Author's response to reviews

Title: Panic disorder and incident coronary heart disease: a systematic review and meta-analysis protocol

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Author's response to reviews: see over
Dear Editors-in-chief,

Please accept the revised manuscript titled “Panic disorder and incident coronary heart disease: a systematic review and meta-analysis protocol” as a submission to Systematic Reviews.

We have accommodated most of the associated editor and reviewer comments, and attach a document with a point to point reply. All changes to the manuscript are highlighted in yellow for ease of location and interpretation. The study has not been submitted for publication or previously published elsewhere, and there is no conflict of interest to declare. All authors contributed significantly to the study and give their consent to the final manuscript.

Once again I thank you for your consideration of this manuscript. With best wishes, sincerely yours

Dr. Phillip J. Tully, PhD
On behalf of the authors
Reply to Associate Editor

Abstract

• Please, delete “…full text inspection and…” from the 2nd sentence. Instead, the 2nd sentence should read as follows: “Authors and reference lists of included studies will also be consulted to identify additional published and unpublished studies.”
Change made as suggested to abstract methods section, page 2.

• Given it is a protocol, the manuscript throughout (including the abstract) should be in the future tense.
Change made as suggested to abstract.

• The abstract Methods text (as well as the manuscript Methods section) needs to adhere the following order: 1) search strategy, 2) eligibility criteria, 3) study selection/screening, 4) data extraction, 5) study quality (risk of bias) assessment, and 6) data synthesis and analysis.
Change made as suggested to abstract.

• Will the authors indicate what study designs (e.g., RCTs, non-RCTs, cohort, case-control studies, cross sectional studies, etc…) they will include in their review? The authors are planning to examine the effect of exposure (panic disorder), not an intervention as applied in experimental settings. They will compare the incidence/risk of CHD (or MI) in the exposed (panic disorder) to non-exposed population (no panic disorder). Therefore, I suspect eligible studies should be of longitudinal cohort design (both retrospective and prospective) where panic disorder precedes the incidence of CHD. Additionally, case-control studies (but not cross-sectional studies) could also estimate the odds ratio (or relative risk – if the incidence of CHD in the control group is low) of CHD associated with the presence of panic disorder.
On page 10 of the revised manuscript we outline the design of eligible studies and expand further to include experimental studies; “Only peer reviewed studies in full-text, conference abstract or doctoral dissertations are eligible for this review if published in English. Observational studies
designed as longitudinal cohort, case–control study, or database registry, and experimental studies designed as randomized controlled trials or non-randomized trials will be eligible for this review. Prospective and retrospective studies will be eligible. We will exclude cross-sectional studies, case series and case reports.”

Cross-sectional studies are excluded from this review.

- In the abstract-discussion, the authors made a very strong statement with respect to etiology: “This systematic review will evaluate the etiological links between panic disorder with incident CHD.” I suggest to use this statement in the context of highlighting future clinical and/or policy implications of the review (here as well as in the Discussion section of manuscript). We have made changes to the Abstract, discussion section, pointing out the potential implications for clinical decision making.

  “An evaluation of the etiological links between panic disorder with incident CHD might inform evidence based clinical practice and policy concerning triaging chest pain patients, diagnostic assessment and psychiatric intervention with panic disorder patients.”

Background

- The authors mention about synthesizing ‘quantitative’ evidence several times throughout the manuscript (e.g., line 168). Given this is the protocol, it is not known in advance, what type of evidence (qualitative or quantitative) will be pooled. I suggest to drop ‘quantitative’ from such sentences.

  Change made as suggested, the term quantitative has been deleted throughout the manuscript.

- It is obvious that most included evidence will be from studies of observational nature (e.g., cohort, case-control), in which temporal sequence of panic disorder and CHD incidence can be ascertained. Is there a concern that by excluding experimental controlled intervention trials (randomized or nonrandomized), the reviewers are at risk of missing any relevant evidence? In other words, is it plausible that experimental randomized or non-randomized interventional controlled trials can inform or provide the relevant evidence sought for this
review? May there be any study scenarios where any given intervention would not confound the association between panic disorder and risk of CHD or that this intervention would not interact with panic disorder to modify the outcome risk?

The study design and inclusion criteria is addressed in the Associate Editor’s comment above, and we have included experimental studies. The revision is listed in the Study design eligibility as follows; “Only peer reviewed studies in full-text, conference abstract or doctoral dissertations are eligible for this review if published in English. Observational studies designed as longitudinal cohort, case–control study, or database registry, and experimental studies designed as randomized controlled trials or non-randomized trials will be eligible for this review. Prospective and retrospective studies will be eligible. We will exclude cross-sectional studies, case series and case reports.”

• Depending on the question above, will the authors exclude or include such studies? Please, explain your rationale for inclusion/exclusion. Please, update your eligibility criteria accordingly.

We agree that experimental designs might provide information pertaining to panic disorder and incident heart disease and could be included. The study design and inclusion criteria has been revised accordingly, page 10.

• Will the authors exclude studies published in non-English language?

Yes non-English studies will be excluded, due to lack of funding for translation.

Methods and Design – Search Strategy

• Will the authors specifically search for grey literature/unpublished studies in any designated database or source? Please, indicate this where appropriate.

No we anticipate EMBASE and PsychINFO will provide unpublished Doctoral theses and unpublished conference abstracts. We clarify on page 9; “The grey literature/unpublished studies will not be searched on an electronic database.”

Methods and Design – Data Items for Collection
• Line 234: Will the authors clarify what ‘absolute categorical numbers’ means? Do they refer to nominator (n of new CHD cases) and denominator counts (N total at baseline without CHD)?

Yes here we are referring to the numerator and denominator and we have clarified accordingly on page 11; “Primary outcome data collected will include CHD, reported either as categorical numbers (numerator and denominator)”

• For patient populations (Line: 232), will the authors extract data on comorbidities at baseline?

We will extract data on comorbidities at baseline as specified in the revised manuscript page 11, covariates will include comorbid hypertension, hypercholesterolemia and diabetes

• For patient populations (Line: 232), will the authors extract data on risk factors for CHD?

We will extract data for risk factors for CHD including comorbid hypertension, hypercholesterolemia and diabetes, revised manuscript page 11.

• For the endpoints, will the authors extract mortality data and related summary measures of association (e.g., RRs, ORs, HRs) and associated 95% CIs?

This was stated on page 11 “or the statistical effect size (i.e. risk ratio, hazard ratio, incidence rate ratio, odds ratio) and the 95% confidence interval (CI).”

Methods and Design – Synthesis of Data and Summary Measures

• This section needs some reorganization. Please, put the subsections in the following order:

a) Analysis plan (how the results will be organized qualitatively in tables and text; what will be the summary effect measures from individual studies)

b) Meta-analysis (details on pooling; choice of pooling model; pooled effect measures; assessment of statistical heterogeneity I2 etc…)

c) Sensitivity and subgroup analysis
We have made substantial revisions to this section rearranging the sub-sections, and then further clarification the information to be described in this meta-analysis.

d) Publication bias assessment

See specific comments below:

• The ‘Risk of Bias’ subsection does not belong in this section. Please, place it right after the ‘Data Items for Collection’ section. It should have the same level heading as ‘Data Items for Collection’ section’. Please provide this tool in a separate supplementary file.

Change made as suggested. The RTI item bank is listed in Supplemental File 2 of the revised manuscript.

• Line 245: “…which is a more conservative…” revise as follows: “…which provides a more conservative…”

Change made as suggested, revised manuscript page 13.

• Effect estimates of included studies will be adjusted for different covariates. Moreover, some studies will report risk ratios, some others odds ratios. Will the authors consider this aspect when pooling these measures in their meta-analyses? How will the authors address the pooling if there are marked differences in the adjustment methods across the studies with respect to chosen covariates and the effect measures? Will they pool ORs and RRs, or stratify studies reporting risk ratios from those reporting odds ratios? Will they pool unadjusted and adjusted estimates together?

We will pool together odds ratios, risk ratios and hazard ratios. It is specified on page 15 that our sensitivity analyses will check the appropriateness of this method. “Because of possible under or overestimation of effect sizes, we will adopt Loef and Walach’s [56] methodology for sensitivity analyses and apply the natural logarithms of calculated values and calculate the standard errors based on 95% CIs.”

We will pool unadjusted effect sizes followed by adjusted effect sizes. We have clarified in the revision as follows, page 13, “In the first instance we will pool together the unadjusted effect
sizes for each CHD outcome (permitting age and sex adjustment). In the second instance we will pool together the unadjusted and most adjusted effect sizes for each CHD outcome.”

• Will the authors move the paragraph on statistical heterogeneity (I square, etc) in Lines 271-274 up somewhere along the Lines 242-249, where meta-analysis technicalities are discussed? Then, the subsection heading ‘Assessment of Heterogeneity’ should be replaced with ‘Sensitivity Analysis’ subheading (see below).

The paragraph on statistical heterogeneity has been moved as suggested.

• The authors need to use sensitivity and subgroup analysis terms apart and consistently without mixing them. For example, sensitivity analysis is used to assess the robustness of the pooled estimate across study characteristics (e.g., study design, risk of bias, follow up length, outcome measurement methods) as opposed to subgroup analysis which is used to assess the variation of the effect estimate across population characteristics (e.g., in-patients, co-morbidity, age, gender, etc…).

We have made substantial revisions to this section and further clarified our planned sub-group analyses and sensitivity analyses.

• The authors may create two separate subsections of ‘sensitivity analysis’ and ‘subgroup analysis.’

Subtitles for sub-group analysis and sensitivity analyses made as suggested.

• Lines 255-264 should belong to ‘sensitivity analysis’ subsection.

Change made as suggested, this section has been moved to the sensitivity analysis section.

• Consolidate all relevant text scattered in different places, in subsections of ‘sensitivity analysis’ and ‘subgroup analysis.’

Change made as suggested, we have made substantial revisions and clarified our planned sub-group analyses and sensitivity analyses.
• Are the authors planning to assess an overall quality of evidence (‘strength of evidence’) for their primary outcome using the GRADE system?

We will assess overall strength of evidence for each CHD endpoint according to the GRADE system. On page 16 of the revised manuscript we have added the following section; “The proposed review will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [56] to determine the quality of evidence and the strength of recommendations. The GRADE guidelines will be applied separately to each of the CHD endpoints, providing a summary of findings tables with qualitative description as either; high, moderate, low or very low.”
Reviewer: Karina Davidson

Major Compulsory Revisions

1) Please consider removing 'symptomatic CHD' or angina as an appropriate category of incident CHD. Without any objective indication of CHD but that a clinician is reporting that there is angina pectoris, there could be a major confound between the patient of panic symptoms and the patient report of chest pain.

We have clarified on page 10 of the revised manuscript the definition of our primary CHD endpoint, primary CHD is inclusive of physician or cardiologist diagnosed CHD and we have removed the qualifier “angina” and “chest pain” (CHD endpoint levels 1-4), acknowledging that there might be some bias in this endpoint if CHD is not further specified. We further clarify the secondary endpoints as fatal CHD (verified death for CHD, levels 1-4), and fatal or non-fatal MACE (CHD level 1).

1. Major Adverse Cardiac Events – defined as documented death due to CHD, cardiac arrest (including ventricular fibrillation), sudden-cardiac death or myocardial infarction (fatty 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 ischemia 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.

- Minor Essential Revisions

2) Please consider an additional sensitivity analysis that restricts to only those studies with clinician-diagnosed panic disorder, and one then that restricts to only those studies with self-report of panic symptoms.

We clarify on page 14 of the revised manuscript the planned sub-group analyses. Sub-group analyses will be performed for the primary CHD endpoint on psychiatric classification level: (1) studies utilizing anxiety neurosis diagnoses versus all other anxiety classifications; (2) studies
utilizing self-report symptoms versus all others; (3) studies utilizing panic disorder versus all others.

- Discretionary Revisions

3) I believe the bolding in the references is not in conformance with the Author instructions.

We have updated the references accordingly for the revised submission.

4) Please consider adding to Table 1 the exact number and types of symptoms required to meet panic disorder criteria, for those not familiar with the DSM 5th edition scoring procedure. This could be added as a footnote to Table 1.

This is a good suggestion. We have added the number of symptoms required for a panic disorder diagnosis and further diagnostic qualifiers as a footnote to Table 1 of the revised manuscript.