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Association between urinary tin concentration and diabetes in nationally representative sample of US Adults

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Abstract

Background—Animal studies indicate that chronic exposure to certain tin compounds induces pancreatic islet cell apoptosis and glucose intolerance. However, little is known about health effects of environmental tin exposure in humans. We therefore evaluated the association of tin exposure with diabetes in a nationally representative sample of US adults.

Methods—We used data from a nationally representative population (n=3,371) in the National Health and Nutrition Examination Survey 2011–2014. Diabetes (n = 605) was defined as a self-reported physician's diagnosis, a hemoglobin A1c level ≥ 6.5%, a fasting plasma glucose ≥ 126 mg/dL, or a two-hour plasma glucose ≥ 200 mg/dL. Tin concentrations in urine samples were determined by inductively coupled plasma mass spectrometry. We used logistic regression with sample weights to estimate the odds ratios (ORs) of diabetes and 95% confidence intervals (CIs).

Results—Urinary tin concentrations were higher in individuals with diabetes (weighted median: 0.58 μg/L) than those without diabetes (0.39 μg/L). After adjustment for urinary creatinine and

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Declarations

Competing interests: none

Authors' contributions: WB has full access to all of the data in this study and assumes responsibility for study supervision. WB and BL contributed to the conception and design of the study. BL performed the statistical analyses and drafted the manuscript. All authors contributed to the acquisition, analysis, or interpretation of the data, and critically revised the manuscript for important intellectual content.

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other risk factors of diabetes, the OR of diabetes comparing the highest with lowest quartile of urinary tin concentrations was 1.6 (95% CI, 1.0–2.6; P for trend = 0.02).

Conclusions—Environmental tin exposure was positively and significantly associated with diabetes in US adults.

Keywords

Tin exposure; diabetes; US adults; Human health; Epidemiology

Introduction

Diabetes prevalence is continuously increasing, which causes extensive financial burden and increased mortality risk.[1,2] In recent years, accumulating evidence suggests that environmental factors may be implicated in the development of diabetes.[3,4] These environmental factors are receiving increasing attention because, unlike genetic factors, they are modifiable risk factors that can be used to prevent or slow down the rapid increase of the global diabetes epidemic.

Tin is a widespread but largely understudied heavy metal. Tin compounds exist in inorganic or organic (organotin) forms.[5,6] Inorganic tin has been extensively used as a protective coating in food cans and containers.[7] Organotin compounds have been widely used in agriculture and industry as biocides, antifouling agents, heat stabilizers, and chemical catalysts.[8] Human exposure to tin compounds is mainly from food, beverages, consumer products, and environmental media (air, soil and dust).[8–10] The total daily intake of tin is estimated at 34.6 μg/d for a standard man.[11] The maximum daily tin intake could reach 50,000–60,000 μg for individuals who routinely consume canned food.[6]

Despite the ubiquitous exposure of tin compounds to humans, little is known about whether and how environmental tin exposure affects human health. Organotin compounds, such as tributyltin and triphenyltin, have been identified as emerging metabolism disrupting chemicals based on findings from laboratory studies.[12] Exposure to tin compounds, especially certain organotin compounds, can impair metabolic function,[13] inhibit insulin secretion,[14] and induce pancreatic β-cell dysfunction.[15] Therefore, environmental tin exposure might be a potential contributor to the occurrence of diabetes in humans.

In this study, we used data from the National Health and Nutrition Examination Survey (NHANES) to examine the association of urinary total tin concentrations with diabetes in a nationally representative sample of US adults.

Methods

Study population

NHANES is a complex, multistage probability sampling survey, administered by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC). NHANES data represent the nationwide non-institutionalized U.S. population. NHANES collects abundant data on demographics, socioeconomic status, lifestyle, diet, and medical

conditions. In addition, NHANES also performs extensive health examinations and collects specimens for laboratory tests. NHNAES data are publicly released biannually.[16] NHANES has been approved by the National Center for Health Statistics Ethics Review Board. Written informed consent was obtained from all participants.

In this study, we used data from NHANES 2011–2012 and 2013–2014, because urinary concentrations of tin were only measured in these two cycles. There are 3,451 adults 20 years or older who had available data on diabetes and urinary tin concentrations in total. After excluding pregnant women (n = 37) and individuals whose body mass index (BMI) data were unavailable (n = 43), we finally included 3,371 adult participants in this study.

Exposure assessment

Concentrations of total tin (i.e., organic plus inorganic forms of tin) in urine samples were measured using the inductively coupled plasma- dynamic reaction cell-mass spectrometry at the Inorganic and Radiation Analytical Toxicology Division of Laboratory Sciences, National Center for Environmental Health, CDC.[17] The lower limit of detection (LLOD) of urine tin was 0.090 μg/L. According to NHANES analytic guidance, analytic results (13.2%) that are below the LLOD were assigned values of the LLOD divided by the square root of 2.[17] To account for variable urine dilution, we adjusted for urinary creatinine in all analyses as recommended.[18]

Outcome ascertainment

Diabetes was defined based on a self-reported physician diagnosis, a plasma fasting glucose level of 126 mg/dL or more, a hemoglobin A1c of 6.5% or more, or a two-hour plasma glucose level equal or higher than 200 mg/dL.[2] Trained interviewers collected information of self-reported previous diagnosis of diabetes. Certified technologists measured hemoglobin A1c levels and plasma fasting glucose and administered a two-hour oral glucose tolerance test.

Potential confounders

Standardized questionnaires were used to collect data on age, gender, race/ethnicity, education, family income, dietary information, smoking status, alcohol consumption, physical activity, and medical conditions.[16] Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican and non-Mexican Hispanic), and other race/ethnicity. Education was categorized as less than high school, high school, and higher than high school (college or associates (AA) degree and college graduate or higher). Family income-to-poverty ratio was grouped as ≤ 1.30, 1.31–3.50, and > 3.50.[16] Total energy intake was calculated using the United States Department of Agriculture Automated Multiple-Pass Method.[19] Never smokers were defined as individuals who smoked less than 100 cigarettes in their lifetime; Among those who smoked more than 100 cigarettes, adults who did not smoke at the time of the survey was former smokers, while those who smoked cigarettes at the time of survey were current smokers.[20] Alcohol intake was categorized as 0 g/day, 0.1–27.9 g/day, and ≥ 28 g/day for male, and 0 g/day, 0.1–13.9 g/d, and ≥ 14 g/d for female.[21] Physical activity was assessed using the Global Physical Activity Questionnaire. Metabolic equivalents of task (MET) minutes per week were derived to take into account both the

duration and intensity of different activities[22]. Weight and height were measured and used to calculate BMI.

Statistical analysis

We conducted all the analyses according to NHANES Analytic Guidelines. Appropriate weights and the Taylor series linearization method were used to represent the non-institutionalized U.S. population.[16] We used Chi-square test and ANOVA to compare categorical variables and continuous variables, respectively. Urinary tin concentration was log-transformed prior to the analyses because it was in skewed distribution. Logistic regression was used to estimate odds ratios (ORs) of diabetes according to quartiles of urinary tin concentrations. We adjusted for age, gender, and urinary creatinine in Model 1. Race/ethnicity, family income-to-poverty ratios, education, physical activity, smoking status, alcohol intake, total energy intake, BMI, and HEI-2010 were additionally adjusted in Model 2. Missing data of categorical variables was grouped into a subcategory. To assess linear trends across quartiles of urinary tin concentrations, we calculated the median of log-transformed tin concentrations for each category and fitted the median as a continuous variable in models.

To evaluate effect modification, we conducted interaction and stratified analyses by gender and race/ethnicity. Because chronic kidney disease could affect urinary tin excretion, we conducted a sensitivity analysis by excluding individuals with chronic kidney disease to test the robustness of our findings. The NHANES data did not distinguish diabetes subtypes, so that we conducted another sensitivity analysis by excluding participants who were diagnosed with diabetes before 20 years old (i.e., more likely to have type 1 diabetes).

All statistical analyses were performed using survey procedures of SAS 9.4 package (SAS Institute, Cary, NC). The level of statistical significance (alpha) was set at 0.05.

Results

The final sample consisted of 3,371 participants (50.1% male, average age 48.1 ± 17.5 years; 49.9% female, average age 48.7 ± 17.4 years). The median urinary tin concentration was 0.4 μg/L (interquartile range [IQR], 0.2–0.9 μg/L). Urinary concentrations of tin were higher in older participants, non-Hispanic blacks, and those with less education, lower family income, higher BMI, and less physical activities (Table 1). The weighted prevalence of diabetes was 13.7% (standard error, 0.7%). Higher concentrations of tin were observed in diabetic adults than in non-diabetic adults ($P < 0.001$). The weighted median concentrations of tin in individuals with diabetes vs. those without diabetes were 0.6 μg/L (IQR, 0.3–1.3) vs. 0.4 μg/L (IQR, 0.2–0.8) μg/L. Urinary tin concentrations according to population characteristics are shown in Supplemental Material (Table S1).

We observed an elevated risk of diabetes in association with higher concentrations of urinary tin. After adjustment for demographic, socioeconomic, and lifestyle factors, BMI, and urinary creatinine concentrations, the OR of diabetes was 1.6 (95% CI, 1.0–2.6) comparing the highest quartile of tin with lowest quartile (P for trend 0.02) (Table 2).

Although the associations between urinary tin concentrations and diabetes appeared stronger in female than in male, and stronger in whites than in non-whites, no significant interactions were found. The OR of diabetes comparing the highest with the lowest quartile of urinary tin concentration was 2.1 (95% CI, 1.0–4.5) in female (P for trend 0.03) and 1.3 (95% CI, 0.7–2.7) in male (P for trend 0.57, Table 3). The OR of diabetes for tin was 1.8 (95% CI, 0.9–3.6) in whites (P for trend 0.03) and 1.5 (95% CI, 0.8–2.6) in non-whites (P for trend 0.21, Table 3). The associations of urinary tin concentrations with diabetes did not change appreciably in sensitivity analyses when excluding individuals with chronic kidney disease (Table S2). The associations of urinary tin concentrations with diabetes did not change significantly when excluding individuals who were diagnosed with diabetes before 20 years old (Table S3).

Discussion

In this nationally representative study, higher urinary tin concentrations were significantly associated with an elevated risk of diabetes in US adults, even after adjustment for other major risk factors for diabetes, such as age, gender, socioeconomic status, diet, lifestyle, and BMI.

Humans are widely exposed to tin compounds. In the present study, tin was detected in 86.8% of urine samples. In a study conducted by Feng et al. in China, the detection rate of total tin in urine reached up to 62%.[23] Specific organotin compounds, monobutyltin, dibutyltin, and tributyltin were detected in 53%, 81%, and 70%, respectively, of blood samples of US adults.[24] More noteworthy is that the disruption of metabolic function by exposure to tributyltin in mice occurred at relatively low doses similar to tributyltin levels found in the environment and in humans.[25] Therefore, it is urgent to understand the associations of environmental tin exposures with risk of diabetes, which has important public health and scientific implications.

Although there are no studies reporting the diabetogenic effects of inorganic tin exposure, our findings are in line with previous *in vitro* and *in vivo* studies showing potential diabetogenic effects of certain organotin compounds.[4,26] Animal studies have consistently found that organotin compounds, such as tributyltin, could impair pancreatic function,[13,14] induce insulin resistance,[15,27] and disrupt glucose homeostasis.[28] Tributyltin could induce hepatic inflammation and lipid storage through stimulating peroxisome proliferator-activated receptor gamma (PPAR-γ) and inhibiting estrogen receptors a (ERa).[13] Tributyltin could also induce adipose accumulation through stimulating both PPARγ and ERα protein expression in adipose tissue.[13] These impairments then affect the metabolic functions of pancreatic islets and induce glucose tolerance and insulin resistance.[13] Triphenyltin could disrupt cellular signaling in pancreatic β-cells and impair insulin secretion.[29] Nuclear receptors, including PPAR-γ, ER, retinoic acid X receptor, and glucocorticoid receptor, may be involved in the underlying mechanisms of tin compounds in the development of diabetes, although precise mechanisms need to be further elucidated.[30,31] To date, only one previous study has examined the association between tin exposure and diabetes in humans. In a cross-sectional study in Chinese adults, Feng et al. observed a positive but non-significant association between urinary tin concentration and diabetes, with an OR comparing the

extreme quartiles of 1.30 (0.85–1.98).[23] Of note, the number of diabetes cases (n = 218) was smaller and urinary tin concentrations on average (median tin concentration = 0.27 μg/L) was lower in the study by Feng et al.[23] compared to the current study.

Interestingly, we observed evidence for possible gender and race/ethnic differences for the association between tin exposure and diabetes. The associations between urinary tin concentrations and diabetes seemed stronger in female than in male, although the interaction effects are not statistical significant. One possible explanation for the observed gender differences is exposure to organotin compounds, a known class of endocrine disrupting chemicals that may have gender specific effects on the development of diabetes.[32] Unfortunately, the analytical method used in NHANES does not distinguish between organic and inorganic forms of tin, and additional studies are warranted to distinguish the role of organic vs. inorganic forms of tin in diabetes.

Strengths of our analysis include the use of nationally representative data from NHANES, which allows us to generalize the findings to a broader population. Additionally, the wealth of data from NHANES, including comprehensive information about demographic, socioeconomic, and lifestyle factors, provide the opportunity to adjust for confounding from a variety of diabetes-related risk factors. We acknowledge that there were also several limitations. First, we could not establish a temporal relation or draw causal inference from the observed associations. Longitudinal studies are needed to confirm our findings. Second, the exposure variable in this study is total tin concentration, which is considered a sum of both the organic and inorganic forms of tin compounds. Therefore, contributions from each specific tin compound to the elevated risk of diabetes remains to be determined in future studies. Third, spot urine samples were collected to measure tin concentrations instead of 24-h urine samples due to the perceived challenges and difficulties in sample collection. Finally, although we adjusted for many potential confounders, we cannot rule out the possibility of residual confounding by other unknown factors.

Conclusions

In a nationally representative population, we found that environmental tin exposure was positively and significantly associated with diabetes in US adults. More research is warranted to identify if organic and/or inorganic forms of tin are linked to diabetes, characterize relevant exposure pathways and determine the potential mechanisms, with the ultimate objective to reduce the burden of diabetes on individuals and the society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations

NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
BMI	body mass index
LLOD	the lower limit of detection
MET	Metabolic equivalents of task
OR	Odds ratio
IQR	interquartile range
PPAR-γ	peroxisome proliferator-activated receptor gamma

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Highlights

- Tin was detected in 86.8% of urine samples and the median urinary tin level was 0.4 μg/L.
- Urinary tin concentration was associated with higher risk of diabetes.

Table 1

Characteristics of the Study Population from NHANES 2011–2014 (N = 3,371), According to Quartiles of Urinary Tin Concentrations

Variables	Urinary tin concentrations, μg/L				P
	Quartile 1 (<0.23)	Quartile 2 (0.23–0.47)	Quartile 3 (0.47–1.03)	Quartile 4 (>1.03)	
Number of participants	832	862	837	840	
Age, years	43.3 ± 0.9	47.4 ± 0.8	48.8 ± 0.7	49.9 ± 0.9	0.005
Gender					
Male	48.1 (2.0)	50.2 (1.8)	50.7 (2.3)	45.3 (2.4)	0.32
Female	51.9 (2.0)	49.8 (1.8)	49.3 (2.3)	54.7 (2.4)	
Race/ethnicity					
Non-Hispanic white	69.3 (3.2)	68.9 (3.0)	61.8 (2.7)	63.1 (3.6)	<0.001
Hispanic	14.5 (2.5)	14.4 (2.1)	16.7 (2.3)	13.2 (2.2)	
Non-Hispanic black	6.7 (1.3)	8.3 (1.2)	14.5 (2.1)	17.8 (2.2)	
other	9.6 (1.0)	8.3 (1.1)	7.1 (1.0)	5.9 (1.0)	
Education					
Less than high school	12.3 (1.7)	15.5 (1.4)	16.3 (1.9)	19.1 (2.1)	<0.001
High school	15.3 (1.5)	21.3 (1.8)	22.3 (2.4)	25.2 (2.2)	
College or higher	72.5 (2.1)	63.2 (2.2)	61.4 (3.1)	55.8 (3.0)	
Smoking					
Never smoker	61.5 (2.4)	54.3 (3.2)	54.2 (2.5)	55.3 (2.4)	0.31
Current smoker	17.5 (1.5)	20.9 (2.0)	19.9 (1.5)	20.7 (1.6)	
Ever smoker	21.0 (1.9)	24.8 (2.1)	25.8 (1.7)	24.0 (2.1)	
Family income to poverty ratio					
≤1.30	21.1 (2.1)	18.6 (1.7)	22.5 (2.1)	30.0 (2.7)	<0.001
1.30<PIR<3.50	27.9 (2.2)	33.1 (2.2)	33.1 (2.3)	34.6 (2.5)	
≥3.50	46.0 (3.2)	42.3 (2.6)	35.2 (2.1)	29.1 (3.3)	
Missing	5.1 (1.0)	6.0 (1.4)	9.2 (1.4)	6.3 (1.2)	
Physical activity, MET-min/week					
<600	27.7 (2.0)	33.5 (2.0)	36.0 (2.1)	44.7 (2.6)	<0.001
600–1199	12.5 (1.5)	10.5 (1.5)	12.3 (1.1)	10.6 (1.7)	

Variables	Urinary tin concentrations, μg/L				P
	Quartile 1 (<0.23)	Quartile 2 (0.23–0.47)	Quartile 3 (0.47–1.03)	Quartile 4 (>1.03)	
>1200	59.8 (2.4)	56.0 (2.1)	51.7 (2.2)	44.8 (3.3)	
Alcohol, g/d	14.8 ± 2.0	14.4 ± 1.7	13.9 ± 1.6	11.4 ± 1.7	0.89
Total energy intake, kcal/d	2221.7 ± 47.0	2181.1 ± 33.9	2265.1 ± 60.6	2062.1 ± 30.3	0.66
HEI-2010	53.2±0.5	52.1±0.8	50.5±0.9	49.1±0.7	0.52
BMI					
<25.0	40.5 (2.4)	30.8 (2.1)	29.0 (2.1)	26.1 (2.1)	
25–29.9	33.5 (2.1)	34.5 (2.4)	32.4 (3.2)	33.8 (2.0)	<0.001
>30.0	26.1 (2.1)	34.7 (2.4)	38.6 (2.8)	40.2 (2.1)	
Diabetes					
Yes	8.3 (1.3)	12.7 (1.0)	16.4 (1.9)	18.6 (1.3)	<0.0001
No	91.7 (1.3)	87.3 (1.0)	83.6 (1.9)	81.4 (1.3)	

Abbreviations: BMI, body mass index; MET: metabolic equivalent of task.

Values were weighted means (SEs) for continuous variables and weighted percentages (SEs) for categorical variables except the number of participants.

Table 2

Associations of urinary tin concentrations with diabetes in US adults

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend	OR per unit
Model 1	1 (ref.)	1.3 (0.9–2.0)*	1.8 (1.1–2.9)	2.0 (1.2–3.3)	0.004	1.3 (1.1–1.5)
Model 2	1 (ref.)	1.3 (0.9–1.9)	1.6 (1.0–2.7)	1.6 (1.0–2.6)	0.02	1.2 (1.0–1.4)

*OR; 95% CI in parentheses (all such values).

Model 1: adjusted for age (years), gender (male, female), and urinary creatinine (quartiles).
Model 2: Model1 plus race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and other race), education (less than high school, high school, college or higher), family income (family income to poverty ratio: ≤1.30, 1.31–3.50, >3.50, or missing), cigarette smoking (never, past, current), physical activity (<600, 600–1199, ≥1200), alcohol intake (male: 0, 0.1–27.9 g/d, ≥28 g/d; female: 0, 0.1–13.9 g/d, ≥14 g/d), BMI (<25.0, 25.0–29.9, ≥30.0), total energy intake (quartiles), and HEI-2010 (quartiles).

Table 3

Associations of urinary tin concentrations with diabetes in US adults by gender and race/ethnicity

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend	P for interaction
Gender	Male	1 (ref.)	1.4 (0.8–2.4) *	1.6 (0.7–3.6)	1.3 (0.7–2.7)	0.57	0.25
	Female	1 (ref.)	1.3 (0.7–2.3)	2.0 (1.1–3.5)	2.1 (1.0–4.5)	0.03	
Race/ethnicity	White	1 (ref.)	1.3 (0.7–2.4)	2.0 (1.0–4.0)	1.8 (0.9–3.6)	0.03	0.77
	Non-white	1 (ref.)	1.2 (0.8–1.9)	1.4 (0.8–2.3)	1.5 (0.8–2.6)	0.21	

* OR; 95% CI in parentheses (all such values).

Adjusted for the same covariates as Table 2, except the stratified variable.