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Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women

Y Song[1,2], **R Hauser**[3,4], **FB Hu**[3,5,6], **AA Franke**[7], **S Liu**[2,8,9], and **Q Sun**[5,6]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, USA

[2]Department of Epidemiology, School of Public Health, Brown University, Providence, RI, USA

[3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[4]Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA

[5]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

[6]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[7]Natural Products and Experimental Therapeutics Program, University of Hawaii Cancer Center, Honolulu, Hawaii

[8]Department of Medicine, Alpert School of Medicine, Brown University, Providence, RI, USA

[9]Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

Abstract

OBJECTIVE—Both bisphenol A (BPA) and phthalates are known endocrine-disrupting chemicals for which there is widespread general population exposure. Human exposure occurs through dietary and non-dietary routes. Although animal studies have suggested a potential role of these chemicals in obesity, evidence from human studies is sparse and inconsistent, and prospective evidence is lacking. This study evaluated urinary concentrations of BPA and major phthalate metabolites in relation to prospective weight change.

METHODS—The study population was from the controls in a prospective case-control study of type 2 diabetes in the Nurses' Health Study (NHS) and NHSII. A total of 977 participants provided first-morning-void urine samples in 1996–2002. Urinary concentrations of BPA and nine phthalate metabolites were measured using liquid chromatography–mass spectrometry. Body weights were self-reported at baseline and updated biennially thereafter for 10 years.

Correspondence: Dr Q Sun, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA. qisun@hsph.harvard.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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RESULTS—On average, the women gained 2.09 kg (95% confidence interval (CI), − 2.27 to 6.80 kg) during the 10-year follow-up. In multivariate analysis with adjustment of lifestyle and dietary factors, in comparison with women in the lowest quartile of BPA concentration, those in the highest quartile had 0.23 kg per year (95% CI, 0.07–0.38 kg per year) greater weight gain during the 10-year follow-up (*P*-trend = 0.02). Several phthalate metabolites, including phthalic acid, MBzP and monobutyl phthalate, were also associated with faster prospective weight gain in a dose-response fashion (*P*-trend < 0.01), whereas other phthalates metabolites, including MEP and monoethylhexyl phthalate, were not monotonically associated with body weight change.

CONCLUSIONS—These data suggest urinary concentrations of BPA and certain individual phthalate metabolites that were associated with modestly greater weight gain in a dose-response fashion. These data are consistent with a potential role of BPA and phthalates in obesity, although more prospective data are needed to corroborate these observations.

Keywords

bisphenol A; phthalate; endocrine-disrupting chemicals

Excessive body weight is associated with an increased risk of major chronic diseases including cardiovascular disease, diabetes and certain cancers.[1] Recently, a new policy statement from the American Medical Association has officially recognized obesity as a separate disease, not simply a risk factor of other chronic diseases.[2] Accumulating evidence has suggested that some environmental chemicals possessing endocrine-disrupting properties may lead to adiposity.[3,4] Bisphenol A (BPA) and phthalates are ubiquitous endocrine-disrupting chemicals that have the ability to alter hormone signaling in the body.[5] Both BPA and phthalates are widely used in consumer products and exposure occurs through dietary and non-dietary routes.[6,7] Although animal studies have suggested a role of these chemicals in the etiology of obesity,[8,9] evidence from human studies was inconsistent.[10–23] Furthermore, most of these studies were cross-sectional and no prospective studies in adult populations have been conducted. We aim to evaluate urinary concentrations of BPA and major phthalate metabolites in relation to prospective weight change in the Nurses' Health Study (NHS) and NHSII.

MATERIALS AND METHODS

Study population and sample collection

The NHS was established in 1976 when 121 700 female registered nurses aged 30–55 years were enrolled, whereas in 1989 the younger counterpart NHSII cohort was initiated among a total of 116 686 female registered nurses aged 25–42 years. A total of 18 717 NHS participants aged 53–79 years provided blood and urine samples during 2000–2001. During 1995–2000, blood and urine samples were collected from 29 611 NHSII participants aged 32–52 years. Urine samples were collected without preservative in a polypropylene container and returned to a central biorepository via overnight courier with an icepack and were immediately processed on arrival and aliquoted into polypropylene cryovials, which were stored in the vapor phase of liquid nitrogen freezers at ≤ 130 °C.

During the follow-up period of 2000–2008 in the NHS and 1995–2007 in the NHSII, a total of 971 type 2 diabetes cases were identified and confirmed among participants who provided urine samples in these two cohorts.[24] A control was selected for each case and case-control pairs were matched for age at urine sample collection, race, fasting status, first morning sample, and menopausal status and use of hormone replacement therapy (NHSII only). The study population of the current analysis is from the control population of this case-control study of type 2 diabetes nested in the NHS and NHSII cohorts.[24] All urine samples from the 977 participants were first-morning-void urine collected during 1996–2002. (Of note, in the NHS only, because of technical reasons, concentrations of phthalic acid (PA) were not available for 144 case-control pairs.) The study protocol was approved by the institutional review board of the Brigham and Women's Hospital and the Human Subjects Committee Review Board of Harvard School of Public Health.

Body weight and covariate assessments

Body weight of each individual was self-reported every 2 years. In these cohorts of registered nurses, self-reported body weight was highly accurate: a correlation coefficient of 0.96 was observed between self-reported weight and measured weight among 184 NHS participants.[25] The major outcome of this study was the prospective weight change since urine sample collection (2000–2001 in NHS, 1995–2000 in NHSII) to the most recent follow-up cycle (2010 in NHS, 2009 in NHSII). The most recent body weights available in both NHS and NHSII were body weight at 10-year of follow-up since baseline. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Self-administrated questionnaires were used to collect information on demographics and lifestyle factors including age, cigarette smoking, alcohol drinking and physical activity. Total energy intake and alternative healthy eating index[26] were calculated from the data collected using a validated food frequency questionnaire.

Laboratory measurements

Urinary concentrations of BPA and nine phthalate metabolites (mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), monobutyl phthalate (MBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP) and PA) were measured using liquid chromatography–mass spectrometry.[27,28] The average intra-batch coefficients of variation were < 10% for most metabolites (including creatinine), except MEHP (NHS 11.4%, NHSII 10.0%) and BPA (NHS 11.5%, NHSII 13.0%). We grouped these metabolites according to their parent chemicals: DEHP (di-2-ethylhexyl phthalate) metabolites (MEHP, MEHHP, MEOHP and MECPP) and butyl phthalates metabolites (MBP and MiBP). PA is a nonspecific metabolite that can be derived from all phthalate diesters, and all of the phthalates can be ultimately metabolized to PA, so it is a nonspecific metabolite that is not often measured for this reason.[19–23] To be consistent with previous research on phthalates, we excluded PA in calculation of total phthalate metabolite concentration. To test for potential environmental contamination of samples, we compared measurements of urinary concentrations of phthalate metabolites among samples treated with and without β-glucuronidase and sulfatase in a pilot study.[29] Among 44 NHS and NHSII participants, the two measurements with and

without β-glucuronidase and sulfatase were highly correlated. The intraclass coefficients were >0.99 for MEP, MBP, MEOHP and MBzP, >0.96 for MEHHP and MECPP and >0.94 for MiBP and MEHP, suggesting that the impacts of the use of these enzymes in sample preparation on the measurements of these chemicals were minimal.

Statistical methods

Analysis was conducted among controls to facilitate the generalizability of results to the entire NHS studies and to minimize the impact of diabetes on weight change. Baseline characteristics were summarized according to quartiles of BPA and total phthalate concentrations. Categorical variables were shown as percentages; normal-distributed continuous variables were expressed as the mean (s.d.); and non-normal-distributed continuous variables were shown as median (interquartile range). Missing data of covariates were imputed as medians of the study population (94% participants had valid values of covariates, 6% had 1–4 missing values). General linear regression was used to model the relation of urinary concentrations of BPA and phthalates with BMI at baseline. The basic models were adjusted for urinary creatinine concentration (log-transformed). In the multivariable model, we additionally adjusted for cohort origin (NHS or NHSII), age at baseline (year), menopausal status (yes or no), smoking (never, past, or current smoker), alcohol consumption (g per day, log-transformed), physical activity (MET-hours per week, log-transformed), alternative healthy eating index score and total energy intake (kcal per day). *P*-values for linear trend were obtained by including the median concentration of each quartile as a continuous variable in the regression models. To model prospective annual weight change rate by quartiles of urinary BPA and phthalate concentrations, we used mixed-effect models with product terms between the concentrations and year after baseline. *P*-values for linear trend were obtained by examining an interaction term between follow-up time and median concentration of the quartile in the mixed-effect models. All *P*-values were two sided. Data were analyzed with the SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics of participants are summarized in Table 1. Women with higher urinary concentration of BPA were on average younger, more likely to be current smokers, had lower level of physical exercise, higher concentrations of creatinine and phthalate metabolites, and greater weight gain during follow-up. Similarly, women with higher urinary concentration of total phthalates were on average younger, had lower level of physical exercise, higher concentrations of creatinine and BPA, and greater weight gain during follow-up.

Associations between urinary concentrations of BPA and phthalate metabolites and baseline BMI are shown in Table 2. Urinary BPA concentration was not associated with baseline BMI (*P*-trend = 0.65). Likewise, total phthalate metabolite concentration was not associated with baseline BMI (*P*-trend = 0.58). Sum of butyl phthalates, however, was inversely associated with baseline BMI (*P*-trend = 0.02). The nonspecific metabolite—PA—was positively associated with baseline BMI (*P*-trend = 0.02). The adjusted mean of baseline

BMI for women in the highest quartile of PA was 27.0 (95% CI, 26.1–27.8), whereas the adjusted mean for women in the lowest quartile was 25.5 (95% CI, 24.6–26.3). All other phthalate metabolites were not significantly associated with baseline BMI.

Table 3 presents the associations between quartiles of urinary concentrations of BPA and phthalate metabolites and prospective annual weight change rate. Higher quartiles of urinary BPA concentration were associated with faster weight gain during follow-up (*P*-trend = 0.02). Compared with women in the lowest BPA quartile (median: 3.61 nmol l^{-1}), those in the highest quartile (median: 21.91 nmol l^{-1}) had 0.23 kg greater annual weight gain (95% CI, 0.07–0.38 kg) during 10 years of follow-up.

Associations between urinary phthalate concentrations and weight gain showed apparent heterogeneity among different metabolites. PA, MBzP and sum of butyl phthalates showed significant associations with faster weight gain during follow-up. Specifically, compared with women in the lowest quartile of PA concentration (median: 212 nmol l^{-1}), those in the highest quartile (median: 1326 nmol l^{-1}) had 0.33 kg per year faster weight gain (95% CI, 0.15–0.50 kg; *P*-trend = 0.001). Compared with women in the lowest quartile of MBzP concentration (median: 20 nmol l^{-1}), those in the highest quartile (median: 252 nmol l^{-1}) had 0.42 kg per year faster weight gain (95% CI, 0.26–0.57 kg; *P*-trend <0.001). Compared with women in the lowest quartile of sum of butyl phthalates (median: 67 nmol l^{-1}), those in the highest quartile (median: 481 nmol l^{-1}) had 0.34 kg per year faster weight gain (95% CI, 0.18–0.50 kg; *P*-trendo0.001). In contrast, MEP and DEHP metabolites were not associated with weight change in a monotonic fashion (*P*-trend = 0.27 and 0.42, respectively). For the sum of all metabolites, higher total phthalate concentration (excluding PA) was associated with faster weight gain during follow-up (*P*-trend = 0.05).

In a secondary analysis when the analyses were stratified by age (Supplementary Appendix Table 1), the trends of BPA and MBP were attenuated to lack of statistical significance probably due to diminished statistical power, although PA and MBzP were still significantly associated with faster weight gain in young and old women, respectively. When we further stratified the analysis by baseline BMI levels, we observed a similar pattern that overall associations were attenuated, although in certain strata statistically significant relationships remained (Supplementary Appendix Table 2). We also conducted an analysis evaluating the probability of gaining >10% body weight during follow-up as an alternative study outcome. In this analysis with largely diminished power (body weights assessed at 2–8 years of follow-up did not contribute to this analysis), we did not observe significant associations (data not shown).

DISCUSSION

To our knowledge, this is the first report of prospective associations between BPA and phthalates and weight change. In the current study among US women, we observed that higher urinary concentrations of BPA and certain phthalate metabolites (PA, MBzP and butyl phthalates) were significantly associated with modestly faster weight gain during follow-up. Other phthalate metabolites, including MEP and DEHP metabolites, were not monotonically associated with rate of weight gain. Analyses stratified by baseline age or

BMI generated somewhat heterogeneous results probably due to lower statistical power, although positive, significant associations remained in certain strata.

Previous cross-sectional studies observed significant correlations between urinary BPA concentration and obesity in children[10–15] and adults,[16–18] with adjustment of potential confounders. In addition, the association in children differed by age (association observed in older but not younger children[12,14]), gender (in girls but not boys[11,14]) and race/ethnicity (in whites but not other races[10,15]). Evidence for adults in this regard was generated from the NHANES[16,18] and a Chinese community-based survey.[17] These studies found significant association of higher BPA concentrations with general obesity and abdominal obesity: odds ratios comparing the highest quartile with the lowest ranged from 1.50 to 1.76. Our current study did not demonstrate the same cross-sectional correlation between urinary BPA concentration and BMI at baseline. Likewise, in the EPIC-Norfolk cohort, baseline BPA concentrations were not correlated with BMI.[30] The discrepancy regarding the cross-sectional correlations between BPA and adiposity may be due to the heterogeneous routes of exposure in different populations and the presence and amounts of these chemicals in foods across countries,[7,31,32] various confounding patterns unique to study populations, or chance, especially for smaller studies. Nonetheless, the cross-sectional evidence cannot help establish the temporal relationship between BPA exposure and body weight. Similarly, evidence for phthalate exposures in relation to obesity is exclusively from cross-sectional investigations among children[19,21,23] and adults,[20–22] and the results were highly inconsistent. Two studies found association between low molecular weight metabolites (for example, MEP) and BMI in children,[15,16] but the association was not replicated in another study.[21] These studies also reported sex heterogeneity of the association between phthalate metabolites and obesity. For example, studies based on NHANES data found that MEP, MBzP, MEHHP and MEOHP were associated with larger waist circumference in men, but not in women.[21,22] A study in a Swedish population found the opposite in that a positive association between MiBP with waist circumference was observed in women but not in men.[20] Lastly, a cross-sectional study using NHANES data found inverse association between MBP concentration and BMI in older women.[21] The current study extends this research to elucidate the longitudinal relationships between these chemicals and weight change and provides supportive evidence that these pollutants are potential obesogens.[33]

Several mechanisms have been proposed to explain potential biological pathways of BPA and phthalate exposure leading to obesity. *In vitro* studies have suggested that BPA exposure induces the differentiation of 3T3-L1 fibroblasts into adipocytes, and accelerates the adipocyte conversion process.[34] Moreover, BPA exposure was shown to cause triacylglycerol accumulation in adipocytes, which is associated with obesity and metabolic syndrome.[35] Animal models also show that BPA exerts estrogenic effects through binding to estrogen receptor-β to cause insulin resistance and obesity.[36]

Phthalates are a group of chemicals with heterogeneous structures, and may have diverse effect on health outcomes.[37] Previous animal studies document that phthalate exposures, predominantly DEHP, as well as its main metabolites, may lead to weight gain through a peroxisome proliferator-activated receptor (PPAR)-mediated pathway that promotes adipocyte maturation.[38,39] Meanwhile, limited evidence also suggests that metabolites of

different parent phthalates may have various capacities of activating PPARs,[40] and it is largely unknown regarding the biological effects of certain minor metabolites, such as PA. Nonetheless, more mechanistic insights are needed to explain the heterogeneity of associations with body weight observed in the previous and current studies.[19–23] It is worth noticing that some nonlinear relations were observed for certain phthalate metabolites in the analyses, which have also been previously described for other endocrine disrupting chemicals.[41,42] However, such nonlinear relations need to be interpreted with caution.

There are several limitations in the current study. First, as the biologic half-lives of BPA and phthalates are relatively short, a single measurement of urine levels may not be able to represent long-time exposure levels. Specifically, in NHS and NHSII population, Townsend *et al.* found that within-person variability of urinary BPA concentrations was quite high (intraclass correlation coefficient = 0.14), whereas most of the phthalate metabolites showed moderate within-person stability (intraclass correlation coefficient = 0.39–0.55).[43] Meanwhile, an investigation demonstrated that BPA levels in a single urine sample might still be reasonably informative for categorizing participants' long-term exposure levels.[44] Ideally, use of multiple 24-h urine samples collected through an extended period of time is required to estimate long-term exposures, although in large epidemiological investigations it is challenging to obtain such data. Second, there might be potential contamination from sample containers or during sample processing. However, as indicated above, the impacts of the use of β-glucuronidase and sulfatase on the measurements of these chemicals were shown to be minimal. The correlation of PA measurements was somewhat weaker (intraclass correlation coefficient = 0.82), although any misclassification of the true PA concentration is likely to be non-differential because contamination by environmental phthalates was unrelated with true exposures. Third, the current study only included women, most of whom are white. Future studies in other populations are warranted. Fourth, because the understanding of predictors of BPA and phthalate exposure is limited, we cannot exclude the possibility of residue confounding by factors beyond the ones we controlled for in the models.

In conclusion, we observed that higher urinary concentrations of BPA, PA, MBzP and butyl phthalates were significantly associated with faster weight gain in US women. The results are consistent with an etiological role of BPA and phthalates in the pathogenesis of obesity, although we cannot exclude the possibility of chance findings, especially when associations were attenuated in stratified analyses. Future large-scale studies with repeated assessments of the levels of these chemicals are needed to replicate these observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of participants by quartiles of urinary BPA and total phthalate metabolite concentrations

Characteristics	***BPA***				***Total phthalates***			
	Q1	***Q2***	***Q3***	***Q4***	***Q1***	***Q2***	***Q3***	***Q4***
n	244	244	243	244	244	244	245	244
Age, mean (s.d.), years	57.6 (12.0)	54.8 (11.2)	51.1 (9.9)	51.7 (10.2)	57.9 (12.3)	53.5 (10.8)	52.3 (10.4)	51.4 (9.8)
NHS, no. (%)	131 (53.7)	110 (45.1)	76 (31.3)	81 (33.2)	135 (55.3)	99 (40.6)	88 (35.9)	78 (32.0)
White, no. (%)	235 (96.3)	237 (97.1)	239 (98.4)	239 (98.0)	240 (98.4)	236 (96.7)	240 (98.0)	236 (96.7)
Smoking status, no. (%)								
Nonsmokers	140 (57.4)	145 (59.4)	147 (60.5)	137 (56.2)	143 (58.6)	132 (54.1)	150 (61.2)	145 (59.4)
Past smokers	93 (38.1)	81 (33.2)	75 (30.9)	86 (35.3)	84 (34.4)	90 (36.9)	77 (31.4)	84 (34.4)
Current smokers	10 (4.1)	18 (7.4)	20 (8.2)	21 (8.6)	17 (7.0)	22 (9.0)	16 (6.5)	15 (6.2)
Alcohol consumption, median (IQR), g per day	1.0 (0.0–5.6)	1.5 (0.0–4.7)	0.9 (0.0–3.8)	0.9 (0.0–4.9)	1.5 (0.0–5.6)	0.9 (0.0–5.2)	0.9 (0.0–3.5)	1.1 (0.0–4.7)
AHEI, median (IQR)	53.0 (45.3–59.6)	51.3 (44.9–60.0)	52.9 (45.1–58.8)	51.5 (43.7–58.6)	53.1 (45.5–61.1)	51.8 (44.6–58.7)	51.9 (44.9–59.6)	51.5 (45.1–58.0)
Physical exercise, median (IQR), MET-hours per week	12.9 (4.2–23.4)	12.1 (4.6–25.3)	11.9 (4.6–25.9)	11.1 (5.5–21.4)	13.8 (5.1–24.8)	12.2 (4.6–26.2)	11.5 (5.2–21.7)	10.9 (3.9–22.1)
Creatinine, median (IQR), $mgdl^{-1}$	57.1 (38.7–75.7)	61.3 (46.5–92.7)	92.0 (65.6–127.1)	108.5 (71.8–157.3)	52.3 (37.6–68.0)	71.3 (51.2–98.3)	92.6 (62.6–125.9)	107.3 (65.7–157.0)
BPA, median (IQR), nmol l^{-1}	3.6 (2.6–4.5)	6.4 (5.8–7.3)	10.5 (9.0–12.1)	21.9 (16.8–35.7)	6.0 (3.9–9.3)	7.6 (4.5–12.9)	9.0 (6.1–15.0)	10.6 (6.5–18.6)
Total phthalates, median (IQR), nmol l^{-1}	835 (503–1392)	1261 (647–2212)	1513 (941–2559)	1742 (911–3531)	500 (346–602)	962 (841–1109)	1688 (1495–1975)	4094 (2952–6402)
Phthalic acid, median (IQR), nmol l^{-1}	307 (210–433)	430 (254–729)	570 (352–926)	742 (433–1266)	250 (181–373)	364 (273–570)	602 (430–901)	1007 (664–1600)
Weight at year 0, mean (s.d.), kg	71.0 (14.8)	71.5 (15.1)	70.7 (16.0)	70.3 (13.7)	72.2 (15.8)	70.0 (14.5)	71.0 (14.3)	70.4 (14.9)
10-year weight change, mean (s.d.), kg	0.7 (7.3)	2.1 (9.0)	2.8 (8.7)	2.9 (8.5)	0.9 (9.6)	2.1 (8.0)	3.0 (8.7)	2.4 (7.1)

Abbreviations: AHEI, alternative healthy eating index; BPA, bisphenol A; IQR, interquartile range; MET, metabolic equivalent; NHS, Nurses' Health Study. Conversion factor: BPA (nmol l^{-1})×0.228 = BPA (μg l^{-1}).

Table 2

Associations between urinary concentrations of BPA and phthalate metabolites and baseline BMI

Chemical	*Quartile*	*Median concentration (nmol l^{-1})*	*BMI (kg m^{-2})*	
			Model 1	*Model 2*
BPA	Q1	3.61	26.1 (25.4–26.8)	25.7 (25.0–26.4)
	Q2	6.40	26.2 (25.5–26.9)	26.3 (25.6–27.0)
	Q3	10.53	26.3 (25.6–27.0)	26.2 (25.5–26.9)
	Q4	21.91	26.0 (25.3–26.7)	26.2 (25.4–26.9)
	P-trend[a]		0.77	0.65
Phthalic acid	Q1	212	25.6 (24.8–26.4)	25.5 (24.6–26.3)
	Q2	369	26.0 (25.2–26.8)	26.1 (25.3–26.9)
	Q3	641	25.9 (25.1–26.6)	25.6 (24.8–26.4)
	Q4	1326	26.8 (26.0–27.6)	27.0 (26.1–27.8)
	P-trend		0.04	0.02
MEP	Q1	88	26.3 (25.6–27.0)	26.1 (25.4–26.8)
	Q2	321	25.8 (25.1–26.5)	25.6 (24.9–26.3)
	Q3	725	26.6 (25.9–27.3)	26.7 (26.0–27.4)
	Q4	2198	25.9 (25.2–26.6)	25.9 (25.1–26.6)
	P-trend		0.65	0.78
MBzP	Q1	20	26.3 (25.6–27.1)	26.4 (25.7–27.2)
	Q2	47	26.0 (25.3–26.7)	26.1 (25.4–26.8)
	Q3	90	26.6 (25.9–27.3)	26.5 (25.7–27.2)
	Q4	252	25.6 (24.8–26.3)	25.3 (24.5–26.1)
	P-trend		0.16	0.05
Sum of butyl phthalates[b]	Q1	67	26.4 (25.7–27.1)	26.4 (25.6–27.2)
	Q2	140	26.8 (26.1–27.5)	26.8 (26.1–27.5)
	Q3	249	25.8 (25.1–26.5)	25.6 (24.9–26.4)
	Q4	481	25.5 (24.8–26.2)	25.4 (24.6–26.2)
	P-trend		0.03	0.02
DEHP metabolites[c]	Q1	115	26.3 (25.5–27.0)	26.2 (25.4–26.9)
	Q2	204	26.5 (25.8–27.1)	26.5 (25.8–27.2)
	Q3	353	25.6 (24.9–26.3)	25.7 (25.0–26.4)
	Q4	870	26.3 (25.5–27.0)	26.1 (25.3–26.8)
	P-trend		0.98	0.70
Total phthalates[d]	Q1	500	26.6 (25.9–27.4)	26.6 (25.9–27.4)
	Q2	962	25.9 (25.2–26.6)	25.7 (25.0–26.4)
	Q3	1688	26.1 (25.4–26.8)	26.0 (25.3–26.7)
	Q4	4094	25.9 (25.2–26.6)	25.9 (25.2–26.7)
	P-trend		0.43	0.58

Abbreviations: BMI, body mass index; BPA, bisphenol A; DEHP, di-2-ethylhexyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate. Conversion factor: BPA (nmol l^{-1})×0.228= BPA (μg l^{-1}). Numbers are least square means (95% CI) of baseline body mass index (kg

m^{-2}). Model 1: adjusted for urinary creatinine concentration. Model 2: adjusted for urinary creatinine concentration, cohort origin, age, menopausal status, smoking, physical activity, alcohol consumption, AHEI and total energy intake.

[a] P-values for linear trend were obtained by including the median concentration of each quartile as continuous variables in the regression models.

[b] Include MBP and MiBP.

[c] Include MEHP, MEHHP, MCEPP and MEOHP.

[d] Include MEP, MBzP, MBP, MiBP, MEHP, MEHHP, MCEPP and MEOHP.

Table 3

Prospective annual weight change rate by quartiles of urinary BPA and phthalate metabolite concentrations

Chemical	*Quartile*	*Median concentration (nmol l^{-1})*	*Weight change rate (kg per year)*	
			Model 1	*Model 2*
BPA	Q1	3.61	0.00 (reference)	0.00 (reference)
	Q2	6.40	0.16 (0.00 to 0.31)	0.15 (0.00 to 0.31)
	Q3	10.53	0.21 (0.05 to 0.36)	0.18 (0.03 to 0.34)
	Q4	21.91	0.23 (0.08 to 0.39)	0.23 (0.07 to 0.38)
	P-trend[a]		0.01	0.02
Phthalic acid	Q1	212	0.00 (reference)	0.00 (reference)
	Q2	369	0.16 (−0.01 to 0.33)	0.19 (0.02 to 0.36)
	Q3	641	0.17 (0.00 to 0.34)	0.21 (0.04 to 0.38)
	Q4	1326	0.30 (0.13 to 0.47)	0.33 (0.15 to 0.50)
	P-trend		0.002	0.001
MEP	Q1	88	0.00 (reference)	0.00 (reference)
	Q2	321	− 0.01 (−0.16 to 0.15)	− 0.01 (−0.17 to 0.15)
	Q3	725	0.15 (−0.01 to 0.30)	0.16 (0.01 to 0.32)
	Q4	2198	0.09 (−0.07 to 0.25)	0.08 (−0.07 to 0.24)
	P-trend		0.23	0.27
MBzP	Q1	20	0.00 (reference)	0.00 (reference)
	Q2	47	0.29 (0.13 to 0.44)	0.29 (0.13 to 0.44)
	Q3	90	0.35 (0.20 to 0.51)	0.33 (0.17 to 0.48)
	Q4	252	0.45 (0.29 to 0.60)	0.42 (0.26 to 0.57)
	P-trend		<0.001	< 0.001
Sum of butyl phthalates[b]	Q1	67	0.00 (reference)	0.00 (reference)
	Q2	140	0.19 (0.04 to 0.34)	0.19 (0.03 to 0.34)
	Q3	249	0.24 (0.09 to 0.40)	0.21 (0.06 to 0.37)
	Q4	481	0.37 (0.22 to 0.52)	0.34 (0.18 to 0.50)
	P-trend		o0.001	< 0.001
DEHP metabolites[c]	Q1	115	0.00 (reference)	0.00 (reference)
	Q2	204	0.04 (−0.12 to 0.19)	0.03 (−0.13 to 0.18)
	Q3	353	0.28 (0.12 to 0.43)	0.27 (0.12 to 0.43)
	Q4	870	0.07 (−0.08 to 0.23)	0.08 (−0.07 to 0.24)
	P-trend		0.55	0.42
Total phthalates[d]	Q1	500	0.00 (reference)	0.00 (reference)
	Q2	962	0.08 (−0.07 to 0.24)	0.09 (−0.07 to 0.24)
	Q3	1688	0.18 (0.02 to 0.33)	0.21 (0.06 to 0.37)
	Q4	4094	0.17 (0.02 to 0.33)	0.17 (0.02 to 0.33)
	P-trend		0.05	0.05

Abbreviations: BPA, bisphenol A; DEHP, di-2-ethylhexyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate. Conversion factor: BPA (nmol l^{-1}) ×0.228=BPA (μg l^{-1}). Numbers are adjusted for prospective weight change rate (kg per year) and 95% CI, relative to the rate of

individuals in the first quartile. Model 1: adjusted for urinary creatinine concentration. Model 2: adjusted for urinary creatinine concentration, cohort origin, age, menopausal status, smoking, physical activity, alcohol consumption, AHEI, total energy intake and baseline body weight.

[a] P-values for linear trend were obtained by examining an interaction term between follow-up duration and median concentration of the quartiles in the mixed-effects models.

[b] Include MBP and MiBP.

[c] Include MEHP, MEHHP, MCEPP and MEOHP.

[d] Include MEP, MBzP, MBP, MiBP, MEHP, MEHHP, MCEPP and MEOHP.