Author’s response to reviews

Title: Trends of blood pressure and heart rate in normal pregnancies: A systematic review and meta-analysis

Authors:
Lise Loerup (loerup.lise@bcg.com)
Rebecca Pullon (rm.pullon@gmail.com)
Lucy Mackillop (Lucy.MacKillop@ouh.nhs.uk)
Jacqueline Birks (jacqueline.birks@csm.ox.ac.uk)
Susannah Fleming (susannah.fleming@phc.ox.ac.uk)
Stephen Gerry (stephen.gerry@csm.ox.ac.uk)
Peter Watkinson (peter.watkinson@ndcn.ox.ac.uk)

Version: 1 Date: 13 Jul 2019

Author’s response to reviews:

13th July 2019

Dear Editor,

Thank you for the opportunity to revise our manuscript. We are pleased that the reviewers recognise the importance of our work. We are grateful for the suggestions of the reviewers and have incorporated these where possible, which we believe has improved our paper. We have answered each point in line below.

Yours faithfully

Peter J Watkinson MD
Associate Professor of Intensive Care Medicine
Reviewer #1

Jagadissan Moodley: this is well, written and well carried out systematic review. My only comments would be is to add to your possible limitations the impact of race on blood pressure it is not clear whether all the studies reviewed, recruited a variety of race groups or homogenous population group. Blood pressure levels are reported to be higher in Black race groups. Although comment is made about maternal age, it is well known that blood pressures in adolescents tend to be lower than there adult counterparts.

Thank you, we have added this point to our limitations (lines 388-391).

The finding that diastolic BP taken manually were higher than that in automated devices may possible be due to some health care providers using the 4th Koratoff sound as the cut-off these possible should be under your limitations

Thank you, we have added this interesting observation to our discussion (line 430-31).

Reviewer #2

Nelson Wang: There was significant statistical heterogeneity in the analyses, which not only reflects potential differences in the patient populations but also methodological differences between studies. Unfortunately, there was little data available on the patient populations, so the between study differences could not be more accurately explained. Differences in measurements of gestational age, blood pressure measurement and heart rate are also important. Even differences in the time of day, can have a large impact on blood pressure readings. If the heterogeneity was able to be explained by the patient characteristics or differences in measurements, then the results would be of more merit.

Thank you. We agree that a key finding of our study is that the published studies are heterogeneous and do not provide sufficient information to allow this heterogeneity to be suitably explored (lines 341-344, 357-363. We believe it is important for clinicians to appreciate the current state of the available literature (lines 343-344) and what this data shows when summarised.
I do not think the authors should have included participants who subsequently developed gestational hypertension or pre-eclampsia because these patients would likely have much higher blood pressure readings. It also goes against the purpose to establish a reference range for healthy women.

We discuss this issue lines 373-377. We include participants who subsequently develop gestational hypertension or pre-eclampsia in line with our (peer-reviewed and published) protocol as pragmatically these participants would be managed using the standard reference ranges up to the point of diagnosis. It would of course have been ideal to undertake our pre-specified subgroup analysis excluding these patient readings after diagnosis. As we discuss lines 376-377, studies did not provide this information, so this analysis could not be undertaken. As we note, lines 422-24, the proportion of participants was small (generally <10%) and so their effect is likely to be minimal. Removing these participants would also be problematic, as the effect is to truncate the top end of the blood pressure distribution – so biasing reference ranges downwards.(1) We aimed (as stated in our peer-reviewed protocol and lines 101-2) to include women recruited as healthy.

What is also concerning is that some studies had BP and HR trajectories in the opposite direction to the overall trend. There should be some attempt at explaining, perhaps in a table, the BP and HR trends within each study. The authors could then provide a thoughtful discussion about which of these studies would be more appropriate as a reference range.

Thank you for noticing these individual study trajectories within our figures, which we think adds to our paper. We have identified the studies as suggested (lines 287-289 and 322-323).

The authors should propose mechanisms to account for their SBP/DBP changes they observed.

Thank you – we have added a sentence about underlying mechanisms (lines 393-395), but have been cautious as we do not wish to over-interpret our findings.

Overall, I appreciate the lack of high quality evidence in this space, and the authors should be commended on their attempt at undertaking this difficult task. The paper should focus more on the individual studies, and try to bring light to those that are high quality and provide a reference range using these studies. I would also suggest a formal statistician review from the journal.
Thank you, we have added a section in the discussion (lines 366-371) directing readers towards our two analyses of higher quality studies, (as specified in our published protocol) neither of which greatly affected our outcomes.

Reviewer #4

Paolo Eusebi: Methods for summarizing evidence are adequate and well-described.

Thank you. We are pleased the reviewer is happy with our methods.

QUADAS-2 is supposed to be used in diagnostic meta-analyses. Furthermore is not meant for building quality scores. I recommend to use Newcastle Ottawa Scale or ROBINS-I among all the possible tools for the complex evaluation of study quality in non-randomized settings.

We agree that ideally we would have used a published quality score specific to the type of studies we were including. However, we did not find a score that suited the study designs that we were interested in, or assessed key aspects of study quality in this field. Therefore we decided to adapt the QUADAS-2, which we found to most closely match our desired score, by modifying the questions to suit the studies we were interested in. This adaptation of the QUADAS-2 scoring system was pre-defined before extracting any information from the studies, and was accepted in the published (peer-reviewed) study protocol. We had previously considered both ROBINS-I and the Newcastle Ottawa scale (and have previously used Newcastle Ottawa successfully). Since receiving the review, we have attempted to implement the Newcastle Ottawa Scale and ROBINS-I, as recommended, however it proved not to be feasible. The ROBINS-I is focused on non-randomised intervention studies, and therefore the majority of the questions are not relevant and not possible to answer (for example ‘Was the intervention implemented successfully for most participants?’). Similarly the Newcastle Ottawa Scale is designed to assess the quality of studies which investigate the effect of exposures on outcomes, and this did not work in the type of studies we have included. On balance, we are confident that the quality score we have used is a good measure which identifies the low and high quality studies in our review. Furthermore, we have attempted to make the process as scientifically robust as possible, by pre-defining the scoring system, and publishing the study protocol.
Potential limits of the study are not discussed, and I think that the cut-off of 50 patients for the study inclusion should at least be reported.

We have discussed potential limitations (lines 351-391) and added text to highlight the exclusion of studies containing <50 participants.

There were deviations from protocol?

Thank you. We have been explicit in the methods section where analyses not identified in the protocol were undertaken.

References: