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Commentary

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Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis

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Abstract

This commentary is an author response to Lu and Wang, regarding the manuscript entitled 'Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: Systematic review and meta-analysis'. We address their concern regarding duplication of studies in the meta-analysis and the quality of included studies.

Dear editor,

We thank Dr. Lu and Dr. Wang for their comments regarding our systematic review and meta-analysis on cardiovascular disease in offspring exposed to gestational diabetes mellitus *in utero*.[1] Their comments highlight important considerations regarding study quality in systematic review and meta-analyses and statistical methods put in place to address low-quality studies.

Although we have already specified our methodology regarding including publications of multiple cohorts in the meta-analysis, we appreciate the opportunity to provide further clarity. There has been the understanding that the cohort publications published by Krishnaveni *et al.*, Tam *et al.* and Vohr *et al.*, which we have included in our systematic review, have been doubly reported in the meta-analysis.[2-9] In our methods under the 'included studies' header, it states that 'when the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis'. We only used the publications of Krishnaveni *et al.*[4] and Tam *et al.* [7] in our meta-analysis as these studies have data on the most recent follow-up (i.e., 15 years of age for both cohorts).[3,7] The publications that have been mentioned in the previous commentary are only reported as supplementary data (Supplementary Table 1) but not in the meta-analyses. The Vohr *et al.* studies are also only reported in the supplementary data. We included 59 studies from 54 cohorts in our systematic review, and only 25 studies were used in the meta-analysis (Fig. 1). The reasons for not including 34 studies in the meta-analysis include but are not limited to: (1) reporting the cohort at an earlier follow-up and thus not being the most recent publication with the oldest follow-up age (in the case of Krishnaveni and Tam studies); (2) some studies not reporting a control group value (in the case of Vohr *et al.*[9]); (3) studies only including adjusted mean values that we could not incorporate in a meta-analysis due to limitation in the number of studies; (4) being unable to include median and interquartile range values in the analysis. While we endeavoured to contact authors for unadjusted and unknown values in the meta-analysis, we received a 44% response rate. It would be counter-intuitive to exclude these studies all together after trying to contact the authors for appropriate data; it seemed best to report these data in a supplementary table if it was not suitable for the analysis, thereby providing readers a more comprehensive review of the literature. Furthermore, in our protocol, we were interested in subgroup analyses stratified by childhood, adolescence and adulthood to determine if any of the cardiovascular risk factors appeared at certain points during the lifecourse in offspring exposed to Gestational diabetes mellitus *in utero*. However, we did not have sufficient number of studies to complete any subgroup analyses. We have addressed this in our discussion.

The second point mentioned by Lu and Wang regarding using only high-quality studies in a meta-analysis is an important one to address. While we have included studies of varying study quality, we must emphasise that our methods address how we handle low-quality studies. All 59 included studies have been verified by two authors and underwent quality assessment using the Newcastle–Ottawa Scale (NOS), which is a recommended quality assessment tool used for observational studies. The NOS broadly assesses study quality, including study selection, definition and comparability of cases and controls, assessment and reporting of outcome. We only found nine studies of low quality. We performed sensitivity analyses to omit all

low-quality studies from the meta-analysis, thereby assessing whether these studies would have influenced the effect size of the outcomes. Performing a quality assessment of studies and performing sensitivity analyses are common protocols for many meta-analyses.[10,11] Sensitivity analyses were done for only four outcomes, as these were the only outcomes that included low-quality studies. Our sensitivity analysis tables reported as supplementary data show that there was no significant difference between the effect estimates when removing the low-quality studies, based on I^2 and chi-square value. Therefore, the effect size of our meta-analysis is unaffected by these low-quality studies. Henceforth, the heterogeneity in these analyses needs to be explored in other avenues, including through visual analysis of funnel plots for heterogeneity (which in our analysis were all standard), through performing analyses with values adjusted for important covariates and subgroup analysis (both actions that we were unable to do).

Including all relevant studies and reporting them allow for an extensive scope of the literature, and it is important to assess and report which of this literature is high, moderate and low quality to ensure that clinical decision-making is based on the best-quality evidence.

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