Exposure and Health
https://doi.org/10.1007/s12403-021-00439-z

ORIGINAL PAPER

Mediation Effect of Metal Mixtures in the Association Between Socioeconomic Status and Self-rated Health Among US Adults: A Weighted Quantile Sum Mediation Approach

Juwel Rana[1,2,3] · **Stefano Renzetti**[4] · **Rakibul Islam**[3,5] · **Metodi Donev**[6] · **Kai Hu**[7] · **Youssef Oulhote**[8]

Received: 3 June 2021 / Revised: 3 September 2021 / Accepted: 7 October 2021

Abstract

This study aimed to examine the association between socioeconomic status (SES) and self-rated health (SRH) among US adults and the extent to which blood and urinary metal mixtures explain this association. We used 14 years of repeated cross-sectional data that consists of seven consecutive NHANES cycles from 2003 to 2016 ($n=9497$). 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 effect of SES on SRH was examined by linear regression model. The direct effect of SES on blood and urinary metal mixtures was examined by the weighted quantile sum (WQS) regression with repeated holdout validation method, and the average causal mediation effects of blood and urinary metal mixtures were examined by model-based causal mediation technique. Results showed that SES indicators [education β: 0.17; 95% Confidence Interval (CI): 0.15, 0.18; employment β: 0.16; 95% CI: 0.12, 0.21; and FMPIR β: 0.09; 95% CI: 0.08, 0.11] were significantly positively, and 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 in the US adults. The novel finding was the mechanism between SES and SRH that exposure to heavy metals may explain socioeconomic inequalities in SRH in the US general population. Longitudinal studies are needed to corroborate this study results.

Keywords Metal mixtures · Self-rated health · Causal mediation · NHANES

✉ Juwel Rana
juwelranasoc@gmail.com

Stefano Renzetti
stefano.renzetti@unibs.it

Rakibul Islam
rakib.islam@monash.edu

Metodi Donev
metodidonev21@gmail.com

Kai Hu
kaihu1991@gmail.com

Youssef Oulhote
youlhote@umass.edu

1 Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

2 Department of Public Health, School of Health and Life Sciences, North South University, Dhaka 1229, Bangladesh

3 South Asian Institute for Social Transformation (SAIST), Dhaka 1205, Bangladesh

4 Department of Molecular and Translational Medicine, Università degli Studi di Brescia, Brescia, Italy

5 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia

6 Department of Quantitative Methods in Public Health, EHESP School of Public Health, Paris, France

7 School of Geography and Sustainable Development, University of St Andrews, St Andrews, UK

8 Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts Amherst, Amherst, MA 01003, USA

Published online: 08 November 2021

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 (Phelan et al. 2010; Suresh et al. 2011). People with higher SES have access to better healthcare, nutritious food, better housing, healthier lifestyles, and less stressful events, therefore, reporting better health status (Power et al. 1998; Adler and Rehkopf 2008; Phelan et al. 2010; Platts and Gerry 2017). Furthermore, they are more likely to avoid environmental exposures and have multiple channels to prevent themselves from being continuously exposed to environmental contaminants (Evans and Kantrowitz 2002; Brender et al. 2011; Morello-Frosch et al. 2011; Tyrrell et al. 2013). This unequal distribution of exposure to environmental contaminants 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 Kim 2010; Tyrrell et al. 2013; Cullati et al. 2014).

Epidemiological studies have shown that people who are highly exposed to a range of environmental pollutants 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 Kim 2010; Mendy et al. 2012; Chowdhury et al. 2018). Two previous studies assessed the effects of exposure to heavy metals measured in urine on SRH and found that people with higher concentrations of heavy metals were more likely to rate their health as poor, fair, and good compared to people with lower concentration (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. (Evans and Kim 2010; Chakraborty et al. 2011). However, empirical studies on the mechanism of socioeconomic inequalities in SRH with reference to metal mixtures are very limited (Chakraborty et al. 2011; Shiue 2015). Likewise, 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).

The observed association between SES and health effects of metal mixtures is overlooked in previous studies, which focused on single metal exposure analysis (Mendy et al. 2012; Tyrrell et al. 2013; Awata et al. 2017). To our best knowledge, no study has examined the effects of both blood and urinary metal mixtures on SRH and its mediating role in the associations between SES and SRH using a novel and innovative mixture model. 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 populations (NHANES 2018).

This study sample consisted of seven consecutive NHANES cycles: 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016. Two earlier cycles (1999–2000 and 2001–2002) and the latest cycle 2017–2018 of NHANES were not included in this study as some of the important heavy metals were not measured in the earlier cycles and were not yet released in the 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 ($n = 5986$) because NHANES considers aged 20 years and older as adults. We dropped the samples with missing data in SRH ($n = 1042$), SES, and confounders ($n = 1112$) via listwise deletion. Thus, the final eligible analytic sample was 9794 (Fig. 1). Detailed information on NHANES questionnaires, datasets, and related documentation is available on the NHANES website (NHANES 2018).

Blood and Urinary Heavy Metal Mixtures and Creatinine Measurements

Measurements of Metal Mixtures Exposures

Venous whole blood samples were collected by phlebotomists and blood concentration of lead, mercury, and cadmium was measured in each included cycle of NHANES by an Inductively Coupled Plasma Mass Spectrometer

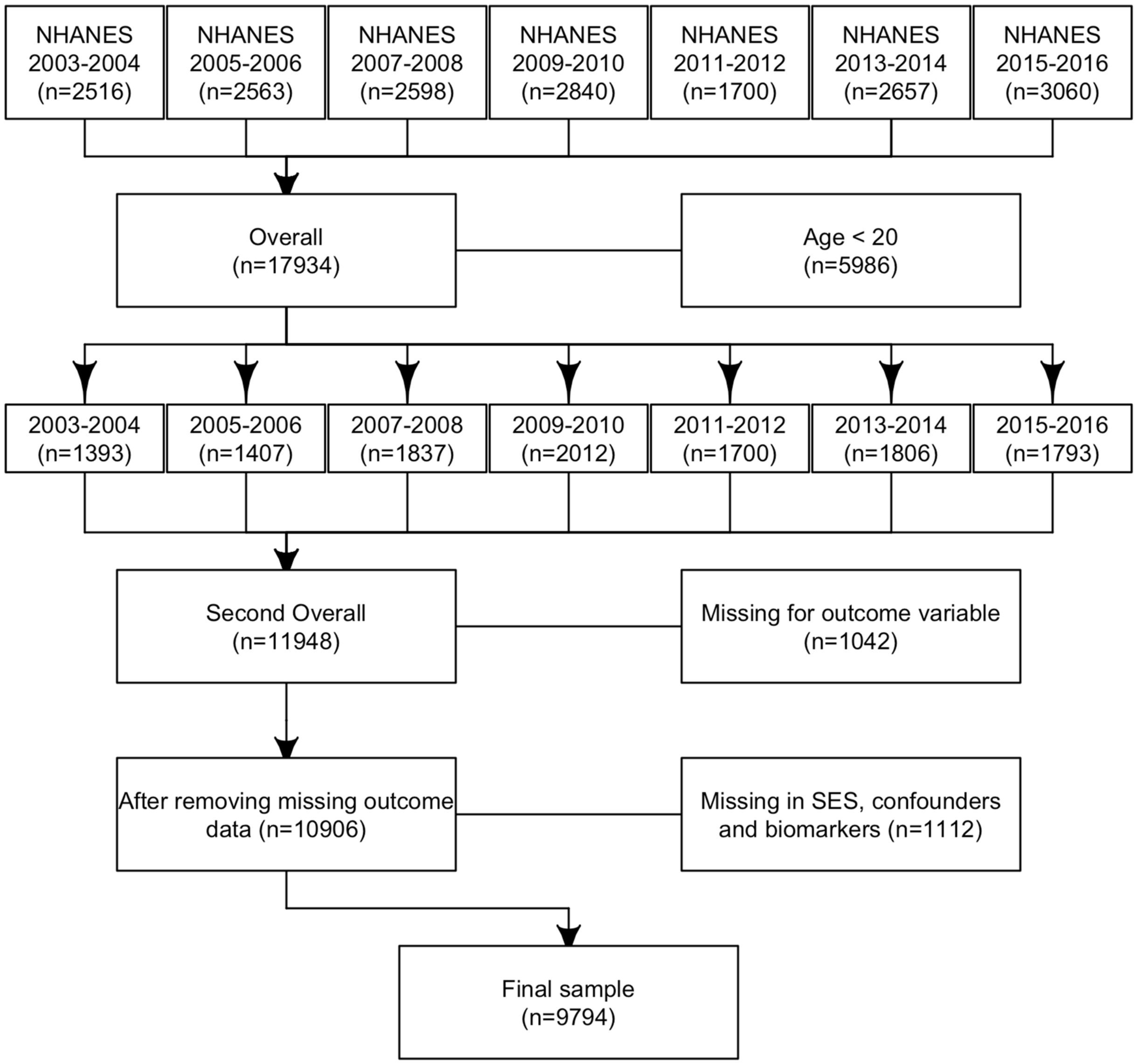

Fig. 1 Schematic diagram of analytic sample selection in NHANES 2003–2016, US

with Dynamic Reaction Cell Technology (ELAN® DRC II), details are published elsewhere (NHANES 2015, 2018; CDC 2018). Urinary concentrations of ten heavy metals (UAs: arsenic, UBa: barium, UCd: cadmium, UCs:cesium, UCo: cobalt, UPb: lead, UHg: mercury, UMo: molybdenum, UTl: thallium, UW: 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, the 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). Blood concentrations of three heavy metals (BCd: cadmium, BHg: mercury, BPb: lead) were available for each included cycle of NHANES. We used the imputed values provided by NHANES for metal concentrations below the limit 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.

Socioeconomic Status (SES) Measurements

SES was measured employing commonly used indicators: educational attainment, family income to poverty ratio (FMPIR), and employment status of the participants

(Phelan et al. 2010; Suresh et al. 2011; Arcaya et al. 2015). 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 (0.00 to 5.00), was calculated by dividing family income by poverty guidelines of the Department of Health and Human Services 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). 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 argued 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 line graphs and heatmap, respectively. SRH and metal concentration trends were tested using the Spearman rank correlation coefficient (Gauthier 2001). Based on existing literature, 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 (Evans and Kantrowitz 2002; Hill and Needham 2006; Mendy et al. 2012; Tyrrell et al. 2013; Brailsford et al. 2018).

Statistical models were developed in three steps. In the first step, the total effect of SES on SRH was measured using a linear regression model 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 mixtures represented by the WQS index.

In the second step, a WQS regression model was used to examine the direct associations between SES and SRH (the arrow pointing to SRH from SES in Fig. 2), including metal mixtures (WQS index) and adjusted for the 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 measured in urine and three metals measured in blood. The calculated weight for each chemical represented how much a single chemical contributed to the WQS index of metals.

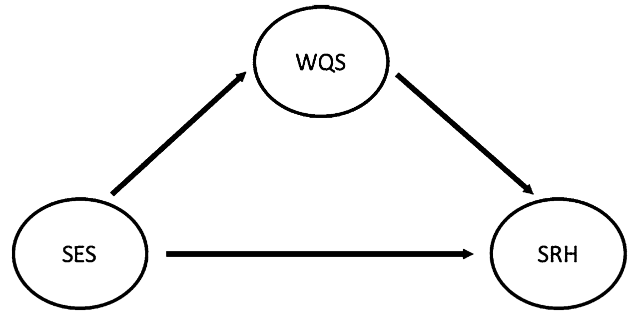

Fig. 2 Path diagram of the causal effect of SES on SRH mediated by metal mixtures represented by the WQS index (mediating metal mixture are summarized to a single mediator using WQS index)

The WQS regression involves splitting 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. WQS regression was fitted through the gWQS R package (Renzetti et al. 2019).

As a final step, the average causal mediation effect was estimated under sequential ignorability assumption using model-based inference of *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 (mediator) in step 2 as the dependent variable (Bellavia et al. 2019) to estimate the effect represented by the arrow pointing to the WQS index 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 using general estimation algorithm. Confidence intervals (CIs) for all estimated regression parameters were assessed using bootstrap resampling. The exposure-mediator interactions were also tested for estimating the causal mediation effect of metal mixtures, which were null. 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 aged between 40 and 49 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 2010 cycle to the 2016 cycle. The highest prevalence of unemployment rates (37–43%) were 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%).

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

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

National Health and Nutrition Examination Surveys (NHANES) Cycles								
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 ($n = 9794$)
Age group								
20–29	18.1%	18.6%	18.8%	19.1%	19.3%	19.0%	18.3%	18.8%
30–39	20.6%	19.7%	18.5%	17.7%	16.5%	17.1%	16.7%	18.1%
40–49	22.9%	23.2%	20.4%	19.8%	18.7%	17.8%	18.4%	20.1%
50–59	18.2%	18.8%	18.3%	18.6%	20.1%	18.8%	18.5%	18.8%
60–69	10.7%	12.1%	13.1%	12.9%	13.1%	14.9%	15.2%	13.2%
70–80	9.4%	7.6%	10.9%	12.0%	12.3%	12.5%	13.0%	11.1%
Gender								
Men	48.9%	49.0%	47.9%	49.9%	49.1%	49.6%	48.4%	49.0%
Women	51.1%	51.0%	52.1%	50.1%	50.9%	50.4%	51.6%	51.0%
Ethnicity								
Non-Hispanic White	74.5%	74.0%	72.6%	70.2%	69.0%	67.9%	66.9%	70.6%
Black	10.7%	10.6%	10.3%	10.8%	10.5%	10.6%	10.2%	10.5%
Hispanic	3.2%	3.5%	4.7%	4.3%	7.0%	4.6%	6.1%	4.8%
Other race	11.6%	11.8%	12.3%	14.7%	13.4%	16.9%	16.8%	14.0%
Education level								
Less than 9th grade	6.1%	6.1%	6.4%	5.6%	5.7%	4.3%	5.5%	5.6%
9–11th Grade	10.8%	11.3%	13.4%	12.2%	8.9%	9.5%	8.0%	10.5%
High School Grad/GED or equivalent	29.0%	23.5%	24.2%	24.5%	20.4%	22.0%	20.5%	23.3%
Some College or AA degree	32.7%	32.7%	29.2%	31.9%	31.2%	32.8%	33.3%	32.0%
College graduate or above	21.4%	26.4%	26.8%	25.9%	33.9%	31.4%	32.7%	28.5%
Employment status (at last week of the survey)								
Unemployed	31.4%	31.3%	33.9%	36.1%	41.7%	37.2%	35.5%	35.4%
Employed	68.6%	68.7%	66.1%	63.9%	58.3%	62.8%	64.5%	64.6%
Family income-to-poverty ratio (FMPIR)								
≤ 1.30	19.6%	17.9%	19.3%	20.5%	23.5%	23.6%	20.0%	20.7%
1.31–3.50	39.3%	37.2%	36.0%	38.1%	35.0%	34.5%	38.0%	36.8%
> 3.5	41.1%	44.9%	44.7%	41.4%	41.5%	41.9%	41.9%	42.5%

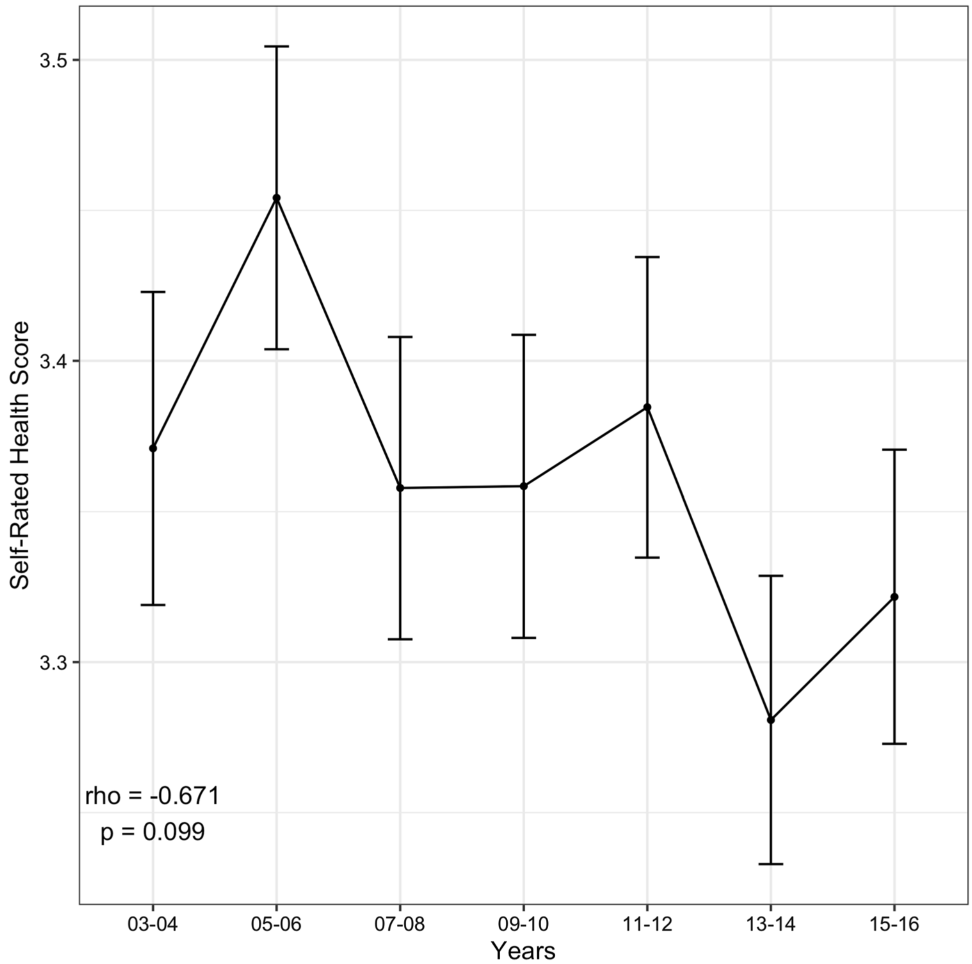

Fig. 3 Trends of SRH score in the US adult populations, NHANES 2003–2016 (The Spearman rank correlation coefficient and *p*-value are also shown)

cycles are shown in Fig. 3. 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.

Trends of Blood and Urinary Heavy Metal Concentrations and Correlations

The trends of creatinine-adjusted ten urinary heavy metal concentrations in seven consecutive NHANES cycles (2003 to 2016) are depicted in Fig. 4. Blood and urinary lead, cadmium, and urinary mercury concentrations remarkably decreased across all seven NHANES cycles ($p < 0.05$). In addition, a significant decreasing trend was found for blood mercury and urinary Cesium.

An overall decreasing trend in urinary concentrations of arsenic, barium, and molybdenum 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 also showed a non-significant overall decreasing trend. Conversely, cobalt and thallium had an increasing trend over the seven cycles, but only cobalt was significant ($p = 0.012$).

A correlation heatmap shows the pairwise Spearman correlations among blood and urinary heavy metals in the US adults (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 urinary cesium and lead (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 Effect of SES on SRH

Table 2 shows the total effect of SES on SRH, and SES indicators were significantly positively 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.

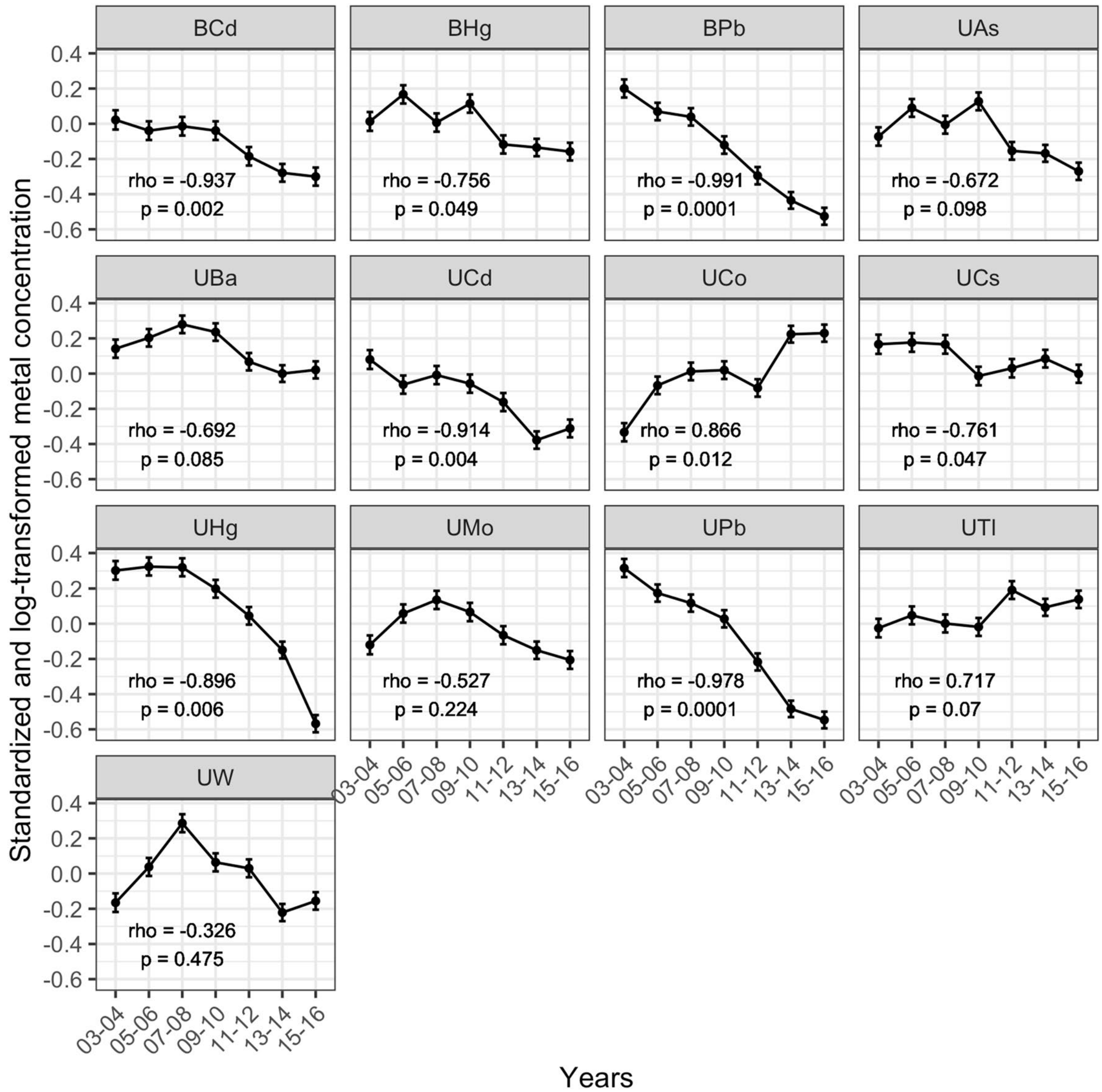

Fig. 4 Trends of blood and urinary heavy metal concentrations in the US adult population, NHANES 2003–2016. The Spearman rank correlation coefficients and *p*-values are shown for each metal

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 effect of SES on SRH was consistently significant, but slightly attenuated after further adjustments for both blood and urinary metal mixtures (mediator) and 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 with a higher index of metal mixtures concentrations in their blood or urine were more likely to have poorer SRH compared to participants with a lower index of metal mixture concentrations.

The estimated metals weight for the repeated holdout WQS index is shown in Fig. 6. This suggests that blood and urinary cadmium (Weighted 0.99 and 0.75 respectively) and urinary thallium (Weighted 0.22) were the two highest weighted heavy metals in SRH.

SES was inversely significantly associated with the WQS index of mixtures, indicating socioeconomic inequalities in metal mixtures exposure (Table 4). Results suggest that participants with higher FMPIR (β: −0.06, 95% CI: −0.09, −0.04) and education (β: −0.03, 95% CI: −0.04, −0.02) are exposed to lower levels of metal mixtures in their urine compared to participants who report

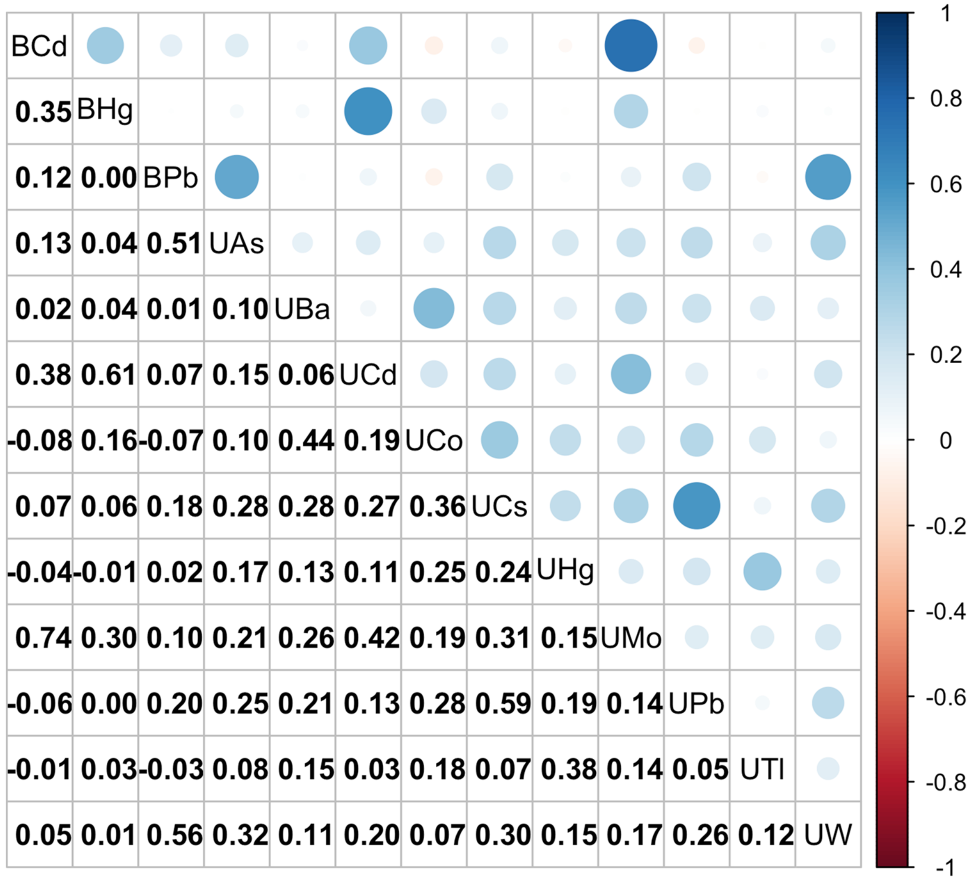

Fig. 5 Pairwise Spearman correlations among blood and urinary heavy metals in the US adult populations, NHANES 2003–2016

Table 2 Total effect of SES on SRH in the US adult populations, NHANES 2003–2016

Self-rated health[a] ($n=9794$)		
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

[a]OLS model was adjusted for age, race, gender, and NHANES cycles

Table 3 Direct effect of SES and WQS index on SRH in the US adult populations, NHANES 2003–2016

Self-rated health[a] ($n=9794$)		
SES	Blood metals Beta-coefficients (95% CI)	Urine metals Beta-coefficients (95% CI)
WQS Index	−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)

CI Confidence Interval

[a]WQS regression model was adjusted for age, race, gender, and NHANES cycles

lower levels of FMPIR and education. We observed a similar result with employment status.

Mediation Effect of WQS Index

To disentangle 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 urinary heavy metal mixtures (Table 5 shows the mediated proportion of the effects ranged from 0.6 to 2.1%).

The only non-significant mediated effect was for urinary metal mixtures when considering the association between employment and SRH. Alternatively, the association

Table 4 Indirect effect of SES on SRH in the US adult populations, NHANES 2003–2016

Heavy metal mixtures[a] ($n=9794$)		
SES	Blood metals Beta-coefficients (95% CI)	Urine metals Beta-coefficients (95% CI)
Education	−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)

CI Confidence Interval

[a]OLS model was adjusted for age, race, gender, and NHANES cycles

between SES and SRH was significantly mediated by the WQS index.

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 adults and the mediating effect of multiple blood and urinary metal mixtures in this association. Our findings show that the overall trend of SRH scores in US adults was downward from 2003 to 2014. In addition, our results show that creatinine-adjusted urinary concentrations of cobalt and thallium increased in the period between 2003

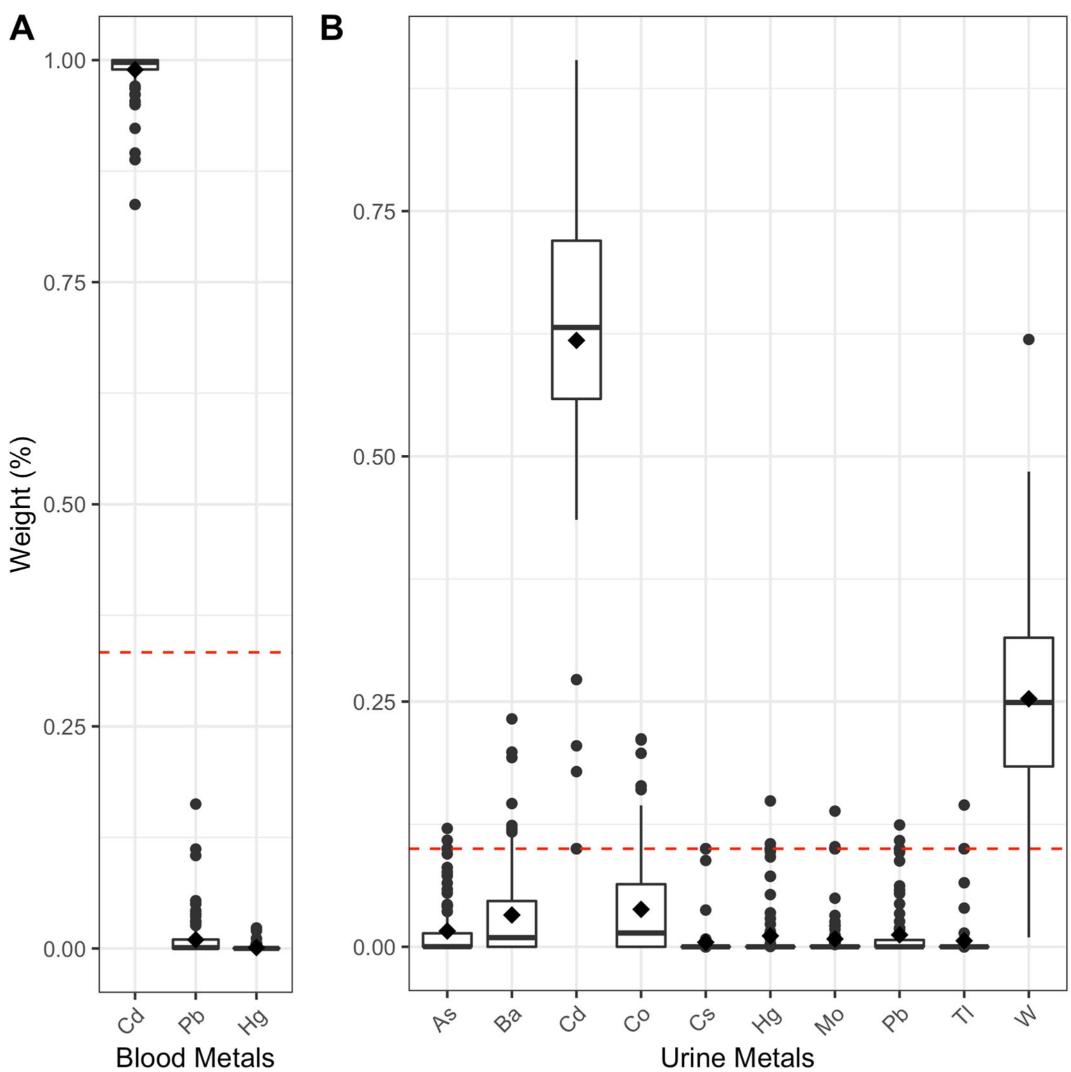

Fig. 6 Distribution of blood (**A**) and urine (**B**) Repeated holdout WQS index weights on SRH in the US adult population, NHANES 2003–2016. The dashed red lines represent the prespecified cutoff to discriminate between significant and non-significant weights equal to the inverse of the number of elements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

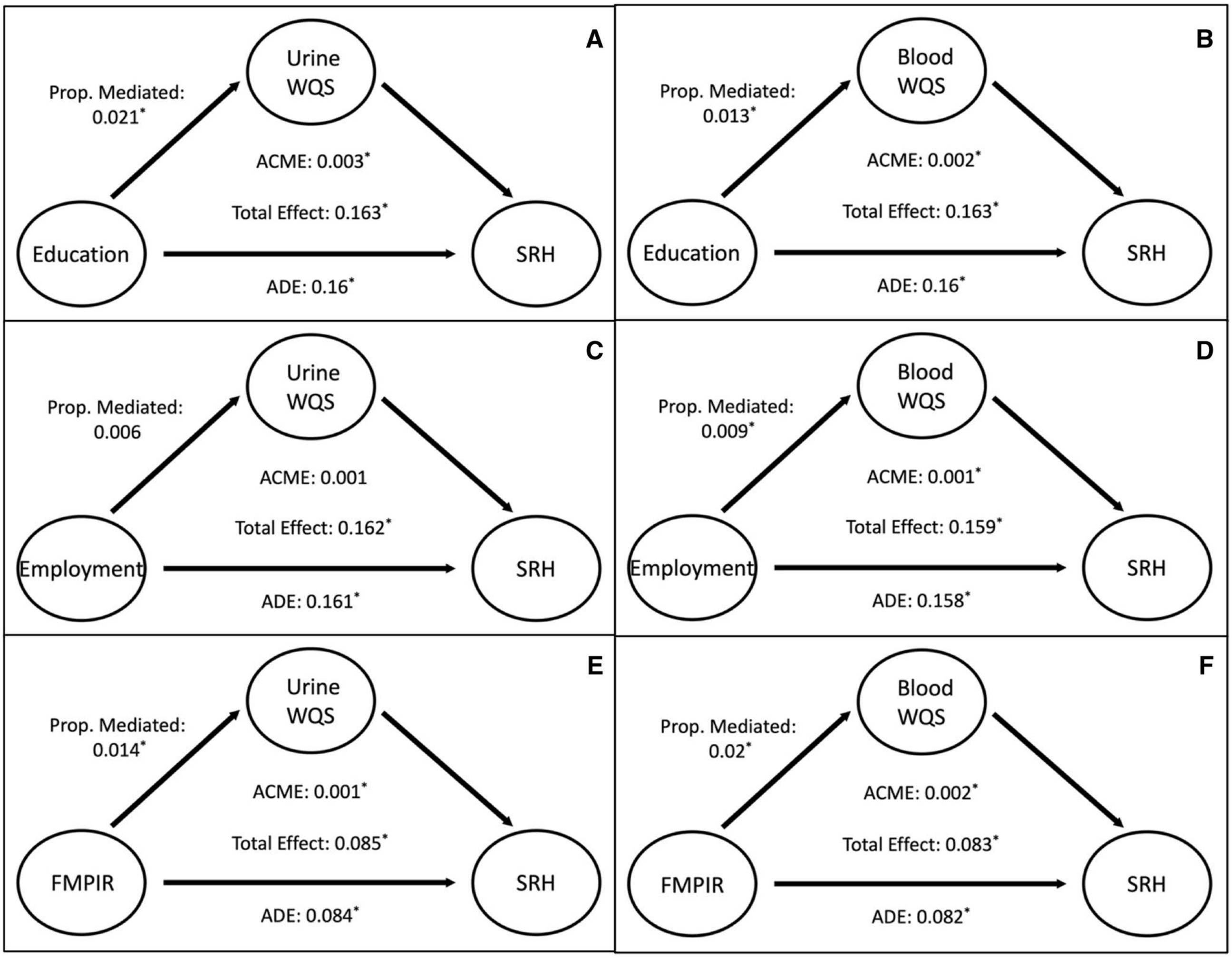

Fig. 7 Mediation effect of WQS index of heavy metal mixtures on SES and SRH

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

	Blood Metals			Urine Metals		
	Education	Employment	FMPIR	Education	Employment	FMPIR
Average direct effect	0.16 (0.143, 0.178)	0.158 (0.117, 0.199)	0.082 (0.068, 0.095)	0.160 (0.140, 0.180)	0.161 (0.120, 0.201)	0.084 (0.071, 0.096)
Average causal mediated effect	0.002 (0.001, 0.003)	0.001 (0.0003, 0.003)	0.002 (0.001, 0.002)	0.003 (0.0001, 0.007)	0.001 (– 0.001, 0.003)	0.001 (0.0001, 0.002)
Proportion mediated	0.013 (0.008, 0.018)	0.009 (0.001, 0.017)	0.02 (0.011, 0.028)	0.021 (0.0001, 0.042)	0.006 (– 0.006, 0.018)	0.014 (0.0001, 0.028)
Total effect	0.163 (0.145, 0.180)	0.159 (0.118, 0.200)	0.083 (0.070, 0.096)	0.163 (0.144, 0.183)	0.162 (0.121, 0.202)	0.085 (0.072, 0.098)

and 2016. However, blood and urinary concentration of cadmium, mercury, and lead markedly decreased in this period. SES indicators were positively associated with SRH after adjusting for age, race, gender, and NHANES cycles. SES indicators 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 association between SES and SRH was 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, 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 adults. 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). Furthermore, 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 people from higher SES 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 disentangle 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 patterns 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. The effect of each SES indicator was mediated 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 (single 2007–2008 NHANES cycle) and used a conventional statistical and mediation method, which were unable to examine simultaneous effects of common metals due to complex exposure patterns, high collinearities, and interactions among metals and their combined causal mediation effect (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 and causal mediation 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 SRH (Evans and Kantrowitz 2002; Evans and Kim 2010; Brailsford et al. 2018).

The major strengths of our study are the application of mixture analysis method-WQS with repeated holdout validation approach, and causal mediation technique to examine mediating role of blood and urinary metal mixtures in SES and SRH 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 mediation effect of metal mixtures in the association between SES and SRH. However, our results were highly significant but small effect sizes, which suggests that it is highly likely that such associations and mediating effects truly exist. Another possible limitation would be using creatinine-adjusted urinary concentrations of heavy metals as an environmental exposure. Urinary concentration may not always be the most valid indicator for assessing environmental exposure, depending on the elimination half-time of each studied heavy metal. However, we used blood metals, a better biomarker for heavy metal exposure assessment that has similar effects. Nevertheless, the NHANES dataset only contains heavy metal exposure 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 was positively associated with SRH in the US general adults. We also found that SES was inversely associated with blood and urinary concentration of heavy metal mixtures. 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 infer that socioeconomic inequalities in SRH in the US may be explained by the exposure to multiple heavy metal mixtures. Therefore, 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. Nevertheless, we suggest with reference to previous studies that neighborhoods with high rate 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. Thus, crafting public health interventions specifically tailored to these disadvantaged communities would be a successful way of preventing the combined detrimental effects of metal mixtures on SRH due to double burden of disparities in SES and exposure to heavy metal mixtures.

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.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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. In addition, 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.

Declarations

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

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