

## Review Article

## Bisphenol A exposure and associations with obesity among adults: a critical review

Sarah J Oppeneer<sup>1,\*</sup> and Kim Robien<sup>2</sup><sup>1</sup>Office of Minority Health and Health Disparities, Lombardi Comprehensive Cancer Center, Georgetown University, 1000 New Jersey Avenue SE, Washington, DC 20003, USA: <sup>2</sup>Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC, USA

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**Abstract***Objective:* To review the literature on bisphenol A (BPA) exposure and obesity in human populations.*Design:* Systematic review of the literature via searches of PubMed, EMBASE, Web of Science and reference lists for articles published to 1 August 2014.*Setting:* China, Italy, Japan, Republic of Korea, Sweden, UK, USA.*Subjects:* Adults ( $\geq 18$  years).*Results:* Eighteen articles were identified and included in the review. Twelve studies included secondary evaluations of BPA exposure and BMI, and six studies evaluated body composition as the primary outcome. All analyses were cross-sectional and no study included in the review received a positive quality rating (twelve negative, six neutral). Eight studies observed a statistically significant positive association between urinary or serum BPA levels and BMI, and ten studies observed no association. Studies where BMI was a primary outcome and studies of neutral quality were more likely to observe an association.*Conclusions:* Study results are conflicting and significant methodological issues limit the ability to draw conclusions from these studies. Prospective studies that measure BPA exposure and changes in body weight and composition are needed to establish temporality, causality and the direction of any observed associations.**Keywords**  
Obesity  
Environmental  
Bisphenol A

Being overweight or obese contributes to an increased risk for many chronic diseases, including CVD, type 2 diabetes and some cancers<sup>(1,2)</sup>. Since 1980, worldwide prevalence of obesity has almost doubled<sup>(3)</sup>. While excess energy intake and a sedentary lifestyle are known risk factors for gaining weight, there has been increasing interest in the effects that environmental chemicals may have on the development of obesity<sup>(4)</sup>. Food and water provide us with essential nutrients; however, food and water are also sources of exposure to environmental chemicals, including pesticides<sup>(5,6)</sup>, food packaging and processing-derived contaminants such as bisphenol A (BPA) and phthalates<sup>(7–15)</sup>, and naturally occurring contaminants such as arsenic<sup>(16,17)</sup>. Chemicals detected in the food and water supply include endocrine-disrupting chemicals, a class of chemicals that interfere in some way with the normal functioning of the endocrine system and includes chemicals that may alter hormonal regulation of body weight.

First synthesized in 1891, BPA is now one of the highest-volume chemicals produced<sup>(18)</sup>, resulting in widespread human exposure<sup>(19)</sup>. BPA is used as a component of polycarbonate plastics and in epoxy resins<sup>(18)</sup>. The list of products currently made with polycarbonate plastics or lined with epoxy resins is extensive, and includes food and beverage storage containers and packaging<sup>(20)</sup>. The use of BPA in food packaging, along with the ability of BPA to leach into the food<sup>(7)</sup>, has led many to believe that diet is a major route of human BPA exposure<sup>(7–12)</sup>. BPA has also been found in products made from recycled paper<sup>(21)</sup>, dust particles<sup>(22–24)</sup>, thermal receipt paper<sup>(25,26)</sup>, soil, tap water and surface water<sup>(27–32)</sup>.

In 2002, Baillie-Hamilton<sup>(33)</sup> put forth a hypothesis that endocrine-disrupting chemicals could contribute to weight gain and that the historical toxicological emphasis on weight loss as an indicator of toxicity could have resulted in weight gain going largely unnoticed as an adverse effect

\*Corresponding author. Email sjo36@georgetown.edu

of exposure to endocrine-disrupting chemicals. These observations, and results from animal and *in vitro* studies, have led to increased interest in evaluating the potential for environmental exposures to act as 'obesogens'. Obesogens were defined by Grun and Blumberg as 'molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity'<sup>(34)</sup>.

*In vitro* studies have shown that BPA has the ability to bind to thyroid hormone receptors<sup>(35)</sup> and human studies have observed associations between higher BPA levels and altered levels of thyroid hormones<sup>(36–40)</sup>. Thyroid hormones regulate basal metabolism and the impact of even small alterations to thyroid hormone levels on body composition is evidenced by weight changes in patients with thyroid dysfunction<sup>(41–43)</sup>. Another mechanism by which BPA exposure may lead to weight gain is through activation of PPAR $\gamma$ . PPAR $\gamma$  is highly expressed in adipose tissue and regulates adipocyte differentiation and lipid metabolism<sup>(44)</sup>. *In vitro* data suggest BPA has the ability to bind to PPAR $\gamma$ , which could trigger increased adipocyte differentiation and/or uptake of lipids by adipocytes, thus influencing body composition<sup>(45–47)</sup>.

Findings from animal studies on the association between BPA exposure and weight gain have been inconsistent<sup>(4)</sup>, which can likely be attributed to variability in methodologies, doses, exposure routes and outcomes, and differences between species and genders<sup>(48)</sup>. A 2012 report from the National Institute of Environmental Health Sciences concluded there is suggestive evidence that BPA may act as an obesogen, but that further research is required<sup>(49)</sup>. The majority of research on the association between BPA and weight gain to date has focused on *in utero* and early-life exposures. Exposure to low levels of BPA perinatally<sup>(50–58)</sup>, and during adolescence<sup>(59,60)</sup>, has been shown to result in increased weight in rodents. Few studies have evaluated the risk of obesity associated with BPA exposure in adult animals.

It is important for practitioners and researchers working to reduce obesity rates to be aware of the presence of non-nutrient exposures in the diet and the potential for these exposures to contribute to risk for becoming overweight or obese. The present systematic review summarizes the currently available literature evaluating the association between BPA levels and risk of overweight or obesity in adult human populations ( $\geq 18$  years). Limitations of current studies and recommendations for future studies will also be addressed.

## Methods

The Population, Intervention, Comparison, and Outcome (PICO) method<sup>(61)</sup> was used to construct a focused research question for the systematic review, which was 'What is the risk or prevalence of obesity (outcome) among human adults ( $\geq 18$  years) (population) who have

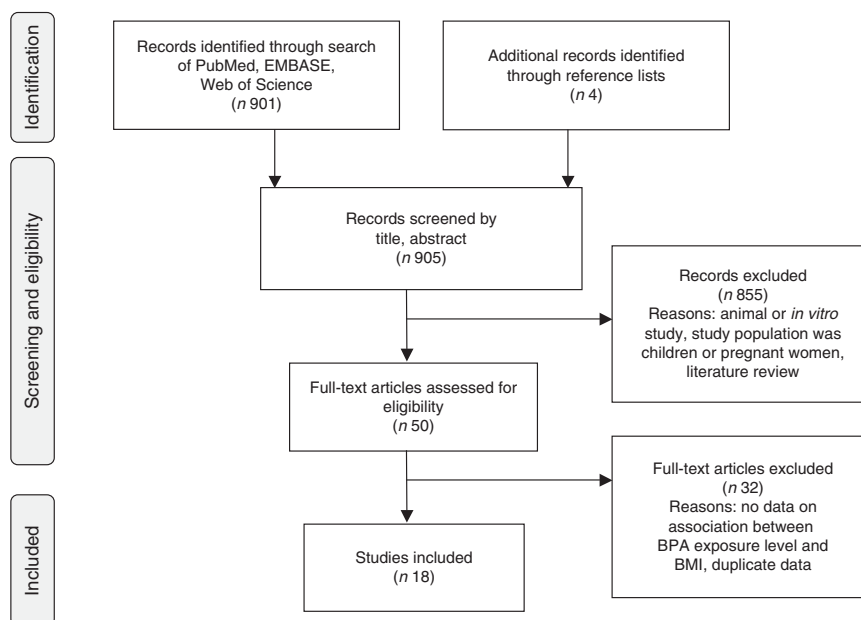
higher BPA exposure (intervention/exposure) compared with those who have low BPA exposure (comparison)?'

To be included in the systematic review, a study had to be published in a peer-reviewed journal, written in English and report data on the association between urine or serum BPA levels and BMI ( $\text{kg}/\text{m}^2$ ) in an adult population ( $\geq 18$  years). BMI was not required to be the primary outcome evaluated in the study. Studies were excluded if they did not present data for the association (with corresponding *P* value and/or confidence interval) between BPA exposure and BMI (e.g. correlation, linear regression, logistic regression). Studies that included pregnant women were excluded.

For the review, systematic searches of PubMed, EMBASE and Web of Science to 1 August 2014 were performed using the keywords 'body weight', 'body size', 'body composition', 'BMI', 'fat mass', 'overweight' or 'obesity' and 'Bisphenol A' or 'BPA'. The search was limited to English articles, excluded conference abstracts and identified 901 articles. Data on associations with other markers of obesity and weight gain, such as waist circumference (WC) and weight, are included in the results presented in the current systematic review. However, data on these outcomes were not a requirement for inclusion because very few studies evaluated these outcomes. Studies that presented duplicate data from the same study population from an already included study were excluded. In each case, the article where BMI was a primary outcome of interest was included in the review<sup>(62–64)</sup>. Two articles evaluated US National Health and Nutrition Examination Survey (NHANES) data with BMI as the primary outcome. Both studies were included in the systematic review because of differences in analysis approaches, study years included in the analyses and no obvious reason to justify including one over the other<sup>(62,63)</sup>.

Titles, abstracts and articles were then reviewed for relevance to the research question. Fourteen articles were found to be eligible for inclusion<sup>(62–75)</sup>. Four additional articles were identified in reference lists<sup>(76–79)</sup>, for a final total of eighteen included articles. Reasons for exclusion included: not the study population of interest, no data on association between BPA levels and BMI, duplicate data, animal or *in vitro* study, review article and other (e.g. laboratory methods validation, did not evaluate BPA, etc.; Fig. 1).

Using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist as a guide<sup>(80)</sup>, the following information, if available, was abstracted from each study: first author; year of publication; study location; study design; study population (age, gender, health status); exposure assessment; body composition measurement methods; data analysis approach; and study results related to body composition and BPA levels. Data analysis approach was included to evaluate consistencies in analysis methods and to evaluate assessments of potential confounders. For exposure assessment



**Fig. 1** Article identification flow diagram (BPA, bisphenol A)

methods, article abstraction focused on the type of biospecimens collected, reported materials used in collection, storage and processing, and BPA assay methodology.

Article quality was assessed using a quality rating system adapted from the rating system developed by the Academy of Nutrition and Dietetics<sup>(81)</sup>. Study design classification was based on the data analysis approach. For example, studies that evaluated data collected at the same time point from a cohort study were classified as cross-sectional. To receive a positive quality study rating, at least five of the validity criteria (questions) had to be met. Specifically, methods had to be appropriate and adequately described for subject selection, comparability of study subjects (appropriate control of confounders) and measurement of BPA levels (exposure) and body composition (BMI – outcome). A study with five or more ‘no’ or ‘unclear’ answers to the validity questions was rated as negative quality. When an article contained insufficient information to ascertain a clear ‘yes’/‘no’ for meeting a criterion, it was classified as ‘unclear’ and was considered as not meeting the criterion. All other studies were classified as neutral quality.

## Results

To date, eighteen studies have presented data on associations between urinary or serum BPA levels and body composition<sup>(62–79)</sup>. Table 1 summarizes the studies and their findings. Thirteen studies were cross-sectional<sup>(62–64,67,68,71–73,75–78)</sup>, two were case–control<sup>(65,70)</sup> and two were prospective cohort studies<sup>(66,74)</sup>, but all data analyses were cross-sectional. One of the cohort studies did prospectively

evaluate rate of weight change, but only evaluated the association between BMI and urinary BPA levels at baseline<sup>(74)</sup>. The studies were conducted in the USA ( $n\ 5$ )<sup>(62,63,70,74,77)</sup>, Republic of Korea ( $n\ 5$ )<sup>(71,72,75,76,78)</sup>, China ( $n\ 2$ )<sup>(64,67)</sup>, Italy ( $n\ 2$ )<sup>(65,66)</sup>, Japan ( $n\ 2$ )<sup>(68,73)</sup>, Sweden ( $n\ 1$ )<sup>(79)</sup> and the UK ( $n\ 1$ )<sup>(70)</sup>. For six of the articles, body composition (BMI, WC and/or weight) was the primary outcome of interest<sup>(62–64,67,71,74)</sup>. Seven studies included only women<sup>(65,67,69,73,74,77,78)</sup>, nine of the studies were in general adult populations<sup>(62–64,66,67,70,71,75,76)</sup>, one study included men and women  $\geq 60$  years<sup>(72)</sup> and another included only 70-year-old men and women<sup>(79)</sup>.

All studies evaluated associations using a single cross-sectional measurement of BPA, but biospecimen collection, laboratory assay methodology and data analysis approaches varied across the studies. Six studies measured serum BPA levels; four using a competitive ELISA<sup>(65,68,73,78)</sup>, one using HPLC paired with an electrochemical detector<sup>(77)</sup> and one using LC and tandem MS (LC–MS/MS)<sup>(79)</sup>. Ten studies measured total BPA in spot urine samples<sup>(62–64,67,70–72,74–76)</sup>, one study used the geometric mean for two spot samples collected during the same *in vitro* fertilization cycle<sup>(69)</sup> and one study measured total BPA in a 24 h urine sample<sup>(66)</sup>. Urinary BPA levels were measured using GC–MS<sup>(63)</sup> and/or HPLC and tandem MS (HPLC–MS/MS)<sup>(62–64,66,67,71,72,74)</sup>.

Data analysis approaches included correlation<sup>(65,67–69,73,75–78)</sup>,  $\chi^2$  tests<sup>(65,70)</sup>, ANOVA<sup>(73)</sup>, linear regression<sup>(62,64,66,71,74,79)</sup>, logistic regression<sup>(62–64)</sup> and unspecified analysis approach<sup>(72)</sup>. Differences in data analysis approaches limited the ability to perform meta-analyses.

The six studies that measured serum BPA concentrations observed wide ranges of serum BPA levels across study participants. While Tarantino *et al.* observed means

**Table 1** Human studies evaluating BMI in relation to bisphenol A in adult populations ( $\geq 18$  years)

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Serum BPA measurement studies ( <i>n</i> 6) Bloom <i>et al.</i> <sup>(77)</sup> USA (California)	To evaluate associations between serum BPA, peak oestradiol levels, and number of oocytes retrieved during IVF	Women undergoing IVF Age: 28–44 years <i>n</i> 41 No additional exclusion/inclusion criteria specified except for having serum BPA and serum oestradiol levels or number of oocytes retrieved	Cross-sectional	Spot blood samples Serum BPA HPLC with electrochemical detector LOD = 0.3 ng/ml Collection and storage materials: PET serum separator Vacutainer tubes, PP storage cryovials	Mean (sd) BMI (kg/m <sup>2</sup> ): 24.3 (4.9) Mean (sd) BPA (ng/ml): 7.22 (14.2) Median BPA (ng/ml): 2.53 Pearson correlation (BPA, BMI): $r = -0.12$ , $P = 0.44$	None	D – negative
Kim <i>et al.</i> <sup>(78)</sup> Republic of Korea	To evaluate associations between BPA levels and BMD and biochemical bone markers related to osteoporosis	Postmenopausal women receiving treatment for osteoporosis Age: 50–82 years <i>n</i> 51 Excluded women taking medications that alter bone or Ca metabolism, and women with cancer or other systemic disease	Cross-sectional	Spot blood samples Serum BPA Competitive ELISA Quantitative range: 0.50–10 ng/ml Collection and storage materials: No information provided	Mean (sd) BMI (kg/m <sup>2</sup> ): 23.0 (2.7) Mean (sd) BPA (ng/ml): 1.44 (0.52) Pearson correlation (BPA, BMI): $r = 0.008$ , $P = 0.96$	None	D – negative
Olsen <i>et al.</i> <sup>(79)</sup> Sweden	To evaluate whether there is an association between circulating BPA and phthalate levels and Framingham Risk Score and/or cardiovascular risk factors included in the score	Men and women Age: 70 years <i>n</i> 1016 No additional exclusion/inclusion criteria specified except age and location of residence	Cross-sectional	Fasting spot blood samples Serum BPA Isotope LC–MS/MS LOD = 0.2 ng/ml (unclear if this is for BPA, phthalates or all chemicals analysed) Collection and storage materials: No information provided	Mean (sd) BMI (kg/m <sup>2</sup> ): 27.0 (4.3) WHR (sd): 0.90 (0.075) Mean/median BPA: Not provided Linear regression, $\beta$ (95% CI) (ng/ml): BPA = 0.085 (–0.19, 0.36)	Gender, serum cholesterol, serum TAG, hypertension, smoking, diabetes	D – negative
Takeuchi <i>et al.</i> <sup>(73)</sup> Japan	To evaluate whether serum BPA levels are associated with serum hormone levels in women with ovarian dysfunction and obesity	Non-obese women with normal menstrual cycles: Mean (se) age = 27.5 (0.7) years <i>n</i> 19 Obese women with normal menstrual cycles: Mean (se) age = 28.8 (2.0) years <i>n</i> 7 Women with hyperprolactinaemia: Mean (se) age = 27.7 (2.6) years <i>n</i> 7 Women with hypothalamic amenorrhoea: Mean (se) age = 25.1 (1.0) years <i>n</i> 21 Non-obese women with PCOS: Mean (se) age = 26.5 (1.5) years <i>n</i> 13 Obese women with PCOS: Mean (se) age = 24.7 (1.9) years <i>n</i> 6 Exclusions were unclear, but it appears use of medications and abnormal thyroid hormone levels were exclusionary criteria	Cross-sectional	Fasting spot blood samples Serum BPA Competitive ELISA LOD: Not provided Collection and storage materials: No information provided	Mean (se) BMI (kg/m <sup>2</sup> ): Non-obese women with normal menstrual cycles = 19.7 (0.3) Obese women with normal menstrual cycles = 28.5 (1.7) Patients with hyperprolactinaemia = 20.8 (1.0) Women with hypothalamic amenorrhoea = 19.2 (0.6) Non-obese PCOS = 19.1 (0.6) Obese PCOS = 31.3 (3.0) Mean (se) BPA (ng/ml): Normal menstrual cycles = 0.71 (0.09) Obese women with normal menstrual cycles = 1.04 (0.09) Patients with hyperprolactinaemia = 0.83 (0.12) Women with hypothalamic amenorrhoea = 0.84 (0.10) Non-obese PCOS = 1.05 (0.10) Obese PCOS = 1.17 (0.16) Correlation (BPA, BMI): $r = 0.50$ , $P < 0.001$ Among normal women serum BPA levels were higher in obese women <i>v.</i> non-obese women, $P < 0.05$	None	D – negative

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Takeuchi and Tsutsumi <sup>(68)</sup> Japan	To evaluate associations between urinary BPA levels and gender and sex-hormone levels	Healthy women: Mean (SE) age = 28.7 (0.7) years n 14 PCOS women: Mean (SE) age = 25.7 (1.4) years n 16 Healthy men: Mean (SE) age = 29.4 (1.1) years n 11 No exclusion/inclusion criteria specified	Cross-sectional	Spot blood samples Serum BPA Competitive ELISA LOD: Not provided Collection and storage materials: No information provided	Mean (SE) BMI (ng/ml): Healthy women = 19.4 (0.3) PCOS women = 22.4 (0.9) Healthy men = 21.2 (1.1) Mean (SE) BPA (ng/ml): Healthy women = 0.64 (0.10) PCOS women = 1.49 (0.11) Healthy men = 1.04 (0.10) Correlation – women only (BPA, BMI): $r = 0.30$ , $P > 0.05$ Correlation – all participants (BPA, BMI): $r = 0.32$ , $P > 0.05$	None	D – negative
Tarantino <i>et al.</i> <sup>(65)</sup> Italy	To evaluate whether serum BPA levels are associated with insulin resistance, hepatic steatosis, hyperandrogenism severity and spleen size in women with PCOS	Women Cases: Mean (SD) age = 27.7 (6.8) years n 40 women with PCOS Controls: Mean (SD) age = 26.2 (3.9) years n 20 age-matched healthy, normal-weight women who worked at hospital Excluded smoking, alcohol consumption, pregnancy, hypothyroidism, hyperprolactinaemia, Cushing's disease, non-classical congenital adrenal hyperplasia, use of oral contraceptives in previous 6 months, also use of insulin-sensitizing agents, glucocorticoids, anti-androgens, ovulation agents, anti-obesity drugs, presence of any acute viral, bacterial or fungal infection, any type of chronic liver disease, arthritis, bronchial asthma, IBS, cancer	Case-control *Analysis is cross-sectional	Spot blood sample Serum BPA Competitive ELISA LOD: Not provided. Compared increased levels (>0.45 ng/ml) with lower levels (<0.45 ng/ml) Chose cut-off based on 95th percentile in controls Collection and storage materials: No information provided	Mean (SD) BMI (kg/m <sup>2</sup> ): Cases = 28.1 (7.7) Controls = 22.1 (1.8) Median (range) BPA (ng/ml): Cases = 0.7 (0.1–6.0) Controls = 0.1 (0.1–0.6) Among women with PCOS, BMI did not differ between those with BPA levels <0.45 ng/ml v. those with levels about the cut-off point ( $P = 0.30$ ) BMI was significantly correlated ( $r = 0.27$ , $P = 0.04$ ) with serum BPA measurements Only one control had BPA level above 0.45 ng/ml	None	D – negative

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Total urinary BPA measurement studies (n 12) Carwile and Michels <sup>(62)</sup> USA	To evaluate whether urinary BPA levels were associated with general (BMI) and central (WC) obesity	US NHANES 2003–2006 Men and women Age: 18–74 years n 2747 Excluded women who were pregnant and participants missing urinary BPA or creatinine data	Cross-sectional	Fasting spot urine samples Total BPA HPLC–MS/MS LOD 2003–2004 = 0.36 ng/ml LOD 2005–2006 = 0.40 ng/ml Urinary BPA levels were evaluated as quartiles Q1: ≤1.1 ng/ml Q2: 1.2–2.3 ng/ml Q3: 2.4–4.6 ng/ml Q4: ≥4.7 ng/ml Collection and storage materials: According to CDC Laboratory Procedure Manual efforts are made to avoid contamination of samples, including using PP collection containers, and borosilicate glass or PP storage containers and vials	Mean BMI: Not provided Mean (IQR) BPA (µg/g creatinine): 2.05 (1.18–3.33) BMI (kg/m <sup>2</sup> ) definitions: Recommended = BMI < 25.0 Overweight = 25.0 < BMI ≤ 29.9 Obese = BMI ≥ 30.0 Overweight BMI v. Recommended BMI, Q4 BPA v. Q1 BPA: OR = 1.31 (95% CI 0.80, 2.14) Obese BMI v. Recommended BMI, Q4 BPA v. Q1 BPA: OR = 1.76 (95% CI 1.06, 2.94) BMI and urinary BPA (continuous) change in BMI by BPA quartile, kg/m <sup>2</sup> (95% CI): Q1 = Reference Q2 = 1.48 (0.46–2.51) Q3 = 1.69 (0.62, 2.76) Q4 = 1.56 (0.25, 2.87) ( <i>P</i> <sub>trend</sub> = 0.18) WC definitions for elevated: ≥102 cm (men) ≥88 cm (women) Elevated WC v. Normal WC, Q4 BPA v. Q1 BPA: OR = 1.58 (95% CI 1.03, 2.42)	Sex, age, race/ethnicity, education, smoking, creatinine	D – neutral
Galloway <i>et al.</i> <sup>(66)</sup> Italy	To evaluate whether urinary BPA levels were associated with serum oestrogen and testosterone levels	InCHIANTI prospective cohort study Men and women Age: 20–74 years n 715 No additional exclusion/inclusion criteria specified except age and location of residence	Cohort *Analysis is cross-sectional	2 h collection urine samples Total BPA HPLC–MS/MS LOD/LOQ = 0.50 µg/l Evaluated as covariate, not exposure/outcome association Collection and storage materials: No information provided. Unspecified type of plastic container was used for urine sample collection	Mean BPA (95% CI) (ng/ml): 3.59 (3.42, 3.77) Mean BMI: Not provided Mean BPA (95% CI) (µg/d): BMI 18.5–25.0 kg/m <sup>2</sup> : 5.67 (5.22, 6.16) reference BMI 25.0–30.0 kg/m <sup>2</sup> : 5.84 (5.43, 6.27) ( <i>P</i> = 0.30) BMI 30.1–34.9 kg/m <sup>2</sup> : 5.66 (5.04, 6.34) ( <i>P</i> = 0.37) BMI ≥ 35.0 kg/m <sup>2</sup> : 4.85 (3.94, 5.98) ( <i>P</i> = 0.73) β (95% CI): WC (cm) = 0.006 (0.002, 0.011) ( <i>P</i> = 0.013) Weight (kg) = 0.006 (0.002, 0.010) ( <i>P</i> = 0.003)	Age, sex, study site *24 h urine sample-concentration adjustment not needed	D – neutral

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Ko <i>et al.</i> <sup>(71)</sup> Republic of Korea	To evaluate whether urinary BPA levels are associated with WC	Men and women Mean (sd) age baseline: 44.3 (14.6) years <i>n</i> 1030 Inclusion/exclusion criteria not provided	Cross-sectional	Unclear type of urine sample. Appears to be spot urine sample Total BPA HPLC-MS/MS LOD/LOQ: Not provided BPA quartiles: Q1: <0.85 µg/ml Q2: 0.85–1.41 µg/ml Q3: 1.41–2.59 µg/ml Q4: ≥2.59 µg/ml Collection and storage materials: No information provided. Unspecified type of plastic container was used for urine sample collection	Mean (range) BPA (µg/ml): 1.04 (0.2–198.7) Mean (sd) BMI (kg/m <sup>2</sup> ): 24.0 (3.4) Mean (sd) BMI (kg/m <sup>2</sup> ) by BPA quartile: Q1 = 24.0 (3.6) Q2 = 23.7 (3.2) Q3 = 24.0 (3.4) Q4 = 24.2 (3.6) ( <i>P</i> = 0.16) BMI (continuous), <i>B</i> (se) <i>P</i> value: 0.19 (0.03) 0.01 Mean (sd) body fat (%) by BPA quartile: Q1 = 27.3 (6.7) Q2 = 26.4 (5.7) Q3 = 26.2 (6.3) Q4 = 26.2 (6.5) ( <i>P</i> = 0.74) Body fat (continuous), <i>B</i> (se) <i>P</i> value: 0.11 (0.05) 0.04 Mean (sd) weight (kg) by BPA quartile: Q1 = 62.8 (10.9) Q2 = 63.0 (11.6) Q3 = 64.4 (12.0) Q4 = 65.3 (12.5) ( <i>P</i> = 0.07) Weight (continuous), <i>B</i> (se) <i>P</i> value: 0.04 (0.03) 0.08 Mean (sd) WC (cm) by BPA quartile: Q1 = 84.0 (8.5) Q2 = 84.0 (8.6) Q3 = 84.5 (8.3) Q4 = 85.6 (10.7) ( <i>P</i> = 0.007) WC (continuous), <i>B</i> (se) <i>P</i> value: 0.56 (0.03) 0.05 WC definitions for elevated: ≥90 cm (men) ≥85 cm (women) Elevated WC v. Normal WC, Q4 BPA v. Q1 BPA: OR = 1.93 (95% CI 1.31, 2.86) Mean (sd) HC (cm) by BPA quartile: Q1 = 94.5 (6.1) Q2 = 94.3 (6.2) Q3 = 95.1 (6.4) Q4 = 95.9 (7.0) ( <i>P</i> = 0.03) HC (continuous), <i>B</i> (se) <i>P</i> value: 0.06 (0.04) 0.13	Age, sex, urinary creatinine (WC logistic regression model additionally adjusted for education, income, alcohol intake and smoking status)	D – negative

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Lee <i>et al.</i> <sup>(72)</sup> Republic of Korea	To evaluate whether urinary BPA levels were associated with liver enzyme concentrations using repeated measures	Men and women Age: $\geq 60$ years <i>n</i> 478 Excluded participants who visited study centre only once, with no blood and urine samples available, and those who reported currently having viral hepatitis, fatty liver disease, liver cancer or any other type of liver disease	Cross-sectional *Analysis of BMI is cross-sectional	Multiple spot urine samples were collected, but BMI was compared only with spot urine sample collected at baseline Total BPA HPLC–MS/MS LOD = 0.005 $\mu\text{g/l}$ Collection and storage materials: Unspecified type of container was used for urine sample collection and storage	Mean BMI: Not provided Mean (sd) BPA ( $\mu\text{g/g}$ creatinine): Men = 0.88 (1.33) Women = 1.28 (1.95) Mean (sd) BPA ( $\mu\text{g/g}$ creatinine) by BMI category: <23.0 $\text{kg/m}^2$ = 1.09 (1.31) 23.0–24.9 $\text{kg/m}^2$ = 1.10 (1.87) >25.0 $\text{kg/m}^2$ = 1.28 (2.02)	None	D – negative
Melzer <i>et al.</i> <sup>(70)</sup> UK	To evaluate the association between urinary BPA levels and incident CAD	EPIC-Norfolk cohort Men and women Age: 40–74 years Cases: <i>n</i> 758 Controls: <i>n</i> 861 Excluded participants with diabetes and/or a history of MI or stroke at baseline	Nested case–control *Analysis is cross-sectional	Spot urine sample Total BPA HPLC–MS/MS LOQ = 0.50 $\text{ng/ml}$ Collection and storage materials: No information provided	Mean (sd) BMI ( $\text{kg/m}^2$ ): Cases = 27.2 (3.8) Controls = 26.2 (3.4) Mean (sd) BPA ( $\text{ng/ml}$ ): Cases = 1.23 (2.95) Controls = 1.39 (3.02) BPA v. BMI category BPA $\leq 1.243$ $\text{ng/ml}$ : BMI < 18.4 $\text{kg/m}^2$ , 0.43 % BMI 18.4–24.9 $\text{kg/m}^2$ , 38.2 % BMI 25.0–29.9 $\text{kg/m}^2$ , 47.0 % BMI 30.0–34.9 $\text{kg/m}^2$ , 12.9 % BMI > 35 $\text{kg/m}^2$ , 1.5 % BPA > 1.243 $\text{ng/ml}$ : BMI < 18.4 $\text{kg/m}^2$ , 0.0 % BMI 18.4–24.9 $\text{kg/m}^2$ , 33.7 % BMI 25.0–29.9 $\text{kg/m}^2$ , 52.8 % BMI 30.0–34.9 $\text{kg/m}^2$ , 11.3 % BMI > 35 $\text{kg/m}^2$ , 2.2 % $\chi^2$ test: $P = 0.21$	None *Did not adjust for urine concentration	D – neutral
Mok-Lin <i>et al.</i> <sup>(69)</sup> USA (Massachusetts)	To evaluate pre- and peri-conception urinary BPA concentrations with oocyte and oestradiol production among women undergoing IVF	Women partners of couples seeking infertility evaluation and treatment Age: 21–44 years <i>n</i> 84 Excluded women using donor oocytes or embryos or who underwent cryo–thaw cycles	Cross-sectional	Two spot urine samples from same IVF cycle; used geometric mean of the two SG-adjusted urinary BPA concentrations Total BPA HPLC–MS/MS LOD = 0.4 $\text{ng/ml}$ Collection and storage materials: PP collection containers. Storage container details not provided	Mean (sd) BMI ( $\text{kg/m}^2$ ): 24.0 (5.1) Mean (sd) BPA ( $\text{ng/ml}$ ): 3.97 (5.9) Unspecified model correlation: $r = -0.06$ , $P = 0.61$	None BPA levels were SG-adjusted	D – negative



Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Shankar <i>et al.</i> <sup>(63)</sup> USA	To evaluate whether urinary BPA levels were associated with obesity (BMI and WC) by gender and race/ethnicity	NHANES 2003–2008 Men and women Age: ≥20 years n 3967 Excluded participants with self-reported history of CVD, missing data on education, smoking status, serum glucose levels, SBP or DBP, BMI and/or cholesterol levels	Cross-sectional	Spot urine samples Total BPA Analysis method depends on year: GC–MS or HPLC–MS/MS LOD = 0.1–2 ng/ml per 100 µl urine Urinary BPA levels were evaluated as quartiles BPA quartiles: Q1: <1.10 ng/ml Q2: 1.10–2.10 ng/ml Q3: 2.11–4.20 ng/ml Q4: >4.20 ng/ml Collection and storage materials: According to CDC Laboratory Procedure Manual efforts are made to avoid contamination of samples, including using PP collection containers, and borosilicate glass or PP storage containers and vials	Mean BMI: Not provided Mean WC: Not provided Mean (sd) BPA (ng/ml): Men = 3.97 (0.21) Women = 3.90 (0.26) Overall population BPA v. BMI ≥ 30.0 kg/m <sup>2</sup> , Q4 BPA v. Q1 BPA: OR = 1.69 (95% CI 1.30, 2.20) (P < 0.0001) Overall population BPA v. WC ≥ 88 cm (women)/102 cm (men), Q4 BPA v. Q1 BPA: OR = 1.59 (95% CI: 1.21–2.09) (P = 0.0009) Urinary BPA levels were significantly associated with higher odds of obesity (BMI or WC), regardless of race/ethnicity or gender	Age, sex, race/ethnicity, education, smoking, alcohol intake, physical inactivity, diabetes, hypertension, serum TC *Did not adjust for urine concentration	D – neutral
Song <i>et al.</i> <sup>(74)</sup> USA	To evaluate urinary concentrations of BPA and major phthalate metabolites in relation to prospective weight change in the NHS and NHS II	Controls from nested case–control study in NHS and NHS II Women n 977 Mean (sd) baseline age (years): BPA Q1 = 57.6 (12.0) BPA Q2 = 54.8 (11.2) BPA Q3 = 51.1 (9.9) BPA Q4 = 51.7 (10.2)	Cohort (nested case–control) *Analysis of BPA and BMI association is cross-sectional	Spot first morning void urine samples Total BPA LC–MS/MS LOD: Not provided Urinary BPA levels were evaluated as quartiles BPA quartiles (median, IQR) (µg/l): Q1 = 0.82 (0.59–1.03) Q2 = 1.46 (1.32–1.66) Q3 = 2.39 (2.05–2.76) Q4 = 4.99 (3.83–8.14) Collection and storage materials: PP collection and storage containers Weight change = Weight at most recent follow-up – weight at urine sample collection (~9–14 years apart)	Median (IQR) BPA (µg/l): Q1 = 0.82 (0.59–1.03) Q2 = 1.46 (1.32–1.66) Q3 = 2.39 (2.05–2.76) Q4 = 4.99 (3.83–8.14) Mean (95% CI) BMI (kg/m <sup>2</sup> ): Q1 = 26.1 (25.4, 26.8) Q2 = 26.2 (25.5, 26.9) Q3 = 26.3 (25.6, 27.0) Q4 = 26.0 (25.3, 26.7) (adjusted for creatinine) (baseline BMI) Mean (95% CI) BMI (kg/m <sup>2</sup> ): Q1 = 25.7 (25.0, 26.4) Q2 = 26.3 (25.6, 27.0) Q3 = 26.2 (25.5, 26.9) Q4 = 26.2 (25.4, 26.9) (P <sub>trend</sub> = 0.65) Weight change rate (95% CI): Q1 = Reference Q2 = 0.15 (0.00, 0.31) Q3 = 0.18 (0.03, 0.34) Q4 = 0.23 (0.15, 0.50) (P <sub>trend</sub> = 0.02)	Creatinine, cohort origin, age at baseline, smoking, alcohol consumption, physical activity, alternative healthy eating index, total energy intake	D – neutral

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Wang <i>et al.</i> <sup>(64)</sup> China	To evaluate whether urinary BPA levels were associated with obesity (BMI and WC) or insulin resistance	Men and women Age: $\geq 40$ years $n$ 3390 Excluded participants with self-reported liver diseases (e.g. hepatitis, cirrhosis, cancer)	Cross-sectional	Spot morning urine samples Total BPA HPLC-MS/MS LOD = 0.30 ng/ml (below were assigned value of 0.15) Urinary BPA levels were evaluated as quartiles BPA quartiles (ng/ml): Q1: $\leq 0.47$ Q2: 0.48–0.81 Q3: 0.82–1.43 Q4: $> 1.43$ Collection and storage materials: No information provided	Median (IQR) BPA (ng/ml): 0.81 (0.47–1.43) (mean not provided) Mean (sd) BMI ( $\text{kg}/\text{m}^2$ ): 24.9 (3.6) (adjusted for gender) BMI ( $\text{kg}/\text{m}^2$ ) definitions: Recommended: BMI $< 24.0$ Overweight: $24.0 \leq \text{BMI} < 28.0$ Obese: BMI $\geq 28.0$ Overweight BMI v. Recommended BMI, Q4 BPA v. Q1 BPA: OR = 1.24 (95% CI 0.97, 1.59) Obese BMI v. Recommended BMI, Q4 BPA v. Q1 BPA: OR = 1.50 (95% CI 1.15, 1.60) BMI and urinary BPA (continuous), mean (sd) BMI ( $\text{kg}/\text{m}^2$ ) by BPA quartile: Q1 = 24.6 (3.6) Q2 = 24.9 (3.8) Q3 = 24.8 (3.6) Q4 = 25.1 (3.5) ( $P_{\text{trend}} < 0.001$ ) WC definitions for elevated: $\geq 90$ cm (men) $\geq 85$ cm (women) Elevated WC v. Normal WC, Q4 BPA v. Q1 BPA: OR = 1.28 (95% CI 1.03, 1.60) WC and urinary BPA (continuous), mean (sd) WC (cm) by BPA quartile: Q1 = 86.6 (9.9) Q2 = 87.7 (9.8) Q3 = 87.1 (9.8) Q4 = 87.9 (9.6) ( $P_{\text{trend}} < 0.001$ )	Age, sex, urinary creatinine, smoking, alcohol consumption, education, SBP, HDL-C, LDL-C, TC, CRP, FPG, fasting serum insulin, serum ALT and GTT	D – neutral
Yang <i>et al.</i> <sup>(75)</sup> Republic of Korea	To evaluate if associations between BPA levels and markers of oxidative stress and inflammation differ by gender and/or postmenopausal status	Men and women Age: Range not specified Mean (sd) age: Men = 49.5 (8.6) years Premenopausal women = 45.9 (3.9) years Postmenopausal women = 57.0 (7.1) years $n$ 485 Excluded subjects who reported a history of disease that could be associated with oxidative stress biomarker levels, such as cancer, heart disease, tuberculosis, hepatitis, arthritis and asthma	Cross-sectional	Fasting (12 h) spot morning urine samples Total BPA HPLC-MS/MS LOD = 0.063 ng/ml (per 500 $\mu\text{l}$ urine) Collection and storage materials: No information provided	Mean (IQR) BPA ( $\mu\text{g}/\text{g}$ creatinine): Men = 0.52 (0.12–1.75) Premenopausal women = 0.61 (0.24–1.86) Postmenopausal women = 0.58 (0.11–1.82) Mean (sd) BMI ( $\text{kg}/\text{m}^2$ ): Men = 24.6 (2.6) Premenopausal women = 23.0 (2.7) Postmenopausal women = 23.8 (3.0) Unspecified correlation model (BPA, BMI): $r = -0.042$ , $P = 0.358$ Unspecified correlation model (BPA, weight): $r = -0.079$ , $P = 0.085$	Creatinine	D – negative

Table 1 Continued

Study and country	Study objective	Population	Study design	Exposure assessment	Results	Covariates	Study quality*
Yang <i>et al.</i> <sup>(76)</sup> Republic of Korea	To evaluate associations between BPA levels and genetic polymorphisms (UGT, SULT), sister chromatid exchange and endocrine-related disorders	Men and women who visited the hospital for regular check-up Age: Range not specified Mean (sd) age: Men = 48.9 (10.7) years Women = 47.5 (12.3) years <i>n</i> 172 Excluded participants who were occupationally exposed to BPA, but approach for defining this was not provided	Cross-sectional	Spot morning urine samples Total BPA HPLC–fluorescence detector LOD: Not provided Collection and storage materials: No information provided	Mean (sd) BPA (ng/ml): Men = 6.88 (3.72) Women = 5.61 (3.16) Mean (sd) BMI (kg/m <sup>2</sup> ): Men = 24.5 (3.7) Women = 23.6 (4.7) Unspecified model: <i>P</i> = 0.08	None	D – negative
Zhao <i>et al.</i> <sup>(67)</sup> China	To evaluate whether urinary BPA levels are associated with body composition, serum oestrodial, leptin and osteocalcin levels, and BMD	Healthy premenopausal women Age: 20–55 years <i>n</i> 282 Excluded postmenopausal women and women who reported taking medications that alter bone metabolism or body weight	Cross-sectional	Spot urine samples Total BPA HPLC–MS/MS LOD: Not provided Collection and storage materials: No information provided	Mean (se) BPA (ng/ml): 2.27 (0.32) Mean (se) BMI (kg/m <sup>2</sup> ): 21.2 (0.2) BMI v. BPA: <i>r</i> = 0.24, <i>P</i> < 0.001 WC v. BPA: <i>r</i> = 0.30, <i>P</i> < 0.001 HC v. BPA: <i>r</i> = 0.27, <i>P</i> < 0.001 WHR v. BPA: <i>r</i> = 0.149, <i>P</i> < 0.001 Fat mass v. BPA: <i>r</i> = 0.350, <i>P</i> < 0.001 Weight v. BPA: <i>r</i> = 0.186, <i>P</i> = 0.001	Age *Did not adjust for urine concentration	D – negative

BPA, bisphenol A; IVF, *in vitro* fertilization; BMD, bone mineral density; PCOS, polycystic ovary syndrome; WC, waist circumference; CAD, coronary artery disease; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase; IBS, irritable bowel syndrome; NHANES, National Health and Nutrition Examination Survey; InCHIANTI, Invecchiare in Chianti, ageing in the Chianti area; EPIC, European Prospective Investigation on Cancer and Nutrition; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, quartile; LOD, limit of detection; PET, polyethylene terephthalate; PP, polypropylene; CDC, Centers for Disease Control and Prevention; LOQ, limit of quantification; SG, specific gravity; IQR, interquartile range; HC, hip circumference; WHR, waist-to-hip ratio; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; CRP, C-reactive protein; FPG, fasting plasma glucose; ALT, alanine aminotransferase; GTT,  $\gamma$ -glutamyl transpeptidase.

Quality score does not necessarily reflect the study quality for the primary outcomes of the study. Outcome evaluations and data analysis quality evaluations were evaluated specifically for the presented associations between BMI and BPA, which were often not the primary outcome of interest in some of these studies.

\*Academy of Nutrition and Dietetics Evidence Analysis Manual<sup>(81)</sup>.

<0.70 ng/ml<sup>(65)</sup>, Bloom *et al.* observed a mean of 7.22 ng/ml and a median of 2.53 ng/ml<sup>(77)</sup>. Three of the studies reported a limit of detection (LOD) or limit of quantification (LOQ)<sup>(77–79)</sup>, but only Bloom *et al.* reported the number of participants below the LOD/LOQ (13.6%)<sup>(77)</sup>.

Mean or median urinary BPA levels in spot urine samples were difficult to compare across studies given that some studies reported means<sup>(62,63,67,69,70,75,76)</sup>, some reported medians<sup>(64,74)</sup> and some reported levels unadjusted for concentration<sup>(63,67,69,70,76)</sup>, while others reported creatinine-adjusted concentrations<sup>(62,64,75)</sup>. LOD/LOQ were relatively similar across studies and ranged from 0.063 to 0.50 ng/ml. Four studies did not report an LOD/LOQ<sup>(67,71,74,76)</sup>. Most studies reported frequent detection of BPA in urine samples. Seven studies did not report the number of samples below the LOD/LOQ. In three of these studies, data presented in the paper indicated detectable urinary BPA levels in at least 75%<sup>(64)</sup>, 90%<sup>(63)</sup> and 95%<sup>(66)</sup> of the population. Among studies that reported the frequency of BPA detection in participants' urine, detection ranged from 77.9 to 97.5% of samples<sup>(62,69,70,75,76)</sup>.

Among the studies that measured serum BPA, results were conflicting. Two studies<sup>(65,73)</sup> observed positive correlations between serum BPA levels and BMI. The other four studies did not observe an association between serum BPA concentrations and BMI<sup>(68,77–79)</sup>. Only one of these studies reported adjusting for potential confounders, such as age or health status<sup>(79)</sup>.

Among the six studies that did not evaluate BMI as the primary outcome compared with urinary BPA levels, one study observed associations between body composition and urinary BPA levels<sup>(66)</sup> and five observed no association<sup>(69,70,72,75,76)</sup>. Galloway *et al.* did not find BMI to be statistically significantly associated with urinary BPA levels measured in a 24 h urine collection. However, WC (continuous) and weight (continuous) were statistically significantly positively associated with 24 h urinary BPA levels<sup>(66)</sup>. Melzer *et al.* did not find an association between BMI and urinary BPA category ( $\leq 1.243$  ng/ml *v.*  $> 1.243$  ng/ml), although there was a higher percentage of overweight and obese participants (66.3%) in the high BPA category compared with the low BPA category (61.8%)<sup>(70)</sup>.

Four of the six studies where body composition was the primary outcome observed statistically significant positive associations between BMI and urinary BPA levels<sup>(62–64,67)</sup>. Zhao *et al.*<sup>(67)</sup> observed statistically significant positive correlations (adjusted for age) between urinary BPA levels and BMI, WC and hip circumference in premenopausal women. Wang *et al.* found a small, but statistically significant, positive trend between spot urine BPA levels and both BMI (continuous) and WC (continuous)<sup>(64)</sup>. That study observed marginally statistically higher odds of being overweight ( $24 \text{ kg/m}^2 \leq \text{BMI} < 30.0 \text{ kg/m}^2$ , OR = 1.24; 95% CI 0.97, 1.59) among participants in the highest BPA quartile (total urinary BPA  $> 1.43$  ng/ml) compared with

those in the lowest quartile (total urinary BPA  $\leq 0.47$  ng/ml), and being in the highest BPA quartile was associated with 50% higher odds of being obese (BMI  $\geq 30.0 \text{ kg/m}^2$ ; 95% CI 1.15, 1.60) compared with those in the lowest BPA quartile. Wang *et al.* also observed higher odds of elevated WC ( $\geq 85$  cm in women,  $\geq 90$  cm in men) among participants in the highest BPA quartile (OR = 1.20; 95% CI 1.03, 1.60) compared with those in lowest BPA quartile. The study by Song *et al.* found no association between cross-sectional BMI and urinary BPA levels measured at baseline. However, that study did observe a statistically significant positive association between urinary BPA levels and annual weight change rate (quartile 4 *v.* quartile 1:  $\beta = 0.23$  kg/year, 95% CI 0.07, 0.38)<sup>(74)</sup>. Similarly, Ko *et al.* observed inconsistent results depending on analysis approach and measure of body composition used<sup>(71)</sup>. Regardless of analysis approach, WC was associated with urinary BPA levels. Conversely, hip circumference and weight were not associated with urinary BPA levels, regardless of analysis approach. Percentage body fat and BMI were associated with urinary BPA when evaluated as continuous variables only.

Using NHANES 2003–2008 data, Shankar *et al.* found higher odds of general obesity (BMI  $\geq 30.0 \text{ kg/m}^2$ ; OR = 1.69; 95% CI 1.30, 2.20) and central obesity (WC  $\geq 88$  cm in women,  $\geq 102$  cm in men; OR = 1.59; 95% CI 1.21, 2.09) among those in the highest BPA quartile compared with those in the lowest BPA quartile<sup>(63)</sup>. Carwile and Michels performed analyses using NHANES 2003–2006 data and the findings were consistent with those of Shankar *et al.* Those in the highest urinary BPA level quartiles (total urinary BPA  $> 4.20$  ng/ml) had higher odds of being overweight ( $25.0 \text{ kg/m}^2 \leq \text{BMI} < 30.0 \text{ kg/m}^2$ ; OR = 1.31; 95% CI 0.80, 2.14) or obese (BMI  $\geq 30.0 \text{ kg/m}^2$ ; OR = 1.76; 95% CI 1.06, 2.94) and having an elevated WC ( $\geq 88$  cm in women,  $\geq 102$  cm in men; OR = 1.58; 95% CI 1.03, 2.42) compared with participants in the first quartile (total urinary BPA  $< 1.10$  ng/ml). While higher urinary BPA levels were associated with general and central obesity in this study, there was not a clear linear pattern to the association<sup>(62)</sup>.

Twelve of the eighteen studies were rated as negative quality<sup>(65,67–69,71–73,75–79)</sup>, six were neutral quality<sup>(62–64,66,70,74)</sup> and none were positive quality. The lack of positive quality studies was typically due to limitations and issues related to BPA exposure measurement (validity question 5), temporality problems (validity question 6) and/or lack of evaluation of confounding factors (validity question 7). Among the twelve negative quality studies, only three observed statistically significant associations between urinary or serum BPA levels and any measure of body composition<sup>(67,71,73)</sup>, while four<sup>(62–64,66)</sup> of the six neutral quality studies observed statistically significant associations. All six of the serum BPA studies received a negative quality rating<sup>(65,68,73,77–79)</sup>, while four of the twelve urinary BPA studies received a negative quality rating<sup>(67,69,75,76)</sup>.

No study, regardless of whether serum BPA or urinary BPA was measured, met the criteria for adequate exposure measurement (question 6).

## Discussion

Overall, the literature evaluating the association between BPA levels and obesity is conflicting and inconclusive. Eight out of the eighteen studies observed a positive association between urinary or serum BPA levels and BMI. Among studies that indicated a lack of association, all but one were secondary analyses and all but one were rated negative quality. Significant limitations were present in all eighteen studies included in the present systematic review. No study received a positive quality rating and, thus, all results should be interpreted with caution. Of note, higher-quality studies were more likely to report a positive association between BPA levels and BMI, and all studies that evaluated BMI as a primary outcome observed statistically significant positive associations.

Our findings are consistent with another recently published systematic review by Lakind *et al.*<sup>(82)</sup>. However, the Lakind *et al.* review included duplicate data, pregnant women, adolescents and children, which further complicated their interpretation of the results. The previous review did not evaluate how the study results differed by quality, methods and whether BMI was the primary outcome. The present review also includes three studies<sup>(71,72,74)</sup> not included in the Lakind *et al.* review.

The data presented in all eighteen studies included in the current systematic review were single, cross-sectional measurements of both BPA levels and body composition. The one exception was an analysis of rate of weight change, but that study also had only a single spot urine sample<sup>(74)</sup>. Cross-sectional data have an inherent inability to distinguish temporality, so researchers are not able to determine whether differences in observed BPA exposure levels are causally related to current body composition. An additional concern with cross-sectional data is that they only reflect very recent exposures and for many chronic health conditions (including the development of obesity) long-term exposure is most relevant. This is particularly true for BPA, which is generally considered to be absorbed, metabolized and excreted within 24 h of exposure<sup>(48,83,84)</sup>, and within-person BPA levels are highly variable over time<sup>(85–87)</sup>. Studies have demonstrated high intra-individual variation in urinary BPA levels from spot samples collected at multiple time points on the same day and across multiple days or years<sup>(85,86)</sup>. Single-day 24 h urine samples have been shown to also have high intra-individual variability across days. All studies included in the present review used a spot serum, spot urine or a single-day 24 h urine sample to determine BPA levels.

Biomarkers (urine or serum) are currently the only available method for assessing BPA exposure level.

Actual results are difficult to compare across studies because of differences in BPA assay methodologies and observed BPA levels. Six studies measured serum BPA level which, regardless of assay method, is currently not considered to be the most appropriate method for measuring BPA exposure due to concerns regarding specimen contamination and the inability of current assay methods and equipment to accurately measure the low levels of BPA that are typically present in serum<sup>(10,11,26,88–90)</sup>. BPA is a non-persistent chemical that is found at nano- to picomolar concentrations in serum, which increases the potential for extraneous sample contamination to influence serum measurements<sup>(48,91,92)</sup>. Urinary BPA levels are much higher and consist largely of conjugated BPA, which can only be formed *in vivo*, thus acting as a marker for ruling out contamination by extraneous sources<sup>(88)</sup>. In fourteen of the studies<sup>(64,66–73,75–79)</sup>, including five of six studies that measured serum BPA levels, the manuscripts lacked sufficiently detailed information to determine whether BPA-free materials were used to collect, process and store biospecimens. Failure to use BPA-free laboratory materials could lead to sample contamination and inaccurate BPA measurements, particularly with serum measurements<sup>(64,65,67,68,73,88)</sup>. This could result in non-differential misclassification of exposure, which may attenuate observed associations, and should be addressed in future studies. Further complicating interpretations is the lack of reporting of LOD/LOQ and the number of participants who had undetectable levels of BPA in collected samples, which is essential information for evaluating the BPA assessment method and comparing study results.

Given the limitations in measuring low-level BPA metabolites in serum, many researchers consider total urinary BPA to be the preferred approach for measuring BPA exposure<sup>(48,88,91,92)</sup>. However, it is important to note that studies measuring total urinary BPA levels do not directly test the association between internal unconjugated BPA (biologically active) exposure and body composition. Total urinary BPA measures primarily conjugated BPA, which is no longer biologically active and is readily excreted in the urine<sup>(20,48,93,94)</sup>.

It has been suggested that BPA exhibits a non-monotonic dose–response relationship, where very low levels and very high levels are the ranges in which BPA exposure may adversely affect health<sup>(95)</sup>. However, the broad range of reported urinary and serum BPA levels in currently available studies and the lack of a quality control programme for BPA measurements have been a challenge for testing this hypothesis and defining the cut-off point for low-level BPA exposures. Reliable testing methodology for unconjugated serum BPA is required to fully test this hypothesis. Results were recently published from a round robin including four laboratories with previous experience in environmental chemical analysis<sup>(96)</sup>. The round robin was established to specifically evaluate and address improvements to serum assay methodologies

and standardization of assay protocols. Results indicate that unconjugated serum BPA can be measured using strict protocols for collection, storage and processing materials and appropriate laboratory methodologies.

It is currently unclear whether there is any exposure level at which no adverse health effects occur. Adding to the complexity of evaluating BPA exposures and health outcomes in population-based studies is that nearly all human populations are exposed to low levels of BPA. There is generally no 'unexposed' group to compare with the 'exposed' population. Prospective population-based studies evaluating different levels of exposure could help elucidate if there are thresholds at which BPA is associated with health outcomes. The lack of an unexposed control group makes it difficult to interpret study findings because a lack of a statistically significant association could mean either: (i) there is no true association; or (ii) any BPA exposure is harmful.

Data analysis approaches varied widely across studies, which likely contributes to the inconclusive findings in the present systematic review. Few of the studies provided sufficient details on their approach to the data analysis. Two major issues were the use only of correlation, especially Pearson's correlation, and a failure to adjust for relevant covariates. BPA levels generally are not normally distributed in human populations, even after log transformation, which makes Pearson's correlation an inappropriate analysis approach. Very high outliers have the ability to skew associations, particularly in studies with smaller sample sizes. Most studies showed a range that log transformation would not have sufficiently corrected, thus complicating the interpretation of study results.

Additionally, all of the studies included in the systematic review failed to collect data and/or evaluate important potential covariates, such as dietary factors and correlated chemical exposures. Eating greater quantities of food should theoretically lead to greater potential for BPA exposure, but also higher energy intake, and thus increase the risk of being overweight or obese. Additionally, other chemical exposures found in the human environment are also suspected of being endocrine-disrupting obesogens. As an example, diet is also thought to be the primary route of exposure to phthalates<sup>(14,15)</sup>, which are often added to food packaging materials to increase flexibility and resilience<sup>(15,97–100)</sup>. Phthalate exposure has also been associated with increased risk of obesity<sup>(49,101,102)</sup>. Data indicate that most people are exposed to both BPA and phthalates, making it difficult to evaluate the individual effects of BPA without considering associations with phthalates<sup>(103)</sup>. Future studies should consider overall energy intake and correlated chemical exposures when evaluating the association between BPA and body weight/composition.

While cross-sectional studies have important limitations, there are challenges to evaluating the health effects of BPA exposure using other study designs. If biospecimens are

collected as part of a case-control study, the biospecimen collection would occur after the health event of interest has occurred (as the presence or absence of the health effect determines study eligibility) and thus BPA measurements would not reflect long-term exposure or establish the temporality necessary for the determination of causality. In order to optimally address the association between BPA exposure and risk of obesity, new prospective cohort studies are needed in which biospecimens are collected at regular intervals using appropriate procedures and materials to minimize the risk of sample contamination. However, these studies are very expensive, require a large number of study participants for sufficient statistical power and require years of observation time. Many of the existing longitudinal, prospective cohort studies have not collected urine samples, or if they have, the samples are single spot urine samples and/or the samples were not collected using BPA-free materials.

Obesity is a multifactorial health condition and collaboration among obesity researchers from a variety of disciplines (including toxicology, nutrition and epidemiology) is essential. Future research evaluating associations between exposures to obesogenic chemicals, such as BPA, and body composition would benefit from including obesity researchers with expertise in nutrition and physical activity. Studies investigating the association between BPA exposure and changes in body weight or composition must consider the multifactorial nature of obesity and collect and evaluate additional potential confounders or effect modifiers, including dietary intake and concurrent chemical exposures. Reducing the cost of measuring BPA exposure will allow for BPA measurements in large prospective observational studies and for repeated measurements to evaluate longer-term exposure patterns. Research is needed to clarify sources of human BPA exposure and how exposure levels vary over time. This would provide insight for appropriate sample collection and may allow for the development of data collection tools, such as a questionnaire, that could be used to estimate relative BPA exposure in large population-based observational studies. Longitudinal studies that prospectively measure BPA exposures and changes in body weight and composition are needed to establish temporality and causality, and the direction of any observed associations. Finally, improving the accuracy of serum BPA measurements, especially at low levels, will allow researchers to directly test the association between unconjugated BPA levels and body composition and determine if levels of internal exposure are sufficient to adversely affect health.

## Conclusion

Currently available evidence is inconclusive with regard to the association between adult BPA exposure and risk of

being overweight or obese. Significant methodological issues limit the ability to draw firm conclusions from these studies. However, the lack of high-quality research findings does not mean that there are no health effects. The evidence of widespread human exposure to BPA makes it imperative that the health consequences of BPA exposure be fully evaluated.

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