ized to one of the exercise programs or to the control condition, and differential effects on outcomes should be attributed to this factor. The children’s fatness was reduced because of the exercise programs offered to those groups. Mediation analysis (ie, testing factors posited to be in the causal pathway) can suggest how those changes may have occurred based on contemporaneous, collinear data with varying precision. Mediation analyses on these data are in progress.

As expected, puberty (ie, thelarche or gonadarche stage) was a predictor in the insulin resistance models (insulin area under the curve, P < .001; fasting insulin, P < .001; Matsuda index, P = .002). The adrenarche variable was not significant in any model. At the request of Short, we conducted an analysis of the interaction of thelarche or gonadarche stage (classified as Tanner I, II, or III and above) with the group × time interaction in the insulin resistance models, adjusting for cohort, sex, and race. An interaction was detected only for fasting insulin, such that differential change from baseline to posttest between exercise groups and control was detected only in Tanner stage III or above. In more developed children, similar decreases in fasting insulin were seen in the low-dose (adjusted mean difference, −18.2 [95% CI, −23.8 to −10.6] µU/mL) and high-dose (−15.8 [95% CI, −23.0 to −8.5] µU/mL) exercise groups (each P < .001 vs the control group). Thus, more developed children might be more responsive to exercise. However, of 3 insulin resistance indicators, only 1 showed evidence of pubertal moderation. These exploratory analyses provide scant support for the hypothesis that pubertal stage affects the benefits of aerobic training in obese children. Conclusions should be tempered by the exploratory nature of these additional analyses.

Catherine L. Davis, PhD
Jennifer L. Waller, PhD
Norman K. Pollock, PhD

Author Affiliations: Departments of Pediatrics (Drs Davis and Pollock) (cadavis@georgiahealth.edu) and Biostatistics (Dr Waller), Medical College of Georgia, Augusta.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and all 3 reported receiving grants from the National Institutes of Health.


Bisphenol A and Obesity in Children and Adolescents

To the Editor: Dr Trasande and colleagues1 concluded that “Urinary [bisphenol A] BPA concentration was significantly associated with obesity in this cross-sectional study of children and adolescents. Explanations of the association cannot rule out the possibility that obese children ingest food with higher BPA content or have greater adipose stores of BPA.”

The authors also examined other environmental phenols and did not find an association with obesity, stating that “The absence of an association between body mass/obesity and levels of other environmental phenols argues for a specificity of association.”

The problem is that BPA is a lipophilic compound and would have a propensity to be stored in fat, leading to an increased amount in the urine of obese children. Bisphenol A has a water solubility of 120 to 300 mg/L (practically insoluble in water).2,3 On the other hand, phenols as a group have a great range in solubility. For example, phenol is soluble in water at 83 g/L.3 The authors do not discuss the solubility of the other phenol compounds, which would have to be comparably lipophilic to draw the conclusion that the association is specific. In addition, the study was limited by only measuring urine concentrations of BPA, which may not reflect the serum level.

It was appropriate for Trasande et al1 to suggest that obese people may have higher stores of BPA in their fat. If this is indeed the case, then obesity would result in higher levels of BPA in the urine and would not be the cause of obesity but rather the result.

Robert L. Brent, MD, PhD, DSc

Author Affiliation: Department of Pediatrics, Jefferson Medical College, Philadelphia, Pennsylvania (rbrent@nemours.org).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported being a consultant for the Food and Drug Administration, Centers for Disease Control and Prevention, and National Institutes of Health; providing expert testimony in vaccine litigation as a defense expert for the US government; and receiving travel expenses for meetings of the Teratology Society, Institute of Medicine, National Council for Radiation Protection, The Fetus as a Patient, Health Physics Society, and International Academy of Perinatal Medicine from his university account.


In Reply: In our analysis of data from the 2003-2008 National Health and Nutrition Examination Survey (NHANES), we found associations of urinary BPA (but not other chemically similar environmental phenols) with body mass index z score and obesity in children and adolescents, whether the urinary concentration was categorized in quartiles or analyzed as a continuous variable. Dr Brent asserts that we failed rather the result.

Robert L. Brent, MD, PhD, DSc

Author Affiliation: Department of Pediatrics, Jefferson Medical College, Philadelphia, Pennsylvania (rbrent@nemours.org).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported being a consultant for the Food and Drug Administration, Centers for Disease Control and Prevention, and National Institutes of Health; providing expert testimony in vaccine litigation as a defense expert for the US government; and receiving travel expenses for meetings of the Teratology Society, Institute of Medicine, National Council for Radiation Protection, The Fetus as a Patient, Health Physics Society, and International Academy of Perinatal Medicine from his university account.


In Reply: In our analysis of data from the 2003-2008 National Health and Nutrition Examination Survey (NHANES), we found associations of urinary BPA (but not other chemically similar environmental phenols) with body mass index z score and obesity in children and adolescents, whether the urinary concentration was categorized in quartiles or analyzed as a continuous variable. Dr Brent asserts that we failed to account for the lipophilic nature of BPA and therefore its propensity to be stored in the adipose tissue of obese individuals (especially compared with other environmental phenols), invalidating our use of their urinary concentrations as tests of specificity.
To reinforce his assertion, Brent suggests that BPA has low water solubility. However, one of his citations actually states that BPA is “moderately soluble” in water. More recent reviews by the World Health Organization estimate BPA solubility in water to be 0.5 to 1.3 mmol/L. Furthermore, it is important to reflect on the metabolic transformation of BPA in humans. After dietary ingestion, BPA undergoes first-pass glycosylation in the liver, a process that increases its urinary excretion as water-soluble glucuronide conjugates. The NHANES analytic method used to measure BPA quantifies total (conjugated and unconjugated) BPA.

The lipophilicity of BPA compared with the other environmental phenols can be evaluated by comparing the chemicals’ octanol and water partition coefficients—the higher the coefficient, the more lipophilic the compound. Compared with benzophenone-3, triclosan, and 4-tert-octylphenol, BPA has a much lower partition coefficient ($K_{ow}$, 2.2-3.4), and therefore is less likely to be stored in fat than the other phenols. Thus, it was appropriate to examine associations of urinary BPA alongside urinary concentrations of other environmental phenols, as we did in our study.

Brent’s comment presents an opportunity to reinforce that our specificity tests have limits intrinsic to the cross-sectional design. Absent controlled human experiments that intentionally provide BPA doses to individuals and examine weight gain, observational, longitudinal studies are needed to examine whether BPA may be associated with obesity or whether obese children simply excrete more BPA. If further research reveals that the latter is more likely, our study raises concerns that obese children may be susceptible to adverse neurodevelopmental and respiratory effects that have been associated with BPA exposure in children.

Leonardo Trasande, MD, MPP
Teresa M. Attina, MD, PhD, MPH
Jan Blustein, MD, PhD

Author Affiliations: Department of Pediatrics, New York University School of Medicine, New York (Dr Trasande and Attina) (leonardo.trasande@nyumc.org); and New York University Wagner School of Public Service, New York (Dr Blustein).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


©2013 American Medical Association. All rights reserved.