Do exposure to heavy metals mediate the associations between socioeconomic indicators and self-rated health among the US adult Populations: A Weighted Quantile Sum Mediation Approach

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Abstract

This study aimed to examine the associations between socioeconomic status (SES) and self-rated health (SRH) among US general adult populations and the extent to which blood and urinary metal mixtures explain these associations. We used 14 years of repeated cross-sectional data that consists of seven consecutive NHANES cycles from 2003-04 to 2015-16 (N = 9497). SRH was measured using a 5-point Likert scale, and SES was measured by Family Income to Poverty Ratio (FMPIR), levels of education, and employment status. Blood concentration of lead, mercury, and cadmium, and urinary concentrations of ten heavy metals (arsenic, barium, cadmium, cesium, cobalt, lead, mercury, molybdenum, thallium, tungsten) were used as metal mixtures. The total effects of SES on SRH were examined by linear regression. The direct effects of SES on metal mixtures were examined by weighted quantile sum (WQS) regression with Repeated Holdout Validation method, and causal mediation effect of mixtures was examined by model-based causal mediation technique. Results showed that SES (education $\beta$: 0.17; 95% CI: 0.15, 0.18; employment $\beta$: 0.16; 95% CI: 0.12, 0.21; and FMPIR $\beta$: 0.09; 95% CI: 0.08, 0.11) were positively, and the WQS indices of blood and urine metal mixtures (blood $\beta$: -0.04; 95% CI: -0.05, -0.03, urine $\beta$: -0.07; 95% CI: -0.13, -0.004) were significantly inversely associated with SRH in the US adult population. The novel finding was the mechanism between SES and SRH that exposure to heavy metals may explain socioeconomic inequalities in SRH in the US. Longitudinal studies are needed to corroborate this study results.

Introduction

People with a higher socioeconomic status (SES: higher educational attainment, having a greater wealth, and being employed in a white-collar job) are more likely to have better self-rated health (SRH) and higher life expectancy compared to those from lower SES groups (Hill and Needham 2006; Phelan et al. 2010; Suresh et al. 2011; Vonneilich et al. 2019). Firstly, people with higher SES have access to proper healthcare, nutritious food, better housing, healthier lifestyles, and less stressful events, therefore, reporting better health status (Power et al. 1998; Frankenberg and Jones 2004; Adler and Rehkopf 2008; Phelan et al. 2010; Suresh et al. 2011; Zajacova and Dowd 2011; Platts and Gerry 2017; Vonneilich et al. 2019; Budhathoki et al. 2020). Secondly, they are more likely to avoid environmental exposures and have multiple channels to prevent themselves from being continuously exposed to environmental toxins (Evans and Kantrowitz 2002; Brender et al. 2011; Chakraborty et al. 2011; Morello-Frosch et al. 2011; Bell and Ebisu 2012; Tyrrell et al. 2013). This unequal distribution of exposure to environmental toxins is partially due to differences in SES in the population, especially occupation, income, and education. Thus, people with low SES confront environmental injustice and health inequalities (Evans and Kantrowitz 2002; Evans and Kim 2010; Morello-Frosch et al. 2011; Bell and Ebisu 2012; Tyrrell et al. 2013; Cullati et al. 2014).

Epidemiological studies have shown that people who are highly exposed to a range of environmental toxins tend to have poor health status, as indicated by higher prevalence of respiratory disease, obesity, hypertension, cardiovascular disease, diabetes, cancer, liver damage, kidney ailment, vision impairment,
and lower cognitive function in adults (Evans and Kantrowitz 2002; Evans and Kim 2010; Mendy et al. 2012; Cullati et al. 2014; Chowdhury et al. 2018). Two previous studies assessed the effects of toxic heavy metals on SRH and found that people with higher exposures to urinary heavy metals were more likely to rate their health as poor, fair, and good (Shiue 2015; Brailsford et al. 2018). Hence, some scholars theoretically argued that non-social environmental factors, such as exposure to pollutants, may constitute a significant pathway connecting SES and SRH, which has not yet been measured and studied empirically (Evans and Kantrowitz 2002; Evans and Kim 2010; Chakraborty et al. 2011). Moreover, most of the existing studies were limited to examine the effect of a single metal biomarker on health outcomes (Shiue 2013, 2015; Nigra et al. 2016; Brailsford et al. 2018; Moody et al. 2018).

The observed association between SES and the combined effects of metals is often overlooked in previous studies (Mendy et al. 2012; Tyrrell et al. 2013; Awata et al. 2017; Brailsford et al. 2018). To our best knowledge, no study has examined both blood and urinary metal mixture effects on SRH and its mediating role in the associations between SES and SRH using the mixture approach. Thus, this study aimed to examine the association between SES and SRH among US general adult populations and to what extent this association is explained by blood and urinary metal mixtures applying the weighted quantile sum (WQS) mediation approach.

Materials And Methods

Study Population and Data Sources

We used 14 years of repeated cross-sectional data (2003-2016) from the National Health and Nutrition Examination Survey (NHANES), which includes the consistent format of demographic, socioeconomic, dietary, and health-related questions over the years. NHANES is conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) based on a multistage probability cluster sampling design to ensure a representative sample in noninstitutionalized US residents (NHANES 2018).

This study sample consisted of seven consecutive NHANES cycles: 2003-04, 2005-06, 2007-08, 2009-10, 2011-12, 2013-14, and 2015-16. Two earlier cycles (1999-2000 and 2001-2002) and the latest cycle 2017-2018 of NHANES were not included in this study since some of the important heavy metals were not measured in the earlier cycles and were not yet released latest cycle.

A total of 17,934 participants had blood, and urinary measurements of heavy metals in the included seven consecutive cycles of NHANES. We excluded participants aged less than 20 years old (n=5,986) because NHANES consider 20+ as the adult population. We also dropped the samples with missing data in the self-rated health (n=1,042), SES, and confounders (n=1,112) via listwise deletion. The final eligible analytic sample was 9,794 (Fig. 1). Detailed information on NHANES questionnaires, datasets, and related documentation is available at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Fig. 1: Schematic diagram of analytic sample selection in NHANES 2003-2016, US
Blood and Urinary Heavy Metal Mixtures and Creatinine Measurements

Measurements of Metal Mixtures Exposures

Blood concentration of lead, mercury, and cadmium was measured in each included cycle of NHANES by an Inductively Coupled Plasma Mass Spectrometer with Dynamic Reaction Cell Technology (ELAN® DRC II) the National Center for Environmental Health. Venous whole blood samples were collected by phlebotomists, and details are published elsewhere (NHANES 2015, 2018; CDC 2018). Urinary concentrations of ten heavy metals (arsenic, barium, cadmium, cesium, cobalt, lead, mercury, molybdenum, thallium, tungsten) were measured in each included cycle of NHANES. Inductively coupled-plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) was employed to analyze all the heavy metals concentration in urine by the Division of Laboratory Sciences, National Center for Environmental Health, Atlanta, Georgia (NHANES 2015, 2018; CDC 2018). The urinary concentrations of heavy metals were measured in micrograms per liter (ug/L) (NHANES 2018) and standardized by creatinine concentration to account for urine dilution (Mendy et al. 2012). We used the imputed values provided by NHANES for metal concentrations below limits of detection to be consistent with CDC's National Report on Human Exposure to Environmental Chemicals (CDC 2018). All blood and urinary heavy metal concentrations were log-transformed due to highly skewed distributions (Shiue 2015).

Socioeconomic Status (SES) Measurements

Socioeconomic status (SES) was measured employing commonly used indicators: educational attainment, family income to poverty ratio (FMPIR), and employment status of the participants (Hill and Needham 2006; Phelan et al. 2010; Suresh et al. 2011; Arcaya et al. 2015; Vonneilich et al. 2019). In NHANES, the levels of education were categorized as five ordinal categories (less than 9th grade, 9-11th grade, high school graduate, some college or associate in arts (AA) degree, and college graduate or higher) (NHANES 2018). FMPIR, a continuous value, is calculated by dividing family income by poverty guidelines of the Department of Health and Human Services (HHS) specific to the survey year (NHANES 2018). The employment status was a dichotomous variable: being currently employed=1 and unemployed=0 (NHANES 2018). We did not use a composite index of SES measures because these indicators tend to have different pathways of causation in relation to exposures to heavy metals (Brailsford et al. 2018). SES indicators were used as continuous exposures except for employment to develop statistical models in this study.

Self-rated Health (SRH) Measure

The overall SRH, a globally recognized subjective indicator of general health status, was considered as the outcome variable in this study (Suresh et al. 2011; Brailsford et al. 2018; Vonneilich et al. 2019). SRH was measured using a 5-point Likert scale. The highest score 5 denotes excellent SRH and the lowest score 1 denotes poor SRH. DeMaris notes that with a large degree of freedom, ordinal variables "with at
least five levels" can be treated as "approximately interval" in ordinary least squares (OLS) regression (DeMaris 2002).

**Statistical Analysis**

Descriptive statistics are presented as frequencies and percentages. Trends of SRH and exposure to heavy metals across all seven cycles and the pairwise correlations of blood and urine heavy metals are presented in a heatmap. SRH and metal concentration trends were tested using the Spearman rank correlation coefficient (Gauthier 2001). Statistical models were developed in three steps. We adjusted for age, gender, race/ethnicity, and year of the survey related to SES, heavy metals exposure, and SRH as confounders in all multivariable analyses.

In the first step, the total effect of SES on SRH was measured through a linear regression adjusted for the aforementioned confounders. This allowed us to estimate the effect due to both paths represented in fig. 2, described by the straight arrow pointing from SES to SRH, representing all potential mechanisms, and the path that goes through the metal mixture represented by the weighted quantile sum (WQS) index.

In the second step, a WQS regression model was used to examine the direct associations of SES with SRH (the arrow pointing to SRH from SES in Fig. 2), adjusting for mixtures of heavy metals effects (WQS index) and aforementioned confounders for each biological matrix. A WQS approach in conjunction with linear function considering SRH as the continuous outcome was employed, which considered all the measured heavy metals and included heavy metals were constrained to have the same direction of effects for SRH (Carrico et al. 2015; Czarnota et al. 2015a, b). The WQS regression model calculated a weighted index, a linear combination of the different metals standardized into quintiles, which denoted the whole-body burden of all ten metals. The calculated weight for each chemical represented how much a single chemical contributed to the WQS index of metals.

WQS regression involves the split of the dataset in a training and validation part on which the weight and the regression parameters occur, respectively (usually 40% of the data are used for the test and 60% for validation). In order to use all the observations to estimate both the weights and the regression coefficients, a repeated holdout validation was implemented (Tanner et al. 2019). A hundred repeated holdout validations were performed besides the 100 bootstraps to estimates the weights. The repeated holdout procedure also allowed us to characterize better distribution of the weights associated with each mixture element.

**Fig. 2.** Path diagram of the causal effect of SES on SRH mediated by metal mixture represented by the WQS index.

As a final step, the average causal mediation effect was estimated using a formal mediation analysis using the Mediation package in R (Tingley et al. 2014). The average indirect effect of SES on SRH through a linear regression model was measured where we considered the estimated WQS index in step 2 as the dependent variable (Bellavia et al. 2019; Renzetti et al. 2019) to estimate the effect represented by
the arrow pointing to WQS from SES of Fig. 2. The impact of WQS on SRH was then estimated through a linear regression model (arrow pointing to SRH from WQS in Fig. 2). The product of these two effects provides the estimate of the average indirect association between SES and SRH. Confidence intervals for all estimated regression parameters were assessed using bootstrap resampling. We applied two-sided statistical tests assuming a significance level of 5%. All analyses accounted for survey weights and were performed in R version 4.1.0 (R Core Team 2021).

Results

Study Population Characteristics

The overall characteristics of the study population are presented in Table 1. A total of 9794 US adults aged 20-80 years were included in the analysis. The highest percentage (20.1%) of respondents were between 40-49 years old, and the lowest percentage of respondents were between 70-80 years old. There was almost similar proportion of men and women. The sampling from other racial/ethnic groups increased across the seven cycles. The percentage of participants with college or university level education increased from the 2009-10 cycle to 2016 cycle. The highest prevalence of unemployment rate (37%-43%) was recorded between 2009 and 2014. Overall, about 21% respondents belong to FMPIR <=1.30 and these percentages increased consistently until 2014 (20.5% to 23.6%).

Table 1: Characteristics of the US adult (20-80 years old) populations in NHANES 2003-2016 (n= 9794; %=weighted)

Trends of Self-Rated Health in the US Adult Population

The trends of average SRH score reported by 9794 US adults across seven consecutive NHANES 2003-2016 cycles are shown in Fig. 3. The highest score 5 denotes excellent self-rated physical health, while the lowest score 1 refers to poor physical health. A general decreasing trend of SRH was found through the Spearman rank correlation coefficient (rho = -0.671; p = 0.099. SRH scores showed a downward trend from 2003 to 2014.

Fig. 3: Trends of SRH score in the US adult populations, NHANES 2003-2016 (The Spearman rank correlation coefficient and p-value are also shown)

Trends of Blood and Urinary Heavy Metals Concentration and Correlations

The trends of creatinine-adjusted ten urinary heavy metals concentration in seven consecutive NHANES cycles (2003 to 2016) are depicted in Fig.4. Blood and urinary lead (BPb, UPb), cadmium (BCd, UCd), and urinary mercury (BHg, UHg) concentrations remarkably decreased across all seven NHANES cycles (p < 0.05). A significant decreasing trend was also found for blood Hg and urinary Cesium (Cs).

Fig. 4: Trends of blood and urinary heavy metals concentration in the US adult population, NHANES 2003-2016. The Spearman rank correlation coefficients and p-values are shown for each metal.
An overall decreasing trend in urinary concentrations of Arsenic (UAs), Barium (UBa), and Molybdenum (UMo) was also observed, particularly in the last three cycles (2011-12, 2013-14, and 2015-16). However, the trends were not statistically significant. Urinary Tungsten (UW) also showed a non-significant overall decreasing trend. Conversely, Cobalt (UCo) and Thallium (UTl) had an increasing trend over the seven cycles, but only UCo was significant (p=0.012).

**Fig. 5:** Pairwise Spearman correlations among blood and urinary heavy metals in the US adult populations, NHANES 2003-2016

A correlation heatmap shows the pairwise Spearman correlations among blood and urinary heavy metals in the US adult population (Fig. 5). Overall, we have observed weak to strong positive correlations among blood and urinary metals with a range of 0 to 0.59, with the strongest correlation between UCs and UPb (r=0.59) within the urine metals, while blood metal correlations ranged from 0 to 0.35. However, we have observed weak negative correlations among few bloods and urinary metals.

### Total Effects of SES on SRH

Table 2 shows the total effects of SES on SRH, and SES characteristics were positively significantly associated with SRH after adjusting for age, race, gender, and NHANES cycles (Table 2). Participants with higher levels of education (β: 0.17; 95% CI: 0.15, 0.18), being employed (β: 0.16; 95% CI: 0.12, 0.21) and with a higher FMPIR (β: 0.09; 95% CI: 0.08, 0.11) were more likely to have better SRH compared to their counterparts, which suggests socioeconomic inequalities in SRH.

**Table 2:** Total effects of SES on SRH in the US adult populations, NHANES 2003-2016

*a*OLS model was adjusted for age, race, gender, and NHANES cycles.

### Direct and Indirect Effects of SES and WQS Index on SRH

Tables 3 and 4 show the direct and indirect effects of SES and WQS index on SRH, respectively, for blood and urine metals. The direct effects of SES on SRH were consistently significant after further adjustments for both blood and urine metal mixtures (mediator) along with other potential confounders (Table 3). The WQS indices of blood and urine metal mixtures (blood β: -0.04; 95% CI: -0.05, -0.03, urine β: -0.07; 95% CI: -0.13, -0.004) were significantly inversely associated with SRH. It indicates that the participants who have a higher index of metal mixtures concentrations in their blood or urine were more likely to have poorer SRH than participants who have a lower index of metal mixtures concentration.

**Table 3:** Direct effects of SES and WQS index on SRH in the US adult populations, NHANES 2003-2016

*a*WQS regression model was adjusted for age, race, gender, and NHANES cycles. CI: Confidence Interval

The estimated metals weight for the Repeated Holdout WQS index is shown in Fig.6. This suggests that both blood and urine Cd (Weighted 0.99 and 0.75 respectively) and urine Tl (Weighted 0.22) were the two
highest weighted heavy metals in SRH.

**Fig 6**: Distribution of blood (A) and urine (B) Repeated Holdout WQS index weights on SRH in the US adult population, NHANES 2003-2016. The dashed red lines represent the prespecified cutoff to discriminate between significant and non-significant weights equal to the inverse of the number of elements in the mixture. Models were adjusted age, race, gender, education, employment, FMPIR, and NHANES cycles.

SES was inversely associated with the WQS index of mixtures that also indicates socioeconomic inequalities in exposure to metal mixtures (Table 4). Results suggest that participants with higher FMPIR ($\beta$: -0.06, 95% CI: -0.09, -0.04) and education ($\beta$: -0.03, 95% CI: -0.04, -0.02) are exposed to lower levels of metal mixtures in their urine compared to participants who report lower levels of FMPIR and education. We observed a similar result with employment status.

**Table 4**: Indirect effects of SES on SRH in the US adult populations, NHANES 2003-2016

$^a$OLS model was adjusted for age, race, gender, and NHANES cycles. CI: Confidence Interval

**Mediation Effect of WQS Index**

To untangle the causal relationship between SES, metal mixtures, and SRH, we examined the average causal mediation effect of the WQS index on SRH and presented it in Fig.7A-F. We observed a statistically significant but weak average indirect effect for SES through blood and urine heavy metal mixtures (Table 5 shows the mediated proportion of the effects ranged from 0.6% to 2.1%).

**Fig. 7**: Mediation effect of WQS index of heavy metals mixtures on SRH

The only non-significant mediated effect was for urine metal mixtures when considering the association between employment and SRH. Alternatively, the association between SES and SRH was significantly mediated by the WQS index.

**Table 5**: Estimates of the total, direct and mediated effect of SES on SRH.

**Discussion**

This is the first study, to our best knowledge, that used one of the novel multipollutant approaches (WQS regression) to examine the association between SES and SRH among US general adult populations and the mediating effect of multiple blood and urinary metal mixtures in these associations. Our findings show that the overall trend of SRH scores in US adults was downward from 2003 to 2014. Our results show that creatinine-adjusted urinary concentrations of cobalt and thallium increased in the period between 2003 and 2016. However, blood and urinary concentration of cadmium, mercury, and lead markedly decreased in this period. The SES indicators were positively associated with SRH after adjusting for age, race, gender, and NHANES cycles. SES were inversely associated with exposure to the WQS index of blood and urinary metal mixtures, and this WQS index was also inversely associated with
SRH. In other words, the associations between SES and SRH were significantly mediated by the WQS index of blood and urinary metal mixtures, although the effect sizes were small.

Consistent with previous studies, our findings show that SRH had substantially deteriorated between 2003 and 2016, which was more pronounced between 2011 and 2016 (Salomon et al. 2009; Shiue 2015). This deterioration in SRH over the years may be explained by the growing socioeconomic and racial inequalities in health and SRH in the US (Suresh et al. 2011; Zajacova and Dowd 2011; Tellez-Plaza et al. 2012; Beck et al. 2014; Vonneilich et al. 2019), which is confirmed by our empirical assessment of significant positive association between SES and SRH.

Studies suggest that over the years, the successful public health interventions in the US have led to a substantial decrease in the environmental exposure to heavy metals (Muntner et al. 2005; Tellez-Plaza et al. 2012; Ruiz-Hernandez et al. 2017), which is consistent with our results. (Tellez-Plaza et al. 2012; Shiue 2013, 2015; Ruiz-Hernandez et al. 2017). However, there are socioeconomic inequalities in the environmental exposure to heavy metal mixtures in the US adult populations. In other words, people from the lower SES group are significantly more exposed to environmental heavy metal mixtures compared with those from the higher SES group, leading to higher burden of environmental and health inequalities, which is in agreement with previous studies (Evans and Kim 2010; Phelan et al. 2010; Brender et al. 2011; Chakraborty et al. 2011; Morello-Frosch et al. 2011; Bell and Ebisu 2012; Tyrrell et al. 2013; Brailsford et al. 2018). People throughout their life are exposed to multiple heavy metals, which are widely dispersed in the environment, such as in food, substandard housing, industrial fumes, water, and air (Billionnet et al. 2012; Alloway 2013; Braun et al. 2016; Awata et al. 2017). These multiple metals can introduce interactions between correlated metals, model misspecification, confounding by co-pollutants, and overlooking synergistic or antagonistic effects in single pollutant analytic method (Billionnet et al. 2012; Braun et al. 2016). The unequal distribution of exposure to metal mixtures is because higher SES people may have multiple channels to avoid continuous exposure and reduce metal mixtures (Evans and Kantrowitz 2002; Brender et al. 2011; Chakraborty et al. 2011; Bell and Ebisu 2012; Tyrrell et al. 2013).

To untangle the complex relationship among SES, environmental exposure to metal mixtures, and SRH, we used a novel and innovative multipollutant WQS approach to overcome these complex pattern of metal exposures and understand the mechanism of socioeconomic inequalities in SRH (Billionnet et al. 2012; Braun et al. 2016; Bellavia et al. 2019; Renzetti et al. 2019). Our mediation analysis shows that the environmental metal mixtures mediated the association between SES and SRH. Each of them mediated this relationship in its unique way. For example, SES indicators, including education level, employment status, and FMPIR, were associated with the blood and urinary concentration of mixtures. On the other hand, the blood and urinary metal mixtures were also associated with SRH. Therefore, the association between SES and SRH may be explained by the exposure to multiple metal mixtures. People from the lower SES group were exposed to higher levels of metal mixtures and thus had lower SRH. A previous study explored heavy metals exposure as a mediator in the relationship between SES and SRH (Brailsford et al. 2018). This study was, however, conducted on a much smaller sample (singly 2007-2008 NHANES cycle) and used a conventional statistical method that was unable to examine simultaneous effects of
common metals due to complex exposure patterns, high collinearities, and interactions among metals (Billionnet et al. 2012; Taylor et al. 2016; Wang et al. 2018; Rana 2019; Zhang et al. 2019). Our study has a much larger sample size (seven cycles of NHANES from 2003 to 2016) and first time empirically measured metal mixtures as mediator applying a novel mixture analysis method. The results from our study strongly support the theory that the embodiment of heavy metals plays a substantial mediating role in the association between SES and SHR (Evans and Kantrowitz 2002; Evans and Kim 2010; Brailsford et al. 2018).

The main strengths of our study are the application of mixture analysis method-WQS with Repeated Holdout Validation approach, and mediating role of blood and urinary metal mixtures using large sample size and the high quality of the NHANES data with availability of detailed information about the demographic and socioeconomic characteristics of the participants. The blood and urinary heavy metals were also measured under rigorous laboratory quality control conditions, which ensures reliability and comparability of the concentrations from different years (CDC 2018; NHANES 2018). The main limitation is that although our sample size was quite big, the data came from multiple cross-sectional surveys conducted between 2003 and 2016. Therefore, it may not be possible to make strong causal inferences about the associations between SES and SRH and causal mediation effects of metal mixtures. However, our results were highly significant but small effect sizes, which suggests that it is highly likely that such associations, modifying, and mediating effects truly exist. Another possible limitation would be the use of creatinine-adjusted urinary concentrations of heavy metals as an indicator for environmental exposure. Depending on the elimination half-time of each studied heavy metal, urinary concentration may not always be the most valid indicator for assessing environmental exposure. However, we used blood metals, a better biomarker for heavy metal exposure assessment that has similar effects. Nevertheless, the NHANES dataset is the only one that contains this information for thousands of people, and there is evidence suggesting that the urinary concentrations of heavy metals from NHANES reflect the population level environmental exposure to a great extent (Mendy et al. 2012; CDC 2018; Wang et al. 2018; Zhang et al. 2019).

**Conclusion**

Our study found that SES were positively associated with SRH in the US adult population. We also found that the SES were inversely associated with blood and urinary concentration of heavy metal mixtures in the US population. The novel finding was the mechanism between SES and SRH that the heavy metal mixtures may play a mediating role in the association between SES and SRH. We can, therefore, infer that socioeconomic inequalities in SRH in the US may be explained by the exposure to multiple heavy metal mixtures. It could be a viable mechanism of SES inequalities in SRH.

Further research and longitudinal studies are needed to corroborate this study results and to make robust causal inferences. We suggest with reference to previous studies that neighborhoods with high concentration of poverty and people of low income and education are extremely vulnerable to the higher exposure to toxic heavy metals and their deleterious effects on SRH (Evans and Kantrowitz 2002; Evans
and Kim 2010; Brender et al. 2011; Morello-Frosch et al. 2011; Tyrrell et al. 2013; Ard et al. 2016; Brailsford et al. 2018). Thus, crafting public health interventions specifically tailored to these disadvantaged communities (Evans and Kantrowitz 2002; Adler and Rehkopf 2008; Evans and Kim 2010; Brender et al. 2011; Chakraborty et al. 2011; Tyrrell et al. 2013; Brailsford et al. 2018) would be a successful way of preventing the combined damaging effects of metal mixtures on SRH that low SES and heavy metal mixtures have together.

Declarations

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Conflicts of interest/Competing interests

The authors have no known conflict/competing interests that could have influenced the results of this study.

Availability of data and material

All data files are available from the NHANES program of the National Center for Health Statistics: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Codes are available from the corresponding author on reasonable request.

Authors' contributions

JR: conceptualization, formal analysis, methodology, visualization, writing—original draft, writing—review & editing. SR: methodology, visualization, writing—review & editing. RI: writing—review & editing. MD: writing—original draft, writing—review & editing. KH: writing—original draft, writing—review & editing. YO: Supervision, writing—review & editing.
References

Adler NE, Rehkopf DH (2008) US Disparities in Health: Descriptions, Causes, and Mechanisms. Annu Rev Public Health 29:235–252. https://doi.org/10.1146/annurev.publhealth.29.020907.090852

Alloway BJ (2013) Heavy Metals in Soils: Trace Metals and Metalloids in Soils and their Bioavailability. Springer Dordrecht Heidelberg

Arcaya MC, Arcaya AL, Subramanian SV (2015) Inequalities in health: definitions, concepts, and theories. Glob Health Action 38:261–271. https://doi.org/10.3402/gha.v8.27106

Ard K, Colen C, Becerra M, Velez T (2016) Two mechanisms: The role of social capital and industrial pollution exposure in explaining racial disparities in self-rated health. Int J Environ Res Public Health 13:. https://doi.org/10.3390/ijerph13101025

Awata H, Linder S, Mitchell LE, Delclos GL (2017) Association of dietary intake and biomarker levels of arsenic, cadmium, lead, and mercury among asian populations in the United States: NHANES 2011–2012. Environ Health Perspect 125:314–323. https://doi.org/10.1289/EHP28

Beck AN, Finch BK, Lin S-F, et al (2014) Racial disparities in self-rated health: Trends, explanatory factors, and the changing role of socio-demographics. Soc Sci Med 104:163–177. https://doi.org/10.1016/j.socscimed.2013.11.021

Bell ML, Ebisu K (2012) Environmental Inequality in Exposures to Airborne Particulate Matter Components in the United States. Environ Health Perspect 120:1699–1704. https://doi.org/10.1289/ehp.1205201

Bellavia A, James-Todd T, Williams PL (2019) Approaches for incorporating environmental mixtures as mediators in mediation analysis. Environ Int 123:368–374. https://doi.org/10.1016/j.envint.2018.12.024

Billionnet C, Sherrill D, Annesi-Maesano I (2012) Estimating the Health Effects of Exposure to Multi-Pollutant Mixture. Ann Epidemiol 22:126–141. https://doi.org/10.1016/j.annepidem.2011.11.004

Brailsford JM, Hill TD, Burdette AM, Jorgenson AK (2018) Are Socioeconomic Inequalities in Physical Health Mediated by Embodied Environmental Toxins? Socius 4:1–9. https://doi.org/10.1177/2378023118771

Braun JM, Gennings C, Hauser R, Webster TF (2016) What Can Epidemiological Studies Tell Us about the Impact of Chemical Mixtures. 6–9

Brender JD, Maantay JA, Chakraborty J (2011) Residential proximity to environmental hazards and adverse health outcomes. Am J Public Health 101:. https://doi.org/10.2105/AJPH.2011.300183

Budhathoki SS, Bhandari A, Gurung R, et al (2020) Stunting Among Under 5-Year-Olds in Nepal: Trends and Risk Factors. Matern Child Health J 24:39–47. https://doi.org/10.1007/s10995-019-02817-1
Carrico C, Gennings C, Wheeler DC, Factor-Litvak P (2015) Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. J Agric Biol Environ Stat 20:100–120. https://doi.org/10.1007/s13253-014-0180-3

CDC (2018) Fourth National Report on Human Exposure to Environmental Chemicals Updated Tables, March 2021. Washington

Chakraborty J, Maantay JA, Brender JD (2011) Disproportionate proximity to environmental health hazards: Methods, models, and measurement. Am J Public Health 101:27–36. https://doi.org/10.2105/AJPH.2010.300109

Chowdhury R, Ramond A, O'Keeffe LM, et al (2018) Risk Factors for Detection, Survival, and Growth of Antibiotic-Resistant and Pathogenic Escherichia coli in Household Soils in Rural Bangladesh. Am J Respir Crit Care Med 16:e302–e315. https://doi.org/10.1186/s12940-017-0272-y

Cullati S, Rousseaux E, Gabadinho A, et al (2014) Factors of change and cumulative factors in self-rated health trajectories: A systematic review. Adv Life Course Res 19:14–27. https://doi.org/10.1016/j.alcr.2013.11.002

Czarnota J, Gennings C, Colt JS, et al (2015a) Analysis of environmental chemical mixtures and non-hodgkin lymphoma risk in the NCI-SEER NHL Study. Environ Health Perspect 123:965–970. https://doi.org/10.1289/ehp.1408630

Czarnota J, Gennings C, Wheeler DC (2015b) Assessment of weighted quantile sum regression for modeling chemical mixtures and cancer risk. Cancer Inform 14:159–171. https://doi.org/10.4137/CIN.S17295

DeMaris A (2002) Regression Models. In: M. Wiederman and, Whitley.Mahwah B (eds) Handbook for Conducting Research on Human Sexuality. Lawrence Erlbaum, New Jersey, pp 255–87

Evans GW, Kantrowitz E (2002) Socioeconomic Status and Health: The Potential Role of Environmental Risk Exposure. Annu Rev Public Health 23:303–331. https://doi.org/10.1146/annurev.publhealth.23.112001.112349

Evans GW, Kim P (2010) Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status-health gradient. Ann N Y Acad Sci 1186:174–189. https://doi.org/10.1111/j.1749-6632.2009.05336.x

Frankenberg E, Jones NR (2004) Self-Rated Health and Mortality: Does the Relationship Extend to a Low Income Setting? Author (s): Elizabeth Frankenberg and Nathan R. Jones Source: Journal of Health and Social Behavior, Vol. 45, No. 4 (Dec., 2004), pp. 441-452 Published by. J Health Soc Behav 45:441–452
Gauthier TD (2001) Detecting trends using Spearman's rank correlation coefficient. Environ Forensics 2:359–362. https://doi.org/10.1006/enfo.2001.0061

Hill TD, Needham BL (2006) Gender-specific trends in educational attainment and self-rated health, 1972-2002. Am J Public Health 96:1288–1292. https://doi.org/10.2105/AJPH.2004.061119

Mendy A, Gasana J, Vieira ER (2012) Urinary heavy metals and associated medical conditions in the US adult population. Int J Environ Health Res 22:105–118. https://doi.org/10.1080/09603123.2011.605877

Moody EC, Coca SG, Sanders AP (2018) Toxic Metals and Chronic Kidney Disease: a Systematic Review of Recent Literature. Curr Environ Heal reports 5:453–463. https://doi.org/10.1007/s40572-018-0212-1

Morello-Frosch R, Zuk M, Jerrett M, et al (2011) Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff 30:879–887. https://doi.org/10.1377/hlthaff.2011.0153

Muntner P, Menke A, DeSalvo KB, et al (2005) Continued decline in blood lead levels among adults in the United States: The national health and nutrition examination surveys. Arch Intern Med 165:2155–2161. https://doi.org/10.1001/archinte.165.18.2155

NHANES (2018) NHANES-Questionnaires, datasets, and related documentation. https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. Accessed 1 Jan 2021

NHANES (2015) NHANES 2015–2016 laboratory methods, centers for disease control and prevention. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2015. Accessed 1 Jan 2021

Nigra AE, Ruiz-Hernandez A, Redon J, et al (2016) Environmental Metals and Cardiovascular Disease in Adults: A Systematic Review Beyond Lead and Cadmium. Curr Environ Heal reports 3:416–433. https://doi.org/10.1007/s40572-016-0117-9

Phelan JC, Link BG, Tehranifar P (2010) Social Conditions as Fundamental Causes of Health Inequalities: Theory, Evidence, and Policy Implications. J Health Soc Behav 51:S28–S40. https://doi.org/10.1177/0022146510383498

Platts LG, Gerry CJ (2017) Social inequalities in self-rated health in Ukraine in 2007: The role of psychosocial, material and behavioural factors. Eur J Public Health 27:211–217. https://doi.org/10.1093/eurpub/ckw143

Power C, Matthews S, Manor O (1998) Inequalities in self-rated health: Explanations from different stages of life. Lancet 351:1009–1014. https://doi.org/10.1016/S0140-6736(97)11082-0

R Core Team (2021) R: A language and environment for statistical computing
Rana J (2019) Comparison of Different Methods to Handle Chemical Mixtures in Environmental Epidemiology Studies. EHESP School of Public Health, France

Renzetti S, Gennings C, Curtin P (2019) gWQS: An R Package for Linear and Generalized Weighted Quantile Sum (WQS) Regression. R package:1–21

Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, et al (2017) Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004. Int J Epidemiol 46:1903–1912. https://doi.org/10.1093/ije/dyx176

Salomon JA, Nordhagen S, Oza S, Murray CJL (2009) Are Americans feeling less healthy? the puzzle of trends in self-rated health. Am J Epidemiol 170:343–351. https://doi.org/10.1093/aje/kwp144

Shiue I (2015) Urinary arsenic, heavy metals, phthalates, pesticides, polycyclic aromatic hydrocarbons but not parabens, polyfluorinated compounds are associated with self-rated health: USA NHANES, 2011–2012. Environ Sci Pollut Res 22:9570–9574. https://doi.org/10.1007/s11356-015-4604-6

Shiue I (2013) Urinary environmental chemical concentrations and vitamin D are associated with vision, hearing, and balance disorders in the elderly. Environ Int 53:41–46. https://doi.org/10.1016/j.envint.2012.12.006

Suresh S, Sabanayagam C, Shankar A (2011) Socioeconomic Status, Self-Rated Health, and Mortality in a Multiethnic Sample of US Adults. J Epidemiol 21:337–345. https://doi.org/10.2188/jea.JE20100142

Tanner EM, Bornehag CG, Gennings C (2019) Repeated holdout validation for weighted quantile sum regression. MethodsX 6:2855–2860. https://doi.org/10.1016/j.mex.2019.11.008

Taylor KW, Joubert BR, Braun JM, et al (2016) Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology: Lessons from an Innovative Workshop. Environ Health Perspect 124:. https://doi.org/10.1289/ehp547

Tellez-Plaza M, Navas-Acien A, Caldwell KL, et al (2012) Reduction in cadmium exposure in the United States population, 1988-2008: The contribution of declining smoking rates. Environ Health Perspect 120:204–209. https://doi.org/10.1289/ehp.1104020

Tingley D, Yamamoto T, Hirose K, et al (2014) Mediation: R package for causal mediation analysis. J Stat Softw 59:1–38. https://doi.org/10.18637/jss.v059.i05

Tyrrell J, Melzer D, Henley W, et al (2013) Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ Int 59:328–335. https://doi.org/10.1016/j.envint.2013.06.017

Vonneilich N, Lüdecke D, von dem Knesebeck O (2019) Educational inequalities in self-rated health and social relationships – analyses based on the European Social Survey 2002-2016. Soc Sci Med 112379.
Table 1: Characteristics of the US adult (20-80 years old) populations in NHANES 2003-2016 (n= 9794; %=weighted)
### Characteristics

|                          | 2003-2004 (n=1204) | 2005-2006 (n=1224) | 2007-2008 (n=1504) | 2009-2010 (n=1615) | 2011-2012 (n=1325) | 2013-2014 (n=1514) | 2015-2016 (n=1408) | Overall (n=9794) |
|--------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|-----------------|
| **Race**                 |                     |                     |                     |                     |                     |                     |                     |
| White                    | 74.5%               | 74.0%               | 72.6%               | 70.2%               | 69.0%               | 67.9%               | 66.9%               | 70.6%           |
| Other                    | 25.5%               | 26.0%               | 27.4%               | 29.8%               | 31.0%               | 32.1%               | 33.1%               | 29.4%           |
| **Employment status**    |                     |                     |                     |                     |                     |                     |                     |                 |
| Employed                 | 31.4%               | 31.3%               | 33.9%               | 36.1%               | 41.7%               | 37.2%               | 35.5%               | 35.4%           |
| Unemployed               | 68.6%               | 68.7%               | 66.1%               | 63.9%               | 58.3%               | 62.8%               | 64.5%               | 64.6%           |
| **Family income-to-poverty ratio (FMPIR)** |                     |                     |                     |                     |                     |                     |                     |                 |
| .30                      | 19.6%               | 17.9%               | 19.3%               | 20.5%               | 23.5%               | 23.6%               | 20.0%               | 20.7%           |
| 1-3.50                   | 39.3%               | 37.2%               | 36.0%               | 38.1%               | 35.0%               | 34.5%               | 38.0%               | 36.8%           |
| 5                        | 41.1%               | 44.9%               | 44.7%               | 41.4%               | 41.5%               | 41.9%               | 41.9%               | 42.5%           |

#### Table 2: Total effects of SES on SRH in the US adult populations, NHANES 2003-2016

| SES                                | Beta-coefficients (95% CI) | p-value |
|------------------------------------|----------------------------|---------|
| Education                          | 0.17 (0.15, 0.18)          | <0.001  |
| Employed vs. unemployed            | 0.16 (0.12, 0.21)          | <0.001  |
| FMPIR                              | 0.09 (0.08, 0.11)          | <0.001  |
OLS model was adjusted for age, race, gender, and NHANES cycles.

**Table 3: Direct effects of SES and WQS index on SRH in the US adult populations, NHANES 2003-2016**

|                        | Self-rated health<sup>a</sup> (n=9794) |
|------------------------|----------------------------------------|
| **SES**                | Blood metals                           | Urine metals                           |
| WQS Index              | Beta-coefficients (95% CI)             | Beta-coefficients (95% CI)             |
|                        | -0.04 (-0.05, -0.03)                   | -0.07 (-0.13, -0.004)                  |
| Education              | 0.16 (0.14, 0.18)                      | 0.16 (0.14, 0.18)                      |
| Employed vs. unemployed| 0.16 (0.12, 0.20)                      | 0.16 (0.12, 0.20)                      |
| FMPIR                  | 0.08 (0.07, 0.10)                      | 0.08 (0.07, 0.10)                      |

<sup>a</sup>WQS regression model was adjusted for age, race, gender, and NHANES cycles. CI: Confidence Interval

**Table 4: Indirect effects of SES on SRH in the US adult populations, NHANES 2003-2016**

|                        | Heavy metal mixtures<sup>a</sup> (n=9794) |
|------------------------|------------------------------------------|
| **SES**                | Blood metals                             | Urine metals                             |
| Education              | Beta-coefficients (95% CI)               | Beta-coefficients (95% CI)               |
|                        | -0.03 (-0.04, -0.02)                     | -0.02 (-0.03, -0.01)                     |
| Employed vs. unemployed| -0.05 (-0.08, -0.03)                     | -0.03 (-0.05, 0.0003)                    |
| FMPIR                  | -0.04 (-0.05, -0.04)                     | -0.02 (-0.03, -0.02)                     |

<sup>a</sup>OLS model was adjusted for age, race, gender, and NHANES cycles. CI: Confidence Interval

**Table 5: Estimates of the total, direct and mediated effect of SES on SRH.**

|                        | Blood Metals | Urine Metals |
|------------------------|--------------|--------------|
| **Average direct effect| 0.16         | 0.158        |
|                        | (0.143, 0.178)| (0.117, 0.199)|
| **Average causal mediated effect** | 0.002 (0.001, 0.003) | 0.002 |
|                        | (0.0003, 0.003) | (0.001, 0.002) | (0.0001, 0.007) |
| **Proportion mediated**| 0.013        | 0.009        |
|                        | (0.008, 0.018) | (0.001, 0.017) | (0.011, 0.028) |
| **Total effect**       | 0.163        | 0.159        |
|                        | (0.145, 0.180) | (0.118, 0.200) | (0.070, 0.096) |
|                        |              | 0.083        |
|                        |              | (0.070, 0.096) | (0.144, 0.183) |
|                        |              | 0.163        |
|                        |              | (0.121, 0.202) | (0.072, 0.098) |
Figures

Figure 1
Schematic diagram of analytic sample selection in NHANES 2003-2016, US

Figure 2
Path diagram of the causal effect of SES on SRH mediated by metal mixture represented by the WQS index.
Figure 3

Trends of SRH score in the US adult populations, NHANES 2003-2016 (The Spearman rank correlation coefficient and p-value are also shown)
Figure 4

Trends of blood and urinary heavy metals concentration in the US adult population, NHANES 2003-2016. The Spearman rank correlation coefficients and p-values are shown for each metal.
Figure 5

Pairwise Spearman correlations among blood and urinary heavy metals in the US adult populations, NHANES 2003-2016
Figure 6

Distribution of blood (A) and urine (B) Repeated Holdout WQS index weights on SRH in the US adult population, NHANES 2003-2016. The dashed red lines represent the prespecified cutoff to discriminate between significant and non-significant weights equal to the inverse of the number of elements in the mixture. Models were adjusted age, race, gender, education, employment, FMPIR, and NHANES cycles.
Figure 7

Mediation effect of WQS index of heavy metals mixtures on SRH