


Lorenzo D. Botto
Joseph Mulinare
Division of Birth Defects and Developmental Disabilities
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, GA 30333

THE AUTHORS REPLY

We thank Botto and Mulinare (1) for their observations. They suggest that our recent paper (2) should have concluded more strongly that our data were consistent with evidence for the interaction of MTHFR genotype with maternal vitamin use in determining infant spina bifida risk. We concluded that we observed only "minimal evidence" for an interaction between infant MTHFR genotype and maternal vitamin use in determining spina bifida risk. This discrepancy in conclusions appears to be based on the analytic approach we chose versus the one that Botto and Mulinare suggest. They indicate that our analytic approach should have emphasized the 2 x 4 table. Those analyses and results were, in fact, included in our paper (2, p. 34).

Given that the analytic approach used should be consistent with the underlying hypothesis, we did not emphasize the 2 x 4 approach because we believed that it did not directly address our hypothesis. In our underlying model of this potential association, we hypothesized, based on accumulating evidence (3), that infants with the TT genotype for MTHFR would be at increased risk of spina bifida, ignoring the influence of maternal vitamin intake. (Our results, however, did not strongly support this hypothesis (odds ratio = 1.5, 95 percent confidence interval: 0.9, 2.5).) We further hypothesized that elevations in maternal serum folate levels resulting from periconceptional supplementation with folic acid could improve the activity of the poorly functioning MTHFR enzyme. Thus, our hypothesis predicted that spina bifida risk for infants homozygous for the TT genotype (compared with those with the CC genotype) would be lower in the group of infants whose mothers used vitamins, possibly lowered to no risk, compared with the group of infants whose mothers did not use vitamins. The 2 x 2 table analysis we used (2, table 2) directly assessed this hypothesis. In contrast, the 2 x 4 analytic approach uses a different reference group, i.e., infants with the CC genotype whose mothers used vitamins.

Our results pointed in the hypothesized direction. However, differences in risk were not substantial or "statistically significant," and therefore we found only weak support for the hypothesis. That is, compared with infants with the CC genotype, the odds ratios for spina bifida among infants with the TT genotype were 1.2 (95 percent confidence interval: 0.4, 4.0) for infants whose mothers used vitamins and 1.6 (95 percent confidence interval: 0.8, 3.1) for infants whose mothers were considered nonusers.

Although we chose to emphasize this particular analytic approach, we also recognized that other approaches to analyzing these data might be of interest to readers, and we therefore presented results of the 2 × 4 analysis suggested by Botto and Mulinare (1), as well as sufficient data to allow the reader to make other similar analytic comparisons.

We agree with Botto and Mulinare that our data lacked the power to obtain precise risk estimates for the 2 × 4 approach. It was not designed to specifically investigate that approach. Our analysis was consistent with what we hypothesized to be the underlying mechanism of a relation between vitamins, genotype, and risk. However, we do not know what the underlying biologic relation is hypothesized to be using the model suggested by Botto and Mulinare.

REFERENCES


Gary M. Shaw
March of Dimes Birth Defects Foundation
California Birth Defects Monitoring Program
Emeryville, CA 94608

Rima Rozen
Departments of Human Genetics, Pediatrics, and Biology
McGill University
Montreal Children's Hospital
Montreal, Quebec, Canada H3Z 2Z3

Richard H. Finnell
Department of Veterinary Anatomy and Public Health
College of Veterinary Medicine
Texas A&M University
College Station, TX 77843

Cathy R. Wasserman
Community and Family Health
Maternal and Child Health
Washington State Department of Health
Olympia, WA 98504

Edward J. Lammer
Division of Medical Genetics
Children's Hospital
Oakland, CA 94609

Am J Epidemiol Vol. 150, No. 3, 1999