TWO AUTHORS REPLY

We are grateful to Dr. Cardwell and Dr. Patterson (1) for their interest in our work (2) and would like to reply to their 3 major points of concern.

First, Cardwell and Patterson claim that our meta-analysis on birth weight and later risk of type 1 diabetes contains only a small portion of relevant studies. To support their concerns, they name 11 studies (3–13) that were not included but are suggested by them to ''contain relevant data'' (1, p. 529). In fact, however, 10 of these studies had to be excluded from our analysis, although primarily identified, because unfortunately they do not contain relevant data for a quantitative synthesis: 1 paper does not contain any numerical information on birth weight (3), 2 studies give only adjusted estimates (4, 5), 4 studies report only mean birth weight (6–9), 1 study reports an odds ratio without confidence interval (10), 1 study uses unjustified arbitrary cutoff points (e.g., 3.1 kg) to stratify birth weight (11), and 1 paper reports only standard deviation scores of birth weight (12). Altogether, these failures of data reporting, which lead to unsuitability for meta-analysis, rather seem to support the necessity of exact data presentation in original articles. Only 1 of the 11 studies was not covered by our search strategy although containing relevant data (13). However, the inclusion of this study's unadjusted risk estimate for type 1 diabetes after high birth weight (odds ratio = 1.65, 95% confidence interval: 0.83, 3.26) even slightly strengthened the pooled odds ratio of 1.18 (95% confidence interval: 1.10, 1.27) in our analysis and did not disturb the high between-study homogeneity ($I^2 = 0\%$). Moreover, although reporting bias can never be completely excluded, for overestimation, as also suggested by Cardwell and Patterson, a selective ''overreporting'' of associations with high birth weight would be necessary. This, however, is highly unlikely because, in the great majority of reports, neither birth weight nor even high birth weight was the primary focus of the respective studies.

The second criticism is related to an important problem in meta-analyses of associations between birth weight and later outcomes in general, that is, the fact that individual studies often report adjusted estimates for which different reference categories were used. It is argued by Cardwell and Patterson (1) that pooling these adjusted estimates might have exaggerated the pooled adjusted estimate that we, however, calculated for orientating purposes only, as stated in the paper. However, we now have made the following additional calculation to make the pooled adjusted and unadjusted estimates more comparable. We calculated an unadjusted pooled estimate for those 6 studies that reported adjusted data, but here we used the same reference categories for birth weight as used by the authors themselves in their studies to calculate the adjusted odds ratios. The resulting pooled unadjusted odds ratio for type 1 diabetes after high birth weight was 1.27 (95% confidence interval: 0.98, 1.65), which was still smaller than the pooled adjusted odds ratio of 1.43 (95% confidence interval: 1.11, 1.85) from the same studies. Although these calculations are only of orientating character, they show that irrespective of which reference category is used, adjustment for confounders strengthens the association between high birth weight and later risk of type 1 diabetes.

Third, Cardwell and Patterson (1) support concerns that we also addressed in the Discussion of our paper (2) when criticizing that the multiple inclusion of cases might have contributed to the high homogeneity of the pooled estimate for high birth weight. This argument, however, does not speak against our meta-analysis but against the quality of original reports (as shown above), where respective information on multiple inclusion of data in different reports is rarely given. For example, in the only cohort study, the inclusion of cases from a former study is only vaguely indicated by the authors (14), and therefore their impact remains speculative for investigators who perform a meta-analysis. Moreover, the study from Yorkshire (15) cited by Cardwell and Patterson is irrelevant in this context because it did not contribute cases to the analysis of an association between high birth weight and risk of type 1 diabetes.

Taken together, after careful consideration of all the arguments provided by Cardwell and Patterson (1), we think that they do not invalidate the main result of our meta-analysis, showing that a highly reproducible and biologically plausible association exists between high birth weight and the risk of later type 1 diabetes.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

References

1. Cardwell CR, Patterson CC. Re: "Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis" [letter]. *Am J Epidemiol*. 2009;170(4):529–533.
2. Harder T, Roepke K, Diller N, et al. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. *Am J Epidemiol*. 2009;169(12):1428–1436.
3. Bache I, Bock T, Vølund A, et al. Previous maternal abortion, longer gestation, and younger maternal age decrease the risk of type 1 diabetes among male offspring. *Diabetes Care*. 1999; 22(7):1063–1065.
4. Wadsworth EJ, Shield JP, Hunt LP, et al. A case-control study of environmental factors associated with diabetes in the under 5s. *Diabet Med*. 1997;14(5):390–396.
5. Svensson J, Carstensen B, Mortensen HB, et al. Early childhood risk factors associated with type 1 diabetes—is gender important? *Eur J Epidemiol*. 2005;20(5):429–434.
6. Podar T, Onkamo P, Forsen T, et al. Neonatal anthropometric measurements and risk of childhood-onset type 1 diabetes. DiMe Study Group. *Diabetes Care*. 1999;22(12):2092–2094.
7. Bock T, Pedersen CR, Vølund A, et al. Perinatal determinants among children who later develop IDDM. *Diabetes Care*. 1994;17(10):1154–1157.
8. Malcova H, Sumnik Z, Drevinek P, et al. Absence of breast-feeding is associated with the risk of type 1 diabetes: a case-control study in a population with rapidly increasing incidence. *Eur J Pediatr.* 2006;165(2):114–119.
9. Visalli N, Sebastiani L, Adorisio E, et al. Environmental risk factors for type 1 diabetes in Rome and province. *Arch Dis Child*. 2003;88(8):695–698.
10. Gimeno SG, De Souza JM. IDDM and milk consumption. A case-control study in São Paulo, Brazil. *Diabetes Care*. 1997;20(8):1256–1260.
11. Hathout EH, Beeson WL, Ischander M, et al. Air pollution and type 1 diabetes in children. *Pediatr Diabetes*. 2006;7(2): 81–87.
12. Dahlquist GG, Pundziute-Lyckå A, Nyström L. Birthweight and risk of type 1 diabetes in children and young adults: a population-based register study. *Diabetologia*. 2005;48(6): 1114–1117.
13. Sipetić S, Vlajinac H, Kocev N, et al. Early infant diet and risk of type 1 diabetes mellitus in Belgrade children. *Nutrition*. 2005;21(4):474–479.
14. Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with risk of childhood onset type 1 diabetes: a UK regional retrospective cohort study. *Diabet Med*. 2005;22(2): 200–206.
15. McKinney PA, Parslow R, Gurney KA, et al. Perinatal and neonatal determinants of childhood type 1 diabetes: a case-control study in Yorkshire, U.K. *Diabetes Care*. 1999;22(6): 928–932.

Thomas Harder and Andreas Plagemann (e-mail: andreas.plagemann@charite.de)

Clinic of Obstetrics, Division of "Experimental Obstetrics," Charité—University Medicine Berlin, Campus Virchow-Klinikum, Berlin 13353, Germany

DOI: 10.1093/aje/kwp190; Advance Access publication July 1, 2009