



# Differential fat accumulation in early adulthood according to adolescent-BMI and heavy metal exposure

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## Abstract

**Introduction:** Heavy metals such as Lead (Pb) and Mercury (Hg) can affect adipose tissue mass and function. Considering the high prevalence of exposure to heavy metals and obesity in Mexico, we aim to examine if exposure to Pb and Hg in adolescence can modify how fat is accumulated in early adulthood.

**Methods:** This study included 100 participants from the ELEMENT cohort in Mexico. Adolescent Pb and Hg blood levels were determined at 14–16 years. Age- and sex-specific adolescent BMI Z-scores were calculated. At early adulthood (21–22 years), fat accumulation measurements were performed

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(abdominal, subcutaneous, visceral, hepatic, and pancreatic fat). Linear regression models with an interaction between adolescent BMI Z-score and Pb or Hg levels were run for each adulthood fat accumulation outcome with normal BMI as reference.

Results: In adolescents with obesity compared to normal BMI, as Pb exposure increased, subcutaneous (p-interaction = 0.088) and visceral (p-interaction < 0.0001) fat accumulation increases. Meanwhile, Hg was associated with subcutaneous (p-interaction = 0.027) and abdominal (p-interaction = 0.022) fat deposition among adolescents with obesity.

Conclusions: Heavy metal exposure in adolescence may alter how fat is accumulated in later periods of life.

#### KEYWORDS

fat distribution, heavy metals, lead, mercury, obesogens

## INTRODUCTION

Heavy metals such as lead (Pb) and Mercury (Hg) are elements with a relatively high atomic weight and density compared to water (Tchounwou et al., 2012). These metals are considered priority metals of public health significance because of their degree of toxicity (Balali-Mood et al., 2021). Heavy metals are cataloged as systemic toxicants since they induce multiple organ damage, even at lower levels of exposure, through their ability to accumulate in vital organs (Tchounwou et al., 2012). Also, they are widely dispersed in the environment, through soil, water, air, dust, human food, and manufacturing products, so people could be exposed to a myriad of metals throughout their lifetime (Heindel & Blumberg, 2019). The effects of heavy metals on children's health have been extensively studied (Al Osman et al., 2019; Trentacosta & Mulligan, 2020). Among the most recognized damages, Pb exposure has been associated with neurological effects such decreased neurological function, behavioral disturbance, and alterations in neuromotor and neurosensory function in children. Recently, Pb exposure has been associated with shorter sleep duration in adolescents (Jansen et al., 2019) and with hepatic steatosis and hepatocellular damage in young Mexicans (L et al., 2021). Similar to Pb, Hg exposure has also been associated with neurodevelopmental effects (Bose-O'reilly et al., 2010).

In Mexico, the prevalence of children with higher blood lead levels ( $\geq 5 \mu\text{g}/\text{dl}$ ) is 21.8% (Télez-Rojo et al., 2019), far surpassing those reported in other countries, such United States where the prevalence of intoxication in 2012 was 2.5% (Tsoi et al., 2016). Until now the principal non-occupational source of exposure to Pb in the general Mexican population is cooking or storing foods in lead-glazed ceramics (Télez-Rojo et al., 2019). On the other hand, although Hg is a global contaminant of concern (World Health Organization (WHO) 2006), though little is known about exposures in the Mexican population. Though it is unclear the burden of disease imposed by Hg in Mexico, a study in Mexico City reported widespread exposures in children with a mean of blood Hg level of  $1.8 \pm 1.7 \mu\text{g}/\text{L}$ , with seafood considered the principal source of exposure (Basu et al., 2014).

Additionally to these effects, recently Pb and Hg have been considered obesogens since they have adipotropic effects in the adipose tissue (Tinkov et al., 2021). In vivo and in vitro studies demonstrated that heavy metals can affect adipose tissue mass and function through modulation of adipogenesis via peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and CCAAT/enhancer-binding protein (C/EBP) expression (Egusquiza & Blumberg, 2020). However, the effects of heavy metals on adipogenesis are biphasic and dose-dependent, varying from an increased adipogenesis at lower-dose exposure (C et al., 2016; CN et al., 2018; Park et al., 2017; Lee, 2018; X et al., 2018) to the inhibition of adipose tissue differentiation at higher doses, observed as an "anti-obesogenic" effect (Rizzetti et al., 2019). This anti-obesogenic effect has been demonstrated especially for Hg via the reduction of adipocyte size (Rizzetti et al., 2019; Kawakami et al., 2012), adipokine secretion, and the activation of apoptosis through induction of oxidative stress (Chauhan et al., 2019) and regulation of adipogenesis-related genes (L et al., 2017).

Aforementioned observations are important because there is evidence that early stages of life such as fetal life, infancy, childhood and adolescence are critical windows of time where environmental exposures can have a long-term phenotypic effect (Rauschert et al., 2017; Wells, 2006). Therefore, the weight gain in these stages could be an important predictive of later obesity risk (Simmonds et al., 2016). Additionally, adolescence is one of the life periods where fat deposition peaks (Wells, 2006), a time of rapid growth where significant changes in the amount and distribution of adipose tissue occur (Mihalopoulos et al., 2010). It has been demonstrated that adolescents with obesity are 5 times more likely to become obese adults compared to adolescents without obesity (Simmonds et al., 2016).

Multiple environmental factors can affect obesity susceptibility and body fat accumulation (Goossens, 2017). Obesity is currently one of the leading public health problems since it is a major contributor to the global burden of chronic diseases including cardiovascular disease, non-alcoholic fatty liver disease, type 2 diabetes mellitus, and certain types of cancer (Ng et al., 2014). In Mexico, all age groups are affected by obesity, with the prevalence in children and adolescents being one of the highest worldwide (17.5% and 14.6%, respectively) (Shamah-Levy et al., 2018). In addition, body fat distribution is a strong metabolic and cardiovascular risk factor (Goossens, 2017). Not all forms of fat distribution possess the same health risks and may have different physiological influences and pathological implications. Particularly, studies have shown that visceral fat mass is associated with cardiometabolic risk, compared with other fat depots (Frank et al., 2019). On the other hand, subcutaneous fat deposition has been associated with insulin resistance (Stefan, 2020), and abdominal fat has been linked with changes in lipid profile, increased blood pressure and hyperinsulinemia (Spolidoro et al., 2013). According to the last National Health and Nutrition Survey in Mexico (ENSANUT, 2018), the prevalence of adults with obesity is 36.1% and the prevalence of abdominal obesity was 81.6% in all adults (Barquera & Rivera, 2020). Hepatic and pancreatic fat are associated with the development of hepatic and pancreatic steatosis, respectively. These fat stores increase the risk of cirrhosis and hepatocellular carcinoma (Chalasanani et al., 2018; Fan & Farrell, 2009); chronic pancreatitis, pancreatic cancer and insulin resistance (N et al., 2019; Singh et al., 2017).

Considering the high prevalence of exposure to heavy metals and obesity in Mexico, it will be important to understand the effects of this environmental exposure during the adolescent developmental period on adipose tissue mass (Holtrup et al., 2017). In addition, we aim to explore how these exposures could interact with the BMI status on the distribution of fat accumulation in a future stage of life. Therefore, the objective of the present study was to examine if exposure to heavy metals (Pb and Hg) has a modification effect on the association of adolescent BMI status and fat accumulation during early adulthood.

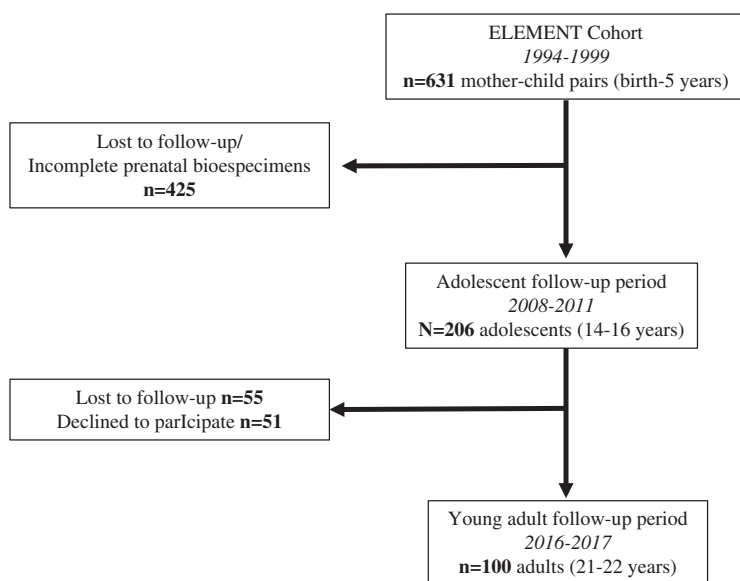


FIGURE 1 Flowchart of the study population

## METHODS

### Study population

The present analysis includes a subsample from the first cohort of the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) (González-Cossío et al., 1997). The cohort began in 1994 with the recruitment of 631 mother-child pairs from three maternity hospitals in Mexico City, Mexico. Details of the cohort are described elsewhere (Perng et al., 2019). Then, during 2008 and 2011, a second follow-up of the cohort was implemented when the participants were between 14 and 16 years of age ( $n = 206$ ). Finally, during 2016 and 2017, when subjects were between 21 and 22 years of age, they were invited to participate in a third follow-up of 100 subjects (Figure 1). Comparison of the original cohort and the analytical sample has been described elsewhere (Cantoral et al., 2019); no significant differences were found except for the duration of maternal education (Table S1). The analysis of the present study was restricted to 92 participants who had available data of blood Pb levels and 79 participants who had available data on blood Hg levels during adolescence (2008-2011), and measurements of fat accumulation at early adulthood (waist circumference, visceral and subcutaneous fat, hepatic and pancreatic fat fraction).

The Ethics, Biosafety, and Research Committees of the National Institute of Public Health, Mexico approved the study (approval number 1377). Participants provided written informed consent at each wave of the study. No incentives were given for the participation of the subjects, except that the result of the Magnetic Resonance Image (MRI) were delivered to the participants.

### Outcomes: Fat accumulation assessment in early adulthood

At the early adulthood follow-up, measurements of different fat accumulation were performed:

**Abdominal fat:** Abdominal fat was determined by waist circumference (WC) measured twice to the nearest 0.1 cm with a SECA (model 201, Hamburg, Germany) measuring tape within the facilities of the research center. Elevated WC (abdominal obesity) was defined using the International Diabetes Federation (IDF) criteria for adults (men  $\geq 94$  cm, women  $\geq 80$  cm (International Diabetes Federation, 2006).

In order to estimate subcutaneous, visceral, hepatic and pancreatic fat, Magnetic Resonance Imaging (MRI) was carried out using a Philips Achieva 3.0 T MR-scanner (Achieva 3.0, Philips Healthcare, Best, The Netherlands). A certified radiologist and biomedical engineer who were "blinded" to each participant's BMI status and metal exposure implemented the MRI. A detailed description of imaging and post-processing procedures have been published elsewhere (Kinner et al., 2016; Nasr et al., 2017; Yokoo et al., 2011).

**Subcutaneous and visceral fat:** Subcutaneous adipose tissue area (SAA) and Visceral adipose tissue area (VAA) were quantified using abdominal MRI images with T1 and T2 sequences in the axial plane acquired. VAA was measured at the level of the L2-L3, L3-L4 vertebral superior endplate at the umbilicus level, with three slices obtained superior, and one slice inferior at 40 mm intervals (16 cm window); VAA was distinguished from SAA based on the abdominal wall muscle layer. Visceral and subcutaneous fat areas ( $\text{cm}^2$ ) were measured separately, and images were analyzed using the Analyze v14.0 software (AnalyzeDirect Inc., Kansas, USA). Measurements of volumes from these regions have been recently reported (OY et al., 2020).

**Hepatic fat:** Hepatic fat was determined by the quantification of fatty liver (% of hepatic triglyceride content) by MRI, a validated methodology considered the most accurate non-invasive method for measuring (Roldan-Valadez et al., 2010). In order to estimate hepatic triglyceride content, we estimated proton density fat fraction (PDFF). We defined the presence of steatosis using the American Association for the Study of Liver Diseases (AASLD) cut-off point of 5% (hepatic triglyceride level of 55.6 mg/g) corresponding to the 95th percentile of the distribution of liver fat in healthy subjects (Chalasanani et al., 2018).

**Pancreatic fat:** Pancreatic fat was determined by the estimation of pancreatic triglyceride content by MRI scanner, a validated methodology considered the most accurate non-invasive method for measuring (Roldan-Valadez et al., 2010). We estimated proton density fat fraction (PDFF) and we defined the presence of pancreatic steatosis using cut-off point of 6.2% pancreatic fat (Singh et al., 2017).

## Exposure: Adolescence-BMI Z-Score

At the adolescent period (14–16 years of age), trained personnel performed the anthropometric measurements in duplicate. Weight and height were measured using a Tanita digital scale (Tanita Co. Tokyo, Japan) with a height rod (model WB-3000 m). Weight and height were recorded to the nearest 0.1 kg and 0.5 cm, respectively. The observed values were averaged. BMI was calculated as weight in kg divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). To provide comparable indices with other international studies of weight status, age- and sex-specific BMI Z-scores were calculated using the 2007 World Health Organization (WHO) reference growth standard; BMI status was defined as underweight ( $< -2\text{SD}$ ), normal ( $-2\text{SD}$  to  $+1\text{SD}$ ), overweight ( $> +1\text{SD}$  to  $< +2\text{SD}$ ) and obesity ( $> +2\text{SD}$ ) (M de O et al., 2007).

## Effect modification variable: Adolescence heavy metal exposure

Adolescent whole blood samples were collected (at 14–16 years of age) into vials certified for trace metals analysis and stored at  $4^\circ\text{C}$  until analysis, using standardized protocols and

after at least 8 h of fasting. Pb were quantified using graphic-furnace atomic-absorption spectroscopy (model 3000; PerkinElmer, Chelmsford, Massachusetts, USA) at the research facilities of the American British Cowdray Hospital in Mexico City. All blood Pb samples were above the limit of detection and the precision of this instrument was within  $\pm 1 \mu\text{g}/\text{dl}$  (Afeiche et al., 2011). Analytical measurement of total blood Hg content was carried out using a Direct Mercury Analyzer 80 (DMA-80, Milestone Inc., CT) as previously described (Paruchuri et al., 2010). The analytical detection limit was less than  $1 \mu\text{g}/\text{L}$  per measure. Quality control measures included daily instrument calibration, procedural blanks, replicates, and several certified reference materials.

Other variables used in the analyses were collected from the cohort's historical records such as child's sex and mother's education. Socioeconomic status (SES) was reported by the mothers at the recruitment through a validated questionnaire consisting of thirteen questions (AMAI).

## Statistical analysis

First, bivariate correlations were used to test relationships among the interest variables. We conducted a descriptive analysis of the main characteristics of the study sample. The categorical variables are expressed as frequencies and proportions, and the continuous variables are presented as means or medians, according to their distribution. We estimated statistical differences between the general characteristics of the subjects by Adolescence-BMI Z-score status using Chi-square or Fisher's exact tests for the categorical variables; and ANOVA or Kruskal Wallis test for the continuous variables depending on their distribution. As Pb and Hg had a skewed distribution to the right, both were log-transformed.

The different fat accumulation at early adulthood by adolescent BMI Z-score statuses was assessed running a linear model to estimate the p-trend from the different BMI status. Additionally, we generated linear regression models with an interaction between BMI Z-score status (underweight, normal, overweight and obesity) and Pb or Hg levels (log Pb and log Hg levels) for each adulthood outcome (abdominal, subcutaneous, visceral, hepatic and pancreatic fat). Normal BMI status was considered as reference. Assumptions were tested after running the models (data not shown).

We considered a significance level  $p < 0.05$  for the tests and regressions and  $p < 0.1$  for the interaction term. All the analyses were performed in STATA 15 statistical software (StatCorp LLC, College Station, TX, USA).

## RESULTS

General characteristics of the participants are described in Table 1. Of the total sample, 54% were male; the mean age at adolescence was 14 years old. The majority were low Socio Economic Status (SES) (52%), and 42% had mothers with a high school education level. The median of Pb levels was  $3.1 \mu\text{g}/\text{dl}$  and  $1.3 \mu\text{g}/\text{L}$  for Hg blood levels. The percentage of adolescents with higher blood Pb levels ( $\geq 5 \mu\text{g}/\text{dl}$  established as the current Mexican reference level in children) (Secretaría de Salud, 2000) was 13%. In addition, the percentage of adolescents with higher blood Hg levels ( $\geq 2 \mu\text{g}/\text{L}$ ) (Ye et al., 2016) was 21%. Among 100 adolescents, 6% had underweight, 46% normal weight, 37% overweight, and 11% obesity according to the BMI Z-score cut points; male adolescents had higher overweight and obesity percentages. Measurements of blood Pb and Hg levels were not statistically significantly correlated. No correlations were found between BMI Z-score and heavy metals lev-

**TABLE 1** Characteristics of participants by age- and sex-specific adolescent BMI Z-score status during adolescence ( $n = 100$ )

	Adolescent BMI Z-score <sup>a</sup>					<i>p</i> -value
	Overall ( $n = 100$ )	Underweight ( $n = 6$ )	Normal ( $n = 46$ )	Overweight ( $n = 37$ )	Obesity ( $n = 11$ )	
Age (years), mean (SD)	13.7 (0.6)	13.7 (0.5)	13.7 (0.6)	13.6 (0.6)	13.5 (0.5)	0.8787
Sex, <i>n</i> (%)						0.3000
Male	54 (54.0)	5 (83.3)	21 (46.7)	21 (56.7)	7 (63.3)	
Female	46 (46.0)	1 (16.7)	25 (54.3)	16 (43.2)	4 (36.4)	
Maternal education, <i>n</i> (%)						0.1350
< 8 years (secondary or primary)	24 (24.0)	1 (16.7)	16 (34.8)	7 (18.9)	1 (9.1)	
9–11 years (some high school)	42 (42.0)	1 (16.7)	22 (47.8)	14 (37.8)	5 (45.5)	
12 years (completed high school)	25 (25.0)	4 (66.6)	6 (13.0)	11 (29.7)	4 (36.4)	
> 12 years (more than high school)	9 (9.0)	0 (0)	3 (4.4)	5 (13.5)	1 (9.1)	
Socioeconomic status						0.5760
Low	52 (52.0)	2 (33.3)	22 (47.8)	21 (56.7)	7 (63.6)	
Medium	48 (48.0)	4 (66.6)	24 (51.2)	16 (43.3)	4 (36.4)	
Pb blood levels, median (IQR)	3.1 (2.2–4.5)	3.3 (2.6–5.1)	3.0 (2.0–4.8)	3.2 (2.3–3.9)	4.2 (2.3–4.9)	0.6199
% $\geq 5 \mu\text{g}/\text{dl}$ ( $n = 92$ , %)	13 (14.4)	1 (16.6)	7 (15.0)	4 (10.9)	1 (9.0)	0.6250
Hg blood levels, median (IQR)	1.3 (0.9–2.1)	1.2 (1.1–1.3)	1.3 (0.9–1.9)	1.4 (0.9–2.2)	1.3 (1.0–2.3)	0.9824
% $\geq 2 \mu\text{g}/\text{L}$ ( $n = 79$ , %)	21 (26.7)	1 (16.6)	10 (21.7)	7 (18.9)	3 (27.3)	0.9490

Note: Statistical significance was assessed using ANOVA or Kruskal Wallis tests for continuous variables and Chi2 or Fisher's Exact tests for the categorical variables according to their distribution.

Abbreviations; BMI; Body Mass Index; Hg; Interquartile Range.; IQR; lead; Mercury; Pb; SD; Standard Deviation.

<sup>a</sup>Age- and sex-specific BMI Z-scores were calculated using the 2007 World Health Organization (WHO) reference growth standard; BMI status was defined as underweight ( $-2\text{SD}$ ), normal ( $-2\text{SD}$  to  $+1\text{SD}$ ), overweight ( $> +1\text{SD}$  to  $< +2\text{SD}$ ) and obesity ( $> +2\text{SD}$ ).

els; in addition none of the fat deposition variables were correlated with Pb and Hg levels (Table 2).

Table 3 presents the mean values of variables measured for fat accumulation at early adulthood by adolescent BMI Z-score status. As expected, all means increased as BMI status changed from underweight/normal/overweight/obesity ( $p$ -trend =  $< 0.05$ ). When we introduced the interaction term (BMI status  $\times$  log Pb or log Hg) into the model, we observed that adolescent BMI status modifies the association between adolescent heavy metal exposure and fat accumulation in early adulthood. In those who had obesity during adolescence, there was a different pattern of subcutaneous ( $p$ -interaction = 0.088) and visceral ( $p$ -interaction =  $< 0.0001$ ) fat accumulation, such that as Pb increased there was higher fat accumulation, whereas there was a null association in the normal BMI category (Table S2 and Figure 2). Similarly, in the case of Hg, the accumulation pattern of abdominal ( $p$ -interaction = 0.022) and subcutaneous ( $p$ -interaction = 0.027) fat was different in those with obesity during adolescence, compared to the normal BMI category (Table S3). Additionally, we observed (Figure 3) that in those who presented overweight during adoles-

TABLE 2 Bivariate correlation matrix

	1	2	3	4	5	6	7	8
1 Lead	1.0000							
2 Mercury	-0.0418	1.0000						
3 BMI Z-score	0.0418	0.0088	1.0000					
4 Abdominal fat	0.0508	-0.0513	0.6094*	1.0000				
5 Subcutaneous fat	0.0402	-0.0793	0.5148*	0.8554*	1.0000			
6 Visceral fat	-0.0005	-0.1560	0.3683*	0.7002*	0.6633*	1.0000		
7 Hepatic fat	0.0995	-0.0618	0.2865*	0.5252*	0.4604*	0.5112*	1.0000	
8 Pancreatic fat	-0.1633	-0.0143	0.1922	0.3180*	0.2849*	0.3076*	0.5443*	1.0000

Note; Spearman's rho.

\* $p < 0.05$ .

TABLE 3 Descriptive statistics Mean (SD) and Median (IQR) of fat accumulation in early adulthood by adolescent BMI Z-score status ( $n = 100$ )

	Fat accumulation at early adulthood				
	Abdominal (cm) mean (SD)	Subcutaneous (cc) median (IQR)	Visceral (cc) median (IQR)	Hepatic (%) median (IQR)	Pancreatic (%) median (IQR)
Overall	88.5 (12.1)	228 (176–317)	47.1 (32–66.4)	1.4 (0.7–3.7)	3.1 (1.7–5.8)
<i>Adolescent BMI Z-score</i>					
Underweight	76.2 (12.5)	111 (45–224)	35.4 (12.2–50.0)	0.9 (0.7–3.6)	1.8 (1.6–8.0)
Normal	82.7 (7.7)	189 (154–252)	39.4 (27.7–53.8)	1.2 (0.6–1.7)	2.8 (1.7–4.7)
Overweight	93.3 (8.9)	258 (214–329)	52.5(44.0–76.0)	1.9 (0.8–3.7)	5.6 (1.9–13.8)
Obesity	103.4 (15.9)	381.5 (195–539)	64.5 (34.3–90.7)	5.6 (1.9–13.8)	5.3 (2.6–9.6)
<i>p-trend<sup>a</sup></i>	0.000	0.000	0.015	0.005	0.052

Abbreviations: BMI; Body Mass Index; Hg; Interquartile Range.; IQR; lead; Mercury; Pb; SD; Standard Deviation.

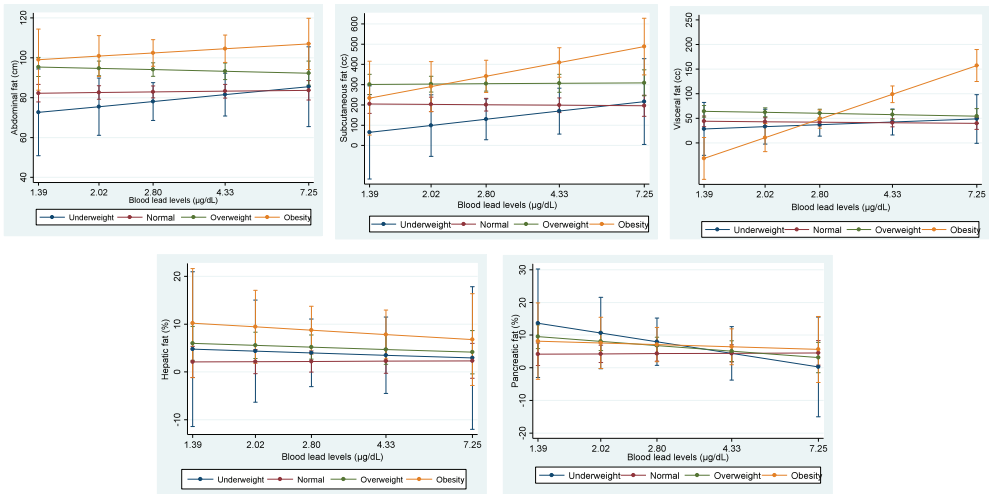
<sup>a</sup>Statistical significance was assessed using linear regression models.

cence; there was an opposite pattern for all types of fat accumulation (this can be mainly observed in visceral, hepatic and pancreatic fat), such that as blood Hg levels increased, there was a lower fat accumulation. However, although these results are consistent, they are not statistically significant. Figure 2 and Figure 3 show the different early adulthood patterns of fat accumulation (abdominal, subcutaneous, visceral, hepatic and pancreatic fat) by adolescent BMI as Pb or Hg levels increased.

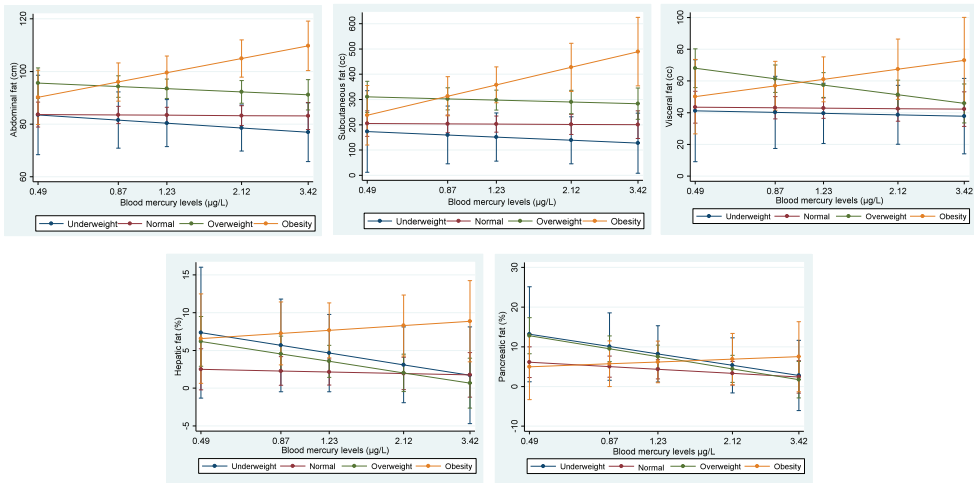
## DISCUSSION

We documented in this study population, which was nested in a cohort study, that heavy metal exposure in adolescence is associated with the way in which fat is accumulated within the body in later periods of life (early adulthood). Specifically, we observed that in adolescents with obesity, as Pb (p-interaction = 0.088) or Hg (p-interaction = 0.027) exposure increase, subcutaneous fat deposition increases, whereas there is no association in those with normal BMI. In the case of Pb, visceral fat (p-interaction = 0.000) also increases for those with obesity in adolescence; meanwhile, the relationship with Hg is also observed in the abdominal fat (p-interaction = 0.022). We did not observe any interaction effect in the hepatic or pancreatic fat accumulation. Considering the high prevalence of exposure





**FIGURE 2** Early adulthood fat accumulation by adolescent BMI category and blood lead levels. The  $\beta$  estimates, 95% CIs and  $p$ -values were determined using linear regression models of blood lead levels (log transformed) in adolescence and fat accumulation in early adulthood with the effect modification of adolescent BMI status. Normal BMI z-score status was the reference.  $p$ -value < 0.1 for interaction were found with subcutaneous and visceral fat. Blood lead levels were run as logarithmic values, in the graphic the values are presented as their normal measurement value ( $\mu\text{g/L}$ )



**FIGURE 3** Early adulthood fat accumulation by adolescent BMI category and blood mercury levels. The  $\beta$  estimates, 95% CIs and  $p$ -values were determined using linear regression models of blood mercury levels (log transformed) in adolescence and fat accumulation in early adulthood with the effect modification of adolescent BMI status. Normal BMI z-score status was the reference.  $p$ -value < 0.1 for interaction were found with abdominal and subcutaneous fat. Blood mercury levels were run as logarithmic values, in the graphic the values are presented as their normal measurement value ( $\mu\text{g/L}$ )

to heavy metals and obesity in Mexico (Holtrup et al., 2017; Wells, 2006), these results highlight that heavy metal exposures may increase, and modify the way that fat is accumulated within the body. In particular, the effects were more striking for visceral fat which is associated with increased cardiometabolic risk, compared with other fat depots (Frank et al., 2019).

The median Pb levels in our study were 3.1  $\mu\text{g}/\text{dl}$  (IQR 2.2–4.5), higher than the current U.S. average of 1.2  $\mu\text{g}/\text{dl}$ . Our results suggest that the Pb exposure differentially affects subcutaneous and visceral fat in obese adolescents. These results are consistent with previous epidemiological studies. A cross sectional study in 5558 adults reports a positive association between Pb blood levels with BMI and obesity in women (Wang et al., 2015). In another birth cohort study in 442 mother-child pairs of US urban population, findings suggest that maternal elevated Pb exposure was associated with increased risk of intergenerational child body mass index (Wang et al., 2019). However, in another birth cohort study with 299 young children, Pb blood levels were associated with smaller BMI at ages 2–3 years (Cassidy-Bushrow et al., 2016). It is important to highlight to the best of our knowledge, no previous study has investigated the associations of Pb exposure with subcutaneous and visceral obesity.

On the other hand, the median Hg levels in this sample was 1.3  $\mu\text{g}/\text{L}$  (IQR 0.9 – 2.1), which is lower than the last adolescents' geometric mean reported in the Korean National Health and Nutrition Examination Survey (KNHANES) of 1.93  $\mu\text{g}/\text{L}$  (Shin et al., 2018), but higher than those reported for US adolescents of 0.73  $\mu\text{g}/\text{L}$  (SD 0.91) (Chen et al., 2019). In the case of Hg, our results suggest that the exposure affects abdominal and subcutaneous fat in obese adolescents. In support, a previous cross-sectional study with elderly Koreans living in coastal areas reported a positive association between blood mercury and waist-to-hip ratio (You et al., 2010). However, in the KNHANES, blood Hg was positively associated with visceral adiposity but negatively associated with body fat percentage (Park et al., 2017; Park & Lee, 2012). According to the WHO data on background Hg levels in the general population are < 5  $\mu\text{g}/\text{L}$  (Basu et al., 2018). However, the recent focus on the health impact of exposure to Hg is more on chronic, low or moderate grade exposure for the danger and effects of low grade Hg exposure (Ye et al., 2016).

To the best of our knowledge, this study is the first to assess if exposure to Pb and Hg in adolescence can modify how fat is accumulated in adulthood. While the underlying mechanisms are still not well understood, there is biological plausibility for heavy metals in obesity pathogenesis. There are a few mechanisms studied by *in vivo* and *in vitro* studies that may underlie the association between Pb exposure and the differential fat accumulation. It is known that Pb effectively accumulates in human adipose tissue (C et al., 2020); *in vivo* and *in vitro* studies have demonstrated that Pb exposure resulted in a significant increase in bone marrow adiposity characterized by increased adipocyte size and number through upregulation of PPAR $\gamma$  gene expression (EE et al., 2016). The effects of mercury exposure on the adiposity have also been demonstrated. *In vitro* studies have shown the impact of Hg exposure in adipokine secretion through the formation of a lower number of adipocytes and clumped lipid droplets as well as activation of apoptosis through induction of oxidative stress and systemic inflammation (Chauhan et al., 2019). In addition, mercury exposure causes disturbances in carbohydrate and lipid metabolism. These effects, caused by mercury exposure, could lead to an increased risk of the development of obesity-related metabolic disorders (Shin et al., 2018; Chen et al., 2006). We hypothesize that the mechanism of interaction observed in this study, which was mainly restricted to obese adolescents, is due to the obesity-induced changes in adipose tissue microenvironment. Adipocyte hypertrophy leads to cell death, which contributes to increased production of proinflammatory cytokines, the development of chronic low-grade inflammation, metabolic dysfunction and oxidative stress (Fuster et al., 2016; Wu et al., 2020). Such physiological changes may render adipocytes more vulnerable to subsequent chemical exposures, such as Pb or Hg.

It is important to mention that we observed a different pattern from what we expected to find in overweight adolescents, such that as Hg exposure increases, all fat type of depo-

sition decrease; however, these results are not statistically significant but are consistent. This pattern does not necessarily imply that Hg protects against fat accumulation among overweight adolescents, though is consistent with what has been described by Tinkov A. et al, [REFERENCE # HERE] as a biphasic adipogenic response to heavy metal exposure. They postulated that with low-level exposures to heavy metals, individuals may up-regulate key adipogenic factors, such as PPAR $\gamma$ , thus promoting excessive adipogenesis and contributing to obesity. With higher exposures to metals, adipogenesis may be inhibited through the down-regulation of C/EBPs and PPAR $\gamma$ , and these may be associated with ultimate toxic effects of the metals because of pro-inflammatory and pro-oxidant activities (Tinkov et al., 2021).

Some limitations of our study mainly related to our limited sample size should be mentioned. First, the modest sample size could have decreased the precision of our associations and limited statistical power. Nevertheless, we were able to detect statistically significant associations that were consistent across the different fat accumulation biomarkers we used and consistent with findings from other studies. Second, we decided to raise  $p$  value for interaction to  $p < 0.1$ , therefore results from this study should be interpreted with caution. Third, we were not able to perform stratified analysis by sex. Considering that this variable is a determinant in the way fat is stored during adolescence (Holtrup et al., 2017; Wells, 2006), we recommend that this work be a starting point to future analyses in larger analytic samples. An important strength of the present study includes that we used multiple biomarkers of fat accumulation. Not all forms of fat distribution possess the same health risks; for example, higher concentrations of visceral relative to subcutaneous adipose tissue are associated with greater metabolic risks (Frank et al., 2019). Childhood and adolescent obesity are strongly correlated with adult obesity; however, our results demonstrate how the increased exposure to heavy metals may increase and can modify the way that fat is accumulated within the body in later periods of life. Additionally, our study sample in Mexico City represents a particularly vulnerable segment of the population not well-represented in the literature.

Many obesogens appear to induce a variety of effects and, therefore, may be acting through multiple mechanisms (Egusquiza & Blumberg, 2020). However, despite the evidence, obesogens exposure (including heavy metals) are not commonly included as an obesity prevention intervention (Perng et al., 2021). Thus, there is an urgent need to understand how these environmental factors may be determinants contributing to obesity and the capacity for fat deposition to best implement effective prevention and therapeutic approaches (Egusquiza & Blumberg, 2020). In any case, early detection of heavy metal exposures in critical stages of life, policy regulations that limit the production and release of heavy metals into the environment, as well as an epidemiological surveillance system may aid in the development of preventive public health obesity strategies.

## CONCLUSION

These findings may be indicative of an important role of heavy metal exposure in alterations of energy homeostasis and excessive adiposity. Quantifying the impact of exposure to metals is crucial for identifying risk factors with environmental origins for obesity and its comorbidities and developing more targeted public health interventions.

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## CONFLICT OF INTEREST

The authors have no conflicts to disclose, and certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## AUTHOR CONTRIBUTIONS

All listed authors have read and contributed to the manuscript substantially and have accepted the final submitted version. Larissa Betanzos-Robledo: analyzed and interpreted of data, drafted the work and writing original draft and edit final work. Martha M. Téllez-Rojo: definition, conceptualization, editing the work and resources. Hector Lamadrid-Figueroa: formal analysis, and visualization. Ernesto Roldan-Valadez: analysis, visualization, and resources. Karen E. Peterson: definition, conceptualization, and editing the work. Erica C. Jansen: investigation, writing original draft, and edit final work. Nil Basu: validation analysis and editing. Alejandra Cantoral: interpreted of data, drafted the work and writing original draft and edit final work.

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## REFERENCES

- Afeiche, M., Peterson, K. E., Sánchez, B. N., Cantonwine, D., Lamadrid-Figueroa, H., Schnaas, L., Ettinger, A. S., Hernández-Avila, M., Hu, H., & Téllez-Rojo, M. M. (2011). Prenatal lead exposure and weight of 0- to 5-year-old children in Mexico city. *Environmental Health Perspectives*, *119*, 1436–1441.
- Al Osman, M., Yang, F., & Massey, I. Y. (2019). Exposure routes and health effects of heavy metals on children. *Biometals*, *32*, 563–573.
- AMAI, Niveles Socioeconómicos AMAI.
- Holtrup, B., Church, C. D., & Berry, R., Colman, R., Jeffery, E., Bober, J., & Rodeheffer, M. S. (2017). Puberty is an important developmental period for the establishment of adipose tissue mass and metabolic homeostasis. *Adipocyte*, *6*, 224–233.
- Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M. R., & Sadeghi, M. (2021). Toxic mechanisms of five heavy metals; mercury, lead, chromium, cadmium, and arsenic. *Frontiers in Pharmacology*, *12*, . Epub ahead of print 13 April <https://doi.org/10.3389/FPHAR.2021.643972>
- Barquera, S., & Rivera, J. A. (2020). Obesity in Mexico; rapid epidemiological transition and food industry interference in health policies. *The Lancet Diabetes & Endocrinology*, *8*, 746.
- Basu, N., Horvat, M., & Evers, D. C. (2018). A state-of-the-science review of mercury biomarkers in human populations worldwide between 2000 and 2018. *Environmental Health Perspectives*, *126*. Epub ahead of print 1 October <https://doi.org/10.1289/EHP3904>
- Basu, N., Tutino, R., Zhang, Z., Cantonwine, D. E., Goodrich, J. M., Somers, E. C., Rodriguez, L., Schnaas, L., Solano, M., Mercado, A., Peterson, K., Sánchez, B. N., Hernández-Avila, M., Hu, H., & Maria Téllez-Rojo, M. (2014). Mercury levels in pregnant women, children, and seafood from Mexico City. *Environmental Research*, *135*, 63.
- Bose-O'reilly, S., Mccarty, K. M., Steckling, N., & Lettmeier, B. (2010). Mercury exposure and children's health. *Current Problems in Pediatric and Adolescent Health Care*, *40*, 186.

- Camsari, C., Folker, J. K., & McGee, D. (2016). Effects of periconception cadmium and mercury co-administration to mice on indices of chronic diseases in male offspring at maturity. *Environmental Health Perspectives*, *125*, 643–650.
- Freire, C., Vrhovnik, P., & Fiket, Ž. (2020). Adipose tissue concentrations of arsenic, nickel, lead, tin, and titanium in adults from GraMo cohort in Southern Spain; An exploratory study. *Science of the Total Environment*, *719*, . Epub ahead of print 1 June. <https://doi.org/10.1016/J.SCITOTENV.2020.137458>
- Cantoral, A., Contreras-Manzano, A., & Luna-Villa, L. (2019). Dietary sources of fructose and its association with fatty liver in mexican young adults. *Nutrients*, *11*, . Epub ahead of print 1 March <https://doi.org/10.3390/nu11030522>
- Cassidy-Bushrow, A. E., Havstad, S., Basu, N., Ownby, D. R., Park, S. K., Ownby, D. R., Johnson, C. C., & Wegienka, G. (2016). Detectable blood lead level and body size in early childhood. *Biological Trace Element Research*, *171*, 41.
- Chalasan, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., Harrison, S. A., Brunt, E. M., & Sanyal, A. J. (2018). The diagnosis and management of nonalcoholic fatty liver disease; practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*, *67*, 328–357.
- Chauhan, S., Dunlap, K., & Duffy, L. K. (2019). Effects of methylmercury and theaflavin digallate on adipokines in mature 3T3-L1 adipocytes. *International Journal of Molecular Sciences*, *20*, . Epub ahead of print 1 June <https://doi.org/10.3390/IJMS20112755>
- Chen, R., Xu, Y., Xu, C., Shu, Y., Ma, S., Lu, C., & Mo, X. (2019). Associations between mercury exposure and the risk of nonalcoholic fatty liver disease (NAFLD) in US adolescents. *Environmental Science and Pollution Research*, *26*, 31384–31391.
- Martini, C. N., Gabrielli, M., & Bonifacio, G. (2018). Lead enhancement of 3T3-L1 fibroblasts differentiation to adipocytes involves ERK, C/EBP $\beta$  and PPAR $\gamma$  activation. *Molecular and Cellular Biochemistry*, *437*, 37–44.
- Beier, E. E., Holz, J. D., & Sheu, T. J. (2016). Elevated lifetime lead exposure impedes osteoclast activity and produces an increase in bone mass in adolescent mice. *Toxicological Sciences*, *149*, 277–288.
- Egusquiza, R. J., & Blumberg, B. (2020). Environmental obesogens and their impact on susceptibility to obesity; new mechanisms and chemicals. *Endocrinology*, *161*, . Epub ahead of print 1 <https://doi.org/10.1210/ENDOCR/BQAA024>
- Fan, J. -. G., & Farrell, G. C. (2009). Epidemiology of non-alcoholic fatty liver disease in China. *Journal of Hepatology*, *50*, 204–210.
- Frank, A. P., De Souza Santos, R., Palmer, B. F., & Clegg, D. J. (2019). Determinants of body fat distribution in humans may provide insight about obesity-related health risks. *Journal of Lipid Research*, *60*, 1710.
- Fuster, J. J., Ouchi, N., Gokce, N., & Walsh, K. (2016). Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. *Circulation Research*, *118*, 1786.
- González-Cossío, T., Peterson, K. E., Saniñ, L. -. H., Fishbein, E., Palazuelos, E., Aro, A., Hernández-Avila, M., & Hu, H. (1997). Decrease in birth weight in relation to maternal bone-lead burden. *Pediatrics*, *100*, 856–862.
- Goossens, G. H. (2017). The Metabolic phenotype in obesity; fat mass, body fat distribution, and adipose tissue function. *Obesity Facts*, *10*, 207.
- Heindel, J. J., & Blumberg, B. (2019). Environmental obesogens; mechanisms and controversies. <https://doi.org/10.1146/annurev-pharmtox-010818-021304>, *59*, 89–106.
- International Diabetes Federation (2006). IDF consensus worldwide definition of the metabolic syndrome. Epub ahead of print 2006. 10.14341/2071-8713-4854.
- Jansen, E. C., Dunietz, G. L., Dababneh, A., Peterson, K. E., Chervin, R. D., Baek, J., O'brien, L., Song, P. X. K., Cantoral, A., Hu, H., & Téllez-Rojo, M. M. (2019). Cumulative childhood lead levels in relation to sleep during adolescence. *Journal of Clinical Sleep Medicine*, *15*, 1443–1449.
- Park, J. S., Ha, K. H., & He, K., Kim, D. J. (2017). Association between blood mercury level and visceral adiposity in adults. *Diabetes & Metabolism Journal*, *41*, 113–120.
- Lee, K. (2018). Blood mercury concentration in relation to metabolic and weight phenotypes using the KNHANES 2011–2013 data. *International Archives of Occupational and Environmental Health*, *91*, 185–193.
- Kinner, S., Reeder, S. B., & Yokoo, T. (2016). Quantitative imaging biomarkers of NAFLD. *Digestive Diseases and Sciences*, *61*, 1337–1347.
- Betzanos-Robledo, L., Cantoral, A., & Peterson, K. E. (2021). Association between cumulative childhood blood lead exposure and hepatic steatosis in young Mexican adults. *Environmental Research*, *196*, . Epub ahead of print 1 May <https://doi.org/10.1016/J.ENVRES.2021.110980>
- Jagannathan, L., Jose, C. C., & Tanwar, V. S. (2017). Identification of a unique gene expression signature in mercury and 2,3,7,8-tetrachlorodibenzo- p-dioxin co-exposed cells. *Toxicology Research*, *6*, 312–323.
- de Onis, M., & Onyango, A. W. (2007). Development of a WHO growth reference for school-aged children and adolescents. *Bulletin of the World Health Organization*, *85*, 660–667.
- Mihalopoulos, N. L., Holubkov, R., Young, P., Dai, S., & Labarthe, D. R. (2010). Expected changes in clinical measures of adiposity during puberty. *Journal of Adolescent Health*, *47*, 360–366.

- Shah, N., Rocha, J. P., & Bhutiani, N. (2019). Nonalcoholic fatty pancreas disease. *Nutrition in Clinical Practice*, 34(Suppl 1), S49–S56.
- Nasr, P., Forsgren, M. F., & Ignatova, S. (2017). Using a 3% proton density fat fraction as a cut-off value increases sensitivity of detection of hepatic steatosis, based on results from histopathology analysis. *Gastroenterology*, 153, 53–55.e7.
- Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E. C., Biryukov, S., Abbafati, C., Abera, S. F., Abraham, J. P., Abu-Rmeileh, N. M. E., Achoki, T., Albuhairan, F. S., Alemu, Z. A., Alfonso, R., Ali, M. K., Ali, R., Guzman, N. A., ... Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013; a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, 384, 766–781.
- Bello-Chavolla, O. Y., Antonio-Villa, N. E., & Vargas-Vazquez, A. (2020). Metabolic Score for Visceral Fat (METS-VF), a novel estimator of intra-abdominal fat content and cardio-metabolic health. *Clinical Nutrition*, 39, 1613–1621.
- Park, S., & Lee, B. - K. (2012). Body fat percentage and hemoglobin levels are related to blood lead, cadmium, and mercury concentrations in a Korean adult population (KNHANES 2008–2010). *Biological Trace Element Research*, 151, 315–323.
- Paruchuri, Y., Siuniak, A., Johnson, N., Levin, E., Mitchell, K., Goodrich, J. M., Renne, E. P., & Basu, N. (2010). Occupational and environmental mercury exposure among small-scale gold miners in the Talensi–Nabdam District of Ghana's Upper East region. *Science of the Total Environment*, 408, 6079–6085.
- Perng, W., Cantoral, A., Soria-Contreras, D. C., Betanzos-Robledo, L., Kordas, K., Liu, Y., Mora, A. M., Corvalan, C., Pereira, A., Cardoso, M. A., Chavarro, J. E., Breton, C. V., Meeker, J. D., Harley, K. G., Eskenazi, B., Peterson, K. E., & Tellez-Rojo, M. M. (2021). Exposure to obesogenic endocrine disrupting chemicals and obesity among youth of Latino or Hispanic origin in the United States and Latin America: A lifecourse perspective. *Obesity Reviews*, 22(Suppl 3), Epub ahead of print 1 June <https://doi.org/10.1111/OBR.13245>
- Perng, W., Tamayo-Ortiz, M., & Tang, L. (2019). Early life exposure in Mexico to environmental toxicants (ELEMENT) project. *BMJ Open*, 9. Epub ahead of print 1 August <https://doi.org/10.1136/bmjopen-2019-030427>
- Rauschert, S., Kirchberg, F. F., Marchioro, L., Koletzko, B., Hellmuth, C., & Uhl, O. (2017). Early programming of obesity throughout the life course: a metabolomics perspective. *Annals of Nutrition & Metabolism*, 70, 201–209.
- Singh, R. G., Yoon, H. D., & Wu, L. M. (2017). Ectopic fat accumulation in the pancreas and its clinical relevance: a systematic review, meta-analysis, and meta-regression. *Metabolism*, 69, 1–13.
- Rizzetti, D. A., Corrales, P., Piagette, J. T., Uranga-Ocio, J. A., Medina-Gomez, G., Peçanha, F. M., Vassallo, D. V., Miguel, M., & Wiggers, G. A. (2019). Chronic mercury at low doses impairs white adipose tissue plasticity. *Toxicology*, 418, 41–50.
- Roldan-Valadez, E., Favila, R., Martínez-López, M., Uribe, M., Ríos, C., & Méndez-Sánchez, N. (2010). In vivo 3T spectroscopic quantification of liver fat content in nonalcoholic fatty liver disease; Correlation with biochemical method and morphometry. *Journal of Hepatology*, 53, 732–737.
- Secretaría de Salud. NORMA Oficial Mexicana NOM-199-SSA1-2000, Salud ambiental. Niveles de plomo en sangre y acciones como criterios para proteger la salud de la población expuesta no ocupacionalmente. (2000).
- Shamah-Levy, T., Vielma-Orozco, E., Heredia-Hernández, O., Romero-Martínez, M., Mojica-Cuevas, J. C. - N. L., & Santaella-Castell, J. A. R. - D. J. (2018). Encuesta Nacional de Salud y Nutrición 2018–19; Resultados Nacionales.
- Shin, Yi-Y., Ryu, In-K., Park, Mi-J., & Kim, S. - H. (2018). The association of total blood mercury levels and overweight among Korean adolescents; analysis of the Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2013. *Korean Journal of Pediatrics*, 61, 121–128.
- Simmonds, M., Llewellyn, A., Owen, C. G., & Woolacott, N. (2016). Predicting adult obesity from childhood obesity: A systematic review and meta-analysis. *Obesity Reviews*, 17, 95–107.
- Spolidoro, J. V., Pitrez Filho, M. L., Vargas, L. T., Santana, J. C., Pitrez, E., Hauschild, J. A., Bruscatto, N. M., Moriguchi, E. H., Medeiros, A. K., & Piva, J. P. (2013). Waist circumference in children and adolescents correlate with metabolic syndrome and fat deposits in young adults. *Clinical Nutrition*, 32, 93–97.
- Stefan, N. (2020). Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinology*, 8, 616–627.
- Kawakami, T., Hanao, N., & Nishiyama, K. (2012). Differential effects of cobalt and mercury on lipid metabolism in the white adipose tissue of high-fat diet-induced obesity mice. *Toxicology and Applied Pharmacology*, 258, 32–42.
- Tchounwou, P. B., Yedjou, C. G., & Patlolla, A. K. (2012). Heavy metals toxicity and the environment. *Experientia Supplementum*, 101, 133.
- Téllez-Rojo, M. M., Bautista-Arredondo, L. F., Trejo-Valdivia, B., Cantoral, A., Estrada-Sánchez, D., Kraiem, R., Pantic, I., Rosa-Parra, A., Gómez-Acosta, L. M., Romero-Martínez, M., Cuevas-Nasu, L., Shamah-Levy, T., Fuller, R., & Tamayo-Ortiz, M. (2019). Reporte nacional de niveles de plomo en sangre y uso de barro vidriado en población infantil vulnerable. *Salud Pública De Mexico*, 61, 787.

- Tellez-Rojo, M. M., Bautista-Arredondo, L. F., & Trejo-Valdivia, B. Análisis de la distribución nacional de intoxicación por plomo en niños de 1 a 4 años. *Implicaciones para la política nacional*. Salud Publica Mex.
- Tinkov, A. A., Aschner, M., Ke, T., Ferrer, B., Zhou, Ji-C., Chang, J.-S., Santamaría, A., Chao, J. C.-J., Aaseth, J., & Skalny, A. V. (2021). Adipotropic effects of heavy metals and their potential role in obesity. *Faculty Reviews*, 10, . Epub ahead of print 26 <https://doi.org/10.12703/R/10-32>
- Trentacosta, C. J., & Mulligan, D. J. (2020). New directions in understanding the role of environmental contaminants in child development; Four themes. *New Directions for Child and Adolescent Development*, 2020, 39–51.
- Tsoi, M. -. F., Cheung, C. -. L., Cheung, T. T., & Cheung, B. M. Y. (2016). Continual decrease in blood lead level in Americans: United States National Health Nutrition and Examination Survey 1999-2014. *American Journal of Medicine*, 129, 1213–1218.
- Wang, G., Dibari, J., Bind, E., Steffens, A. M., Mukherjee, J., Azuine, R. E., Singh, G. K., Hong, X., Ji, Y., Ji, H., Pearson, C., Zuckerman, B. S., Cheng, T. L., & Wang, X. (2019). Association between maternal exposure to lead, maternal folate status, and intergenerational risk of childhood overweight and obesity. *JAMA Network open*, 2, e1912343.
- Wang, N., Chen, C., & Nie, X. (2015). Blood lead level and its association with body mass index and obesity in China – Results from SPECT-China study. *Science Reports*, 5, 1–11.
- Wells, J. C. K. (2006). The evolution of human fatness and susceptibility to obesity; an ethological approach. *Biological Reviews of the Cambridge Philosophical Society*, 81, 183–205.
- World Health Organization (WHO). (2006). Fifth session of the Intergovernmental Forum on Chemical Safety – Final report, Accessed 15 February 2022 <https://www.who.int/publications/m/item/fifth-session-of-the-intergovernmental-forum-on-chemical-safety-final-report>
- Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., ... Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine*, 180, 934.
- Wang, X., Mukherjee, B., & Park, S. K. (2018). Associations of cumulative exposure to heavy metal mixtures with obesity and its comorbidities among U.S. adults in NHANES 2003-2014. *Environment International*, 121, 683–694.
- Ye, B.-J., Kim, B.-G., Jeon, M.-J., Kim, Se.-Y., Kim, H.-C., Jang, T.-W., Chae, H.-J., Choi, W.-J., Ha, M.-N., & Hong, Y.-S. (2016). Evaluation of mercury exposure level, clinical diagnosis and treatment for mercury intoxication. *Annals of Occupational and Environmental Medicine*, 28, . Epub ahead of print <https://doi.org/10.1186/S40557-015-0086-8>
- Yokoo, T., Shiehmorteza, M., Hamilton, G., Wolfson, T., Schroeder, M. E., Middleton, M. S., Bydder, M., Gamst, A. C., Kono, Y., Kuo, A., Patton, H. M., Horgan, S., Lavine, J. E., Schwimmer, J. B., & Sirlin, C. B. (2011). Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. *Radiology*, 258, 749–759.
- You, C.-H., Kim, B.-G., Kim, J.-M., Yu, S.-D., Kim, Y.-M., Kim, R.-B., & Hong, Y.-S. (2010). Relationship between blood mercury concentration and waist-to-hip ratio in elderly Korean individuals living in coastal areas. *Journal of Preventive Medicine and Public Health*, 44, 218–225.
- Chen, Y. W., CF, H., & KS, T. (2006). The role of phosphoinositide 3-kinase/Akt signaling in low-dose mercury-induced mouse pancreatic beta-cell dysfunction in vitro and in vivo. *Diabetes*, 55, 1614–1624.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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