Author's response to reviews

Title: Predicting developmental outcomes in premature infants by term equivalent MRI: systematic review and meta-analysis

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Author's response to reviews: see over
Dear Dr. David Moher,

Thank you for reviewing the manuscript MS:5966080711653312 entitled: Predicting developmental outcomes in premature infants by term equivalent MRI: systematic review and meta-analysis, that we had submitted for publication in your journal. We have read the comments of the reviewers with interest, and revised the manuscript accordingly.

Please find the revised draft of the manuscript included. We have marked the adjustments that have been made in the revised manuscript.

Our responses to the comments of the referees are stated below.

Referee #1: The data suggests that presence of moderate/severe WM injury has a very good positive likelihood ratio, and absence of any WM/brain injury has a very good negative likelihood ratio, certainly more than clinical or any other imaging modes that we use now for preterm babies. Thus this data supports use of MRI at term for preterm babies, but of course whether this alters clinical management is a different question, however, accurate the test is. This was not the aim of this review. Please include this in the discussion.

Response:
We have added the following text to the discussion section (page 12 line 270-276): “The data in our meta-analysis suggest that presence of moderate/severe WMA has higher positive likelihood ratio, and absence of any WMA has a higher negative likelihood ratio than any other test that we now use for preterm infants (i.e. cranial ultrasound or neurological examination). The prognostic accuracy of WMA finding on MRI therefore supports the use of MRI for preterm infants. However, whether this alters clinical management is a different question. Answering this question was beyond the scope of our meta-analysis.”

Secondly, the review does not include any quantitative biomarkers – like MR spectroscopy and DTI/NODDI and it is likely that the accuracy of MR biomarkers will continue to improve with increasing use of these techniques. This needs to be mentioned in the discussion.

Response:
We have included the examples of MR spectroscopy and DTI/NODDI in the discussion section as ‘future promising techniques’ (page 15, line 361-364): “or other promising MRI techniques that might show moderate prognostic accuracy in the near future (i.e. MR spectroscopy, diffusion tensor imaging –DTI- and neurite orientation dispersion and density imaging –NODDI-).”

Referee #2:
Inclusion criteria may provide the requirements for MRI machine and scanner reference standards. How to define “mild, moderate or severe brain abnormalities”? Are the definitions for included studies similar or same? Please specify.

Response:
The studies describing mild moderate or severe brain abnormalities use the terms ‘brain injury’ (Augustine et al. 2008), ‘brain pathology’ (Setanen et al. 2013) or ‘white mater lesions’ (de Bruine et al. 2011). We reviewed all these articles again to be sure that all these different definitions of ‘brain abnormalities’ were capturing similar MRI findings. We concluded that this was the case. All included studies report WMA as one of the findings. The differences between studies can be found in including IVH and/or increased ventricle size as one of the outcomes as well. Therefore ‘brain abnormality’ is a composite finding of WMA and a variety of two other findings. We did want to include this MRI finding as this reflects common practice in which WM abnormalities together with other abnormalities are taken into consideration. Articles all categorize into three groups according to the most pathological finding in the MRI. They often refer to the article of Maunu et al. (Brain and ventricles in very low birth weight infants at term: a comparison among head circumference, ultrasound, and magnetic resonance imaging. Pediatrics 2009; 123: 617–26) for the definition of mild, moderate or severe brain abnormality.

In the manuscript (Page 14, lines 331 to 336), we added: “This is probably the case in studies describing ‘brain abnormalities’. Although these studies all consequently report WMA as one of the MRI findings, these studies use a composite of other MRI findings as well (i.e. IVH and/or increased ventricle size). Despite the heterogeneity of the definition ‘brain abnormality’, we did want to include this MRI finding as this reflects common practice in which WMA together with other abnormalities are taken into consideration.”

The authors used QUADAS-2 assessment tool to evaluate the risk of bias. To my knowledge, some meta-analysis studies for prognostic accuracy are still using QUADAS. What is the difference, and how to choose?

To answer this question we cite the article published by the QUADAS-2 Group (reference #10 in our manuscript: Whiting PF et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. 2011 Ann Intern Med).

‘In 2003, the QUADAS tool for systematic reviews of diagnostic accuracy studies was developed. Experience, anecdotal reports, and feedback suggested areas for improvement; therefore, QUADAS-2 was developed. This tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. Signalling questions are included to help judge risk of bias. The QUADAS-2 tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. This tool will allow for more transparent rating of bias and applicability of primary diagnostic accuracy studies.’

We look forward to your final decision on the manuscript.

Yours sincerely,
Janneke van ’t Hooft
on behalf of all authors

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