Reviewer's report

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

Version: 1 Date: 8 December 2014

Reviewer: Alexander Tsertsvadze

Reviewer's report:

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follows: “Authors and reference lists of included studies will also be consulted to identify additional published and unpublished studies.”

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

• 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.

• 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.

• 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).

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.

Methods and Design – Eligibility Criteria
• 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 non-randomized), 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?
• 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.
• Will the authors exclude studies published in non-English language?

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.

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)?
• For patient populations (Line: 232), will the authors extract data on comorbidities at baseline?
• For patient populations (Line: 232), will the authors extract data on risk factors for CHD?
• For the endpoints, will the authors extract mortality data and related summary measures of association (e.g., RRs, ORs, HRs) and associated 95% CIs?

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
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.

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

- 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?

- 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 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…).

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

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

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

Methods and Design – Grading overall quality of evidence

- Are the authors planning to assess an overall quality of evidence (‘strength of evidence’) for their primary outcome using the GRADE system?