Reviewer's report

Title: Do Prescription Stimulants Increase the Risk of Adverse Cardiovascular Events?: A Systematic Review

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Reviewer: Sanne A. E. Peters

Reviewer's report:

The authors aimed to systematically review the available evidence on the potential risk for cardiovascular events associated with prescription stimulants. The authors conclude that current evidence on this issue and limited and that future research needs to be performed. The paper is of interest and addresses an important issue as the use of stimulants has been increasing over the last decade. However, some additional remarks remain.

Introduction:
The introduction is quit and not to the point. The authors may consider to shorten the length of the introduction. Also, the paper may be much more appealing by addressing the two examples of drugs that are under strict regulation in an earlier stage.

Results:
The authors state that 350 papers were excluded based on abstract and title. This is a lot and an overview of reasons for exclusion should be provided.

Page 9: the authors state that the results from the study from Schelleman were not adjusted for confounding and selection bias. The reviewer wonders whether any analysis could have been performed given the absence of events. Also, adjustment for selection bias is generally not possible in epidemiological research. How do the authors think this adjustment would look like?

Review of additional evidence:
The pathophysiological evidence is of interest but may warrant further explanations. Why do stimulants increase blood pressure, induce vasospasms, vasculitis and arrhythmia. Only stating that they do cause events seems unsufficient.

Why are the studies on medical and nonmedical use described in this section not included in the systematic review?

Discussion:
The discussion section is long and not to the point. Especially the sections proposed strategies may be substantially reduced.

Page 15: the authors state that RCT's will not be the best way to answer this
question. However, this seems to contradict with the conclusion where the authors state that clinical trials may have a role to determine safety. Clinical trials are generally designed to address efficacy and not safety. The authors should reconsider this statement.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests