Endocrine (2018) 61:258–266
https://doi.org/10.1007/s12020-018-1623-3

ORIGINAL ARTICLE

Gender-specific differences of interaction between cadmium exposure and obesity on prediabetes in the NHANES 2007–2012 population

Fei Jiang[1] · Xueyuan Zhi[1] · Miao Xu[1] · Bingyan Li[2] · Zengli Zhang[1]

Received: 9 April 2018 / Accepted: 30 April 2018 / Published online: 30 May 2018

Abstract

Purpose Data from National Health and Nutrition Examination Survey (NHANES) for the years 2007–2012 were used to evaluate the interactions of cadmium (Cd) exposure with being overweight/obesity on the risk of prediabetes among adults 20 years older.

Methods A total of 3552 subjects were included in the analysis. Urinary cadmium levels (UCd) was used as a biomarker for long-term exposure to Cd. Additive interaction was estimated using relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (S).

Results Following covariates adjustments, we found significant associations of UCd with higher prediabetes prevalence, and this association was more apparent in males (Q4 vs Q1: OR = 1.95, 95%CI: 1.34–2.84); while overweight/obesity was associated with prediabetes both in males and in females. Additionally, there was a significant interaction between Cd exposure and being overweight/obesity on prediabetes risk among males (RERI = 1.18, 95% CI: 0.42–1.93; AP = 0.35, 95% CI: 0.12–0.58; S = 2.00, 95% CI: 0.92–4.34).

Conclusions Our results suggest that being overweight/obesity may substantially amplify the adverse effects of long-term cadmium exposure on prediabetes risk, and this interaction is more severe in male adults. Further studies are needed to confirm these findings.

Keywords Cadmium · Obesity · Prediabetes · Interaction

Introduction

According to the International Diabetes Federation, 425 million adults worldwide were living with diabetes in 2017, and type 2 diabetes (T2D) accounts for roughly 90% of all diabetes cases [1]. Prediabetes, typically defined as blood glucose concentrations below diabetes thresholds but above normal, is associated with a higher risk of diabetes and its complications [2]. More importantly, there is accumulating data suggesting damage on end organs already at the prediabetic stage, such as kidneys, eyes, blood vessels and the heart [3, 4]. A host of factors can lead to dysglycemia, including unhealthy lifestyle, poor dietary habits and family history. In addition, accumulating evidence has indicated that environmental chemicals may also contribute to the development of diabetes [5].

Cadmium (Cd), a heavy metal, is a recognized endocrine disrupting chemicals released in the environment by natural or thropogenic activities [6, 7]. The major sources of Cd for general population are cigarette smoke and diet [8]. After uptake from the environment and deposition in the kidney with a half-life between 10–30 years, an extremely small amount of Cd is excreted in urine, due to a lack of excretory mechanism. Consequently, urinary Cd levels (UCd) can serve as a biomarker of long-term exposure for individuals

These authors contributed equally: Fei Jiang, Xueyuan Zhi.

✉ Zengli Zhang
zhangzengli@suda.edu.cn

[1] Department of Occupational and Environmental Health, School of Public Health, Medical College of Soochow University, 199 Renai Road, Suzhou 215123, China

[2] Department of Nutrition and Food Hygiene, School of Public Health, Medical College of Soochow University, 199 Renai Road, Suzhou 215123, China

[9]. A range of negative health consequences have been proposed to be associated with chronic Cd exposure, including T2D [10–13]. Both epidemiological and experimental studies showed that Cd exposure was associated with hyperglycemia, reduced serum insulin and T2D. The exact mechanism involved in the Cd-induced glucose homeostasis has not been extensive explored. However, accumulation of Cd in β-cells, alteration expression of glucose transport genes in adipocytes and augment of gluconeogenesis in renal and hepatic cells might give explanations that Cd likely has multiple effects in multiple tissues to contribute to glucose homeostasis [14–16].

Obesity is an independent risk factor of T2D, and prevention of excessive weight gain represents a critical means for T2D management [17, 18]. Accumulating evidence suggests that oxidative stress and inflammation as a link between obesity and T2D [19, 20]. Moreover, oxidative stress and inflammation are also implicated in the pathogenesis and development of adverse effects resulting from Cd exposure. In addition, a recent research identifies an interaction of Cd exposure and dietary antioxidant and anti-inflammation intake on markers of systemic inflammation and oxidative stress [21]. Considering the relationship of oxidative stress and inflammation, obesity and Cd exposure, it is conceivable to hypothesize that obesity would modify the association between Cd exposure and prediabetes.

The present study examined the modification by obesity on the association of exposure to Cd with the risk of prediabetes in the National Health and Nutrition Examination Survey (NHANES) population from 2007 through 2012 utilizing a cross-sectional study design.

Materials and methods

Study population

Participants enrolled in this study were merged from three cycles of the NHANES (2007–2008, 2009–2010, and 2011–2012), a cross-sectional survey designed to estimate the prevalence of health, nutrition and potential risk factors in the United States (Fig. 1). Survey participants were interviewed and invited for a clinical examination. Physical examinations and laboratory testing using blood or urine samples were conducted in the Mobile Examination Centers. All data from the website of the National Center for Health Statistics were retrieved.

To analyze the effects of urinary cadmium and body mass index (BMI) on prediabetes, we included the subjects 20 years older ($n = 17{,}713$), and excluded subjects with missing data of race, the poverty income ratio (PIR), BMI, urinary cadmium, physical activity information, smoking status, alcohol use or prediabetes information. Therefore, our final sample size was 3552.

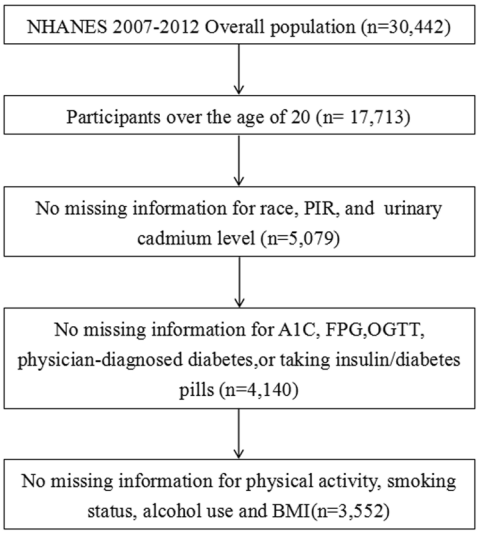

Fig. 1 Flow chart of participants included in the interaction analysis of urinary cadmium and obesity on prediabetes in the NHANES 2007–2012 population

Outcome

Case definition of prediabetes was based on guidelines of the American Diabetes Association. The outcome of variable prediabetes was defined as any one of the following: 5.7% ≤ hemoglobin A1c < 6.5%, fasting plasma glucose (FPG) between 5.6 and 7.0 mmol/L, 2-h plasma glucose between 7.8 and 11.1 mmol/L during an oral glucose tolerance test.

Urinary cadmium (UCd)

Urine samples were collected as part of the surveys examination components. The measurement of urine cadmium concentrations was described in detail elsewhere. UCd concentrations were adjusted using the concentration of creatinine in urine to account for the effect of urinary dilution. Creatinine-corrected Cd was expressed as μg Cd/g creatinine.

Covariates

Age, race/ethnicity, sex, ratio of family income to poverty, physical activity, smoking status and alcohol consumption were obtained by self-reported. The PIR was calculated by dividing household income by the poverty guidelines specific to the survey year. We also evaluated the PIR as a potential confounder in categories: low (<1), middle (1–2) and high (≥2). Participants self-reported their daily activity,

leisure-time activities and sedentary activities using questions based on the Global Physical Activity Questionnaire. Participants without moderate-to-vigorous-intensity physical activity were classified as inactive, while those with moderate-to-vigorous-intensity physical activity were classified as active. Participants were asked if they have smoked at least 100 cigarettes in their entire life to classify their smoking status. Those who answered "Yes" were asked if they now smoke cigarettes every day, some days or not at all. Current smokes were those who have smoked at least 100 cigarettes during their lifetime and smoked every day or some days during the time of interviews. Former smokers were those who have smoked at least 100 cigarettes during their lifetime but did not smoke currently. Non-smokers were those who reported never have smoked 100 cigarettes during their lifetime. Alcohol consumption was surveyed and participants who, in their entire life, never had at least 12 drinks were defined as never drinkers. Participants who had at least 12 drinks in their entire life were defined as drinkers. BMI was calculated as weight in kilograms divided by the square of height in meters. For adults aged 20 years and above, obesity was defined as a BMI of 30 kg/m^2 or greater. Overweight was defined as a BMI of 25.0–29.99 kg/m^2, normal weight was defined as a BMI of 18.5–24.99 kg/m^2, according to the WHO definition. For the additive effect analysis, underweight adults were not included because they compromise a small proportion of the sample (~1.8%).

Statistical analysis

SAS 9.1.3(SAS Institute Cary, NC) was used for the analysis and calculations performed in this study. Weighted means and standard deviation were calculated for continuous variables, weighted frequency for categorical variables. Differences in continuous variables and categorical variables were assessed by Student *t* test and Pearson chi-square test separately. Logistic regressions were used to determine the association of prediabetes with quartiles of urinary cadmium (μg Cd/g creatinine) and BMI (underweight/normal/overweight/obese). Model I represented the unadjusted data. In model II, the data were adjusted for gender, age, race/ethnicity, PIR. In model III, the results were adjusted for model II plus smoking status, alcohol consumption, physical activity and urinary cadmium level or BMI. We also calculated the odds ratios (OR) and 95% confidence interval (CI) for the urinary cadmium and prediabetes across strata of BMI. The additive model was used to explore whether biological interaction was present or not. The additive interaction between being overweight/obese and high urinary cadmium exposure in association with prediabetes were assessed by testing whether the estimated joint effect of two risk factors was greater than the sum of the independent effect estimates for being overweight/obesity and high urine cadmium exposure, respectively. To assess additive interaction, the relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP) and synergy index (S) were calculated. In the absence of additive interaction, RERI and AP are equal to 0 and S is equal to 1.

Results

Table 1 displayed the baseline characteristics of the participants > 20 years of age from NHANES 2007–2012. The average age of the study subjects was 46.70 ± 17.57 years, and 50.2% were male. Compared with individuals without prediabetes, those with prediabetes had significantly higher BMI, urinary cadmium levels, and were more likely to be older, male, a former smoker and less activity.

Independent association of Cd exposure and BMI with prediabetes

The independent associations of abnormal BMI and UCd with prediabetes prevalence were presented in Table 2. Compared with the lowest quartile, the ORs for prediabetes were increased in the 2nd, 3rd, and 4th quartiles of UCd in the unadjusted model. Following covariates adjustments, the ORs for prediabetes remained elevated in the 3rd and 4th quartiles of UCd, and the 4th quartiles of UCd hold the highest OR for prediabetes (adjusted OR = 1.64, 95% CI: 1.25–2.15). When stratified by gender, significant relationship between urinary cadmium and prediabetes was mainly apparent among men. Both overweight and obesity were associated with an increased prevalence rate of prediabetes (adjusted OR = 1.85, 95% CI: 1.53–2.23 of being overweight, adjusted OR = 3.20, 95% CI: 2.63–3.90 of obesity), and stratified analysis by gender indicated that these associations were consistent in men and women..

Interaction effect between Cd exposure and BMI on prediabetes

For further interaction analysis, individuals within the lowest quartile of urinary cadmium concentration were defined as low exposure group, and individuals within the 2nd, 3rd, and 4th quartiles were classified as high exposure group.

In total population, no significance was observed for the interaction between Cd exposure and overweight/obesity, despite stratified analysis showed significant correlation of prediabetes with high Cd exposure among overweight/obese participants (Table 3; adjusted OR = 1.30, 95% CI: 1.03–1.64).

Table 1 Characteristics of NHANES 2007–2012 participants included in the current study

	Overall		With prediabetes		Without prediabetes		*P*-value
	N	Mean or frequency	*N*	Mean or frequency	*N*	Mean or frequency	
Age (yr)	3552	46.70 ± 17.57	1420	53.68 ± 16.66	2132	42.04 ± 16.59	<0.0001
20–39	1429	40.2	332	23.4	1107	51.9	<0.0001
40–59	1145	32.2	522	36.8	623	29.2	
60+	978	27.5	576	40.6	402	18.9	
Male/Female	1783/1769	50.2/49.8	774/646	54.5/45.5	1009/1123	47.3/52.7	<0.0001
BMI		28.15 ± 6.29		29.70 ± 6.59		27.11 ± 5.85	<0.0001
Race							0.0019
Mexican American	507	14.3	201	14.2	306	14.4	
Other Hispanic	359	10.1	144	10.1	215	10.1	
Non-Hispanic White	1710	48.1	650	45.8	1060	49.7	
Non-Hispanic Black	689	19.4	321	22.6	368	17.3	
Other Race	287	8.1	104	7.3	183	8.6	
Poverty income ratio							0.0947
<1	737	20.7	292	20.6	445	20.9	
1–2	898	25.3	386	27.2	512	24.0	
≥2	1917	54.0	742	52.3	1175	55.1	
Smoke							<0.0001
Non-smoker	1942	54.7	705	49.6	1237	58.0	
Former-smoker	844	23.8	407	28.7	437	20.5	
Current-smoker	766	21.6	308	21.7	458	21.5	
Physical activity (Yes/No)	1803/1749	50.8/49.2	632/788	44.5/55.5	1171/961	54.9/45.1	<0.0001
Drink (Yes/No)	2651/901	74.6/25.4	1020/400	71.8/28.2	1631/501	76.5/23.5	0.0017
Urinary cadmium (μg/g creatinine)		3.49 ± 3.72		4.14 ± 3.72		3.05 ± 3.65	<0.0001

BMI body mass index

In males, stratified analysis by BMI also indicated that significant association for Cd exposure was only apparent for the overweight/obesity group (adjusted OR = 1.90, 95% CI: 1.38–2.62). High exposure to cadmium showed a positive interaction with being overweight/obesity on prediabetes. Men with a combination of being overweight/obesity and high exposure to cadmium had a significantly higher risk of prediabetes compared with normal-weight males with low exposure (adjusted OR: 3.36, 95% CI: 2.02–5.57). The independent ORs for being overweight/obesity alone and high cadmium exposure alone were 1.84 (95% CI: 1.08–3.14) and 1.34 (95% CI: 0.78–2.28), respectively. The corresponding RERI, AP and S were 1.18 (95% CI: 0.42–1.93), 0.35 (95% CI: 0.12–0.58) and 2.00 (95% CI: 0.92–4.34), respectively. About 35% of the OR of being prediabetes was attributed to the interaction effect.

No significant interaction of high Cd exposure with being overweight/obesity was found in females.

Discussion

In a large, nationally representative sample of adults ≥ 20 years of age, we found that chronic Cd exposure was associated with higher prediabetes prevalence, and this association was more strong among males. Additive interaction between being overweight or obese and UCd on prediabetes was detected in men but not in women. These results showed that exposure to Cd may be a susceptible factor for prediabetes in males with overweight or obesity.

The association between Cd exposure and T2D has been proposed and explored recently. However, few

Table 2 Associations of Cd exposure and BMI with prediabetes

		With/without	Model I OR (95%CI)	*P*-value	Model II OR (95%CI)	*P*-value	Model III OR (95%CI)	*P*-value
Total								
UCd	Q1	227/662	1.00	–	1.00	–	1.00	–
	Q2	323/563	1.67(1.37–2.05)	<0.0001	1.18(0.94–1.47)	0.1512	1.23(0.98–1.55)	0.0709
	Q3	408/481	2.47(2.03–3.02)	<0.0001	1.39(1.11–1.76)	0.0051	1.48(1.16–1.88)	0.0016
	Q4	462/426	3.16(2.59–3.86)	<0.0001	1.47(1.15–1.88)	0.0022	1.64(1.25–2.15)	0.0003
BMI	underweight	17/50	0.90(0.51–1.59)	0.7247	0.95(0.51–1.75)	0.8567	0.85(0.45–1.57)	0.59
	Normal	303/805	1.00	–	1.00	–	1.00	–
	Overweight	534/731	1.94(1.63–2.31)	<0.0001	1.80(1.49–2.17)	<0.0001	1.85(1.53–2.23)	<0.0001
	obesity	566/546	2.75(2.31–3.29)	<0.0001	3.02(2.49–3.66)	<0.0001	3.20(2.63–3.90)	<0.0001
Male								
UCd	Q1	113/332	1.00	–	1.00	–	1.00	–
	Q2	191/256	2.19(1.65–2.91)	<0.0001	1.61(1.20–2.17)	0.0018	1.61(1.21–2.23)	0.0016
	Q3	221/224	2.90(2.18–3.85)	<0.0001	1.69(1.24–2.32)	0.0010	1.77(1.27–2.46)	0.0007
	Q4	249/197	3.71(2.80–4.93)	<0.0001	1.69(1.20–2.37)	0.0024	1.95(1.34–2.84)	0.0005
BMI	Underweight	9/18	1.16(0.51–2.63)	0.7256	0.96(0.40–2.34)	0.9339	0.87(0.36–2.11)	0.7552
	Normal	164/380	1.00	–	1.00	–	1.00	–
	Overweight	321/375	1.95(1.57–2.51)	<0.0001	1.88(1.46–2.42)	<0.0001	1.98(1.53–2.56)	<0.0001
	obesity	280/236	2.75(2.14–3.54)	<0.0001	2.92(2.23–3.83)	<0.0001	3.2(2.42–4.24)	<0.0001
Female								
UCd	Q1	94/350	1.00	–	1.00	–	1.00	–
	Q2	139/301	1.72(1.27–2.33)	0.0005	1.08(0.78–1.49)	0.6645	1.08(0.77–1.51)	0.6699
	Q3	194/249	2.90(2.16–3.90)	<0.0001	1.37(0.98–1.91)	0.0628	1.43(1.01–2.03)	0.0436
	Q4	219/223	3.66(2.72–4.91)	<0.0001	1.30(0.92–1.84)	0.1383	1.34(0.92–1.96)	0.1254
BMI	Underweight	8/32	0.76(0.34–1.70)	0.5094	0.97(0.41–2.28)	0.9394	0.92(0.39–2.18)	0.8463
	Normal	139/425	1.00	–	1.00	–	1.00	–
	Overweight	213/356	1.83(1.42–2.36)	<0.0001	1.76(1.33–2.33)	<0.0001	1.79(1.34–2.37)	<0.0001
	obesity	286/310	2.82(2.20–3.62)	<0.0001	3.29(2.48–4.36)	<0.0001	3.42(2.56–4.57)	<0.0001

UCd urinary cadmium levels, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval, *Q1–Q4* quartile 1–quartile4

Model I: no adjustments; Model II: adjustments for age, gender, race/ethnicity and PIR; Model III: Model II plus smoking status, alcohol consumption, physical activity and urinary cadmium or BMI

investigations have examined the relationship between Cd exposure and prediabetes. Nie et al. demonstrated that blood Cd levels (BCd) was positively related to the prevalence of prediabetes in 5544 Chinese adults [22]. Using the lowest tertile of BCd as the reference, BCd in the upper tertile had a positive correlation with lgFPG and significant positive trend was also observed. However, no association between BCd and diabetes was detected. An examination of 8722 subjects from NHANES III (1988–1994) revealed that UCd were significantly and dose-dependently associated with both impaired fasting glucose and diabetes when adjusted for age, sex, ethnicity, and BMI [23]. Wallia et al. also detected a non-linear association between higher UCd and prediabetes in a study involving 2398 participants aged ≥ 40 years [24]. Our present study also observed significant association between UCd and prediabetes in the whole subjects after adjustments for age, ethnicity, gender, PIR, BMI, smoking status, alcohol use and physical activity. Stratified analysis by gender showed that the increased prediabetes risk seemed to be greater for men. The gender-specific differences was similar with the prior study which revealed association between UCd and diabetes prevalence as well as blood glucose level in males, while these relations were not significant in females [25].

Obesity is a well-established risk factor for T2D. In the current study, we also found that being overweight/obesity was associated with an increase in odds ratio for prediabetes. When stratified by gender, the significant association still existed. There is a growing body of literature showed that the development of T2D could be postponed or sometimes prevented in obese individuals through weight loss produced by behavioral treatment, medication or surgery therapies [17, 18], which strengthened the importance of weight management in prevention of prediabetes and diabetes. Furthermore, we investigated the interactions of being overweight/obese with exposure to Cd in affecting the

Table 3 Additive interactions between Cd exposure and being overweight/obesity on prediabetes

	BMI	Cadmium	stratified OR (95% CI) *	Interaction analyses			
				Adjusted OR (95% CI) *	RERI (95% CI) #	AP (95% CI) #	S (95% CI) #
Total							
	Normal	Low exposure	1.00	1.00	0.21 (−0.49–0.91)	0.064 (−0.16–0.28)	1.10 (0.77–1.57)
		High exposure	1.44(0.90–2.29)	1.44(0.90–2.29)			
	Overweight/obesity	Low exposure	1.00	2.63(1.74–4.00)			
		High exposure	1.30(1.03–1.64)	3.28(2.20–4.91)			
Male							
	Normal	Low exposure	1.00	1.00	1.18 (0.42–1.93)	0.35 (0.12–0.58)	2.00 (0.92–4.34)
		High exposure	1.34(0.78–2.28)	1.34(0.78–2.28)			
	Overweight/obesity	Low exposure	1.00	1.84(1.08–3.14)			
		High exposure	1.90(1.38–2.62)	3.36(2.02–5.57)			
Female							
	Normal	Low exposure	1.00	1.00	−0.079 (−1.34–1.18)	−0.022 (−0.36–0.32)	0.97 (0.62–1.53)
		High exposure	1.54(0.79–3.01)	1.54(0.79–3.01)			
	Overweight/obesity	Low exposure	1.00	3.17(1.63–6.16)			
		High exposure	1.15(0.82–1.61)	3.64(1.92–6.88)			

BMI body mass index, *OR* odds ratio, *CI* confidence interval, *RERI* relative excess risk due to interaction, *AP* attributable proportion due to interaction, *S* synergy index

*adjustments for age, gender, race/ethnicity, PIR, smoking status, alcohol consumption and physical activity

#statistically significant with RERI > 0 and AP > 0 indicating additive interaction

risk of prediabetes. A significant interaction was observed in males, and stratified analyses by BMI indicated that the relationships of Cd exposure with prediabetes were confined to overweight/obesity group. The potential mechanisms were not clear and inflammation and oxidative stress might be involved.

Oxidative stress has been recently recognized as a key mechanism in insulin resistance. The ability of cadmium to induce oxidative stress has been established in animal and in vitro studies, and substantiated in some epidemiologic studies [26, 27]. Affecting antioxidant enzymes and depleting antioxidant scavengers is involved in Cd induced oxidative stress. Gamma glutamyl transferase (GGT) is particular an informative biomarker for assessing systemic oxidative stress levels. Lee et al suggested a link between long-term Cd exposure and increases in systemic oxidative stress using GGT and other biomarkers [28]. Pizzino et al. found an increased expression of malondialdehyde and decreased expression of total antioxidant capacity, in parallel with elevated insulin resistance, when male adolescents exposed to Cd [29]. In addition, several parameters of glycemic metabolism were alleviated by oestradiol and antioxidants [30, 31]. Additionally, in adipocytes, fat accumulation increased Nox activity and endoplasmic reticulum stress led to increased ROS production [32]. A recent study showed that in obese patients, antioxidant defense were lower than normal weight participants and were characterized by enhanced levels of reaction oxygen or nitrogen species [33]. Thus, it is possible to explain the modification that individuals with overweight/obese may be more susceptible to Cd exposure-associated prediabetes as seen in our results. Inflammation appears to be another important mechanism associated with the interaction. Accumulating data revealed that chemokines, including C-reaction protein (CRP), TNF-α, IL-6, were elevated in obese and T2D subjects [20, 34, 35]. In addition, improvement in insulin sensitivity induced by weight loss was accompanied by a decrease in the expression of pro-inflammatory genes [36–38]. Similarly, Cd exposure was positively associated with the systemic inflammation markers. The relationship between Cd exposure and inflammation has been explored to be an important mechanism in cadmium-related cardiovascular disease [39]. In NHANES III, Lin et al. identified UCd was associated with elevated CRP, as well as fibrinogen, another marker of inflammation [40]. Cheung et al. observed a positive association between BCd and alkaline phosphatase (ALP) [41]. Consistently, Colacino et al confirmed the associations between cadmium exposure and CRP and ALP, and they also uniquely identified that relationships were strongest among individuals with lower anti-inflammatory and antioxidant nutrients diet [21]. In hence, provoking inflammation by Cd exposure and obesity might be another potential mechanism for the observed interaction.

To our knowledge, it is the first study reporting the gender-specific interaction between obesity and Cd exposure on prediabetes. The mechanisms for this gender-specific interaction are unclear, although there is growing literature on the differing associations between Cd exposure and health for males and females. Multiple factors may contribute to this sex difference. It was reported that maternal Cd exposure could alter fetal DNA methylation in a sex-specific manner [42]. In vivo, an environmental dose of cadmium at early stages of life caused gut microbiota alterations, accelerated hepatic lipid metabolism, and led to life-long metabolic consequences in a sex-dependent manner [43]. Moreover, Cd has also been shown to interact with sex hormones [44]. Another study showed that Cd had an impact on sexual maturation and hormone levels [45]. These findings might partially explain such discrepancy by gender. Although we observed that the joint effect of Cd exposure and obesity on prediabetes was evident in males, the mechanisms accounting for gender-specific interactions still warrant further investigation. Nevertheless, the interaction revealed in our study suggest that personal action (weight management) might matters while exposure to cadmium are well beyond the control of individuals. Evidence that individual healthy choices can improve the health condition has been provided by Esposito et al. in population suffering with particulate matter air pollution, another public health threatening [46].

A limitation of this study is a use of a cross-sectional nature of NHANES. Hence, a cause-effect relationship could not be determined in the present study. Also, the association with diabetes was not included in the analysis given the potential influence of sustained hyperglycemia on renal Cd excretion. Furthermore, our results may be affected by the residual confounding. For instance, PIR is a commonly used indicator of socio-economic status, however, the PIR may not reflect the accurate socio-economic status. Our results are also limited by the universality due to the study constrained in US. Rice and vegetables were the main sources of dietary Cd intake, however, our results are limited by no adjustment for the diet, due to the lack of composition of each food item. Nevertheless, a major strength of this study lies in the large, well-characterized sample population, with available measures of exposure and control for potentially important covariates, including smoking status, alcohol use and physical activity. Further, we report for the first time the signi12ficant effect modification by obesity on the role of Cd on prediabetes, potentially providing evidence in support of weight loss for Cd exposed individuals and reduction of Cd exposure of the general public.

Conclusion

Our results may have important public health implications considering the current obesity epidemic and high exposure to Cd worldwide. The results add to the evidence linking exposure to Cd with prediabetes. Furthermore, the results suggest that overweight and obesity may augment the risk of prediabetes triggered by exposure to Cd in men. Prevention strategies for prediabetes aimed at both reducing Cd exposure and normal weight management may exceed the expected benefits based on targeting the risk factors separately. Further studies will be needed to investigate the temporality of obesity relative to Cd exposure and onset of disease.

Acknowledgements This study was supported by the National Natural Science Foundation of China (No.81703209, No.81773414, and No.81673151), Postdoctoral Science Foundation of Jiangsu Province, China Postdoctoral Science Foundation (No.2017M621823), and A Project Funded by the Priority Academic Program Development to Jiangsu Higher Education Institutions (PAPD).

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. International Diabetes Federation, IDF Diabetes Atlas, (2018) http://www.diabetesatlas.org/. Accessed 9 April 2018
2. C.M. Edwards, K. Cusi, Prediabetes: a worldwide epidemic. Endocrinol. Metab. Clin. North. Am. **45**, 751–764 (2016)
3. B. Brannick, S. Dagogo-Jack, Prediabetes and cardiovascular disease: pathophysiology and interventions for prevention and risk reduction. Endocrinol. Metab. Clin. North. Am. **47**, 33–50 (2018)
4. A.G. Tabak, C. Herder, W. Rathmann, E.J. Brunner, M. Kivimaki, Prediabetes: a high-risk state for diabetes development. Lancet **379**, 2279–2290 (2012)
5. K.A. Thayer, J.J. Heindel, J.R. Bucher, M.A. Gallo, Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. Environ. Health Perspect. **120**, 779–789 (2012)
6. I. Iavicoli, L. Fontana, A. Bergamaschi, The effects of metals as endocrine disruptors. J. Toxicol. Environ. Health B. Crit. Rev. **12**, 206–223 (2009)
7. S. Satarug, S.H. Garrett, M.A. Sens, D.A. Sens, Cadmium, environmental exposure, and health outcomes. Environ. Health Perspect. **118**, 182–190 (2010)
8. S. Satarug, Long-term exposure to cadmium in food and cigarette smoke, liver effects and hepatocellular carcinoma. Curr. Drug. Metab. **13**, 257–271 (2012)
9. A.A. Tinkov, T. Filippini, O.P. Ajsuvakova, J. Aaseth, Y.G. Gluhcheva, J.M. Ivanova, G. Bjorklund, M.G. Skalnaya, E.R. Gatiatulina, E.V. Popova, O.N. Nemereshina, M. Vinceti, A.V. Skalny, The role of cadmium in obesity and diabetes. Sci. Total Environ. **601-602**, 741–755 (2017)
10. J.C. Erie, J.A. Good, J.A. Butz, D.O. Hodge, J.S. Pulido, Urinary cadmium and age-related macular degeneration. Am. J. Ophthalmol. **144**, 414–418 (2007)
11. G.L. Ginsberg, Cadmium risk assessment in relation to background risk of chronic kidney disease. J. Toxicol. Environ. Health A **75**, 374–390 (2012)
12. J.M. Lavado-Garcia, L.M. Puerto-Parejo, R. Roncero-Martin, J.M. Moran, J.D. Pedrera-Zamorano, I.J. Aliaga, O. Leal-Hernandez, M.L. Canal-Macias, Dietary intake of cadmium, lead and mercury and its association with bone health in healthy premenopausal women. Int. J. Environ. Res. Public. Health **14**, 1437 (2017).
13. S.C. Larsson, N. Orsini, A. Wolk, Urinary cadmium concentration and risk of breast cancer: a systematic review and dose-response meta-analysis. Am. J. Epidemiol. **182**, 375–380 (2015)
14. J.C. Han, S.Y. Park, B.G. Hah, G.H. Choi, Y.K. Kim, T.H. Kwon, E.K. Kim, M. Lachaal, C.Y. Jung, W. Lee, Cadmium induces impaired glucose tolerance in rat by down-regulating GLUT4 expression in adipocytes. Arch. Biochem. Biophys. **413**, 213–220 (2003)
15. M.M. El, M.R. Raja, X. Zhang, K.W. MacRenaris, S. Bhatt, X. Chen, M. Urbanek, T.V. O'Halloran, W.J. Lowe, Accumulation of cadmium in insulin-producing beta cells. Islets **4**, 405–416 (2012)
16. K.D. Chapatwala, M. Hobson, D. Desaiah, B. Rajanna, Effect of cadmium on hepatic and renal gluconeogenic enzymes in female rats. Toxicol. Lett. **12**, 27–34 (1982)
17. S. Mohammad, J. Ahmad, Management of obesity in patients with type 2 diabetes mellitus in primary care. Diabetes Metab. Syndr. **10**, 171–181 (2016)
18. L. Khaodhiar, S. Cummings, C.M. Apovian, Treating diabetes and prediabetes by focusing on obesity management. Curr. Diab. Rep. **9**, 348–354 (2009)
19. E.J. Henriksen, M.K. Diamond-Stanic, E.M. Marchionne, Oxidative stress and the etiology of insulin resistance and type 2 diabetes. Free Radic. Biol. Med. **51**, 993–999 (2011)
20. N. Esser, S. Legrand-Poels, J. Piette, A.J. Scheen, N. Paquot, Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res. Clin. Pract. **105**, 141–150 (2014)
21. J.A. Colacino, A.E. Arthur, K.K. Ferguson, L.S. Rozek, Dietary antioxidant and anti-inflammatory intake modifies the effect of cadmium exposure on markers of systemic inflammation and oxidative stress. Environ. Res. **131**, 6–12 (2014)
22. X. Nie, N. Wang, Y. Chen, C. Chen, B. Han, C. Zhu, Y. Chen, F. Xia, Z. Cang, M. Lu, Y. Meng, B. Jiang, J.M. D, Y. Lu, Blood cadmium in Chinese adults and its relationships with diabetes and obesity. Environ. Sci. Pollut. Res. Int. **23**, 18714–18723 (2016)
23. G.G. Schwartz, D. Il'Yasova, A. Ivanova, Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. Diabetes Care **26**, 468–470 (2003)
24. A. Wallia, N.B. Allen, S. Badon, M.M. El, Association between urinary cadmium levels and prediabetes in the NHANES 2005-2010 population. Int. J. Hyg. Environ. Health **217**, 854–860 (2014)
25. H.S. Son, S.G. Kim, B.S. Suh, D.U. Park, D.S. Kim, S.D. Yu, Y. S. Hong, J.D. Park, B.K. Lee, J.D. Moon, J. Sakong, Association of cadmium with diabetes in middle-aged residents of abandoned metal mines: the first health effect surveillance for residents in abandoned metal mines. Ann. Occup. Environ. Med. **27**, 20 (2015)
26. Z.A. Shaikh, T.T. Vu, K. Zaman, Oxidative stress as a mechanism of chronic cadmium-induced hepatotoxicity and renal toxicity and protection by antioxidants. Toxicol. Appl. Pharmacol. **154**, 256–263 (1999)

27. J. Liu, W. Qu, M.B. Kadiiska, Role of oxidative stress in cadmium toxicity and carcinogenesis. Toxicol. Appl. Pharmacol. **238**, 209–214 (2009)
28. D.H. Lee, J.S. Lim, K. Song, Y. Boo, D.J. Jacobs, Graded associations of blood lead and urinary cadmium concentrations with oxidative-stress-related markers in the U.S. population: results from the third National Health and Nutrition Examination Survey. Environ. Health Perspect. **114**, 350–354 (2006)
29. G. Pizzino, N. Irrera, A. Bitto, G. Pallio, F. Mannino, V. Arcoraci, F. Aliquo, L. Minutoli, C. De Ponte, P. D'Andrea, F. Squadrito, D. Altavilla, Cadmium-induced oxidative stress impairs glycemic control in adolescents. Oxid. Med. Cell Longev. **2017**, 6341671 (2017)
30. I. Abdelaziz, M.I. Elhabiby, A.A. Ashour, Toxicity of cadmium and protective effect of bee honey, vitamins C and B complex. Hum. Exp. Toxicol. **32**, 362–370 (2013)
31. J. Mladenovic, B. Ognjanovic, N. Dordevic, M. Matic, V. Knezevic, A. Stajn, Z. Saicic, Protective effects of oestradiol against cadmium-induced changes in blood parameters and oxidative damage in rats. Arh. Hig. Rada Toksikol. **65**, 37–46 (2014)
32. S. Furukawa, T. Fujita, M. Shimabukuro, M. Iwaki, Y. Yamada, Y. Nakajima, O. Nakayama, M. Makishima, M. Matsuda, I. Shimomura, Increased oxidative stress in obesity and its impact on metabolic syndrome. J. Clin. Invest. **114**, 1752–1761 (2004)
33. I. Savini, M.V. Catani, D. Evangelista, V. Gasperi, L. Avigliano, Obesity-associated oxidative stress: strategies finalized to improve redox state. Int. J. Mol. Sci. **14**, 10497–10538 (2013)
34. G.S. Hotamisligil, P. Arner, J.F. Caro, R.L. Atkinson, B.M. Spiegelman, Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J. Clin. Invest. **95**, 2409–2415 (1995)
35. C. Phosat, P. Panprathip, N. Chumpathat, P. Prangthip, N. Chantratita, N. Soonthornworasiri, S. Puduang, K. Kwanbunjan, Elevated C-reactive protein, interleukin 6, tumor necrosis factor alpha and glycemic load associated with type 2 diabetes mellitus in rural Thais: a cross-sectional study. BMC Endocr. Disord. **17**, 44 (2017)
36. H.P. Kopp, C.W. Kopp, A. Festa, K. Krzyzanowska, S. Kriwanek, E. Minar, R. Roka, G. Schernthaner, Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. Arterioscler. Thromb. Vasc. Biol. **23**, 1042–1047 (2003)
37. C. Holdstock, L. Lind, B.E. Engstrom, M. Ohrvall, M. Sundbom, A. Larsson, F.A. Karlsson, CRP reduction following gastric bypass surgery is most pronounced in insulin-sensitive subjects. Int. J. Obes. (Lond.). **29**, 1275–1280 (2005)
38. E.S. Abd, A.M. Saiem, Impact of weight loss on oxidative stress and inflammatory cytokines in obese type 2 diabetic patients. Afr. Health Sci. **16**, 725–733 (2016)
39. A. Navas-Acien, E. Selvin, A.R. Sharrett, E. Calderon-Aranda, E. Silbergeld, E. Guallar, Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation **109**, 3196–3201 (2004)
40. Y.S. Lin, D. Rathod, W.C. Ho, J.J. Caffrey, Cadmium exposure is associated with elevated blood C-reactive protein and fibrinogen in the U. S. population: the third national health and nutrition examination survey (NHANES III, 1988-1994). Ann. Epidemiol. **19**, 592–596 (2009)
41. B.M. Cheung, K.L. Ong, L.Y. Wong, Elevated serum alkaline phosphatase and peripheral arterial disease in the United States National Health and Nutrition Examination Survey 1999-2004. Int. J. Cardiol. **135**, 156–161 (2009)
42. M. Kippler, K. Engstrom, S.J. Mlakar, M. Bottai, S. Ahmed, M.B. Hossain, R. Raqib, M. Vahter, K. Broberg, Sex-specific effects of early life cadmium exposure on DNA methylation and implications for birth weight. Epigenetics **8**, 494–503 (2013)
43. Q. Ba, M. Li, P. Chen, C. Huang, X. Duan, L. Lu, J. Li, R. Chu, D. Xie, H. Song, Y. Wu, H. Ying, X. Jia, H. Wang, Sex-dependent effects of cadmium exposure in early life on gut microbiota and fat accumulation in mice. Environ. Health Perspect. **125**, 437–446 (2017)
44. C. Nagata, Y. Nagao, C. Shibuya, Y. Kashiki, H. Shimizu, Urinary cadmium and serum levels of estrogens and androgens in postmenopausal Japanese women. Cancer Epidemiol. Biomark. Prev. **14**, 705–708 (2005)
45. S. De Craemer, K. Croes, N. van Larebeke, S. De Henauw, G. Schoeters, E. Govarts, I. Loots, T. Nawrot, V. Nelen, E. Den Hond, L. Bruckers, Y. Gao, W. Baeyens, Metals, hormones and sexual maturation in Flemish adolescents in three cross-sectional studies (2002-2015). Environ. Int. **102**, 190–199 (2017)
46. K. Esposito, G. Bellastella, M.I. Maiorino, D. Giugliano, Particulate matter air pollution: individual choices for improving cardiometabolic well-being. Endocrine **59**, 495–498 (2018)