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RESEARCH ARTICLE

Association of bisphenol A exposure with overweight in the elderly: a panel study

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Abstract Bisphenol A (BPA) is an ubiquitous chemical, which is an endocrine disruptor. Recent epidemiological studies have suggested a relationship between BPA exposure and body weight. However, most of these studies were cross-sectional and not on elderly people. We conducted a panel study with repeated measurements to evaluate the relationship between BPA and overweight in elderly people. A total of 560 elderly participants aged ≥60 years were recruited in Seoul from 2008 to 2010. Urinary BPA levels and body mass index (BMI, kg/m^2) were measured at every visit. We defined a BMI ≥25 as overweight and examined the relations between urinary BPA and BMI or overweight. Repeated measures analysis was performed after adjusting for age, sex, low-density lipoprotein cholesterol levels, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine levels, and the status of diabetes mellitus. The geometric mean of BPA was 0.67 μg/g creatinine. The odds ratio (OR) of overweight was 1.17 (95 % confidence interval [CI] 1.04–1.32) per interquartile range increase of log-transformed BPA. When stratified based on sex, we observed a significant association in women (OR 1.25; 95 % CI 1.09–1.45) but not in men (OR 0.97; 95 % CI 0.77–1.22). The ORs of overweight increased with quartiles of BPA in women (quartile 2 vs 1: OR 1.54; 95 % CI 1.02–2.32, 3 vs 1: OR 1.70; 95 % CI 1.10–2.62, and 4 vs 1: OR 1.81; 95 % CI 1.13–2.92). Our results suggest that urinary BPA levels are significantly associated with overweight in elderly women but not elderly men.

Keywords Bisphenol A · BMI · Overweight · Elderly people · Sex difference · Panel study

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Introduction

Bisphenol A (4,40-isopropylidenediphenol, BPA) is an endocrine disruptor, which acts similar to estrogen and is widely used in daily life (Rogers et al. 2013). The production volume of BPA increased from 2.8 million metric tons in 2002 to 5.5 million metric tons in 2011 (Rochester 2013). As a result of ubiquitous use of BPA, human exposure to BPA has been so prevalent that 92.6 % of the population of the USA who were older than 6 years old was reported to have detectable BPA in urine according to a report from the National Health and Nutrition Examination Survey (NHANES) (Calafat et al. 2008).

The geometric mean of BPA was 1.51 μg/L in the 2011–2012 NHANES (CDC 2014). The Korean National Environmental Health Survey reported that the BPA concentration was 0.97 μg/g creatinine in adults older than 19 years (men, 0.90 μg/g creatinine; women, 1.05 μg/g creatinine) in 2011.

Recent studies have shown evidence for a relation between exposure to BPA and chronic disease. Sabanayagam et al. (Sabanayagam et al. 2013) reported a positive association between urinary BPA and diabetes, and this association was stronger among women and obese subject. Bae et al. (Bae et al. 2012) suggested that urinary BPA was associated positively with hypertension. Because obesity is a common risk factor for many chronic diseases, including diabetes and cardiovascular disease (Aballay et al. 2013), this suggests that obesity plays a role in the association between BPA exposure and chronic disease.

Epidemiological studies have shown that BPA exposure in childhood is linked to obesity of children (Bhandari et al. 2013; Li et al. 2013; Trasande et al. 2012; Wang et al. 2012a). Using the NHANES 2003–2008 data, Trasande et al. (Trasande et al. 2012) and Bhandari et al. (Bhandari et al. 2013) suggested that BPA concentrations are associated with body mass index (BMI) and the prevalence of obesity. Harley et al. (Harley et al. 2013) showed that BPA concentrations in 9-year-old children are positively associated with BMI, waist circumference, fat mass, and overweight/obesity. Cross-sectional studies in adults also showed that high-level exposure to BPA is related to obesity (Carwile and Michels 2011; Ko et al. 2014; Shankar et al. 2012; Wang et al. 2012b). A recent study showed that BPA was positively associated with weight change during 10 years in American adult women using data of the Nurses' Health Study (NHS) and NHSII (Song et al. 2014).

Several studies have suggested a biological pathway between BPA and obesity, but the mechanism of the metabolic action of BPA on adipocytes is still unclear (Alonso-Magdalena et al. 2011; Nadal 2013). BPA acts through phosphatidylinositol 3-kinase (PI 3-kinase), resulting in accelerated terminal adipocyte differentiation (Boucher et al. 2014; Masuno et al. 2005; Masuno et al. 2002), and stimulates triacylglycerol accumulation in mature adipocytes (Wada et al. 2007). Suppression of adiponectin release (Ben-Jonathan et al. 2009; Hugo et al. 2008) and a change in hypothalamic action (Mackay et al. 2013) have been suggested as other possible mechanisms.

Although many studies have shown a relationship between BPA and obesity in childhood and adulthood, to the best of our knowledge, there are no studies on the effect on obesity in the elderly population from exposure to BPA. Therefore, we examined the association between BPA exposure and obesity in elderly people using a panel study with repeated measurements.

Materials and methods

Study design and participants

The Korean Elderly Environmental Panel (KEEP) study is an epidemiological study with 560 participants who were aged 60 years or older and regularly visited a community welfare center located in Seongbuk-gu, Seoul, Korea. The study period was from August 2008 to August 2010. Five repeated examinations were performed during this period: twice in 2008 (from August to December 2008 and from October 2008 to January 2009), once in 2009 (from April to October 2009), and twice in 2010 (from March to August 2010 and from July to August 2010). At initial examination, we recruited participants by visiting community welfare center, explaining and taking consent about study personally. At repeated study, we did follow-up survey for initially recruited participants. We finally analyzed 558 people (total of 1571 samples) for this study after excluding subjects without available measurements for urinary BPA and BMI.

Urine samples were obtained and physical examinations were performed at each visit from 10:00–12:00 h. We collected spot urine and took physical examination at each visit: 558 samples in first visit, 471 samples in second visit, 316 samples in third visit, 181 samples in fourth visit, and 45 samples in fifths visit. During the five repeated follow-up study period, 87 participants had spot urine sample and physical examination only once, 155 had twice, 135 had three times, 136 had four times, and 45 five times. Missing value in urine sample or physical examination had excluded in analysis.

Participants were interviewed with a structured questionnaire at the initial visit regarding demographic characteristics, lifestyle behavior, environmental exposure, and dietary intake. All of the participants provided informed consent, and the study plan was approved by the institutional review board of Seoul National University Hospital (IRB no. H-0804-045-241).

Measurement of urinary BPA concentrations

We collected spot urine samples (50 mL) in conical tubes (SPL Lifesciences, Pocheon, Gyunggi-do, Korea) from each participant who fasted more than 8 h before the examination. These samples were divided into four 12-mL tubes, stored at −20 °C in a freezer, and carried to the laboratory (NeoDin Medical Institute, Seoul, Korea) within 90 min. Blank, standard solution, quality control materials (48th G-EQUAS A and B), and urine samples were placed into a tube in 500-mL aliquots. These aliquots were buffered with 30 μL 2 M sodium acetate (pH 5.0) and spiked with 25 μL ISTD BPA (RING-13C12, 99 %, Cambridge Isotope Lab., Inc, Tewksbury, MA, USA) and 10 μL β-glucuronidase/sulfatase type HP-2S from *Helix pomatia* (Sigma, St. Louis, MO,

USA). We incubated samples at 37 °C for 3 h to deconjugate the glucuronidated BPA, added 100 μL 2 N HCl and 4 mL ethyl acetate, and centrifuged at 1736×*g* for 5 min. The extract was dried with nitrogen gas and reconstituted with 1 mL high-performance liquid chromatography (HPLC)-grade H_2O in a 2-mL glass vial. We subsequently used liquid–liquid extraction. The analytic column was an Agilent Eclipse plus C18 (3.5 μm, 2.1×100 mm) (Agilent technologies, Santa Clara, CA, USA). The mobile phase was acetonitrile/water (60:40, *v*/*v*) at a flow rate of 0.4 mL/min. We measured urinary BPA concentrations using HPLC tandem mass spectrometry (HPLC: Agilent 1200, USA; MS/MS: Agilent 6410 Triple Quad LCMS, Agilent, USA). We measured total BPA, including free and conjugated BPA. The limit of detection was determined at the lowest concentration to detect a signal-to-noise ratio of 3. The LOD for urinary BPA was 0.01 μg/L and BPA level with below the LOD was coded as half the LOD (0.005 μg/L).

Anthropometric measurements

Trained health technicians measured body weight (kg) and height (cm) following standardized procedures for all of the participants. BMI was calculated as body weight in kilograms divided by height in meters squared. Overweight was defined as 25 kg/m^2 or over using criteria of the World Health Organization (WHO 2004).

Dietary assessment

A trained dietary interviewer used a food frequency questionnaire (FFQ) to assess dietary intake for the past year, and this included 114 food items at the first visit. The frequency of servings was classified into nine categories: never or seldom, once a month, two to three times a month, one to two times a week, three to four times a week, five to six times a week, once a day, twice a day, and three or more times a day. The portion size of the food items was classified as follows: small, medium, or large. The FFQ method has been previously validated (Oh et al. 2007). Dietary intakes of nutrients and food groups were analyzed using CAN-pro 3.0 software (The Korean Nutrition Society, Seoul, Korea). Nutrient intake was adjusted for total energy intake by the residual method to avoid bias because of the simple relationship between nutrient intake and total energy intake (WC 1998).

Data analysis

Urinary BPA was adjusted by creatinine to account for variation in urinary flow for each individual. We determined arithmetic means of urinary BPA and their statistical significance for each demographical characteristic from the initial visit using ANOVA. Because urinary BPA concentrations were not normally distributed, log-transformed BPA values were used in analysis. We constructed repeated measurements analysis models using generalized estimating equations to determine odds ratios of overweight by increasing levels of urinary BPA. In generalized estimating equations model, we used log-transformed BPA in each visit and quartiles of the concentration of urinary BPA in each visit measurement were defined with the cut points of 0.35, 0.67, and 1.09 μg/g of creatinine for men and 0.39, 0.76, and 1.42 μg/g of creatinine for women, respectively. We include overweight for outcome in generalized estimating equations analysis from each visit physical examination.

Multivariate modeling was used with covariates, which were associated with BMI in univariate analysis (age [years], sex [male and female], diabetes mellitus [diagnosed or fasting blood glucose ≥100]) or were previously reported in relation to obesity (low-density lipoprotein cholesterol level [mg/dL], alcohol consumption [yes or no], regular exercise [yes or no], total calorie intake [kcal], fatty acid intake [g/day], and urinary cotinine concentrations [mg/g]) (Chen et al. 2008; Shankar et al. 2012; Shin et al. 2013; Trasande et al. 2012). We used urinary cotinine concentrations to represent direct and indirect smoking instead of smoking questionnaires.

In addition, we conducted sensitivity analysis after excluding participants with log-transformed BPA>mean+3 standard deviation (SD) or < mean −3 SD. Assuming that the average BPA level from five visits represent chronic exposure, we performed additional analysis using average BPA levels of each participant. We conducted additional analysis using weight values yielded by inverse probability of attaining a follow-up response to adjust the non-random loss of follow-up due to different number of repeated measures (McCracken et al. 2010; Robins et al. 1995).

All analyses applied two-sided tests and we considered a p value lower than 0.05 as statistically significant. Statistical analyses were conducted using R version 2.15.2 (The Comprehensive R Archive Network: http://cran.r-project.org) and SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Participants' characteristics at the first visit and mean BPA levels are shown in Table 1. The mean age of 558 participants was 70.5 years (range, 60–87 years) and the ratio of men to women was approximately one-third. Overweight was present in 43 % of participants. We observed higher BMI with higher mean of BPA, but this was not significant.

The arithmetic and geometric mean, minimum, maximum, and quartiles of urinary BPA at each visit all are shown in Supplemental Material Table S1. The arithmetic and geometric

Table 1 Demographic properties of the study population from the first visit of participants (n=558)

		Numbers	Percentage (%)	Mean BPA levels ±STD (μg/g crea)	p value
Sex	Men	146	26.16	0.96±1.42	0.052
	Women	412	73.84	1.32±2.06	
Age group	60 to 69	249	44.62	1.39±2.31	0.183
	70 to 79	286	51.25	1.11±1.53	
	>80	23	4.12	0.93±1.38	
Smoking	Never	477	85.48	1.24±1.93	0.951
	Past	36	6.45	1.14±1.30	
	Current	31	5.56	1.22±2.33	
	Missing	14	2.51		
Alcohol consumption	No	420	75.27	1.29±2.05	0.218
	Yes	121	21.68	1.05±1.36	
	Missing	17	3.05		
Regular exercise	No	202	36.2	1.33±2.21	0.383
	Yes	342	61.29	1.18±1.72	
	Missing	14	2.51		
Body mass index	<18.5	6	1.08	0.82±0.57	0.563
	18.5–24.9	310	55.56	1.14±1.78	
	25.0–29.9	218	39.07	1.35±2.18	
	>30.0	24	4.3	1.40±1.06	

mean of BPA in all samples was 1.34 and 0.67 μg/g of creatinine, respectively. Overweight was present in 44.4 % of all samples.

There was a significant increase in prevalence of overweight with log-transformed BPA exposure per interquartile range increase (IQR 0.96 μg/g of creatinine) with the assumption of a monotonic relationship between BPA levels and overweight (Table 2). When adjusted by age, sex, low-density lipoprotein cholesterol levels, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine concentrations, and diabetes, the odds ratio (OR) and 95 % confidence interval (CI) was 1.17 (1.04, 1.32) per IQR increase in log-transformed BPA. Stratification by sex showed a significant association in women (OR 1.25; 95 % CI 1.09, 1.45), but there was no significant association in men.

Finally, we performed generalized estimating equations analysis using quartiles of urinary BPA because there was a non-linear association between BMI and urinary BPA in graphical analysis (Fig. 1). Women in the highest quartile for urinary BPA had almost twice the odds for the prevalence of obesity (OR 1.81; 95 % CI 1.13, 2.92) compared with women in the lowest quartile, but there were no significant associations in men (OR 0.91; 95 % CI 0.41, 2.04).

To evaluate relations between acute and chronic exposure measurements, we performed Pearson correlations between a single measurement and the average measurement of five samples. The correlation coefficients ranged from 0.36 to 0.95, suggesting that a single measurement of urinary BPA could represent chronic exposure in these study subjects (Supplemental Material, Table S2). When we performed analysis using the average urinary BPA of each subject, significant results were also shown for women, but not for men (Supplemental Material, Table S3). Results were essentially unchanged when we excluded participants

Table 2 Odds ratios for overweight according to log-transformed bisphenol A levels per interquartile range increase using generalized estimating equations model

	Total (n=1571)	Women (n=1189)	Men (n=382)
Not adjusted	1.15 (1.05, 1.26)	1.18 (1.07, 1.31)	1.02 (0.86, 1.22)
Age and sex adjusted	1.14 (1.05, 1.25)	1.18 (1.06, 1.31)	1.02 (0.86, 1.22)
Additional adjustment[a]	1.17 (1.04, 1.32)	1.25 (1.09, 1.45)	0.97 (0.77, 1.22)

[a] Additionally adjusted by age, sex, low-density lipoprotein cholesterol level, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine concentrations, and diabetes

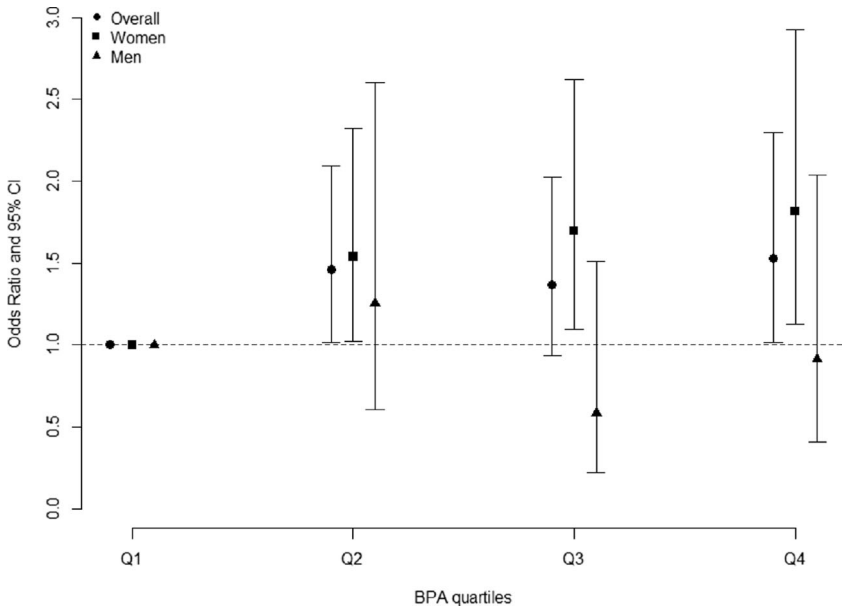

Fig. 1 Odds ratios and 95 % confidence intervals for overweight according to quartile bisphenol A levels. *Q* quartile, *CI* confidence interval. Additionally adjusted for age, sex, low-density lipoprotein cholesterol levels, alcohol consumption, regular exercise, total calorie intake, fatty acid intake, urinary cotinine concentrations, and diabetes

with log-transformed BPA >3.23 (mean +3 SD) or<−4.03 (mean −3 SD) (Supplemental Material, Tables S4 and S5). Upon weighting or not weighting inverse probability of attaining a follow-up response, we found no difference in direction and significant of effect estimate (Supplemental Material, Table S6).

Discussion

We found that urinary BPA levels were significantly associated with overweight in elderly women after adjustment for possible confounders, but not in the men. This finding is consistent with animal studies where exposure to BPA led to more persistent increase in weight in females than in males (Rubin 2011; Rubin and Soto 2009).

Previous epidemiological studies have also reported an association between BPA exposure and obesity, but a sex difference was not consistent. Carwile and Michels (Carwile and Michels 2011), using 2003–2006 NHANES data, and Shankar et al. (Shankar et al. 2012), using 2003–2008 NHANES data, observed higher BPA exposure associated with general and central obesity in women and men. A recent study showed that BPA concentrations were positively associated with waist circumference in Korean women, but not in men (Ko et al. 2014). Song et al. (Song et al. 2014) found that the highest quartile of BPA compared with the lowest quartile had weight gain (0.23 kg per year) during a 10-year follow-up in American women using NHS and NHSII.

In children, Trasande et al. (Trasande et al. 2012) examined 2003–2008 NHANES data and found that the OR for obesity was 2.53 (95 % CI 1.72, 3.74). Another study reported that BPA levels are associated with BMI, weight circumference, and overweight/obesity in children using the CHAMACOS cohort study (Harley et al. 2013). Trasande et al. (Trasande et al. 2012) and Harley et al. (Harley et al. 2013) found significant associations between BPA and obesity in boys and girls. A previous report showed that the highest quartiles of BPA level compared with the lowest quartile significantly increased the risk of obesity using 2003–2008 NHANES data (OR 2.55; 95 % CI 1.65, 3.95) and this finding was predominant in boys compared with girls (Bhandari et al. 2013). BPA and BMI were found to be significantly associated in Chinese school students aged 8–15 years, and this result remained significant in girls, but not in boys (Wang et al. 2012a). Li et al. (Li et al. 2013) observed that high urine BPA levels were associated with overweight only in girls, but not in boys.

The biology of the sex difference in the association between BPA levels and obesity can be explained in several ways. First, the reason for this sex difference may be due to different responses of the energy balance system to BPA exposure. Female mice exposed to a high dose of BPA have reduced proopiomelanocortin transcription, leading to increasing dietary intake and decreased energy expenditure, which results in more weight gain or body fat. In contrast, male mice do not gain more weight or body fat (Mackay et al. 2013). Second, we assume that different numbers of estrogen receptors may cause a sex-specific relationship because BPA acts on estrogen receptors, which could lead to obesity (Alonso-Magdalena et al. 2006; Ben-Jonathan et al. 2009; Hugo et al. 2008) Postmenopausal women have a relatively higher number of estrogen receptors than men (Ishunina et al. 2000). This finding is similar to a previous study, which reported that BPA-induced health effects, such as oxidative stress and inflammation by BPA, are predominant in postmenopausal women (Yang et al. 2009). Third, women have more

body fat than men when they have the same BMI (Jackson et al. 2002). Therefore, women may have higher BPA levels than men because BPA may be stored in adipose tissue (Fernandez et al. 2007; Stahlhut et al. 2009).

Several studies have suggested a biological pathway between BPA and obesity, but a definite pathway is still not clear. The first possible mechanism is that BPA is associated with adipocyte maturation and triacylglycerol accumulation in adipocytes. Insulin binds to receptors in preadipocytes, resulting in activated PI 3-kinase, which promotes terminal differentiation of preadipocytes into adipocytes (Gregoire et al. 1998; Xia and Serrero 1999). Masuno et al. (Masuno et al. 2005; Masuno et al. 2002) suggested that BPA acts through PI 3-kinase, resulting in accelerated terminal adipocyte differentiation and triacylglycerol accumulation in adipocyte. The second possible mechanism is associated with adiponectin and inflammatory cytokines. Hugo et al. (Hugo et al. 2008) and Ben-Jonathan et al. Ben-Jonathan et al. (2009) suggested that binding BPA to estrogen receptors in adipose tissue inhibits adiponectin, which is an adipocyte-specific hormone that protects against obesity. Third, BPA is thought to affect the hypothalamic arcuate nucleus, which regulates food intake and energy balance. Early life BPA exposure acts as obesogen in the adult by decreasing the metabolic rate and reducing proopiomelanocortin neurons in the hypothalamic arcuate nucleus, and this results in increased food intake (Mackay et al. 2013).

With regard to metabolism of BPA, BPA is metabolized into BPA conjugates with glucuronic acid in the liver to become a water-soluble compound and minor amounts of BPA form BPA-sulfate (Matthews et al. 2001). BPA conjugates formed in the liver are delivered to the kidney and are rapidly excreted in the urine and their half-life in humans is less than 6 h (Volkel et al. 2005; Volkel et al. 2002). However, some researchers have suggested that BPA could be accumulated in body fat. Using the 2003–2004 NHANES data, Stahlhut et al. (2009) observed that BPA levels did not rapidly decline with longer fasting times, which is opposite to the expected pattern. They explained that the half-life of BPA is longer than previously reported because BPA stored in body tissue, such as fat, is released over time. A recent study showed similar findings in that urinary BPA patterns in five subjects over a 48-h period of fasting had fluctuations in BPA levels and these levels did not decline to below the detection limit (Christensen et al. 2012). Rudel et al. (2011) studied 20 participants who received fresh food intervention and showed that the decrease in BPA levels was less than predicted from pathway-based estimates of BPA intake. BPA was reported to be present in adipose tissue in adult women, with a mean value of 3.16 ng/g of adipose tissue (Fernandez et al. 2007). Therefore, there is a possibility that adipose tissue could store BPA, which influence the release of BPA.

Many previous epidemiological studies were based on cross-sectional data, which used measurement of a single spot urine sample (Bhandari et al. 2013; Carwile and Michels 2011; Shankar et al. 2012; Trasande et al. 2012; Wang et al. 2012a). Whether a single measurement of BPA can represent long-term exposure of BPA is controversial. Because BPA has a short half-life in the human body, urinary levels of BPA may provide estimated exposure of only a few previous days (Dekant and Volkel 2008). However, if a study sample has a large number of subjects and they are randomly collected, a single spot sample of BPA may represent the average exposure of the population (Ye et al. 2008). Because we measured urinary BPA five times repeatedly during 3 years, we performed Pearson's correlation between each measurement and the average value from five times was calculated. The correlation coefficients were 36–95 %, suggesting that variability within persons is small and a single measurement is representative of chronic exposure when BPA is measured at the same hour of the day after fasting more than 8 h. When we performed reanalysis using average BPA concentrations for each participant, the results were not different from analysis with single measurements.

Wang et al. (2014) proposed that overweight and obese children have higher urinary BPA concentrations than normal weight children because overweight and obese children consume more canned food and drinks. Fat (margarine, oils, shortening, butter, and animal fats) consumption is associated with increased urinary concentrations of BPA (Mervish et al. 2014). However, in our study, after adjusting for caloric intake and fatty acid intake, the association between BPA and obesity remained significant.

The primary strength of our study is that this is the first report of an association of urinary BPA and obesity for elderly people. Second, our study was a panel study design, which includes repeated samples, which enabled between- and within-subject variation to be taken into account. Third, when we excluded samples with extreme BPA concentrations for sensitivity analysis, the relationships were not different from results including the outliers.

Our study has several limitations. First, our results provide limited interpretation for a causative role of BPA in a change in body weight because of the nature of cross-sectional measures, despite the approach of repeated measures design. Second, our study population was elderly people (≥60 years). Therefore, our results cannot be directly applied to the general population because elderly people could be different in terms of effects from BPA exposure. Third, we did not collect data on waist circumference. Therefore, we could not show an association between BPA and abdominal obesity, which may be more relevant to chronic disease. Fourth, we could not exclude the possibility that overweight subjects had a higher BPA level because BPA could store and accumulate in fat cell. In addition, women could have different metabolism routes which lead to more store of BPA in fat cell.

Conclusion

Our results indicate that an increase in BPA concentrations is related to a risk of obesity in elderly women, but not in men. Efforts for lowering exposure to BPA are important to improve health, particularly in elderly women.

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Conflict of interest The authors declare that they have no conflict of interests.

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