

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Global cardiovascular risk assessment in the primary prevention of cardiovascular disease in adults: systematic review of systematic reviews
AUTHORS	Collins, Dylan; Tompson, Alice; Onakpoya, Igbo; Roberts, Nia; Ward, Alison; Heneghan, Carl

VERSION 1 - REVIEW

REVIEWER	Claudio Borghi University of Bologna
REVIEW RETURNED	31-Aug-2016

GENERAL COMMENTS	<p>The paper is focused on an important topic that cannot have a solution through the current literature nice it would deserve a randomized, long term observation of the impact of CV risk scores that has probably never done in an appropriate way.</p> <p>This strong limitation of very clear in the manuscript that is one additional demonstration that the favorable impact of the compliance and knowledge of the results of risk scores can be only presumed. This does not mean that it is not real, simply is lacking of evidence.</p> <p>Minor problems</p> <ol style="list-style-type: none">1. Since the main interest of the manuscript is emphasize a limitation of the current epidemiological methodology, this should be more clearly stated in the introduction.2. The manuscript should be shortened through a better integration of the information in the pictures with the text.3. An attempt should be made to add or replace one figure with one reporting the impact of any single study on the different variables considered.4. On the other hand the discussion should report that the use of the risk equations is finalized to the identification of risk profiles and the definition of the target of interventional and consequent strategies. The estimate of the results of the impact of interventions is matter or RCT.5. However the assessment of the reliability of CV risk scores in terms of prevention is probably out of the purposes of the scores and this can explain the paucity of data and should be emphasized in the introduction and discussion.
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REVIEWER	Olalekan Uthman University of Warwick, UK
REVIEW RETURNED	16-Sep-2016

GENERAL COMMENTS	The authors of the manuscript identified, critically appraised, and summarized existing systematic reviews on the impact of global
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	<p>cardiovascular risk. The paper has potential to add to body knowledge related to cardiovascular disease prevention</p> <p>1. The searches are outdated and will need to be updated. At least one additional relevant systematic review has been published. "Dyakova M, Shantikumar S, Colquitt JL, Drew CM, Sime M, MacIver J, Wright N, Clarke A, Rees K. Systematic versus opportunistic risk assessment for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2016 Jan 29;(1):CD010411. PMID: 26824223"</p> <p>2. The post-hoc meta-analyses, may be not reflect the true prevention effect, since the authors did not actively search for primary studies published after the publication of those systematic reviews. Instead, the existing systematic reviews could have been used as the starting point for identifying potentially relevant studies and additional searches conducted for randomized controlled trials published after the last searches for each of the systematic reviews included in the overview.</p> <p>Minor comments</p> <p>3. Inclusion – page 4, line 91. "We included systematic review of controlled or ..", Do the authors mean "randomized controlled"?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The paper is focused on an important topic that cannot have a solution through the current literature nice it would deserve a randomized, long term observation of the impact of CV risk scores that has probably never done in an appropriate way.

This strong limitation of very clear in the manuscript that is one additional demonstration that the favourable impact of the compliance and knowledge of the results of risk scores can be only presumed. This does not mean that it is not real, simply is lacking of evidence.

Response: We thank you for your thoughtful and valuable contribution to our work.

Minor problems

Point 1. Since the main interest of the manuscript is emphasize a limitation of the current epidemiological methodology, this should be more clearly stated in the introduction.

Response: We agree with this point , and have updated the last sentence of the introduction (page 4 line 78) to include:

"We chose to conduct a systematic review of systematic reviews because they can be used to synthesize evidence for a given intervention on a diversity of outcomes, in addition to identifying limitations in the methodology and quality of existing systematic reviews."

Point 2. The manuscript should be shortened through a better integration of the information in the pictures with the text.

Response: The current literature on this topic is of poor quality and highly variable. We have therefore provided a comprehensive description of the methods and the findings and covered only the most important outcomes.

Point 3. An attempt should be made to add or replace one figure with one reporting the impact of any single study on the different variables considered.

Response: This point is not compatible with evidence synthesis. The impact of individual studies is illustrated in the forest plots, organised by outcome – standard practice in systematic review methodology. Our appendix also includes a table that lists every primary study, their salient characteristics, the review which reports them, and the outcomes they report. Illustrating the impact of one single study could be misleading – the pooled results and the individual results in the context of the forest plot provide a more complete picture allowing the reader to compare and contrast findings.

Point 4. On the other hand the discussion should report that the use of the risk equations is finalized to the identification of risk profiles and the definition of the target of interventional and consequent strategies. The estimate of the results of the impact of interventions is matter or RCT.

Response: We agree with this point and have therefore added the following sentence (page 4 line 73) to the introduction:

“Although calibration and discrimination studies of prognostic risk score models are important, trials on the prospective use of risk scores in practice are required to determine their impact on patient outcomes.”

Point 5. However the assessment of the reliability of CV risk scores in terms of prevention is probably out of the purposes of the scores and this can explain the paucity of data and should be emphasized in the introduction and discussion.

Response: We agree with the point and have added the following sentences to the introduction (page 4, line 73):

“Although calibration and discrimination studies of prognostic risk score models are important, trials on the prospective use of risk scores in practice are required to determine their impact on patient outcomes.”

; and the discussion (page 14, line 343):

“We speculate that paucity of data may be explained by the assumption that accuracy of risk scores is a proxy for effectiveness, therefore undermining rationale for further study. While mechanical prediction, such as the use global cardiovascular risk assessment, is generally a superior method of data combination than clinical judgment, (46) it is unknown whether this holds true for cardiovascular risk. Moreover, clinicians still rely on clinical judgment to integrate risk scores within the broader context of the patient—especially for risk factors that are not included in the risk assessment algorithm—therefore risk stratification is not strictly a practice that can be replaced with mechanical prediction. The uncertainty around the clinical utility of this practice has been highlighted by UK general practitioners ,who expressed that broad implementation created considerable confusion, and emphasized the need for guidance to be updated to reflect how risk scores are actually used. (15)”

Reviewer: 2

The authors of the manuscript identified, critically appraised, and summarized existing systematic reviews on the impact of global cardiovascular risk. The paper has potential to add to body knowledge related to cardiovascular disease prevention

Response: We thank you for your valuable review and recommendations to improve our work.

Point 1. The searches are outdated and will need to be updated. At least one additional relevant systematic review has been published.

“Dyakova M, Shantikumar S, Colquitt JL, Drew CM, Sime M, MacIver J, Wright N, Clarke A, Rees K. Systematic versus opportunistic risk assessment for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2016 Jan 29;(1):CD010411. PMID: 26824223”

Response: We have updated our searches to 25 October 2016 using the same methods described in our manuscript, and have updated our manuscript and figure to reflect this. While our search did identify the above mentioned review, it did not meet our pre-specified inclusion criteria as outlined in our published protocol on PROSPERO (Registration CRD42015019821), specifically the a priori definition of global risk score.

Point 2. The post-hoc meta-analyses may be not reflect the true prevention effect, since the authors did not actively search for primary studies published after the publication of those systematic reviews. Instead, the existing systematic reviews could have been used as the starting point for identifying potentially relevant studies and additional searches conducted for randomized controlled trials published after the last searches for each of the systematic reviews included in the overview.

Response: Importantly we did not diverge from our registered protocol and search for individual primary studies. However, to make this limitation more clear, we have added the following to the limitations section of the discussion (page 15, line 366) :

“Our post hoc analysis of primary studies reported by included systematic review should be interpreted with caution. Its purpose is to better appraise and synthesize the primary studies which are already available in the systematic review literature, and therefore it does not represent the conclusions from a systematic review of individual primary studies, and it is possible that further primary studies exist.”

Minor comments

Point 3. Inclusion – page 4, line 91. “We included systematic review of controlled or ..”, Do the authors mean “randomized controlled”?

Response: We have changed the sentence on page 4 (line 92) to:

“We included systematic reviews of studies of any design that included adults (18 years of age or older) with no history of cardiovascular disease (including atrial fibrillation).”