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REVIEW ARTICLE

Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events

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Background. Substantial healthcare resources are devoted to panic disorder (PD) and coronary heart disease (CHD); however, the association *between these conditions remains controversial. Our objective was to* conduct a systematic review of studies assessing the association between PD, related syndromes, and incident CHD.

Method. Relevant studies were retrieved from Medline, EMBASE, SCOPUS and PsycINFO without restrictions from inception to January 2015 supplemented with hand-searching. We included studies that reported hazard ratios (HR) or sufficient data to calculate the risk ratio and 95% confidence interval (CI) which were pooled using a random-effects model. Studies utilizing self-reported CHD were ineligible. Twelve studies were included comprising 1 131 612 persons and 58 111 incident CHD cases.

Results. PD was associated with the primary incident CHD endpoint [adjusted HR (aHR) 1.47, 95% CI 1.24–1.74, $p < 0.00001$] even after excluding angina (aHR 1.49, 95% CI 1.22–1.81, $p < 0.00001$). High to moderate quality evidence suggested an association with incident major adverse cardiac events (MACE; aHR 1.40, 95% CI 1.16–1.69, $p = 0.0004$) and myocardial infarction (aHR 1.36, 95% CI 1.12–1.66, $p = 0.002$). The risk for CHD was significant after excluding depression (aHR 1.64, 95% CI 1.45–1.85) and after depression adjustment (aHR 1.38, 95% CI 1.03–1.87). Age, sex, length of follow-up, socioeconomic status and diabetes were sources of heterogeneity in the primary endpoint.

Conclusions. Meta-analysis showed that PD was independently associated with incident CHD, myocardial infarction and MACE; however, reverse causality cannot be ruled out and there was evidence of heterogeneity.

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Key words: Aetiology, anxiety disorder, anxiety neurosis, coronary heart disease, meta-analysis, myocardial infarction, panic attack, panic disorder, systematic review.

Introduction

Panic disorder (PD) is among the most prevalent anxiety disorders in the community (Wittchen *et al.* 2011) signifying a major public health burden in terms of economic costs (Coley *et al.* 2009) and disability worldwide (Baxter *et al.* 2014). Although anxiety has been clinically linked with coronary heart disease (CHD) for more than 100 years (Walsh, 1912), the nexus between PD and CHD remains tenuous and is yet to be clarified by means of a systematic review.

Part of the suspicion concerning an aetiological association is that persons with PD report a myriad of symptoms overlapping those with CHD (Carmin *et al.* 2008). Moreover, persons with PD persist in emergency department presentations (Fleet *et al.* 1997) and outpatient examinations for chest pain (Rutledge *et al.* 2001) despite negative diagnostic results from coronary catheterization, electrocardiogram or serum markers of myocardial damage (Rohacek *et al.* 2012). A second cause for scepticism of the link between PD and CHD, and a caveat to interpreting the extant evidence base, is reverse causality. Specifically, persons with PD may be simply experiencing somatic symptoms of undiagnosed coronary conditions such as coronary spasm, microvascular angina and coronary slow-flow (Vural *et al.* 2009), therefore it is plausible that PD partly represents a misdiagnosis. The inconsistency in collective findings to date (Bowen *et al.* 2000; Bringager *et al.* 2008; Walters *et al.* 2008; Janszky *et al.* 2010; Cheng *et al.* 2013), coupled with the high coronary healthcare utilization by PD patients (Fleet *et al.* 1997), indicates that a meta-analysis is both timely and warranted. This review

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aims to synthesize the quantitative evidence base regarding PD, panic attacks and incident CHD. The reporting of this review conforms to the PRISMA guidelines (Liberati *et al.* 2009); a review protocol is described elsewhere [PROSPERO CRD42014014891] (Tully *et al.* 2015).

Method

Search strategy

One systematic search of the Medline, EMBASE, SCOPUS and PsycINFO electronic databases was performed from database inception without language restrictions and text explosion, the last search was on 2 January 2015 incorporating Ovid week 5 December 2014 (Supplementary Table S1). Hand search was performed of the reference lists of prior qualitative reviews (Beitman *et al.* 1993; Hemingway & Marmot, 1999; Fleet *et al.* 2000; Katerndahl, 2008) and articles selected for full text review, and the principal investigators of studies were contacted to clarify data if required.

Eligibility criteria

Population: The population of interest was persons with PD at baseline but without verified or known CHD at this time from the general, cardiology or psychiatric population (inpatients and outpatients). PD must be reported according to a recognized criteria including the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or the International Classification of Diseases (ICD-10), or determined by a standardized interview (e.g. Structured Clinical Interview), or diagnosis made by a qualified professional (e.g. psychiatrist), or medical records. Studies reporting PD ± other anxiety disorders were eligible as were studies reporting anxiety neurosis [the diagnostic precursor to PD in ICD-10 (Feighner *et al.* 1972)] ± other anxiety disorders. Validated self-report measures of panic attack or panic-attack symptoms were also eligible to determine dose-response associations (Nicholson *et al.* 2006).
Comparator/control: The comparator group consisted of persons without PD or related conditions at baseline and without verified or known CHD at this time from the general, cardiology or psychiatric population (inpatients and outpatients).
Outcomes: Incident CHD was considered in any of the following categories:

(1) Major adverse cardiac events (MACE) – defined as documented death due to CHD, cardiac arrest (including ventricular fibrillation), sudden cardiac death or myocardial infarction (MI) (fatal or non-fatal).
(2) Structural coronary artery disease – as evidenced by obstructive coronary artery disease (⩾50% stenosis) on coronary angiography and/or subsequent coronary revascularization.
(3) Ischaemic heart disease – clinical evidence of myocardial ischaemia on ECG (transient ST/T wave changes), myocardial scintigraphy (reversible defect), echocardiography (transient wall motion abnormality) or cardiac magnetic resonance imaging (perfusion defect or transient wall motion abnormality), either during a spontaneous episode or a provocative stress stimulus.
(4) Other CHD – physician- or cardiologist-diagnosed CHD.

Only studies reporting verified CHD endpoints were eligible (e.g. ICD-10 coding of hospital admission, death certificate, cardiologist or physician diagnosis). In studies reporting multiple CHD outcomes we initially extracted the most common CHD endpoint for primary analyses (categories 1–4), and the secondary endpoints of fatal CHD (categories 1–4), and fatal or non-fatal MACE including MI (category 1).
Study design: Prospective longitudinal cohort, case-control study, database registry, randomized controlled trials (RCTs), or retrospective studies were eligible.
Exclusion: Studies utilizing patient self-report to determine incident CHD were ineligible. Studies reporting neurocirculatory asthenia, cardiac neurosis, effort syndrome or Da Costa's syndrome were ineligible as they preceded the formulation of anxiety neurosis and PD nomenclature and are conceptualized under multiple psychosomatic disorders (Taylor, 2001).

Data extraction process, risk of bias, and strength of recommendations

Two reviewers (P.J.T., S.C.) independently screened titles and abstracts of all the retrieved bibliographical records for eligibility. In the case of title/abstract disagreements, the study was subjected to full-text review. The RTI item bank (Viswanathan & Berkman, 2012) was utilized to identify methodological bias at the primary CHD outcome level. Risk of bias was independently undertaken by two reviewers (P.J.T., S.C.) and disagreements adjudicated by consensus after discussion. Adjudication of the strength of evidence was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with GRADE Profiler 3.6.1 (The GRADE Working Group, 2013).

Statistical analysis

In studies where an effect size was not reported we extracted the individual cell data for each CHD

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outcome and calculated the risk ratio (RR) and 95% confidence interval (CI) with Cochrane RevMan version 5.3 (raw data provided as a footnote to Supplementary Table S2). Otherwise the original data was reported as hazard ratios (HRs) and 95% CIs. Each of the HR and RR estimates were pooled together using random-effects models utilizing the DerSimonian & Laird method (1986). Because of possible under- or over-estimation of the calculated RRs we adopted Loef & Walach's (2012) methodology for sensitivity analyses applying the natural logarithms of these values. Heterogeneity was evaluated with the I^2 statistic: $I^2 = 0$–60% (not important to moderate), $I^2 > 60\%$ (substantial statistical heterogeneity) (Higgins & Green, 2008).

Sensitivity analyses and meta-regression was performed with Comprehensive Meta-Analysis 2.0. Sensitivity analyses examined the effect sizes stratified by depression co-morbidity, depression adjustment, and exclusion of depression. Sensitivity analyses also stratified studies according to the inclusion of unstable angina and/or angina pectoris in the primary CHD endpoint. Meta-regression was performed to determine possible sources of heterogeneity. A random-effects model was used to combine studies within each subgroup according to the following psychiatric-level variables: inclusion of psychiatric inpatients, anxiety neurosis, disorders *v.* PD symptoms. Meta-regression was utilized to assess the effects of gender (categorical and % of females in the sample) and the effects of age (categorical <50 years and mean age of the study population). Meta-regression also considered covariates and general study characteristics as possible sources of heterogeneity: adjustment for exercise, tobacco smoking, alcohol use, socioeconomic status, diabetes, cholesterol, hypertension, retrospective design, length of follow-up (<2 years, 2–10 years, >10 years), and region of recruitment. To evaluate the presence of publication bias, the test of Egger *et al.* (1997), and the funnel plot including the trim-and-fill method outlined by Duval & Tweedie (2000) were inspected. Effect size graphs were constructed using Microsoft Excel (Microsoft Corp., USA).

Results

Study selection and characteristics

The search yielded 2386 citations from which 83 were reviewed in detail, 71 were excluded and 12 articles were retained (Fig. 1). Ineligible studies were excluded most commonly for not reporting PD (30 studies) and cross-sectional design (28 studies). The 12 articles comprised a pooled sample of 11 31 612 persons and 58 111 CHD events (study characteristics given in Supplementary Table S2). Briefly, the 12 participating studies originated from three regions, North America (five studies), Europe (six studies) and Asia (one study). The median sample size was 41 660 participants per study (S.D. ± 1 36 929.6). The median patient age across studies was 36.5 ± 11.6 years and the median percent of females in the individual studies was 42 ± 31.2%. Common CHD risk factors in the samples included dyslipidaemia (median 22.8% prevalence), hypertension (median 21.2% prevalence) whereas diabetes was uncommon (median 3.6% prevalence); however, five studies did not report suitable subgroup data in participants without CHD at baseline. PD was assessed according to diagnostic interview (two studies), database codes (six studies) and self-report questionnaires (three studies) and was unclear in one study. Baseline sampling was conducted until 2004. Follow-up time ranged from 1 to 37 years (median 7 years).

Assessment of risk of bias and precision

The adjudication of risk of bias is provided in Supplementary Table S3. There were six prospective studies and six retrospective studies, and clear inclusion criteria were only stated in seven studies. An attempt to adjust for baseline differences between groups was made in six studies. The study outcome was clearly defined in all 12 studies but blinding to PD groups could not be determined in nine studies. Generally, however, CHD outcomes were assessed with reliable methods and studies tended to be sufficiently powered to identify differences between groups. A source of funding was identified in eight studies.

PD and incident CHD outcome

The analysis of the primary least-adjusted CHD endpoint was calculated from 11 studies (10 97 916 persons and 56 862 CHD events). There was evidence of high-level heterogeneity between estimates ($I^2 = 87\%$). The pooled unadjusted HR was highly significant (HR 1.62, 95% CI 1.45–1.82, $p < 0.00001$). Pooling the bivariate and multivariate adjusted effect sizes from all 12 studies (11 31 612persons and 58 111 CHD events) attenuated the effect size by 15% and remained highly significant [adjusted HR (aHR) 1.47, 95% CI 1.24–1.74, $p < 0.00001$]; however, there was substantial heterogeneity between estimates ($I^2 = 94\%$) (Fig. 2). The first sensitivity analysis was restricted to adjusted risk estimates only which remained significant (aHR 1.45, 95% CI 1.22–1.73, $p < 0.0001$). The second sensitivity analysis excluding angina pectoris and unstable angina in the CHD endpoint was largely unchanged

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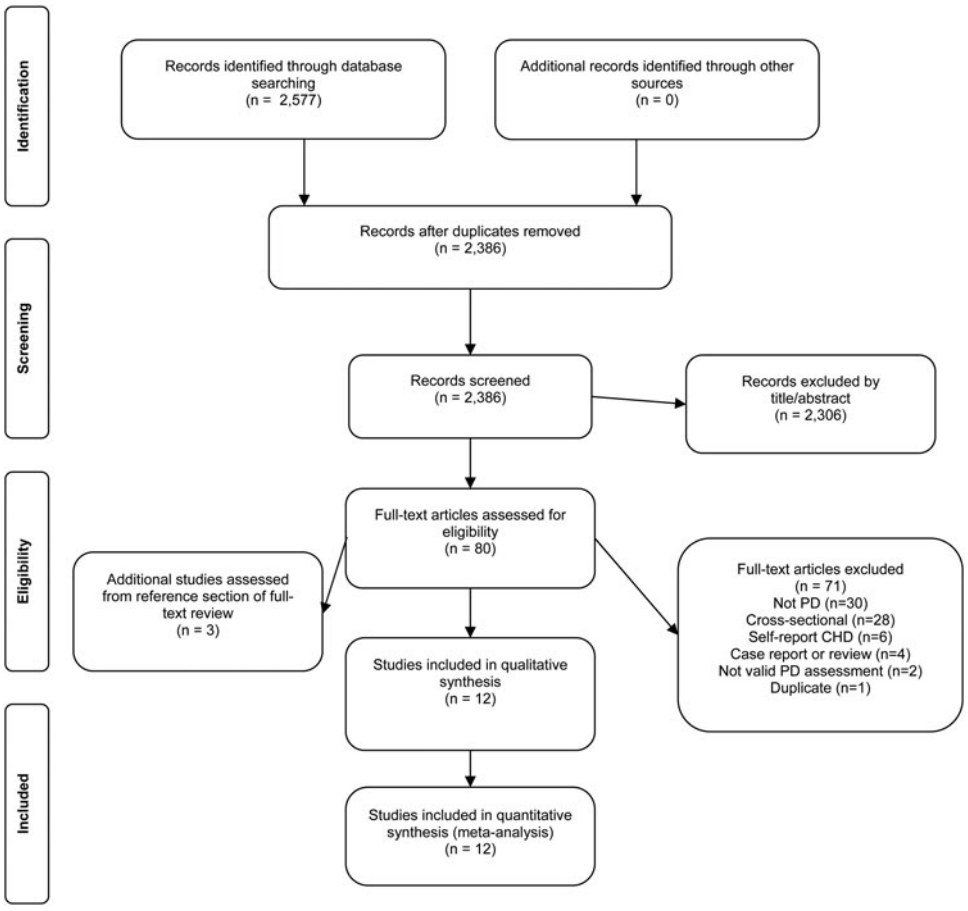

Fig. 1. PRISMA flow chart showing the number of studies at each stage of the systematic review, reasons for exclusion, and the total number of retained studies. CHD, Coronary heart disease; PD, panic disorder.

(aHR 1.49, 95% CI 1.22–1.81, $p < 0.00001$); however, the pooled estimate was based on only eight studies.

PD and incident MACE and MI

Incident MI was the most common individual endpoint with a total of 18 541 MI events reported in 9 53 888 persons obtained from six studies. There was evidence of high-level heterogeneity between estimates ($I^2 = 86\%$). The unadjusted model suggested a 47% increased risk for MI in least-adjusted analyses (95% CI 1.17–1.86, $p = 0.001$). Adding multivariate adjusted effects attenuated the effect size by 11% (aHR 1.36, 95% CI 1.12–1.66, $p = 0.002$, $I^2 = 85\%$) (Fig. 3).

The review protocol specified that we would examine MACE (Tully *et al.* 2015). Specifically, the MACE analyses added the findings of Albert *et al.* (2005) and the combined fatal CHD and MI results of Kawachi *et al.* (1994), otherwise data were the same as for MI events. The analysis of MACE provided similar results (aHR 1.40, 95% CI 1.16–1.69, $p = 0.0004$, $I^2 = 83\%$).

PD and fatal CHD

Fatal CHD was infrequently reported and there was a non-significant increased risk in unadjusted analyses from four studies (HR 1.39, 95% CI 0.75–2.59, $p = 0.29$). Multivariate adjustment was performed in one study (Walters *et al.* 2008) and inclusion of the aHR did not change the non-significant association (aHR 1.39, 95% CI 0.69–2.79, $p = 0.35$, $I^2 = 83\%$).

Sensitivity analysis

The first sensitivity analyses corroborated that the calculated RRs and 95% CIs for two studies (Bringager *et al.* 2008; Rohacek *et al.* 2012) were equivalent to the HRs and 95% CIs calculated from the applied natural logarithms of these values (Loef & Walach, 2012). Sensitivity analysis was then performed for analyses stratified by depression. The risk for CHD remained significant in studies excluding depression (aHR 1.64, 95% CI 1.45–1.85, $I^2 = 73\%$) but was substantially reduced in studies which adjusted for depression (aHR 1.38, 95% CI 1.03–1.87, $I^2 = 98\%$). The

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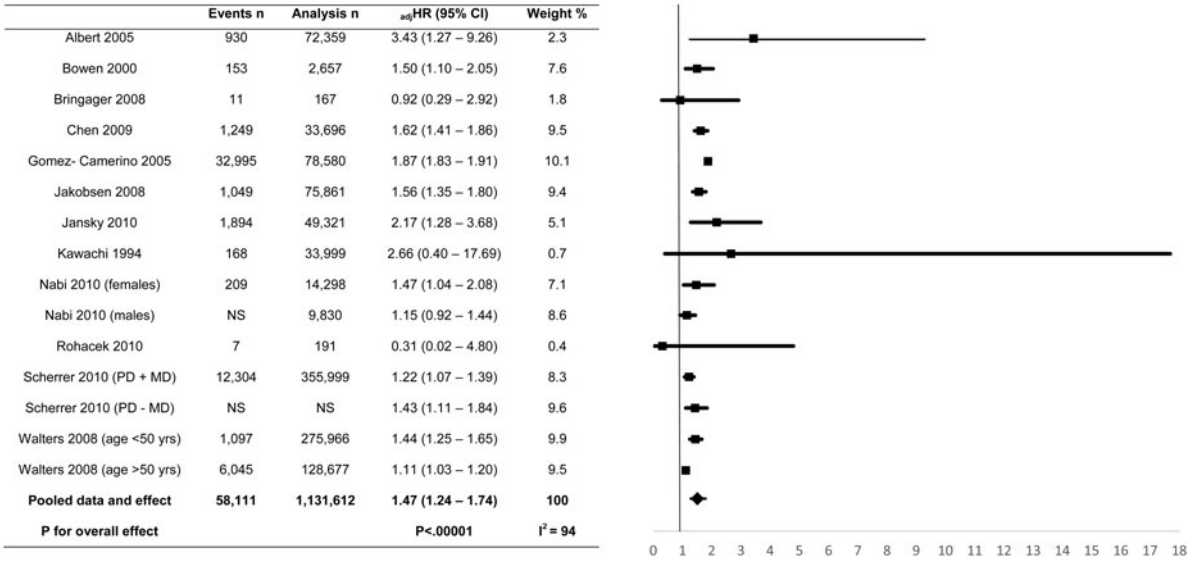

Fig. 2. Forest plot of adjusted and weighted hazard ratios for incident coronary heart disease (CHD) (primary endpoint). Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased CHD risk for persons with panic disorder (PD). GRADE assessment = low. GRADE, Grading of Recommendations Assessment, Development and Evaluation; NS, not specified; MD, major depression.

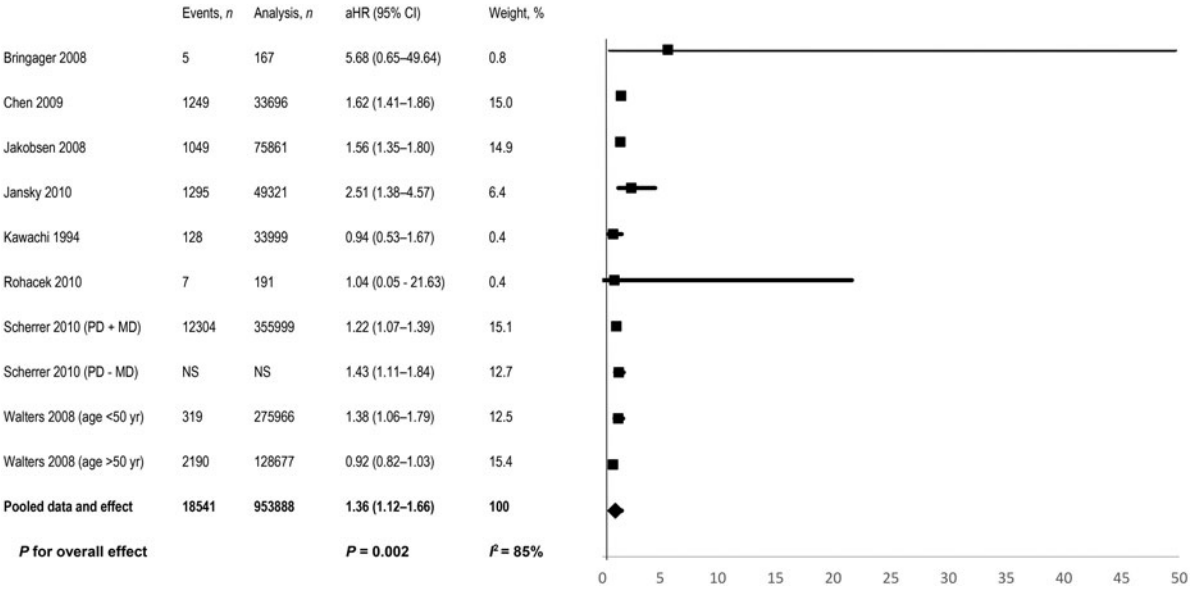

Fig 3. Forest plot of adjusted and weighted hazard ratios for incident myocardial infarction (MI) (secondary endpoint). Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased MI risk for persons with panic disorder (PD). GRADE assessment = high. GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, major depression.

effect sizes for co-morbid PD depression indicated a 79% increased CHD risk; however, this estimate was based on only two studies and substantial heterogeneity remained (aHR 1.79, 95% CI 0.85–3.76, $I^2 = 99\%$).

Meta-regression

Meta-regression of the primary CHD endpoint according to psychiatric-variable study characteristics are shown in Fig. 4. No psychiatric-level variables were identified as a source of between-study heterogeneity.

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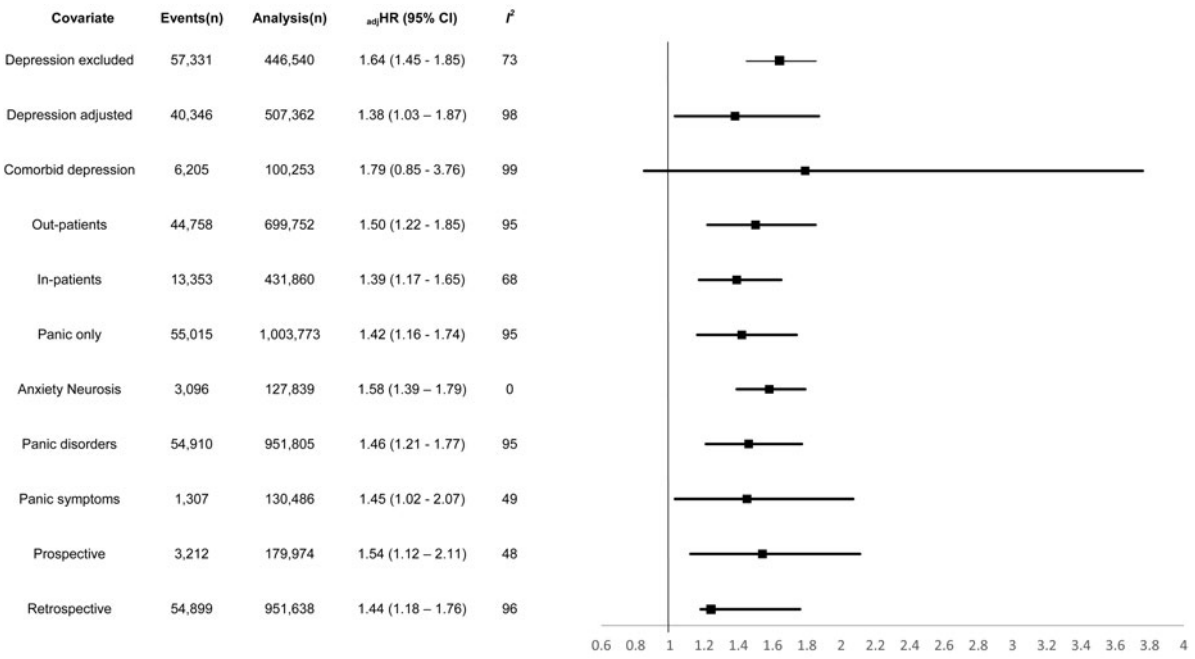

Fig. 4. Forest plot of adjusted hazard ratios (aHR) for incident coronary heart disease (CHD) by psychiatric-level panic disorder (PD) study characteristics. aHR with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased CHD risk for persons with PD.

Meta-regression of the primary CHD endpoint according to general study characteristics are shown in Fig. 5. The analysis of gender and age >50 years as categorical variables did not reveal heterogeneity. However, analyses using the median % suggested that the attributable PD-CHD risk increased with the percentage of females in the study (point estimate for slope 0.002, S.E. = 0.0001, $p = 0.003$) and decreased with the age of participants (point estimate for slope −0.029, S.E. = 0.002, $p < 0.00001$). In terms of psychosocial and CHD risk-factor adjustment we found that adjustment for socioeconomic status and diabetes were sources of between-study heterogeneity. A trend towards between-study heterogeneity was also evident for alcohol covariate adjustment ($p = 0.15$). We also observed length of follow-up as a source of heterogeneity ($I^2 > 10$ years = 25%, 2–10 year = 63%, <2 years = 48%, $p = 0.001$).

The meta-regression results for the MACE endpoint are shown in Supplementary Table S4 (psychiatric moderators) and Supplementary Table S5 (study-level moderators). These results indicated that source of statistical or methodological heterogeneity included adjustment for depression and exercise, and the study region.

GRADE assessment of quality of evidence and publication bias

The assessment of each CHD endpoint according to the GRADE criteria (Guyatt *et al.* 2008) is shown in Supplementary Table S6. The quality of evidence was generally low and this was attributable to imprecision in the estimates, plausible confounding and the absence of a dose-response gradient effect. MI was the only endpoint rated as high-quality evidence where there was evidence of a dose-response gradient effect.

A funnel plot of selected studies and imputed studies on the primary outcome did not suggest the presence of publication bias (Supplementary Fig. S1). Egger's test showed a trend towards significant asymmetry ($p = 0.07$). The fail-safe N shows that another 2314 null studies are needed for the p value to exceed 0.05. According to the trim-and-fill test the association between PD and CHD remains significant after imputing possible missing studies (HR 1.75, 95% CI 1.72–1.79).

Discussion

General findings

In the first meta-analysis reporting the association between PD and verified CHD we observed a 47% increased risk of developing CHD, a 36% increased MI risk, a 40% MACE risk and a non-significant association with fatal CHD in persons with PD. However, there was considerable statistical heterogeneity between study estimates for the primary endpoint that was related to length of follow-up, population age,

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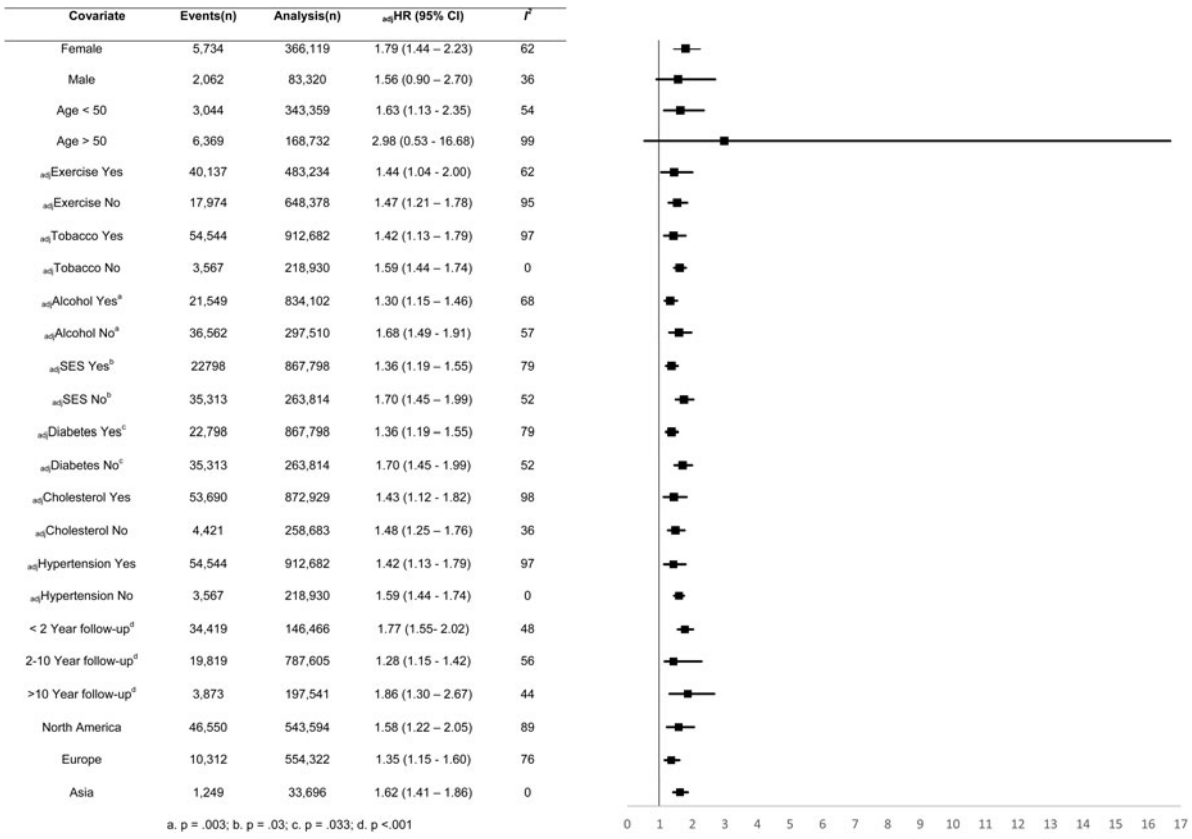

Fig. 5. Forest plot of adjusted hazard ratios (aHR) for incident coronary heart disease (CHD) by general panic disorder (PD) study characteristics. aHR with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased CHD risk for persons with PD. SES, Socioeconomic status.

gender, socioeconomic status and diabetes. For the MACE endpoint, heterogeneity was related to adjustment for depression and exercise, and the study region. Incomplete and biased reporting was also evident; five studies did not list clear inclusion criteria, blind adjudication of CHD endpoints could not be determined in nine studies. None of the retained studies had performed coronary catheterization on all participants to rule out coronary disease as specified in the review protocol (Tully *et al.* 2015) although three studies employed a clinical examination of participants to identify overt CHD (Bringager *et al.* 2008; Janszky *et al.* 2010; Rohacek *et al.* 2012). Consequently, the manner in which PD has been investigated in relation to incident CHD cannot rule out reverse causality.

Reverse causality

One study excluded CHD events in the early follow-up period, but this was only the first 6 months (Bowen *et al.* 2000). In addition Jansky *et al.*'s (2010) longitudinal cohort was performed among 18- to 20-year-old Swedish military conscripts making reverse causality biases unlikely in such a young population. The symptoms of PD and CHD substantially overlap and it is plausible that PD may aggravate underlying coronary disease (Sardinha *et al.* 2009). Here it was evident that the largest pooled HR without heterogeneity was evident in the studies with >10 years follow-up, a marginally higher risk than studies with <2 years follow-up. Together these findings suggest that PD populations are at an increased risk of CHD in both the longer term and more immediate term. However, the heightened CHD risk in the short-term (2-year) period might represent different mechanisms. For example, it is plausible that immediate CHD risk reflects a tendency toward misdiagnosis of PD (Tully, 2015), such as a lower tendency to ascribe CHD admissions to PD in older persons. It is also possible CHD is misdiagnosed in circumstances of psychological stress. Along these lines, takotsubo cardiomyopathy is notably associated with sympathetic activation and cardiac beta-receptor stimulation, often mimicking ST segment elevation MI (Tsuchihashi *et al.* 2001).

PD subtypes and dose-response relationship

We did not find evidence of a dose-response relationship between PD and CHD, only between PD and MI. Effect sizes for PD symptoms were comparable

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to studies assessing PD and there was no evidence of between-study heterogeneity. A previous meta-analysis of non-specific anxiety reported a 26% overall increased CHD risk ($I^2 = 74\%$), a 48% increased fatal CHD risk, and a non-significant association with MI (Roest *et al.* 2010). However, there were too few studies to report anxiety disorder effect sizes separately from anxiety symptoms in the previous review (Roest *et al.* 2010). Such findings contrast those evident here where we observed the largest risk attributable to be for incident CHD risk followed by MI whereas the fatal CHD association was non-significant. It is possible that methodological differences account for such discrepancies. First, we did not include studies comprising persons with established CHD at baseline which is problematic for establishing aetiological associations independent of reverse causality. Moreover, we did not include studies with self-reported CHD which is subject to recall biases among anxiety populations (Goodwin *et al.* 2009). One such study reported a three- to four-fold higher risk of stroke and CHD events in persons with panic attacks (Smoller *et al.* 2007). A second possibility explaining the divergence in findings from previous reviews is the relatively large sample sizes here (median 41 660 participants per study).

Our finding that studies comprising anxiety neurosis had higher effect sizes than PD alone points to the possibility that time of publication, period of recruitment and historical changes to psychiatric nomenclature may affect the purported CHD risk. Given that anxiety neurosis was the precursor to PD (Feighner *et al.* 1972) but contains generalized anxiety symptoms, this raises the possibility that generalized anxiety could be associated with incident CHD (Goodwin *et al.* 2009; Scherrer *et al.* 2010). As such the effect of generalized anxiety and anxiety phenotypes upon CHD risk warrants further study. Given the broad inclusion of anxiety neurosis, PD and panic symptoms, it is not known whether findings relate to more general constructs shared between depression and anxiety such as negative affect which is considered the defining feature of anxiety and depression disorders (Goldberg *et al.* 2011).

Sensitivity analyses with depression adjustment

The importance of depression to CHD is well known (Glozier *et al.* 2013; Ladwig *et al.* 2014) although methodological inconsistencies have been highlighted (Nicholson *et al.* 2006; Kuper *et al.* 2009). Here adjustment for depression and antidepressant medication attenuated CHD risk attributable to PD by 24% compared to studies excluding depression. The modifying effect of depression on PD risk for CHD is comparable to that reported in a recent review of post-traumatic stress disorder (Edmondson *et al.* 2013). In a meta-analysis of six studies Edmondson *et al.* (2013) found that incident CHD risk was attenuated by 28% with depression adjustment. Previous systematic reviews concerning depression have reported CHD risks in the range of 30–90% (Kuper *et al.* 2002; Rugulies, 2002; Wulsin & Singal, 2003; Nicholson *et al.* 2006; Gan *et al.* 2014) with the smallest effect size reported in the most recent and largest sample of 8 93 850 persons (Gan *et al.* 2014). In fact many of the meta-regression analyses here exceeded the total sample of prior depression reviews, (Kuper *et al.* 2002; Rugulies, 2002, Wulsin & Singal, 2003; Nicholson *et al.* 2006) some of which have included only prospective studies. Indeed, recent decades have focused almost exclusively on depression disorders (Berkman *et al.* 2003) which remain the primary psychiatric intervention in established CHD populations. By comparison, the importance of post-traumatic stress disorder and anxiety disorders to cardiovascular health is emerging more recently (Sardinha *et al.* 2009; Edmondson *et al.* 2013; Chalmers *et al.* 2014; Tully & Baune, 2014; Tully *et al.* 2014).

PD intervention

The frontline treatments for PD include cognitive-behavioural therapy (Lessard *et al.* 2012), serotonergic reuptake inhibitors (Van Apeldoorn *et al.* 2013), benzodiazepines (Moylan *et al.* 2012), and their combination such as collaborative care (Archer *et al.* 2012). It remains unclear whether the treatment of PD, by any modality, has a significant beneficial effect lowering the incidence of CHD. However, it was demonstrated recently in the IMPACT trial that collaborative depression care led to a 48% reduction in MACE at 7-year follow-up in persons without established CHD (Stewart *et al.* 2014). By contrast, two recent RCTs indicate that collaborative anxiety disorder management is feasible in primary-care populations with substantial cardiovascular co-morbidity (Roy-Byrne *et al.* 2010; Huffman *et al.* 2014).

Potential mechanisms of cardiopathogenesis

The hypothesized mechanisms underlying PD and CHD association include platelet abnormalities and inflammation (Sardinha *et al.* 2009), diminished heart rate variability (Yeragani *et al.* 1993; Kemp *et al.* 2012), change in the QRS complex (Yeragani *et al.* 2007) and especially the QT interval (Pohl & Yeragani, 2001; Yeragani *et al.* 2002; Sullivan *et al.* 2004). More recent evidence has also indicated links between PD and atrial fibrillation (Cheng *et al.* 2013). It is possible that PD and panic attacks may lead to higher sympathetic discharge and myocardial ischaemia (Fleet *et al.* 2005, 2014). Certainly, associations between

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PD and microvascular disorders including coronary slow-flow (Vural *et al.* 2009), microvascular angina (Roy-Byrne *et al.* 1989) and arterial stiffness (Cicek *et al.* 2012) have been reported. Further, it was recently shown that mental stress-induced myocardial ischemia was associated with microvascular constriction quantitated as peripheral arterial tonometry ratio but not angiographic burden of coronary disease (Ramadan *et al.* 2013). In addition to such mechanisms behavioural factors including a preponderance of smoking (Isensee *et al.* 2003), alcohol use (Hoertel *et al.* 2013), overt exercise-avoidance behaviours (Muotri & Bernik, 2014) or heightened sensitivity to cardiorespiratory symptoms (Ramos *et al.* 2014) might explain links between PD and CHD.

Strengths and limitations

The strengths of this review include the standardized extraction and rating conducted by two independent reviewers. The findings hold relevance for clinicians given that this review excluded studies adopting self-reporting of CHD. The findings of this review are presented with several limitations including that high risk of bias was particularly evident for unclear or unblinded determination of CHD outcome, the absence of clear inclusion criteria, retrospective design, and extent to which studies adjusted for between-group differences at baseline. Another limitation is that the original studies precluded an evaluation of whether the chronicity and severity of PD or frequency of panic attacks were discretely associated with incident CHD outcomes. Only the meta-regression analyses comparing psychiatric in- and out-patients might be a crude marker of PD severity. However inpatient ICD-10 codes for PD might also be associated with more severe psychiatric problems including psychosis and bi-polar disorder. Another limitation is potential regional bias as no studies were eligible from Africa, South East Asia, Asia Pacific or South America. Finally, there may be other unknown biases in the original studies not captured by our sensitivity analyses to determine heterogeneity.

Conclusion

In conclusion, high-quality evidence assessed by GRADE criteria suggested that PD was a risk factor for incident MI although heterogeneity remained. Moderate evidence supported an association between PD and MACE. By contrast, low-quality evidence assessed by GRADE indicated an association between PD and CHD and no association between PD and fatal CHD. These findings are tempered by the heterogeneity between study estimates and risk of biases especially reverse causality. Given the latter possibility, future research is required to examine bi-directional mechanisms of cardiopathogenesis evident in persons with PD and subclinical coronary artery disease and to evaluate further the cardiovascular effects of panic attacks and incident CHD.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715000963.

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Declaration of Interest

None.

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