RESPONSE TO COMMENT ON SCHOLTENS ET AL.

Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism. Diabetes Care 2019;42:381–392

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As described in our article (1), the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study and HAPO Follow-up Study (HAPO FUS) allowed examination of associations between maternal glucose levels during a 75-g oral glucose tolerance test (OGTT) at ~28 weeks' gestation, across the continuum, with child glucose metabolism at ages 10–14 years. The comment by Hulman (2) on our article (1) raises questions about exploratory trajectory analyses that complemented main regression analyses of these secondary predictors and outcomes.

First, regarding exploration of a cubic model, after the fasting blood draw, the HAPO protocol specified recording the number of minutes following glucose consumption for two subsequent blood draws: times ranged 50–70 min and 110–130 min. Using times in minutes as reported, cubic fits were explored, along with linear and quadratic models that included both fixed and random effects. Cubic models in general did not converge and thus were not reported.

Second, regarding the reported quadratic models, the comment (2) and additional reports (3) describe a rise in glucose during a 2-h OGTT, followed by a decline. It is therefore surprising that reporting a quadratic fit, given the available data, would be considered problematic (2); certainly linearity would not suffice and cubic models did not converge. Model fit criteria (4,5) identified the reported quadratic model as the best fit, given those explored for the available HAPO data. We agree with Hulman (2) that four or more time points could facilitate more accurate polynomial or spline fits.

Third, Hulman (2) states that further investigation of clinical relevance of glucose response patterns is required before changing current guidelines. Perhaps our conclusion was misunderstood; we are not advocating immediate change in current guidelines based on exploratory trajectory analyses using limited time points in HAPO data. Rather, we pointed out that the pattern of maternal glucose response, in conjunction with individual analyses of fasting, 1-h, and 2-h maternal glucose values, indicate that the full range, and likely fluctuation, of maternal glucose measures are associated with offspring metabolic outcomes.

Fourth, regarding the direct comparison of child impaired glucose tolerance for trajectory groups B and C, this would certainly be straightforward analytically. Given the exploratory nature of these analyses, we simply chose to interpret associations relative to class A with largest membership that appeared to reflect normal maternal glucose response rather than perform pairwise comparisons for all classes.

Fifth, regarding Fig. 3 (1), we plotted lowess curves within estimated latent class groups to help confirm appropriateness of a quadratic shape for the available data. We acknowledge that plots of the estimated quadratic trajectories would also be informative.

Undoubtedly, maternal glucose response during an OGTT is more dynamic than captured by available HAPO data. Trajectory models were explored to complement analyses that emphasized individual associations of fasting, 1-h, and 2-h maternal glucose across the continuum with offspring metabolic outcomes. We agree that increased granularity of timed glucose measures in future studies would enhance physiological understanding and potential clinical utility of well-calibrated models of pregnancy OGTT data.

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