Environmental Pollution xxx (2018) 1–9

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

# Associations of multiple plasma metals with incident type 2 diabetes in Chinese adults: The Dongfeng-Tongji Cohort☆

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## ARTICLE INFO

*Article history:*
Received 13 December 2017
Received in revised form
16 January 2018
Accepted 16 January 2018
Available online xxx

*Keywords:*
Titanium
Arsenic
Selenium
Prospective study
Type 2 diabetes

## ABSTRACT

The long-term associations between multiple metals and incident diabetes are uncertain. We aimed to examine the relationship between plasma concentrations of 23 metals and the incidence of type 2 diabetes among Chinese senior adults. We quantified fasting plasma concentrations of 23 metals by inductively coupled plasma mass spectrometry among 1039 incident diabetes cases and 1039 controls (age and sex matched) nested in a prospective study, the Dongfeng-Tongji cohort. Both cases and controls were free of diabetes at baseline (2008–2010), incident diabetes were identified using the following criteria: fasting glucose ≥ 7.0 mmoL/l; or hemoglobin A1c (HbA1c) ≥ 6.5%; or self-reported physician diagnosis of diabetes or use of anti-diabetic medication during the follow-up visits in 2013. In the conditional logistic regression models, the multivariable adjusted ORs (95% CIs) of diabetes across quartiles (Q1–Q4) of metal concentrations were as follows: titanium, 1.00, 0.92, 1.31, 1.38 (1.00–1.91, $P_{\text{trend}} = 0.011$); selenium, 1.00, 1.08, 1.45, 1.27 (0.93–1.74, $P_{\text{trend}} = 0.05$); and antimony, 1.00, 0.79, 0.77, 0.60 (0.44–0.83, $P_{\text{trend}} = 0.002$). Arsenic was significantly associated with diabetes in the crude model (ORs comparing extreme quartiles 1.30; 1.02–1.65; $P_{\text{trend}} = 0.006$), but was not significant after adjustment for socio-demographic factors. No significant associations were found for other metals. In conclusion, titanium and selenium were positively while antimony was negatively associated with incident diabetes.

## 1. Introduction

Diabetes is a major non-communicable disease globally, and the prevalence has increased dramatically over the past several decades, particularly in the developing countries (Guariguata et al., 2014). More than 415 million people were afflicted with diabetes in 2015, and about one fourth of them were Chinese (International Diabetes Federation, 2017). Even though unhealthy dietary pattern and sedentary lifestyles are well-established risk factors for diabetes, accumulating evidence has indicated that environmental chemicals (e.g., heavy metals) may also play important roles in the development of diabetes (Thayer et al., 2012). In daily life, the general population is commonly exposed to multiple metals through dietary intake, water drinking, inhalation of ambient air, and dermal contact of consumable goods (Nordberg et al., 2014; Rehman et al., 2018). Some existing human studies explored the association of single metals (e.g., arsenic (Brauner et al., 2014; Huang et al., 2014; Kuo et al., 2015), selenium (Bleys et al., 2007; Laclaustra et al., 2009; Park et al., 2012), nickel (Liu et al., 2015), manganese (Shan et al., 2016), zinc (Shan et al., 2014)) with

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☆ This paper has been recommended for acceptance by Dr. Chen Da.

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https://doi.org/10.1016/j.envpol.2018.01.046

Please cite this article in press as: Yuan, Y., et al., Associations of multiple plasma metals with incident type 2 diabetes in Chinese adults: The Dongfeng-Tongji Cohort, Environmental Pollution (2018), https://doi.org/10.1016/j.envpol.2018.01.046

diabetes and obtained mixed findings. For example, a Denmark cohort study showed that exposure to low-level arsenic in drinking water is associated with an increased risk of diabetes (Brauner et al., 2014), while in the Strong Heart Study in the U.S., this positive association was found for lower levels of urine monomethylarsonate proportion but not total arsenic (Kuo et al., 2015). Trace elements including selenium, manganese, and zinc are involved in various metabolic characteristics and biological functions (Nordberg et al., 2014). However, few epidemiological studies have been conducted to examine the relation of diabetes with those trace elements except selenium. Cross-sectional data of the U.S. National Health and Nutrition Examination Surveys (NHANES) suggested that serum selenium levels were positively associated with prevalence of diabetes (Bleys et al., 2007; Laclaustra et al., 2009), whereas higher toenail selenium levels were associated with a lower risk of incident type 2 diabetes in two U.S. cohorts (Park et al., 2012). Moreover, the exact physiological roles of other metals (e.g. titanium, antimony) in the human body are still unclear.

Furthermore, few studies investigated the diabetes risk related to simultaneous exposures to multiple metals, where people are naturally exposed to in the real-world scenario. Recently, some national surveys (e.g. the NHANES study) have explored the cross-sectional association between multiple-metals exposure and diabetes (Moon, 2013; Menke et al., 2016). Given that cross-sectional design could not provide temporal relation, prospective studies are warranted to validate the association. Therefore, we conducted a large case-control study nested within a cohort to systematically investigate whether plasma concentrations of multiple metals are associated with incident risk of type 2 diabetes.

## 2. Materials and methods

### 2.1. Study population

The detail of participant selection process is shown in Supplementary Fig. 1. All study participants were from the Dongfeng-Tongji (DFTJ) cohort, an ongoing prospective study launched in Shiyan City, China (Wang et al., 2013). Dongfeng Motor Corporation (DMC) is one of the largest auto corporation in China. The Retirement Office and the Social Insurance Center of DMC provided a list of all alive retired employees ($n = 31,000$) in 2008, who were senior adults with the mean age of 63 years old. These participants were invited to participate in the study, and 27,009 agreed (response rate 87%) and responded to questionnaires, underwent physical examinations, and provided baseline blood specimens from September 2008 to June 2010. The participants were invited to a follow-up examination in 2013 with a follow-up rate of 96.2% ($n = 25,978$). Totally, we identified 1515 incident diabetes patients after 4.6 years of follow-up. After excluding participants with baseline cardiovascular disease or cancer or insufficient blood samples, a total of 1039 incident cases were included in the study. We randomly selected controls from participants who were free of diabetes, cardiovascular disease and cancer at baseline and during follow-up, and they were 1:1 matched on age (within five years) and sex to incident diabetes cases.

### 2.2. Covariates

Data on socio-demographic factors, lifestyle habits, health status and medical history were interviewed by trained investigators with structured questionnaires. Trained personnel measured standing height, weight, waist circumference with subjects wearing light indoor clothing and without shoes. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Participants were defined as adherence to regular physical activity if they regularly exercised for half an hour on at least 5 days per week. Fasting blood was drawn for laboratory examination of serum lipids, fasting glucose, and renal function. Fasting plasma glucose levels were measured via glucose oxidase method with Aeroset automatic analyzer (Abbott Laboratories. Abbott Park, Illinois, USA), and serum lipids were measured with the ARCHITECTCi8200 automatic analyzer (ABBOTT Laboratories. Abbott Park, Illinois, USA). The HbA1c level was assessed with high-performance liquid chromatography (D-10 System; Bio-Rad Laboratories, Hercules, CA, USA). Impaired fasting glucose (IFG) was defined as fasting plasma glucose [FPG] $\geq 6.1$ and $< 7.0$ mmol/L. We defined hyperlipidemia as triglyceride $\geq$2.26 mmol/L, or total cholesterol $\geq$6.22 mmol/L, or HDL< 1.04 mmol/L, or LDL $\geq$4.14 mmol/L, or a previous physician diagnosis of hyperlipidemia, or usage of lipid-lowering medication. We assessed blood pressures on the left upper arm of the subjects in a seated position after a brief rest, and hypertension was defined as blood pressure $\geq$140/90 mmHg, or record of anti-hypertensive medication use. We utilized the Modification of Diet in Renal Disease equation to calculate estimated glomerular filtration rate (eGFR) (Ma et al., 2006). The study was approved by the Ethics and Human Subject Committees of Tongji Medical College. Participants gave written informed consents prior to the study.

### 2.3. Metals measurement

In the baseline survey, fasting blood samples were collected with clean EDTA tubes and preserved at $-80\,^{\circ}$C until analysis. The laboratory personnel were blinded to the case and control status during analyses. We determined the plasma concentrations of 23 metals using inductively coupled plasma mass spectrometry (Agilent 7700x ICP-MS; Agilent Technologies, USA), and the detail methods were described previously (Cesbron et al., 2013), with minor modification. The accuracy of ICP-MS was checked by analyzing certified reference agents (ClinChek human plasma controls for trace elements no. 8883 and 8884, Recipe, Munich, Germany) and standard reference materials 1640a (Trace Elements in Natural Water, National Institute of Standards and Technology, Gaithersburg, MD) in every 20 samples. Satisfactory results were obtained by comparing the quantified concentrations with certified reference ranges to guarantee strict quality control. To insure precise and accurate detection of titanium, rubidium, and tungsten (no available certified reference agents), we further utilize a spiked pooled plasma sample (100 samples randomly pooled together) as inter-laboratory comparison. The intra-assay and inter-assay coefficients of variations of plasma metals were all below 10%. The spike recovery rates of these metals range from 82.9% to 105.8%. We pre-cleaned the test tubes by overnight soaking in ultrapure grade 5% $HNO_3$. The detection limits of the plasma metals were within range of 0.0018–0.4992 μg/L. In the samples with metal levels below the detection limit, we imputed the metal levels as half of the detection limit.

### 2.4. Statistical analysis

Descriptive statistics were computed for all demographic and clinical characteristics of the participants. Comparison between the case-controls were performed with *t*-test or Mann-Whitney *U* test (continuous variables), and Chi-square tests (category variables). Given that over 50% participants were under the detection limits for plasma tungsten, tin, and uranium; we excluded these metals in subsequent analyses. Other metals maintained satisfactory detection rates (percentages under detection limits were all less than 13%). In our previous study (Yuan et al., 2017), we have examined

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