Urinary Bisphenol A Concentration and Risk of Future Coronary Artery Disease in Apparently Healthy Men and Women

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Background—The endocrine-disrupting chemical bisphenol A (BPA) is widely used in food and beverage packaging. Higher urinary BPA concentrations were cross-sectionally associated with heart disease in National Health and Nutrition Examination Survey (NHANES) 2003–2004 and NHANES 2005–2006, independent of traditional risk factors.

Methods and Results—We included 758 incident coronary artery disease (CAD) cases and 861 controls followed for 10.8 years from the European Prospective Investigation of Cancer–Norfolk UK. Respondents aged 40 to 74 years and free of CAD, stroke, or diabetes mellitus provided baseline spot urine samples. Urinary BPA concentrations (median value, 1.3 ng/mL) were low. Per-SD (4.56 ng/mL) increases in urinary BPA concentration were associated with incident CAD in age-, sex-, and urinary creatinine–adjusted models (n=1919; odds ratio=1.13; 95% confidence interval, 1.02–1.24; P=0.017). With CAD risk factor adjustment (including education, occupational social class, body mass index category, systolic blood pressure, lipid concentrations, and exercise), the estimate was similar but narrowly missed 2-sided significance (n=1744; odds ratio=1.11; 95% confidence interval, 1.00–1.23; P=0.058). Sensitivity analyses with the fully adjusted model, excluding those with early CAD (<3-year follow-up), body mass index >30, or abnormal renal function or with additional adjustment for vitamin C, C-reactive protein, or alcohol consumption, all produced similar estimates, and all showed associations at P=0.05.

Conclusions—Associations between higher BPA exposure (reflected in higher urinary concentrations) and incident CAD during >10 years of follow-up showed trends similar to previously reported cross-sectional findings in the more highly exposed NHANES respondents. Further work is needed to accurately estimate the prospective exposure-response curve and to establish the underlying mechanisms. (Circulation. 2012;125:1482-1490.)

Key Words: bisphenol A ■ blood lipids ■ body mass index ■ coronary artery disease ■ endocrine disruption
We undertook a nested case-control analysis, measuring uBPA in stored samples from a baseline clinical examination. We compared uBPA concentrations in a case group who later developed CAD with a control group who remained free of CAD during follow-up.

Methods

Study Design

We studied respondents in a well-characterized nested CAD case-control set within the European Prospective Investigation Into Cancer and Nutrition (EPIC)–Norfolk cohort study. EPIC-Norfolk is a prospective population study of 25,663 men and women aged 45 to 79 years, resident in Norfolk, United Kingdom, who completed a baseline questionnaire and attended a clinic examination. The sample was comparable to UK national population samples with respect to many characteristics. Participants were recruited by mail to age/sex registers of general practices. The baseline sample was comparable to UK national population samples with respect to many characteristics. Participants were recruited by mail to age/sex registers of general practices. The baseline sample was comparable to UK national population samples with respect to many characteristics.

Participants

Boekholdt et al selected a CAD case-control set within EPIC-Norfolk, originally with 2 controls matched to each case by sex, age (within 5 years), and date of clinic visit (within 3 months). We used the cases and controls from Boekholdt et al but included only those aged 40 to 74 years and free of diabetes mellitus at baseline with an available urine sample and valid uBPA measure. We selected equal numbers of incident CAD cases and controls, but the aforementioned constraints (especially urine sample availability) did not always allow selection within the Boekholdt original matching (see Statistical Analysis). Diabetes mellitus was excluded (n=84) because associations between uBPA and diabetes mellitus have been reported. We excluded those aged ≥75 years to minimize biases caused by comorbidity and nonrepresentation of seniors in institutions, as with our previous NHANES analyses.

CAD End Points

Participants were identified as having CAD during follow-up if they had a recorded hospital admission and/or died with CAD as an underlying cause during follow-up. All EPIC-Norfolk participants were flagged for death certification at the UK Office of National Statistics, and vital status was obtained for the whole cohort. Participants admitted to a hospital are identified by their unique National Health Service number, which a local health authority in Norfolk links to the Hospital Episode Statistics (including hospital contacts throughout the country). CAD is classified according to the International Classification of Diseases, Ninth Revision codes 410 to 414 or International Statistical Classification of Diseases, Tenth Revision codes I20 to I25. A case is considered if a participant had a hospital diagnosis and/or died of coronary heart disease during the follow-up. In 1996, the EPIC study conducted a validation study of CAD cases ascertained from death certificates and hospital admissions. Confirmation of the cause of death was sought in general practice and hospital notes or the postmortem report. For CAD deaths identified from death certificates, the cause of death was coded as a definite CAD death, possible CAD death, or not a CAD death with the use of standard World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO-MONICA) criteria. Of 39 deaths, 38 were confirmed by inspection of hospital notes. For cases identified on the basis of linkage with hospital admission databases, the admission diagnosis was evaluated by inspection of hospital notes. The event was then coded as a definite myocardial infarction, possible myocardial infarction, or not a myocardial infarction on the basis of the clinical history, ECG changes, and enzyme changes with the use of standard criteria. All 26 patients with a hospital discharge diagnosis of myocardial infarction had either a definite or possible myocardial infarction by WHO-MONICA criteria.

Analysis of uBPA Concentrations

Study participants attended the research clinic and provided a urine sample between March 1993 and April 1998. We followed WHO guidelines in regard to study design to evaluate exposure to BPA using biomonitoring. Analysis of uBPA metabolites was undertaken in 2011 by Brixham Environmental Laboratory, Analytic Chemistry (a division of AstraZeneca PLC) in accordance with Good Laboratory Practice, European Union Directive 89/398/EEC. Because orally administered BPA is considered to be rapidly and completely excreted, urine is the body fluid most appropriate for biomonitoring assessment of BPA exposure. We measured total (free and conjugated) urinary concentrations of BPA on the basis of the methods employed by NHANES and adopted by the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention (ie, sample preparation and online solid-phase extraction coupled with high-performance liquid chromatography/isotope dilution tandem mass spectrometry with peak focusing).

The Good Laboratory Practice–compliant quality control system included reagent blanks, and we confirmed that the EPIC stored samples contained almost exclusively metabolized compound, showing minimal leaching of BPA from collection or storage vessels. Total (free and conjugated) urinary concentrations of BPA were obtained with the use of online, solid-phase extraction coupled with high-performance liquid chromatography/isotope dilution tandem mass spectrometry with peak focusing. Calibration was linear from 0.50 to 100 µg/L ($R^2=0.996$, limit of detection was <0.50 ng/mL uBPA, limit of quantification was 0.50 ng/mL). For the lowest calibration standard gave a signal height/noise ratio >10 (relative SDs <20%, all other standards <15%).

Biochemical Analyses

Nonfasting blood samples were taken by venipuncture into plain and citrate bottles. Blood samples were processed soon after baseline collection at the Department of Clinical Biochemistry, University of Cambridge, by Quotient (http://www.quotientbioresearch.com/) with the use of an Olympus AU640 chemistry analyzer or stored at −80°C. Serum levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured in fresh plasma samples with the RA 1000 (Bayer Diagnostics, Leverkusen, Germany).
low-density lipoprotein cholesterol levels were calculated with the Friedewald formula.\(^9\) C-reactive protein (CRP) concentrations were later measured on thawed baseline plasma from cases and controls. CRP levels were measured with a sandwich-type enzyme-linked immunosorbent assay in which polyclonal rabbit anti-CRP antibodies were used as catching antibodies and biotinylated monoclonal antibodies against CRP (Sanquin Research, Amsterdam, Netherlands) were used as detecting antibodies.\(^20\) Results were related to a standard that consisted of commercially available CRP (Behringwerke AG, Marburg, Germany). Researchers and laboratory personnel had no access to identifiable information and could identify samples by unique identifier only.

**Statistical Analysis**

We applied an analysis approach similar to that used previously in NHANES\(^8\): We assigned a value of 0.28 ng/mL to uBPA assays below the level of accurate detection (n=190 controls and 140 cases reassigned); respondents with “outlier” BPA concentrations >80.1 ng/mL were excluded from the analyses; and we present per-SD uBPA linear estimates of association with incident CAD, adjusted for markers of relative social privilege and conventional CAD risk factors.

Logistic regression models were used to estimate log-odds ratios of case status as a linear function of standardized uBPA concentrations (Z scores). The original EPIC age-, sex-, and clinic date-matched case-control sets\(^3\) were sometimes incomplete (mainly because of urine sample availability): There were 217 of 861 controls (25.2%) with no matched case, and 251 of 758 cases (33.1%) had no matched control. Controls with no matched case had higher uBPA concentrations (OR=1.41; 95% CI, 1.17–1.70; \(P<0.000\)) and were less likely to be obese (compared with normal weight: OR=0.74; 95% CI, 0.55–0.98; \(P=0.020\)) compared with controls with matched cases. Among cases without controls, there were fewer women (OR for women vs men=0.85; 95% CI, 0.76–0.94; \(P=0.001\)). In our main analysis, we therefore analyzed the case-control groups without matching and provide a subanalysis for the matched sets using conditional logistic regression.

Regression models were adjusted for potential confounders, including socioeconomic markers that Calafat and colleagues\(^17\) reported to be associated with BPA concentrations and urinary creatinine to account for urine concentration.\(^21\) Initial adjustment was for the following: age, sex, education (categorized as no qualifications, “O” level or equivalent [15 years], “A” level or equivalent [17 years], and postschool or postdegree qualifications); occupational social class (grouped into uncoded [eg, unemployed], professional, managerial, skilled nonmanual, skilled manual, semi-skilled, nonskilled); and urinary creatinine concentration (in mg/dL). Fully adjusted models were additionally adjusted for body mass index (BMI) (measured weight in kilograms divided by the square of measured height in meters, categorized into the following: underweight [BMI <18.5], recommended [BMI 18.5–24.9], overweight [BMI 25.0–29.9], obese I [BMI 30.0–34.9], obese II [BMI ≥35.0], and unknown BMI); smoking (never smoked, former smoker, current smoker); systolic blood pressure (mm Hg); total cholesterol and unknown BMI); smoking (never smoked, former smoker, current smoker); systolic blood pressure (mm Hg); total cholesterol and unknown BMI); and unknown BMI); smoking (never smoked, former smoker, current smoker); systolic blood pressure (mm Hg); total cholesterol and unknown BMI); smoking (never smoked, former smoker, current smoker); systolic blood pressure (mm Hg); total cholesterol and unknown BMI); smoking (never smoked, former smoker, current smoker); and unknown BMI). Data were available on 861 controls and 758 cases of incident CAD (total n=1619). The mean±SD age of cases was 64.1±7.5 years and of controls was 63.8±7.3 years. There were marginally fewer men in the case group (62.0% versus 66.1% in controls), and fewer had never smoked (Table 1). As expected, CAD risk markers were associated with case status. uBPA concentrations were relatively low. The median uBPA concentration in controls was 1.24 ng/mL and in cases was 1.35 ng/mL (geometric means, 1.23 and 1.39 ng/mL, respectively; 1.304 ng/mL combined). The distributions were strongly skewed with, for example, 12.5% (108/861) of the controls having uBPA concentrations ≥4 ng/mL compared with 16.6% (126/758) of the cases. Among controls (Table 2), those with higher uBPA concentrations (top 50% >1.243 ng/mL versus bottom 50%) tended to be less likely to be from professional or managerial occupational backgrounds, but there were no other differences on demographic or CAD risks.

In logistic models with case-control status as the dependent variable, per-SD (SD=4.56 ng/mL) uBPA linear increases in uBPA concentration were associated with incident CAD in age-, sex-, and urinary creatinine–adjusted models (Table 3, model B; OR per Z score=1.13; 95% CI, 1.02–1.24; \(P=0.017\)). This association remained after additional adjustment for education and occupational groupings (model C; OR=1.14; 95% CI, 1.03–1.26; \(P=0.021\)). With additional adjustment for CAD risk factors (as in model D), the central estimate was similar but narrowly missed conventional 2-sided significance (n=1477; OR=1.11; 95% CI, 1.00–1.23; \(P=0.058\)).

We fitted a generalized additive model with a cubic regression spline to explore the shape of the dose-response curve. This provided marginal evidence of a linear relationship between SD increases in BPA concentration and log-odds of cardiovascular disease (to 4 SDs above the mean BPA concentration, as in our earlier work;\(^8\)) Figure; estimated df=1.001; P for smoothed term=0.068; 6 knots placed at \(-0.5, -0.37, -0.26, -0.08, 0.26, 3.92\). A quadratic model did not provide a better fit (\(P=0.40\)), and inspection of residual plots for the linear and quadratic models did not suggest threshold effects.

**Sensitivity Analyses**

We undertook post hoc sensitivity analyses using separate variations of the fully adjusted (CAD risk factor–adjusted) model (Table 3, models E through K). We excluded the earliest 3 years of follow-up (to remove those close to CAD onset at uBPA sample collection; model E). We excluded those with a BMI ≥30, given the suggestion that obesity may be a key factor (model F). We adjusted for serum creatinine and excluded those with elevated concentrations, mainly removing impaired renal function, which may result in biased uBPA measures (model G). In addition, we adjusted for vitamin C concentrations, a marker of dietary quality (particularly high fruit and vegetable intake) (model H); adjusted for CRP...
concentrations (reflecting inflammation) (model I); adjusted for liver enzymes to account for liver cell function effects (model J); and adjusted for units of alcohol consumed at the time of baseline interview (model J). None of these analyses changed estimates materially, and all associations reached $P<0.05$.

Finally, our cases and controls were originally drawn in matched sets on the basis of date of birth, sex, and date of clinic visits categories. Due to the limited availability of urine specimens, we ignored matching in the above analysis: Estimating a conditional (matched) logistic model on the subset with at least 1 matched pair, per SD increases in uBPA were associated with incident CAD (OR $= 1.34$; CI 1.12–1.62; $P=0.0015$).

### Discussion

In NHANES 2003–2004 and again in NHANES 2005–2006, higher uBPA concentrations were associated with heart disease (pooled $P<0.001$). A major limitation of the NHANES analyses is their cross-sectional nature, making it theoretically possible, for example, that CAD patients might have changed their behaviors and incidentally increased their BPA.
exposure. To strengthen the evidence for causal inference, we conducted the longitudinal study presented here, which provides the first report of similar trends in associations between higher BPA exposure (evidenced as higher uBPA metabolite concentrations) and incident CAD. The prospective design adopted shows that such reverse causation cannot account for BPA-CAD associations.

The concentrations of uBPA seen in this sample are relatively low: The overall median value was 1.3 ng/mL compared with 2.7 ng/mL (interquartile range, 1.3–5.4 ng/mL) in the US NHANES 2003–2004 study in which the uBPA association with cardiovascular disease was first identified. The relative paucity of more highly exposed study subjects clearly reduces our power to detect true associations, which makes our results more noteworthy. This reduced power may explain the marginal loss of 2-sided significance for the fully adjusted unmatched linear model. In our NHANES 2003–2004 analysis, the SD of uBPA was 6.68 ng/mL and produced a (per-SD) OR of 1.39 (95% CI, 1.18–1.63; \( P = 0.001 \)) for cardiovascular diagnoses in fully

| Table 2. Sociodemographic and Coronary Artery Disease Risk Factor Status by Lower and Higher Urinary Bisphenol A Concentration (Dichotomized at uBPA=1.243 ng/mL) in Controls |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Lower uBPA Concentration ≤1.243 ng/mL | Higher uBPA Concentration >1.243 ng/mL | Unadjusted \( P \) |
| N | 842 | 842 | |
| Age, y | 63.8 (7.19) | 63.8 (7.38) | 0.91 |
| Male sex, % | 62.9 | 62.8 | 0.99 |
| Smoking status, % | | 0.42 |
| Never | 8.1 | 10.5 |
| Past | 48.5 | 45.9 |
| Current | 43.5 | 33.8 |
| Education, % | | 0.072 |
| No qualifications (<15 y of schooling) | 36.9 | 42.0 |
| “O” level or equivalent (15 y) | 6.7 | 9.6 |
| “A” level or equivalent (17 y) | 41.9 | 37.0 |
| Postschool or postdegree qualification | 15.6 | 11.5 |
| Occupational social class, % | | 0.034 |
| Professional | 8.3 | 7.8 |
| Managerial | 40.3 | 32.1 |
| Skilled nonmanual | 15.0 | 17.8 |
| Skilled manual | 21.6 | 25.2 |
| Semiskilled | 10.0 | 14.0 |
| Nonskilled | 4.6 | 2.5 |
| Uncoded | 0.2 | 0.7 |
| Physical activity, % | | 0.49 |
| Inactive | 30.5 | 34.6 |
| Moderately inactive | 29.2 | 26.3 |
| Moderately active | 23.0 | 20.9 |
| Active | 17.4 | 18.3 |
| Body mass index categories, kg/m² | | 0.21 |
| <18.4 | 0.43% | 0.0% |
| 18.4–24.9 | 38.2% | 33.7% |
| 25.0–29.9 | 47.0% | 52.8% |
| 30.0–34.9 | 12.9% | 11.3% |
| >35 | 1.5% | 2.2% |
| LDL-C, mmol/L | 4.06 (1.04) | 4.11 (0.97) | 0.45 |
| HDL-C, mmol/L | 1.36 (0.39) | 1.36 (0.41) | 0.93 |
| Total cholesterol, mmol/L | 6.31 (1.30) | 6.28 (1.08) | 0.78 |
| Triglycerides, mmol/L | 2.03 (1.68) | 1.87 (1.02) | 0.097 |
| Systolic blood pressure, mm Hg | 138.4 (16.6) | 137.8 (17.6) | 0.59 |

Data are presented as arithmetic mean (SD) or percentage. uBPA indicates urinary bisphenol A; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

*Unadjusted \( \chi^2 \) or \( t \) test estimate.
Table 3. Logistic Regression Estimates of Odds Ratios (95% Confidence Intervals) per SD Increase in Urinary Bisphenol A Concentrations (SD=4.56 ng/mL) With Incident Coronary Artery Disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Definition</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Age, sex (n=1619)</td>
<td>1.13</td>
<td>1.02–1.24</td>
<td>0.018</td>
</tr>
<tr>
<td>B</td>
<td>Age, sex, urinary creatinine (n=1619)</td>
<td>1.13</td>
<td>1.02–1.24</td>
<td>0.017</td>
</tr>
<tr>
<td>C</td>
<td>B plus education level and occupational group (n=1579)</td>
<td>1.14</td>
<td>1.03–1.26</td>
<td>0.012</td>
</tr>
<tr>
<td>D</td>
<td>C plus cardiovascular risk factors* (n=1477)</td>
<td>1.11</td>
<td>1.00–1.23</td>
<td>0.058</td>
</tr>
</tbody>
</table>

*Adjusted as in C and with the following additional variables: BMI, cigarette smoking, average of the 2 systolic blood pressure readings (in mm Hg), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and level of physical activity.

Any misclassification of longer-term BPA body burden is likely to have resulted in a smaller (diluted) estimate of the individual’s tertiary BPA categorization.24 Nepomnaschy et al25 measured stability of BPA over 2-week intervals in first-voided urine samples from 60 women and found a Spearman correlation of 0.5, indicating that within-individual BPA exposures were generally stable over periods of weeks. Ye et al26 similarly reported changes between spot measures during each day and across 7 days but concluded that spot samples may adequately reflect population average exposures.

Although humans can rapidly eliminate BPA when it is provided as a single bolus,27 continuous external BPA exposure through diet appears to lead to sustained concentrations that are detectable in serum or plasma. A recent study in which deuterated BPA was used found that the half-life of BPA was 6 times longer for diet-fed mice than for those who received a bolus, a phenomenon consistent with an inhibitory effect of food on first-pass metabolism.28 Stahlhut et al29 reported the population half-life of BPA to be considerably >6 hours on the basis of NHANES data on fasting times. The supposition is that BPA, which is lipophilic, is redistributed to lipid-rich tissues, from which slow release may occur. However, there is an absence of human pharmacokinetic data for BPA to fully explain these findings, and extrapolations from animal studies have been hindered by species-specific differences in the metabolism and toxicity of BPA30 and by the multiple potential routes by which humans may be exposed, including dermal exposure31 and inhalation of dusts, which would avoid first-pass metabolism. Once ingested, BPA is metabolized in the intestines and liver,32 with the major metabolite BPA-monoglucuronide eliminated in humans via urine but in rats via bile. Glucuronidation and enterohepatic recirculation also show differences between rodents, primates, and humans, although the effect of this on pharmacokinetics is not yet clear.33
The strength of association between BPA and CAD; the true association is likely to be stronger. Some\textsuperscript{34} have suggested that BPA disease associations are driven by higher dietary intakes, which would result in obesity-related risks and incidental higher BPA excretions. However, our sensitivity analyses show that exclusion of those with obesity and adjustment for blood lipid concentrations and levels of physical activity have little effect on the association, making such an explanation unlikely. Similarly, the lack of effect of adjustment for vitamin C makes diets poor in fruits and vegetables an unlikely explanation.\textsuperscript{35} Liver and kidney function changes, resulting in altered BPA metabolism or excretion, are also possible confounding factors, but excluding those with high blood creatinine concentrations or adjusting for liver enzymes sensitive to cell damage shows these as unlikely explanations. In any observational study, it is impossible to exclude the possibility that some unmeasured confounder is present. It is clear, however, that any such confounder must be independent of classic CAD risk factors.

There are several potential mechanisms by which BPA could plausibly raise CAD incidence rates. BPA and metabolites have well-documented estrogenic, antiandrogenic,\textsuperscript{36} and additional receptor-mediated modes of toxicity.\textsuperscript{36} Given the known receptor-mediated effects of estrogen on cardiovascular tissues, it is biologically plausible that BPA might exert estrogenic effects or antagonize endogenous estrogens in cardiovascular tissues by binding to soluble or membrane-bound estrogen receptors.\textsuperscript{37}

The mean uBPA concentration in our study was 3.65 ng/mL. With the assumption of an average 24-hour urine volume for adults of 1600 mL, a 100% excretion rate, and a total blood volume of 6 L, this would give an estimated BPA blood concentration in the nanograms per milliliter range.\textsuperscript{38} A recent study has reported positive associations between increased BPA exposure and in vivo estrogenic activity,\textsuperscript{18} suggesting the potential for BPA to exert estrogenic effects in vivo.

The half-maximal inhibitory concentration for receptor binding of BPA to human ER<sub>α</sub> and ER<sub>β</sub> is in the low micromolar range when calculated in vitro, and, if extrapolated directly to the in vivo situation (without considering competitive binding to serum-binding proteins, for instance), this would imply low ER occupancy rates in blood and potential target tissues. However, BPA binds to other estrogen-related receptors with high affinity, including the estrogen-related receptor-α (ERR<sub>α</sub>, ER<sub>β</sub>) that control many estrogen-mediated activities. The half-maximal inhibitory concentration for receptor binding of BPA to human ER<sub>α</sub> and ER<sub>β</sub> is in the low micromolar range when calculated in vitro, and, if extrapolated directly to the in vivo situation (without considering competitive binding to serum-binding proteins, for instance), this would imply low ER occupancy rates in blood and potential target tissues. However, BPA binds to other estrogen-related receptors with high affinity, including the estrogen-related receptor-α (ERR<sub>α</sub>, ER<sub>β</sub>) that control many estrogen-mediated activities.

Other potential mechanisms of BPA toxicity may be relevant to the results presented here. Maxi-K channels and the β1 subunit in particular\textsuperscript{45} play key roles in regulating smooth muscle excitability and are estrogen sensitive. BPA in the micromolar range activates Maxi-K (K<sub>Ca1.1</sub>) ion channels in human coronary smooth muscle cells in culture to a degree sufficient to hyperpolarize the membrane potential.\textsuperscript{46} Laboratory exposure studies have shown that BPA can induce liver and oxidative cellular damage,\textsuperscript{47} disrupt pancreatic β-cell function,\textsuperscript{48} and have obesity-promoting effects,\textsuperscript{49} all of which could plausibly contribute toward CAD risk. Certain BPA derivatives including bisphenol A diglycidyl ether (BADGE) are peroxisome proliferator-activated receptor-γ antagonists.\textsuperscript{50} Peroxisome proliferator-activated receptor-γ agonists may activate or inhibit ion channel activity in vessel walls directly,\textsuperscript{51} providing an alternative mechanism worthy of further investigation.

Much remains unknown about the mechanisms involved in the BPA-CAD association in humans. Future scientific work in humans is, of course, constrained by ethical limits and the practicality of repeated BPA exposure measures in long-term and larger follow-up studies. Without these constraints, controlled trials would be needed to prove causation in humans, but such evidence is almost certainly beyond reach.
Conclusions
Associations between higher BPA exposure (reflected in higher urinary concentrations) and incident CAD during in >10 years of follow-up in the EPIC-Norfolk study showed trends similar to previously reported cross-sectional findings in the more highly exposed NHANES 2003–2004 and 2005–2006 study respondents. More work is needed to accurately estimate the shape of the dose-response relationship. Work is also needed to identify the mechanism underlying the association between higher BPA exposure and incident CAD.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Bisphenol A (BPA) is a synthetic molecule widely used in plastics and epoxy resins in can linings, from which it can leach to contaminate food and beverages. It is present in >95% of the population and is of public health concern because many studies have reported effects at low exposure levels as a hormone mimic in animal and laboratory investigations, although these effects are contested. There is little direct human evidence on BPA toxicokinetics, which appears to differ from that in laboratory models and may be influenced by concurrent food intake. A cross-sectional association between higher urinary BPA and cardiovascular disease was first noted in 2008 and was independently replicated in 2010 in the US population–representative National Health and Nutrition Examination Survey study. We show here for the first time that associations between higher BPA excretion and incident coronary artery disease during a 10.8-year follow-up show similar trends. Higher body mass index could represent higher food intakes and incidentally higher BPA exposure, but adjustment for or exclusion of those with obesity or high serum lipid concentrations has little effect on estimates. There is initial data that BPA may be associated with expression of estrogen related receptors in vivo and may be antiandrogenic, but a firm mechanism for the coronary artery disease association is unknown. Evidence on high BPA exposures from occupational studies is scarce. For clinicians, this study suggests that BPA is worth investigating further, especially given the feasibility of control and the limits of experimentation for potential hazards. The US Food and Drug Administration is already committed to reducing BPA residues in food and provides guidance on how to do so on its Web pages.
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