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Research Article

Mixture analysis of associations between environmental and workplace toxins and liver damage and telomere length, stratified by race/ethnicity

Ning Ma[1], *Rowena Yip*[2], *Mark Woodward*[3,4], *Sara Lewis*[2], *Michael Crane*[5], *Artit Jirapatnakul*[2], *Costica Aloman*[6], *Meena B. Bansal*[1], *Douglas Dieterich*[1], *Louis Gros*[2], *Damaskini Valvi*[5], *Elena Colicino*[5], *David Yankelevitz*[2], *Claudia Henschke*[2], *Andrea D. Branch*[1,*]

[1] *Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA*
[2] *Department of Diagnostic, Molecular and Interventional Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA*
[3] *The George Institute for Global Health, School of Public Health, Imperial College London, London, W12 7RZ, UK*
[4] *The George Institute for Global Health, University of New South Wales, Sydney, 2000, Australia*
[5] *Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA*
[6] *Department of Medicine, Division of Gastroenterology and Hepatobiliary Diseases, Westchester Medical Center, Valhalla, 10595, USA*

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ABSTRACT

This study aimed to identify the worst "bad actors" in mixtures of pollutants contributing to liver damage and shorter telomeres in the U.S. population, using weighted quantile sum (WQS) modeling with stratification by race/ethnicity. We conducted a comprehensive cross-sectional analysis of mixtures of pollutants in National Health and Nutrition Examination Survey datasets: (1) 33,979 adults with blood levels of cadmium (Cd), lead (Pb), and mercury, including subsets with measurements of per-/polyfluoroalkyl substances (PFAS), and polychlorinated biphenyls (PCBs)/polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs); and (2) 7360 adults with measurements of telomeres, Cd, and Pb. Multivariable-adjusted WQS regression examined associations between WQS mixture indices and liver injury (alanine aminotransferase (ALT)-elevation), advanced liver-fibrosis (LF), and telomere length. WQS_{metal} indices were associated with advanced-LF in all racial/ethnic groups. The top contributor was Cd in the total population and in non-Hispanic Whites (NHW), while Pb was the top contributor in non-Hispanic Blacks (NHB). The $WQS_{metal\text{-}PCB\text{-}PCDD/F}$ index was associated with ALT-elevation, with PCB126, Cd and Pb as

* Corresponding author.
E-mail: andrea.branch@mssm.edu (A.D. Branch).

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main contributors; the odds ratio (OR) per decile was 1.50 (95 % CI, 1.26–1.78), while the OR per decile of the $WQS_{metal\text{-}PFAS}$ index was 1.03 (95 % CI, 0.98–1.05), not significant. WQS_{metal} indices were associated with shorter telomeres. Cd was main contributor associated with advanced-LF in NHW, while Pb was the major bad actor in NHB, suggesting that NHB may be especially susceptible to Pb toxicity. Metals were associated with shorter telomeres. Metal and PCB/PCDD/F mixtures were associated with ALT-elevation. Heavy metals and organic chemicals may contribute to liver-related morbidity and healthcare disparities.

Introduction

Liver disease claims over a million lives each year (Asrani et al., 2019). Many of these deaths could be prevented by reducing chronic liver injury. Environmental and workplace toxins, including heavy metals (cadmium (Cd); lead (Pb); and mercury (Hg)), polychlorinated biphenyls (PCBs) and other "forever chemicals", are associated with liver injury (Cave et al., 2010; Tinkov et al., 2023), but additional data are needed to identify the most significant hepatotoxins and define the mechanisms of pathogenesis. It is likely that environmental exposures contribute to liver-related healthcare disparities. Heavy metals (Cd and Pb) are unevenly distributed geographically and are often higher in lower and middle-income countries (Levin et al., 2021; Sripada and Lager, 2022) and in communities of color (Cassidy-Bushrow et al., 2017). PCB concentrations are significantly higher in urban and industrial areas compared to rural areas (Othman et al., 2022). In the United States, African Americans have the higher blood levels of PCBs then Caucasians (Wesselink et al., 2019). However, additional data about specific exposures and vulnerabilities are needed for public health planning.

Most end-stage liver disease and liver-related mortality result from liver scarring (liver fibrosis (LF)), which can progress to cirrhosis, liver failure, and liver cancer (Dulai et al., 2017; Ng et al., 2023). Liver biopsy is the gold standard for diagnosing LF (Berger et al., 2019); but in population-level studies, LF and the risk of serious liver-related events are often estimated by using composite indices of non-invasive markers (Loomba and Adams, 2020), with or without a requirement for alanine aminotransferase (ALT) elevation. Composite fibrosis indices plus ALT elevation have area under the receiver operating characteristic curves (AUROCs) over 0.82 for identifying high risk individuals in community settings (Hagström et al., 2020). In this study, to maximize clinical relevance, we used a combination of composite fibrosis indices and ALT elevation to define our main endpoint, advanced-LF. We also examined associations between pollutants and ALT elevation, a widely-used clinical indicator of liver injury.

Toxic exposures have multiple injurious effects on cells. Environmental pollutants, including 1,4-dioxane and benzidine (Niehoff et al., 2019) and heavy metals, Pb (Pawlas et al., 2015) and Cd (Xia et al., 2022), are associated with telomere shortening, which can reflect oxidative stress and chronic inflammation (Barnard et al., 2019). Shorter telomeres on peripheral blood mononuclear cells are associated with LF in patients with viral hepatitis (Hoare et al., 2010) and with LF (Kim et al., 2018) and increased mortality in people with steatotic (fatty) liver disease (Korkiakoski et al., 2022). Germline mutations in the telomerase pathway increase the risk of liver cirrhosis (Calado et al., 2011; Hartmann et al., 2011).

We (Ma et al., 2023) and others (Han et al., 2022), demonstrated that high (4th quartile) blood levels of Cd, a class I carcinogen (Alexander et al., 2009), are associated with fibrosis and other indicators of liver injury, consistent with data showing that Cd levels in urine are associated with liver-related outcomes (Hong et al., 2021; Hyder et al., 2013). We also found that high blood levels of Pb are associated with advanced-LF (≥ F3) uniquely in non-Hispanic Black (NHB), and not in other racial/ethnic groups (Ma et al., 2023) and demonstrated that over 95 % of U.S. adults with LF had PCB blood levels in the 4th quartile (Ma et al., 2023). These studies examined toxins individually, but real-world exposures typically involve multiple chemicals. Newly developed statistical techniques, such as weighted quantile sum (WQS) regression modeling, allow the components of mixtures to be examined collectively (Renzetti et al., 2019) and can identify the main "bad actors". These methods reduce dimensionality and adjust for additive, synergistic and/or antagonistic effects among toxins (Renzetti et al., 2019).

The primary objective of this study was to use WQS modeling to analyze real-world exposures to pollutants and to identify the main contributors to advanced-LF and to liver injury (defined by ALT elevation) in the total population and in members of individual racial/ethnic groups. The secondary objectives were to determine the consistency of results of WQS and multivariable logistic regression (MVL) models and to analyze the relationships between toxic exposures and telomere length and between telomere length and advanced-LF. Toxins were selected based on data completeness and reported associations with liver disease.

1. Methods

1.1. *Study population and data sources*

The mixture analyses were conducted in 33,979 adults (age ≥ 20 years) with blood levels of Cd, Pb and Hg in National Health and Nutrition Examination Survey (NHANES) 2003–2018 as

well as in three subsets with additional data: (1) 10,257 adults with data on four per- and polyfluoroalkyl substances (PFAS); (2) 12,847 adults with data on urine levels of eight metals; and (3) 1043 adults with data on 34 PCBs and six polychlorinated dibenzo-*p*-dioxins (PCDD) and dibenzofuranes (PCDF). Analyses of peripheral blood mononuclear cell telomere length and blood levels of Pb and Cd were conducted on 7360 adults with data in NHANES 1999–2002 (Fig. 1). Analysis of de-identified NHANES data is exempt from IRB review (Johnson et al., 2013).

1.2. *Definition of liver injury and fibrosis*

Liver injury was defined as ALT elevation (≥ 40 IU/L, men; ≥ 31 IU/L, women) (Ma et al., 2023). Advanced-LF was defined as ALT elevation and Fibrosis-4 (FIB-4) ≥ 2.67 and/or Forns Index ≥ 6.9 and/or Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) ≥ 1.5 (Hagström et al., 2020).

1.3. *Covariates*

The age range was 20–85 years. Sex and race/ethnicity (non-Hispanic White (NHW), NHB, Mexican American (MA), and other race (O)) were self-reported. Smoking status, alcohol use, body mass index (BMI), poverty and diabetes were defined as before (Ma et al., 2023). Smoking categories were past/current and never. Alcohol use categories were lifetime abstainers, former drinkers, non-excessive current drinkers, and excessive current drinkers. BMI categories were normal weight (<25 kg/m^2), overweight (25≤ BMI <30 kg/m^2), and obese (≥30 kg/m^2). Diabetes was self-reported, and/or hemoglobin A1c ≥ 6.5 %, and/or fasting plasma glucose ≥ 126 mg/dL. Poverty was a family poverty-income-ratio < 1 (Ma et al., 2023). Viral hepatitis was past/current infection with hepatitis B virus (HBV), positive core antibody or surface antigen; or infection with hepatitis C virus (HCV), positive RNA or antibody (Ma et al., 2023). Blood levels of Pb, Cd, Hg, PFAS, and lipid-adjusted plasma levels of PCBs/PCCD/Fs and urine levels of eight heavy metals were analyzed as continuous (log-transformed) and binary variables (quartiles (Q)1–3 versus Q4). Telomere length was determined by quantitative polymerase chain reaction (PCR) as described elsewhere (Rattan et al., 2022). Telomere length was categorized as quartiles.

1.4. *Statistical methods*

Univariable and multivariable logistic (MVL) regression and WQS regression models were used to examine associations between exposures and outcomes. MVL models were used to assess the independent association of each compound with advanced-LF or ALT elevation, adjusting for covariates. The survey estimation commands for logistic regressions in SAS OnDemand for Academics (SAS Institute Inc., Cary, NC, USA) added sample weights, allowing the results to be extrapolated to the housed and non-institutionalized U.S. population. Age standardization estimates were obtained through the direct method and were standardized to the 2000 US census population. Differences between groups were assessed using *t* statistics.

The "gWQS" package in R (version 4.1.0) was used to evaluate the collective impact of toxic mixtures and to identify the primary drivers (Carrico et al., 2015). The dataset was randomly divided into training and validation sets (40 % vs. 60 %). In the training set, toxic component weights (w_i) were derived through 100X bootstrapping; weights ranged from 0 to 1 and summed to 1. The WQS index was then calculated by averaging the weights across the bootstrap sets and multiplying them by the toxic component's decile of concentration (q_i) : WQS index = $\sum_{i=1}^{c} \overline{w_i} q_i$. Associations between the indices and liver endpoints were then evaluated in the validation set using WQS regression models. Sensitivity analysis was conducted by using Least Absolute Shrinkage and Selection Operator (Lasso) regression, a machine learning technique that encourages variables selection in model by adding a penalty term (Tibshirani, 1996). For dioxin-like PCBs and PCDD/Fs, a sensitivity analysis was conducted using Toxic Equivalent Quantity (TEQ) estimates. TEQs were calculated using the 2005 World Health Organization's toxic equivalency factors (TEFs) for dioxin-like compounds (Van den Berg et al., 2006). The TEQ for each specimen was determined by summing the products of the concentration of each congener and its corresponding TEF. Missing values of covariates (<10 %) were addressed using multiple imputation by chained equations (Yuan, 2010). Statistical significance was a two-sided *P* value <0.05.

2. Results

2.1. *Study group*

NHANES provides cross-sectional data about the residential population of the United States. In this study, we analyzed data on NHANES participants with the following data: (1) blood levels of Pb, Cd and Hg (n = 33,979); (2) blood levels of Pb, Cd, Hg and four PFAS (n = 10,257); (3) urine levels of eight metals (Pb, Cd, barium, cesium, cobalt, antimony, thallium, tungsten) and blood levels of Pb, Cd, and Hg (n = 12,847); (4) blood levels of Pb, Cd, Hg, 34 PCBs and six PCDD/Fs (n = 1043); and (5) blood levels of Pb and Cd and telomere length (n = 7360) (Fig. 1). The characteristics of the NHANES participants with data about the various toxins and telomere length are presented in Appendix A Table S1a-S1e.

2.2. *Blood levels of heavy metals and MVL analysis of risk factors for advanced-LF and ALT elevation*

Among NHB, high (Q4 vs Q1–3) blood levels of Pb were associated with advanced-LF in an MVL model that adjusted for the survey cycle, age, sex, BMI, smoking status, alcohol use, diabetes, and poverty. The odds ratio (OR) for high (Q4 vs Q1–3) Pb was 2.26 (95 %CI, 1.37–3.74) (Table 1). NHB persons were both more likely to have high blood levels of Pb (Fig. 2) and they had a higher risk of advanced-LF when exposed to high Pb than NHW or any other racial/ethnic group (Table 1). In an analysis that excluded participants with viral hepatitis exposure, high Pb remained associated with advanced-LF in NHB (OR = 2.39; 95 % CI, 1.18–4.86) (Appendix A Table S2). When analyzed as a continuous variable, Pb was associated with advanced-LF in NHB in a dose-dependent manner (Appendix A Table S3), but Pb was not associated with advanced-LF in any other racial/ethnic group, whether when

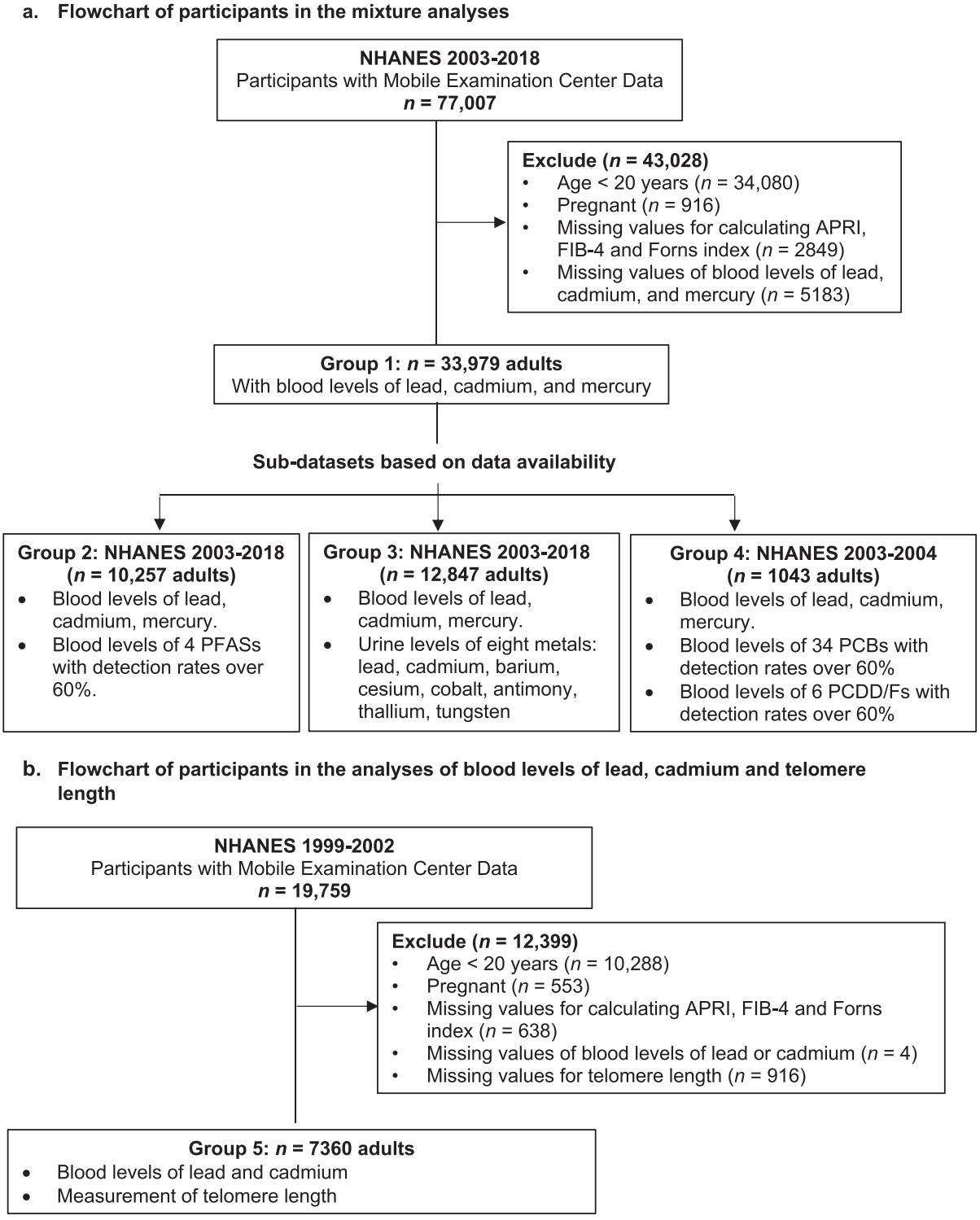

Fig. 1 – Flowcharts showing the five groups of participants. (a) Flowchart of 33,979 adult participants in the National Health and Nutrition Examination Survey (NHANES, 2003–2018) included in the analyses of mixtures of toxins. Group 1: **participants had data on blood levels of cadmium, lead and mercury;** group 2: **a subset of 10,257 adults had data on blood levels of four PFAS (PFOS, PFOA, PFHxS, PFNA);** group 3: **a subset of 12,847 adults had data on urine levels of eight metals (lead, cadmium, barium, cesium, cobalt, antimony, thallium, tungsten); and** group 4: **a subset of 1043 adults had data on blood levels of 34 PCBs and six PCDD/Fs. (b)** Group 5: **flowchart of 7360 adult participants in NHANES 1999–2002 with data on telomere length of blood cells and blood levels of cadmium and lead. Abbreviations: PFAS: per- and polyfluoroalkyl substances; PFOS: Perfluorooctane sulfonic acid; PFOA: Perfluorooctanoic acid; PFHxS: Perfluorohexane sulfonic acid; PFNA: Perfluorononanoic acid; PCB: polychlorinated biphenyls; PCDD: polychlorinated dibenzo-*p*-dioxins (PCDD); and PCD: polychlorinated dibenzofuranes.**

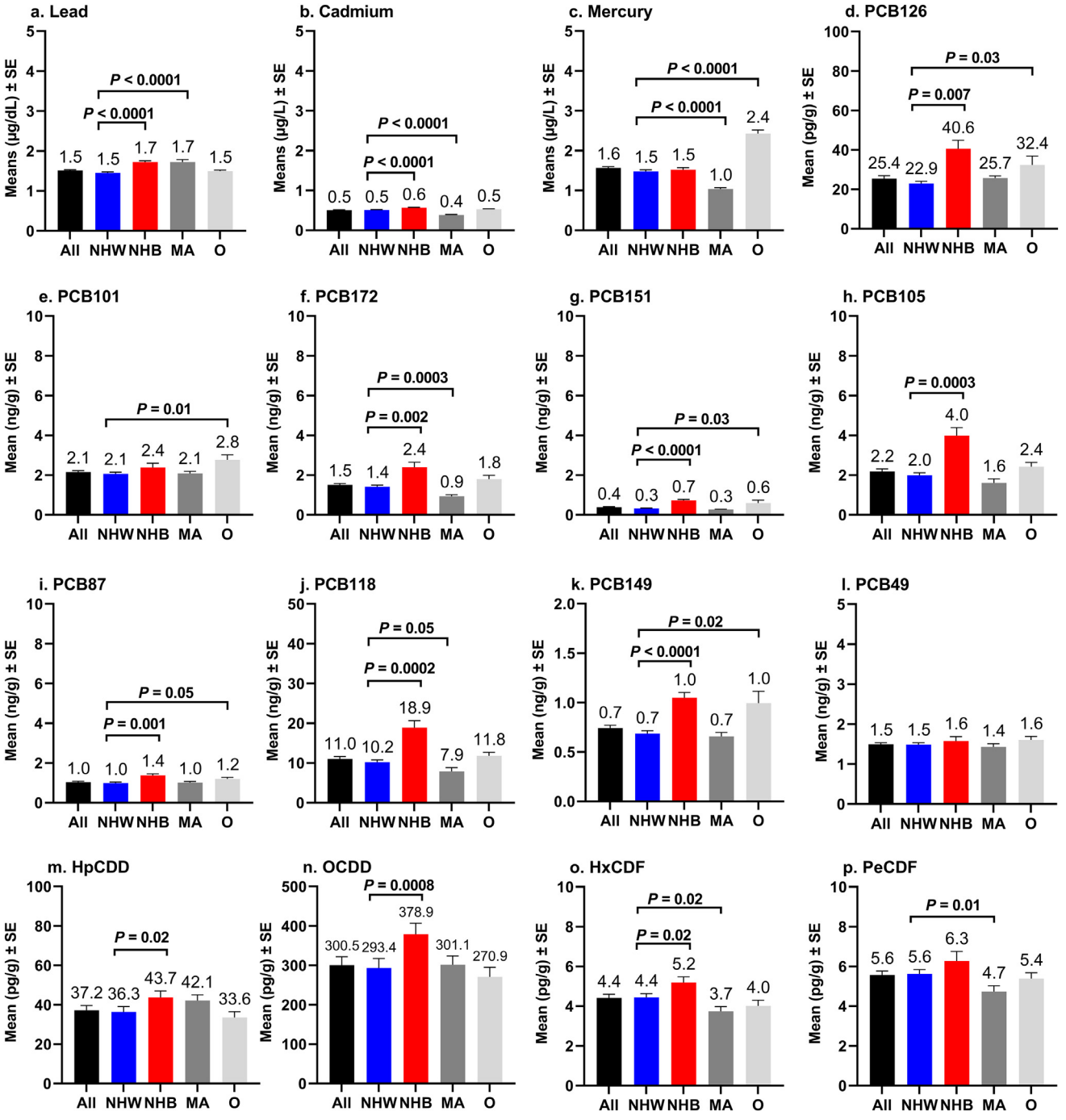

Fig. 2 – Age-standardized weighted means of blood levels of toxins stratified by race/ethnicity. Age-standardized weighted means of blood levels of (a) lead, Pb; (b) cadmium, Cd; (c) mercury, Hg; (d) PCB126; (e) PCB101; (f) PCB172; (g) PCB151; (h) PCB105; (i) PCB87; (j) PCB118; (k) PCB149; (l) PCB49; (m) HpCDD; (n) OCDD; (o) HxCDF; (p) PeCDF, stratified by race/ethnicity, showing results for the total group (all), non-Hispanic White (NHW, blue), non-Hispanic Black (NHB, red), Mexican American (MA, grey), and other (O, light grey) racial/ethnic groups. Panels a, b, and c were based on the data in group 1, and the rest of panels were based on data in group 4. Differences between groups were tested by univariate *t* statistic at a significance level of two-sided *P* value < 0.05. Abbreviation: HpCDD: 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; OCDD: 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; PCB: polychlorinated biphenyls; HxCDF: 1,2,3,4,7,8-hexachlorodibenzofura; PeCDF: 2,3,4,7,8-pentachlorodibenzofuran; SE: Standard Error.

Table 1 – Odds ratios from multivariable logistic regression models with the outcome of advanced liver fibrosis with blood levels of three metals included as independent variables (Q1–3 and Q4) with stratification by race/ethnicity.

Cohorts	OR (95 % CI)				
Sample size (*n*)	Total (33,979)	NHW (15,091)	NHB (7046)	MA (5532)	O (6310)
Advanced fibrosis (weighted %)	**496 (1.19)**	**207 (1.19)**	**118 (1.41)**	**90 (1.38)**	**81 (0.87)**
Survey cycle	**1.09**	**1.12**	1.01	1.08	1.04
	(1.04, 1.15) †	**(1.05, 1.20) †**	(0.93, 1.10)	(0.96, 1.22)	(0.90, 1.21)
Age (per 10 years)	**1.44**	**1.39**	**1.40**	**1.55**	**1.93**
	(1.33, 1.57) ‡	**(1.23, 1.57) ‡**	**(1.21, 1.63) ‡**	**(1.27, 1.89) ‡**	**(1.67, 2.23) ‡**
Gender					
Female	Reference				
Male	**1.62**	**1.68**	1.51	1.61	1.40
	(1.21, 2.18) †	**(1.11, 2.56) ***	(0.94, 2.44)	(0.87, 3.01)	(0.75, 2.62)
Diabetes					
No	Reference				
Yes	**2.60**	**3.12**	0.73	**2.12**	**3.11**
	(2.00, 3.38) ‡	**(2.18, 4.47) ‡**	(0.46, 1.17)	**(1.19, 3.79) ***	**(1.66, 5.80) †**
BMI					
Normal	Reference				
Overweight	0.94	0.87	1.21	1.16	0.89
	(0.63, 1.42)	(0.49, 1.54)	(0.68, 2.16)	(0.55, 2.44)	(0.42, 1.88)
Obese	1.02	0.90	1.02	1.19	1.68
	(0.72, 1.43)	(0.56, 1.44)	(0.56, 1.86)	(0.56, 2.52)	(0.78, 3.63)
Alcohol use					
Lifetime abstainers	Reference				
Former drinkers	0.97	0.74	**2.58**	0.71	1.53
	(0.61, 1.53)	(0.38, 1.42)	**(1.08, 6.18) ***	(0.25, 2.01)	(0.67, 3.47)
Non-excessive current drinkers	1.08	1.00	1.83	0.82	1.05
	(0.70, 1.67)	(0.54, 1.87)	(0.71, 4.75)	(0.25, 2.65)	(0.42, 2.63)
Excessive current drinkers	**2.13**	1.86	**3.06**	1.97	**2.79**
	(1.32, 3.44) *	(0.90, 3.83)	**(1.24, 7.58) ***	(0.62, 6.22)	**(1.02, 7.65) ***
Smoking status					
Never	Reference				
Past/current	1.30	1.43	0.99	1.37	0.98
	(0.95, 1.80)	(0.90, 2.29)	(0.59, 1.68)	(0.71, 2.64)	(0.48, 2.02)
Poverty					
No	Reference				
Yes	1.18	0.93	**2.12**	0.98	0.92
	(0.89, 1.56)	(0.58, 1.48)	**(1.35, 3.34) †**	(0.52, 1.84)	(0.46, 1.83)
Blood Lead (Pb)					
Q1–3	Reference				
Q4	1.24 (0.89,	1.19	**2.26**	0.71	1.12
	1.73)	(0.75, 1.90)	**(1.37, 3.74) †**	(0.37, 1.39)	(0.59, 2.11)
Blood Cadmium (Cd)					
Q1–3	Reference				
Q4	**2.01**	**2.07**	**1.73**	**2.08**	**2.19**
	(1.45, 2.78) ‡	**(1.27, 3.36) ***	**(1.04, 2.86) ***	**(1.13, 3.82) ***	**(1.18, 4.08) ***
Blood Mercury (Hg)					
Q1–3	Reference				
Q4	0.80	0.86	1.01	0.54	0.68
	(0.58, 1.12)	(0.53, 1.40)	(0.60, 1.71)	(0.25, 1.16)	(0.40, 1.17)

Multiple imputation was performed in multivariate logistic regression models. *$P < 0.05$, †$P < 0.001$, ‡$P < 0.0001$. Advanced fibrosis was defined as ALT elevation and APRI ≥1.5 and/or FIB-4 ≥ 2.67 and/or Forns ≥6.9. Abbreviations: ALT: alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index; FIB-4: fibrosis-4; OR: odds ratio; CI: confidence interval; BMI: body mass index; NHW: non-Hispanic White; NHB: non-Hispanic Black; MA: Mexican American; O: other race; Q: quartile.

analyzed as a categorical or continuous variable (Table 1, Appendix A Tables S2 and S3). In contrast to high Pb, high Cd was associated with advanced-LF in the total population and in all racial/ethnic groups, with ORs ranging from 1.73 to 2.19. Hg was not associated with advanced-LF in any group. Diabetes was associated with advanced-LF in the total population and in NHW, MA and O, but not in NHB (OR = 0.73; 95 % CI, 0.46–1.17), underscoring the distinctiveness of the factors associated with advanced-LF in NHB (Table 1).

In an investigation of factors associated with ALT elevation, high Pb (Q4 vs Q1–3) had an OR of 1.24 (95 % CI, 1.01–1.53) and high Cd had an OR of 1.25 (95 % CI, 1.03–1.55) in NHB. Neither high Pb nor high Cd was significantly associated with ALT elevation in any other group. Q4 blood levels of Hg were asso-

ciated with ALT elevation in the total population and in MA (Appendix A Table S4).

2.3. WQS analysis of blood levels of metals and liver endpoints

Spearman correlations between Pb and Cd ranged up to 0.4 (Appendix A Fig. S1); thus, WQS modeling was used to identify the true "bad actors" (Carrico et al., 2015). WQS_{metal} indices were determined for all group 1 participants (n = 33,979) and for each racial/ethnic group. The indices were significantly associated with advanced-LF in the total population and in NHW, NHB, and MA in models that adjusted for age, sex, smoking status, alcohol use, BMI, poverty, and diabetes. ORs ranged from 1.12 (95 % CI, 1.01–1.24) per decile of the WQS_{metal} index in MA to 1.40 (95 % CI, 1.21–1.64) in NHB (Fig. 3). Pb was the most significant contributor in NHB, while Cd was the most significant contributor in the total population and in the other racial/ethnic groups (Fig. 3). Among NHB, the OR of advanced-LF for participants in the top decile of the WQS_{metal} index was 20.7 (95 % CI, 5.6–85.8) (Fig. 3). In other analyses, the WQS_{metal} indices were significantly associated with ALT elevation in the total population, NHW, NHB and MA. Pb was the major contributor in NHB and MA, while Hg and Pb were the top contributors in the total population (Appendix A Table S5).

2.4. WQS analysis of metal-PFAS indices and liver endpoints

Spearman correlations between blood levels of metals and PFAS are shown in Appendix A Fig. S2. In group 2 participants (n = 10,257), the WQS_{metal} index was significantly associated with advanced-LF (OR = 1.17 (95 % CI, 1.03–1.32)) and ALT elevation (OR = 1.03 (95 % CI, 1.00–1.07)), after adjusting with age, sex, smoking status, alcohol use, poverty and diabetes, consistent with results in group 1, while the WQS_{PFAS} index was not associated with either advanced-LF or ALT elevation (Appendix A Figs. S3 and S4). The OR of the $WQS_{metal\text{-}PFAS}$ index was similar to that of the WQS_{metal} index for the association with advanced-LF; Cd was the major contributor (Appendix A Fig. S4). Sample size limitations precluded stratification by race/ethnicity with outcome of advanced-LF. Neither the $WQS_{metal\text{-}PFAS}$ index nor the WQS_{PFAS} index was associated with ALT elevation in most racial/ethnic groups (Appendix A Figs. S5 and S6, respectively).

2.5. WQS analysis of blood and urine metals and liver endpoints

Spearman correlations among heavy metals in blood and urine are shown in Appendix A Fig. S7. In group 3 participants (n = 12,847), the WQS indices of heavy metals in a) blood, b) urine, and c) blood and urine were all significantly associated with both advanced-LF and ALT elevation. The index of the combination of blood and urine metals had the highest adjusted ORs: 1.15 (95 % CI: 1.03–1.29) for advanced-LF and 1.06 (95 % CI: 1.02–1.10) for ALT elevation; blood and urine Cd were the major contributors (Appendix A Figs. S8 and S9). Sample size limitations precluded stratification by race/ethnicity with outcome of advanced-LF. The indices were not associated with ALT elevation in most individual racial/ethnic groups (Appendix A Figs. S10 and S11).

2.6. WQS analysis of PCBs, PCDD/Fs, metals in blood and ALT elevation

Before conducting a mixture analysis, 34 PCBs, six PCDD/Fs and three heavy metals (Pb, Cd, and Hg) were analyzed individually for associations with ALT elevation in the total group (group 4, n = 1043) with adjustment for age, sex, and race/ethnicity (Appendix A Table S6). PCB209 was excluded from the subsequent mixture analysis because its concentration is inversely related to ALT elevation. Spearman correlations among the remaining pollutants are shown in Appendix A Fig. S12. The $WQS_{metal\text{-}PCB\text{-}PCDD/F}$ index was significantly associated with ALT elevation in the total population of group 4: OR = 1.50 per decile (95 % CI, 1.26–1.78), reaching an OR of 38.4 (95 % CI, 8.0–179.0) in the top decile, after adjusting for age, sex, and race/ethnicity. PCB126, Cd, Pb, PCB101, PCB172, Hg and 1,2,3,4,6,7,8-heptachlororodibenzo-*p*-dioxin (HpCDD) were the primary contributors. PCB126 had the highest weight by far (Fig. 4). Sample size limitations precluded analysis with outcome of advanced-LF.

In a comparison of ORs for the associations between ALT elevations and WQS indices in groups 2 and 4, the $WQS_{metal\text{-}PCB\text{-}PCDD/F}$ index had the highest value, followed by the $WQS_{PCB\text{-}PCDD/F}$ index. The ORs of the indices for mixtures that included PCBs/PCDD/Fs were higher than those that included PFAS (Fig. 4), after adjusting for age, sex, and race/ethnicity. These results underscore the importance of heavy metals and selected persistent organic pollutants as potential drivers of liver injury.

An additional WQS analysis of the metal-PCB-PCDD/F mixture was carried out because many pairs of PCBs have correlation coefficients exceeding 0.7 (Appendix A Fig. S12). In this case, components with weights over 0.005 may be significant contributors (Carrico et al., 2015). Several additional compounds are above this threshold and might be considered significant contributors (Fig. 4). Lasso regression modeling was used as an additional alternative approach for identifying chemicals positively associated with ALT elevation. In general agreement with the $WQS_{metal\text{-}PCB\text{-}PCDD/F}$ index, PCB126, PCB172, HpCDD, Cd, and Hg were selected, in addition to PCB151, PCB105, and octachlorodibenzo-*p*-dioxin (OCDD) (Appendix A Table S7).

In the TEQ analysis of dioxin-like PCBs and PCDD/Fs, the association between ALT elevation and the TEQ values of PCB 105, 118, 126, HpCDD, and OCDD was highly significant (OR = 1.89 (95 % CI, 1.09–3.26) per 10 pg/g TEQ) when the TEQ values were treated as a continuous variable, after adjusting for age, sex, and race/ethnicity. The association was also highly significant when the TEQ values were treated as a categorical variable. Compared to participants with TEQ values in Q1, those in Q3 and Q4 had ORs of 3.43 (95 % CI, 1.80–6.56) and 3.21 (95 % CI, 1.90–5.41), respectively, after adjusting for age, sex, and race/ethnicity (Appendix A Table S8). Notably, PCB 105, 118, 126, HpCDD, and OCDD were significantly associated with ALT elevation in both the single-chemical analysis (Appendix A Table S6) and in the WQS mixture analysis (Fig. 4), indicating that these compounds are major contrib-

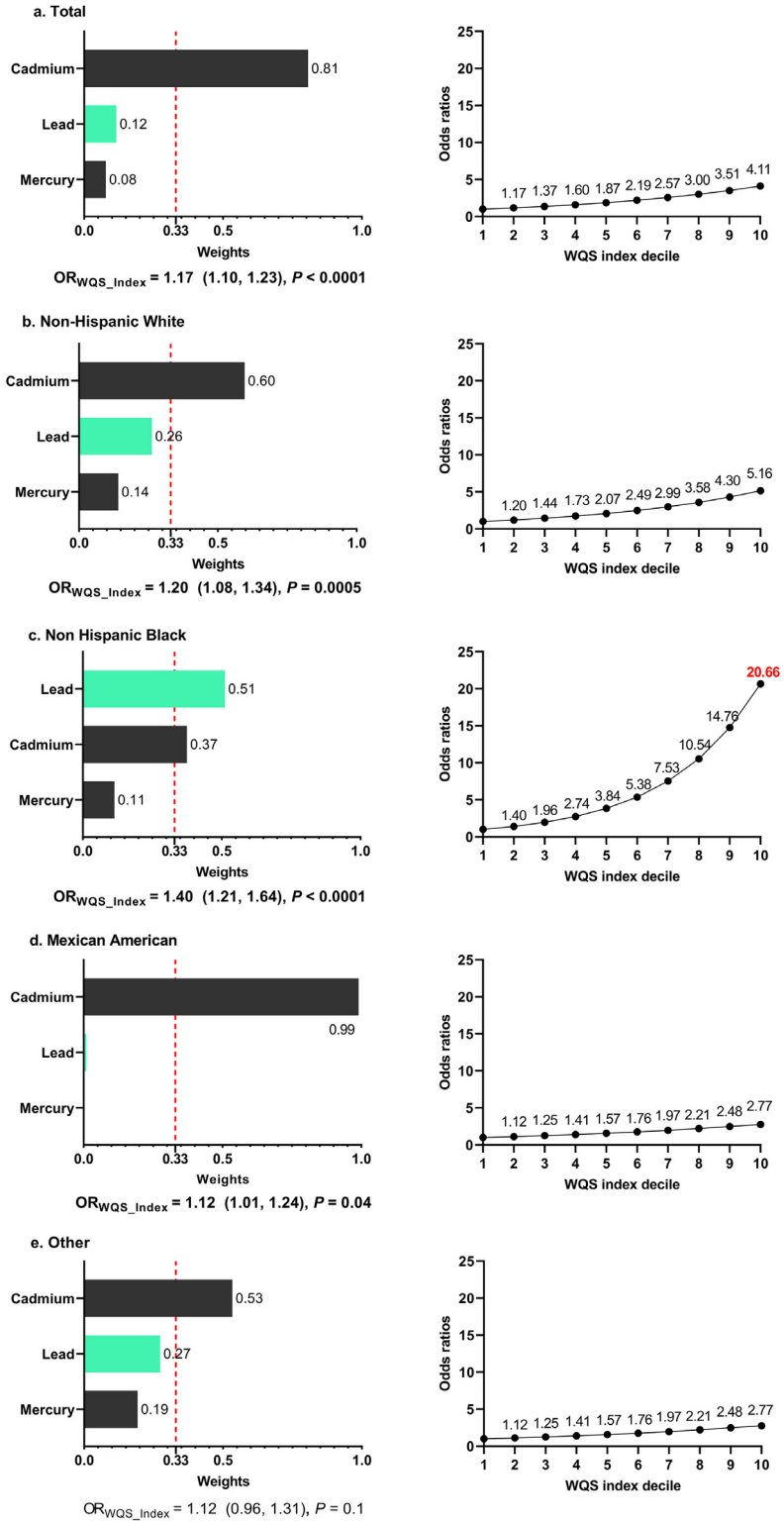

Fig. 3 – Weights of the components and estimated odds ratios per decile of the WQS_{metal} indices with the outcome of advanced liver fibrosis in group 1. Blood levels of metals (lead, cadmium and mercury) were analyzed in weighted quantile sums (WQS) models with the outcome of advanced liver fibrosis (ALT elevation plus FIB-4 ≥ 2.67 and/or Forns ≥ 6.9 and/or APRI ≥ 1.5). By default, metals in the mixture were considered significant if their weights exceeded the inverse of the number of elements in the mixture, which is 1/3 (0.333), indicated by the red dashed line. Weights and the estimated odds ratios (OR) per decile of the WQS_{metal} indices are reported for the total population. (a) total; (b) Non-Hispanic White, (NHW); (c) Non-Hispanic Black (NHB); (d) Mexican American (MA); (e) Other racial/ethnic group. Weights of lead are colored green. Data of blood levels of cadmium, lead and mercury were not normally distributed and were log-transformed in the analysis.

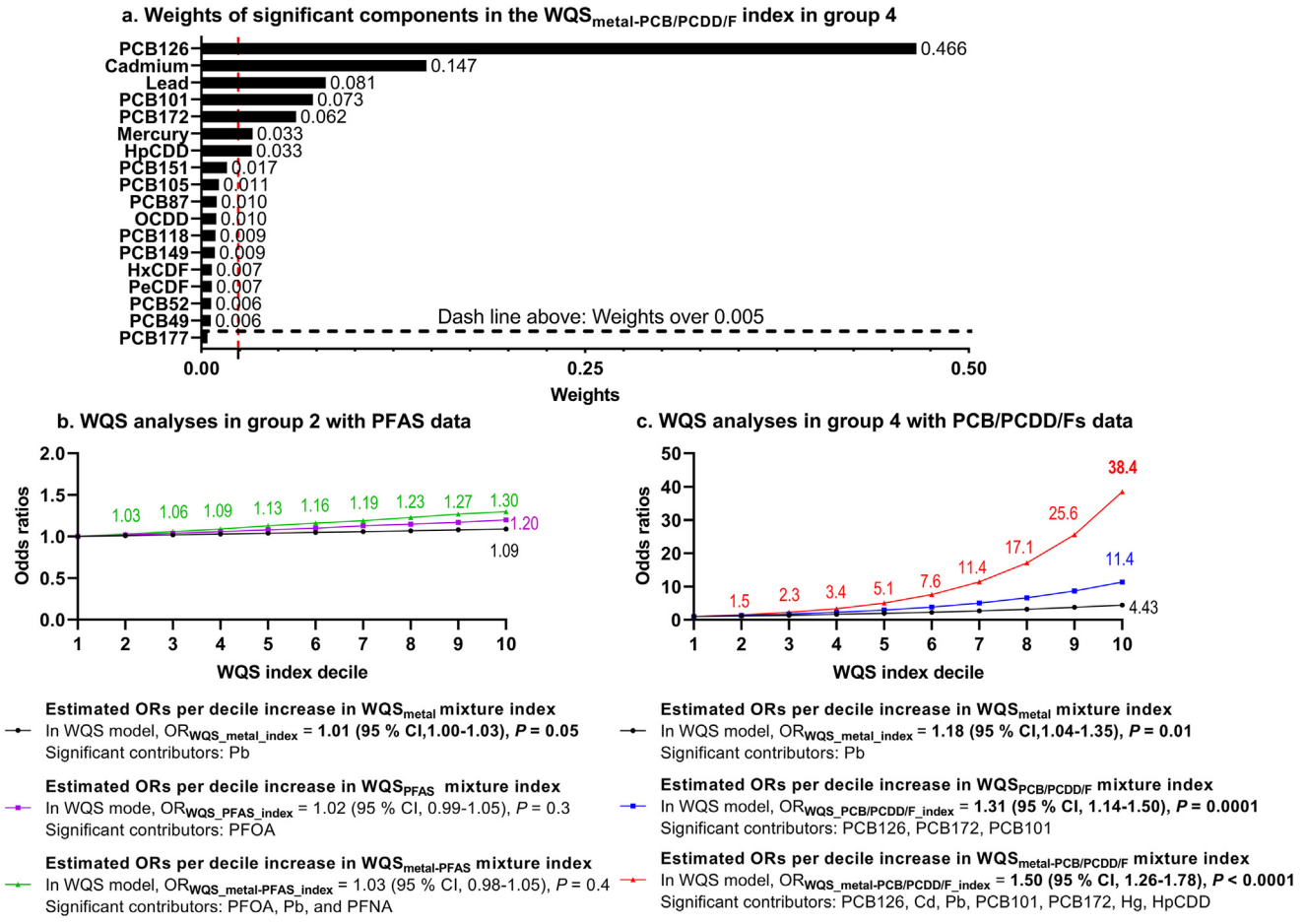

Fig. 4 – Weights of significant components in the $WQS_{metal\text{-}PCB/PCDD/F}$ index (a) and ORs by decile of WQS indices with the outcome of ALT elevation (b and c). (a) Bar plot showing the weights of significant components in the $WQS_{metal\text{-}PCB/PCDD/F}$ index. The significant components exceed to the inverse of the number of elements in the mixture, which was 1/42 = 0.024, red dash line. Components with weights over 0.005 may be significant contributors (horizontal dash black line). Non-significant components were not plotted. (b) Graph of group 2 data (which include blood metals and PFAS) showing the ORs of the WQS indices by decile for the outcome of ALT elevation after adjusting for age, sex, and race/ethnicity; (c) graph of group 4 data (which include blood metals and PCB/PCDD/Fs) showing the ORs of the WQS indices by decile for the outcome of ALT elevation after adjusted with age, sex, and race/ethnicity. Limited by the sample size, the covariates included only age, sex, and race/ethnicity. Abbreviations: PCDF: polychlorinated dibenzofurans.

utors to liver disease risk, aligning with our primary findings. An analysis that included all of the dioxin-like PCBs and PCDD/Fs in our dataset that have reported TEQ values did not show a significant association with ALT elevation (Appendix A Table S9).

2.7. *Racial/ethnic disparities in toxin levels*

NHB had higher blood levels of liver toxicants than NHW, as indicated by their higher age-standardized weighted mean blood levels of Pb, Cd, PCB126, PCB172, HpCDD, and OCDD (Fig. 2).

2.8. *Blood levels of Pb, Cd, and telomere length*

NHANES 1999–2002 included 7360 adults with measurements of both blood levels of Pb and Cd and blood cell telomere length (Fig. 1, Appendix A Table S1e). In an MVL model, telomere length had an inverse relationship with advanced-LF. Compared to Q4, the adjusted ORs for Q3 to Q1 varied from 4.31 to 5.28, indicating a higher risk of advanced-LF with decreasing telomere length (Fig. 5a). Sample size limitations precluded stratification by race/ethnicity. Telomere length was not significantly associated with ALT elevation (Appendix A Fig. S13). Heavy metals were associated with short (Q1) telomere length in WQS models in the total population, OR=1.12 (95 % CI, 1.08–1.17) and in NHW and NHB; Cd was the top contributor (Fig. 5b).

3. Discussion

In this comprehensive cross-sectional study, we investigated associations between toxin levels in prospectively-collected specimens and liver scarring (advanced-LF) and liver injury

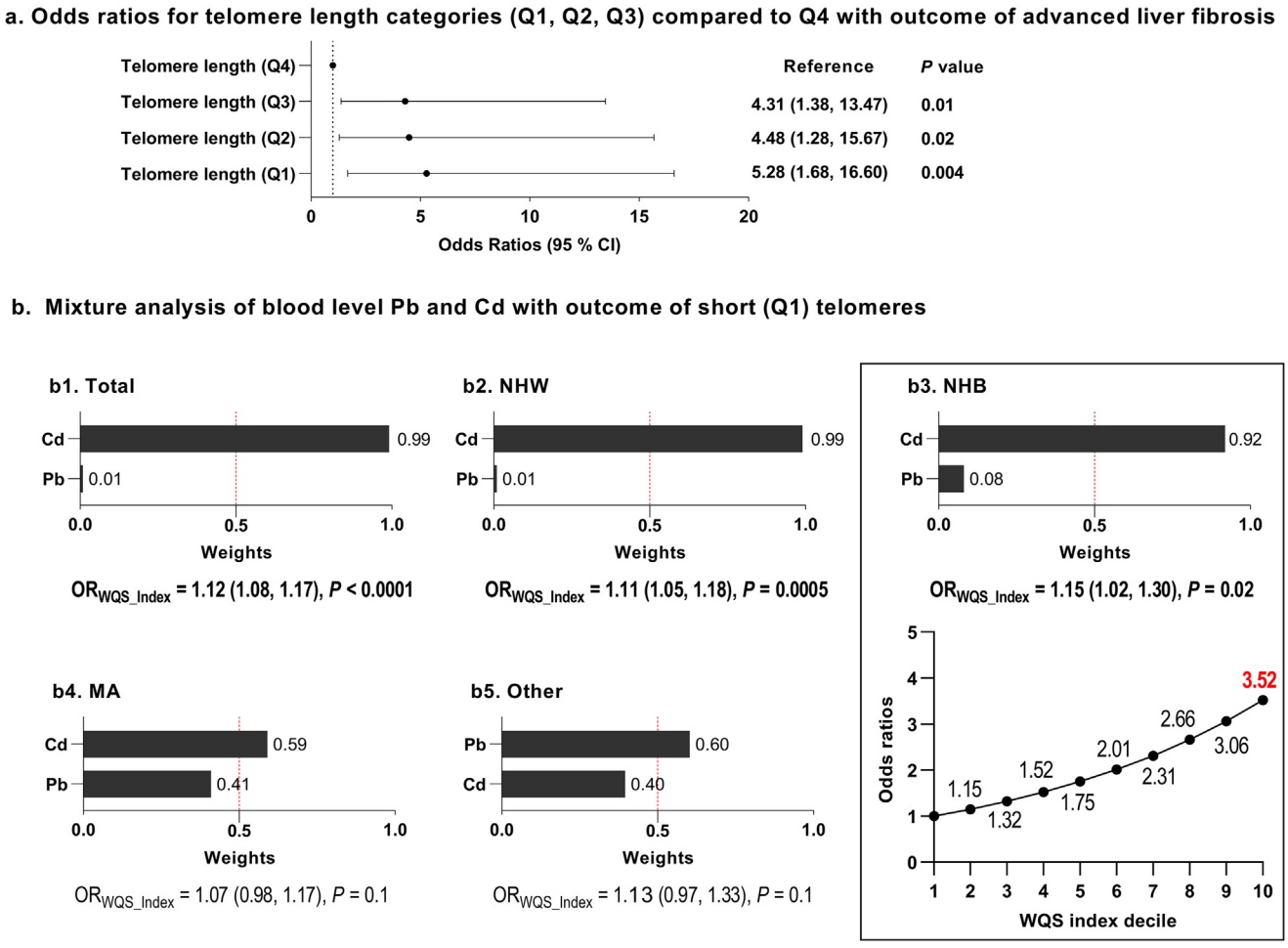

Fig. 5 – MVL analysis of the relationship between telomere length and advanced fibrosis (a) and analysis of the relationship between the WQS metal index and short telomeres (b). (a) Plot of the ORs from MVL models analyzing the relationship between telomere length by quartile [reference was Q4 telomere] and advanced fibrosis adjusted for age, sex, diabetes, body mass index, alcohol use, smoking status, and poverty. (b) WQS models analyzing the relationship between WQS indices of blood levels of lead (Pb) and cadmium (Cd) and short (Q1) telomeres, with adjustment for age, sex, smoking status, alcohol use, body mass index and diabetes. Bar graphs indicate the weights of significant contributors (indicated by the red dotted line) in the total population and in individual racial/ethnic groups. By default, metals were considered significant if their weights exceeded the inverse of the number of elements in the mixture, which is 1/2 (0.5), indicated by a red dotted line. ORs are per decile of WQS index scores. Data of blood levels of cadmium and lead were not normally distributed and were log-transformed in the analysis. Abbreviations: MVL: multivariable logistic regression.

(ALT elevation) in adults in the United States. We analyzed 53 toxins with blood and/or urine levels measured in NHANES. Four findings have public health importance.

First, Pb exposure was associated with advanced-LF in both MVL and WQS models in NHB and in no other racial/ethnic group. The high ORs and their concordance suggest that NHB may have a heightened vulnerability to the hepatotoxic effects of Pb, but additional research is needed to examine the possibility that Pb is a proxy for other exposures. NHB have a high frequency of a variant of the arylsulfatase A gene (Taylor et al., 2016) that increases susceptibility to Pb toxicity in cultured cells (Poretz et al., 2000). This, or other genetic factors, could contribute to the unique risk profile of NHBs for advanced-LF, which included high Pb levels but did not include diabetes in this study or in prior studies (Browning et al., 2018; Ma et al., 2023). Heightened susceptibility to toxins may extend beyond Pb, as indicated by data showing that NHB who smoke develop lung cancer at a younger age and with fewer pack-years of smoking than NHW (Prosper et al., 2020).

Second, blood levels of many hepatotoxins were higher in NHB than in NHW, consistent with published findings (Ma et al., 2023). These results identify a potential source of liver-related healthcare disparities that could be addressed through public health measures. The higher blood levels of toxins in NHB could reflect greater exposure, greater intake, greater absorption, or greater retention in the body.

Third, WQS models confirmed the importance of Cd toxicity in the total population and in major subgroups. In WQS models, both urine and blood levels of Cd were associated with

advanced-LF and ALT elevation and blood levels of Cd were also associated with shorter telomeres.

Fourth, the group of persistent organic pollutants that include PCBs and PCDD/Fs had a much higher OR for ALT elevation than PFAS (1.31 vs. 1.02), establishing the importance of reducing levels of PCBs and structurally-related compounds, even as the important efforts to reduce PFAS are carried out. Although PCB manufacturing was banned in the United States in 1979, production continued in other parts of the world until 2001. A recent study identified 149 different PCBs that can be derived from commercial products still being manufactured (Hannah et al., 2022). Once created, PCBs can persist in the environment for long periods (van den Berg et al., 2017).

PCB126 was the most significant contributor to ALT elevation in WQS models that included PCBs and PCDD/Fs, highlighting the importance of this potent dioxin-like toxicant. PCB126 was only a minor constituent of commercial PCB products (Frame et al., 1996), but it contributed 37 %–59 % of the liver toxic equivalents (Iwata et al., 2004). PCB126 was classified as group 1 carcinogen by the International Agency for Research on Cancer (Lauby-Secretan et al., 2016). It is a high affinity ligand of the aryl hydrocarbon receptor (AhR). Activation of AhR by PCB126 results in liver steatosis and altered metabolism (Shen et al., 2019; Zhang et al., 2012).

4. Strengths and limitations

The strengths include the use of: (1) clinically-meaningful endpoints to evaluate hepatotoxic effects, (2) nationally representative NHANES data, (3) two complementary statistical approaches, WQS and MVL modeling, and (4) stratification by race/ethnicity. Limitations include: (1) the lack of biopsy data to confirm fibrosis stage, which we mitigated by analyzing both ALT elevation and well-validated composite indices of advanced-LF, (2) sample size limitations that precluded stratification by race/ethnicity in several cases, (3) the inability to directly compare certain exposures because toxicants were measured in non-overlapping groups, (4) the cross-sectional design of NHANES, which precludes an investigation of causality, and (5) the WQS method is sensitive to collinearity among components, which can affect the stability and interpretability of the weights assigned to each component. For the highly correlated PCB/PCDD/Fs data, we mitigated this by using lower weight cutoffs for significant components and by conducting sensitivity analyses using Lasso Regression and TEQ mixture analysis to confirm the primary results.

5. Conclusions

WQS analysis of common pollutants revealed that metal mixture indices are significantly associated with liver damage and shorter telomeres. Pb is the main contributor of the mixture indices associated with advanced-LF and ALT elevation in NHB and with ALT elevation in MA. Cd was the main contributor to the associations between the mixture indices and advanced-LF and shorter telomere length in the total population. Several PCBs and dioxin-like compounds, most notably PCB126, are the primary contributors to the association between the mixture indices and liver injury. The results suggest that African Americans may be especially susceptible to the toxic effect of Pb. Future safety regulations may need to be adjusted to ensure that standards protect people with heightened vulnerability. The results highlight the opportunity to reduce the burden of liver disease by reducing exposure to environmental pollutants.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ning Ma: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Rowena Yip:** Writing – review & editing, Methodology, Conceptualization. **Mark Woodward:** Writing – review & editing, Methodology, Conceptualization. **Sara Lewis:** Writing – review & editing, Methodology, Conceptualization. **Michael Crane:** Writing – review & editing, Methodology, Conceptualization. **Artit Jirapatnakul:** Writing – review & editing, Methodology, Conceptualization. **Costica Aloman:** Writing – review & editing, Methodology, Conceptualization. **Douglas Dieterich:** Writing – review & editing, Methodology, Conceptualization. **Louis Gros:** Writing – review & editing, Methodology, Conceptualization. **Damaskini Valvi:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Elena Colicino:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **David Yankelevitz:** Writing – review & editing, Methodology, Conceptualization. **Claudia Henschke:** Writing – review & editing, Methodology, Conceptualization. **Andrea D. Branch:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization, Funding acquisition.

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Appendix A Supplementary data

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jes.2024.08.020.

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