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Relationship Between Urine Bisphenol-A Level and Declining Male Sexual Function

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ABSTRACT: The adverse effect of bisphenol-A (BPA) on the male reproductive system observed in animal studies has not been well examined in human populations. BPA is potentially a serious public health problem because of its widely detected presence in the human body. This study was conducted among 427 male workers in regions where high levels of BPA exposure existed. All participants provided urine samples, which were tested for BPA concentration using high-performance liquid chromatography. Male sexual dysfunction was ascertained using standard male sexual function inventories. Male sexual dysfunction was measured in 4 domains using 7 indices. After controlling for potential confounders using linear regression, increasing urine BPA level was associated with worsening male sexual function on a continuous scale. All 7 indices demonstrated this negative linear correlation. Increasing urine BPA level was associated with decreased sexual desire ($P < .001$), more difficulty having an erection ($P < .001$), lower ejaculation strength ($P < .001$), and lower level of overall satisfaction with sex life ($P < .01$). A similar negative correlation was also observed among participants exposed to BPA from only environmental sources (no occupational exposure to BPA), although the estimates in this group were less stable because of a smaller sample size. Our results reveal a correlation between a biological measure of urine BPA level and declining male sexual function. This finding may enhance the understanding of the BPA effect in human populations, and may have important public health implications given the widespread human exposure to BPA.

Key words: BPA, epidemiology, cohort study, male reproductive system, sexual dysfunction.

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Bisphenol-A (BPA) is an ingredient in manufacturing polycarbonate plastic and epoxy resins and a highly suspected endocrine disruptor (Kuehn, 2007). BPA is now contained in a wide variety of consumer products, from baby bottles, plastic containers, and the resin lining of cans for food and beverages, to dental sealants (Chapin et al, 2008; National Toxicology Program, 2008). People are exposed to BPA by using BPA-containing plastic products (Carwile et al, 2009). Because of its widespread presence in the environment and consumer products, humans are constantly exposed to BPA. In US representative samples, BPA was detected in more than 92% of spot urine samples (Calafat et al, 2008; Chapin et al, 2008), and similar urine BPA levels in the populations of other countries have also been reported (Kim et al, 2003; Matsumoto et al, 2003; Miyamoto and Kotake, 2006).

BPA exhibits both estrogenic and antiandrogenic effects in animal studies (Sohoni and Sumpter, 1998; Lee et al, 2003; Xu et al, 2005; Sun et al, 2006; Richter et al, 2007; Wetherill et al, 2007; Chapin et al, 2008). Its endocrine bioactivities demonstrated in animal studies make it a potential human endocrine disruptor. BPA has been reported in in vitro and in vivo studies to affect the male reproductive system, including androgen receptors (ARs), male sex hormone levels, male reproductive organs including testes and epididymis, sperm and seminal vesicles, prostate gland, and sperm production (Richter et al, 2007; National Toxicology Program, 2008; Bouskine et al, 2009; Salian et al, 2009a,b; Li et al, 2010). Changes in sexual behavior such as reduced

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latency and frequency of intromission have been reported in rodents exposed to BPA (Farabollini et al, 1999; Dessi-Fulgheri et al, 2002; Worley et al, 2002; Richter et al, 2007; vom Saal et al, 2007; Wetherill et al, 2007; Chapin et al, 2008; Palanza et al, 2008). However, human studies of the reported effects of BPA on the reproductive system remain largely absent, as pointed out by 2 US government panels convened by the National Toxicology Program and the National Institute of Environmental Health and Sciences (Kuehn, 2007; vom Saal et al, 2007; Chapin et al, 2008), respectively.

Epidemiological studies with findings on the BPA effect on human endpoints are needed to evaluate the risks of BPA to the human population. Recently, we reported an increased risk of reduced male sexual function associated with occupational exposure to BPA (Li et al, 2010). However, in the reported study, BPA exposure was based on the classification of BPA exposure in the workplace compared to those without BPA exposure in the workplace. In the present study, we used urine BPA level as a biological measure of individual BPA exposure level among a subgroup of workers who provided urine specimens for assays. We examined whether the level of BPA in urine, a biological marker of BPA exposure, is related to male sexual dysfunction to confirm or refute the previous reported association between a high BPA exposure in the workplace and the risk of male sexual dysfunction (Li et al, 2010). If the urine biomarker of BPA exposure is associated with male sexual dysfunction, it will provide additional evidence to support the reported finding of an increased risk of male sexual dysfunction associated with high BPA exposure (Li et al, 2010).

Materials and Methods

A more detailed description of the study population, recruitment, and ascertainment of BPA exposure, outcomes, and other risk factors can be found elsewhere (Li et al, 2010). The following are the descriptions of the study methods relevant to the current study.

Study Population

The study was conducted among workers in 4 regions of China. The regions were chosen because there were factories where BPA or epoxy resin was manufactured. Epoxy resin manufacturers use BPA as one of their raw materials. Therefore, workers with exposure to high BPA levels in the workplace could be identified and recruited for the study. We also identified and recruited workers from factories with no occupational exposure to BPA in the work environment in the same regions. Among 888 workers identified, 514 (58%) agreed to participate.

Two Chinese academic and research institutions in Shanghai participated in data collection for the study. This study was approved by the Institutional Review Boards of Kaiser Permanente as well as the 2 Chinese collaborating institutions. An informed consent form was obtained from participants before their participation in the study.

Urine BPA Level

All participants were asked to provide urine samples for analysis of urine BPA levels. For workers with BPA exposure in the workplace, 2 spot urine samples from each participating worker were collected during each of the following time periods: before and after their work shift, respectively. For workers without BPA exposure in the workplace, only 1 spot urine sample was collected because their work shift should not have an effect on their urine BPA levels. For each urine sample, the total urine BPA concentration (free plus conjugated species) was measured using high-performance liquid chromatography (HPLC) as described previously (Yang et al, 2003; He et al, 2009). Briefly, urine samples were mixed with phosphorous acid buffer and β-glucuronidase (Sigma Chemical Co, St Louis, Missouri) for hydrolyzation. Afterwards, samples were extracted twice with ether (HPLC grade; Dikma, Lake Forest, California) and supernatants were evaporated with nitrogen gas. The residue was dissolved in 60% acetonitrile and analyzed by HPLC with fluorescence detection. The limit of detection (LOD) was 0.31 μg/L, which was comparable to LODs reported in previous studies (Calafat et al, 2008). The assay was conducted by coauthors at the Department of Occupational Health and Toxicology, School of Public Health & WHO Collaborating Center for Occupational Health, Fudan University, Shanghai, China. Detailed methodology involved in the assay has been published elsewhere (He et al, 2009).

Urine BPA level was measured by both volume-based (μg/L) and creatinine-corrected (μg/g creatinine) concentrations. To adjust for urine volume, we used creatinine-corrected (μg/g creatinine) BPA concentration in the analyses. To make the measurement more stable, we used the average of BPA levels for workers who provided both preshift and postshift urine samples. Fifty-eight participants who did not provide urine samples were excluded from this analysis.

Outcome Measurement

Sexual functioning among participating male workers was ascertained through an in-person interview. Questions about sexual function were based on the International Index of Erectile Function and the Brief Male Sexual Function Inventory (O'Leary et al, 1995; Rosen et al, 1997; Mykletun et al, 2006). These instruments have been used in the Chinese population in many previously reported studies (He et al, 1976; Yu et al, 2007; Guo et al, 2009; Wang et al, 2009; Xie et al, 2009).

We ascertained sexual function for the following domains: sexual desire (1 measurement), erectile function (3 measurements), orgasmic function (2 measurements), and overall satisfaction with sex life (1 measurement). Participants provided answers about their sexual function based on a discrete scale (0–10 or 1–4). To determine the impact of current

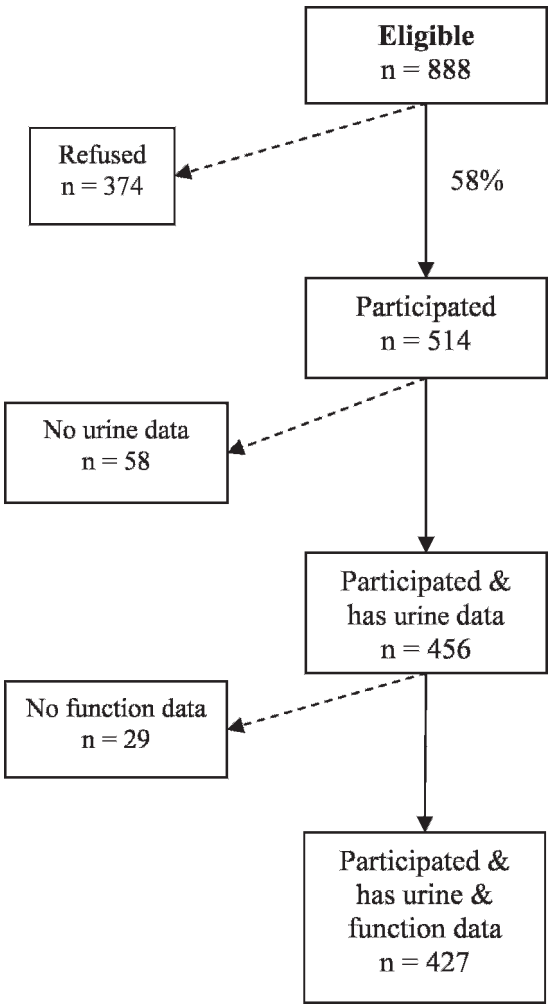

Figure. Recruitment and inclusion of subjects.

urine BPA level on sexual function, we ascertained sexual function during the past 6 months. Twenty-nine participants who did not provide answers to sexual function questions, largely because of their lack of sexual activities, were excluded, thus leaving 427 subjects in the final analysis. A detailed description of recruitment and inclusion of participants is presented in the Figure.

Through the in-person interview, we also ascertained information on potential confounders, including 1) demographic characteristics; 2) factors that may influence sexual function, including smoking, alcohol use, chronic diseases, and exposure to other chemicals and heavy metals; and 3) occupational history.

Analyses

General linear regression was used to examine the correlation between urine BPA level and the scale of sexual function after adjustment for potential confounders. The coefficient was used to measure the strength of the association between urine BPA level and declining male sexual function, and its associated *P* value was used to determine whether the correlation was statistically significant. Because of the skewed distribution of urine BPA data and reported sexual function scales, these variables were included in the regression model after $\log_{10}$ transformation, except for the 2 sexual function outcomes with a scale of 1–4. For the $\log_{10}$ transformation of urine BPA levels, as conventionally accepted practice, values of 0 were imputed as LOD/($\sqrt{2}$) (Calafat et al, 2008; Hornung and Reed, 1990). For sexual function outcomes with scales ranging from 0 to 10, in order to use the 0 values, the scale was shifted up by 1 unit (1–11) prior to $\log_{10}$ transformation.

Results

Table 1 presents a description of characteristics in relation to urine BPA concentration in the study population. The largest difference in urine BPA concentration was associated with exposure to BPA in the workplace. Workers who had previously worked in the chemical industry were more likely to work currently in the BPA-exposed factories, which themselves are also part of the chemical industry. Thus, the higher BPA level among those with a history of exposure to other chemicals reflects their current exposure to BPA in the workplace. That was also the case for employment history, where those with occupational BPA exposure were more likely to be in the category of 1–5 years of employment. Smokers had a higher urine BPA level than nonsmokers and those who were 25–30 and 40–45 years old had a higher urine BPA concentration because of a larger proportion of workers with occupational BPA exposure in these age groups. However, these differences were not statistically significant. A history of chronic disease and alcohol use, which could adversely impact the male reproductive system, was not related to urine BPA concentration.

Table 2 shows the associations between urine BPA level and 7 measures of male sexual function in 4 categories (sexual desire, erectile function, orgasmic function, and overall satisfaction with sex life). After adjustment for potential confounders, increasing urine BPA level was associated with decreasing male sexual function for all 7 measures. The dose-response correlation was statistically significant for 6 of them: a higher urine BPA level was associated with reduced sexual desire ($P < .001$), lowered ability to have an erection ($P = .05$), increased difficulty in having an erection ($P < .001$) or ejaculation ($P = .02$), lower ejaculation strength ($P < .001$), and lower overall satisfaction with sex life ($P = .003$). An increased urine BPA level was also associated with reduced ability to have an erection hard enough for penetration. However, this correlation did not reach statistical significance (Table 2). To assess the appropriateness of model choices, we repeated the

Table 1. *Distribution of urine bisphenol-A by characteristics of workers*

Characteristic	Category	No.[a]	BPA, μg/g Cr		
			Median	Interquartile Range (25th–75th percentiles)	*P* Value
Age, y	≤25	32	2.7	(0.0–18.0)	.07
	25–30	93	18.6	(1.6–55.0)	
	30–35	105	6.6	(0.2–26.8)	
	35–40	86	4.8	(0.0–37.9)	
	40–45	48	12.6	(0.0–135.4)	
	>45	63	1.1	(0.0–135.9)	
Education	≤Junior high	126	6.4	(0.0–553.6)	.18
	Senior high	228	9.8	(0.0–36.3)	
	≥College	73	3.5	(0.0–22.7)	
Married	No	59	5.4	(0.4–25.9)	.50
	Yes	368	7.8	(0.0–54.5)	
Employment history, y	<1	42	9.4	(0.5–172.6)	.002
	1–5	122	14.5	(0.1–92.9)	
	≥5	263	4.7	(0.0–30.6)	
History of chronic disease[b]	No	330	7.2	(0.0–42.1)	.67
	Yes	97	7.2	(0.0–38.8)	
Ever exposed to other chemicals or heavy metals[c]	No	272	3.9	(0.0–24.4)	<.001
	Yes	155	20.8	(0.9–121.3)	
Current smoker	No	134	2.3	(0.0–77.7)	.09
	Yes	293	10.0	(0.0–38.8)	
History of alcohol intake	No	317	7.2	(0.0–40.7)	.81
	Yes	110	7.6	(0.0–43.1)	
Occupational exposure to BPA	No	254	1.2	(0.0–11.4)	<.001
	Yes	173	53.7	(8.6–558.9)	

Abbreviations: BPA, bisphenol-A; Cr, creatinine.

[a] The number in each category may not match the total number because of missing values.

[b] Diseases that may impact male sexual function, including urogenital diseases, autoimmune diseases, endocrine disorders, hypertension and other cardiovascular diseases, kidney diseases, and injury to genital organs.

[c] Includes organic solvents, pesticides/herbicides, and heavy metals (eg, lead, mercury).

analysis using ordinal logistic regression, accounting for multiple levels for outcomes. The findings based on ordinal logistic regression were essentially the same as those obtained based on linear regression: increasing urine BPA levels were associated with increased risk of male sexual dysfunction.

To remove the potential confounding effect of previous exposure to other chemicals or heavy metals on the observed association between urine BPA level and male sexual dysfunction, we reanalyzed the data after restricting to participants who did not have a history of exposures to other chemicals or heavy metals. The linear correlation remained (Table 3).

To assess whether the observed association exists among those who had only environmental exposure to BPA, we conducted another analysis restricted to those participants who did not have BPA exposure in the workplace. As shown in Table 4, although the sample size in this analysis was reduced significantly, the association between urine BPA level and measures of male sexual function revealed a similar trend to that shown in Table 2. However, many of the estimates were no longer statistically significant because of the markedly reduced sample size. In addition, our sensitivity analysis indicated that these estimates changed noticeably after outliers were excluded. Therefore, these estimates were not stable and should be interpreted accordingly.

Discussion

Studying the effect of BPA in the human population carries significant public health urgency and could help establish prevention strategies and regulatory policies. Although animal studies have repeatedly demonstrated that BPA has both estrogenic and antiandrogenic effects, studies examining BPA's endocrine-disrupting effects on the human reproductive system have been largely absent. We recently reported an association between exposure to high BPA levels in the workplace and increased risk of male sexual dysfunction (Li et al, 2010). However, the exposure to BPA was measured based on the status of occupational exposure to BPA, not on biological measures.

In this study, we examined the association between BPA exposure and the risk of male sexual dysfunction

Table 2. *Urine bisphenol-A concentration[a] and male sexual function*

Sexual Function in the Past 6 Months	No.	Adjusted β Coefficient for BPA[b]	*P* Value
Sexual desire			
Level of sex drive[c]	423	−0.016[d]	<.001
Erectile function			
Ability to have an erection[e]	425	−0.023	.05
Ability to have an erection hard enough for penetration[e]	424	−0.015	.24
Difficulty level of having an erection[f]	419	0.022[d]	<.001
Orgasmic function			
Difficulty level of ejaculating[f]	393	0.015[d]	.02
Level of ejaculation strength[c]	393	−0.017[d]	<.001
Overall satisfaction with sex life			
Level of satisfaction[c]	390	−0.010[d]	.003

[a] μg/g creatinine, $\log_{10}$-transformed.
[b] Adjusted for age, marital status, and presence of chronic diseases. Additional adjustment for education, employment history, previous exposure to other chemicals or heavy metals, smoking, drinking, and study site did not change results.
[c] Scale 0–10, with 10 indicating highest level of function.
[d] Using $\log_{10}$-transformed sexual function score.
[e] Scale 1–4, with 4 indicating highest ability.
[f] Scale 0–10, with 10 indicating most difficulty.

Table 3. *Urine bisphenol-A concentration[a] and male sexual function in workers with no previous exposure to other chemicals or heavy metals*

Sexual Function in the Past 6 Months	No.	Adjusted β Coefficient for BPA[b]	*P* Value
Sexual Desire			
Level of sex drive[c]	271	−0.018[d]	.001
Erectile function			
Ability to have an erection[e]	271	−0.032	.04
Ability to have an erection hard enough for penetration[e]	270	−0.032	.06
Difficulty level of having an erection[f]	268	0.020[d]	.01
Orgasmic function			
Difficulty level of ejaculating[f]	245	0.011[d]	.14
Level of ejaculation strength[c]	245	−0.014[d]	.01
Overall satisfaction with sex life			
Level of satisfaction[c]	243	−0.013[d]	.009

[a] μg/g creatinine, $\log_{10}$-transformed.
[b] Adjusted for age, marital status, and presence of chronic diseases. Additional adjustment for education, employment history, smoking, drinking, and study site did not change results.
[c] Scale 0–10, with 10 indicating highest level of function.
[d] Using $\log_{10}$-transformed sexual function score.
[e] Scale 1–4, with 4 indicating highest ability.
[f] Scale 0–10, with 10 indicating most difficulty.

Table 4. *Urine bisphenol-A concentration[a] and male sexual function in workers without BPA exposure in the workplace*

Sexual Function in the Past 6 Months	No.	Adjusted β Coefficient for BPA[b]	*P* Value
Sexual Desire			
Level of sex drive[c]	253	−0.016[d]	.01
Erectile function			
Ability to have an erection[e]	253	−0.001	.97
Ability to have an erection hard enough for penetration[e]	252	0.010	.66
Difficulty level of having an erection[f]	248	−0.013[d]	.16
Orgasmic function			
Difficulty level of ejaculating[f]	225	−0.010[d]	.14
Level of ejaculation strength[c]	225	−0.015[d]	.05
Overall satisfaction with sex life			
Level of satisfaction[c]	223	−0.012[d]	.04

[a] μg/g creatinine, $\log_{10}$-transformed.
[b] Adjusted for age, marital status, and presence of chronic diseases. Additional adjustment for education, employment history, previous exposure to other chemicals or heavy metals, smoking, drinking, and study site did not change results.
[c] Scale 0–10, with 10 indicating highest level of function.
[d] Using $\log_{10}$-transformed sexual function score.
[e] Scale 1–4, with 4 indicating highest ability.
[f] Scale 0–10, with 10 indicating most difficulty.

using the urine BPA level among participants who provided urine specimens for assays. In addition to having individual biomarkers of BPA exposure level, the current study allowed us to examine dose-response correlations between urine BPA level (on a continuous scale) and measurement scores of various indices of male sexual function. We observed a dose-response association (a linear correlation) between increasing urine BPA level and declining male sexual function (Table 2). The observed negative association was consistent across all categories measuring male sexual function. This finding is also consistent with the results in the recently reported study, in which BPA exposure was not based on measurement of biomarkers. This consistency both between studies and within the study strengthens the findings from both studies and supports the argument for an underlying effect of exposure to BPA on the risk of male sexual dysfunction in the human population.

Our observed correlation between urine BPA level and the risk of male sexual dysfunction in the human population is also supported by the results from both in vitro and in vivo studies, even at low dose levels similar to current human environmental exposure levels (Richter et al, 2007). BPA has been shown consistently to have both antiandrogenic and estrogenic effects (Sohoni and Sumpter, 1998; Lee et al, 2003; Xu et al, 2005; Sun et al, 2006; Bonefeld-Jorgensen et al, 2007; Richter et al,

2007; Wetherill et al, 2007; Chapin et al, 2008). For example, in vivo studies have shown that rodents exposed to BPA displayed changes in sexual behavior ranging from reduced latency and frequency of intromission (Farabollini et al, 1999; Dessi-Fulgheri et al, 2002; Worley et al, 2002; Richter et al, 2007). In addition, underlying mechanisms for such observed associations have been demonstrated in both in vitro and in vivo studies, including BPA's effect on ARs, male sex hormone levels, male reproductive organs including testes and epididymis, sperm and seminal vesicles, prostate gland, and sperm production (Richter et al, 2007; Bouskine et al, 2009; Li et al, 2009; Salian et al, 2009a,b). Several studies have shown that BPA acts as an AR antagonist that interrupts the normal AR binding activity and interaction between AR and endogenous androgens (Wetherill et al, 2007). It is conceivable that normal male sexual functions such as libido and erectile and orgasmic functions can be adversely impacted if BPA interferes with the function of endogenous androgen and its receptors. BPA has also been shown to interfere with the function of Leydig cells, resulting in a reduction of testosterone biosynthesis and Sertoli cells, resulting in impaired spermatogenesis (Akingbemi et al, 2004; Li et al, 2009; Salian et al, 2009a). BPA has also been shown to affect various tissue and cell structures of male sexual organs through several mechanisms, including possible epigenetic effects (Richter et al, 2007; Wetherill et al, 2007). Finally, the estrogenic effect of BPA could potentially interfere with the hormonal balance and sensitivity of the receptors, thus leading to sexual dysfunction. Therefore, our observed association between BPA exposure and the risk of male sexual dysfunction is biologically plausible and supported by findings from experimental studies.

Although the present study has many strengths, including a biological measurement of urine BPA level, a study population specifically designed to study the effect of BPA exposure, and the ability to ascertain and control for potential confounders, there were a few limitations that need to be kept in mind when interpreting the results. One such limitation was the relatively low participation rate due to, among other demands, the requirement of providing biological specimens. Nevertheless, we have examined the potential participation bias in the previously published paper (Li et al, 2010), concluding that no apparent evidence of biased participation was present that would explain the observed association.

The present finding of an association between urine BPA levels and an increased risk of impaired male sexual function is most likely to reflect the effect of current BPA exposure because of the relatively fast metabolism of BPA in the body (Chapin et al, 2008). Although it is difficult to determine the causal sequence between BPA exposure and sexual dysfunction because both BPA exposure and sexual function were ascertained simultaneously, it is unlikely that impaired sexual function would have led to a higher BPA exposure.

Although creatinine-adjusted BPA concentration was used in the analysis, using original volume-based concentration without adjustment for creatinine level (unadjusted) produced the same results.

In conclusion, the results from this study provide evidence of a correlation between increased urine BPA levels and declining male sexual function. Our finding further supports our previously reported association between exposure to BPA and the risk of male sexual dysfunction (Li et al, 2010). Although we showed a similar trend among workers without occupational BPA exposure, the observed association among those exposed only to BPA from environmental sources requires further examination.

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