychol Med* 1992; 22(4):939-949.

(11) Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012; 345:e4933.

(12) Cox DR. Regression models and life-tables. *J R Stat Soc [Ser B]* 1972; 34:187-220.

(13) Bradford Hill A. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine* 1965; 58:295-300.

(14) Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998; 55(7):580-592.

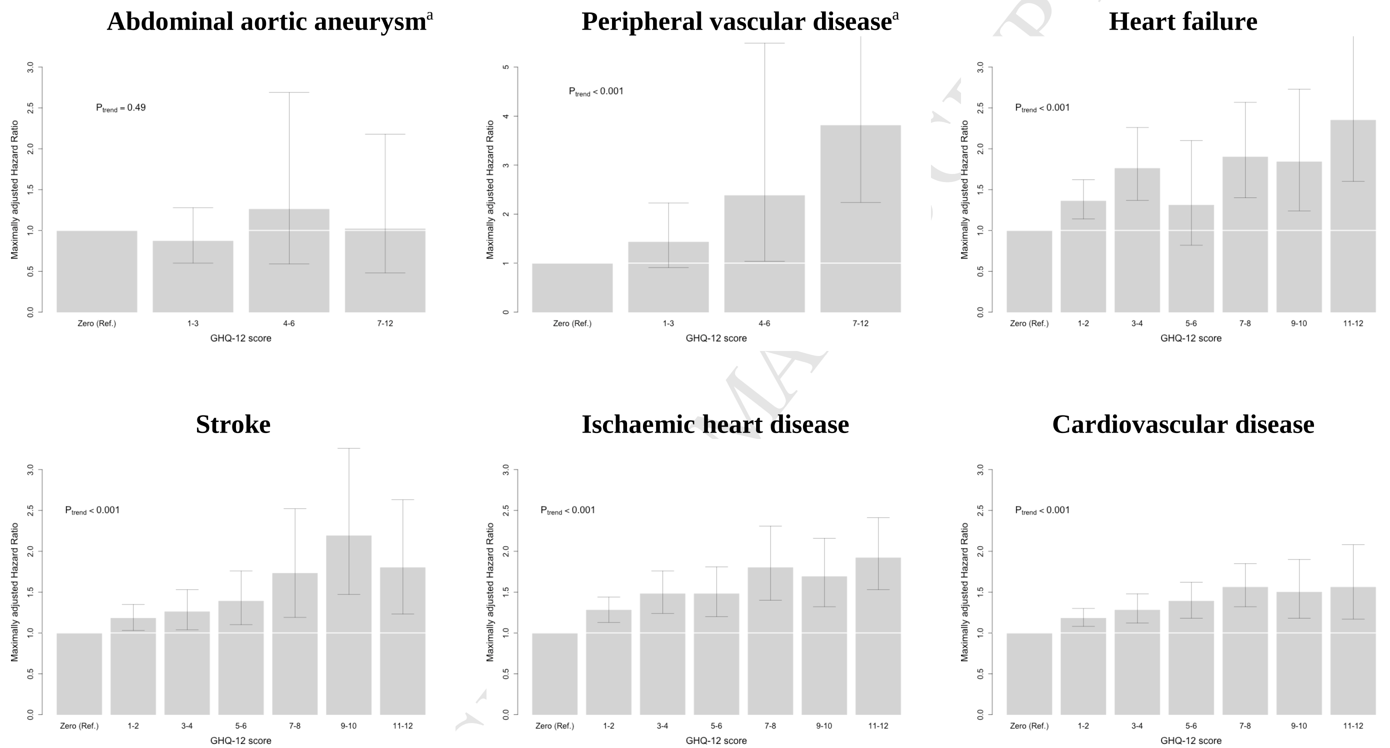
(15) Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. *Am J Cardiol* 2005; 96(7):1016-1021.

**Table 1. Hazard ratios (95% confidence intervals) for the association between psychological distress and mortality from cardiovascular disease phenotypes: individual participant meta-analysis of sixteen prospective cohort studies**

| | Deaths | N | Distress classification (GHQ score) | | | | $P_{trend}$ |
|---|---|---|---|---|---|---|---|
| | | | Asymptomatic (0) | Subclinically symptomatic (1-3) | Symptomatic (4-6) | Highly symptomatic (7-12) | |
| **Abdominal aortic aneurysm** | | | | | | | |
| Minimally-adjusted[a] | 220 | 166631 | 1 (ref) | 1.01 (0.73, 1.41) | 1.36 (0.77, 2.43) | 1.46 (0.83. 2.58) | 0.69 |
| Maximally-adjusted[b] | 162 | 109680 | 1 | 0.85 (0.58, 1.24) | 1.22 (0.57, 2.61) | 0.97 (0.45, 2.07) | 0.49 |
| **Peripheral vascular disease** | | | | | | | |
| Minimally-adjusted | 247 | 166631 | 1 | 1.48 (1.06, 2.06) | 1.93 (1.19, 3.12) | 3.62 (2.43, 5.38) | <0.001 |
| Maximally-adjusted | 147 | 109680 | 1 | 1.31 (0.85, 2.02) | 2.37 (1.01, 5.57) | 3.39 (1.97, 5.82) | <0.001 |
| **Heart failure** | | | | | | | |
| Minimally-adjusted | 1948 | 166631 | 1 | 1.54 (1.30, 1.83) | 1.79 (1.44, 2.22) | 2.36 (1.77, 3.14) | <0.001 |
| Maximally-adjusted | 1236 | 109680 | 1 | 1.41 (1.18, 1.69) | 1.43 (1.05, 1.94) | 1.76 (1.37, 2.26) | <0.001 |
| **Stroke** | | | | | | | |
| Minimally-adjusted | 2225 | 166631 | 1 | 1.23 (1.12, 1.36) | 1.56 (1.36, 1.80) | 1.93 (1.66, 2.23) | <0.001 |
| Maximally-adjusted | 1343 | 109680 | 1 | 1.16 (1.02, 1.32) | 1.44 (1.20, 1.73) | 1.53 (1.25, 1.87) | <0.001 |
| **Ischaemic heart disease** | | | | | | | |
| Minimally-adjusted | 4519 | 166631 | 1 | 1.44 (1.31, 1.58) | 1.73 (1.54, 1.94) | 2.19 (1.88, 2.55) | <0.001 |
| Maximally-adjusted | 3019 | 109680 | 1 | 1.31 (1.16, 1.47) | 1.48 (1.26, 1.73) | 1.71 (1.45, 2.02) | <0.001 |
| **All cardiovascular disease** | | | | | | | |
| Minimally-adjusted | 5922 | 166631 | 1 | 1.34 (1.25, 1.43) | 1.60 (1.47, 1.74) | 2.08 (1.79, 2.42) | <0.001 |
| Maximally-adjusted | 3806 | 109680 | 1 | 1.19 (1.09, 1.30) | 1.36 (1.20, 1.653) | 1.50 (1.27, 1.76) | <0.001 |
| | | | | | | | |

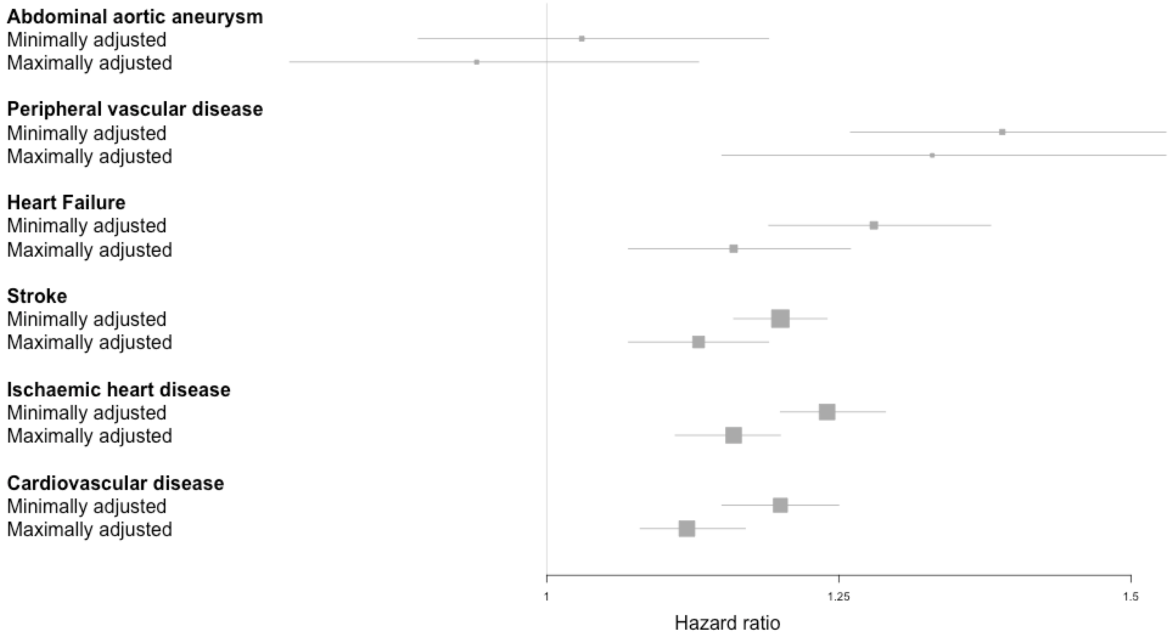
[a]Models adjusted for age and sex. [b]Models adjusted for age, sex, hypertension, diabetes, occupational social class, smoking status, frequency of alcohol consumption, body mass index, and self-reported longstanding illness.

**Figure 1. Maximally-adjusted hazard ratios (95% confidence intervals) for the association between increasing levels of psychological distress and mortality from a range of cardiovascular disease phenotypes: individual participant meta-analysis of sixteen prospective cohort studies**




Maximally adjusted models are adjusted for age and sex plus hypertension, diabetes, occupational social class, smoking status, frequency of alcohol consumption, body mass index, and self-reported longstanding illness. [a]Fewer distress categories owing the lower number of deaths relative to the other outcomes. Analytical samples are as per table 1.

**Figure 2. Forest plot illustrating the association between one standard deviation increase (disadvantage) in psychological distress and mortality from a range of cardiovascular disease phenotypes: individual participant meta-analysis of sixteen prospective cohort studies**




Minimally-adjusted hazard ratios are adjusted for age and sex. Maximally adjusted models are adjusted for age and sex plus hypertension, diabetes, occupational social class, smoking status, frequency of alcohol consumption, body mass index, and self-reported longstanding illness. Analytical samples are as per table 1. The gender-specific standard deviation for distress was 2.42 in men and 2.77 in women.