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Response to commentary by Rhew and colleagues on: Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence

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We thank Rhew and colleagues for their letter(1) regarding our recently published article.(2) Their concern is that we indicated in our methods that we used an inverse variance weighted method to combine summary measures with random-effects models to account for between-study heterogeneity. However, in our pooled analysis of the effects of selective serotonin reuptake inhibitors (SSRIs) on venous thromboembolism (VTE) risk, we employed a fixed-effect model. Based on their re-analysis using a random-effects model, the data suggested that SSRIs may not be associated with an increased risk of VTE. Indeed, this is correct. However, this statement does not mean we employed a random-effects model in every single analysis in our report. Our main analysis employed random-effects models in the presence of substantial heterogeneity, but in other subsidiary analyses where heterogeneity was low, studies shared one common effect, and in the presence of a limited number of studies, we employed fixed-effects models. We should have also indicated this in the methods section. Comparing users of antidepressants with non-users (6 studies), we employed a random effects model. Heterogeneity was substantial (I^2=79%, 53 to 90%; p<0.001). We also used a random-effects model in the sensitivity analysis that excluded case-control designs, as heterogeneity was substantial (I^2=85%, 61 to 94%; p<0.001). In subgroup analyses by type of risk estimate reported (hazard ratios vs odds ratios), type of VTE (deep vein thrombosis vs pulmonary embolism), gender, and class of antidepressants, we utilized fixed-effects models as the number of studies were few and degree of heterogeneity ranged from low to moderate. In comparing depression with no depression (3 studies), we used a fixed-effects model as heterogeneity was low (I^2=0%, 0 to 90%; p=0.44).

In quantifying heterogeneity using the I^2, there remains the question of how much is too much heterogeneity and when does one apply random-effects models. Higgins and colleagues suggest that the categorization of I^2 values would not be appropriate for all circumstances, but do tentatively assign I^2 values of 25%, 50%, and 75% to mean low, moderate, and high heterogeneity respectively.(3) In the exploration of variability across studies, the I^2 quantification of heterogeneity is just one component of this; the most important is the variability in the clinical and methodological aspects. Higgins and colleagues report that the interpretation of an estimated degree of heterogeneity across

several studies will vary according to whether the estimates show the same direction of effect.(3) In our analyses of the effects of specific antidepressants on VTE risk, this was based on a subgroup analysis. We employed fixed-effects models because of the limited number of studies for each class of antidepressant, the degree of heterogeneity ranged from low to high, and the studies shared one common effect. The studies were not heterogeneous from a clinical and methodological point of view and it was reasonable to assume they shared a common effect, which is a criterion for employing a fixed-effect model.(4) Moreover, the majority of the estimates for each study in the subgroup had the same direction of effect. The heterogeneity of sample sizes of included studies is another criterion that is taken into consideration when deciding to employ a fixed- or random-effects model.(4) When one study is larger than one or more smaller studies, a fixed-effects model is preferable.(5) Furthermore, if there are few studies available for pooling, a random-effects model will provide poor estimates of the width of the distribution of intervention or exposure effects.(6) Given that our data fulfilled these criteria, a fixed-effect model was therefore a better approach for this analysis. We would consider an I^2 of 58.43% to be moderate and not high. Nevertheless, considering the inconsistent effect estimates based on random- and fixed-effects models, the association between SSRIs and VTE cannot be claimed to be robust. Rhew and colleagues further suggested that based on their re-analysis,(1) the inconsistent estimates reported could have broad clinical implications and there may be no concern for the therapeutic use of SSRIs related to VTE as an adverse event. In our report, we also estimated 95% prediction intervals of the pooled estimates of the associations and these contained values below 1. As we have reported, this implies that although on average there seemed to be evidence of associations of depression and antidepressant use with VTE risk, this may not always be so in other studies. The associations may be causal or just be due to confounding. We have not proposed any guideline recommendations or changes as a result of these findings. The overall evidence is based on limited number of studies, characterized by heterogeneity, and deserves further exploration and as we have clearly reported, further studies are still warranted to establish the role of depression and antidepressant use in VTE development, their potential causative pathways, and if there is a class effect of antidepressants on VTE. Furthermore, additional research is needed to ascertain whether it is depression or antidepressant use which drives an increase in VTE risk.

Disclosure of interest

The authors report no conflicts of interest.

References

1. Rhew K, Reams VZ, Brown JD, Winterstein AG. Commentary on: Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. Ann Med. 2018

2. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. Ann Med. 2018;50(6):529-537

3. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560

4. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc. 2015 Sep;13(3):196-207

5. Murad MH, Montori VM, Ioannidis JPA, et al. Fixed-effects and random-effects models. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' guide to the medical literature. A manual for evidence-based clinical practice. 3rd ed. New York: McGraw-Hill, 2015

6. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.