

Association of Urinary Bisphenol A Concentration With Medical Disorders and Laboratory Abnormalities in Adults

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BISPHENOL A (BPA) IS ONE OF the world's highest production-volume chemicals, with more than 2 million metric tons produced worldwide in 2003 and annual increase in demand of 6% to 10% annually.¹ Bisphenol A is used extensively in epoxy resins lining food and beverage containers and as a monomer in polycarbonate plastics in many consumer products. Widespread and continuous exposure to BPA, primarily through food but also through drinking water, dental sealants, dermal exposure, and inhalation of household dusts, is evident from the presence of detectable levels of BPA in more than 90% of the US population.²⁻⁴

Most studies of the health effects of BPA have focused on well-documented estrogenic activity,⁵ but reports have highlighted additional modes of action,⁶ including liver damage,⁷⁻¹¹ disrupted pancreatic β -cell function,¹² thyroid hormone disruption,¹³ and obesity-promoting effects.¹⁴ The potential for low-dose effects¹⁵ has added to the con-

Context Bisphenol A (BPA) is widely used in epoxy resins lining food and beverage containers. Evidence of effects in animals has generated concern over low-level chronic exposures in humans.

Objective To examine associations between urinary BPA concentrations and adult health status.

Design, Setting, and Participants Cross-sectional analysis of BPA concentrations and health status in the general adult population of the United States, using data from the National Health and Nutrition Examination Survey 2003-2004. Participants were 1455 adults aged 18 through 74 years with measured urinary BPA and urine creatinine concentrations. Regression models were adjusted for age, sex, race/ethnicity, education, income, smoking, body mass index, waist circumference, and urinary creatinine concentration. The sample provided 80% power to detect unadjusted odds ratios (ORs) of 1.4 for diagnoses of 5% prevalence per 1-SD change in BPA concentration, or standardized regression coefficients of 0.075 for liver enzyme concentrations, at a significance level of $P < .05$.

Main Outcome Measures Chronic disease diagnoses plus blood markers of liver function, glucose homeostasis, inflammation, and lipid changes.

Results Higher urinary BPA concentrations were associated with cardiovascular diagnoses in age-, sex-, and fully adjusted models (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.18-1.63; $P = .001$ with full adjustment). Higher BPA concentrations were also associated with diabetes (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.21-1.60; $P < .001$) but not with other studied common diseases. In addition, higher BPA concentrations were associated with clinically abnormal concentrations of the liver enzymes γ -glutamyltransferase (OR per 1-SD increase in BPA concentration, 1.29; 95% CI, 1.14-1.46; $P < .001$) and alkaline phosphatase (OR per 1-SD increase in BPA concentration, 1.48; 95% CI, 1.18-1.85; $P = .002$).

Conclusion Higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the community-dwelling adult population.

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troverly about possible hazards and whether currently recommended exposure thresholds require revision.¹⁶⁻¹⁹

Debate about the health effects of BPA in humans has been hindered by the lack of epidemiologic data of sufficient statistical power to detect low-dose effects.⁴ The US National Health and Nutrition Examination Survey (NHANES) 2003-

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2004 recently released the only large-scale data on urinary BPA concentrations.²⁰ Because orally administered BPA is rapidly and completely excreted, urine is considered the body fluid most appropriate for assessment of BPA exposure.²¹ The highly water-soluble major BPA metabolite, BPA-monoglucuronide, is formed in the gut wall and liver and is rapidly removed from the blood by the kidneys, with terminal half-lives of less than 6 hours after oral administration.²¹

Given the previous animal evidence, we hypothesized that higher urinary BPA concentrations would be associated with adverse health effects, especially in the liver and in relation to insulin, type 2 diabetes, and obesity in humans. Because of the paucity of direct human evidence, however, we undertook analyses of all 8 of the reported major diagnostic groupings available in the NHANES 2003-2004 data (including cardiovascular and respiratory conditions for which 3 questions each are available on subdiagnoses). We also examined a preselected list of 8 blood-based clinical measures reflecting liver function, glucose homeostasis, inflammation, and lipid changes.

METHODS

Data were from NHANES 2003-2004.²² NHANES surveys assess the health and diet of the noninstitutionalized US population and are administered by the National Center for Health Statistics. NHANES was approved by the National Centers for Health Statistics institutional review board, and all participants provide written informed consent.

Assessment of BPA Concentrations

NHANES includes biomonitoring for exposure to a range of environmental toxins.²³ A one-third random subset of NHANES 2003-2004 participants supplied urine samples that were then analyzed for BPA concentration. A spot urine sample was collected from each participant. Total (free and conjugated) urinary concentrations of BPA were measured at the Division of Environmental Health Laboratory Sciences (National Center for Environmental Health, Centers for Disease Control and

Prevention) using online solid-phase extraction coupled with high-performance liquid chromatography–isotope-dilution tandem mass spectrometry with peak focusing. A comprehensive quality control system, including reagent blanks, was used to ensure that samples were not contaminated during handling, storage, and analysis.²⁴ For BPA concentrations below the level of detection (116/1455 [8%]), a value of 0.3 ng/mL was assigned by NHANES; we used this value in our analyses.

Health Outcomes

Participants aged 20 years and older were asked “Has a doctor or other health professional ever told you that you have . . .” for angina, arthritis, asthma, cancer, chronic bronchitis, coronary heart disease, emphysema, heart attack, liver disease (any kind), stroke, or thyroid disease. Participants 18 years and older were asked about asthma and diabetes. Because of low numbers, emphysema (n=20) was combined with chronic bronchitis. Similarly, we combined diagnosed and borderline diabetes and grouped the cardiovascular conditions (reported angina, coronary heart disease, and heart attack). We included all available common conditions (ie, those with ≥ 40 cases) in the analyses, covering 8 major disease categories after grouping.

We analyzed concentrations of the following 8 blood serum analytes: C-reactive protein, quantified using latex-enhanced nephelometry; γ -glutamyltransferase (GGT), using an enzymatic rate method; lactate dehydrogenase, using an enzymatic rate method; alkaline phosphatase, using a 2-amino-2-methyl-1-propanol buffer; triglycerides, measured enzymatically following hydrolysis; low-density lipoprotein cholesterol (LDL-C), calculated from measured values of total cholesterol, triglycerides, and high-density lipoprotein cholesterol; fasting glucose, using spectrophotometric measurement of reduced nicotinamide adenine dinucleotide concentration; and fasting insulin, using a 2-site immunoenzymometric assay. Details of analyte extraction and measurement are available at <http://www.cdc.gov/nchs/nhanes.htm>.

Two derived glucose homeostasis indices were used: steady-state β -cell function, calculated from fasting levels of glucose and insulin using the computerized version of the updated homeostasis model assessment (HOMA2),²⁵ and HOMA2 insulin resistance, the reciprocal of insulin sensitivity, also calculated using the HOMA2 model.

Statistical Analysis

NHANES 2003-2004 used a complex cluster sample design, with some demographic groups (including Mexican Americans and groups in low socioeconomic positions) oversampled to ensure adequate representation. To account for this complex sampling, weighted estimates of population parameters were computed, following the NHANES Analytic and Reporting Guidelines (September 2006). For most analyses, population weights for the BPA measurement sample (subsample C of the medical examination) were used. Sampling errors were estimated by the Taylor series (linearization) method to account for stratification and clustering using the provided “masked variance pseudo-psu” and “pseudo-stratum” variables. This procedure produced the same geometric mean and variance estimates as those published by the National Center for Environmental Health³ (ie, geometric mean BPA concentrations for age group 20 to 59 years, 2.6 μ g/L; 95% confidence interval [CI], 2.3 to 2.9). Data on levels of LDL-C, glucose, and insulin were available in a random subsample assigned to fast (n=653); for these analyses, a specific fasting specimen weight was used as directed. Analyses were conducted by 3 authors (I.A.L., W.E.H., D.M.) using Stata SE version 9.2 (Stata-Corp, College Station, Texas); $P < .05$ was considered statistically significant.

Using the sample weights in a classical design-based analysis of survey data provides asymptotically unbiased estimates of population parameters but can lead to inefficiency (ie, inflation of standard errors).²⁶ An overall inefficiency coefficient of 34% was calculated for our NHANES 2003-2004 BPA data set using equation 3.7 in Korn and Graubard.²⁶

To assess the sensitivity of our findings to the weighting method, we repeated all analyses using a partial weighting approach in which the unweighted regression model was augmented with exogenous design variables.²⁶ There were no substantive changes in the model inferences (see eSupplement at <http://www.jama.com>).

Because the diseases of interest are rare in children, we restricted our analyses to respondents aged 18 through 74 years (of those randomly selected by NHANES 2003-2004 for measurement of BPA concentration) to focus on health effects in adults. The upper age cutoff was chosen to minimize problems of comorbidity and nonrepresentation of seniors in institutions. We excluded 1 respondent because of a missing urinary creatinine concentration, resulting in an included sample of 1455 respondents.

We used logistic regression to estimate odds ratios (ORs) of physician-diagnosed diseases (as the dependent variable) per 1-SD increase in BPA concentrations and used linear regression to estimate associations between logged levels of blood analytes and standardized BPA concentrations.

Regression models were adjusted for a broad range of potential confounders, including socioeconomic factors that Calafat et al³ have shown to be associated with BPA and urinary creatinine concentrations.²⁷ Variables included were race/ethnicity (from self-description and categorized into Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race [including multiracial]); education (categorized as <high school, high school diploma [including General Educational Development], and >high school); annual household income (in 3 approximately equal-sized categories [$< \$25\,000$, $\$25\,000$ - $\$55\,000$, and $> \$55\,000$], plus a fourth category for missing values [$n=92$]); smoking (from self-reported status and categorized as never smoked, former smoker, smoking some days, and smoking every day, plus unknown, because the questions were asked of those aged ≥ 20 years [$n=177$]); body mass index (BMI) (calculated as weight in kilo-

grams divided by height in meters squared and categorized as underweight [< 18.5], recommended weight [18.5 - 24.9], overweight [25.0 - 29.9], obese I [30.0 - 34.9], or obese II [≥ 35.0], with a final category for participants with missing values [$n=25$]); waist circumference (in quintiles, with $n=60$ in a group with missing values); and urinary creatinine concentration in mg/dL.

We carried out 5 sets of sensitivity analyses, which were identified post hoc to test the robustness of our findings. First, to assess whether increased levels of liver enzymes reflect normal induction of enzymes or a clinically relevant abnormality, we used NHANES reference ranges, established from wellness participants with an age mix similar to that of NHANES participants. Ranges were 36 to 113 U/L for alkaline phosphatase, 93 to 198 U/L for lactate dehydrogenase, and 10 to 65 U/L for GGT in men and 8 to 36 U/L in women (to convert values for all 3 analytes to $\mu\text{kat/L}$, multiply by 0.0167).²⁸ Second, to investigate whether the presence of the diseases found to be associated with BPA concentrations might have been associated with altered BPA exposure (perhaps through greater consumption of sugar-free foods or drinks from plastic containers by individuals trying to manage their obesity or diabetes), we examined associations of BPA with increased levels of liver enzymes in respondents in 2 subgroups: those reporting neither cardiovascular disease nor diabetes, and those with BMI less than 25. Third, because alcohol intake might confound associations of BPA concentration with increased levels of liver enzymes, we conducted our analyses again including data on self-reported daily alcohol consumption. Fourth, we tested whether the association between BPA concentrations and cardiovascular disease was robust to adjustment for the effects of lipid levels (LDL-C and triglycerides). Fifth, to explore the possibility that our findings were due to higher exposure to a wider set of xenoestrogenic compounds and not specific to BPA concentrations, we repeated our models including other known xenoestrogenic compounds.

We also have explored a range of alternative approaches to accounting for the sampling design, the skewed distribution of BPA concentrations, and the correction of urinary creatinine concentrations (see eSupplement at <http://www.jama.com>).

Power Calculations

Power calculations for presence of diagnoses were conducted using the approach proposed by Hsieh et al²⁹ for simple logistic regression models. For continuous outcomes, the power calculations were performed using the PS power and sample size program.^{30,31} The sample provided 80% power to detect unadjusted ORs of 1.4 for diagnoses of 5% prevalence per 1-SD change in BPA concentration (or, for 10% prevalence, unadjusted ORs of 1.3). For liver enzymes and insulin, the detectable effect sizes for 80% power are given by standardized regression coefficients of 0.075 and 0.11, respectively.

RESULTS

The study sample included 694 men and 761 women (TABLE 1). Weighted but unadjusted mean urinary BPA concentrations were similar by sex, but for some variables ranges were wider. For example, mean BPA concentrations in participants at recommended weight (BMI 18.5-24.9) were 3.91 ng/mL (95% CI, 3.34 to 4.48), compared with 6.93 ng/mL (95% CI, 4.39 to 9.47) in those in the obese II category (BMI ≥ 35).

Weighted mean BPA concentrations adjusted for age and sex (FIGURE) appeared higher in those who reported diagnoses of cardiovascular diseases (including coronary heart disease, heart attack, and angina) and diabetes. To explore this further, we estimated the ORs of reporting a diagnosis of these conditions by z scores of BPA concentration, using adjusted logistic regression models including age, sex, and urinary creatinine concentrations and fully adjusted models including these covariates plus race/ethnicity, education, income, smoking, BMI, and waist circumference (TABLE 2). Overall, patterns of linear association in all mod-

els were similar to those in the Figure. A 1-SD increase in BPA concentration was associated with increased ORs of reporting cardiovascular disease (angina, coronary heart disease, or heart attack combined) (OR, 1.39; 95% CI, 1.18 to 1.63; $P=.001$ with full adjustment) and diabetes (OR, 1.39; 95% CI, 1.21 to 1.60; $P<.001$). Associations with the individual cardiovascular diagnoses were all significant. No asso-

ciations with the other diagnoses were observed.

When using an alternative exposure metric of dividing BPA concentrations into quartiles in the fully adjusted models, participants in the highest BPA concentration quartile had an OR of 2.89 (95% CI, 1.07 to 7.78; $P=.04$) for cardiovascular disease compared with those in the lowest quartile. Similarly, those in the highest BPA concentration quartile

had an OR of 2.43 (95% CI, 1.35 to 4.38; $P=.006$) for diabetes compared with those in the lowest quartile.

TABLE 3 presents results of adjusted regression models of logged levels of blood analytes by z scores of BPA concentration. In fully adjusted models, associations were observed between BPA concentrations and logged levels of alkaline phosphatase ($P=.01$), lactate dehydrogenase ($P=.04$), and GGT ($P=.001$). Initial associations (adjusted for age, sex, and urinary creatinine level) with levels of C-reactive protein disappeared on further adjustment. Levels of fasting glucose and insulin were associated with BPA concentration in models adjusted for age, sex, and urinary creatinine concentration but not in models with full adjustment. No associations with levels of LDL-C or triglycerides were observed.

Sensitivity Analyses

We first reran our models to assess the ORs for having clinically above-normal concentrations of each of the liver enzymes. In adjusted models, we found that a 1-SD increase in BPA concentration was associated with clinically above-normal concentrations of GGT ($n=129$ above normal; weighted 8.8% prevalence; OR, 1.29; 95% CI, 1.14 to 1.46; $P<.001$), alkaline phosphatase ($n=58$ above normal; weighted 2.6% prevalence; OR, 1.48; 95% CI, 1.18 to 1.85; $P=.002$), and lactate dehydrogenase ($n=20$ above normal; 1% prevalence; OR, 1.40; 95% CI, 0.96 to 1.72; $P=.08$).

In participants reporting neither cardiovascular disease nor diabetes (excluding $n=190$), BPA concentration remained associated with clinically abnormal concentrations of lactate dehydrogenase (OR per 1-SD increase in BPA concentration, 1.31; 95% CI, 1.06 to 1.62; $P=.01$) and GGT (OR per 1-SD increase in BPA concentration, 1.22; 95% CI, 1.02 to 1.45; $P=.03$). In those with BMI less than 25 ($n=501$), BPA concentration was associated with increased concentrations of GGT ($\beta=0.09$; 95% CI, 0.01 to 0.18; $P=.03$).

Models including measures of alcohol consumption included a smaller

Table 1. Sample Characteristics Including Mean Bisphenol A Concentrations (N = 1455)

Characteristic	Unweighted, No.	Weighted	
		Percentage of Sample ^a	Mean BPA Concentration (95% CI), ng/mL
Sex			
Men	694	48.2	4.53 (3.98 to 5.08)
Women	761	51.8	4.66 (3.67 to 5.65)
Age group, y			
18-29	449	23.5	5.69 (4.74 to 6.64)
30-39	244	20.4	4.38 (3.20 to 5.57)
40-49	252	22.8	4.17 (3.18 to 5.16)
50-59	182	17.7	4.98 (3.85 to 6.12)
60-74	328	15.7	3.41 (2.41 to 4.41)
Race/ethnicity			
Mexican American	324	8.5	4.45 (3.48 to 5.41)
Other Hispanic	57	4.3	4.74 (2.86 to 6.62)
Non-Hispanic white	690	69.2	4.45 (3.73 to 5.17)
Non-Hispanic black	313	11.6	6.50 (5.45 to 7.55)
Other (including multiracial)	71	6.4	2.83 (2.03 to 3.63)
Level of education			
Less than high school diploma	430	18.1	5.00 (3.99 to 6.00)
High school diploma (including GED)	356	25.9	4.91 (4.02 to 5.80)
Some college education	669	56.1	4.32 (3.57 to 5.07)
Household annual income			
<\$25 000	457	21.8	5.38 (4.19 to 6.58)
\$25 000-\$55 000	457	32.2	5.25 (4.38 to 6.11)
>\$55 000	449	41.0	3.72 (3.08 to 4.37)
Unknown	92	5.0	4.11 (2.51 to 5.71)
BMI^b			
Low weight (<18.5)	31	2.1	3.81 (2.86 to 4.77)
Recommended weight (18.5-24.9)	469	33.6	3.91 (3.34 to 4.48)
Overweight (25.0-29.9)	448	30.4	4.18 (3.43 to 4.92)
Obese I (30.0-34.9)	283	20.0	5.10 (3.97 to 6.24)
Obese II (≥ 35)	199	12.2	6.93 (4.39 to 9.47)
Unknown	25	1.6	3.89 (1.86 to 5.92)
Cigarette smoking			
Never smoked ^c	640	48.8	4.37 (3.52 to 5.22)
Former smoker	311	22.6	4.53 (3.82 to 5.24)
Some days	63	4.4	3.72 (3.00 to 4.44)
Every day	264	20.5	5.00 (3.88 to 6.12)
Unknown	177	3.8	6.69 (5.59 to 7.79)

Abbreviations: BMI, body mass index; BPA, bisphenol A; CI, confidence interval; GED, General Educational Development.

^aPercentages may not sum to 100 because of rounding.

^bCalculated as weight in kilograms divided by height in meters squared.

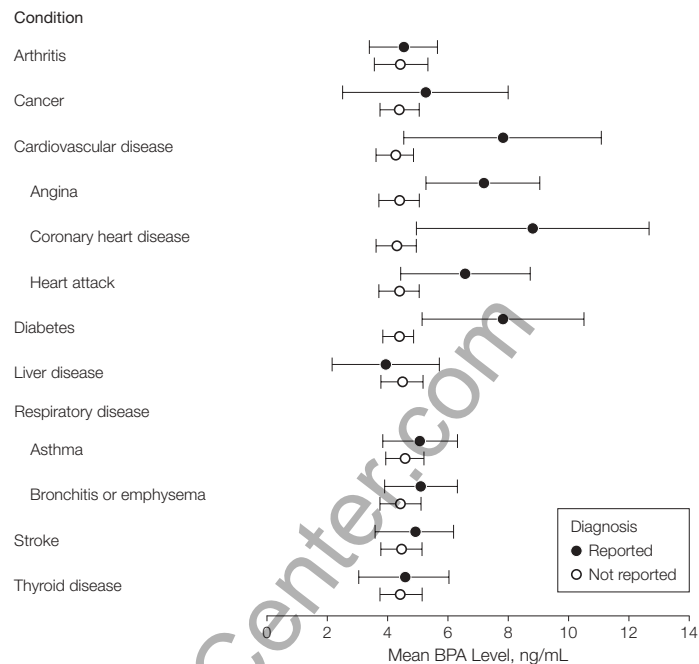
^cIncluded those who had ever smoked <100 cigarettes.

number of participants (n=1029) because of item nonresponse and because those younger than 20 years were not questioned. In models including self-reported daily alcohol consumption, BPA concentration remained associated with increased concentrations of GGT ($\beta=.06$; 95% CI, 0.02 to 0.10; $P=.007$).

In models adjusted for triglyceride levels, a 1-SD change in BPA concentration was associated with increased odds of reporting cardiovascular disease (OR, 1.41; 95% CI, 1.20 to 1.65; $P<.001$) and diabetes (OR, 1.38; 95% CI, 1.20 to 1.58; $P<.001$). Models adjusted for levels of triglycerides plus LDL-C had a reduced number of participants (data for the fasting subsample only), but overall trends were similar: a 1-SD increase in BPA concentration was associated with increased odds of reporting diabetes (n=635; OR, 1.40; 95% CI, 1.02 to 1.93; $P=.04$). However, the association with cardiovascular disease became nonsignificant, although the trend was similar (n=546; OR, 1.22; 95% CI, 0.80 to 1.88; $P=.33$).

Finally, we found that including measured concentrations of other phenols (4-tert-octyl phenol, benzophenone, and triclosan) did not affect the relationship between BPA concentration and disease or levels of blood analytes, and these compounds were not themselves associated with these outcomes. For example, in adjusted models the OR of reporting cardiovascular disease associated with a 1-SD score change in 4-tert-octyl phenol concentrations was 1.10 (95% CI, 0.79 to 1.54; $P=.55$) and of reporting diabetes was 0.93 (95% CI, 0.64 to 1.36; $P=.71$). A 1-SD score change in 4-tert-octyl phenol concentrations was not associated with changes in concentrations of the 3 liver enzymes; eg, for GGT, the β coefficient for 4-tert-octyl phenol per 1-SD change was 0.00 (95% CI, -0.03 to 0.04; $P=.78$). In fully adjusted BPA models with the addition of standardized 4-tert-octyl phenol and triclosan concentrations, the OR for reporting cardiovascular disease with a 1-SD score change in BPA concentration was 1.38 (95% CI, 1.18 to 1.61; $P<.001$) and for diabetes was 1.40 (95% CI, 1.22 to 1.60). BPA concentration remained associ-

Figure. Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions



Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

ated with logged levels of GGT ($\beta=.06$; 95% CI, 0.03 to 0.10; $P=.002$).

COMMENT

In this study we aimed to assess whether increased urinary BPA concentrations were associated with adverse health effects in the general US adult population. This analysis made use of the first large-scale and high-quality population-representative data set to become available. After adjusting for potential confounders, we found that higher BPA concentrations were associated with diagnoses of cardiovascular disease and diabetes. We also found associations between higher BPA concentrations and clinically abnormal concentrations of the 3 liver enzymes examined, namely GGT, alkaline phosphatase, and lactate dehydrogenase. Importantly, we observed no associations with the other common conditions examined, suggesting specificity of the associations. A series of sensitivity analyses provided further support for the specificity of the associations found.

Controversy has surrounded the risk that BPA poses to humans, because estimates extrapolated from animal studies³² have demonstrated significant species-specific differences in both metabolism and toxicity³² and also because of the multiple potential routes of human exposure. Ingestion of oral doses of BPA in rats and humans leads to first-pass metabolism in the intestine and liver to yield the major metabolite, BPA-monoglucuronide.³³ Transdermal exposure and inhalation of airborne dust will largely avoid first-pass metabolism, which is also limited in neonates.³⁴ While BPA-monoglucuronide is eliminated in the bile in rodents, in humans it is eliminated principally in the urine, and both gastrointestinal tract glucuronidation and enterohepatic recirculation differ between rats and humans. Modeling the pharmacokinetics of BPA is further complicated by a lack of human exposure studies, which are restricted for ethical reasons and by the difficulties in finding individuals completely unexposed to BPA from the environment. The human

experimental exposures that do exist have mostly been to single high doses.⁴ Calculations to predict actual human exposure levels based on animal exposure studies have reported mean circulating concentrations of both unconjugated and conjugated BPA.⁴

These models suggest that exposure among the general US population is likely to exceed the 50- $\mu\text{g}/\text{kg}$ per day reference dose currently recommended by the US Environmental Protection Agency and that exposure is most likely through continuous, multiroute exposure, prin-

cipally diet, but also through transdermal exposure and inhalation of airborne dust. These results confirm estimates made from early-morning urine samples collected from 48 women, which were used to estimate an intake of 0.6 to 71.4 $\mu\text{g}/\text{d}$.³⁵ A study of Japanese university students between 1992 and 1999 compared urinary BPA concentrations with dietary intake to suggest that canned beverages constitute a major dietary source.³⁶

Because human health effects are most likely associated with long-term, low-

dose exposure, the relevance of single measurements of urinary BPA concentrations has been questioned. From the few pharmacokinetic studies of human BPA metabolism, near-complete urinary excretion has been shown to occur within 24 hours of a single high dose.³⁷ Mahalingaiah et al³⁸ examined temporal variability in urinary concentrations and found that although a second sample could improve the sensitivity of predicting an individual's longer-term exposure status, a single urinary measurement showed moderate sensitivity for

Table 2. Odds Ratios of Diseases and Conditions Associated With a 1-SD Increase in Bisphenol A Concentration

Disease/Condition	Unweighted, No./Total	Weighted %	Model 1 ^a		Model 2 ^b	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Arthritis	312/1273	22.98	0.99 (0.77 to 1.28)	.96	0.97 (0.78 to 1.21)	.75
Cancer	77/1275	6.77	1.12 (0.85 to 1.48)	.38	1.14 (0.86 to 1.52)	.33
Cardiovascular disease	79/1272	4.76	1.36 (1.16 to 1.60)	.001	1.39 (1.18 to 1.63)	.001
Angina	42/1274	2.66	1.26 (1.10 to 1.44)	.002	1.28 (1.09 to 1.50)	.006
Coronary heart disease	46/1276	2.83	1.41 (1.09 to 1.82)	.01	1.63 (1.18 to 2.26)	.006
Heart attack	42/1277	2.79	1.33 (1.08 to 1.64)	.01	1.40 (1.11 to 1.78)	.008
Diabetes	136/1455	7.94	1.40 (1.21 to 1.63)	<.001	1.39 (1.21 to 1.60)	<.001
Liver disease	55/1274	3.89	0.77 (0.40 to 1.49)	.42	0.74 (0.37 to 1.44)	.35
Respiratory disease						
Asthma	174/1454	12.35	1.02 (0.89 to 1.18)	.75	0.98 (0.84 to 1.14)	.80
Bronchitis or emphysema	81/1274	6.47	1.03 (0.81 to 1.30)	.82	0.98 (0.74 to 1.29)	.87
Stroke	40/1278	2.35	0.99 (0.83 to 1.19)	.95	0.97 (0.74 to 1.27)	.82
Thyroid disease	115/1275	10.03	1.13 (0.89 to 1.43)	.30	1.09 (0.88 to 1.37)	.40

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for age, sex, and urinary creatinine concentration.

^bAdjusted for age, sex, race/ethnicity, education, income, smoking, body mass index, waist circumference, and urinary creatinine concentration.

Table 3. Linear Regression Coefficients of Logged Analytes Associated With a 1-SD Increase in Bisphenol A Concentration^a

Analyte	Unweighted, No.	Model 1 ^b		Model 2 ^c	
		β (95% CI)	P Value	β (95% CI)	P Value
C-reactive protein	1390	0.09 (0.02 to 0.15)	.02	0.02 (-0.02 to 0.06)	.24
Glucose homeostasis					
Insulin ^d	661	0.11 (0.01 to 0.21)	.04	0.07 (0.00 to 0.15)	.06
Glucose ^d	655	0.02 (0.00 to 0.03)	.02	0.01 (-0.01 to 0.04)	.37
HOMA2 ^d					
β -Cell function	652	0.05 (-0.03 to 0.12)	.20	0.03 (-0.01 to 0.07)	.09
Insulin resistance	652	0.11 (0.01 to 0.21)	.03	0.07 (-0.01 to 0.15)	.07
Lipids					
LDL-C ^d	639	0.00 (-0.05 to 0.05)	.93	-0.01 (-0.06 to 0.03)	.58
Triglycerides	1376	0.02 (-0.04 to 0.08)	.45	0.01 (-0.04 to 0.05)	.79
Liver enzymes					
Alkaline phosphatase	1378	0.03 (0.02 to 0.05)	.001	0.02 (0.01 to 0.04)	.01
γ -Glutamyltransferase	1377	0.08 (0.03 to 0.12)	.002	0.06 (0.03 to 0.10)	.001
Lactate dehydrogenase	1374	0.02 (0.01 to 0.03)	.007	0.01 (0.00 to 0.03)	.04

Abbreviations: CI, confidence interval; HOMA2, updated homeostatic model assessment; LDL-C, low-density lipoprotein cholesterol.

^aCoefficients represent change in logged analyte level for each 1-SD change in bisphenol A concentration.

^bAdjusted for age, sex, and urinary creatinine concentration.

^cAdjusted for age, sex, urinary creatinine concentration, race/ethnicity, education, income, smoking, body mass index, and waist circumference.

^dLevels were measured in a random subsample assigned to fast; models with these outcomes were weighted to allow for this.

predicting the individual's tertile categorization. This temporal variability in urinary BPA concentrations is likely to have resulted in underestimation of the true strengths of association with the outcomes in our analyses.

BPA has long been thought to act via relatively loose binding to the estrogen receptor, and this mode of action has been incorporated in pharmacokinetic models; however, recent evidence suggests that BPA also binds strongly to the estrogen-related receptor γ , the function of which is unknown.⁶ Although the major metabolite BPA-monoglucuronide lacks estrogenic activity, the generation of estrogenically active metabolites following oxidative cleavage of BPA has been reported in vitro in rat liver microsomal fractions,³⁹ although the in vivo significance of this pathway is not yet clear. Bindhumol et al⁷ found BPA-induced oxidative stress in rat hepatocytes with oral intake over a 30-day period, and hepatocyte damage has been reported in a number of other experimental contexts.⁸⁻¹¹ Lipid accumulation has been shown in adipocyte and hepatoma cell lines exposed to BPA.⁴⁰ A variety of other effects of BPA have been noted, including disrupted pancreatic β -cell function, which produces insulin resistance in mice exposed to oral BPA doses well below the lowest observed adverse effect level currently considered by the Environmental Protection Agency.¹² Four days of low-dose BPA injections also produced insulin resistance in mice.⁴¹

Other studies have identified associations between environmental toxins, body weight, and diabetes,^{42,43} and it has been proposed that exposure to some environmental pollutants may initiate or exacerbate the development of obesity¹⁴ and associated health problems.⁴⁴ We found an apparently wide range of BPA concentrations across BMI categories, with weighted but unadjusted mean BPA concentrations of 3.91 ng/mL (95% CI, 3.34 to 4.48) in participants with BMI of 18.5 to 24.9 compared with 6.93 ng/mL (95% CI 4.39 to 9.47) in those with BMI of 35 or more (Table 1). However, formal testing of logged BPA concentrations adjusted for age, sex, and urinary creati-

nine concentrations showed no significant differences between the categories (data available from the authors on request). Although a possible explanation for our findings is that the increased dietary intakes associated with obesity also result in higher intakes of BPA and consequent morbidity, the observed disease and liver enzyme changes were present after adjusting for both BMI and waist circumference. Crucially, the association with GGT was present after excluding overweight and obese participants. An association of BPA concentration with GGT concentration also was present in those without cardiovascular disease or diabetes, suggesting that "reverse causation" (in which the presence of these diseases might have led to greater exposure or to some form of altered BPA excretion) is also unlikely.

Exposure to BPA also might be an indicator of exposure to multiple xenobiotics, including other endocrine disruptors—but, as presented, adjustment for other environmental phenols and known xenoestrogens including 4-tert-octyl phenol and triclosan made no difference to the observed outcomes, suggesting a specific effect mediated by BPA. We also have explored a range of alternative approaches to accounting for the sampling design, the distribution of BPA concentrations, and the correction of urinary creatinine concentrations (see eSupplement at <http://www.jama.com>), all of which point to our results being robust.

The main limitation of our analyses is their cross-sectional nature: longitudinal data demonstrating that high BPA concentrations predict later onsets of biochemical change or diagnoses would strengthen the evidence. A further limitation is that we have examined a broad hypothesis of associations between higher BPA concentrations and adverse effects on health status, including tests of association with 8 major diagnostic groupings (with 3 questions each about cardiovascular and respiratory conditions) and 8 blood-based assays. Our approach, justified by this being the first large-scale study, may have resulted in false-positive associations. Although false-positive inverse associations be-

tween BPA concentrations and outcomes were theoretically as likely, none were found.

Independent replication is now needed to confirm the associations reported. Because our analyses are based on urinary concentrations of BPA, which reflect recent exposure, studies based on repeat measurements over weeks, months, or even years would improve the assessment of longer-term exposure. Given the many routes of exposure to BPA, direct measures of dermal contact or of contact with contaminated foods, beverages, and dusts would be very difficult to undertake. A further issue is that although the previous animal-model literature provides evidence of the mechanisms underlying effects on liver cells (and therefore liver enzymes) and insulin signaling (and therefore diabetes, as previously discussed), the mechanisms underlying the effect on prevalence of cardiovascular disease are not obvious. If the associations reported here are confirmed in independent studies, more work will be needed to identify the mechanisms of action linking long-term, low-dose BPA exposure to adverse outcomes in humans. Given the substantial negative effects on adult health that may be associated with increased BPA concentrations and also given the potential for reducing human exposure, our findings deserve scientific follow-up.

CONCLUSIONS

Using data representative of the adult US population, we found that higher urinary concentrations of BPA were associated with an increased prevalence of cardiovascular disease, diabetes, and liver-enzyme abnormalities. These findings add to the evidence suggesting adverse effects of low-dose BPA in animals. Independent replication and follow-up studies are needed to confirm these findings and to provide evidence on whether the associations are causal.

Author Contributions: Drs Lang and Melzer had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lang, Galloway, Depledge, Wallace, Melzer.

Analysis and interpretation of data: Lang, Galloway, Scarlett, Henley, Wallace, Melzer.

Drafting of the manuscript: Lang, Galloway, Melzer. **Critical revision of the manuscript for important intellectual content:** Lang, Galloway, Scarlett, Henley, Depledge, Wallace, Melzer.

Statistical analysis: Lang, Henley, Melzer.

Administrative, technical, or material support: Galloway, Scarlett, Wallace.

Study supervision: Depledge.

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Additional Information: An eSupplement is available at <http://www.jama.com>.

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