Author's response to reviews

Title: Early Life Opportunities for Prevention of Diabetes in Low and Middle Income Countries

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Version: 3 Date: 3 October 2012

Author's response to reviews: see over
**Response to reviewers comments to manuscript “Early Life Opportunities for Prevention of Diabetes in Low and Middle Income Countries”; Mark A Hanson, Peter D Gluckman, Ronald CW Ma, Priya Matzen and Regien G Biesma (MS: 8960644767329980)**

Dublin, 03 October 2012

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<th>Comment reviewer</th>
<th>Discretionary Revisions</th>
<th>Response</th>
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<td>1. In the section entitled '1) early life influences on diabetes risk' – 2nd paragraph, the authors suggest that there is a 'substantial body of knowledge' that suggests that 'environmental factors act in early life via epigenetic factors...'. This is quite a strong statement, and while I agree that currently the epigenetic pathway is the most plausible mechanism, I am not sure that others would agree that the body of knowledge is 'substantial' at least not yet in humans. The authors may wish to consider re-wording this statement.</td>
<td>We have amended this statement</td>
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<td>2. A single reference is provided in support, to Gluckman et al (16), a viewpoint which discusses the predictive adaptive response, where although mentioned, epigenetic processes are not the main focus of the article. Providing direct reference to papers that review epigenetic pathways would help support the authors' statement.</td>
<td>Suggest that we add another reference which specifically addresses epigenetics and mismatch: Godfrey KM, Lillycrop KA, Burdge G, Gluckman PD, Hanson MA (2007). Epigenetic mechanisms and the Mismatch Concept of the Developmental Origins of Health and Disease. Pediatric Research 61(5 Pt2):5R-10R</td>
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<td>3. Section 4) Intervening from conception. Yes, interventions to prevent excessive weight gain during pregnancy have not been promising. But earlier in the text, the authors also discuss the importance of GDM. Interventions in GDM do appear to be of benefit in terms of birthweight (Gillman MV Diabetes Care 2010, Landon MB NEJM 2009), and maybe worth a mention.</td>
<td>We have added the references with regard to interventions in GDM and beneficial effects on birthweight (Landon MB et al, NEJM 2009; 361(14): 1339-48)(Gillman MW et al, Diabetes Care 2010; 33(5): 964-8)</td>
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<td>4. The authors discuss observational data associating pre-conception maternal health on offspring outcomes. Trial data provide stronger evidence for causality, so they may also want to quote recent subgroup analysis of the SUMMIT trial, (Sebayang Eur J Clin Nutr 2011) which suggested that mothers who were better nourished (as assessed by upper arm circumference), had a better response, in terms of offspring birthweight, to micronutrient supplementation than those who were not.</td>
<td>We agree with the reviewer and have added important experimental studies, such as Sebayang (2011) and Tobias DK et al (2012)</td>
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<td>5. The authors suggest improving health literacy in youth is the key. The deWalt review quoted points out that many of the studies that claim to measure health literacy are measuring literacy per se. So I'm not clear how the authors define health literacy, and if it is so closely related to general literacy, how they see this intervention being successfully</td>
<td>We have included a sentence specifically focusing on the relation between woman's health literacy and her own and her children's health outcomes and strategies to improve that.</td>
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implemented outside the school setting.

6. Discussion: seeing the big picture. Given the long lag time between a potential intervention and hard cardiometabolic outcome, the authors suggest using surrogates to determine efficacy. Some, such as the occurrence or severity of GDM, do have a supporting evidence base, others, for example epigenetic marks in cord blood, currently do not. The authors may wish to separate out surrogates for which there is supporting evidence from those where research is still required. They also discuss healthier trajectories of growth in the first two years of life as a surrogate, but what do they mean by this? Should we be constraining growth in these early years in those of low birthweight for example?

We have amended this to make the point clearer and added a ref to the issue of postnatal growth trajectory as a marker. We feel that further discussion of the question of whether infant growth should be constrained is rather outside the scope of the present review.

Minor essential revisions

7. Section 5) Potential early life interventions – intervening before conception is critical. References appear mismatched to the text. ‘There is considerable data from experimental studies in a range of animal species and prospective studies in humans that a mother’s diet and body composition before and in early pregnancy are related to phenotypic characteristics of the child, such as adiposity at birth and in childhood, and markers of cardiovascular risk such as carotid IMT’ (ref 64 and 65). But both these references discuss diabetes during and after pregnancy.

We have replaced with the following references:

8. Similarly, the figure quotes references Godfrey (18) and Sattar (19). I think these should be Godfrey (19), and Sattar (42).

This is correct and the references for the figure have been changed accordingly.

9. A table summarizing the major clinical and experimental data will increase the objectivity of the article and serves as a quick reference to non-experts.

We feel that this will overburden the review with references whilst providing little insight for the reader. We have attempted to refer to reviews as well as key original papers in order to guide the reader. Thus we would prefer not to include another table, unless the Editor rules that it is essential.

10. Similarly, the article mentions a broad range of prevention strategies including weight management before pregnancy, nutritional intervention during pregnancy, breast feeding after pregnancy, avoidance of childhood obesity and community-based program to enhance health literacy. A schematic diagram showing the optimal stages when these strategies can be introduced, illustrated by some examples, and their potential benefits on both mother and offspring will be useful.

We have modified the figure to illustrate the transgenerational effects and potential benefit of intervention during pregnancy.
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<th>11. This reviewer found figure 1 difficult to interpret - what do the peaks and troughs represent for these trajectories? It is useful to state explicitly that the y-axis represents the risk of NCD in the offspring while the boxes in the graph represent the maternal stresses during her life course and effects on pregnancies. The author also has to explain more clearly how each subsequent pregnancy will drive the risk of the offspring on an upward trajectory (p.9).</th>
<th>We have revised the figure addressing both point 10 and 11.</th>
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<td>12. The authors have not mentioned the growing importance of emotional deprivation during perinatal period and psychological stress during pregnancy on perinatal programming.</td>
<td>We understand this point but, to due justice to this large area would mean expanding the review substantially. In addition, the links with NCDs are less clear than for the other aspects of programming which we have discussed.</td>
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| 13. There are several examples where a broad statement was made without explanation or specific details, e.g:  
- P16, What is cardiovascular Q test and bleep test?  
- P8, Recent animal data now also raise the possibility of paternal transmission of diabetes risk between generations [29] - what next?  
- P9, Experimentally feeding pregnant animals a high fat diet gives rise to offspring who become overweight and who demonstrate a range of metabolic and functional disorders similar to the human metabolic syndrome and which are also associated with epigenetic changes [32] - there are many epigenetic mechanisms and a brief description is needed for completeness for non-experts. It will be useful to replace some of these general statements with more details | P16: We agree and have simplified this section and deleted the example of the Q test  
P8: We did not fully understand this comment, but have extended the statement to make the implications clearer  
P9: We have extended this statement. |