Association of Bisphenol A With Diabetes and Other Abnormalities

To the Editor: Dr Lang and colleagues[1] reported that higher levels of urinary bisphenol A (BPA) were associated with type 2 diabetes and cardiovascular diseases in a cross-sectional analysis of US National Health and Nutrition Examination Survey (NHANES) data. While these findings have public health importance, I am concerned about the classification of diabetes in this study, in which the authors combined self-reported diagnosed diabetes and borderline diabetes as a single group of diabetes.

To my knowledge, a majority of patients who were classified as borderline diabetes by interviewers in NHANES data did not have evidence of taking diabetes medications or meeting plasma glucose criteria for diabetes by the American Diabetes Association. Selective recall of diabetes due to increased exposure to suspected diabetic agents such as fat and some chemicals is possible in participants with borderline diabetes. For this reason, it would be better to eliminate those participants with borderline diabetes from the analysis to clarify the association between BPA and diabetes.

In addition, because it is likely that only some of the participants with borderline diabetes actually represent diabetes, the concentrations of BPA should show an increasing trend from the nondiabetic group to the borderline diabetes group to the diabetes group if BPA is indeed a causative agent of type 2 diabetes. The authors should present the means of concentrations for those 3 groups. The absence of such a trend would not support a causative association of BPA with diabetes.

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1. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA*. 2008;300(11):1303-1310.

To the Editor: In their study, Dr Lang and colleagues[1] found that higher urinary concentrations of BPA were associated with diabetes. Based on animal studies, the authors had hypothesized that BPA exposure would be positively associated with type 2 diabetes. However, NHANES, the database used in this study, does not distinguish between type 1 and type 2 diabetes. Although it is likely that most of the participants with diabetes had type 2, it is probable that some of them had type 1.

The authors pointed out that BPA has been found to disrupt pancreatic β-cell function in animals; this may have implications for not only type 2 but also type 1 diabetes. Bisphenol A has also been found to disrupt thyroid hormone,[2] and people with type 1 diabetes have a 2 to 3 times higher risk of thyroid dysfunction than the general population.[3] In some studies, type 1 diabetes has also been epidemiologically associated with insulin resistance[4] and higher body mass index,[5] also consistent with animal studies of BPA.

The authors suggested follow-up studies to confirm their findings. It may be worthwhile to conduct further studies that focus on BPA and type 1 diabetes, in addition to type 2 diabetes.

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To the Editor: From a cross-sectional analysis of urinary chemical concentrations and health status in the general US adult population, Dr Lang and colleagues[1] reported that BPA was associated with cardiovascular diagnoses, diabetes, and abnormal liver enzyme concentrations. However, the potential for false positives, briefly mentioned but not analyzed, is substantial when the complete Centers for Disease Control and Prevention (CDC) design is examined.

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Letters Section Editor: Robert M. Golub, MD, Senior Editor.

The CDC NHANES (2003-2004)[2,3] measured 275 environmental chemicals and a wide range of health outcomes. Although the study by Lang et al focused on 1 chemical and 16 health outcomes (8 patient-reported medical outcomes and 8 clinical chemistry measurements), counting to determine how many questions were at issue and in how many ways these questions can be statistically analyzed is important.

Focusing only on the health outcomes selected by the authors, the analysis forms a 16×275 composite set of questions. However, there are more than 8 ways that the medical outcomes can be examined since 2 of the outcomes have subgroups, any 1 or combination of which could result in an association. Likewise, there are more than 8 ways the clinical measurements can be examined because additional measurements and derived outcomes were reported. Overall, we counted 32 possible outcomes.

From the perspective of the complete CDC study design, there are $32 \times 275 = 8800$ questions at issue. In addition, there is a large list of possible confounder variables; we counted 10. The authors used 2 regression models to adjust for confounders, but with 10 confounders, there are 1024 possible different adjustment models. Considering the complete list of questions at issue and confounders, the model space could be as large as approximately 9 million models.

Given the number of questions at issue and possible modeling variations in the CDC design, the findings reported by the authors could well be the result of chance. The authors acknowledged as much for only 16 questions for BPA alone, and we amplify their warning by pointing out the conceptually much larger CDC grand design. There could easily be a flood of articles reporting chance results. We note that *JAMA* recently published an article reporting an association between arsenic and diabetes using the same database.[4]

We think it is a good time to step back and consider the entire CDC study for the large, planned study that it is and develop a statistical analysis strategy that takes into account the large number of questions at issue.

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In Reply: Dr Wei and Ms Howard and Dr Howard comment on the observed association between BPA and diabetes in our study. Respondents to the NHANES 2003-2004 were asked, "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Our analyses included 124 respondents replying yes plus 12 recorded as borderline. In fully adjusted models, geometric mean concentration of urinary BPA in the no group was 2.45 ng/mL (95% confidence interval [CI], 2.26-2.65 ng/mL); in the small borderline group, 5.97 ng/mL (95% CI, 4.01-8.88 ng/mL); and in the yes group, 2.86 ng/mL (95% CI, 2.42-3.37 ng/mL). Excluding the borderline response attenuated outcomes slightly in fully adjusted models: the odds ratio (OR) for responding yes vs no was 1.19 (95% CI, 1.00-1.41; $P = .05$) per 1-SD increase in BPA concentration. This equated to an OR of 2.38 (95% CI, 1.14-4.98; P for trend $= .03$) for a yes response in the upper vs lower 25% of BPA concentrations.

Type 1 or type 2 diabetes is not separately identified in NHANES 2003-2004, but only 17 participants reported ages at diabetes onset younger than 30 years. Excluding these persons with young onset had little effect. The OR for older onset diabetes was 1.36 (95% CI, 1.15-1.61) per 1-SD increase in BPA concentrations. We agree with Howard and Howard that studies of BPA in both type 1 and type 2 diabetes are justified.

Dr Young and Ms Yu comment on the implications of multiple statistical testing. Such criticism of observational studies is not new.[1] Given the prior evidence on BPA, we followed the emerging model emphasizing discovery and explanation, asserting that multiple analyses are a necessary part of observational research and that replication is the solution to establishing the validity of new findings.[2]

In our analyses of 16 outcomes, we found associations (significant at $P < .05$) with 5 outcomes (2 diseases and 3 liver enzymes). Explanatory variable selection was based on a priori knowledge rather than automatic variable selection procedures; the latter might have introduced many more comparisons.

In the age group originally studied (18-74 years), associations between urinary BPA concentrations and concentrations of the liver enzymes lactate dehydrogenase, alkaline phosphatase, and γ-glutamyltransferase were present. In further analyses of the NHANES 2003-2004 data in the 12- to 17-year-old age group, BPA associations in the same direction were found with the first 2 of these 3 enzymes.[3] This similarity of findings across independent samples of differing ages suggests the original findings were robust. The findings in adolescents also suggest that the associations between BPA and liver enzyme concentrations are not a result of adult disease (through reverse causation).

On the broader topic of multiple comparisons and the NHANES toxicology program, the chemicals assessed are those causing most concern for human health. The numbers of independent, scientifically interesting comparisons

are likely to be far smaller than the theoretical maximum suggested by Young and Yu. Analyses emphasizing discovery plus replication are scientifically valid and in the interests of safeguarding public health.

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Termination of Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest

To the Editor: As authors of the article that was the subject of the Editorial by Drs Sanders and Kern,[1] we disagree with their assertion that clinical rules for terminating treatment have a way of becoming a self-fulfilling prophecy. All patients in cardiac arrest (excluding those with an advanced directive or obvious signs of death) deserve an adequate attempt at resuscitation using the best available techniques and strategies. Nothing in our study should be construed as proposing that patients should receive anything less. However, when determined efforts at resuscitation fail to reestablish a pulse on the scene—as is frequently the case—it appears that nothing is gained by rushing the patient to the hospital for further efforts at resuscitation.

Concerns have been raised about whether the practice of allowing paramedics to cease efforts in the out-of-hospital setting may undermine their efforts to achieve successful resuscitations. The converse may be true. Encouraging high-speed transport may encourage paramedics to prematurely abort useful on-scene efforts in favor of rushing to the hospital. Paramedics are better able to administer quality cardiopulmonary resuscitation (CPR) on scene rather than in the back of an ambulance traveling at high speeds.[2] Seattle has reported the highest rate of survival from out-of-hospital cardiac arrest (OHCA) (16.3%)[1] even though for 3 decades Seattle's paramedics have been authorized to cease futile cardiac resuscitations in the out-of-hospital setting.[3]

Cardiac resuscitations succeed or fail on the scene. If bystanders fail to promptly call emergency medical services (EMS), if CPR is not begun as quickly as possible, if defibrillation is delayed, and if the patient does not promptly receive definitive care, survival is extremely unlikely, no matter how sophisticated the closest hospital may be.

To this end, we agree that OHCA should be made a reportable disease. Every city should collect and analyze its own performance data to determine what improvements must be made to its own EMS systems to increase survival rates from OHCA. The Cardiac Arrest Registry to Enhance Survival (CARES) used in our study is explicitly designed for this purpose, and it is available to any community that wants to use it.

Finally, we would like to clarify that the derivation of the original basic life support rule[4] was conducted independently by the research group from Toronto, Ontario. The derivation of the advanced life support rule[5] was also led by the Toronto group in collaboration with the Ontario Prehospital Life Support (OPALS) study group.

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In Reply: We agree with Dr Sasson and colleagues and the 2005 American Heart Association Guidelines[1] cited in our Editorial that patients in cardiac arrest unresponsive to CPR and advanced cardiac life support in the out-of-hospital setting do not need to be transported to a hospital.[1] This is consistent with the clinical practice at the University of Arizona Sarver Heart Center. However, we do not feel that a termination-of-resuscitation (TOR) rule is necessary for a team of well-educated health care professionals to determine that the patient will not respond to further resuscitation treatment. Clinicians make the decision to terminate resuscitation for both in-hospital and out-of-hospital cardiac arrest based on individual patient factors, local system factors, and arrest factors and circumstances. Clinicians must have knowledge of the prognostic factors for survival as well as changes in the science of resuscitation.

We have a number of concerns about recommending a universal TOR rule. The study by Nichol et al[2] showed that there is at least a 5-fold difference in survival from cardiac arrest