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Relationships Between Urinary Metals and Diabetes Traits Among Mexican Americans in Starr County, Texas, USA

Margaret C. Weiss[1,2] · Yu-Hsuan Shih[1] · Molly Scannell Bryan[3,4] · Brian P. Jackson[5] · David Aguilar[6] · Craig L. Hanis[6] · Maria Argos[1,4] · Robert M. Sargis[2,4,7,8]

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Abstract

Hispanics/Latinos have higher rates of type 2 diabetes (T2D), and the origins of these disparities are poorly understood. Environmental endocrine-disrupting chemicals (EDCs), including some metals and metalloids, are implicated as diabetes risk factors. Data indicate that Hispanics/Latinos may be disproportionately exposed to EDCs, yet they remain understudied with respect to environmental exposures and diabetes. The objective of this study is to determine how metal exposures contribute to T2D progression by evaluating the associations between 8 urinary metals and measures of glycemic status in 414 normoglycemic or prediabetic adults living in Starr County, Texas, a Hispanic/Latino community with high rates of diabetes and diabetes-associated mortality. We used multivariable linear regression to quantify the differences in homeostatic model assessments for pancreatic β-cell function, insulin resistance, and insulin sensitivity (HOMA-β, HOMA-IR, HOMA-S, respectively), plasma insulin, plasma glucose, and hemoglobin A1c (HbA1c) associated with increasing urinary metal concentrations. Quantile-based g-computation was utilized to assess mixture effects. After multivariable adjustment, urinary arsenic and molybdenum were associated with lower HOMA-β, HOMA-IR, and plasma insulin levels and higher HOMA-S. Additionally, higher urinary copper levels were associated with a reduced HOMA-β. Lastly, a higher concentration of the 8 metal mixtures was associated with lower HOMA-β, HOMA-IR, and plasma insulin levels as well as higher HOMA-S. Our data indicate that arsenic, molybdenum, copper, and this metal mixture are associated with alterations in measures of glucose homeostasis among non-diabetics in Starr County. This study is one of the first to comprehensively evaluate associations of urinary metals with glycemic measures in a high-risk Mexican American population.

Keywords Diabetes · Metals · Metalloids · Endocrine disruptors · Chemical mixtures · Glucose · Insulin

Introduction

Diabetes mellitus exerts a significant individual health burden while imposing a critical threat to public health. It is currently estimated that 34.2 million people in the USA have diabetes, with an additional 88 million adults with pre-diabetes and at high risk of developing diabetes [1]. This disease's societal toll in the USA is significant, with diabetes-associated health costs estimated to be $327 billion annually [2]. Critically, the burden of diabetes disproportionately impacts communities of color. In the USA, Hispanics/Latinos have the highest lifetime risk of developing

✉ Robert M. Sargis
rsargis@uic.edu

1 School of Public Health, University of Illinois at Chicago, Chicago, IL, USA

2 College of Medicine, University of Illinois at Chicago, Chicago, IL, USA

3 Institute for Minority Health Research, University of Illinois at Chicago, Chicago, IL, USA

4 Chicago Center for Health and Environment, Chicago, IL, USA

5 Department of Earth Sciences, Dartmouth College, Hanover, NH, USA

6 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA

7 Section of Endocrinology, Diabetes, and Metabolism, Jesse Brown Veterans Affairs Medical Center, Chicago, IL, USA

8 Division of Endocrinology, Diabetes, and Metabolism, University of Illinois at Chicago, 835 S. Wolcott, Suite E625, M/C 640, Chicago, IL 60612, USA

diabetes, with 80% higher rates of the disease than non-Hispanic whites [3]. Furthermore, Hispanics/Latinos disproportionately suffer from diabetes-associated complications [3]. Starr County, Texas, a primarily Hispanic/Latino community along the Rio Grande River, has some of the highest rates of diabetes in the USA [4]. The reasons behind these disparities are poorly understood; however, emerging evidence linking environmental toxicants to diabetes raises the potential that disproportionate exposure to these chemicals may contribute to disease disparities [5–7]. Among diabetogenic toxicants, metals and metalloids are implicated as potential risk factors; however, their specific associations with diabetes-related traits remain incompletely characterized [8].

Multiple metals and metalloids are required for normal physiological function. Among these, zinc, copper, and selenium are essential cofactors for enzymes and critical structural elements of proteins [9]. Of particular note is the role of zinc in the processing and packaging of insulin, a hormone essential for maintaining normal levels of blood sugar [10]. In contrast, elements such as arsenic and cadmium have no known role in human physiology and can disrupt normal cellular function and increase disease risk. Among these toxic metals and metalloids, some can be classified as endocrine-disrupting chemicals (EDC), exogenous chemicals, or mixtures of chemicals that interfere with hormone action [11]. Several EDCs have been shown to alter insulin secretion or action, disrupt whole-body glucose homeostasis, and are associated with increased diabetes risk [6, 7, 12].

Previous population-based studies suggest associations among various urinary metals and diabetes morbidity. Specifically, arsenic, zinc, selenium, vanadium, manganese, copper, lead, and cadmium have been linked to increased diabetes prevalence in highly exposed populations [8, 13–15]. In addition, epidemiologic data have also shown relationships among cobalt, nickel, copper, molybdenum, cadmium, and lead, with altered fasting blood glucose and other diabetes markers [16, 17]. Studies have also found that even essential nutrients can be diabetogenic at high doses, including vanadium, selenium, and molybdenum [18, 19]. Despite this, there are gaps in knowledge with regard to the specific effects of metal/metalloid exposures on diabetes development. Of these prior epidemiologic studies, most were conducted in populations with known elevated exposures and only evaluated the effect of single metals independently. Additionally, the impact of metal/metalloid exposures and their mixtures has not been completely characterized in diverse ethnic groups, including high-risk Mexican Americans, despite their markedly elevated disease rates.

To address current gaps in knowledge, this study aimed to evaluate the relationships among a comprehensive panel of urinary metal concentrations, individually and as a mixture, with diabetes-related traits among normoglycemic/prediabetic Hispanics/Latinos living in Starr County, Texas, USA. Critically, Starr County residents have a 70% lifetime risk of developing diabetes and one of the highest diabetes-associated mortality rates in the country [4, 20, 21]. This lifetime risk is 20% higher than the general US population of Hispanics/Latinos, and we hypothesize that environmental factors may play a role in this disparity [22].

Methods

Study Population and Design

The population for this analysis included Mexican American individuals from Starr County, Texas, who had participated in a previous study of novel diabetes risk factors [20], and individuals participating in an ongoing study of the gut microbiome and progression of dysglycemia [23]. Briefly, a systematic survey, largely representative of the age and sex distribution of the Starr County population, was conducted in 3,085 households within 309 blocks in Starr County from 2002 to 2006 to determine the frequency of diabetes. Predominantly from those who answered the survey, 1200 individuals (selected to include approximately half with diabetes) returned for a follow-up examination of novel diabetes risk factors in 2010–2014 [20]. Of these participants, 412 individuals were randomly selected for urinary metal analyses. The sample size was then supplemented with an additional 157 individuals (identified from the original survey) without known diabetes participating in an ongoing study of the gut microbiome on the progression of dysglycemia [21]. In total, 569 individuals were selected for urinary metal analyses, of which 414 participants without diabetes and without missing data on exposures, outcomes, and covariates were included in the present study.

Assessment of Outcomes

One 10-mL EDTA vacutainer of whole blood was collected at fasting in order to measure hemoglobin A1c (HbA1c) (Siemens DCA Vantage Analyzer point-of-care device, Malvern, PA), fasting plasma glucose (FPG), and fasting plasma insulin (Roche Cobas Analyzer, Chicago, IL) concentrations at enrollment. FPG was measured using a YSI 2300 STAT Plus Glucose and Lactate analyzer (YSI Life Sciences, Yellow Springs, Ohio). Steady-state insulin-glucose relationships were assessed using the homeostatic model assessments (HOMA) of β-cell function (HOMA-B), insulin sensitivity (HOMA-S), and insulin resistance (HOMA-IR). HOMA-B was calculated using $\frac{I_0\left[\frac{pmol}{L}\right]*3.33}{G_0\left[\frac{mmol}{L}\right]-3.5}$; HOMA-S was calculated using $\frac{22.5*18}{G_0\left[\frac{mg}{dL}\right]*I_0\left[\frac{\mu g}{mL}\right]}$; and HOMA-IR was calculat-

ing using $\frac{G_0\left[\frac{nmol}{L}\right]*I_0[\frac{\mu U}{mL}]}{22.5}$ [24], where I_0 represents fasting insulin and G_0 represents fasting glucose. In the present analyses, we evaluated diabetes status, HbA1c, FPG, 2-h blood glucose, HOMA-B, HOMA-S, HOMA-IR, and fasting plasma insulin with urinary metal levels as described below.

Assessment of Exposure

Urinary evaluation of metal concentrations is a well-accepted method to evaluate the burden of metals in individuals. Specifically, urinary evaluation represents exposure from multiple sources and assesses chemicals with short half-lives. Although each metal has different excretory pathways, for example manganese in bile, urinary evaluation is still well accepted to determine exposures in individuals [25–31]. Spot urine samples were collected from each participant. Following collection, samples were immediately placed on ice, centrifuged within 30 min, aliquoted, and placed in a − 20 °C freezer. At the end of each day, samples were stored at − 70 °C until shipment to Dartmouth College where analyses were performed. The urine samples were analyzed for 19 elements—beryllium (Be), aluminum (Al), vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), molybdenum (Mo), cadmium (Cd), tin (Sn), antimony (Sb), mercury (Hg), lead (Pb), and uranium (U)—using the trace element analysis core at Dartmouth College. Briefly, samples were diluted tenfold in 1% HNO_3 and analyzed on an 8900 ICP-QQQ mass spectrometer (Agilent, Santa Clara, CA) utilizing helium and oxygen modes (for Be, Cd, on-mass and V, As, Se, mass-shifted). The ICP-MS was calibrated using NIST-traceable multi-element standards (Inorganic Ventures, Christiansburg, VA) with seven calibration standard concentrations spanning the expected concentration range. Quality control included initial and continuing calibration checks, laboratory check solutions (past proficiency samples from the Center for Toxicology, Quebec, Canada), and reference materials (normal level urine, UTAK, Valencia, CA). We assigned calibration values from the instrument for concentrations below the limit of detection (LOD). A summary of quality control results and the method detection limits, calculated as 3 sigma of repeated blank concentrations run across the sample batches, is shown in Supplementary Table 1. The fraction of samples below the LOD for each metal were as follows: Be (99.04%), Al (87.48%), V (47.9%), Cr (94.50%), Mn (36.86%), Fe (47.18%), Co (2.75%), Ni (75.24%), Cu (0%), Zn (0.28%), As (0%), Se (0%), Mo (0%), Cd (0.69%), Sn (67.68%), Sb (50.21%), Hg (84.73%), U (67.54%), and Pb (46.49%). Only elements with < 50% of samples below the LOD were retained for analysis. Urinary creatinine was quantified from spot urine samples using DetectX Urinary Creatinine Kit (Arbor Assays, Ann Arbor, Michigan). Urinary metal concentrations were standardized by creatinine concentration to account for differences in participants' hydration status.

Assessment of Covariates

Self-reported participant characteristics, including age (years), sex (male, female), years of education, employment status (full time, part time, unemployed, retired, or disabled), smoking status (current, former, never), pack-years of smoking, height (m), weight (kg), diabetes medication usage (no medication; insulin only; oral hypoglycemic agent only; other injectable hypoglycemic agent only; insulin and oral agent; insulin and other injectable; oral agent and other injectable; insulin, oral agent, and other injectable), and alcohol consumption (yes, no), were available from the baseline questionnaire administered to subjects. Participant's height in meters and weight in kilograms were used to calculate body mass index (kg/m^2).

Statistical Analyses

Demographic characteristics were summarized among the 414 participants overall. The median and interquartile range (IQR) for urinary metal concentration are presented overall. Correlations among the urinary metal concentrations were assessed using Spearman's rank correlation coefficients.

All multivariable models were adjusted for a priori confounders, including urinary creatinine, sex (male, female), age (years), smoking status (current, former, never), pack-years of smoking, BMI (kg/m^2), and alcohol consumption (yes, no) [32]. To evaluate non-linear associations, we constructed quartiles of exposure based on each metal's distribution in the overall study sample. The first quartile, representing participants with the lowest exposure levels, was used as the reference group. The p value for trend was obtained by modeling the quartiles of exposure as an ordinal variable. For continuous diabetes traits, natural log-transformation was used due to skewed distributions. Multivariable linear regression models were utilized to estimate percent changes in HOMA measures (i.e., HOMA-B, HOMA-S, and HOMA-IR), plasma insulin, and FPG as $(e^{(\ln 2 \times \beta)} - 1) \times 100\%$ with respect to quartiles of metal concentrations. We restricted the analyses of these continuous measures to participants without diabetes. Multicollinearity between metals was not detected based on the variance inflation factor. A sensitivity analysis was conducted for analyses of mercury and arsenic to account for fish consumption by additionally including urinary arsenobetaine concentration (a proxy of seafood intake) as a covariate in the regression model due to their exposure source being fish and other marine organisms, which may themselves confer metabolic protection [33].

A quantile-based g-computation approach was implemented to assess the effect of metal mixtures on diabetes traits [34]. Quantile-based g-computation is a novel mixture method used to evaluate environmental mixtures and identify the mixture components driving phenotypic outcomes. In the current analyses, each metal was first categorized into quartiles, and then empirical weights were evaluated for each metal through a generalized linear regression model (binomial distribution for diabetes status and Gaussian distribution for log-transformed diabetes traits). Negative and positive weights were generated since the metal mixture included both essential trace and toxic metals. Weights were interpreted as the proportion of the negative or positive partial effect due to a specific metal. The overall effect of the metal mixture (ψ) with each outcome was estimated based on a marginal structural model via g-computation algorithms with a bootstrap of 1,000 iterations. The estimator, ψ, was calculated by summing the regression coefficients of the 8 included metals and interpreted as the OR of diabetes/pre-diabetes (or the change in log-transformed diabetes traits) corresponding to a simultaneous increase in all metals by one quartile.

SAS software version 9.4 (SAS Institute Inc., Cary, NC) was utilized to perform all analyses with the exception of the g-computation analyses, which were implemented using the qgcomp R package [34].

Table 1 Selected participant characteristics

Characteristic	Overall ($N=414$)
Age, mean ± SD	47.03 ± 9.07
Gender, *n* (%)	
Male	99 (23.91)
Female	315 (76.09)
BMI, mean ± SD	31.58 ± 6.58
Education years, mean ± SD	10.38 ± 3.68
Employment Status, n (%)	
Full time	252 (60.87)
Part time	98 (23.67)
Not employed	42 (10.14)
Retired	18 (4.35)
Disabled	4 (0.97)
Smoking status, n (%)	
Current	67 (16.18)
Former	52 (12.56)
Never	295 (71.26)
Pack-year, mean ± SD	2.90 ± 10.01
Alcohol drinking, n (%)	
Yes	137 (33.09)
No	277 (66.91)

Results

Descriptive Statistics

Table 1 shows the characteristics of the 414 participants from Starr County, Texas. Most of the participants were women (76%), never smokers (71%), and not alcohol consumers (67%). Supplemental Table 2 summarizes the distribution of 8 urinary metal concentrations overall. Urinary metals showed low to moderate correlations, with Spearman's rank correlation coefficients ranging from 0.09 to 0.70 (Supplemental Table 3).

Steady-State of Insulin-Glucose Dynamics

Table 2 summarizes the associations between urinary metal concentrations and HOMA assessments of insulin resistance and sensitivity as well as β-cell function among individuals without diabetes. First, a higher concentration of urinary total arsenic was associated with reduced HOMA-β (p for trend = 0.03) and HOMA-IR (p for trend = 0.02) and increased HOMA-S (p for trend = 0.02). A dose-dependent association was observed for increased urinary molybdenum with reduced HOMA-β (p for trend = 0.09), reduced HOMA-IR (p for trend = 0.048), and increased HOMA-S (p for trend = 0.049). Individuals with higher urinary copper had reduced HOMA-β compared to those with lower copper (p for trend = 0.046). Lastly, cadmium showed borderline statistically significant effects for reduced HOMA-β (p for trend = 0.08).

Plasma Insulin and Fasting Plasma Glucose

Because HOMA estimates may be influenced by FPG or fasting insulin levels, we examined associations with each component of the HOMA calculations separately. The associations of urinary metal concentrations with plasma insulin are summarized in Supplemental Table 4. Findings of this analysis mirror what we found for HOMA measures. Specifically, an inverse association with plasma insulin was observed for arsenic and molybdenum. Supplemental Table 5 summarizes the effect of urinary metal exposure and FPG among patients without diabetes. In these analyses, metals/metalloids appeared to exert minor effects on glucose. These data collectively suggest that associations between urinary metal levels and steady-state estimates of insulin-glucose dynamics using HOMA measurements are principally driven by alterations in insulin levels.

Metal Mixture

Utilizing quantile-based g-computation, exposure to the 8 metal mixtures was significantly associated with alterations in HOMA-β, HOMA-IR, HOMA-S, and plasma insulin when increasing all metals by one quartile (Table 3). A higher

Table 2 Percent difference (95% CI) of HOMA measures[c] with quartile of urinary metal concentrations ($N=414$)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p_{trend}
Arsenic, µg/L[b]	< 2.97	2.97–4.86	4.86–7.42	> 7.42	
HOMA-B	Ref	− 6.96 (− 16.11, 3.18)	− 16.10 (− 24.16, − 7.17)	− 8.26 (− 17.05, 1.46)	0.028
HOMA-S	Ref	21.25 (3.51, 42.03)	34.49 (15.23, 56.98)	17.53 (0.75, 37.10)	0.02
HOMA-IR	Ref	− 17.55 (− 29.62, − 3.41)	− 25.66 (− 36.31, − 13.22)	− 14.90 (− 27.05, − 0.72)	0.02
Cadmium, µg/L	< 0.20	0.20–0.36	0.36–0.63	> 0.63	
HOMA-B	Ref	− 5.25 (− 14.64, 5.18)	− 3.56 (− 13.40, 7.40)	− 10.67 (− 20.24, 0.05)	0.084
HOMA-S	Ref	4.33 (− 11.13, 22.48)	3.62 (− 12.18, 22.25)	14.70 (− 3.63, 36.52)	0.151
HOMA-IR	Ref	− 4.15 (− 18.36, 12.53)	− 3.43 (− 18.15, 13.95)	− 12.77 (− 26.72, 3.83)	0.154
Cobalt, µg/L	< 0.13	0.13–0.19	0.19–0.33	> 0.33	
HOMA-B	Ref	5.17 (− 4.96, 16.39)	− 4.40 (− 13.64, 5.82)	6.41 (− 3.97, 17.91)	0.594
HOMA-S	Ref	− 8.41 (− 21.56, 6.93)	10.98 (− 4.98, 29.63)	− 8.57 (− 21.85, 6.96)	0.777
HOMA-IR	Ref	9.24 (− 6.44, 27.55)	− 9.98 (− 22.93, 5.16)	9.40 (− 6.49, 27.99)	0.779
Copper, µg/L	< 6.27	6.27–9.87	9.87–1306	> 13.06	
HOMA-B	Ref	− 6.05 (− 15.23, 4.13)	− 8.03 (− 17.18, 2.14)	− 10.23 (− 19.26, − 0.20)	0.046
HOMA-S	Ref	13.85 (− 2.77, 33.32)	9.45 (− 6.81, 28.56)	16.02 (− 1.39, 36.50)	0.130
HOMA-IR	Ref	− 12.15 (− 24.98, 2.88)	− 8.62 (− 22.20, 7.34)	− 13.83 (− 26.76, 1.40)	0.129
Lead, µg/L	< 0.35	0.35–0.55	0.55–0.91	> 0.91	
HOMA-B	Ref	− 3.19 (− 12.53, 7.15)	− 9.63 (− 18.64, 0.37)	− 4.43 (− 13.92, 6.10)	0.251
HOMA-S	Ref	8.73 (− 6.97, 27.08)	14.18 (− 2.82, 34.16)	7.27 (− 8.64, 25.95)	0.347
HOMA-IR	Ref	− 8.03 (− 21.31, 7.49)	− 12.48 (− 25.52, 2.84)	− 6.84 (− 20.66, 9.39)	0.342
Molybdenum, µg/L	< 30.63	30.63–46.96	46.96–72.09	> 72.09	
HOMA-B	Ref	− 10.52 (− 19.06, − 1.07)	− 3.72 (− 13.09, 6.66)	− 11.14 (− 19.70, − 1.67)	0.087
HOMA-S	Ref	15.54 (− 0.90, 34.71)	1.82 (− 12.94, 19.09)	22.80 (5.17, 43.38)	0.049
HOMA-IR	Ref	− 13.43 (− 25.75, 0.94)	− 1.82 (− 16.06, 14.84)	− 18.60 (− 30.29, − 4.95)	0.048
Selenium, µg/L	< 33.38	33.38–51.73	51.73–69.52	> 69.52	
HOMA-B	Ref	− 2.61 (− 11.99, 7.78)	1.21 (− 8.59, 12.06)	− 1.41 (− 11.08, 9.32)	0.978
HOMA-S	Ref	5.72 (− 9.49, 23.49)	− 2.65 (− 16.72, 13.80)	1.31 (− 13.52, 18.69)	0.870
HOMA-IR	Ref	− 5.45 (− 19.05, 10.45)	2.68 (− 12.17, 20.04)	− 1.31 (− 15.76, 15.62)	0.872
Zinc, µg/L	< 238.63	238.63–405.75	405.75–660.88	> 660.88	
HOMA-B	Ref	− 9.58 (− 18.22, − 0.04)	− 4.32 (− 13.60, 5.95)	− 11.19 (− 19.94, − 1.49)	0.071
HOMA-S	Ref	12.82 (− 3.31, 31.64)	0.84 (− 13.79, 17.95)	13.78 (− 2.99, 33.44)	0.276
HOMA-IR	Ref	− 11.43 (− 24.09, 3.35)	− 0.81 (− 15.20, 16.03)	− 12.15 (− 25.10, 3.04)	0.276

[a]All models adjusted for sex, age, smoking status, pack-year smoking, BMI, alcohol consumption, years of education, and employment status

[b]Total arsenic calculated as the sum of DMA, MMA, and inorganic arsenic

[c]*HOMA-B*, HOMA beta cell function; *HOMA-S*, HOMA insulin sensitivity; *HOMA-IR*, HOMA insulin resistance

Table 3 Combined effects of metal mixture on diabetes-related measures ($N=414$)

	% Change (95% CI)	*p* value
HOMA-B	− 7.9 (− 14.39, − 0.92)	0.033
HOMA-S	12.08 (0.93, 24.46)	0.028
HOMA-IR	− 10.78 (− 19.66, − 0.92)	0.034
Plasma insulin	− 11.1 (− 20.18, − 0.98)	0.034
Fasting plasma glucose	0.09 (− 1.54, 1.75)	0.915

[a]All models were adjusted for sex, age, smoking status, pack-year smoking, BMI, alcohol consumption, years of education, and employment status

[b]Correspond to a simultaneous increase in all metals by one quartile

concentration of the total metal mixture was associated with reduced HOMA-β ($p=0.03$), plasma insulin ($p=0.03$), and HOMA-IR ($p=0.03$) and increased HOMA-S ($p=0.03$). Analysis of each metal's proportional positive or negative contributions to the joint effect supported the results found in the multivariable linear regression (Supplemental Figs. 1–5).

Discussion

In this study, we investigated the associations between creatinine-standardized urinary concentrations of 8 metals/metalloids with diabetes-related traits in a cohort of 414

normoglycemic/prediabetic Mexican Americans living in Starr County, Texas, USA. We found urinary arsenic and molybdenum to be associated with reduced β-cell function, insulin resistance, and plasma insulin along with increased insulin sensitivity. Additionally, copper was associated with reduced β-cell function. Furthermore, increased urinary cadmium showed a non-significant trend toward reduced HOMA-β. Lastly, the ultimate 8 metal mixture was associated with alterations in measures of HOMA, and the weighted directionality of the individual metals within the mixture matched the findings of the individual metal regressions. To the best of our knowledge, this is one of the first studies to evaluate multiple metals individually and as a mixture with continuous diabetes measures in a homogenous, high-risk Hispanic/Latino population.

Arsenic is a well-studied, toxic metalloid found in many human water and food sources around the globe [35]. Water supplies in the USA have low to moderate levels of arsenic relative to the World Health Organization (WHO) standard of < 10 μg/L [36]. Despite this, Starr County, Texas, has been noted to have groundwater arsenic levels above the WHO standard [37]. Fish and rice consumption are other potential sources for arsenic exposure and studies have shown that minority populations, including Hispanics/Latinos, consume higher amounts of both fish and rice that could lead to disproportionate exposures to arsenic [38]. There is robust research on arsenic's effect on diabetes risk, but few studies are conducted in low exposure, minority populations. Additionally, minimal studies focus on the pathophysiology of diabetes to discern the mechanisms by which arsenic impacts diabetes risk. Many studies conducted in high arsenic exposure regions have revealed increased prevalence and incidence of type 2 diabetes [39, 40], with multiple systematic reviews and meta-analyses corroborating a link between arsenic exposure and increased type 2 diabetes risk. A meta-analysis by Sung et al. evaluated 38 studies and showed a significant association with arsenic exposure and diabetes risk [41]. Furthermore, Navas-Acien et al. reviewed 19 epidemiological studies in both high and low arsenic exposure groups and found consistent results for an increased risk of diabetes in highly exposed regions, but further studies being needed for low exposure groups [42]. These population-based studies are supported by both in vivo and in vitro studies that have shown that arsenic disrupts insulin synthesis and secretion due to β-cell toxicity [12, 43–46], which also support our findings indicating a significant reduction in β-cell function and fasting insulin among individuals in Starr County with the highest levels of urinary arsenic.

Molybdenum is an essential trace element that is a cofactor for several enzymes required for normal human physiology. Although it is necessary for human life, there is evidence that high concentrations are toxic, and acute toxic doses result in immediate clinical symptoms, including diarrhea, anemia, gout, and psychosis [47]. Individuals in Starr County could be exposed to molybdenum through a variety of sources. The most common source of molybdenum is food derived from plants and dairy products. Drinking water exposure is common in areas with industrial waste containing molybdenum, especially from mining, which is prominent in Southern Texas and along the Rio Grande River [28, 48]. Lastly, there is evidence that Hispanics/Latinos living in the USA are more likely to work in high-risk occupations for environmental chemical exposures, including solvents, metals, and pesticides [49].

The observed association between higher urinary molybdenum levels and alterations in HOMA measures (including reduced HOMA-β, HOMA-IR, and fasting insulin and increased HOMA-S) is consistent with some previous epidemiological studies. Specifically, an analysis of the Study of Women's Health Across the Nation (SWAN) cohort found a significant inverse association between urinary molybdenum and HOMA-IR, but it did not find any association with HOMA-β [50]. In other cohort studies, urinary molybdenum was associated with increased diabetes prevalence, with molybdenum levels higher in those with diabetes compared to individuals with normoglycemia [8]. In contrast, other studies have found positive associations between molybdenum and increased HOMA-IR in participants without diabetes in both US and Chinese populations [16, 51]. These studies were not performed in Hispanic/Latino populations.

In addition to this epidemiological literature, there are cell-based, animal, and human data that support mechanistic links between molybdenum and altered glucose-insulin homeostasis. Molybdenum has been shown to reduce insulin secretion in pancreatic β-cells while promoting β-cell apoptosis in both RIN-m5f cells and isolated murine islets through oxidative stress and other mechanisms [52]. This linkage between molybdenum and oxidative stress is supported by data from a cohort study that found a significant association between molybdenum levels and biomarkers of oxidative stress in a general population in Spain [53]. Other studies have found that β-cells have a limited capacity to handle oxidative stress, which may contribute to diabetes pathogenesis when exposed to chemicals that increase free radicals; this association has been further corroborated by a study of oxidative damage due to metals and type 2 diabetes in Chinese adults [51, 54]. Lastly, molybdenum exposure has been linked to other endocrine-disrupting health outcomes with similar mechanisms of toxicity, including infertility, hypertension, and liver dysfunction [55–57].

In addition to arsenic and molybdenum, there is supportive evidence for an impact of copper on pancreatic β-cell function and overall diabetes risk. The most common source of copper exposure in the USA is through drinking water as it leaches into water supplies through copper pipes

[58]. Both individual studies and meta-analyses have found positive associations for serum copper with diabetes prevalence and HbA1c [59, 60]. Other studies have shown that increased copper exposure and alterations in copper metabolism are associated with oxidative stress and increased risk for diabetes mellitus [61]. Furthermore, copper chelation has been proposed as an alternative diabetes treatment [62, 63]. Despite these findings, there is still limited evidence on the pathophysiological impact of copper overload on diabetes, and further studies are clearly needed to explore these relationships further.

Although our assessments of cadmium's links to disrupted glucose-insulin homeostasis did not reach statistical significance, there is evidence that cadmium is associated with metabolic dysfunction. Cadmium has been implicated in diabetes pathogenesis with evidence of cadmium-induced disruptions in adipocyte responses to insulin and pancreatic islet function [64, 65]. Cadmium exposure is widespread through multiple routes, including air pollution as well as agricultural, food, and water contamination [66]. The heavy metal is also found in cigarettes, alloys, pigments, plastics, and batteries. The impact of cadmium exposure on diabetes risk needs to be evaluated further, particularly in high-risk minority populations, as evidence of an effect within general populations is somewhat conflicting [67, 68].

People are simultaneously exposed to multiple metals rather than as isolated elements. In this study, we found an association between the simultaneous exposure to 8 metals as a mixture and alterations of steady-state measures of glycemic status. Additionally, the proportional positive or negative contributions of each metal of the joint effect according to quantile-based g-computation support the findings from the individual regression models. Few studies have investigated the role of metal mixtures on diabetes or diabetes-related traits. A study of 1262 US women in the SWAN cohort utilized adaptive elastic-net models as well as an environmental risk score and found associations of metal mixtures with decreased HOMA-β (higher arsenic and zinc, but lower cobalt) and elevated HOMA-IR (higher copper, lead, and zinc, but lower molybdenum) [50]. Another analysis of the same data observed an association between exposure to 20 metals as a mixture and increased risk of diabetes based on k-mean clustering [69]. As these statistical techniques are novel, future studies are required to corroborate results, but these innovative approaches will illuminate real-world exposure patterns and provide vital information about the physiological consequences of interactions among EDCs.

Strengths and Limitations

This study comprehensively investigated the associations of 8 urinary metals and their mixture with five diabetes-related traits in a US Hispanic/Latino population. In addition, we utilized a novel statistical approach to evaluate the potential combined effects of metals as a mixture. Finally, to our knowledge, our study serves as the first to evaluate these associations in a Mexican American population. Despite these strengths, our study has limitations. The study's cross-sectional nature renders us unable to conclude the temporality of the associations, and the urinary metal levels were measured using a single spot urine sample. Future research that examines diabetes status longitudinally and is able to characterize long-term exposure will allow for a more robust understanding of any causal association between metals/metalloids and diabetic trait trajectories. Furthermore, alternative novel methods for assessing essential mineral status using erythrocytes rather than whole blood may augment assessments of metal/metalloid status [70]. Additionally, as this observational study examined the impacts of metal exposures in non-endemic regions, the exposure levels may not be sufficiently high to see overt effects with our limited sample size. As a result, borderline non-significant associations were observed that should be evaluated both longitudinally and in a larger cohort. In addition, some misclassification of both urinary creatinine and the metals could be possible, as kidney function can be influenced by metal exposure and diabetes status [71]; similarly, increased urinary metal concentrations could be due to increased urinary excretion rather than increased exposure, raising the possibility that associations of higher levels with diabetes traits may reflect reduced cellular and tissue metal/metalloid levels. We also acknowledge that the HOMA measurements may be imperfect markers of glycemic status, as it can be less valid in participants with lean type 2 diabetes mellitus and insulin secretory defects [72]; however, given that the average BMI of our study population was in the obese range and those with diabetes were excluded from HOMA analyses, we expect this to minimally affect our conclusions. We recognize the potential for residual confounding, as some variables that could influence diabetes status were not measured, such as dietary intake of supplements, co-exposure to other environmental pollutants, or other measures of socioeconomic status. We also acknowledge the possibility for inflated type I error, given the multiple tests conducted, but note the consistency of our results across multiple statistical methods and parameterization of glycemic/diabetic status.

Conclusions

In this study of 414 Mexican Americans living in Starr County, Texas, we found a strong association between increased urinary arsenic, molybdenum, copper, and the eight-metal mixture with alterations in steady-state measures of insulin-glucose homeostasis and fasting insulin levels.

While requiring further investigation in prospective studies, these findings illuminate potential roles of these metals/metalloids in the pathogenesis of diabetes or as a marker of active or impending glycemic disruption within this historically high-risk Mexican American population living in Starr County, Texas. Importantly, identifying metals/metalloids that are pathogenically linked to diabetes development in diverse high-risk populations raises the possibility that individual- and policy-based exposure reduction strategies may offer novel approaches for mitigating the devastating burden of diabetes and its complications in vulnerable groups.

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Declarations

Ethical approval RMS declares he has received honoraria from CVS/Health and the American Medical Forum, neither of which relate to the present study.

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