


BMJ Open Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis

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ABSTRACT

Objective Endocrine-disrupting chemicals (EDCs) are viewed as a major potential link between the environment and obesity development. We did a systematic review and meta-analysis to examine the association between exposure to EDCs and obesity.

Data sources, design and eligibility criteria PubMed, Scopus and Web of Science were searched from inception to 6 June 2018 for studies primarily addressing the association between exposure to EDCs after the age of 2 years and anthropometric measures of obesity or body fat. The Newcastle-Ottawa scale was used to assess the risk of bias.

Data extraction and synthesis Two independent reviewers screened and conducted data extraction and synthesis. A third reviewer resolved disagreements.

Results A total of 73 studies investigating bisphenol A (32 286 individuals), organochlorine compounds (34 567 individuals), phthalates (21 401 individuals), polybrominated biphenyls (2937 individuals), polycyclic aromatic hydrocarbons (5174 individuals), parabens (4097 individuals), benzoic acid (3671 individuals) and polyfluoroalkyl substances (349 individuals) met our inclusion criteria. Most had a cross-sectional design and low or medium risk of bias. In qualitative analysis, bisphenol A and phthalates were consistently associated with general and abdominal obesity, in children and adults, and some studies suggested this association was age-dependent and gender-dependent. Meta-analysis indicated a significant association between exposure to bisphenol A and overweight (OR 1.254, 95% CI 1.005 to 1.564), obesity (OR 1.503, 95% CI 1.273 to 1.774) and increased waist circumference (OR 1.503, 95% CI 1.267 to 1.783) in adults, and between exposure to 2,5-dichlorophenol and obesity in children (OR 1.8, 95% CI 1.1018 to 3.184).

Conclusion Most observational studies supported a positive association between obesity and exposure to EDCs. Although causality cannot be determined from these data, they underscore the need to limit human exposure to EDCs in light of the evidence from animal and cell-based studies indicating the effects of these chemicals on adiposity.

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Strengths and limitations of this study

- This systematic review and meta-analysis were conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and used a validated tool for quality assessment of included studies.
- Only human studies primarily addressing the association between exposure to endocrine-disrupting chemicals (EDCs) and obesity were included.
- This systematic review and meta-analysis analysed the association of a broad range of EDCs and measures of generalised and abdominal obesity.
- The meta-analyses were based on a limited number of studies due to the variability in how the measures of association between exposure to EDCs and anthropometric measures of obesity were reported by individual studies.

INTRODUCTION

Obesity is a major worldwide health challenge in multiple perspectives. The physiopathology and clinical impacts of excess body fat (BF) are incompletely understood, and there are many difficulties in developing safe and effective long-term therapeutic strategies.¹ In addition, obesity-related health costs increase at an alarming rate.²

Development of excess weight is the result of a chronic positive energy balance stemming from the complex interaction between genetic, lifestyle, behavioural and environmental factors.³ Data from experimental studies indicate that endocrine-disrupting chemicals (EDCs) influence the development and progression of obesity.⁴ These chemicals, so-called environmental obesogens, are functionally defined by their properties to alter lipid metabolism and inappropriately promote adipogenesis and fat accumulation.⁵ The potential mechanisms underlying their



effects are a major focus of research, and a number of them have been proposed.^{5 6} Obesogens can increase commitment or differentiation of adipocytes from stem cells by activating nuclear receptor signalling pathways that are critical for adipogenesis, such as retinoid X receptor-alpha/peroxisome-proliferator activated receptor gamma^{7 8} and glucocorticoid receptor.⁹ Moreover, obesogens lead to the development of unhealthy adipocytes, with reduced insulin sensitivity and decreased thermogenic capacity.^{10 11} Obesogens may also dysregulate central integration of energy balance and the programming of metabolic setpoints, particularly at critical periods of development, increasing the susceptibility for developing obesity later in life when metabolic homeostasis is challenged by factors such as diet composition and caloric intake.^{12 13} Moreover, exposure to obesogens may lead to a transgenerational thrifty phenotype, possibly caused by changes in chromatin accessibility and organisation.¹²

Several human studies addressed whether exposure to EDCs was associated with obesity. However, their findings were varied. To provide a broad picture of the association between human exposure to different EDCs and obesity, we systematically reviewed human studies addressing the association between exposure to these chemicals outside the prenatal and lactation period and measures of excess body weight or adiposity.

METHODS

Search strategy and selection criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁴

Inclusion criteria were based on the population, exposure, comparison, outcome and study design (PECOS) approach,¹⁵ as follows: (1) population: humans aged over 2 years; (2) exposure: exposure to EDCs assessed by analysis of a biological sample from participants; (3) comparison: participants with higher degrees of exposure versus participants with lower degrees of exposure; (4) outcome: excess weight or adiposity determined by body mass index (BMI), waist circumference (WC) or BF content; and (5) study design: cross-sectional, case-control and cohort studies. We therefore included observational studies addressing the association between exposure to EDCs outside the developmental period and BMI, WC or BF in humans. Studies were excluded if exposure to EDCs was determined by means other than analysis of a biological sample from participants, if exposure was assessed during the prenatal period or lactation, and if a measure of excess weight/adiposity was not considered a primary outcome. Reviews, abstracts, case reports and case series were excluded, in addition to studies addressing the effects of heavy metals, phytoestrogens or the synthetic oestrogen diethylstilbestrol.

PubMed, Scopus and Web of Science were searched from inception to May 3, 2017, and updated on 6 June 6, 2018, with no language restriction, using search terms that were

based on a combination of indexed and free-text terms reflecting the exposure and outcomes of interest to the review, and included the following keywords, which were used in combination to execute the search: “endocrine disrupting, endocrine disruptor, endocrine disrupting chemicals, obesity, overweight, obese, body weight, waist circumference, body mass index, adipogenesis, adipose tissue, adipocyte and obesogenic” (online supplementary appendix A). The reference lists of included articles were also manually searched.

Study selection and data extraction

Study selection was conducted in two phases. In the first phase, three reviewers (BTSB, CMR and NGS) independently screened the titles and abstracts to identify eligible studies according to the PECOS approach. In the second phase, the same two reviewers independently assessed the full-text articles of the eligible studies selected in the first phase. In both phases, disagreements were resolved through discussion, and when there was no consensus, the disagreements were resolved with the participation of a third reviewer (AAA). Data extraction was conducted independently by the same reviewers (BTSB, CMR and NGS) using a predesigned data extraction sheet, with information about sample characteristics, exposure assessment, outcome assessment and risk estimates for relevant comparisons. When necessary to clarify any information, the authors of the included study were contacted by email.

Risk of bias within studies

Risk of bias within studies was assessed using the Newcastle-Ottawa Scale. According to prespecified criteria for risk of bias in sample selection, comparability of subjects in different outcome groups and assessment of outcomes, studies were considered to have a low, medium or high risk of bias (online supplementary appendix B).

Two reviewers independently conducted risk of bias assessment (BTSB and CMR); disagreements were resolved after discussion with a third reviewer (CLL).

Summary measures

The main outcomes assessed in this review were the measures of association between exposure to EDCs and BMI, WC or fat mass.

Meta-analysis

We aggregated the studies into five general groups, according to the type of EDC studied: bisphenol A (BPA), organochlorine (OC) compounds, phthalates (PHTs), brominated compounds (BCs) and other EDCs. Studies assessing OC compounds were further subdivided into those investigating polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), chlorophenol pesticides and triclosan.

The methodological quality of each study was appraised, and sources of heterogeneity, including differences in exposure measurement (eg, categorical vs continuous, any adjustment) and clinical outcome (eg, type

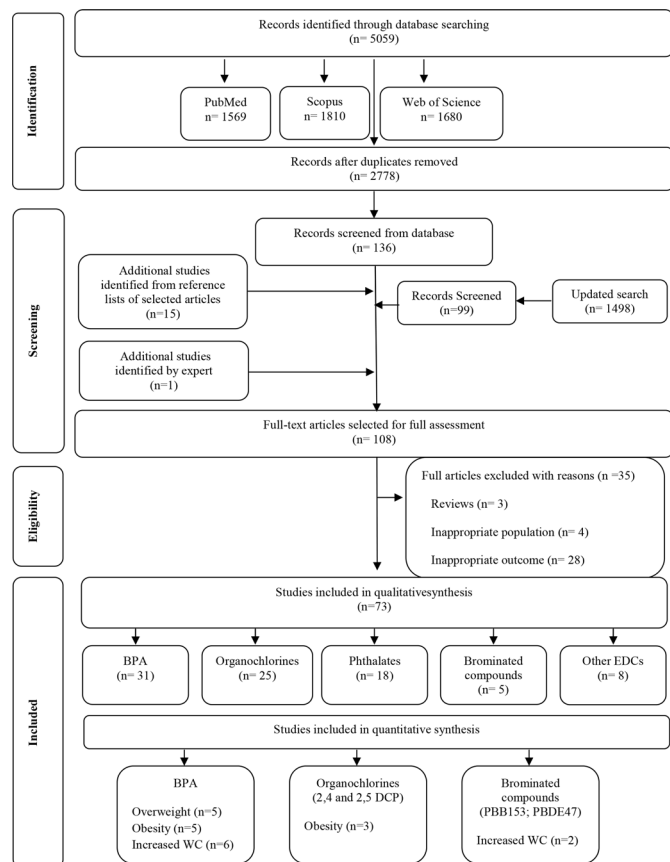


Figure 1 Flow diagram of literature search and selection criteria adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (adapted from Moher *et al*¹⁴). BPA, bisphenol A; DCP, dichlorophenol; EDC, endocrine-disrupting chemical; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; WC: waist circumference.

of anthropometric measure, categorical vs continuous) were identified. For studies with a similar data source, we included only the study with the largest sample size. Meta-analysis was performed when more than a single study per outcome had a similar design, exposure assessment and outcome measures so that we could have a meaningful pooled effect.

As heterogeneity was high among studies reporting continuous outcome data, only three different categorical outcomes were assessed: prevalent overweight, prevalent obesity and prevalent elevated WC. For each exposure (EDC) and outcome, adjusted OR with 95% CIs were extracted and pooled with random-effect model, as we expected some heterogeneity across the studies. Except for BC studies, we considered OR estimates from the highest versus lower EDCs levels. Because the association between exposure to some brominated metabolites and body mass measures in many studies showed an inverted U-shaped relationship, we collected OR estimates from intermediary categories of metabolite levels. Heterogeneity between study results was evaluated with χ^2 test and quantified by I^2 statistic ($I^2 > 75\%$ considered as high heterogeneity).¹⁶ Possible causes of heterogeneity were

explored with additional sensitivity analyses clustering the results by age (children vs adults) or by EDC metabolite/compound. Publication bias was assessed with a funnel plot and by using Egger's regression test (with $p < 0.05$ as an indication of the existence of publication bias). The metan package of STATA V.13.0 software was used for all meta-analysis.

Risk of bias across studies

Clinical heterogeneity of studies was considered by comparing the variability among the participant's characteristics, the assessment of exposure and outcomes. Methodological heterogeneity was assessed by comparing the variability in study design and risk of bias.

Patient and public involvement

No members of the public and patients were directly involved in this study.

RESULTS

A total of 5059 articles were identified; 108 abstracts were selected for full assessment; and 73 studies met our inclusion criteria (figure 1). Thirty studies^{17–46} were conducted in the USA, 17 in Europe,^{47–63} 22 in Asia,^{64–85} 2 in Latin America,^{86 87} 1 in Africa⁸⁸ and 1 in Canada.⁸⁹ In 72 studies, the anthropometric measures of obesity were assessed by trained health professionals, and in one study, weight and height were self-reported.⁷⁷ The qualitative association between exposure to the different EDCs examined and obesity found in these studies is summarised in online supplementary figure 1.

Bisphenol compounds

Thirty-one studies^{17–22 36–40 46–52 63–73 82 86} assessed the association between BPA exposure and obesity (table 1). Three studies^{37 39 71} additionally assessed other bisphenol compounds. Sixteen studies^{18–20 22 36 37 40 46 48 63 65–67 70 71 86} were conducted in children or adolescents, and all but 4^{36 40 46 63} were exclusively cross-sectional. Ten studies^{18–20 22 46 48 63 65 66 86} reported a positive association between exposure to BPA and obesity. In a subgroup analysis based on gender and age, 3 studies^{65 66 86} indicated the association was significant for girls, and 2 of them for girls aged 8–11 years⁶⁵ or 9–12 years.⁶⁶ Moreover, one study²² assessed BF by dual-energy X-ray absorptiometry and found that urinary BPA levels were positively associated with elevated fat mass index in girls but were positively associated with lean body mass in boys. Six studies^{36 37 40 67 70 71} found no association between exposure to BPA and obesity.

Synthesis of data from 3 cross-sectional studies including 5541 children^{20 22 46} indicated that BPA exposure was not significantly associated with prevalent overweight, and synthesis of data from 2 cross-sectional studies including 5230 children^{20 22} indicated that BPA exposure was also not significantly associated with increased WC (figure 2A and table 2).

Table 1 Human studies addressing exposure to BPA and obesity (n=31)

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Carwile <i>et al</i> , 2011 ³⁸	USA	Cross-sectional, 7	To investigate the association between [urinary BPA] and general and central obesity	General adult population, NHANES 2003–2006	Female and male, 18–74 years	2747	Urine BPA (92%) HPLC-MS	BMI, WC	Age, sex, race, education, smoking, urinary creatinine	Higher [urinary BPA] associated with higher BMI and WC
Shankar <i>et al</i> , 2012 ¹⁷	USA	Cross-sectional, 7	To investigate the association between [urinary BPA] and obesity by gender and race/ethnicity	General adult population, NHANES 2003–2008	Female and male, >20 years (mean 44.9±0.4 years)	3967	Urine BPA (NS) HPLC-GC-MS	BMI, WC	Age, gender, race/ethnicity, education, smoking, alcohol intake, physical inactivity, diabetes, hypertension, TC	Positive association between [urinary BPA] and higher BMI and WC, independent of gender and race/ethnicity
Trasande <i>et al</i> , 2012 ¹⁸	USA	Cross-sectional, 7	To investigate the association between [urinary BPA] and body mass outcomes	Children, NHANES 2003–2008	Female and male, 6–19 years	2338	Urine BPA (96.5%) HPLC-MS	BMI (sex-standardised and age-standardised z-score)	Age, sex, race/ethnicity, caregiver education, poverty to income ratio, serum cotinine levels, caloric intake, television watching, urinary creatinine	Significant association between [urinary BPA] and obesity
Wang <i>et al</i> , 2012 ⁶⁴	China	Cross-sectional, 7	To investigate the association between [urinary BPA] and obesity and insulin resistance	General adult population	>40 years	3390	Urine BPA (NS) HPLC-MS	BMI, WC	Age, sex, education, smoking, urinary creatinine, alcohol drinking, systolic blood pressure, HDL-C, LDL-C, TC, TG, hs-CRP, fasting blood glucose and insulin, ALI, GGT	Higher [urinary BPA] associated with higher BMI and WC
Wang <i>et al</i> , 2012 ⁶⁵	China	Cross-sectional, 6	To investigate the association between [urinary BPA] and obesity	Primary and middle school children	Female and male, 8–15 years	259	Urine BPA (84.9%) HPLC-MS	BMI (categories identified according to the Working Group on Obesity in China)	Age, sex, urine specific gravity	Higher [urinary BPA] associated with higher BMI, significant only for girls aged 8–11 years after stratification for age and sex

Continued

Table 1 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Bhandari <i>et al</i> , 2013 ¹⁹	USA	Cross-sectional, 7	To investigate the association between [urinary BPA] and obesity	General paediatric population, NHANES 2003–2008	Female and male, 6–18 years	2664	Urine BPA (NS) HPLC-MS/MS	BMI, OB (BMI > p95)	Age, sex, race/ethnicity, parent/guardian education, urinary creatinine, serum cotinine, moderate physical activity	Higher [urinary BPA] associated with obesity
Eng <i>et al</i> , 2013 ²⁰	USA	Cross-sectional, 7	To investigate the association between [urinary BPA] and measures of adiposity and chronic disease risk factors	General paediatric population, NHANES 2003–2010	Female and male, 6–18 years	3370 (BMI), 2231 (WC), 3321 (WC-to-height), 775 (%BF)	Urine BPA (95.5%) HPLC-MS	BMI categories (OW > p85, OB > p95), WC (> p75 or > p90), WC-to-height (> 0.5), %BF, DXA (> p85, age-adjusted and gender-adjusted)	Age, gender, race/ethnicity, urine creatinine, poverty-to-income ratio, serum cotinine, soda consumption	Higher [urinary BPA] associated with higher odds of obesity (BMI > p95) and abnormal WC-to-height ratio
Li <i>et al</i> , 2013 ⁶⁶	China	Cross-sectional, 6	To investigate the association between [urinary BPA] and overweight/obesity in school-age children	General population of children and adolescents (from a larger national study of pubertal development and health of adolescents)	Female and male, >9 years	1326	Urine BPA (NS) HPLC-fluorescence detection	Weight (OW > p90), BMI, HC, WC, WC-to-height ratio, skinfold thickness	Age, gender, school grade, residence, paternal and maternal education and OW, playing video games, unbalanced diet, junk food consumption, vegetables or fruit consumption, depression scores, sports/activities	Higher [urinary BPA] associated with higher risk of overweight among girls aged 9–12 years, in a dose-dependent fashion

Continued

Table 1 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Harley <i>et al</i> , 2013 ⁴⁶	USA	Cross-sectional, 7, and prospective, 8	To investigate the association between [urinary BPA] anthropometric parameters and prevalent OW/OB in children	Subjects from the CHAMACOS cohort	Male and female, 9 years	311	Urine BPA (NS) HPLC-MS/MS	BMI z-score, BMI categories (OW > p85, OB > p95), WC, BF% (bioimpedance)	Urine-specific gravity, maternal prepregnancy BMI, household income, maternal education level, maternal years of residence in the USA, child's environmental tobacco smoke exposure, soda intake, fast food intake, and sweet consumption at ages 5 and 9 years	[Urinary BPA] at 9 years associated with increased BMI z-score, WC, BF% and prevalent OB/OW at 9 years; [urinary BPA] at 5 years not associated with anthropometric parameters or prevalent OB/OW at 5 or 9 years
Choi <i>et al</i> , 2014 ⁶⁷	South Korea	Cross-sectional, 4	To investigate the association between obesity and POPs	Subjects from a medical college in Seoul	Female, 6–14 years	127 (58 controls, 69 obese)	Urine and serum BPA (NS) GC-MS	BMI (OB > p85)	None	[Serum and urinary BPA] not associated with obesity
Ko <i>et al</i> , 2014 ⁶⁸	South Korea	Cross-sectional, 7	To investigate the association between [urine BPA] and WC	General adult population, from a previous study on integrated exposure to hazardous materials for safety control	Female and male, 44.3±14.6 years	1030	Urine BPA (NS) HPLC-MS	BMI, WC (abdominal OB: > 90 cm for men and > 85 cm for women), %BF*	Age, sex, urinary creatinine (for all outcomes) Age, sex, urinary creatinine, education, income, alcohol consumption, smoking status (for abdominal obesity)	Higher [urinary BPA] associated with higher BMI, WC and BF
Ronn <i>et al</i> , 2014 ⁴⁷	Sweden	Cross-sectional, 6	To investigate the association between [serum BPA] and different indices of obesity	General elderly population	Female and male, 70 years	890 (DXA) and 287 (MRI)	Serum total BPA (98%) isotope liquid chromatography-MS	Fat mass by DXA and MRI	Sex, height, lean mass, smoking, exercise habits, educational level, total daily energy intake, alcohol consumption	[Serum BPA] not associated with fat mass or fat distribution

Continued

Table 1 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Song <i>et al</i> , 2014 ⁴¹	USA	Cross-sectional, 6, and prospective, 8	To investigate the association between [urinary BPA] and prospective weight change during 10-year follow-up	Adult female non-diabetic (control) population from NHS and NHSII	Female, 53–79 years	977	Urine BPA (NS) HPLC-MS	BMI, weight change (kg)	Age, urinary creatinine, cohort origin, menopausal status, smoking, physical activity, alcohol consumption, AHEI and total energy intake	[Urinary BPA] not associated with baseline BMI Higher [urinary BPA] associated with modestly greater weight gain in a dose-dependent fashion
D'Aniello <i>et al</i> , 2015 ⁴⁸	Italy	Cross-sectional, 4	To investigate the association between sleep deprivation/fragmentation, fructose-rich diets and [urinary BPA] and obesity	Children from the teaching hospital and at the local health service outpatient obesity clinics and well-child visits in Salerno	Female and male, 5–16 years	54	Urine total (94.4%) and free BPA (90.7%) GC-MS	BMI (normal p5-p85, OW p85-p95, OB > p95), WC, WC-to-height ratio, WC-to-hip ratio	Urinary creatinine	Higher total and free [urinary BPA] associated with increase in BMI, WC and WC-to-height ratio
Geens <i>et al</i> , 2015 ⁴⁹	Belgium	Cross-sectional, 6	To investigate the association between [urinary BPA] and anthropometric data	OW and obese adults from the Endorup trial (Antwerp University Hospital), lean controls from hospital staff and volunteers	Female and male, >18 years	194	Urine BPA (>99%) GC-MS	BMI, WC	Age, gender, weight loss, urinary creatinine	Higher [urinary BPA] in obese subjects
Lee <i>et al</i> , 2015 ⁴⁹	South Korea	Cross-sectional, 7	To investigate the association between [urinary BPA] and obesity	Participants of the Korean Elderly Environmental Panel study	Female and male, >60 years	558	Urine BPA (NS), average concentration from five samples collected at intervals from 6 to 12 months HPLC-MS	BMI, OW (BMI > 25 kg/m ²)	Age, sex, LDL-C, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine, diabetes	Higher [urinary BPA] significantly associated with OW in elderly women
Milic <i>et al</i> , 2015 ⁵⁰	Serbia	Cross-sectional, 3	To investigate the occurrence of BPA in morning spot urine and the association between [urinary BPA] and obesity	Residents in Novi Sad, Serbia	Female, 19–59 years	145	Urine BPA (29.3%–54.5%) GC-MS	BMI	Urinary creatinine	[Urinary BPA] not associated with OW and OB
Sopon <i>et al</i> , 2015 ⁷⁰	Thailand	Cross-sectional, 5	To investigate exposure of children and adolescents to BPA and the association between [urinary BPA] and obesity	Children and adolescents from two schools in the Patumwan District of Bangkok	Female and male, 3.58–17.17 years	376	Urine BPA (75.3%) HPLC-MS	BMI (OW: z-score > 1.036 or > p85 for age and sex; OB: z-score > 1.64 or > p95 for age and sex)	Urinary creatinine	BPA detection rate significantly higher in obese children, but there was no difference in BPA levels according to BMI category

Continued

Table 1 Continued		Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Authors, year	Country									
Savastano <i>et al</i> , 2015 ⁵¹	Italy	Cross-sectional, 5	To investigate the association between [plasma BPA] and visceral obesity	Adult non-diabetic and Caucasian male, enrolled by routine health survey at the 'Frederico II' University of Naples outpatient facility	Male, 53.5±5.7 years	76	Plasma BPA (NS) ELISA	BMI and WC	Not stated	Increased [plasma BPA] correlated with increased WC
Xue <i>et al</i> , 2015 ⁷¹	India	Cross-sectional, 6	To investigate the association between [urinary POPs] and obesity	Patients from the Endocrinology Outpatient Department of the Amrita Institute of Medical Sciences, Kochi, India	Male and female, 2–14 years	103 (49 OW or obese and 27 normal-weight healthy controls)	Urine BADGE, BADGE.2H2O, TBAFs, BPA, BPS, total BPS (70%–99%) LC-MS	BMI (OW: BMI > p85; OB: BMI > p95)	Age, sex, family income, parent education, physical activity, urinary creatinine	[Urinary bisphenol group compounds] not associated with obesity
Hoepner <i>et al</i> , 2016 ⁴⁰	USA	Cross-sectional, 7, and prospective, 7	To investigate the association between [urinary BPA] at 3 and 5 years, and BMI z-score, FMI, %BF, and WC at 5 and 7 years	Participants from the Columbia Center for Children's Environmental Health New York City birth cohort	Male and female, 3 and 5 years	408	Urine BPA (98%) HPLC-MS/MS	BMI z-score, %BF, FMI, WC	Maternal variables: prepregnancy maternal BMI, race/ethnicity, child variables: sex, birth weight, gestational age at birth, urinary SG, height, (urinary PHT levels)	[Urinary BPA] were not associated with BMI and WC cross-sectionally or prospectively
Vafeiadi <i>et al</i> , 2016 ⁶³	Greece	Cross-sectional, 7, and prospective, 7	To investigate the association between [urinary BPA] at 2.5 and 4.0 years and BMI, WC, skinfold thickness and prevalent obesity at 2.5 and 4.0 years	Subjects from the Rhea Mother-Child Study	Male and female, at 2.5 and 4.0 years	500	Urine BPA (98.8–99.6%) HPLC-EI-MS/MS	BMI, WC, BMI z-score, WC; abdominal obesity (WC > p90), skinfold thickness	Maternal educational level, maternal age, prepregnancy BMI, working status during pregnancy, child sex, z score of birth weight for gestational age and breastfeeding status	[Urinary BPA] at 4 years positively associated with BMI z-score, WC, skinfold thickness and prevalence of obesity [Urinary BPA] at 2.5 years not associated with anthropometric measures at 2.5 years or prevalence of obesity at 4 years

Continued

Table 1 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Hong <i>et al</i> , 2017 ⁷²	South Korea	Cross-sectional, 6	To investigate the association between [urinary EDCs] and insulin resistance and obesity in healthy, reproductive-aged women	Subjects recruited using local advertisement at a community health and service centre and Ewha Womans University Mokdong Hospital outpatient clinic	Female, 30–49 years	296	Urine BPA (NS) HPLC-MS	BMI, WC	Age, smoking, alcohol consumption, TG, TC, HDL-C, urinary creatinine	[Urinary BPA] positively associated with BMI and WC
Li <i>et al</i> , 2017 ²²	USA	Cross-sectional, 6	To investigate the association between [urinary BPA] and body composition	General adult population, NHANES 2003–2006	Male and female, 8–19 years	1860	Urine BPA (NS) HPLC-MS	BF% (DXA)	Age, ethnicity/race, height, caregiver's education, family income to poverty ratio, serum cotinine level, daily calorie intake, television/video watching, computer use, survey year, urinary creatinine	[Urinary BPA] positively associated with lean BMI in boys, and positively associated with elevated FMI in girls. Lower [urinary BPA] associated with lower percentage of trunk fat in girls
Milosevic <i>et al</i> , 2017 ⁵²	Serbia	Cross-sectional, 3	To investigate the association between [urinary BPA] and obesity and abdominal obesity among non-occupationally BPA-exposed women	Residents in the Autonomous Region of Vojvodina, Serbia	Female, 19–50 years	103	Urine BPA (35.9%) GC-MS	BMI, WC, OW/obesity (BMI > 25), WHR, visceral adiposity index	Urinary creatinine	Detectable [urinary BPA] significantly associated with higher WC and WHR. Linear correlation between [urinary BPA] and BMI, WC and WHR among obese women
Hao <i>et al</i> , 2017 ⁷³	China	Cohort, 8	To investigate the association between [urinary BPA] and incident abdominal obesity	Residents in the Songnan Community, Baoshan District, Shanghai, China, free from abdominal obesity at baseline	Male and female, >40 years	888	Urine BPA (NS) HPLC-MS	WC (> 90 cm for men and > 80 cm for women, IDF criteria for Chinese adults) after 4 years	Age, sex, urinary creatinine, BMI, diabetes, smoking, alcohol consumption, education	[Urinary BPA] associated with increased risk of incident abdominal obesity after 4 years

Continued

Table 1 Continued		Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds and method	Outcomes	Adjustment for confounding factors	Main findings
Authors, year	Country									
Deierlein <i>et al.</i> , 2017 ³⁶	USA	Cohort, 9	To investigate the association between [urinary EDCs] and changes in adiposity measurements after 8 years in elementary school-aged girls	Subjects from the puberty cohort studies of the Breast Cancer and Environment Research Program	Female, 6–8 years	1017	Urine BPA (>80%) HPLC-MS	BMI, WC, BF% (bioelectrical impedance analysis)	Age, urinary creatinine, race/ethnicity, site of study, caregiver education, early puberty, baseline weight	[Urinary BPA] not associated with changes in adiposity measurements after 8 years
Kataria <i>et al.</i> , 2017 ³⁷	USA	Cross-sectional, 5	To investigate the association between [urinary bisphenols and PHT] and body mass in children	Children from the General Pediatric Clinic at Bellevue Medical Center	Female and male, 10–13 years	41	Urine BPA, BPS, BPF (NS) HPLC-MS/MS	BMI	Urinary creatinine, gender, age, caloric intake, physical activity	[Urinary bisphenols] not associated with BMI
Yang <i>et al.</i> , 2017 ⁸⁶	Mexico	Cross-sectional, 8	To investigate the association between exposure to BPA and PHTs and obesity	Participants from the 22-year Early Life Exposure in Mexico to Environmental Toxicants cohort	Female and male, 8–14 years	249	Urine BPA (85%) LC-MS/MS	WC, BF (skinfold thickness), BMI z-score	Urine-specific gravity, mother's age, BMI, years of schooling and smoking status, child's age and gender	[Urinary BPA] positively associated with skinfold thickness among girls but not boys
Liu <i>et al.</i> , 2017 ³⁹	USA	Cross-sectional, 7	To investigate the association between [urinary BPA, BPF and BPS] and obesity	General adult population, NHANES 2013–2014	Male and female, >20 years	1521	Urine BPA (94.94%), BPF (65.42%), BPS (90.6%) HPLC-MS/MS	OB and OW defined by BMI, abdominal obesity defined by WC	Age, sex, urinary creatinine, race/ethnicity, education, family income, cigarette smoking, physical activity, total energy intake, BPA, BPF and BPS	[Urinary BPA] associated with general and abdominal obesity
Mouneimne <i>et al.</i> , 2017 ⁸²	Lebanon	Cross-sectional, 5	To investigate the association between [urinary BPA] and metabolic disorders	Residents from the District of the Greater Beirut area, random selection	Male and female, >18 years	501	Urine BPA (89%) HPLC-MS	OB defined by BMI	Gender, education, age, smoking status, physical activity	[Urinary BPA] not associated with obesity

*No description of %BF assessment.

AHEI, Alternative Healthy Eating Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BADGE, bisphenol A diglycidyl ether; BF, body fat; BMI, body mass index; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DR, detection rate; DXA, dual-energy X-ray absorptiometry; EDC, endocrine-disrupting chemical; ELISA, enzyme-linked immunosorbent assay; FMI, fat mass index; GC-MS, gas chromatography–mass spectrometry; GGT, gamma-glutamyl transferase; HA, hypothalamic amenorrhea; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HPLC-El-MS/MS, high performance liquid chromatography/mass spectrometry; HPLC-MS, high performance liquid chromatography–mass spectrometry; HPLC-MS/MS, high performance liquid chromatography–mass spectrometry; hs-CRP, high-sensitivity C reactive protein; IDF, International Diabetes Federation; LC-MS, liquid chromatography–mass spectrometry; LC-MS/MS, isotope dilution–liquid chromatography–tandem mass spectrometry; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSH, Nurses' Health Study II; NS, not stated; OB, obesity; OW, overweight; PCOS, polycystic ovary syndrome; PHT, phthalate; POP, persistent organic pollutant; SG, specific gravity; TBAFs, tetrabutylammonium fluorides; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-to-hip ratio.

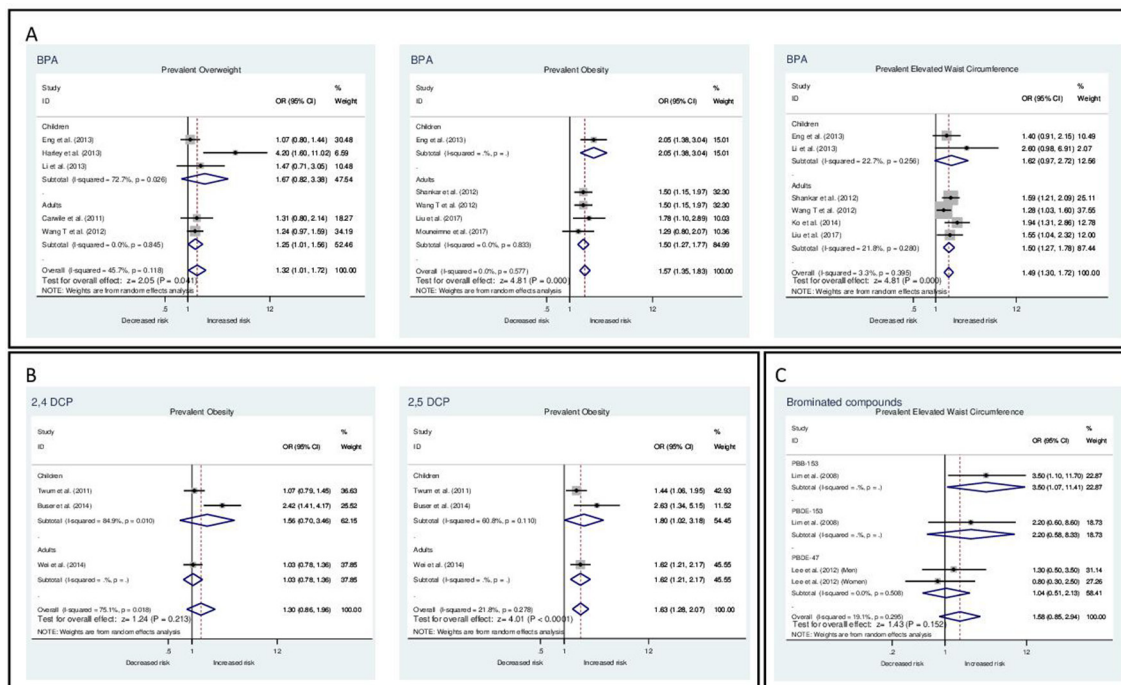


Figure 2 Association between exposure to bisphenol A, 2,4-dichlorophenol, 2,5-dichlorophenol and brominated compounds and anthropometric measures of obesity.

Among 15 studies involving adult participants, 12 studies^{17 21 38 39 49 51 52 64 68 69 72 73} found a positive association between exposure to BPA and obesity. Two of these studies were prospective; one of them²¹ reported that higher urinary levels of BPA were modestly associated with greater weight gain in women, whereas the other⁷³ indicated that BPA exposure was positively associated with incident abdominal obesity in men and women.

Synthesis of data from 2 cross-sectional studies including 3006 adults^{38 64} indicated that BPA exposure was significantly associated with prevalent overweight, with a summary OR of 1.25 (figure 2A and table 2). Synthesis of data from 4 cross-sectional studies including 6248 adults^{17 39 64 82} indicated that BPA exposure was significantly associated with prevalent obesity, with a summary OR of 1.50 (figure 2A and table 2). Moreover, synthesis of data from 4 cross-sectional studies including 6777 adults^{17 39 64 68} indicated a significant association between BPA exposure and increased WC, with a summary OR of 1.50 (figure 2A and table 2).

OC compounds

Twenty-five studies^{23–27 36 42–45 49 53–56 60–62 71 74 80 81 87–89} investigated the association between OC compounds and obesity (table 3). Most obtained data from population-based surveys or other epidemiological studies. Among 12 studies involving children and adolescents,^{23 25 26 36 42 44 53 56 62 71 74 81} 6 reported positive association^{23 25 26 36 53 81}; 4 reported no association^{42 56 71 74}; and 4 reported negative association^{23 44 53 62} between exposure to specific OC compounds and obesity. Sixteen studies included adults; 11 reported positive association^{23 24 27 43 45 53–55 60 61 80}; 4 reported no association^{49 87–89};

and 7 reported negative association^{23 44 45 53–55 60} between OC compounds and measures of increased weight or adiposity. Three studies additionally indicated that the association was age^{26 45 53} or gender^{26 53 55} dependent. Of note, 5 studies^{24 36 55 56 74} had a prospective design. Two of them reported positive association between exposure to OCPs and prospective increases in BMI²⁴ and WC⁵⁵ in adults. One study involving children reported a positive association between exposure to OCPs and prospective changes in adiposity measures in girls aged 6–8 years,³⁶ whereas 2 studies^{56 74} involving children found no association between exposure to OCPs or PCBs and prospective changes in BMI^{56 74} or WC.⁵⁶

The individual OC compounds that were examined varied among the studies, and most assessed more than one compound. However, the association between specific OC compounds and obesity in children and adults was overall inconclusive. Pooled data from 2 studies assessing exposure to 2,4-dichlorophenol (DCP) in childhood^{25 26} and one in adults²⁷ indicated no association with obesity (table 2). Data from 2 studies assessing exposure to 2,5-DCP in childhood^{25 26} indicated a significant association with obesity (figure 2B and table 2).

Phthalates

Eighteen studies^{21 28–31 37 41 57–59 67 72 75 76 83–86} examined the association between exposure to PHTs and obesity (table 4). Seven studies^{30 37 41 67 75 76 86} were conducted in children, 10 in adults^{21 28 31 57–59 72 83–85} and one in both children and adults.²⁹ An overall positive association between exposure to PHTs and measures of excess weight or adiposity was found; only 4 studies

**Table 2** Pooled estimates for the association between BPA, DCP or BC exposure and prevalent OW, OB and abdominal OB defined by WC; random-effect models

EDC	Outcome	Studies (n)	Pooled OR (95% CI)	Heterogeneity					Significance tests of ES=1
				Tau ²	χ ²	Df	I ²	P value	
BPA									
Prevalent OW (subgrouped by age)									
	Overall	5	1.321 (1.012 to 1.724)	0.0382	7.36	4	45.7%	0.118	z=2.05 (p=0.041)
	Children	3	1.666 (0.821 to 3.382)	0.2774	7.32	2	72.7%	0.026	z=1.41 (p=0.157)
	Adults	2	1.254 (1.005 to 1.564)	0.0000	0.04	1	0.0%	0.845	z=2.01 (p=0.045)
Prevalent OB (adults only)									
	Overall	4	1.503 (1.273 to 1.774)	0.0000	0.87	3	0.0%	0.833	z=4.81 (p=0.000)
Prevalent increased WC (subgrouped by age)									
	Overall	6	1.494 (1.298 to 1.720)	0.0011	5.17	5	3.3%	0.395	z=5.59 (p=0.000)
	Children	2	1.623 (0.968 to 2.723)	0.0434	1.29	1	22.7%	0.256	z=1.83 (p=0.067)
	Adults	4	1.503 (1.267 to 1.783)	0.0068	3.84	3	21.8%	0.280	z=4.68 (p=0.000)
2,4-DCP									
Prevalent OB									
	Overall	3	1.299 (0.860 to 1.961)	0.0966	8.04	2	75.1%	0.018	z=1.24 (p=0.213)
	Children	2	1.558 (0.702 to 3.458)	0.2828	6.63	1	84.9%	0.010	z=1.09 (p=0.276)
	Adults	1	1.030 (0.780 to 1.360)	0.0000	0.00	0	–	–	z=0.21 (p=0.835)
2,5-DCP									
Prevalent OB									
	Overall	3	1.629 (1.283 to 2.066)	0.0102	2.56	2	21.8%	0.278	z=4.01 (p=0.000)
	Children	2	1.800 (1.018 to 3.184)	0.1103	2.55	1	60.8%	0.110	z=2.02 (p=0.043)
	Adults	1	1.620 (1.210 to 2.169)	0.0000	0.00	0	–	–	z=3.24 (p=0.001)
BC									
Prevalent elevated WC (subgrouped by BC compound)									
	Overall	4	1.576 (0.846 to 2.938)	0.0778	3.71	3	19.1%	0.295	z=1.43 (p=0.152)
	PBB-153	1	3.500 (1.073 to 11.415)	0.0000	0.00	0	–	–	z=2.08 (p=0.038)
	PBDE-153	1	2.200 (0.581 to 8.329)	0.0000	0.00	0	–	–	z=1.16 (p=0.246)
	PBDE-47	2 (Wm; M)	1.041 (0.508 to 2.132)	0.0000	0.44	1	0.0%	0.508	z=0.11 (p=0.912)

BC, brominated compound; BPA, bisphenol A; DCP, dichlorophenol; df, degree of freedom; EDC, endocrine-disrupting chemical; ES, estimate effect; M, men; OB, obesity; OW, overweight; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; WC, waist circumference; Wm, women.

reported inverse associations,^{29 31 59 86} and 2 reported no association.

Exposure to PHTs was assessed by determining urinary^{21 28–31 37 41 58 59 67 72 75 76 83–86} or serum^{57 67 84} levels of PHT metabolites in all studies. The exact set of metabolites varied among studies. Likewise, the specific PHT metabolites associated with measures of obesity also varied. Of note, 6 studies involving both male and female

children and/or adults reported age-dependent and gender-dependent associations between urinary concentrations of PHT metabolites and measures of excess body weight.^{29 30 57 59 85 86}

Other EDCs

Five studies^{24 32 33 55 60} investigated the association between polybrominated biphenyl (PBB) and obesity

Table 3 Human studies addressing exposure to OC compounds and obesity (n = 25)

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Hue <i>et al</i> , 2007 ⁴⁵	Canada	Cross-sectional, 5	To investigate the association between [plasma OC compounds] and obesity	NS	Male and female, steady body weight, control (n=16), obese (n=19), morbidly obese (n=18)	53	Plasma 14 PCBs (28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) (NS) 11 chlorinated pesticides (β-HCH, HCB, p,p'-DDE, trans-nonachlor, oxychlorodane, cis-nonachlor, aldrin, α-chlorodane, γ-chlorodane) (NS) p,p'-DDT (7.5%) mirex (22.4%) GC-MS	BMI	Age	[Total plasma OC compounds] not correlated with BMI
Dhooge <i>et al</i> , 2010 ⁴³	Belgium	Cross-sectional, 6	To investigate the association between exposure to pollutants and body size	Selection from a stratified clustered multistage design, as a random sample of adolescents and adults residing in the study area	Male and female, 14–15 years and 50–65 years	1679 adolescents, 1583 adults	Serum PCB 118, 138, 153, 180, HCB, p,p'-DDE, CALUX analysis of the dioxin fraction of dioxin-like activity in plasma (NS) GC-ECD	BMI	Adolescents: blood lipids, age, height of father and mother, smoking, sexual maturation (Tanner), food intake. Adults: blood lipids, age, smoking, food intake	[Serum HCB, sum PCB 118, 153, 180] negatively associated with BMI, and [PCB118] positively associated with BMI in adolescents [Serum sum PCB 138, 153, 180] negatively associated with BMI, and [serum HCB, p,p'-DDE and PCB118, dioxin fraction] positively associated with BMI in adult men [Sum PCB138, 153, 180] negatively associated with BMI, and [HCB, p,p'-DDE and PCB118] positively associated with BMI in adult women
Elobeid <i>et al</i> , 2010 ²³	USA	Cross-sectional, 5	To investigate the association between [serum OC compounds] and BMI/WC	General population, NHANES 1999–2002	Male and female, 6 years to > 40 years	2464	Serum HpCDD, OcDD, oxychlorodane, trans-nonachlor, p,p'-DDT (NS) GC-MS	BMI, WC	Serum TC and TG	[Serum p,p'-DDT] positively associated with WC in all subjects [Serum oxychlorodane and HpCDD] positively associated with WC in subjects with detectable levels of these compounds [Serum OcDD] increased with higher WC and BMI [Serum trans-nonachlor] decreased with higher BMI

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Dirinck <i>et al</i> , 2011 ⁵⁴	Belgium	Cross-sectional, 4	To investigate the association between [serum OC compounds] and BMI, WC, fat mass and HOMA-IR	Outpatients from the weight management clinic of the Department of Endocrinology, Diabetology and Metabolism of the Antwerp University Hospital (obese); hospital staff and volunteers (normal-weight controls)	Male and female, 21–60 years (median 40 years)	144	Serum PCB (153, 138, 180, 170, sum PCB), pp-DDE, b-HCH (NS) GC-MS	BMI, WC, FM (total abdominal, visceral abdominal, subcutaneous abdominal), FM%	None	[Serum PCB 153, 180, 180, sum PCB] negatively correlated with BMI, WC, FM%, total and subcutaneous abdominal adipose tissue [Serum b-HCH] positively correlated with BMI, WC, FM%, and total and subcutaneous abdominal adipose tissue
Lee <i>et al</i> , 2011 ²⁴	USA	Cohort, 7	To investigate the association between [serum OC compounds] and adiposity, dyslipidaemia, and insulin resistance over 18 years	Non-diabetic controls from the Coronary Artery Risk Development in Young Adults study	Male and female, 18–30 years at baseline (27.2±3.3 years)	90	Serum 9°C pesticides (44%–100%), 35 PCB congeners (7%–100%) GC/ID-HRMS	BMI	Age, sex, race, TG, TC, HDL-C, HOMA-IR, baseline BMI	[Serum p,p'-DDE] and PCBs with ≥ 7 chlorines predicted higher BMI after 18 years (inverted U-shaped curve across quartiles)
Twum <i>et al</i> , 2011 ²⁵	USA	Cross-sectional, 6	To investigate the association between [urinary OC compounds] and obesity	General population, NHANES 2003–2004, NHANES 2005–2006	Male and female, 6–19 years	6770	Urine 2,4-DCP (92%), 2,5-DCP (99%), ortho-phenylphenol (<40%) HPLC-MS	BMI, obesity (BMI > p95 for sex and age)	Age, gender, race, income, total fat intake	[Urinary 2,5-DCP] associated with childhood obesity
Lee <i>et al</i> , 2012 ⁵⁵	Sweden	Cross-sectional, 6, and prospective, 7	To investigate the association between [plasma POPs] and prevalent abdominal obesity, cross-sectionally and prospectively	Participants from the Prospective Investigation of the Vasculature in Uppsala Seniors	Male and female, 70 years (at baseline)	970 (cross-sectional) 511 (prospective)	Plasma 17 PCB (98.7%–100%) 5°C pesticides (p,p'-DDE, trans-nonachlor, HCB, chlordanes, cis-chlordane) (3.4–100%) HRGC-HRMS	WC, abdominal obesity (WC > 102 cm for men and > 88 cm for women)	Total calorie intake, exercise, smoking, alcohol consumption, TG, TC	[Plasma less chlorinated PCBs, p,p'-DDE and dioxin] associated with abdominal obesity (inverted U-shape relation, particularly in women) [Plasma highly chlorinated PCB] inversely associated with abdominal obesity Similar but weaker associations between [plasma POPs] and development of abdominal obesity after 5 years
Arrebolia <i>et al</i> , 2012 ⁵⁷	Bolivia	Cross-sectional, 3	To describe [serum and adipose tissue OC compounds] in an urban adult population from Bolivia and its association with demographic characteristics	Subjects undergoing non-cancer-related surgery at a general hospital in Santa Cruz de la Sierra	Male and female, >16 years (31.4±12.6 years)	112	Serum and adipose tissue p,p'-DDT (50%), p,p'-DDE (93%), HCB (21%), PCB congeners 138,153,180 (56%–80%) GC-ECD	BMI	None	[Serum and adipose tissue OC compounds] not correlated with BMI

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Ben <i>et al.</i> , 2013 ⁸⁸	Tunisia	Cross-sectional, 4	To describe [serum OC compounds] in the general population of Bizerte, Tunisia, and investigate its association with age, gender and BMI	Subjects visiting the Regional Hospital of Bizerte, in Tunisia	Male and female, >18 years, not pregnant and without critical or heart disease	113	Serum HCB, p,p'-DDE, PCB 153, PCB 180 (100%) Dieldrin, heptachlor, PCB 18, 28, 31, 52, 44 (0%) b-HCH, lindane, p,p'-DDD, p,p'-DDT, PCB congeners 101, 149, 118, 138, 194 (1.7%–95.6%) GC-MS	BMI	Serum lipids	[Serum OCPs and PCB congeners 153, 138, 180 and sum PCB] not associated with BMI
Lankester <i>et al.</i> , 2013 ⁴³	USA	Cross-sectional, 7	To investigate the association between [urinary TCS] and BMI	General population, NHANES 2003–2003	Male and female, >20 years	4037	Urine TCS (75%) HPLC-MS/MS	BMI	Survey year, sex, age, race, poverty index ratio, urinary BPA, urinary cotinine	[Urinary TCS] positively associated with increased BMI
Roos <i>et al.</i> , 2013 ⁶⁰	Sweden	Cross-sectional, 6	To investigate the association between [plasma OC compounds] and abdominal obesity	Subjects aged 70 years randomly chosen from the register of community living from Uppsala, Sweden	Male and female, 70 years	1016	Plasma 16 PCBs, p,p'-DDE, HCB, TNC (>95.5%); O ₆ DD (80.6%); cis-chlordane, trans-chlordane (<10%) HRGC-HRMS	BMI, VAT/SAT ratio (determined by MRI)	Gender, education, exercise habits, smoking	[Plasma less chlorinated PCBs, p,p'-DDE, HCB, TNC] positively associated with both VAT and SAT [Plasma highly chlorinated PCBs] inversely related to both VAT and SAT [Plasma PCB189] correlated with VAT/SAT ratio in an inverted U-shaped manner
Buser <i>et al.</i> , 2014 ²⁶	USA	Cross-sectional, 7	To investigate the association between [urinary POP] and BMI z-score, WC and obesity	General adult population, NHANES 2007–2008 and 2009–2010	Male and female, 6–19 years (mean 12.56±0.1 years)	1298	Urine 2,5-DCP (98.5%), 2,4-DCP (90%), TCS (79%) HRGC-HRMS	BMI z-score, WC, overweight (BMI p85–p95), obesity (BMI > p95)	Age, sex, race/ethnicity, calorie intake, television and video game and computer usage (6–11 years), physical activity (12–19 years), serum cotinine, poverty income ratio, urinary creatinine	[Urinary 2,4-DCP, 2,5-DCP] positively associated with BMI z-score, WC and obesity. After stratification for age, the associations remained significant only in adolescents.
Wei <i>et al.</i> , 2014 ²⁷	USA	Cross-sectional, 7	To investigate the association between [urinary POP] and obesity	General adult population, NHANES 2005–2006, NHANES 2007–2008	Male and female, 20–85 years	2931	Urine 2,4-DCP (92.6%), 2,5-DCP (99%) HPLC-MS	BMI, obesity (BMI ≥ 30 kg/m ²), non-obese (< 30 kg/m ²)	Age, gender, race, income, education, total fat intake, physical activity, urinary creatinine	[Urinary 2,5-DCP] positively associated with obesity
Li <i>et al.</i> , 2015 ⁴⁴	USA	Cross-sectional, 6	To investigate the association between [urinary TCS] and obesity traits	General adult population, NHANES 2003–2010	Female and male, children (6–19 years) and adults (>20 years)	2898 children 2066 adults	Urine TCS (77%–79%) ID-HPLC-MS/MS	BMI and WC	Race/ethnicity, socioeconomic status, serum cotinine, (urinary BPA)	[Urinary TCS] inversely associated with BMI and WC in children and adults

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Zong <i>et al</i> , 2015 ⁴⁵	USA	Cross-sectional, 7	To investigate the association between [serum OC compounds] and body fat	General adult population, NHAES 1999–2004	Female and male, >20 years	2358	Serum p,p'-DDE, p,p'-DDT, b-HCH, HxCDD, OcDD, HpCDF, PCB (126, 138, 153, 169, 170, 180, 187, 194, 196, 199) (30%–69%) HRGC-HRMS	FM% (DXA)	Serum lipids, gender, age, ethnicity, education, physical activity, smoking status, alcohol consumption, history of parity and lactation	[Serum b-HCH, HpCDF, OcDD, PCB128] positively associated with trunk FM% (correlations stronger in subjects >40 years); [serum PCB 138, 153, 169, 170, 180, 187, 194, 196] inversely correlated with FM%
Tang-Péronard <i>et al</i> , 2015 ⁴⁶	Denmark	Cohort, 7	To investigate the association between [serum POP] at 8–10 years of age and changes in measures of obesity at 14–16 years and 20–22 years	Children from the European Youth Heart Study, Danish component	Male and female, 8–10 years at baseline	392	Serum PCB sum (PCB 138, 153, 180), p,p'-DDE, HCB (NS) GC	BMI z-score, WC, %BF	Baseline obesity, breast feeding, maternal educational level, maternal smoking, maternal BMI, pubertal status, physical fitness (maximal work test), dietary intake	[Serum POP] not associated with subsequent changes in measures of obesity
Geens <i>et al</i> , 2015 ⁴⁹	Belgium	Cross-sectional, 6	To investigate the association between [urinary TCS] and anthropometric data and serum thyroid hormones, to evaluate the dynamics of [urinary TCS] during 1 year of weight loss, to estimate daily TCS intake and investigate daily intake differences during weight loss and to evaluate variations in exposure sources according to treatment method for weight loss (bariatric surgery/diet)	OW and obese adults from the Endorup trial (Antwerp University Hospital); lean controls from hospital staff and volunteers	Female and male, >18 years	194	Urine TCS (>90%) HPLC-MS	BMI, WC	Age, gender, weight loss, urinary creatinine	No difference between [urinary TCS] in obese and lean subjects at baseline No significant change of [urinary TCS] during weight loss
Xue <i>et al</i> , 2015 ⁷¹	India	Cross-sectional, 6	To investigate the association between [urinary POPs] and obesity	Endocrinology Outpatient Department of the Amrita Institute of Medical Sciences, Kochi, India	Male and female, 2–14 years	103 (49 OW or obese and 27 normal-weight healthy controls)	Urine TCS (100%) LC-MS	BMI (OW defined by BMI > p85 and obesity defined by BMI > p95)	Age, sex, family income, parent education, physical activity, urinary creatinine	(Urinary TCS) not associated with obesity

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Lee <i>et al</i> , 2016 ³⁴	South Korea	Cohort, 8	To investigate the association between [serum OC compounds] and prospective change of metabolic components of metabolic syndrome	Subjects from the Ewha Birth & Growth Cohort study	Female and male, 7–9 years	214 (158 completed follow-up)	Serum PCB (52, 101, 118, 138, 153, 156, 180), marker PCB (sum 28, 52, 101, 138, 153, 180), dioxin-like PCB (sum 77, 81, 114, 105, 126, 123, 156, 157, 169, 167, 189), nonachlor, HCB, b-HCH, p,p'-DDT, p,p'-DDE (61.68%–99.53%) PCB (1, 3, 4, 15, 19, 28, 37, 77, 81, 104, 105, 114, 123, 126, 155, 157, 167, 169, 188, 189, 202, 205, 206, 208), oxychlorodane, chlordan, heptachlor, heptachlor epoxide, a-HCH, g-HCH, d-HCH, o, p'-DDT, p,p'-DDD, o,p'-DDD, o,p'-DDE (NS) GC-MS	BMI, BMI z-score	Gender, age, monthly household income, baseline BMI, serum lipids	No association between (serum OC compounds) and change in BMI after 1 year
Deierlein <i>et al</i> , 2017 ³⁶	USA	Cohort, 9	To investigate the association between [urinary EDCs] and changes in adiposity measurements after 8 years, in elementary-school-aged girls	Subjects from the puberty cohort studies of the Breast Cancer and Environment Research Programme	Female, 6–8 years	1017	Urine 2,5-DCP (>80%) TCS (>80%) HPLC-MS	BMI, WC, BF% (bioelectrical impedance analysis)	Age, urinary creatinine, race/ethnicity, site of study, caregiver education, early puberty, baseline weight	(Urinary 2,5-DCP and TCS) associated with increase in adiposity measurements after 8 years
Harmouche <i>et al</i> , 2017 ⁸⁰	Lebanon	Cross-sectional, 6	To investigate serum levels of six indicator PCBs and differences in PCBs levels by gender, age and BMI	Students and employees of Saint Joseph University	Female and male, 17–65 years	316	Serum PCB 28, 52, 101, 138, 153, 180 (50%–60%) GC-ECD	BMI, BF% (bioelectrical impedance analyser)	Total serum lipids, age, gender, smoking status, dairy product, fish and shellfish consumption	(Serum sum PCB) associated with OW and OB in and inverted-U shaped manner

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Henriquez-Hernandez <i>et al</i> , 2017 ⁸¹	Spain	Cross-sectional, 4	To investigate the association between exposure to POPs and OB and type two diabetes	Subjects from the Canary Islands Nutrition Survey	Female and male, > 18 years	429	Serum p,p'-DDT (<50%), DDE (<50%), DDD (<50%), p,p'-DDE (85.8%), p,p'-DDD (<50%), aldrin (64.1%), dieldrin (<50%), endrin (68.3%), HCH α (88.1%), HCH β (<50%), HCH δ (<50%), HCH γ (55.7%) PCBs 153 (77.2%), 180 (85.1%), 28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180, 189 (<50%) GC-ECD (OCPs), GC-MS (PCBs)	BMI, waist-to-hip ratio	None	(Serum p,p'-DDE) higher among OW and OB subjects
Karlisen <i>et al</i> , 2017 ⁸²	Denmark	Cross-sectional, 6	To investigate the association between [POPs] and obesity	Subjects from the National Hospital of the Farol Islands	Female and male, 5 years	349	Serum PCB 138, 153, 180 (100%), HCB (100%), p,p'DDE (100%) GC-ECD	BMI z-score, OW (> p85)	Serum lipids, maternal nationality, age at delivery, prepregnancy BMI, smoking during pregnancy, child's gender, exclusive breastfeeding duration, child's fish intake at age 5 years	(Serum OC compounds) inversely associated with BMI z-score
Parastar <i>et al</i> , 2017 ⁸¹	Iran	Cross-sectional, 2	To investigate the association between [urinary pesticides] and obesity in children and adolescents	Selection from households in different areas of Isfahan, Iran	Male and female, 6–18 years	242	Urine 2,4-DCP (94.6%), 2,5-DCP (95%), 2,4,5-TCP (85.1%), 2,4,6-TCP (38%) GC-MS	BMI, BMI z-score, WC	Urinary creatinine, physical activity, fasting blood sugar, blood pressure, TC, HDL-C, LDL-C	[Urinary 2,5-DCP] positively associated with BMI z-score and WC; [urinary 2,4,5-TCP] positively associated with WC; [urinary 2,5-DCP] associated with obesity

Continued

Table 3 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Kalloo <i>et al</i> , 2018 ⁴²	USA	Cross-sectional, 8, and prospective, 8	To investigate the association between [urinary TCS] and adiposity in children	Participants from the Health Outcomes and Measures of the Environment Study, Cincinnati	Male and female, <8 years	218	Urine TCS (NS) HPLC-MS/MS	BMI, WC, %BF	Maternal variables: race, age, education, marital status, household income, age at delivery, BMI, prenatal vitamin use, delivery method, breast feeding, parity, gestational diabetes, hypertensive disorders, urinary cotinine Child variables: age, screen time, diet, physical activity	No association between [urinary TCS] at the ages of 1–5 and 8 and measures of adiposity at the age of 8 years

AT, adipose tissue; BF, body fat; BMI, body mass index; BPA, bisphenol A; CALLUX, chemical activated luciferase gene expression; DCP, dichlorodiphenylchloroethane; DDE, dichlorodiphenylchloroethylene; DDT, dichlorodiphenyltrichloroethane; DR, detection rate; DXA, dual-energy X-ray absorptiometry; EDC, endocrine disrupting chemical; FM, fat mass; GC-ECD, gas chromatography–electron capture detector; GC-ID/HMPS, gas chromatography–isotope dilution/high-resolution mass spectrometer; GC-MS, gas chromatography–mass spectrometry; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; HpCDD, heptachlorodibenzo-p-dioxin; HpCDF, heptachlorodibenzofuran; HPLC-MS, high-performance liquid chromatography–mass spectrometry; HPLC-MS/MS, high-performance liquid chromatography–tandem mass spectrometry; HRGC-HRMS, high-resolution gas chromatography–high-resolution mass spectrometry; HxCDD, hexachlorodibenzo-p-dioxin; HxCDF, hexachlorodibenzofuran; ID-HPLC-MS/MS, isotope dilution–high-performance liquid chromatography–tandem mass spectrometry; LC-MS, liquid chromatography–mass spectrometry; LDL-C, low density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; NS, not stated; OB, obesity; OC, organochlorine, OcDD, octachlorodibenzo-p-dioxin; OCP, organochlorine pesticide; OW, overweight; PCB, polychlorinated biphenyl; PeCDF, pentachlorodibenzofuran; POPs, persistent organic pollutant; SAT, subcutaneous adipose tissue; TC, total cholesterol; TCF, trichlorophenol; TCS, triclosan; TG, triglyceride; TNC, transnonachlorodane; VAT, visceral adipose tissue; W, weight; WC, waist circumference.

Table 4 Human studies addressing exposure to PHTs and obesity (N=18)^{72 83}

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Stahlhut <i>et al</i> , 2007 ²⁸	USA	Cross-sectional, 4	To investigate the association between [urinary PHTs] and abdominal obesity and insulin resistance	General population, NHANES 1999–2002	Male, >18 years	1443	Urine PHT metabolites MBP, MEP, MBzP, MEHP, MEOHP, MEHP (>80%), MNP (25%) HPLC-MS	WC	Age, race/ethnicity, family history of diabetes, dietary fat and caloric intake, physical activity, income, renal function, hepatic function, exposure to tobacco	MBzP, MEHHP, MEOHP and MEP positively associated with increased WC
Hatch <i>et al</i> , 2008 ²⁹	USA	Cross-sectional, 5	To investigate the association between [urinary PHT metabolites] and BMI and WC	General population, NHANES 1999–2002	Male and female, 6–80 years	4836	Urine MEP, MEHP, MBzP, MBP, MEHHP, MEOHP (>80%), MCP, MNP, MOP (<80%) HPLC-MS	BMI, WC	Age, gender, urinary creatinine, height, diet variables, physical activity, race/ethnicity, education, family income, education level, smoking, alcohol consumption, menopausal status, parity, TV/video/computer use	Urinary MBzP] positively associated with BMI and WC in men aged 20–59 years [Urinary MEP] positively associated with BMI and WC in adolescent girls [Urinary MEHP] inversely associated with BMI in adolescent girls and women aged 20–59 years
Lind <i>et al</i> , 2012 ⁵⁷	Sweden	Cohort, 7	To investigate the association between [serum PHT monoester] and measures of adiposity after 2 years	Subjects from the Prospective Investigation of the Vasculature in Uppsala Seniors	Male and female, 70 years	1016	Serum MEP, MIBP, MIBP, MIBP (>96%) LC-MS/MS	Fat mass (DXA and MRI)	Serum TC and TG, education, exercise, smoking	[Serum MIBP] positively associated with WC, total FM, trunk FM, SAT after 2 years in women [MMP] positively associated with trunk fat mass and trunk:leg ratio after 2 years in women
Teitelbaum <i>et al</i> , 2012 ³⁰	USA	Cohort, 7	To investigate the association between [urinary PHT metabolites] and BMI and WC in children	Children from the Growing Up Healthy prospective cohort study	Male and female, 6–8 years	387	Urine MBzP, MIBP, MEOHP, MECPP, MEHP (>97%), HPLC-MS	BMI, BMI after 1 year of PHT exposure measurement	Age at baseline, sex, hours of sedentary activity, day of week for reported sedentary activity, MET hours, total caloric intake, race, ethnicity, family income, parental education	[Urinary MEP] and [urinary sum of low molecular-weight PHTs] positively associated with BMI and WC in overweight girls after 1 year

Continued

Table 4 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Wang <i>et al</i> , 2013 ⁵	China	Cross-sectional, 6	To investigate the association between [urinary PHT metabolites] and BMI and WC in school children	Obese, OW and normal weight (20:10:30) children selected from primary and middle schools in Shanghai, China	Male and female, 8–15 years	259	Urine MEHP, MEOHP, MECPP, MEHHP, MBP, MIBP, MEP, MCMHP, MHBP, MMP, MCHP (≥94.6%) MBzP (38.6%) MINP, MOP (0%) Sum MBP, MHBP, MIBP, MMP, MEP Sum MEHP, MECPP, MEHHP, MEOHP, MCMHP, MCHP, MBzP, RPULC-ESI-MS/MS	BMI, WC, normal weight, OW and OB defined according to age and sex-specific criterion (Working Group on Obesity in China)	Age, sex, urine PHT metabolites, urine specific gravity	MEHP and MEP positively associated with BMI and WC
Choi <i>et al</i> , 2014 ⁶⁷	South Korea	Cross-sectional, 4	To investigate the association between exposure to POPs and obesity	Participants recruited among subjects from a medical college in Seoul	Female, 6–14 years	127 (58 controls, 69 obese)	Urine and serum MEP, DBP, DEHP, MEHP, PA, MBzP (NS) GC-MS	BMI (OB defined by BMI > p85)	None	MEP, DBP and PA positively associated with obesity
Song <i>et al</i> , 2014 ²¹	USA	Cross-sectional, 6, and cohort, 8	To investigate the association between [urinary PHT metabolites] and weight change after 10 years	Adult female non-diabetic (control) population from NHS and NHSII	Female, 53–79 years	977	Urine PA, MEP, MBzP, Sum of butyl PHTs, DEHP metabolites, total PHTs (NS) HPLC-MS	BMI, weight change (kg)	Urinary creatinine, cohort origin, age, menopausal status, smoking, physical activity, alcohol consumption, AHEI and total energy intake	Higher [PHT metabolites] associated with modestly greater weight gain in a dose-dependent fashion
Hou <i>et al</i> , 2015 ⁶	Taiwan	Cross-sectional, 8	To investigate the association between [urinary PHTs] and obesity and pubertal maturity among adolescents	Children and adolescents selected from primary schools in Taipei, Taiwan	Male and female, 6.5–15 years	270	Urine DEHP metabolites (MEHP (78.1%), MEOHP, MEHHP, MECPP (≥99.6%)) LMW PHT metabolites (MMP, MEP, MIBP, MnBP (≥94.8%)) HMW PHT (DEHP metabolites, MBzP (NS)) UPLC-MS/MS	BMI, WC, WHR, skin fold thickness, OB defined by BMI (criteria from Taiwan's Health Promotion Administration and by the Ministry of Health and Welfare)	Age, gender, urinary creatinine	[Urinary PHT metabolites] positively associated with abdominal obesity (assessed by skinfold thickness, WC and WHR), in a dose-response manner

Continued

Table 4 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Medic <i>et al</i> , 2015 ³³	Serbia	Cross-sectional, 5	To investigate the association between [urinary DHEP and DEP] and BMI, WC, plasma lipids and lipoproteins	Volunteers randomly recruited during physical examinations at the Institute of Occupational Medicine of Novi Sad, Serbia	Female, 18–55 years	103	Urine MEP (24.3%) and MEHP (16.5%) GC-MS	BMI, WC	None	[Urinary MEHP] positively associated with WC
Petrovicova <i>et al</i> , 2016 ³⁹	Slovakia	Cross-sectional, 6	To investigate the association between [urinary PHTs], occupation, consumer practices and body composition	Occupationally exposed subjects and non-occupationally exposed from the general population of the Nitra Region in Slovakia	Female and male, >18 years	129 (45 occupational exposed subjects, >82.2%) 35 workers from plastic industry, 49 from the general population)	Urine MEHHP, MEOHP, MEHP, MiBP, MnBP (>82.2%) Sum DEHP HPLC-MS	BMI, WC, FMI, FFMI, HC, WHR, WHHR, WC > 102 cm (male) or > 88 cm (female)	Gender, occupational exposure	[Urinary MEHP] inversely related to WHR, BMI, WHR, HC and WC, and positively related to FFMI among women but not men
Yaghiyan <i>et al</i> , 2016 ³¹	USA	Cross-sectional, 6	To investigate the association between [urinary PHTs] and individual characteristics, including BMI	General population, NHANES 2001–2012	Female and male, > 18 years (non-obese, non-pregnant, and non-diabetic)	6653	Urine DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP), %MEHP (ratio of MEHP to sum of secondary metabolites) (NS) HPLC-MS	BMI, OW (BMI 25.0–29.9)	Age, gender, race, smoking, alcohol use, cancer history, daily caffeine consumption, prescription medication, menopausal status, postmenopausal hormone use	[Urinary MEHP:MEHHP] and [urinary %MEHP] inversely associated with the presence of overweight
Hong <i>et al</i> , 2017 ²	Korea	Cross-sectional, 6	To investigate the association between exposure to EDCs and insulin resistance and obesity in healthy, reproductive-aged women	Women recruited from the community health and service centre and Ewha Womans University Mokdong Outpatient Clinic	Female, 30–49 years	296	Urine MEHHP, MEOHP, MnBP (NS) HPLC-MS	BMI, WC	Age, urinary creatinine, smoking and alcohol status, TG, TC, HDL-C	[Urinary PHTs] not associated with BMI and WC
Kataria <i>et al</i> , 2017 ³⁷	USA	Cross-sectional, 5	To investigate the association between [urinary bisphenols and PHTs] and body mass in children	Children from the General Paediatric Clinic at Bellevue Medical Centre	Female and male, 10–13 years	41	Urine MMP, MEP, MBP, MiBP, MBzP, MCHP, MOP, MCP, MIDP, MNP, MNP, MIDP, MCOP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MHpP (NS) HPLC-MS/MS	BMI	Urinary creatinine, gender, age, caloric intake, physical activity	[Urinary high molecular weight PHT metabolites] positively associated with BMI

Continued

Table 4 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Yang <i>et al</i> , 2017 ⁸⁶	Mexico	Cross-sectional, 8	To investigate the association between exposure to BPA and PHTs and obesity	Participants from the 22-year Early Life Exposure in Mexico to Environmental Toxicants cohort	Female and male, 8–14 years	249	Urine MEP, MBP, MCPP, MIBP, MBzP, MEHP, MEHHP, MEOHP, MECPP (94%–100%) LC-MS/MS	WC, BF (skinfold thickness), BMI z-score	Urine-specific gravity, mother's age, BMI, years of schooling and smoking status, child's age and gender	[Urinary MEHP] positively associated with WC and skinfold thickness. [Urinary MEH] inversely associated with skinfold thickness among boys
Oktar <i>et al</i> , 2017 ⁸⁴	Turkey	Cross-sectional, 1	To investigate the association between [serum and urinary PHTs] and obesity	Patients from the research hospital of Mustafa Kemal University	Male and female, 17–62 years	196	Serum and urine DMP, DEP, DBP, DPP, BBP, DEHP, DOP, GC	BMI, WC	None	[Urinary and serum PHTs] positively associated with BMI and WC
Dong <i>et al</i> , 2017 ⁸⁵	China	Cross-sectional, 5	To investigate the association between [urinary PHT metabolites] and obesity	Participants from the Shanghai Food Consumption Survey 2012	Male and female, >18 years	2330	Urine MMP, MEP, MnBP, MIBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, MCMHP LC-MS/MS	OB and OW defined by BMI, abdominal obesity (\leq 85 cm for men and \geq 80 cm for women)	OB: age, gender, education, marriage, smoking, total caloric intake Abdominal obesity: age, marriage, education, smoking status, BMI, total caloric intake, and total fat intake.	[Urinary MMP, MEHHP, MECPP] associated with abdominal obesity; the association was stronger among young females
Lee <i>et al</i> , 2017 ⁸³	South Korea	Cross-sectional, 6	To investigate the association between [urinary PHTs] and demographic characteristics	Subjects randomly recruited from the population of the Korean National Human Biomonitoring Survey	Male and female, 18–69 years	1870	Urine MnBP, MIBP, MBzP, MCHP, MnOP, MEHP, MEOHP, MEHHP, MINP, MIDP HPLC-MS	OB and OW defined by BMI	Urinary creatinine	[Urinary PHT metabolites] not associated with OB or OW

Continued

Table 4 Continued

Authors, year	Country	Study design, quality	Study objective	Source population	Sex and age	Sample size	Sample, compounds (DR) and method	Outcomes	Adjustment for confounding factors	Main findings
Shoaff <i>et al</i> , 2017 ⁴¹	USA	Cohort, 8	To investigate the association between [urinary PHTs] and measures of adiposity in children	Participants from the Health Outcomes and Measures of the Environment	Male and female, 1 years	219	Urine MEP, MnBP, MiBP; MCPP, MBzP, MEHP, MEHHP, MEOHP, MECPP SumDEHP HPLC-MS/MS Measurements conducted six times, from 1 to 8 years	BMI, WC, %BF at the age of 8 years	Urinary creatinine, maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy BMI, food security, prenatal fruit/vegetable and fish consumption, prenatal vitamin use, child sex, and child age at the 8-year visit	[Urinary MBzP] inversely associated with adiposity; [urinary sum DEHP] at 1 and 5 years associated with decrease and increase in adiposity at 8 years, respectively; [urinary MEP] at 5 and 8 years associated with higher adiposity at 8 years

AHEI, Alternative Healthy Eating Index; BBP, benzyl phthalate; BF, body fat; BMI, body mass index; BPA, bisphenol A; DBP, dibutyl phthalate; DEHP, diethylhexyl-phthalate; DEP, diethyl phthalate; DMP, dimethyl phthalate; DOP, dioctyl phthalate; DPP, dipentyl phthalate; DR, detection rate; DXA, dual-energy X-ray absorptiometry; EDC, endocrine disrupting chemical; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GC-MS, gas chromatography-mass spectrometry; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HMW, high-molecular-weight; HPLC-MS, high-performance liquid chromatography-mass spectrometry; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LMW, low-molecular-weight; MBP, monobutylphthalate; MBzP, monobenzyl phthalate; MCHP, mono-cyclohexyl phthalate; MCMHP, mono(2-carboxymethylhexyl) phthalate; MCOP, monocarboxyisooctyl phthalate; MCP, mono-cyclohexyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, monoethylhexyl phthalic acid; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MET, metabolic equivalent; MHBP, mono-3-hydroxybutyl phthalate; MHP, mono-2-heptyl phthalate; MHP, mono-hexylphthalate; MiBP, mono-isobutyl phthalate; MIDP, mono-8-methyl-1-nonyl-phthalate; MINP, mono-isononyl phthalate; MMP, mono-methyl phthalate; MnBP, mono-n-butyl phthalate; MnOP, mono-n-octyl phthalate; MNP, mono-isononyl phthalate; MOP, mono-n-octyl phthalate; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NS, not stated; OB, obesity; OW, overweight; PA, phthalic acid; PHT, phthalate; POPs, persistent organic pollutant; RPULC-ESI-MS/MS, reversed-phase ultra-performance liquid chromatography-electrospray ionisation-tandem MS; SAT, subcutaneous adipose tissue; TC, total cholesterol; TG, triglycerides; UPLC-MS/MS, ultra-performance liquid chromatography-tandem mass spectrometry; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

(online supplementary table 1). Four studies^{24 32 55 60} were conducted in adults and found no association between exposure to PBB and obesity. Only one study³³ was conducted in children and found an inverse relation between exposure to PBB and BMI z-score. Pooled data from 2 studies^{32 55} indicated that exposure to PBBs was not significantly associated with abdominal obesity (figure 2C and table 2).

Two studies^{34 35} examining the association between polycyclic aromatic hydrocarbons and obesity (online supplementary table 2) were conducted in children and found that exposure to these EDCs was positively associated to obesity, defined on the basis of anthropometric measures.

The association between exposure to parabens and obesity was investigated in 3 studies^{36 71 77} (online supplementary table 2). Xue *et al*⁷¹ reported a positive association between urinary paraben levels and obesity in children, whereas Kang *et al*⁷⁷ studied children and adults and described that urinary parabens levels were positively associated with BMI in adults but not in children. Deierlein *et al*³⁶ found no association between exposure to parabens and prospective changes in adiposity measures among girls. The only study investigating benzoic acid⁷⁸ (online supplementary table 2) described that in adults low urinary 3-PBA levels were positively associated with obesity, whereas high levels were negatively associated.⁷⁸ One study investigated exposure to perfluorinated alkylated substances and reported no association with obesity measures in children⁶² (online supplementary table 2).

Quality Assessment

Quality assessment using the Newcastle-Ottawa Scale indicated that 65% of cross-sectional studies and all prospective studies had low or medium risk of bias (figure 3 and online supplementary table 3). For the studies included in the meta-analysis, no significant publication bias was detected using Egger's regression test or by visual inspection of the funnel plots (online supplementary figure 2), although the small number of studies limited the reliability

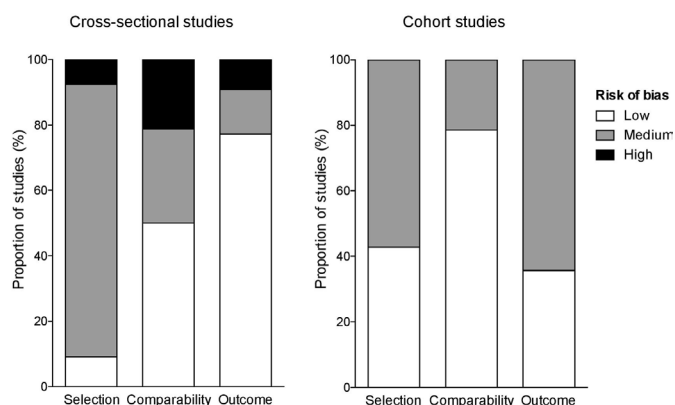


Figure 3 Quality assessment using the Newcastle-Ottawa scale for risk of bias of studies included in the systematic review.

of the tests. Online supplementary table 4 presents the reasons for excluding studies from the meta-analysis.

DISCUSSION

This systematic review of observational studies supports a positive association between exposure to BPA and PHTs and obesity in adults and children outside the early developmental period (aged 2 years or more). Although these data do not establish causation, in light of the evidence from animal and cell-based studies indicating the obesogenic effects of EDCs,⁴ they reinforce the need for continuing discussion on regulation of human exposure to these compounds.

Six previous systematic reviews addressed the association between exposure to EDCs, either during or outside the developmental period, and increased body weight or other measures of adiposity. Three reviews examined specifically BPA; two were inconclusive (including 20⁹⁰ and 18⁹¹ studies), and one indicated a positive association in both children and adults (including 16 studies).⁹² One review summarised preclinical and clinical data on exposure to BPA or PHTs and reported positive associations (including 25 studies),⁹³ whereas two assessed a broad range of EDCs and also reported positive associations (including 24⁹⁴ and 35⁹⁵ studies).

In contrast to the previous reviews, we used a detailed search strategy with no language restriction, and only studies that defined either generalised or regional obesity as a primary outcome were included. Since adiposity, determined by either anthropometric measures or BF quantification, is a multifactor trait, we viewed this would strengthen our findings. Accordingly, most studies were considered to have a low or medium risk of bias with respect to ascertainment of outcome. In addition, we comprehensively summarised data from a total of 73 studies involving bisphenol compounds, OC compounds, PHTs, PBB, polycyclic aromatic hydrocarbons (PAH), parabens, polyfluoroalkyl substances and benzoic acid.

The studies varied in the number of participants, although there did not appear to be a relationship between the number of participants and whether or not an association between exposure to EDCs and obesity was found. They also varied with respect to the precise method to determine serum or urinary levels of EDCs, the confounders for which the results were adjusted and data analysis. We could therefore not accomplish meta-analysis of all data to present overall estimates of the magnitude of the association between EDCs and obesity. However, data from few studies assessing the association between exposure to BPA, dichlorophenols or brominated compounds and measures of adiposity were pooled. Quantitative synthesis of these data revealed a significant positive association between exposure to BPA and overweight, general and central obesity, and between exposure to 2,5-DCP and obesity.

Most studies assessed exposure to BPA by using robust analytical methods to determine its urinary levels,



although only few studies provided detailed information to rule out contamination during sample handling. Urinary BPA levels are considered a more appropriate indicator of exposure when compared with serum/plasma levels.⁹⁶ Circulating BPA is rapidly metabolised into hydrophilic compounds that are conjugated and excreted in urine. This results in several-fold higher urinary BPA metabolites levels than circulating BPA levels.⁹⁶ In addition, conjugated BPA (representing most of urinary total BPA) is not found in extraneous sources, minimising the risk of misleading results due to sample contamination.⁹⁷

A potential concern is that assessment of BPA exposure on the basis of a single urinary and/or serum measurement, as was the case of almost all the included studies, may not be an adequate approach to investigate health outcomes. This is because there may be temporal variability of exposure to BPA, and adverse health effects most likely reflect long-term exposure. Pollack *et al*⁹⁸ reported significant variation of urinary BPA levels over a 2-month period in women of reproductive age. On the other hand, data from other studies suggested that measurement in a single sample was predictive of exposure over 3 months.^{49 99} Moreover, due to its rapid metabolism and excretion, urinary levels of total BPA¹⁰⁰ may not be representative of biologically active BPA, with the potential to affect health. Despite these limitations, it is noteworthy that investigations included in this review were conducted on different populations, and most of them pointed to a positive association between exposure to BPA and body size. Moreover, our meta-analysis of cross-sectional data indicated that exposure to BPA was significantly associated with overweight, general and abdominal obesity in adults.

Studies examining exposure to OC compounds in children and adults indicated an overall positive association with obesity; only data from studies assessing 2,4-DCP and 2,5-DCP exposure were pooled in the meta-analysis and indicated a significant association between exposure to 2,5-DCP and obesity. Many studies investigated more than one compound, but the number of studies examining each specific compound was small, leading to inconclusive findings with respect to the association between specific OC compounds and measures of body weight or fat. In adults, the most frequently studied OC compounds were PCBs and OCPs. The number of participants varied considerably between studies, ranging from 53 to 2931, and larger studies (involving more than 1000 participants) more consistently reported negative associations between highly chlorinated PCBs and obesity^{53–55 60} and positive associations between less chlorinated PCBs^{24 53 55 60 101} and the pesticide p,p'-dichlorodiphenyldichloroethylene with obesity.^{24 53 55 60}

It is noteworthy that some studies reported no association between exposure to specific less chlorinated PCBs and obesity,^{24 88 89 101} whereas a similar number of studies indicated positive associations, mostly with a non-linear dose–response association.^{24 55 60 101} Exposure to specific highly chlorinated PCBs was negatively associated with

obesity in four studies,^{53–55 60} not associated in three studies^{60 88 89} and positively associated in one study.⁵³ This apparent inconsistency in the direction of the associations may be related to the different concentration ranges for these EDCs found in each study, as has been previously discussed.⁵⁵ Accordingly, PCB levels were lower in participants from studies that found no association between exposure to these EDCs and obesity.^{88 89} Therefore, the direction of the associations and also specific features of dose–response association may at least in part reflect the level of exposure of a specific population to these compounds.

Findings from studies investigating exposure to PHTs suggested an overall positive association with obesity, defined by BMI and/or WC, in children/adolescents^{29 30 67 75 76} and adults.^{21 28 29 57 58} Exposure to specific PHT chemicals appeared to be associated with obesity in an age-dependent manner and, although less consistently, in a gender-dependent manner. This was the case of diethyl phthalate (assessed by the urinary levels of its metabolite, monoethyl phthalate), which was positively associated with obesity in all studies involving children/adolescents,^{29 30 67 75 76} but not in adults,^{29 57 58} and which in some studies was associated with obesity only among girls.^{29 30} The possibility of an age-dependent and gender-dependent effect of PHTs is essentially speculative, but has been discussed in the light of its well-established estrogenic¹⁰² and antiandrogenic effects,¹⁰³ which may differently affect male and female subjects at different stages of life. This may also reflect other effects of PHTs that possibly vary in different physiological settings, such as inhibition of thyroid hormone action.¹⁰⁴

Similarly to BPA, PHTs are rapidly metabolised and excreted, and exposure to PHT sources may vary considerably over time.¹⁰⁵ Therefore, a single measurement of PHT metabolites may not reflect long-term exposure to these compounds. However, it was shown that a single measure moderately predicts exposure over some months,^{105 106} with moderate to high sensitivity to allocate individuals into higher ranges of exposures.¹⁰⁶ Another point that deserves discussion is that PHT urinary levels were corrected for variation in urinary dilution differently among the studies, and the best approach for this is still a matter of discussion.¹⁰⁶

There were only five studies^{24 32 33 55 60} addressing the association between exposure to PBBs and obesity, and most reported no association. Too few studies examined PAHs,^{34 35} parabens^{71 77} and pyrethroids.⁷⁸

The association between exposure to some EDCs and obesity raises the question about the potential action of these chemicals as risk factors for obesity-related complications, such as type 2 diabetes and cardiovascular diseases. Because EDCs are lipophilic, they are stored in adipose tissue.¹⁰⁷ Adipose tissue, in turn, is affected in complex ways by EDCs and can also be a source of these chemicals to other key sites of metabolic homeostasis regulation in the setting of uncontrolled lipolysis or intentional weight loss.¹⁰⁸ The direct actions of EDCs

in adipose tissue, in particular, make their relationship to obesity-related complications a complex one. This is because EDCs stored in adipose tissue may act to increase or decrease the risk of these complications. These chemicals may increase the risk of these complications by inducing adipose tissue inflammation independently of obesity or by being released to other tissues and affecting them unfavourably. However, in the scenario where there is no uncontrolled lipolysis, the adipose tissue represents a safe storage site for EDCs, protecting other tissues from their potentially harmful effects.¹⁰⁸

The cross-sectional design of most studies precluded determining causality between exposure to EDCs and obesity. Only a few studies had a prospective design, and notably most supported an association between exposure to EDCs and weight and/or WC increase among adults^{21 24 55 57 73} and children.³⁰ It is also not possible to rule out reverse causality. Since most EDCs are highly lipophilic and stored in adipose tissue, higher levels of these compounds may reflect that obesity is associated with their accumulation. Moreover, it has been argued that obesity or its associated complications could lead to delayed metabolism of EDCs, extending their half-lives and leading to higher levels in serum or urine.¹⁰⁹ It is also possible that obese individuals may be more exposed to EDCs by consuming more food or medications, since exposure to EDCs such as BPA, OC compounds and PHTs may occur by oral ingestion.^{110 111}

Additionally, there is the limitation of testing the association between exposure to specific EDCs and obesity in human studies due to the potential confounders beyond the ones that were controlled for in data analysis. Despite adjusting results for various confounding factors, most studies did not consider potential exposure to multiple EDCs itself. Although this could limit establishing an association between a specific EDC and obesity, in a practical view, this may not be important, since humans are exposed to various EDCs simultaneously in the environment. Moreover, although speculative, it has been argued on the basis of data from cell-based studies¹¹² that the effect of exposure to individual EDCs may be low, but combination exposure may have significant effects.²⁸ On the other hand, it has also been discussed that simultaneous exposure to different EDCs may not simply result in additive effects of single exposure, since these compounds may act differently or even oppositely.^{29 113}

It is also not possible to rule out that the associations between exposure to EDCs and measures of obesity outside the early developmental period examined in this review reflect in fact early life exposure, which may permanently alter gene expression patterns that affect metabolic processes.⁴ Although the circulating half-lives of EDCs are short, current measures of exposure may reflect ongoing exposure since early life, at least for some compounds with still widespread environmental occurrence.

Another methodological limitation was related to meta-analysis conduction. Despite the large number of studies included in this systematic review, only data from a limited

number of them were suitable for quantitative synthesis. Different types of summary effects were first designed, considering both BMI/WC as categorical or continuous variables. However, with multiple exposure metrics and several outcome measures available, heterogeneity among the studies was considerable and precluded their inclusion in the quantitative synthesis.

Finally, the findings from this meta-analysis must be interpreted carefully considering the risk of publication bias. Although we performed funnel plots and Egger's weighted regression to explore the presence of publication bias across studies, these methods are limited when fewer than 10 studies are included in meta-analysis.¹¹⁴ Without reliable graphical evidence or statistical testing, we may suspect of publication bias by using qualitative parameters, such as an inadequate search strategy, and the inclusion of only small studies, mainly with funding from the pharmaceutical industry. However, we used a sensitive and specific search strategy and conducted a comprehensive literature review that enabled the retrieval of relevant published articles, which could decrease the chance of publication bias. However, it cannot be completely ruled out.

CONCLUSION

The findings from the current review indicate a significant association between exposure to BPA and overweight, general and abdominal obesity in adults, and between exposure to 2,5-DCP and obesity in children but are insufficient to support that these EDCs cause obesity in humans due to the cross-sectional design of most included studies. However, given (1) the qualitative similarity of most data from human studies included in this review; (2) the evidence that exposure to BPA,¹¹⁵ OC compounds¹¹⁶ and PHTs¹¹⁷ induces obesity in animals; and (3) the findings from cell-based and in vitro studies indicating that EDCs affect various physiological pathways that may lead to weight gain,⁵ the data from human studies summarised herein should be viewed as evidence of the potential hazards of exposure to EDCs. This is particularly important in the current worldwide scenario of ongoing exposure of children and adults to EDCs, not only to chemicals still used for a wide range of purposes but also to compounds that were banned in many countries but have persistent and ubiquitous occurrence in the environment.

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REFERENCES

- Heymsfield SB, Wadden TA, Mechanisms WTA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med Overseas Ed* 2017;376:254–66.
- Withrow D, Alter DA. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. *Obes Rev* 2011;12:131–41.
- Bouret S, Levin BE, Ozanne SE. Gene-Environment interactions controlling energy and glucose homeostasis and the developmental origins of obesity. *Physiol Rev* 2015;95:47–82.
- Gore AC, Chappell VA, Fenton SE, et al. EDC-2: the endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev* 2015;36:E1–150.
- Grün F, Blumberg B. Endocrine disruptors as obesogens. *Mol Cell Endocrinol* 2009;304:19–29.
- Nadal A, Quesada I, Tuduri E, et al. Endocrine-Disrupting chemicals and the regulation of energy balance. *Nat Rev Endocrinol* 2017;13:536–46.
- Li X, Pham HT, Janesick AS, et al. Triflumizole is an obesogen in mice that acts through peroxisome proliferator activated receptor gamma (PPAR γ). *Environ Health Perspect* 2012;120:1720–6.
- Kanayama T, Kobayashi N, Mamiya S, et al. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. *Mol Pharmacol* 2005;67:766–74.
- Regnier SM, Kirkley AG, Ye H, et al. Dietary exposure to the endocrine disruptor tolylfuaniid promotes global metabolic dysfunction in male mice. *Endocrinology* 2015;156:896–910.
- Regnier SM, El-Hashani N, Kamau W, et al. Tributyltin differentially promotes development of a phenotypically distinct adipocyte. *Obesity* 2015;23:1864–71.
- Shoucri BM, Hung VT, Chamorro-Garcia R, et al. Retinoid X receptor activation during adipogenesis of female mesenchymal stem cells programs a dysfunctional adipocyte. *Endocrinology* 2018;159:2863–83.
- Chamorro-Garcia R, Diaz-Castillo C, Shoucri BM, et al. Ancestral perinatal obesogen exposure results in a transgenerational thrifty phenotype in mice. *Nat Commun* 2012.
- Liu G, Dhana K, Furtado JD, et al. Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: a prospective study. *PLoS Med* 2018;15:e1002502.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
- Morgan RL, Whaley P, Thayer KA, et al. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int* 2018;121:1027–31.
- Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- Shankar A, Teppala S, Sabanayagam C. Urinary bisphenol A levels and measures of obesity: results from the National health and nutrition examination survey 2003–2008. *ISRN Endocrinol* 2012;2012:1–6.
- Trasande L, Attina TM, Blustein J. Association between urinary bisphenol a concentration and obesity prevalence in children and adolescents. *JAMA* 2012;308:1113–21.
- Bhandari R, Xiao J, Shankar A. Urinary bisphenol A and obesity in U.S. children. *Am J Epidemiol* 2013;177:1263–70.
- Eng DS, Lee JM, Gebremariam A, et al. Bisphenol A and chronic disease risk factors in US children. *Pediatrics* 2013;132:e637–45.
- Song Y, Hauser R, Hu FB, et al. Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women. *Int J Obes* 2014;38:1532–7.
- Li J, Lai H, Chen S, et al. Gender differences in the associations between urinary bisphenol A and body composition among American children: The National Health and Nutrition Examination Survey, 2003–2006. *J Epidemiol* 2017;27:228–34.
- Elobeid MA, Padilla MA, Brock DW, et al. Endocrine disruptors and obesity: an examination of selected persistent organic pollutants in the NHANES 1999–2002 data. *Int J Environ Res Public Health* 2010;7:2988–3005.
- Lee D-H, Steffes MW, Sjödin A, et al. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. *PLoS One* 2011;6:e15977.
- Twum C, Wei Y. The association between urinary concentrations of dichlorophenol pesticides and obesity in children. *Rev Environ Health* 2011;26:215–9.
- Buser MC, Murray HE, Scinicariello F. Association of urinary phenols with increased body weight measures and obesity in children and adolescents. *J Pediatr* 2014;165:744–9.
- Wei Y, Zhu J, Nguyen A. Urinary concentrations of dichlorophenol pesticides and obesity among adult participants in the U.S. National health and nutrition examination survey (NHANES) 2005–2008. *Int J Hyg Environ Health* 2014;217:294–9.
- Stahlhut RW, van Wijngaarden E, Dye TD, et al. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. *Environ Health Perspect* 2007;115:876–82.
- Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002. *Environ Health* 2008;7:27.
- Teitelbaum SL, Mervish N, Moshier EL, et al. Associations between phthalate metabolite urinary concentrations and body size measures in New York City children. *Environ Res* 2012;112:186–93.
- Yaghjian L, Carlsson NP, Ghita GL, et al. Associations of individual characteristics and lifestyle factors with metabolism of di-2-ethylhexyl phthalate in NHANES 2001–2012. *Environ Res* 2016;149:23–31.
- Lim J-S, Lee D-H, Jacobs DR. Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003–2004. *Diabetes Care* 2008;31:1802–7.
- Erkin-Cakmak A, Harley KG, Chevrier J, et al. In utero and childhood polybrominated diphenyl ether exposures and body mass at age 7 years: the CHAMACOS study. *Environ Health Perspect* 2015;123:636–42.
- Kim H-W, Kam S, Lee D-H. Synergistic interaction between polycyclic aromatic hydrocarbons and environmental tobacco smoke on the risk of obesity in children and adolescents: the U.S. National health and nutrition examination survey 2003–2008. *Environ Res* 2014;135:354–60.
- Scinicariello F, Buser MC. Urinary polycyclic aromatic hydrocarbons and childhood obesity: NHANES (2001–2006). *Environ Health Perspect* 2014;122:299–303.
- Deierlein AL, Wolff MS, Pajak A, et al. Phenol concentrations during childhood and subsequent measures of adiposity among young girls. *Am J Epidemiol* 2017;186:581–92.
- Kataria A, Levine D, Wertenteil S, et al. Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children. *Pediatr Res* 2017;81:857–64.
- Carwile JL, Michels KB. Urinary bisphenol A and obesity: NHANES 2003–2006. *Environ Res* 2011;111:825–30.
- Liu B, Lehmler H-J, Sun Y, et al. Bisphenol A substitutes and obesity in US adults: analysis of a population-based, cross-sectional study. *Lancet Planet Health* 2017;1:e114–22.
- Hoepner LA, Whyatt RM, Widen EM, et al. Bisphenol A and adiposity in an inner-city birth cohort. *Environ Health Perspect* 2016;124:1644–50.
- Shoaff J, Papandonatos GD, Calafat AM, et al. Early-Life phthalate exposure and adiposity at 8 years of age. *Environ Health Perspect* 2017;125:097008.
- Kaloo G, Calafat AM, Chen A, et al. Early life Triclosan exposure and child adiposity at 8 Years of age: a prospective cohort study. *Environ Health* 2018;17:24.
- Lankester J, Patel C, Cullen MR, et al. Urinary triclosan is associated with elevated body mass index in NHANES. *PLoS One* 2013;8:e80057.
- Li S, Zhao J, Wang G, et al. Urinary triclosan concentrations are inversely associated with body mass index and waist circumference in the US general population: experience in NHANES 2003–2010. *Int J Hyg Environ Health* 2015;218:401–6.

- 45 Zong G, Grandjean P, Wu H, *et al.* Circulating persistent organic pollutants and body fat distribution: evidence from NHANES 1999-2004. *Obesity* 2015;23:1903-10.
- 46 Harley KG, Aguilar Schall R, Chevrier J, *et al.* Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. *Environ Health Perspect* 2013;121:514-20.
- 47 Rönn M, Lind L, Örborg J, *et al.* Bisphenol A is related to circulating levels of adiponectin, leptin and ghrelin, but not to fat mass or fat distribution in humans. *Chemosphere* 2014;112:42-8.
- 48 D'Aniello R, Troisi J, D'Amico O, D'Amico O, *et al.* Emerging pathomechanisms involved in obesity. *J Pediatr Gastroenterol Nutr* 2015;60:113-9.
- 49 Geens T, Dirtu AC, Dirinck E, *et al.* Daily intake of bisphenol A and triclosan and their association with anthropometric data, thyroid hormones and weight loss in overweight and obese individuals. *Environ Int* 2015;76:98-105.
- 50 Milić N, Četojević-Simin D, Milanović M, *et al.* Estimation of in vivo and in vitro exposure to bisphenol A as food contaminant. *Food Chem Toxicol* 2015;83:268-74.
- 51 Savastano S, Tarantino G, D'Esposito V, *et al.* Bisphenol-A plasma levels are related to inflammatory markers, visceral obesity and insulin-resistance: a cross-sectional study on adult male population. *J Transl Med* 2015;13:169.
- 52 Milošević N, Jakšić V, Sudji J, *et al.* Possible influence of the environmental pollutant bisphenol A on the cardiometabolic risk factors. *Int J Environ Health Res* 2017;27:11-26.
- 53 Dhooze W, Den Hond E, Koppen G, *et al.* Internal exposure to pollutants and body size in Flemish adolescents and adults: associations and dose-response relationships. *Environ Int* 2010;36:330-7.
- 54 Dirinck E, Jorens PG, Covaci A, *et al.* Obesity and persistent organic pollutants: possible obesogenic effect of organochlorine pesticides and polychlorinated biphenyls. *Obesity* 2011;19:709-14.
- 55 Lee D-H, Lind L, Jacobs DR, *et al.* Associations of persistent organic pollutants with abdominal obesity in the elderly: the prospective investigation of the vasculature in Uppsala seniors (PIVUS) study. *Environ Int* 2012;40:170-8.
- 56 Tang-Péronard JL, Jensen TK, Andersen HR, *et al.* Associations between exposure to persistent organic pollutants in childhood and overweight up to 12 years later in a low exposed Danish population. *Obes Facts* 2015;8:282-92.
- 57 Lind PM, Roos V, Rönn M, *et al.* Serum concentrations of phthalate metabolites are related to abdominal fat distribution two years later in elderly women. *Environ Health* 2012;11:21.
- 58 Medic Stojanoska M, Milankov A, Vukovic B, *et al.* Do diethyl phthalate (dep) and di-2-ethylhexyl phthalate (DEHP) influence the metabolic syndrome parameters? pilot study. *Environ Monit Assess* 2015;187:526.
- 59 Petrovičová I, Kolena B, Šidlovská M, *et al.* Occupational exposure to phthalates in relation to gender, consumer practices and body composition. *Environ Sci Pollut Res Int* 2016;23:24125-34.
- 60 Roos V, Rönn M, Salihovic S, *et al.* Circulating levels of persistent organic pollutants in relation to visceral and subcutaneous adipose tissue by abdominal MRI. *Obesity* 2012;9.
- 61 Henríquez-Hernández LA, Luzardo OP, Valerón PF, *et al.* Persistent organic pollutants and risk of diabetes and obesity on healthy adults: results from a cross-sectional study in Spain. *Sci Total Environ* 2017;607-608:1096-102.
- 62 Karlsen M, Grandjean P, Weihe P, *et al.* Early-Life exposures to persistent organic pollutants in relation to overweight in preschool children. *Reprod Toxicol* 2017;68:145-53.
- 63 Vafeiadi M, Roumeliotaki T, Myridakis A, *et al.* Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood. *Environ Res* 2016;146:379-87.
- 64 Wang T, Li M, Chen B, *et al.* Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J Clin Endocrinol Metab* 2012;97:E223-7.
- 65 Wang H-xing, Zhou Y, Tang C-xi, *et al.* Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study. *Environ Health* 2012;11:79.
- 66 Li D-K, Miao M, Zhou Z, *et al.* Urine Bisphenol-A level in relation to obesity and overweight in school-age children. *PLoS One* 2013;8:e65399.
- 67 Choi J, Eom J, Kim J, *et al.* Association between some endocrine-disrupting chemicals and childhood obesity in biological samples of young girls: a cross-sectional study. *Environ Toxicol Pharmacol* 2014;38:51-7.
- 68 Ko A, Hwang M-S, Park J-H, *et al.* Association between urinary bisphenol A and waist circumference in Korean adults. *Toxicol Res* 2014;30:39-44.
- 69 Lee M-R, Kim JH, Choi Y-H, *et al.* Association of bisphenol A exposure with overweight in the elderly: a panel study. *Environ Sci Pollut Res Int* 2015;22:9370-7.
- 70 Sopon Pornkunwilaia WN, Jantarac C, Wachrasindhua S, *et al.* Urinary bisphenol A detection is significantly associated with young and obese Thai children. *Asian Biomedicine* 2015;9:363-72.
- 71 Xue J, Wu Q, Sakthivel S, *et al.* Urinary levels of endocrine-disrupting chemicals, including bisphenols, bisphenol A diglycidyl ethers, benzophenones, parabens, and triclosan in obese and non-obese Indian children. *Environ Res* 2015;137:120-8.
- 72 Hong S-H, Sung Y-A, Hong YS, *et al.* Urinary bisphenol A is associated with insulin resistance and obesity in reproductive-aged women. *Clin Endocrinol* 2017;86:506-12.
- 73 Hao M, Ding L, Xuan L, *et al.* Urinary bisphenol A concentration and the risk of central obesity in Chinese adults: a prospective study. *J Diabetes* 2018;10:442-448.
- 74 Lee HA, Park SH, Hong YS, *et al.* The effect of exposure to persistent organic pollutants on metabolic health among Korean children during a 1-year follow-up. *Int J Environ Res Public Health* 2016;13:270.
- 75 Wang H, Zhou Y, Tang C, *et al.* Urinary phthalate metabolites are associated with body mass index and waist circumference in Chinese school children. *PLoS One* 2013;8:e56800.
- 76 Hou J-W, Lin C-L, Tsai Y-A, *et al.* The effects of phthalate and nonylphenol exposure on body size and secondary sexual characteristics during puberty. *Int J Hyg Environ Health* 2015;218:603-15.
- 77 Kang H-S, Kyung M-S, Ko A, *et al.* Urinary concentrations of parabens and their association with demographic factors: a population-based cross-sectional study. *Environ Res* 2016;146:245-51.
- 78 Yoo M, Lim Y-H, Kim T, *et al.* Association between urinary 3-phenoxybenzoic acid and body mass index in Korean adults: 1st Korean national environmental health survey. *Ann Occup Environ Med* 2016;28:2.
- 79 Guo J, Wu C, Lu D, *et al.* Urinary paraben concentrations and their associations with anthropometric measures of children aged 3 years. *Environ Pollut* 2017;222:307-14.
- 80 Harmouche-Karaki M, Matta J, Helou K, *et al.* Serum concentrations of polychlorinated biphenyls (PCBs) in a Lebanese population: ENASB study. *Environ Sci Pollut Res Int* 2017;24:3705-16.
- 81 Parastar S, Ebrahimpour K, Hashemi M, *et al.* Association of urinary concentrations of four chlorophenol pesticides with cardiometabolic risk factors and obesity in children and adolescents. *Environ Sci Pollut Res Int* 2018;25:4516-23.
- 82 Mounaimne Y, Nasrallah M, Khoueiry-Zgheib N, *et al.* Bisphenol A urinary level, its correlates, and association with cardiometabolic risks in Lebanese urban adults. *Environ Monit Assess* 2017;189:517.
- 83 Lee K-M, Kho Y, Kim P-G, *et al.* Urinary levels of phthalate metabolites and associations with demographic characteristics in Korean adults. *Environ Sci Pollut Res Int* 2017;24:14669-81.
- 84 Oktar S, Sungur S, Okur R, *et al.* The relationship between phthalates and obesity: serum and urine concentrations of phthalates. *Minerva Endocrinol* 2017;42:46-52.
- 85 Dong R, Zhou T, Chen J, *et al.* Gender- and age-specific relationships between phthalate exposures and obesity in Shanghai adults. *Arch Environ Contam Toxicol* 2017;73:431-41.
- 86 Yang TC, Peterson KE, Meeker JD, *et al.* Bisphenol A and phthalates in utero and in childhood: association with child BMI z-score and adiposity. *Environ Res* 2017;156:326-33.
- 87 Arrebola JP, Cuellar M, Claire E, *et al.* Concentrations of organochlorine pesticides and polychlorinated biphenyls in human serum and adipose tissue from Bolivia. *Environ Res* 2012;112:40-7.
- 88 Ben Hassine S, Hammami B, Ben Ameer W, *et al.* Concentrations of organochlorine pesticides and polychlorinated biphenyls in human serum and their relation with age, gender, and BMI for the general population of Bizerte, Tunisia. *Environ Sci Pollut Res Int* 2014;21:6303-13.
- 89 Hue O, Marcotte J, Berrigan F, *et al.* Plasma concentration of organochlorine compounds is associated with age and not obesity. *Chemosphere* 2007;67:1463-7.
- 90 Lakind JS, Goodman M, Mattison DR. Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research. *Crit Rev Toxicol* 2014;44:121-50.
- 91 Oppeneer SJ, Robien K. Bisphenol A exposure and associations with obesity among adults: a critical review. *Public Health Nutr* 2015;18:1847-63.
- 92 Rancière F, Lyons JG, Loh VHY, *et al.* Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health* 2015;14:46.



- 93 Stojanoska MM, Milosevic N, Milic N, *et al.* The influence of phthalates and bisphenol A on the obesity development and glucose metabolism disorders. *Endocrine* 2017;55:666–81.
- 94 Tang-Péronard JL, Andersen HR, Jensen TK, *et al.* Endocrine-Disrupting chemicals and obesity development in humans: a review. *Obes Rev* 2011;12:622–36.
- 95 Wang Y, Hollis-Hansen K, Ren X, *et al.* Do environmental pollutants increase obesity risk in humans? *Obes Rev* 2016;17:1179–97.
- 96 Calafat AM, Koch HM, Swan SH, *et al.* Misuse of blood serum to assess exposure to bisphenol A and phthalates. *Breast Cancer Res* 2013;15:403.
- 97 Koch HM, Kolossa-Gehring M, Schröter-Kermani C, *et al.* Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: a retrospective exposure evaluation. *J Expo Sci Environ Epidemiol* 2012;22:610–6.
- 98 Pollack AZ, Perkins NJ, Sjaarda L, *et al.* Variability and exposure classification of urinary phenol and paraben metabolite concentrations in reproductive-aged women. *Environ Res* 2016;151:513–20.
- 99 Mahalingaiah S, Meeker JD, Pearson KR, *et al.* Temporal variability and predictors of urinary bisphenol A concentrations in men and women. *Environ Health Perspect* 2008;116:173–8.
- 100 Thayer KA, Doerge DR, Hunt D, *et al.* Pharmacokinetics of bisphenol A in humans following a single oral administration. *Environ Int* 2015;83:107–15.
- 101 Lee D-H, Lee I-K, Porta M, *et al.* Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National health and nutrition examination survey 1999-2002. *Diabetologia* 2007;50:1841–51.
- 102 Chen F-P, Chien M-H, Chern IY-Y. Impact of low concentrations of phthalates on the effects of 17 β -estradiol in MCF-7 breast cancer cells. *Taiwan J Obstet Gynecol* 2016;55:826–34.
- 103 Christen V, Crettaz P, Oberli-Schrämmli A, *et al.* Antiandrogenic activity of phthalate mixtures: validity of concentration addition. *Toxicol Appl Pharmacol* 2012;259:169–76.
- 104 Ghisari M, Bonefeld-Jorgensen EC. Effects of plasticizers and their mixtures on estrogen receptor and thyroid hormone functions. *Toxicol Lett* 2009;189:67–77.
- 105 Hoppin JA, Brock JW, Davis BJ, *et al.* Reproducibility of urinary phthalate metabolites in first morning urine samples. *Environ Health Perspect* 2002;110:515–8.
- 106 Hauser R, Meeker JD, Park S, *et al.* Temporal variability of urinary phthalate metabolite levels in men of reproductive age. *Environ Health Perspect* 2004;112:1734–40.
- 107 Darbre PD. Endocrine disruptors and obesity. *Curr Obes Rep* 2017;6:18–27.
- 108 Lee Y-M, Jacobs DR, Lee D-H, Lee D-H. Persistent organic pollutants and type 2 diabetes: a critical review of review articles. *Front Endocrinol* 2018;9:712.
- 109 Emond C, Birnbaum LS, DeVito MJ. Use of a physiologically based pharmacokinetic model for rats to study the influence of body fat mass and induction of CYP1A2 on the pharmacokinetics of TCDD. *Environ Health Perspect* 2006;114:1394–400.
- 110 Vandenberg LN, Hauser R, Marcus M, *et al.* Human exposure to bisphenol A (BPA). *Reprod Toxicol* 2007;24:139–77.
- 111 Hauser R, Duty S, Godfrey-Bailey L, *et al.* Medications as a source of human exposure to phthalates. *Environ Health Perspect* 2004;112:751–3.
- 112 Rajapakse N, Silva E, Kortenkamp A. Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. *Environ Health Perspect* 2002;110:917–21.
- 113 Kortenkamp A. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. *Environ Health Perspect* 2007;115 Suppl 1:98–105.
- 114 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- 115 Yang M, Chen M, Wang J, *et al.* Bisphenol A promotes adiposity and inflammation in a nonmonotonic dose-response way in 5-week-old male and female C57BL/6J mice fed a low-calorie diet. *Endocrinology* 2016;157:2333–45.
- 116 Arsenescu V, Arsenescu RI, King V, *et al.* Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environ Health Perspect* 2008;116:761–8.
- 117 Hao C, Cheng X, Xia H, *et al.* The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice. *Biosci Rep* 2012;32:619–29.