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RESEARCH ARTICLE

Associations between mercury exposure and the risk of nonalcoholic fatty liver disease (NAFLD) in US adolescents

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Abstract

Little is known regarding the effects of environmental mercury (Hg) exposure on liver dysfunction in adolescents. We aimed to explore the association between Hg exposure and the risk of nonalcoholic fatty liver disease (NAFLD) in the adolescent population. The cross-sectional associations between blood Hg concentrations and serum alanine aminotransferase (ALT) levels, a surrogate for suspected NAFLD, were evaluated using data from adolescents (aged 12–17 years old) who participated in the National Health and Nutrition Examination Survey (NHANES), 1999–2014. A final sample of 6389 adolescents was analysed. Elevated ALT was defined as > 25 IU/L and > 22 IU/L for boys and girls ≤ 17 years old, respectively. Odds ratios (ORs) of Hg levels in association with serum ALT levels were estimated using a logistic regression after adjusting for gender, age, ethnicity, serum cotinine, body mass index, the poverty income ratio, and NHANES cycles. The median blood Hg level was 0.73 ± 0.91 μg/L amongst US adolescents. In the adjusted model, the ORs of elevated ALT levels of those in the 4th quartile were higher amongst non-Hispanic white adolescents (OR = 1.76, 95% CI 1.20, 2.59; $P = 0.035$) and those who were normal or underweight (OR = 1.41, 95% CI 1.08, 1.85; $P = 0.020$). No association was observed for the other variables. Our results indicate that the positive association between blood Hg exposure and the risk of NAFLD in US adolescents is the highest amongst non-Hispanic white and those who are normal or underweight, regardless of ethnicity. More research is necessary to confirm this association and to clarify the potential mechanisms.

Keywords NHANES · Mercury · Adolescent · Nonalcoholic fatty liver disease (NAFLD) · Alanine aminotransferase

Introduction

Mercury (Hg) is a naturally occurring metal that ubiquitous and persistent in the environment. According to the Agency for Toxic Substances and Disease Registry (ATSDR) 2017 Substance Priority List, Hg is ranked as the third priority pollutant causing global concern to human health. Recently, blood Hg levels amongst adolescents have been investigated worldwide. In Canada, the geometric mean blood level in adolescents was 0.27 μg/L(Lye et al. 2013). In the USA, the average blood Hg concentrations were 0.49 μg/L and 0.53 μg/L for adolescents in the NHANES 2003–2004 and 2009–2010, respectively (Fourth National Report on Human Exposure to Environmental Chemicals 2015). Even low levels of Hg exposure can cause acute and chronic intoxication, affecting the nervous, cardiovascular, reproductive, endocrine, and immune systems (Fernandes Azevedo et al. 2012; Gardner et al. 2010; Minoia et al. 2009; Wong and Cheng 2011; Zhang et al. 2018). Hg is also considered to have structural and functional effects on the liver, which plays a pivotal role in metabolism and detoxification (Choi et al. 2017; Lee et al. 2017). However, the relationship between environmental Hg exposure and liver-related outcomes in humans remains unclear.

Nonalcoholic fatty liver disease (NAFLD) is a condition caused by an accumulation of fat deposits in the hepatocytes exceeding 5% of the weight of the liver, without hepatitis B virus or hepatitis C virus infection, and

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with an ethanol intake of < 20 g/day (Sattar et al. 2014). The prevalence of NAFLD increased from 5.51 to 11.01% according to a previously reported study using NHANES data from 1988 to 2008. It has become the primary form of chronic liver disease worldwide, particularly in Western countries (Le et al. 2017). This trend is of great concern because chronic liver disease may deteriorate to steatohepatitis, cirrhosis, and, eventually, liver failure or liver cancer (Ruhl and Everhart 2015). Recently, several research studies have shown that differential exposures to environmental toxicants may play a role in the increased risk of NAFLD in adults (Cave et al. 2010; Zhai et al. 2017). Children are particularly vulnerable to Hg intoxication due to their physical and biological characteristics compared to adults, which may lead to irreversible damage to the liver (Temple et al. 2016). However, no data currently exist regarding low Hg levels and NAFLD in adolescents.

In the present study, we aimed to utilize nationally representative data from the National Health and Nutrition Examination Survey (NHANES) 1999–2014 to assess the association between Hg exposure and NAFLD risk in adolescents (12- to 17-year-olds). We hypothesized that greater exposure to Hg may contribute to the higher prevalence of NAFLD amongst adolescents.

Materials and methods

Study population

A total of 6389 people were studied during the 15-year period from 1999 to 2014. The NHANES is a cross-sectional study. The participants' basic information, including blood Hg levels, was measured in mobile examination centres. We examined blood Hg concentrations and serum ALT levels amongst 12- to 17-year-olds. The NCHS Research Ethics Review Board approved these NHANES cycles (Futatsuka et al. 1992). Data user agreement was available online (https://www.cdc.gov/nchs/data_access/restrictions.htm). All subjects have written informed consent. All methods conducted conform to the Declaration of Helsinki. The NCHS Research Ethics Review Board approved the NHANES protocol.

Participants in the 15-year period were randomly selected for the detection of blood Hg and serum ALT levels. We intended to exclude the effect of pregnancy on our results, although there were no cases of pregnancy in the studied population. In addition, we also excluded individuals who had positive hepatitis B and hepatitis C antibodies. Finally, 6389 individuals were included in the present study, of whom 3063 were boys and 3326 were girls.

Measurements of blood mercury

The standard method used to detect blood Hg levels was described in detail in previous research (NCHS; National Health and Nutrition Examination Survey; Blood Lead, Cadmium, and Mercury (L06BMT_C); National Center for Health Statistics (NCHS); Centers for Disease Control and Prevention (CDC) 2006). In brief, total blood was collected, transported, and stored in mobile examination centres. Hg was detected with inductively coupled plasma mass spectrometry. The limits of detection for whole blood Hg ranged from 0.14 to 0.2 μg/L in different NHANES cycles.

NAFLD assessment

Serum alanine aminotransferase (ALT) as a transaminase enzyme was mainly found in the liver tissue. Increased ALT levels can be used as a monitoring biomarker for NAFLD (Verma et al. 2013). The serum ALT concentrations of the participants were measured using Beckman UniCel DxC800 Synchron. The cutoff points of ALT amongst the participants aged 12-17 were as follows: high ALT was defined as > 22 IU/L for girls and > 25 IU/L for boys (Schwimmer et al. 2010).

Covariants

The covariants in our study were collected from the questionnaires and body measurements. In the analysis, we first excluded subjects with hepatitis B or C. In addition, we also excluded participants who were drinking; however, the section of the NHANES questionnaire regarding drinking is limited to those over 18 years old, so this information could not be collected. Second, in covariate selection, we integrated age, gender, family income, passive smoking, body mass index (BMI), and cycles into the analysis model to reduce the effect of these factors on the outcomes. Smoking may be associated with nonalcoholic liver disease; thus, cotinine served as a good index of passive smoking and has been widely used in various types of analyses. The method of BMI classification amongst children was that used in a previous study (Cole et al. 2000).

Statistical analysis

The SPSS 20.0 software was used to perform all analyses in the present study. Due to their skewed distributions, the blood mercury and ALT levels were log-transformed. First, normality tests were performed, and quantitative data that satisfied normality were assessed using a *t* test or a one-way analysis of variance. The quantitative data that did not satisfy normality were assessed using the nonparametric test. A chi-square test was selected to compare the classified data. Based on the odd ratio (OR) and 95% confidence interval (CI) results, we

conducted a logistics regression analysis adjusted for the relevant covariates. A stratified analysis was also performed. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Of the 9968 participants in the NHANES 1999–2014, we excluded those who had missing blood Hg (*n* 3414) or missing ALT data (*n* 123). We also excluded subjects with hepatitis B or hepatitis C (*n* 58). The final analytic population included 6389 participants (3063 boys and 3326 girls; Fig. 1).

Table 1 shows the associations between mean blood Hg and participant characteristics. The mean ± standard deviation of blood Hg was 0.73 ± 0.91 μg/L amongst the entire population. Blood Hg levels were lower in 12- to 14-year-olds (mean ± SD, 0.66 ± 0.81 μg/L) than in 15- to 17-year-olds (mean ± SD, 0.79 ± 0.98 μg/L). Blood Hg concentrations were higher in subjects who were in the "other" race category, which included multiracial subjects. Higher blood Hg levels were identified in female participants and in the 1999–2000 survey cycle participants. Other variables, such as weight, PIR, and serum cotinine, were not associated with blood Hg levels.

Table 2 shows that high ALT levels were more common in participants who were aged 15–17, male, Mexican American, and were in the 2013–2014 NHANES cycles. There was no difference in the frequency of participants with different weight statuses, different poverty levels, or serum cotinine between the normal and high ALT groups.

Table 3 shows that blood ALT levels tended to be higher in the highest blood Hg group. However, no significant differences were identified in the overall analysis after adjusting for sex, age, race/ethnicity, PIR, serum cotinine, BMI, and survey cycles. Further stratified analyses were presented for each covariate group separately. We found that in participants who were non-Hispanic white, there was a significant association in the highest blood Hg quartile with higher ALT levels compared to the lowest quartile. aORs were highest amongst non-Hispanic white participants with a risk of elevated ALT compared to the referent and were increased by 76% amongst those in the fourth quartile (OR = 1.76, 95% CI 1.20, 2.59; $P = 0.035$). Similar positive associations were observed between blood Hg levels and ALT levels (OR = 1.41, 95% CI 1.08, 1.85; $P = 0.02$) in participants who were normal or underweight. However, none of the other variables displayed a significant association.

Discussion

Using a large population sample from the US NHANES 1999–2014 survey, we found that blood Hg concentrations were positively associated with serum total ALT levels in adolescents who were non-Hispanic white and normal or underweight, after adjustment for gender, age, ethnicity, PIR, serum cotinine, BMI, and NHANES cycles.

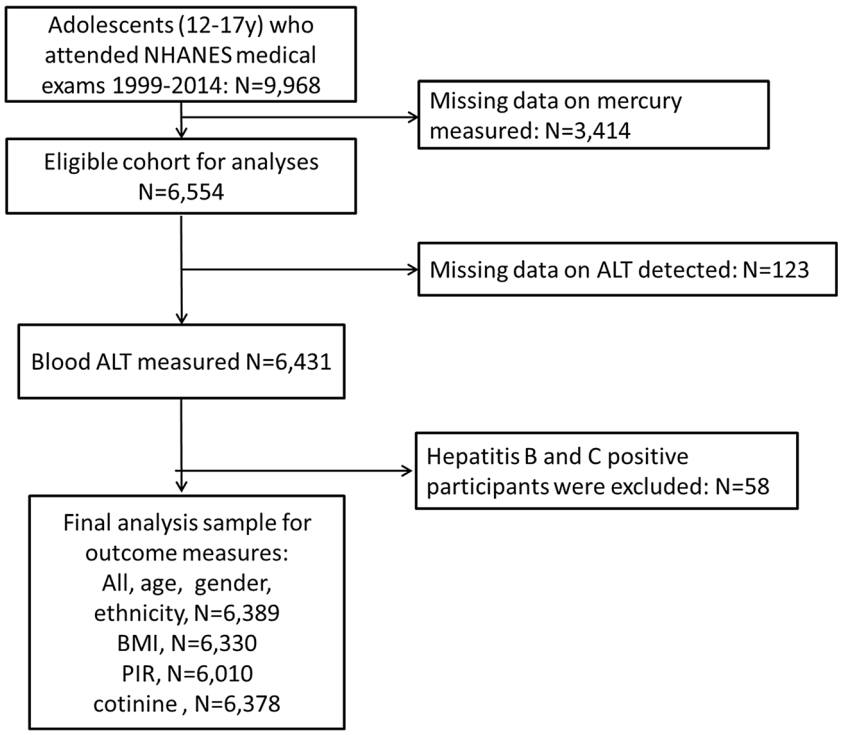

Fig. 1 Eligible participants and those included in the analyses of the associations between blood mercury exposure and risk of nonalcoholic fatty liver disease (NAFLD) in adolescents

Table 1 Blood mercury concentration (mean ± SD) of participants according to demographics

Characteristics	Participants (n)	Blood mercury	*P* value
Overall	6389	0.73 ± 0.91	
Age (years)			< 0.001
12–14	2957	0.66 ± 0.81	
15–17	3432	0.79 ± 0.98	
Gender			0.001
Male	3063	0.71 ± 0.94	
Female	3326	0.75 ± 0.88	
Ethnicity			< 0.001
Mexican American	1836	0.64 ± 0.77	
Other Hispanic	473	0.77 ± 0.83	
Non-Hispanic White	1732	0.67 ± 0.90	
Non-Hispanic Black	1877	0.72 ± 0.76	
Other race—including multi-racial	471	1.31 ± 1.57	
Weight status			0.134
Normal or underweight	3733	0.72 ± 0.89	
Overweight	1430	0.76 ± 0.97	
Obese	1160	0.73 ± 0.88	
PIR			0.902
< 1	1814	0.70 ± 0.85	
≥ 1	4196	0.73 ± 0.90	
Serum cotinine (ng/mL)			0.437
< LOD (0.011)	1389	0.77 ± 1.11	
0.011–10	4479	0.71 ± 0.81	
> 10	510	0.74 ± 1.03	
NHANES cycles			< 0.001
1999–2000	247	0.94 ± 1.27	
2001–2002	295	0.85 ± 0.83	
2003–2004	1496	0.76 ± 0.93	
2005–2006	1417	0.69 ± 0.78	
2007–2008	803	0.64 ± 0.64	
2009–2010	889	0.78 ± 1.12	
2011–2012	817	0.72 ± 0.93	
2013–2014	461	0.67 ± 0.88	

Data were expressed as mean ± standard deviation

Several previous studies have reported on the relationship on the association between Hg exposure and the risk of NAFLD. For instance, One cross-sectional cohort study suggested that multiple environmental pollutions including Hg were individually associated with ALT elevation, total Hg had extremely high detection rates (92.5%) and was positively associated with ALT elevation (Cave et al. 2010). Another study showed an association between blood Hg levels and mild liver dysfunction in the adult Korean population. Specifically, the odds ratios for having serum ALT levels above the median were statistically significant according to the increase of blood Hg (Lee et al. 2014a). Notably, several epidemiological studies showed inconsistent results regarding this association. A population-based cross-sectional mass screening survey showed that the prevalence of liver disease in the methyl mercury polluted area was not significantly increased compared to other areas, and the rate of increased ALT levels was relatively low (Futatsuka et al. 1992). A case-control study of 320 Iranian adolescents found no significant associations between serum Hg levels and ALT levels (Poursafa et al. 2014). Thus, seemingly conflicting results exist regarding this association. Possible explanations may include differences in sample sizes and age groups. Our results revealed that there was a dose-response increase in the risk amongst non-Hispanic whites and normal or underweight groups in US adolescents. We infer that the larger sample size may be more persuasive due to possible biases, even though several covariates were controlled in our analytic models.

Table 2 Characteristics of 6389 US adolescents by alanine aminotransferase (ALT) levels

	Normal ALT	High ALT	*P* value
Age (years)			< 0.001
12–14	89.0% (2631)	11.0% (326)	
15–17	83.6% (2868)	16.4% (564)	
Gender			< 0.001
Male	81.7% (2502)	18.3% (561)	
Female	90.1% (2997)	9.9% (329)	
Ethnicity			< 0.001
Mexican American	81.3% (1492)	18.7% (344)	
Other Hispanic	84.4% (399)	15.6% (74)	
Non-Hispanic White	87.1% (1508)	12.9% (224)	
Non-Hispanic Black	89.5% (1679)	10.5% (198)	
Other race—including multi-racial	89.4% (421)	10.6% (50)	
Wright status			0.558
Normal or underweight	85.6% (3197)	14.4% (536)	
Overweight	86.8% (1241)	13.2% (189)	
Obese	86.2% (1000)	13.8% (160)	
PIR			0.685
< 1	85.8% (1556)	14.2% (258)	
≥ 1	86.2% (3616)	13.8% (580)	
Serum cotinine (ng/mL)			0.440
< LOD (0.011)	85.5% (1187)	14.5% (202)	
0.011–10	86.4% (3870)	13.6% (609)	
> 10	84.7% (432)	15.3% (78)	
NHANES cycles			0.027
1999–2000	86.6% (214)	13.4% (33)	
2001–2002	85.3% (221)	14.7% (38)	
2003–2004	86.8% (1299)	13.2% (197)	
2005–2006	85.3% (1209)	14.7% (208)	
2007–2008	84.3% (677)	15.7% (126)	
2009–2010	85.4% (759)	14.6% (130)	
2011–2012	85.0% (734)	10.2% (83)	
2013–2014	83.7% (386)	16.3% (75)	

High ALT was defined as > 25 IU/L for boys ≤ 17 years and > 22 IU/L for girls ≤ 17 years

The toxic effects of Hg on the liver have been reported in animal models. Lee et al. (2014b) found that a significant increase of ALT levels was observed in mice after being intraperitoneally injected with saline containing 10 mg/kg $HgCl_2$ once a day for 2 weeks compared to a control group. Similarly, Wadaan et al. used male rats treated with drinking water containing 200 ppm $HgCl_2$ for 8 weeks to evaluate blood chemistry and histological changes in the liver. ALT, AST, and GGT were significantly increased in the $HgCl_2$-exposed rats compared to the control. Moreover, conspicuous damage and degenerative and necrotic changes were observed in subtotal liver tissue by histological examination (Wadaan 2009). Although the administration dose and methods applied in the rat models were different, these evidences may support our findings about the positive associations between blood Hg levels and serum ALT levels in adolescents.

In our study, we found a significant association between high blood Hg concentrations and high ALT levels amongst non-Hispanic white adolescents in the USA. Ethnic differences may be ascribed to genetic susceptibility, which can make different population groups with susceptible candidate genes more or less vulnerable to Hg toxicity. Thus far, most Hg studies have focused on environmental factors; however, increasing evidence has raised concerns that genetic factors may play an important role on exposure and health effects (Andreoli and Sprovieri 2017; Basu et al. 2014; Llop et al. 2015). More research is highly warranted to clarify whether non-Hispanic white adolescents comprise a vulnerable group to Hg hepatotoxicity. Our results also show a positive association between blood mercury and ALT levels in the population of normal or underweight individuals. Rothenberg et al. (2015) found that blood mercury levels were

Table 3 Adjusted odds ratio of elevated alanine aminotransferase (ALT) levels with increasing blood mercury concentrations in US adolescents 1999–2014

	N	Quartile of mercury [odd ratio (95% confidence intervals)]				*P* for trend
		1st	2nd	3rd	4th	
All	5941	Reference	1.09 (0.88, 1.36)	1.15 (0.93, 1.41)	1.19 (0.97, 1.47)	0.185
Age (years)						
12–14	2770	Reference	1.15 (0.82, 1.62)	1.20 (0.86, 1.68)	1.23 (0.88, 1.68)	0.780
15–17	3171	Reference	1.10 (0.83, 1.47)	1.09 (0.83, 1.42)	1.17 (0.90, 1.53)	0.231
Gender						
Male	2849	Reference	1.05 (0.80, 1.38)	1.10 (0.85, 1.43)	1.05 (0.80, 1.37)	0.347
Female	3092	Reference	1.21 (0.84, 1.73)	1.25 (0.89, 1.77)	1.44 (1.03, 2.02)	0.311
Ethnicity						
Mexican American	1685	Reference	0.83 (0.58, 1.19)	1.08 (0.77, 1.51)	1.17 (0.82, 1.67)	0.878
Other Hispanic	423	Reference	0.95 (0.40, 2.27)	1.62 (0.74, 3.53)	1.06 (0.48, 2.37)	0.614
Non-Hispanic White	1645	Reference	1.29 (0.86, 1.95)	1.20 (0.78, 1.83)	*1.76 (1.20, 2.59)*	0.035
Non-Hispanic Black	1762	Reference	1.40 (0.88, 2.23)	1.20 (0.78, 1.84)	1.00 (0.63, 1.58)	0.918
Other race—including multi-racial	426	Reference	1.14 (0.39, 3.32)	0.55 (0.19, 1.57)	0.69 (0.30, 1.61)	0.248
Wright status						
Normal or underweight	3516	Reference	1.18 (0.89, 1.56)	1.22 (0.93, 1.59)	*1.41 (1.08, 1.85)*	0.020
Overweight	1344	Reference	1.19 (0.74, 1.91)	1.39 (0.88, 2.18)	1.15 (0.73, 1.81)	0.355
Obese	1081	Reference	0.77 (0.46, 1.27)	0.74 (0.45, 1.21)	0.72 (0.44, 1.17)	0.888
PIR						
< 1	1793	Reference	1.08 (0.73, 1.61)	1.36 (0.93, 1.98)	1.30 (0.88, 1.93)	0.074
≥ 1	4147	Reference	1.08 (0.83, 1.40)	1.05 (0.81, 1.34)	1.16 (0.91, 1.48)	0.658
Serum cotinine (ng/mL)						
< LOD (0.011)	1282	Reference	1.08 (0.69, 1.70)	1.24 (0.79, 1.95)	1.24 (0.80, 1.93)	0.214
0.011–10	4183	Reference	1.16 (0.89, 1.52)	1.10 (0.85, 1.41)	1.23 (0.95, 1.58)	0.642
> 10	473	Reference	0.76 (0.35, 1.62)	1.29 (0.65, 2.59)	0.98 (0.46, 2.08)	0.111
NHANES cycles						
1999–2000	210	Reference	0.64 (0.18, 2.28)	0.58 (0.16, 2.04)	0.40 (0.12, 1.32)	0.250
2001–2002	239	Reference	0.19 (0.04, 0.86)	0.33 (0.10, 1.10)	0.70 (0.25, 1.93)	0.215
2003–2004	1428	Reference	1.26 (0.78, 2.03)	1.25 (0.79, 1.98)	1.30 (0.82, 2.06)	0.673
2005–2006	1358	Reference	1.08 (0.68, 1.73)	1.19 (0.80, 1.78)	1.17 (0.77, 1.78)	0.930
2007–2008	737	Reference	1.35 (0.77, 2.37)	0.86 (0.49, 1.51)	1.02 (0.58, 1.82)	0.819
2009–2010	809	Reference	1.42(0.78, 2.58)	1.09 (0.61, 1.95)	1.29 (0.75, 2.23)	0.765
2011–2012	748	Reference	0.95 (0.47, 1.91)	1.91 (0.95, 3.84)	1.81 (0.86, 3.80)	0.193
2013–2014	411	Reference	0.96 (0.47, 1.95)	1.64 (0.76, 3.56)	1.06 (0.46, 2.42)	0.528

The model was adjusted for gender, age, ethnicity, PIR, serum cotinine, BMI, and NHANES cycles. *PIR* poverty income ratio. Mercury (μg/L): quartile 1 < 0.23, quartile 2 0.23–0.47, quartile 3 0.47–0.82, quartile 4 > 0.82. Italic values indicate statistical significance ($p < 0.05$)

inversely correlated with BMI for adults in the adjusted model, and this trend was also observed in children with limited power that may be due to the small sample size. The mechanistic basis for this inverse association remains unclear. Hg has been reported to be detected in human and rat adipose tissue (Levine et al. 2000; Qin et al. 2010). One reasonable elucidation is that adipose tissue is likely to be a potential reservoir for lipophobic MeHg. The Hg-rich adipocytes leads to low Hg levels in the blood. However, no differences in blood Hg levels were found in different weight statuses in the present study. Thus, additional studies are necessary to identify the underlying reasons that may explain our findings.

Many natural and anthropogenic activities can emit Hg to our environment. Hg pollution is a man-made problem because the proportion of Hg that is emitted by human activities has nearly doubled within the last 100 years(Schuster et al. 2002). Hg is difficult to degrade and can be deposited into aqueous environments as MeHg, the most predominant form of organic Hg. MeHg is more prone to biomagnification in aquatic food chains. Thus, the consumption of contaminated

fish and shellfish is widely considered an important pathway for human exposure to Hg. Numerous studies have indicated that the frequency of Hg-polluted fish consumption was a significant risk factor for prenatal and childhood Hg exposure (Ruggieri et al. 2017). In addition, living in areas away from coal-fired power plants, waste incineration factories, and heavy metal mines and correctly using Hg-containing products (thermometers, sphygmomanometers, fluorescent lamps, batteries, switches) can efficiently reduce Hg exposure. In general, the government should strengthen people's knowledge and awareness of Hg exposure and provide more evidence to support preventive measures for reducing childhood blood Hg levels.

This study has several strengths. First, to our knowledge, this was the first study to identify a positive association between high blood Hg and high ALT levels that was significant and showed the strongest association amongst non-Hispanic white and normal or underweight US adolescents. Second, a large, national sample was included in the analysis of the association to avoid potential bias. Some covariates that may have influenced outcomes were included in our statistical models to offer more accurate and consistent results. Nonetheless, there are several limitations to the present study. First, a criterion standard diagnosis of NAFLD requires a liver biopsy. Due to the liver biopsy was not feasible for the national sample, ALT has been commonly used as a surrogate marker and a screening tool for NAFLD. However, the estimated sensitivity and specificity of ALT for identifying NAFLD remains low compared to liver biopsies(Alkhouri and Feldstein 2016). Second, in light of the cross-sectional nature of our study, we cannot infer any cause-effect relationships between blood Hg and NAFLD. Liver function may affected the blood Hg concentration. Third, although we adjusted for potential confounders in our analysis, some confounders such as physical activity and genetic susceptibility were not recorded and adjusted in this study. Fourth, although we excluded participants with chronic hepatitis, it is possible that we may have included participants who had mild liver dysfunction caused by factors other than mercury exposure. Thus, further prospective studies are warranted to confirm our findings and investigate the underlying causative mechanisms.

Author contribution Runsen Chen and Yang Xu wrote the main manuscript text, Yaqin Shu and Siyu Ma prepared Tables 1, 2, and 3, and Changgui Lu prepared Fig. 1. Cheng Xu and Xuming Mo were responsible for the accuracy of all content in the proof. All authors reviewed the manuscript.

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Availability of data and materials The datasets used and/or analysed during the current study are available from https://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm

Compliance with ethical standards

Ethics approval and consent to participate The consent form was signed by participants in the survey, and participants consented to storing specimens of their blood for future research. The CDC/NCHS Ethics Review Board (ERB) approved the NHANES study and gave approval for public dissemination.

Consent for publication Non applicable. There is no individual level data in our publication.

References

Alkhouri N, Feldstein AE (2016) Noninvasive diagnosis of nonalcoholic fatty liver disease: Are we there yet? Metabolism 65:1087–1095

Andreoli V, Sprovieri F (2017) Genetic Aspects of Susceptibility to Mercury Toxicity: An Overview. Int J Environ Res Public Health 14

Basu N, Goodrich JM, Head J (2014) Ecogenetics of mercury: from genetic polymorphisms and epigenetics to risk assessment and decision-making. Environ Toxicol Chem 33:1248–1258

Cave M, Appana S, Patel M, Falkner KC, McClain CJ, Brock G (2010) Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004. Environ Health Perspect 118:1735–1742

Centers for Disease Control and Prevention (2006) National Center for Health Statistics. National Health and Nutrition Examination Survey. Available at: https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/PBCD_D.htm

Choi J, Bae S, Lim H, Lim JA, Lee YH, Ha M, Kwon HJ (2017) Mercury exposure in association with decrease of liver function in adults: a longitudinal study. J Prev Med Public Health 50:377–385

Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1243

Fernandes Azevedo B, Barros Furieri L, Pecanha FM, Wiggers GA, Frizera Vassallo P, Ronacher Simoes M, Fiorim J, Rossi de Batista P, Fioresi M, Rossoni L, Stefanon I, Alonso MJ, Salaices M, Valentim Vassallo D (2012) Toxic effects of mercury on the cardiovascular and central nervous systems. J Biomed Biotechnol 2012: 949048

Fourth National Report on Human Exposure to Environmental Chemicals UT (2015) Centers for Disease Control and Prevention, Department of Health and Human Services: Atlanta, GA, USA, 2015. Available online: (2015): https://www.cdc.gov/biomonitoring/pdf/fourthreport_updatedtables_feb2015.pdf. Accessed 16 Apr 2018

Futatsuka M, Kitano T, Nagano M, Inaoka T, Arimatsu Y, Ueno T, Wakamiya J, Miyamoto K (1992) An epidemiological study with risk analysis of liver diseases in the general population living in a methyl mercury polluted area. J Epidemiol Community Health 46: 237–240

Gardner RM, Nyland JF, Silbergeld EK (2010) Differential immunotoxic effects of inorganic and organic mercury species in vitro. Toxicol Lett 198:182–190

Le MH, Devaki P, Ha NB, Jun DW, Te HS, Cheung RC, Nguyen MH (2017) Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PLoS One 12:e0173499

Lee H, Kim Y, Sim CS, Ham JO, Kim NS, Lee BK (2014a) Associations between blood mercury levels and subclinical changes in liver

enzymes among South Korean general adults: analysis of 2008-2012 Korean national health and nutrition examination survey data. Environ Res 130:14–19

Lee J, Lee SJ, Lim KT (2014b) Preventive effects of ZPDC glycoprotein (24 kDa) on hepatotoxicity induced by mercury chloride in vitro and in vivo. Cell Biochem Funct 32:520–529

Lee MR, Lim YH, Lee BE, Hong YC (2017) Blood mercury concentrations are associated with decline in liver function in an elderly population: a panel study. Environ Health 16:17

Levine KE, Fernando RA, Lang M, Essader A, Handy RW, Collins BJ (2000) Development of a method for the determination of ultra-trace level mercury in adipose tissue by cold vapour atomic fluorescence spectrometry. J Autom Methods Manag Chem 22:103–108

Llop S, Ballester F, Broberg K (2015) Effect of gene-mercury interactions on mercury toxicokinetics and neurotoxicity. Curr Environ Health Rep 2:179–194

Lye E, Legrand M, Clarke J, Probert A (2013) Blood total mercury concentrations in the Canadian population: Canadian Health Measures Survey cycle 1, 2007-2009. Can J Public Health 104:e246–e251

Minoia C, Ronchi A, Pigatto P, Guzzi G (2009) Effects of mercury on the endocrine system. Crit Rev Toxicol 39:538 author reply 539

Poursafa P, Ataee E, Motlagh ME, Ardalan G, Tajadini MH, Yazdi M, Kelishadi R (2014) Association of serum lead and mercury level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study. Environ Sci Pollut Res Int 21:13496–13502

Qin YY, Leung CKM, Leung AOW, Wu SC, Zheng JS, Wong MH (2010) Persistent organic pollutants and heavy metals in adipose tissues of patients with uterine leiomyomas and the association of these pollutants with seafood diet, BMI, and age. Environ Sci Pollut Res 17:229–240

Rothenberg SE, Korrick SA, Fayad R (2015) The influence of obesity on blood mercury levels for U.S. non-pregnant adults and children: NHANES 2007-2010. Environ Res 138:173–180

Ruggieri F, Majorani C, Domanico F, Alimonti A (2017) Mercury in Children: Current State on Exposure through Human Biomonitoring Studies. Int J Environ Res Public Health 14

Ruhl CE, Everhart JE (2015) Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 41:65–76

Sattar N, Forrest E, Preiss D (2014) Non-alcoholic fatty liver disease. BMJ 349:g4596

Schuster PF, Krabbenhoft DP, Naftz DL, Cecil LD, Olson ML, Dewild JF, Susong DD, Green JR, Abbott ML (2002) Atmospheric mercury deposition during the last 270 years: a glacial ice core record of natural and anthropogenic sources. Environ Sci Technol 36:2303–2310

Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, Sirlin CB (2010) SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology 138:1357–1364 1364 e1-2

Temple JL, Cordero P, Li J, Nguyen V, Oben JA (2016) A guide to non-alcoholic fatty liver disease in childhood and adolescence. Int J Mol Sci 17

Verma S, Jensen D, Hart J, Mohanty SR (2013) Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). Liver Int 33:1398–1405

Wadaan MAM (2009) Effects of mercury exposure on blood chemistry and liver histopathology of male rats. J Pharmacol Toxicol 4:126–131

Wong EW, Cheng CY (2011) Impacts of environmental toxicants on male reproductive dysfunction. Trends Pharmacol Sci 32:290–299

Zhai H, Chen C, Wang N, Chen Y, Nie X, Han B, Li Q, Xia F, Lu Y (2017) Blood lead level is associated with non-alcoholic fatty liver disease in the Yangtze River Delta region of China in the context of rapid urbanization. Environ Health 16:93

Zhang Y, Xu C, Fu Z, Shu Y, Zhang J, Lu C, Mo X (2018) Associations between total mercury and methyl mercury exposure and cardiovascular risk factors in US adolescents. Environ Sci Pollut Res Int 25:6265–6272