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# 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.

**PROSPERO registration number** CRD42018074548.

## 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

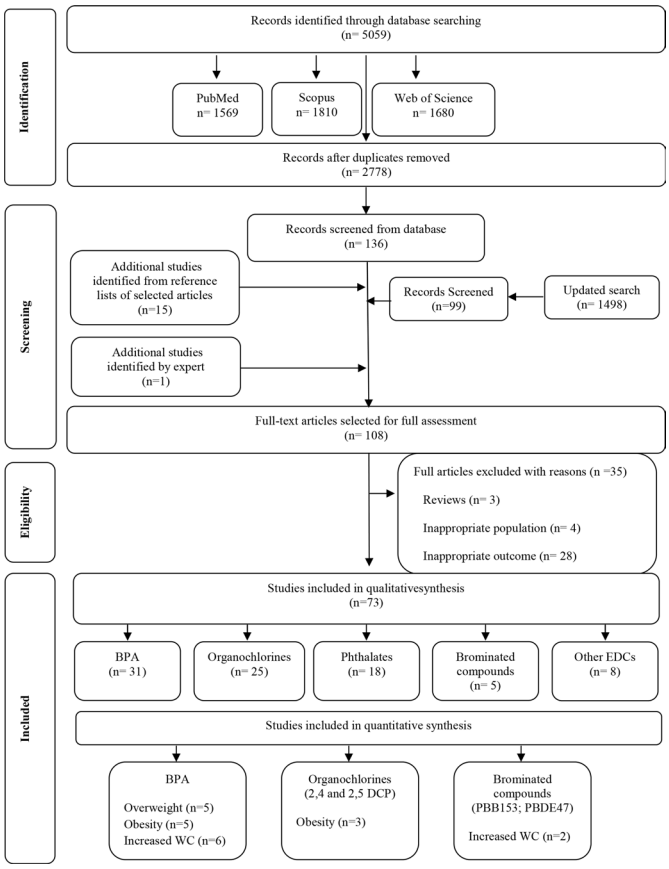


**Figure 1** Flow diagram of literature search and selection criteria adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (adapted from Moher *et al*[14]). BPA, bisphenol A; DCP, dichlorophenol; EDC, endocrine-disrupting chemical; PBB, polybrominated biphenyl; PBDE, polybrominated 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 $\chi^2$ 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 Africa[88] 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 years[65] or 9–12 years.[66] Moreover, one study[22] 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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, ALT, GGT | Higher [urinary BPA] associated with higher BMI and WC |
| Wang *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 2014[21] | 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 *et al*, 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 *et al*, 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 *et al*, 2015[69] | 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 *et al*, 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 *et al*, 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

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| Savastano *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 2017[73] | China | Cohort, 8 | To investigate the association between [urinary BPA] and incident abdominal obesity | Residents in the Songnan Community, Baoshan District, Shangai, 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

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| Deierlein *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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 *et al*, 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-EI-MS/MS, high performance liquid chromatography combined with electrospray ionisation and tandem mass spectrometry; HPLC-GC-MS, high-performance liquid chromatography–gas chromatography/mass spectrometry; HPLC-MS, high performance liquid chromatography-mass spectrometry; HPLC-MS/MS, high performance liquid chromatography-tandem 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; NHSII, 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, tetrabutylamonium fluorides; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-to-hip ratio.

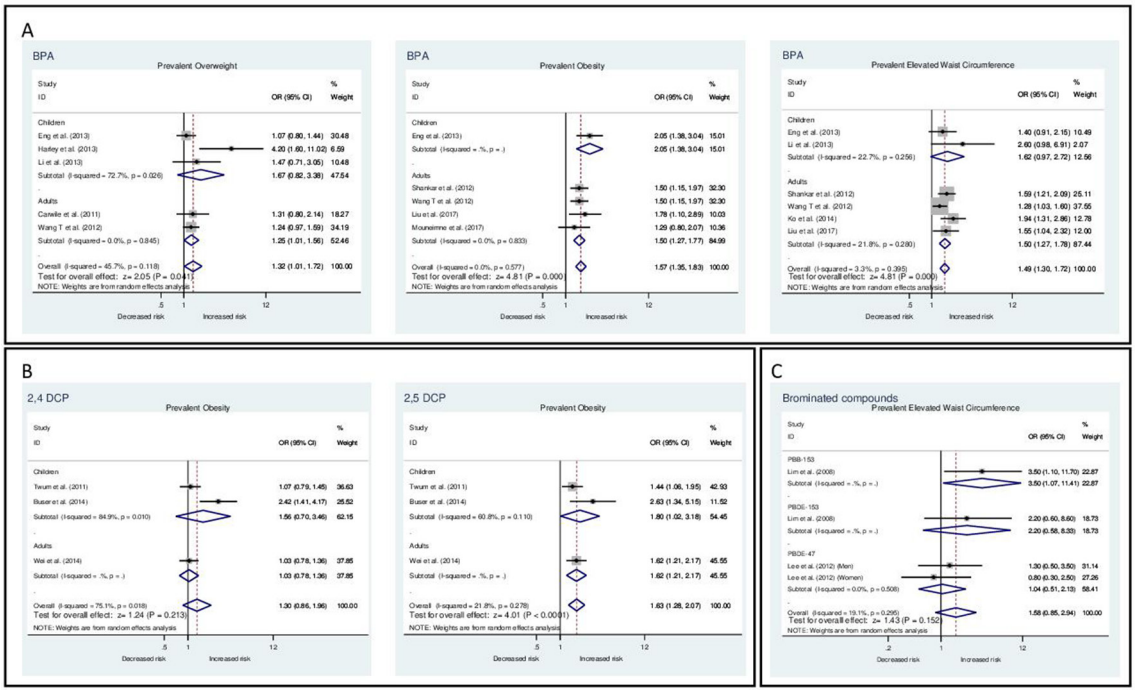


**Figure 2** Association between exposure to bisphenol A, 2,4-dichlorophenol, 2,5-dichlorophenol and brominated compounds and anthropometric measures of obesity.

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 them[21] reported that higher urinary levels of BPA were modestly associated with greater weight gain in women, whereas the other[73] 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 BMI[24] and WC[55] 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 adults[27] 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 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $Tau^2$ | $\chi^2$ | 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 *et al*, 2007[89] | Canada | Cross-sectional, 5 | To investigate the association between [plasma OC compounds] and obesity | NS | Male and female, steady body weight, control 38.8±9.4 years (n=16), obese 38.6±7.6 years (n=19), morbidly obese 44.3±9.2 years (n=18) | 53 | Plasma<br>14 PCBs (28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) (NS)<br>11 chlorinated pesticides (β-HCH, HCB, p,p'-DDE, trans-nonachlor, oxychlordane, cis-nonachlor, aldrin, α-chlordane, γ-chlordane) (NS)<br>p,p'-DDT (7.5%)<br>mirex (22.4%)<br>GC-MS | BMI | Age | [Total plasma OC compounds] not correlated with BMI |
| Dhooge *et al*, 2010[53] | 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<br>PCB 118, 138, 153, 180, HCB, p,p-DDE, CALUX analysis of the dioxin fraction of dioxin-like activity in plasma (NS)<br>GC-ECD | BMI | Adolescents: blood lipids, age, height of father and mother, smoking, sexual maturation (Tanner), food intake.<br>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<br>[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<br>[Sum PCB138, 153, 180] negatively associated with BMI, and [HCB, p,p'-DDE and PCB118] positively associated with BMI in adult women |
| Elobeid *et al*, 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<br>HpCDD, OcDD, oxychlordane, trans-nonachlor, p,p'-DDT (NS)<br>GC-MS | BMI, WC | Serum TC and TG | [Serum p,p'-DDT] positively associated with WC in all subjects<br>[Serum oxychlordane and HpCDD] positively associated with WC in subjects with detectable levels of these compounds<br>[Serum OcDD] increased with higher WC and BMI<br>[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 *et al*, 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<br>PCB (153, 138, 180, 170, sum PCB), pp-DDE, b-HCH (NS)<br>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<br>[Serum b-HCH] positively correlated with BMI, WC, FM%, and total and subcutaneous abdominal adipose tissue |
| Lee *et al*, 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<br>9°C pesticides (44%–100%), 35 PCB congeners (7%–100%)<br>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 *et al*, 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<br>2,4-DCP (92%), 2,5-DCP (99%), ortho-phenylphenol (<40%)<br>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 *et al*, 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<br>17 PCB (98.7%–100%) 5°C pesticides (p,p'-DDE, trans-nonachlor, HCB, chlordane, cis-chlordane(3.4–100%))<br>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)<br>[Plasma highly chlorinated PCB] inversely associated with abdominal obesity<br>Similar but weaker associations between [plasma POPs] and development of abdominal obesity after 5 years |
| Arrebola *et al*, 2012[87] | 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<br>p,p'-DDT (50%), p,p'-DDE (93%), HCB (21%), PCB congeners 138,153,180 (56%–80%)<br>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 *et al*, 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<br>HCB, p,p'-DDE, PCB 153, PCB 180 (100%)<br>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%)<br>GC-MS | BMI | Serum lipids | [Serum OCPs and PCB congeners 153, 138, 180 and sum PCB] not associated with BMI |
| Lankester *et al*., 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<br>TCS (75%)<br>HPLC-MS/MS | BMI | Survey year, sex, age, race, poverty index ratio, urinary BPA, urinary cotinine | [Urinary TCS] positively associated with increased BMI |
| Roos *et al*, 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<br>16 PCBs, p,p'-DDE, HCB, TNC (>95.5%); OcDD (80.6%); cis-chlordane, trans-chlordane (<10%)<br>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<br>[Plasma highly chlorinated PCBs] inversely related to both VAT and SAT<br>[Plasma PCB189] correlated with VAT/SAT ratio in an inverted U-shaped manner |
| Buser *et al*, 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<br>2,5-DCP (98.5%), 2,4-DCP (90%), TCS (79%)<br>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 *et al*, 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<br>2,4-DCP (92.6%), 2,5-DCP (99%)<br>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 *et al*, 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<br>2066 adults | Urine<br>TCS (77%–79%)<br>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 *et al*, 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, PCB126] 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 *et al*, 2015[56] | 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 form 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 *et al*, 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 *et al*, 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 *et al*, 2016[74] | 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<br>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%)<br>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), oxychlordane, chlordane, heptachlor, heptachlor epoxide, a-HCH, g-HCH, d-HCH, o, p'-DDT, p,p'-DDD, o,p'-DDD, o,p'-DDE (NS)<br>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 *et al*, 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<br>2,5-DCP (>80%)<br>TCS (>80%)<br>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 *et al*, 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<br>PCB 28, 52, 101, 138, 153, 180 (50%–60%)<br>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 *et al*, 2017[61] | 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%), HCHα (88.1%), HCHβ (<50%), HCHδ (<50%), HCHγ (55.7%)<br>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%)<br>GC-ECD (OCPs), GC-MS (PCBs) | BMI, waist-to-hip ratio | None | (Serum p,p'-DDE) higher among OW and OB subjects |
| Karlsen *et al*, 2017[62] | 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<br>sum PCB 138, 153, 180 (100%), HCB (100%), p,p'DDE (100%)<br>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 *et al*, 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<br>2,4-DCP (94.6%), 2,5-DCP (95%), 2,4,5-TCP (85.1%), 2,4,6-TCP (38%)<br>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 *et al*, 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<br>TCS (NS)<br>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<br>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; CALUX, chemical activated luciferase gene expression; DCP, dichlorophenol; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; 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/HMRS, gas chromatography–isotope dilution/high-resolution mass spectrometer; GC-MS, gas chromatography–mass spectrometry; HCB, hexachlorobenzene; HCH, hexachlorohexane; 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; TCP, trichlorophenol ; TCS, triclosan; TG, triglyceride; TNC, transnonachlordane; 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 *et al*, 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<br>PHT metabolites<br>MBP, MEP, MBzP, MEHHP, MEOHP, MEHP (>80%), MiNP (25%)<br>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 *et al*, 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<br>MEP, MEHP, MBzP, MBP, MEHHP, MEOHP (>80%), MCP, MNP, MOP (≤80%)<br>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<br>[Urinary MEP] positively associated with BMI and WC in adolescent girls<br>[Urinary MEHP] inversely associated with BMI in adolescent girls and women aged 20–59 years |
| Lind *et al*, 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<br>MEHP, MEP, MiBP, MMP (>96%)<br>LC-MS/MS | Fat mass (DXA and MRI) | Serum TC and TG, education, exercise, smoking | [Serum MiBP] positively associated WC, total FM, trunk FM, SAT after 2 years in women<br>[MMP] positively associated with trunk fat mass and trunk:leg ratio after 2 years in women |
| Teitelbaum *et al*, 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<br>MEP, MBP, MCPP, MBzP, MiBP, MEOHP, MECPP, MEHHP (>97%), MEHP (81%–90%)<br>HPLC-MS | BMI, BMI z-score, WC 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 *et al*, 2013[75] | 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 Shangai, China | Male and female, 8–15 years | 259 | Urine<br>MEHP, MEOHP, MECPP, MEHHP, MBP, MiBP, MEP, MCMHP, MHBP, MMP, MCHP (≥94.6%)<br>MBzP (38.6%)<br>MiNP, MOP (0%)<br>Sum MBP, MHBP, MiBP, MMP, MEP<br>Sum MEHP, MECPP, MEHHP, MEOHP, MCMHP, MCHP, MBzP,<br>RPUPLC-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 *et al*, 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<br>MEP, DBP, DEHP, MEHP, PA, MBzP (NS)<br>GC-MS | BMI (OB defined by BMI > p85) | None | MEP, DBP and PA positively associated with obesity |
| Song *et al*, 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<br>PA, MEP, MBzP, Sum of butyl PHTs, DEHP metabolites, total PHTs (NS)<br>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 *et al*, 2015[76] | 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 Tapei, Taiwan | Male and female, 6.5–15 years | 270 | Urine<br>DEHP metabolites (MEHP (78.1%), MEOHP, MEHHP, MECPP (≥99.6%))<br>LMW PHT metabolites (MMP, MEP, MiBP, MnBP (≥94.8%))<br>MBzP (94.4%)<br>HMW PHT (DEHP metabolites, MBzP (NS))<br>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 *et al*, 2015[58] | 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<br>MEP (24.3%) and MEHP (16.5%)<br>GC-MS | BMI, WC | None | [Urinary MEHP] positively associated with WC |
| Petrovicova *et al*, 2016[59] | 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 occupationally exposed subjects, 35 workers from plastic industry, 49 from the general population) | Urine<br>MEHHP, MEOHP, MEHP, MiBP, MnBP (≥82.2%)<br>Sum DEHP<br>HPLC-MS | BMI, WC, FMI, FFMI, HC, WHR, WHtR, WC > 102 cm (male) or > 88 cm (female) | Gender, occupational exposure | [Urinary MEHP] inversely related to WHtR, BMI, WHR, HC and WC, and positively related to FFMI among women but not men |
| Yaghjyan *et al*, 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<br>DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP), %MEHP (ratio of MEHP to sum of secondary metabolites) (NS)<br>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 *et al*, 2017[72] | 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<br>MEHHP, MEOHP, MnBP (NS)<br>HPLC-MS | BMI, WC | Age, urinary creatinine, smoking and alcohol status, TG, TC, HDL-C | [Urinary PHTs] not associated with BMI and WC |
| Kataria *et al*, 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<br>MMP, MEP, MBP, MiBP, MBzP, MCHP, MOP, MCPP, MIDP, MCNP, MNP, MIDP, MCOP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MHxP, MHpP (NS)<br>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 *et al*, 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<br>MEP, MBP, MCPP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP (94%–100%)<br>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 *et al*, 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<br>DMP, DEP, DBP, DPP, BBP, DEHP, DOP, GC | BMI, WC | None | [Urinary and serum PHTs] positively associated with BMI and WC |
| Dong *et al*, 2017[85] | China | Cross-sectional, 5 | To investigate the association between [urinary PHT metabolites] and obesity | Participants from the Shangai Food Consumption Survey 2012 | Male and female, >18 years | 2330 | Urine<br>MMP, MEP, MnBP, MiBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, MCMHP<br>LC-MS/MS | OB and OW defined by BMI, abdominal obesity (≥ 85 cm for men and ≥ 80 cm for women) | OB: age, gender, education, marriage, smoking, total caloric intake calories, and total fat intake<br>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 *et al*, 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<br>MnBP, MiBP, MBzP, MCHP, MnOP, MEHP, MEOHP, MEHHP, MiNP, MiDP<br>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 *et al*, 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<br>MEP, MnBP, MiBP, MCPP, MBzP, MEHP, MEHHP, MEOHP, MECPP<br>SumDEHP<br>HPLC-MS/MS<br>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 butyl 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, monobuthylphthalate; MBzP, monobenzyl phthalate; MCHP, mono-cyclohexyl phthalate; MCMHP, mono(2-carboxymethylhexyl) phthalate; MCNP, monocarboxylisononyl phthalate; MCOP, mnocarboxyisooctyl 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; MHpP, mono-2-heptyl phthalate; MHxP, 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; RPUPLC-ESI-MS/MS, reversed-phase ultraperformance liquid chromatography–electrospray ionisation–tandem MS; SAT, subcutaneous adipose tissue; TC, total cholesterol; TG, triglycerides; UPLC-MS/MS, ultraperformance 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 study[33] 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 ploycyclic 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 acid[78] (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 children[62] (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 supplemenatry 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 of the tests. Online supplementary table 4 presents the reasons for excluding studies from the meta-analysis.

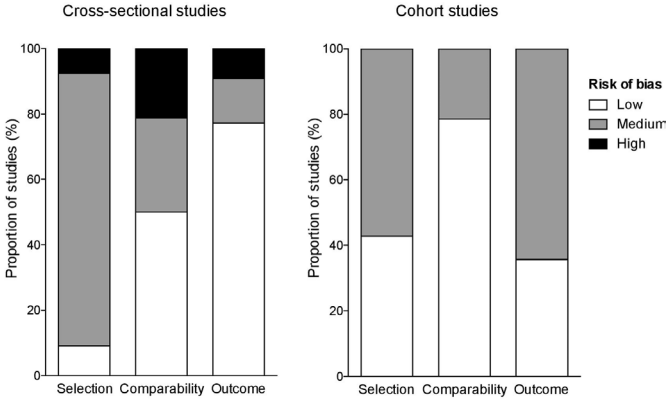


**Figure 3** Quality assessment using the Newcastle-Ottawa scale for risk of bias of studies included in the systematic review.

## 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 20[90] and 18[91] 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 24[94] and 35[95] 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 BPA[100] 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 studyfi.[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 estrogenic[102] 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 studies[112] 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 continous 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 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 compounds[116] and PHTs[117] 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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