Reviewer’s report

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

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Reviewer: Nishi Chaturvedi

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The authors are internationally recognised for providing leadership and novel insights into our understanding of the lifetime determinants of adult disease. Here they apply their conceptual framework, calling on animal and human studies performed by their group and others, to the problem of diabetes in low to middle income countries. They provide strong evidence to support a refocusing of public health intervention strategies to young individuals. Diabetes is a major, if not the main, global public health challenge. Importantly, the authors highlight the roles of both over- and under- nutrition, and of maternal diabetes and obesity, in fuelling future likely trends of diabetes. This manuscript is timely, deserves a wide audience, and is novel.

Discretionary Revisions

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. 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.

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.

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.
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 implemented outside the school setting.

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?

Minor essential revisions

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

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No conflicts of interest