



Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database

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Aims

To determine the risk of coronary heart disease (CHD), acute myocardial infarction (MI), and CHD-related mortality in patients with panic attacks/disorder.

Methods and results

We conducted a cohort study using 650 practices in the 'General Practice Research Database'. We selected all 57 615 adults diagnosed with panic attacks/disorder and a random sample of 347 039 unexposed, frequency matched for sex/age, and measured incidence of CHD, MI, and CHD-related mortality rate. There was a significantly higher incidence of MI following new onset panic in people under 50 years of age, but not in older age groups. There was a higher incidence of CHD for all ages, more marked in those under 50 years, but no significant differences in CHD mortality. Fully adjusted models showed panic attacks/disorder were associated with a significantly increased hazard of MI in those under 50 years (HR 1.38, 95% CI 1.06–1.79) and CHD at all ages (<50 years, HR 1.44, 95% CI 1.25–1.65; \geq 50 years, HR 1.11, 95% CI 1.03–1.20), but no increased hazard of MI over 50 years (HR 0.92, 95% CI 0.82–1.03), and a slightly reduced CHD-mortality at all ages (HR 0.76, 95% CI 0.66–0.88).

Conclusion

New onset panic attacks/disorder were associated with increased hazard of subsequent CHD/MI diagnosis in younger people, but with less effect in people over 50, and a slightly reduced hazard of CHD-related mortality. This may be due to initial misdiagnosis of CHD as panic attacks or an underlying increased risk of CHD with panic attacks/disorder in younger people.

Keywords

Coronary heart disease • Myocardial infarction • Panic-disorder • Cohort study

Introduction

The complex relationship between the 'heart' and the 'mind' has been a subject of much recent debate.¹ Most of this has focused on the relationship between depression and coronary heart disease (CHD)^{2–4} and relatively little large-scale research has considered anxiety disorders. Less is known about the relationship of panic disorder with cardiac disease. This has predominantly been studied in tertiary-care cardiology settings and in the context of

non-cardiac chest pain.⁵ The symptoms of panic attacks can closely mimic those of an acute cardiac event, and there is potentially a complex relationship between them. Panic attacks are a significant public health problem. Panic attacks not meeting full criteria for panic disorder have a prevalence of 1.9% and are associated with substantial morbidity, for example reduced quality of life, increased disability days and increased risk of anxiety disorders, depression, and substance abuse.^{6,7} Panic disorder is defined by the International Classification of Disease,

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10th revision (ICD-10) as recurrent panic attacks not restricted to a particular situation, with comparative freedom from anxiety between attacks.⁸ The dominant symptoms experienced may vary, but sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality are common, associated with a secondary fear of dying, losing control, or going mad.⁸ This serves as a framework for General Practitioners' (GPs) diagnosis of panic disorder, but may not be consistently applied, and not all patients diagnosed with panic disorder by GPs will meet ICD-10 criteria. Panic disorder has a prevalence of around 1.8% in the general population,^{9,10} 5.6–9.2% in primary care,^{11,12} rising to as high as 10–53% in cardiology outpatients and patients with documented CHD.⁵

Few longitudinal studies have been conducted to determine the temporal relationship between panic and cardiac disease, and only two were conducted in primary care/community settings. The first was an analysis of a managed care database in the United States (US) and demonstrated a nearly two-fold risk of diagnosis of CHD in patients with panic disorder.¹³ It however did not include people over 55 years of age, adjusted for limited confounders and did not assess mortality. The second was a recent secondary analysis of the Myocardial Ischemia and Migraine Study (MIMS) on 3369 post-menopausal women enrolled as part of the Women's Health Initiative in the US and demonstrated a more than four-fold increase in hazards of CHD, although with wide confidence intervals (HR 4.2, 95% CI 1.76–9.99).¹⁴ Early work on psychiatric inpatients with panic disorder showed an increased risk of dying from CHD, but this was based on a small sample and not adequately adjusted for confounding factors.¹⁵ More non-specific diagnoses of 'phobic anxiety', 'tension', and 'mental stress' have been shown to be associated with negative coronary outcomes.^{16–20} Well-designed prospective research is needed to establish whether panic disorder is an independent risk factor for the development of CHD.

Our study objectives were to determine the risk of developing CHD, acute myocardial infarction (MI), and mortality from CHD in patients diagnosed with panic disorder or panic attacks.

Methods

Design

Cohort study.

Setting

General practices in the United Kingdom (UK) providing data to the General Practice Research Database (GPRD) in the period April 1990 to April 2002.

Data source

The GPRD consists of the electronic clinical records of all patients registered with up to 650 participating general practices in the UK.²¹ GPRD practices are broadly representative of all practices in the UK in terms of age and sex of patients, practice size, and geographical distribution.²² It includes longitudinal anonymized data on age, gender, medical diagnosis and symptom records, health promotion activity, index of deprivation based on the practice postcode, referrals and prescriptions for each registered individual. Medical diagnoses and

symptoms are entered by GPs using Read and Oxford Medical Information System (OXMIS) codes. For this study we only used practices providing 'up to standard' data, defined as when audits demonstrate that at least 95% of relevant patient encounters are recorded and data meet set quality standards for epidemiological research.

Data verification

The data quality has been demonstrated to be high in independent validation studies.^{22–28} The GPRD prescribing data have been shown to be 95% complete.²⁹ The diagnosis of acute MI has been validated against hospital discharge letters and showed a high level of agreement (>90%).^{29,30}

Participants

'Exposed' participants

All adults aged 16 years and over attending to see their GP with a diagnostic code of panic disorder or panic attacks during the study period.

'Unexposed' participants

A random sample of six unexposed for every 'exposed' case registered with a GP in one of the GPRD study practices during the study period, frequency matched for sex, 10 year age bands, and length of time between registration and study start date. The random sample was selected using computer generation by an independent data manager not involved in the study.

Exclusion criteria

- (1) Previous recorded diagnosis of CHD or panic disorder/panic attacks at any time prior to study entry date.
- (2) Less than a minimum of 6 months of high-quality medical records prior to study entry.

Measurements

Follow-up was from study entry (first consultation with panic, or a random selected 'index date' for unexposed) to exit date (death, left practice, or practice data became non-up-to-standard for quality markers). Exposures: recording of a new diagnosis of a panic attack or panic disorder during the study period (1990–2002). Outcomes: recording of a new CHD diagnosis (including codes for CHD, cardiac ischaemia, angina, acute coronary syndromes, MI, coronary revascularization but not including cerebrovascular disease or heart failure) or MI diagnosis, and CHD-related mortality from study entry (date of first panic attack) up to the last date of record. CHD mortality was determined by searching for CHD-related medical codes recorded from 1 week before date of death. Co-variables: age, sex, quintiles of Carstairs deprivation score based on location of GP practice (a combined measure of social class, car ownership, overcrowding, and employment), smoking (coded as 'current smoker', 'ex-smoker', 'non-smoker', and missing data), heavy alcohol consumption (relevant diagnostic codes or a weekly consumption above 21 units per week for men and 14 units per week for women), obesity (recorded obesity codes or a body mass index >30), past history of depression, anxiety (excluding panic) or severe mental illness (SMI, e.g. schizophrenia, bipolar disorder), number of different types of prescriptions issued in last 6 months (a proxy measure of general co-morbidity), current history of diabetes, cerebrovascular disease, hypertension (relevant diagnostic codes or a blood pressure recorded as >140/90 mmHg for two separate consecutive readings³¹), high cholesterol (relevant diagnostic codes or prescription issued for a Statin drug). We also evaluated possible drug treatments for panic disorder as potential confounding factors, defined as prescriptions issued

for beta adrenoceptor blockers, antidepressants (Selective Serotonin Reuptake Inhibitors, Tricyclic antidepressants and other antidepressants), anxiolytics, hypnotics, and anti-psychotics during the study period.

Sample size

To detect a 30% difference in CHD-related mortality between the two groups with 90% power and a two-sided significance level of 0.05, and assuming a combined CHD and MI annual mortality rate of 287/100 000 UK population in 2001, the minimum number of participants needed was calculated to be 376 750.

Statistical methods

Analysis was conducted using Stata version 9.1.³² Univariate associations between panic and each potential confounder were tested using two-tailed χ^2 , *t*-, and equality of medians tests with a 0.05 significance level. A 'not recorded' category was included for smoking status and deprivation to identify patients with missing data. Incidence rate ratios were calculated from the number of events per 1000 person-years in each age/sex category. Cox proportional hazards modelling was conducted for the outcomes new onset CHD, MI, and CHD-related mortality. The assumption of proportional hazards was checked using log-log survival plots and relative risk ratios. A significant interaction between age and the hazard ratio between groups was found for the outcomes CHD and acute MI. The analyses were therefore stratified into age groups, above and below 50 years. Within each of these two age groups hazard ratios were proportional and there were no further interactions with age. Results are therefore presented stratified by age group above and below 50 years. We further assessed for interactions between age and sex as we felt that there was a potential different effect of gender on the relationship between panic and CHD events in younger (pre-menopausal) women in comparison to older (post-menopausal) women. There was no appreciable clinically important interaction with age and sex for each outcome. We assessed linearity for continuous variables by plotting standardized residuals against the fitted values of each dependent variable, which showed random patterns indicating linearity. To check this, we added nonlinear terms to the model (squares and cubes of the independent variables) and this did not improve the model and we therefore kept the original linear terms.

The Cox proportional hazards models were fitted sequentially, adjusting for each individual potential confounder. Anxiety was highly correlated to both panic and depression and was therefore dropped from the modelling due to co-linearity. Alcohol and obesity were dropped from the final models as they were not contributing to the models and data were incomplete. Drugs prescribed for panic disorder were also dropped from the final model as they are independently associated with depression (they can be prescribed for either disorder), an important confounder included in the model, and this results in potential distortion of the models. Sensitivity analyses were conducted including and excluding participants with missing data for deprivation and smoking, which made no difference to the final models. The final models included adjustments for the following co-variables: age, sex, deprivation, CHD risk factors (smoking, hypertension, high cholesterol, diabetes, cerebrovascular disease), co-morbid psychiatric conditions (depression and SMI), number of prescribed medications. To determine if there was a possible 'dose-response' effect we conducted a sub-group analysis to determine if there was a trend for increasing hazards of CHD events with increasing number of attendances with panic in GP records. The estimated comparative hazards between those with panic attacks/disorder and the

comparison group were adjusted for the possible confounders and for clustering by general practice using robust standard errors.

Results

Sample characteristics

Overall, 57 615 individuals aged 16 years and over were identified with a diagnosis of panic disorder or panic attacks (*Table 1*). Mean age was 43 years and 73% were women. The median follow-up time was 2 years, inter-quartile range 4 years. In our study 89% of deaths had an identifiable cause of death recorded in their GP records. The prevalence of panic disorder/attacks recorded in GP records was 1.1% in our study. We have no comparable external data on GP recorded diagnoses of panic to validate this figure. The median time from panic attack to CHD event was 2.9 years (in those <50 years) and 3.0 years (in those >50 years) for MI diagnoses, 3.3 years (in those <50 years), and 2.8 years (in those >50 years) for CHD diagnoses and 2.6 years for CHD-related mortality. There was some variation between practices in the ratio of exposed (panic) to unexposed groups (median ratio 1:6.7, inter-quartile range 4.8–11.0) as a result of variation in underlying incidence of recorded panic episodes. We adjusted confidence intervals for the effects of clustering within practice using robust standard errors (cluster command in Stata).

Those diagnosed with panic were more likely to be recorded in GP case notes as being smokers, have a history of depression, anxiety or high alcohol intake, have been issued a higher overall number of different prescriptions, or be prescribed beta-blockers, hypnotics, anxiolytics, anti-psychotics, or antidepressants (*Table 1*). They were also statistically more likely to live in a deprived area or have a history of cerebrovascular disease, hypertension, high cholesterol, obesity, or SMI, however the absolute differences in proportions for these variables were small (*Table 1*).

Incidence of myocardial infarction, coronary heart disease, and coronary heart disease-related mortality

Overall there was a significant increase in the incidence of CHD but not MI in those with panic diagnoses. Patients with panic had a higher incidence of MI compared with unexposed patients in younger age groups (<50 years), particularly in young women (aged 16–40 years at study entry), who had a more than three-fold higher incidence of MI compared with unexposed (*Table 2*). For older age groups (>50 years) there was no significant difference in the incidence of MI (*Table 2*). Patients with panic had a higher incidence of CHD for both sexes and at all age groups, but this was most marked in younger age groups, particularly again for young women aged 16–40 years with panic, who again had a three-fold higher incidence of CHD compared with unexposed (*Table 3*). There was an overall significant reduction in crude mortality rate for those with panic, but no significant differences in CHD mortality rates in each age band at all ages and for both men and women (*Table 4*).

Table 1 Sample baseline characteristics

Characteristic	Panic, n (%) (n = 57 615)	Control, n (%) (n = 347 039)	Significance P-value*
Socio-demographic			
Female ^a	41 827 (72.6)	251 933 (72.6)	0.99
Mean age (s.d.) ^a	43 (16)	43 (17)	0.351
Deprivation quintile			
(Most affluent) 0	5975 (10.4)	39 784 (11.5)	<0.001
1	8494 (14.7)	56 602 (16.3)	
2	10 533 (18.3)	64 963 (18.7)	
3	12 415 (21.5)	75 792 (21.8)	
(Most deprived) 4	13 960 (24.2)	75 262 (21.7)	
Not recorded	6238 (10.8)	34 636 (10.0)	
Risk factors for CHD			
Cerebrovascular disease	1058 (1.8)	4091 (1.2)	<0.001
Diabetes	1157 (2.0)	6933 (2.0)	0.869
Hypertension	7532 (13.1)	36 930 (10.6)	<0.001
High cholesterol	2028 (3.5)	8963 (2.6)	<0.001
Obesity	2551 (4.4)	9724 (2.8)	<0.001
Smoking status			
Smoker	9990 (17.3)	37 950 (10.9)	<0.001
Ex-smoker	2337 (4.1)	9990 (2.9)	
Non-smoker	3904 (6.8)	23 324 (6.7)	
Not recorded	41 384 (71.8)	275 865 (79.5)	
Co-morbidity			
Alcohol misuse	2066 (3.6)	4806 (1.4)	<0.001
Anxiety (excluding panic)	16 311 (28.3)	19 592 (5.6)	<0.001
Depression	18 847 (32.7)	36 904 (10.6)	<0.001
Severe mental illness	485 (0.8)	2178 (0.6)	<0.001
Median number of drugs prescribed (min, max)	2 (0, 25)	1 (0, 24)	<0.001
Drugs prescribed			
Beta-blockers	19 769 (34.3)	8878 (2.6)	<0.001
Hypnotics/anxiolytics	25 088 (43.5)	31 040 (8.9)	<0.001
Selective serotonin reuptake inhibitors	22 355 (38.8)	24 245 (7.0)	<0.001
Tricyclic antidepressants	21 390 (37.1)	26 568 (7.7)	<0.001
Antipsychotics	5970 (10.4)	4933 (1.4)	<0.001
Other antidepressants	3543 (6.1)	2906 (0.8)	<0.001

^aThe sample was frequency matched in 10 year age-bands and sex.

*From two-tailed χ^2 , t-, and equality of medians tests.

Multivariable analysis

In the fully adjusted models panic attacks/disorder were associated with a significantly increased hazard of MI in those under 50 years (HR 1.38, 95% CI 1.06–1.79) and CHD at all ages (<50 years, HR 1.44, 95% CI 1.25–1.65; \geq 50 years, HR 1.11, 95% CI 1.03–1.20), but no increased hazard of MI over 50 years (HR 0.92, 95% CI 0.82–1.03), and a slightly reduced CHD-mortality (HR 0.76, 95% CI 0.66–0.88) (Table 5). The increased hazard of CHD with panic was maintained over follow-up time. Sub-group analysis, stratifying by number of panic episodes, showed a significant trend for increasing hazards of CHD at all ages with increasing number of recorded panic episodes (Table 6). There was a similar, but non-significant,

rising trend in the hazard ratio estimates for MI in the 16–50 years age group with increasing panic entries. The absolute number of MI events for this age group was low and the confidence intervals were wide. There was no significant change in hazards of MI in the over 50 years age group with increasing panic entries, and a significant, although slight, reducing trend for hazards of CHD-related mortality with increasing number of panic entries.

Discussion

Our study found a significant association between a new diagnosis of panic attacks/panic disorder by GPs and increased incidence of

Table 2 Incidence of acute myocardial infarction in panic and control groups

	Panic MI events, n (%)	Panic MI incidence rate ^a (95% CI)	Control MI events, n (%)	Control MI incidence rate ^a (95% CI)	Incidence rate ratio (95% CI)
Males					
16–39	8 (0.10)	0.26 (0.13, 0.52)	33 (0.07)	0.26 (0.19, 0.37)	1.00 (0.46, 2.17)
40–49	47 (1.50)	3.55 (2.67, 4.73)	110 (0.58)	1.86 (1.54, 2.24)	1.91 (1.36, 2.69)
50–59	35 (1.62)	4.16 (2.98, 5.79)	179 (1.37)	4.49 (3.88, 5.20)	0.93 (0.65, 1.33)
60–69	45 (3.53)	9.81 (7.32, 13.14)	227 (2.85)	9.40 (8.25, 10.71)	1.04 (0.76, 1.44)
70+	52 (5.32)	19.79 (15.08, 25.97)	246 (4.17)	15.25 (14.34, 18.41)	1.22 (0.90, 1.64)
Females					
16–39	13 (0.07)	0.17 (0.10, 0.29)	15 (0.01)	0.05 (0.03, 0.08)	3.34 (1.59, 7.02)
40–49	30 (0.35)	0.79 (0.55, 1.13)	63 (0.13)	0.40 (0.31, 0.51)	1.98 (1.28, 3.06)
50–59	48 (0.80)	1.88 (1.41, 2.49)	163 (0.45)	1.44 (1.23, 1.68)	1.31 (0.95, 1.80)
60–69	86 (2.26)	5.42 (4.39, 6.70)	355 (1.52)	4.76 (4.29, 5.28)	1.14 (0.90, 1.44)
70+	123 (3.18)	9.61 (8.05, 11.47)	631 (2.61)	9.92 (9.18, 10.73)	0.97 (0.80, 1.18)
Overall	487 (0.85)	2.13 (1.96, 2.34)	2022 (0.58)	2.09 (2.00, 2.18)	1.02 (0.93, 1.13)

MI, myocardial infarction.

^aIncidence of myocardial infarction per 1000 patient years at risk.**Table 3** Incidence of coronary heart disease in panic and control groups

	Panic CHD events, n (%)	Panic CHD incidence, rate ^a (95% CI)	Control CHD events, n (%)	Control CHD incidence rate ^a (95% CI)	Incidence rate ratio (95% CI)
Males					
16–39	32 (0.39)	1.05 (0.74, 1.48)	68 (0.14)	0.53 (0.42, 0.68)	1.95 (1.28, 2.97)
40–49	102 (3.16)	7.82 (6.44, 9.49)	259 (1.36)	4.40 (3.89, 4.97)	1.78 (1.41, 2.23)
50–59	125 (5.78)	15.27 (12.81, 18.20)	431 (3.29)	10.97 (9.99, 12.06)	1.39 (1.14, 1.70)
60–69	145 (11.37)	33.81 (28.73, 39.79)	516 (6.48)	22.03 (20.21, 24.02)	1.54 (1.28, 1.85)
70+	123 (12.58)	49.81 (41.74, 59.44)	537 (9.10)	36.67 (33.70, 39.91)	1.36 (1.12, 1.65)
Females					
16–39	58 (0.29)	0.76 (0.59, 0.99)	74 (0.06)	0.25 (0.20, 0.32)	3.03 (2.15, 4.27)
40–49	175 (2.05)	4.68 (4.03, 5.43)	329 (0.67)	2.10 (1.88, 2.34)	2.23 (1.86, 2.68)
50–59	234 (3.92)	9.38 (8.26, 10.67)	682 (1.89)	6.07 (5.65, 6.56)	1.54 (1.33, 1.79)
60–69	296 (7.80)	19.46 (17.36, 21.81)	1032 (4.42)	14.13 (13.30, 15.03)	1.38 (1.21, 1.57)
70+	365 (9.43)	30.12 (27.19, 33.38)	1559 (6.45)	25.23 (24.01, 26.51)	1.19 (1.07, 1.34)
Overall	1655 (2.87)	7.39 (7.03, 7.75)	5487 (1.58)	5.72 (5.57, 5.87)	1.29 (1.22, 1.37)

CHD, coronary heart disease.

^aIncidence of coronary heart disease per 1000 patient years at risk.

CHD at all ages and acute MI in those <50 years of age only. This was particularly marked in younger women (aged <50 years at date of study entry) diagnosed with panic attacks/disorder. We showed an increased crude hazard of MI in younger people and CHD at all ages, with a greater hazard for those <50 years of age. This increased hazard was reduced slightly after adjusting for a range of potential confounders including age, sex, deprivation, risk factors for CHD, and psychiatric co-morbidity, but remained significant. There was some evidence for an increasing hazard of CHD with increasing frequency of panic entries, which would

support a causal link, although we should be cautious as this was sub-group analysis. These findings could be due to several factors, including initial misdiagnosis of CHD as panic attacks/disorder by GPs or due to a true increase in CHD and acute MI caused by panic disorder, potentially through hypothesized pathways of sympathetic nervous system activation, associated with increased atherogenesis and reduced heart rate variability. The observed increased hazard of CHD with panic was maintained over time, which supports a causal explanation rather than initial misdiagnosis by GPs. While we adjusted for any identified

Table 4 Coronary heart disease mortality rate in panic and control groups

	Panic CHD-related deaths, n (%)	Panic CHD-related mortality rate ^a (95% CI)	Control CHD-related deaths, n (%)	Control CHD-related mortality rate ^a (95% CI)	CHD-related mortality rate ratio (95% CI)
Males					
16–39	1 (0.01)	0.03 (<0.01, 0.23)	9 (0.02)	0.07 (0.04, 0.14)	0.46 (0.06, 3.63)
40–49	11 (0.34)	0.83 (0.46, 1.49)	36 (0.19)	0.61 (0.44, 0.84)	1.36 (0.69, 2.68)
50–59	15 (0.69)	1.76 (1.06, 2.92)	66 (0.50)	1.64 (1.29, 2.09)	1.07 (0.61, 1.88)
60–69	15 (1.18)	3.22 (1.94, 5.33)	133 (1.67)	5.45 (4.60, 6.46)	0.59 (0.35, 1.01)
70+	45 (4.60)	16.77 (12.52, 22.47)	239 (4.05)	15.59 (13.73, 17.69)	1.08 (0.78, 1.48)
Females					
16–39	1 (0.01)	0.01 (<0.01, 0.09)	5 (<0.01)	0.02 (0.01, 0.04)	0.77 (0.09, 6.60)
40–49	5 (0.06)	0.13 (0.05, 0.32)	24 (0.05)	0.15 (0.10, 0.23)	0.87 (0.33, 2.27)
50–59	13 (0.22)	0.51 (0.29, 0.87)	61 (0.17)	0.54 (0.42, 0.69)	0.94 (0.52, 1.72)
60–69	48 (1.26)	2.99 (2.25, 3.97)	200 (0.86)	2.66 (2.32, 3.06)	1.13 (0.82, 1.54)
70+	94 (2.43)	7.22 (5.90, 8.84)	572 (2.37)	8.92 (8.22, 9.68)	0.81 (0.65, 1.01)
Overall	248 (0.43)	1.08 (0.96, 1.23)	1345 (0.39)	1.38 (1.31, 1.46)	0.78 (0.68, 0.90)

CHD, coronary heart disease.

^aCHD-related mortality rate per 1000 patient years at risk.

Table 5 Survival analysis: hazard ratios for new diagnosis of myocardial infarction, coronary heart disease, and coronary heart disease-related mortality in patients with panic attacks/panic disorder

Models	Myocardial infarction		Coronary heart disease		Cardiac mortality All ages; n = 404 643; 1593 events
	Aged <50 years; n = 275 966; 319 events	Aged ≥50 years; n = 128 677; 2190 events	Aged <50 years; n = 275 966; 1097 events	Aged ≥50 years; n = 128 677; 6045 events	
Crude HR (95% CI)	1.77 (1.41, 2.22)	1.02 (0.92, 1.15)	2.01 (1.77, 2.28)	1.31 (1.23, 1.41)	0.86 (0.74, 1.00)
Above adjusted for age, sex, deprivation	1.86 (1.49, 2.33)	1.09 (0.97, 1.22)	2.07 (1.82, 2.35)	1.37 (1.28, 1.47)	0.94 (0.82, 1.09)
Above adjusted for CHD risk factors ^a , depression, SMI, and number of prescribed medications (fully adjusted HR ^b)	1.38 (1.06, 1.79)	0.92 (0.82, 1.03)	1.44 (1.25, 1.65)	1.11 (1.03, 1.20)	0.76 (0.66, 0.88)

HR, hazard ratios; CHD, coronary heart disease.

^aCHD risk factors: smoking, hypertension, high cholesterol, diabetes, cerebrovascular disease.

^bHazard ratio for events in panic vs. control group adjusted for age, sex, deprivation, CHD risk factors, co-morbid psychiatric conditions, and number of prescribed medications.

depression, it is possible that in some patients with panic there may be associated undiagnosed depression, which could in addition be part of the explanation for the excess risk of CHD.

Psychological strain has been associated with increased coronary atherosclerosis, possibly through a mechanism involving excessive sympathetic nervous system activation.^{33,34} Anxiety and panic symptoms (and increased sympathetic autonomic regulation) have been demonstrated to be associated with reduced heart rate variability³⁵ which in turn is associated with acute cardiac events and ventricular arrhythmias.³⁶ In past work, older women with a history of recent panic attacks had no increase in daily life ischaemia detected on ambulatory electrocardiogram monitoring,

but did experience increased chest pain, both ischaemic and non-ischaemic.³⁵ In laboratory studies ‘mental stress’ induced myocardial ischaemia in 50–70% of patients with known CHD³⁷ and there is some evidence that ‘emotional stress’ is a trigger for acute coronary syndromes.³⁸ In addition hyperventilation, a common symptom in panic attacks, can precipitate coronary artery spasm.³⁹ There is limited evidence for the exact neurobiological pathways for increased potential for acute coronary events in panic attacks, but some suggest that there may be surges in cardiac ephedrine secretion and a selective increase in cardiac sympathetic activity during panic attacks, pre-disposing to ventricular arrhythmias.⁴⁰

Table 6 Sub-group analysis: hazards of cardiac outcome stratified by number of panic events

Outcome	Hazards ratio (95% CI) ^a	P-value ^b
MI 16–50 years (MI events = 319)	Baseline	0.10
Control (no panic)	1.30 (0.98–1.74)	
1 panic entry	1.48 (0.87–2.51)	
2 panic entries	1.52 (0.90–2.58)	
3 or more panic entries		
MI ≥ 50 years (MI events = 2190)	Baseline	0.45
Control (no panic)	0.93 (0.82–1.06)	
1 panic entry	0.86 (0.67–1.10)	
2 panic entries	0.89 (0.67–1.18)	
3 or more panic entries		
CHD 16–50 years (CHD events = 1097)	Baseline	0.001
Control (no panic)	1.43 (1.21–1.69)	
1 panic entry	1.39 (1.03–1.88)	
2 panic entries	1.50 (1.16–1.93)	
3 or more panic entries		
CHD ≥ 50 years (CHD events = 6045)	Baseline	0.030
Control (no panic)	1.09 (1.00–1.18)	
1 panic entry	1.13 (0.98–1.31)	
2 panic entries	1.20 (1.04–1.39)	
3 or more panic entries		
CHD-related mortality (CHD deaths = 1593)	Baseline	0.003
Control (no panic)	0.78 (0.66–0.92)	
1 panic entry	0.73 (0.52–1.03)	
2 panic entries	0.67 (0.46–0.98)	
3 or more panic entries		

MI, myocardial infarction; CHD, coronary heart disease.

^aHazard ratio for CHD outcomes in panic vs. control group adjusted for age, sex, deprivation, smoking, hypertension, high cholesterol, diabetes, cerebrovascular disease, depression, severe mental illness, number of prescribed medications, and for clustering by practice using robust standard errors.

^bFrom Wald test of linear trend.

In our study there was limited information on certain confounders such as individual measures of deprivation and ethnicity and incomplete recording of some data, for example smoking. We used area level deprivation as the best available proxy for individual deprivation. Past research has shown that these measures are highly correlated and both are associated to mental health outcomes.⁴¹ We performed a sensitivity analysis for those with missing data on smoking and this had no impact on the models. Our results should nevertheless be interpreted with caution, as while we adjusted the analysis for a range of key confounders, there is still the potential for unmeasured confounding. Our findings may also partly be explained by diagnostic bias, in that some GPs might tend to under-report both CHD and panic disorder

in comparison to others. Our analysis did account to some degree for clustering by GP by adjusting confidence intervals using robust standard errors, however we did not match on GP practice, and did not perform multi-level modelling to account fully for practice effects.

Previous research has found high levels of validity for GPRD diagnoses of MI and CHD compared with hospital records,^{29,30} however the diagnosis of panic attacks/disorder in the GPRD has not been validated. The prevalence of panic in our sample was lower than in studies actively screening GP attenders for psychological disorders including panic disorder.^{11,12} This may be due to some people not reporting their symptoms to their GP, GPs not recognizing symptoms as panic attacks/disorder, or on some occasions GPs recording more non-specific symptom codes associated with panic, such as 'atypical chest pain' or 'palpitations' instead of a panic code. In addition some people with recorded diagnoses of panic attacks/disorder may not meet ICD-10 criteria for panic disorder. This potential misclassification would lead to an underestimation of the effect size in our study. There is however evidence in other work for high levels of agreement between case-finding tools for panic and anxiety disorders and primary care physician diagnoses.⁴² It is arguable that our findings are more relevant to GPs' clinical practice, as we report outcomes associated with diagnostic labels used in general practice rather than strict ICD-10 classification.

Our study was conducted with a very large, representative sample of the UK population, and is the first large controlled cohort study of people with panic attacks/panic disorder selected from a primary care clinical population that is broadly generalizable to other countries with a similar socio-demographic structure. We have found lower levels of risk associated with panic than earlier studies in a managed care database in the United States, which showed a nearly two-fold higher risk of CHD in patients with panic disorder¹³ and in post-menopausal women registered with 10 clinical centres in the Women's Health Initiative, which showed an even greater hazard of CHD.¹⁴ The first study was restricted to patients under 55 years of age, did not adjust for deprivation, untreated depression, or SMI (all of which had significant impact on hazard of CHD in our models), and did not assess CHD-related mortality. In our study despite the increase in risk of CHD and MI in younger people, there was a small but significant reduction in CHD-related mortality in those with panic. There was also a slight reducing trend for CHD-related death with increasing frequency of panic entries. This could be in part as there were few cardiac deaths in younger age groups, where the highest hazard of CHD/MI associated with panic occurred. Another explanation could be that people with panic present earlier or more frequently to their doctor and therefore have their CHD and MI identified and treated, thus reducing future events and CHD-related mortality.

The increased hazard of CHD and acute MI is higher in younger people presenting with panic. Clinicians may be more cautious about excluding CHD when making initial panic diagnoses in older people, and therefore have a lower rate of initial misdiagnosis of CHD as panic. Alternatively it may be that small increases in atherogenesis caused by sympathetic nervous system activation in panic disorder are overtaken by a more dominant underlying age-related atherogenesis in older people, thus masking the relative risk attributed to panic in older age groups.

The findings have significant implications for clinicians. Panic attacks were associated with a significant increased hazard of subsequent diagnosis of CHD and acute MI in those <50 years of age. This may be due to initial misdiagnosis of CHD as panic attacks or a true underlying increased risk of CHD with panic attacks. Clinicians should be vigilant for this possibility when diagnosing and treating people presenting with symptoms of panic.

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