Published in final edited form as:

Environ Res. 2015 April ; 138: 118–129. doi:10.1016/j.envres.2015.01.008.

Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment (LIFE)

Michael S. Bloom^{a,b,*}, Germaine M. Buck Louis^c, Rajeshwari Sundaram^c, Jose M. Maisog^{c,d}, Amy J. Steuerwald^{a,e}, and Patrick J. Parsons^{a,e}

^aDepartment of Environmental Health Sciences, University at Albany School of Public Health, State University of New York, Rensselaer, NY USA

^bDepartment of Epidemiology and Biostatistics, University at Albany School of Public Health, State University of New York, Rensselaer, NY USA

^cDivision of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD USA

^dGlotech, Incorporated, Rockville, MD USA

^eLaboratory of Inorganic and Nuclear Chemistry, Wadsworth Center, New York State Department of Health, Albany, NY USA

Abstract

Evidence suggests that trace exposures to select elements may increase the risk for adverse birth outcomes. To investigate further, we used multiple regression to assess associations between preconception parental exposures to Pb, Cd, and total Hg in blood, and 21 elements in urine, with n=235 singleton birth outcomes, adjusted for confounders and partner's exposure. Earlier gestational age at delivery (GA) was associated with higher tertiles of urine maternal W (−1.22 days) and paternal U (−1.07 days), but GA was later for higher tertiles of maternal (+1.11 days) and paternal (+1.30 days) blood Hg. Additional analysis indicated shorter GA associated with higher paternal urine Ba, W, and U, and with higher maternal blood Pb for boys, but GA was longer in association with higher maternal urine Cr. Birth weight (BW) was lower for higher tertiles of paternal urine Cs (−237.85 g), U (−187.34 g), and Zn (−209.08 g), and for higher continuous Cr (P=0.021). In contrast, BW was higher for higher tertiles of paternal urine As

© 2015 Published by Elsevier Inc.

*Corresponding author: Michael S. Bloom, Ph.D., Department of Environmental Health, Sciences, School of Public Health Rm. #157, One University Place, Rensselaer, NY 12144 USA, Phone: (518) 473-1821, Fax: (518) 474-9899, mbloom@.albany.edu.

ETHICS

This study was conducted based on the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and approved by the Institutional Review Boards at the Eunice Kennedy Shriver National Institute of Child Health and Human Development and participating institutions. The authors declare they have no actual or potential competing financial or non-financial interests.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(+194.71 g) and counterintuitively for maternal blood Cd (+178.52 g). Birth length (BL) was shorter for higher tertiles of urine maternal W (−1.22 cm) and paternal U (−1.10 cm). Yet, higher tertiles of maternal (+1.11 cm) and paternal (+1.30) blood Hg were associated with longer BL. Head circumference at delivery was lower for higher tertiles of paternal urine U (−0.83 cm), and for higher continuous Mo in boys (−0.57 cm). Overall, associations were most consistently indicated for GA and measures of birth size with urine W and U, and paternal exposures were more frequently associated than maternal. Though limited by several factors, ours is the largest multi-element investigation of prospective couple-level trace exposures and birth outcomes to date; the novel observations for W and U merit further investigation.

Keywords

Birth outcomes; elements; environment; metalloids; metals

1. INTRODUCTION

Concern continues to mount for adverse impacts resulting from non-occupational or ‘background’ exposures to environmental agents (ACOG and ASRM, 2013) possibly leading to poorer birth outcomes and life-long sequelae (Stillerman et al., 2008). This includes exposure to non-essential elements that confer no physiologic benefit and are known to be toxic at low doses, such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg). While some elements such as chromium (Cr), copper (Cu), selenium (Se), and zinc (Zn) are essential for normal physiologic function, they are also potentially toxic at higher doses (Domingo, 1994; Fairbrother et al., 2007). Exposure is widespread, via diet, contaminated water, and contaminated air, and having been detected in a majority of specimens collected by U.S. biomonitoring studies (CDC, 2014b) including in pregnant women (Woodruff et al., 2011). Given their potential for reproductive toxicity and widespread nature we conducted an exploratory analysis of trace exposures to select elements and birth outcomes.

Pregnant women and their fetuses are at increased risk for adverse effects from environmental agents (Sutton et al., 2010). Several groups reported associations between maternal exposure to non-essential elements and adverse birth outcomes, but most frequently to high doses of As, Cd, Hg, or Pb encountered in the workplace or associated with residence in so-called ‘endemic’ regions (Wigle et al., 2008). Adverse birth outcomes, including preterm delivery (PD) and low birth weight (LBW) increase lifetime risks for myriad morbidities, including neurodevelopmental complications (Mwaniki et al., 2012), poorer intellectual development (Bergvall et al., 2006), and cardiovascular disease and endocrine disorders (Barker, 2004). Even at term, adult mortality is associated with earlier delivery (Crump et al., 2011). Investigators have described associations between background exposures to toxic and essential elements in pregnant women and birth outcomes (Al-Saleh et al., 2014; Gundacker et al., 2010; Kippler et al., 2012a; Kippler et al., 2012b; Kozikowska et al., 2013; Lee et al., 2010; Lin et al., 2011; Menai et al., 2012; Shirai et al., 2010; Tian et al., 2009; van Wijngaarden et al., 2014; Zhang et al., 2004). However, there are few data to assess the impact of preconception exposures; measurements made during pregnancy are

subject to within-woman variability concurrent to gestation-related physiologic adaptations (Selevan et al., 2000).

Recent evidence substantiates the transgenerational effects of environmental risk factors (Boekelheide et al., 2012), suggesting an important role for preconception parental exposures on birth outcomes. Either through *de novo* generation of reactive oxygen species or depletion of anti-oxidants, excess exposure to metals and metalloids can increase oxidative stress (Ercal et al., 2001; Valko et al., 2005), in turn impacting erasure and programming of epigenetic marks - the dynamic pattern of DNA and histone bound methyl- and acetyl- groups that regulates gene expression (Baccarelli and Bollati, 2009; Ho et al., 2012). Epigenetic germ cell alterations are likely heritable, as demonstrated in spermatozoa (Anway et al., 2005) or through maternal lineage (Newbold et al., 1998; Newbold et al., 2000) in vinclozolin or diethylstilbestrol treated mice, respectively. Alternately, modified reprogramming of epigenetic patterns, which begin only hours after fertilization (Reik et al., 2001), may influence fetal growth and development. Furthermore, many metals and metalloids, including Cd, Pb, Hg, and U are estrogenic, whereas others, such as As, are also anti-estrogenic (Dyer, 2007; Iavicoli et al., 2009), which may further influence epigenetic patterning (Crews and McLachlan, 2006), increasing the prospect for preconception impacts on birth outcomes.

To the best of our knowledge no prior studies assessed pre-conception couple-level exposures to these elements. To begin to address the existing data gap, our aim was to identify associations for further confirmation, between birth outcomes and background or 'trace' exposures to select metals and metalloids. To accomplish this aim we used couples participating in the Longitudinal Investigation of Fertility and the Environment (LIFE), a prospective cohort investigation of environmental factors and human reproduction.

2. MATERIALS AND METHODS

2.1 Study sample

From 2005–2009 a cohort of 501 couples planning pregnancy was recruited from 16 counties in central Michigan and along the Texas Gulf Coast. The details of participant recruitment and data collection were previously described (Buck Louis et al., 2011). In brief, potential participants were identified, using fishing license registries or a commercially available direct marketing data base, from 12 counties in Texas and four in Michigan, respectively, with presumed exposure to persistent organic pollutants (POPs). Inclusion criteria comprised a committed heterosexual relationship, women aged 18–40 years (men 18), English or Spanish speaker, no use of an injectable contraceptive within 12 months, and a menstrual cycle length of 21–42 days. We excluded couples with a sterilized partner or with a prior infertility diagnosis. The present study included 235 singletons born to 347 couples; we excluded two sets of twins, 110 couples experienced a loss, 54 couples did not achieve a pregnancy, and 100 couples withdrew from the study. Participants completed informed consent prior to enrollment, and the study protocol was approved by the Institutional Review Boards at the Eunice Kennedy Shriver National Institute of Child Health and Human Development and participating institutions.

2.2 Data collection

A research nurse visited eligible couples in their homes and enrolled participants following a negative pregnancy test. Blood and ‘spot’ urine specimens were collected into contamination-free 3-mL EDTA purple-top tubes and plastic collection cups, respectively, and stored at -20°C until shipment on dry ice to the analyzing laboratories. A baseline questionnaire was administered, querying demographics, health-related behaviors, medical history, and reproductive histories. Women were instructed in the use of the Clearblue Easy Fertility Monitor to time intercourse more effectively, and allowing for us to capture the date of conception. The monitor stores daily urine estrone-3-glucuronide and luteinizing hormone levels, which we downloaded every 45 days during follow-up home visits. Women were also provided digital Clearblue Easy Pregnancy Tests for use on the day of expected menses. Women were followed until delivery when they completed and returned birth announcements that captured date and sex of birth, weight and length, and head circumference.

2.3 Environmental analyses

Blood specimens were shipped to the Centers for Disease Control and Prevention (Atlanta, GA). The laboratory determined Hg, Pb, and Cd in blood using a method developed for the National Health and Nutrition Examination Survey (NHANES) employing inductively coupled plasma mass spectrometry (ICP-MS), and following a strict quality control (QC) procedure (CDC, 2009). Serum cotinine was measured by liquid chromatography with isotope-dilution tandem mass spectrometry (Bernert et al., 1997), and dichotomized as ‘smoker’ or ‘non-smoker’ at 100 ng/mL (Wall et al., 1988). Total serum lipids were determined using an automated enzymatic method (Akins et al., 1989). Urine specimens were shipped to the New York State Department of Health’s (NYS DOH) Wadsworth Center (Albany, NY), and analyzed for 21 elements including antimony (Sb), As, barium (Ba), beryllium (Be), Cd, cesium (Cs), Cr, cobalt (Co), Cu, Pb, manganese (Mn), molybdenum (Mo), nickel (Ni), platinum (Pt), Se, tellurium (Te), thallium (Tl), tin (Sn), tungsten (W), uranium (U), and Zn, by ICP-MS using a method developed for biomonitoring studies, and following a QC procedure (Minnich et al., 2008). Both the CDC and Wadsworth Center laboratories participate successfully in the NYS DOH’s proficiency testing program for elements in whole blood and urine, and in the CDC’s Lead and Multielement Proficiency (LAMP) program. To minimize bias during statistical analysis we retained instrument-reported values without imputation for those observations below limits of detection (LOD) (Guo et al., 2010; Richardson and Ciampi, 2003; Schisterman et al., 2006).

2.4 Statistical analysis

We characterized distributions and identified outliers for exposures, covariates, and study endpoints, including gestational age at delivery in days (GA), birth weight in kg (BW), birth length in cm (BL), head circumference in cm (HC), ponderal index (PI), and secondary sex ratio (SSR). We defined GA from the date of ovulation, estimated as the date of the fertility monitor recorded LH peak to the reported delivery date. Preterm-delivery (PD) was defined as GA <245 days (<35 weeks) from the date of ovulation (conventionally defined as 37

weeks from last menstrual period date in the absence of ovulation data) (WHO, 1977). Low birth weight (LBW) was defined as <2500 g (WHO, 1977). PI, an indicator of fetal growth proportionality (Landmann et al., 2006), was defined as $100 \times (\text{birth weight}/\text{birth length}^3)$. The SSR is the ratio of live male to female births and typically reflects a male excess (Mathews and Hamilton, 2005). We evaluated unadjusted associations among exposures and birth outcomes using Spearman rank correlations and Mann-Whitney U-tests as appropriate.

We used multiple regression techniques to evaluate adjusted associations between elements and GA, BW, BL, HC, and PI as continuous outcomes. Maternal and paternal exposures were simultaneously entered into regression models and adjusted for maternal age, the difference between maternal and paternal ages (to accommodate the strong positive correlation between partners' age), and for maternal and paternal smoking, income, and race as confounders. We also included total serum lipids as a proxy marker for POPs, an approach we have previously employed (Buck Louis et al., 2012); these compounds distribute to the lipid compartment (Phillips et al., 1989) and have been associated with birth outcomes in this (Robledo et al., 2015) and other study populations (Govarts et al., 2012). Creatinine was entered as a covariate to accommodate urine dilution (Kim et al., 2011). We evaluated covariate-adjusted associations between elements and time of delivery using Cox-proportional hazards models and newborn sex using log-binomial models. Analyses were conducted using tertiles of elements to allow for nonlinear effects, and repeated using log-transformed continuous elements to detect linear trends. To evaluate differences by newborn sex, we used additional regressions incorporating product terms between continuous log-transformed maternal or paternal elements and infant sex, adjusted for serum lipids and creatinine.

Due to limited specimen volume, elements in blood (1.1%) and urine (8.9%), creatinine (4.5%), and lipids (1.5%) data were missing for some participants. To preserve sample size, we implemented a Markov Chain Monte Carlo (MCMC)-based multiple-imputation procedure under an assumption of 'missing at random' (Horton and Kleinman, 2007). We defined significance as $P < 0.05$ and SAS v.9.3 (SAS Institute, Inc. Cary, NC) was used for statistical analysis.

3. RESULTS

3.1 Univariate and bivariate analyses

Distributions of sociodemographic and reproductive factors are presented in Table 1 and the study birth outcomes are described in Table 2. The sample was mostly non-Hispanic white, college-educated, and reported high-income. Distributions for maternal and paternal elements, including tertiles are provided by Tables 3 and 4, respectively. Few values were measured above the LODs for urine Be (8.5%), Mn (20.5%), Ni (16.7%), Te (1.4%), and Pt (0.0%), and so we did not consider these further. We detected mostly weak, positive pairwise correlations among elements (data not shown), and levels were also mostly weakly, and positively correlated between mothers and fathers, except for urine Cu and Zn (data not shown). Bivariate associations between elements and continuous birth outcomes adjusted for only creatinine (in urine) or age (Cd, Pb, and Hg) are reported for mothers in Supplemental Table 1 and for fathers in Supplemental Table 2, and dichotomous birth outcomes are

reported in Supplemental Table 3. Differences in GA were not detected by tertiles of maternal exposures using log-rank tests (data not shown), although higher paternal urine W was related to earlier delivery ($P=0.05$).

3.2 Multivariable analyses

We used linear regression to assess adjusted relations between GA and elements (Table 5), excluding three outliers. Maternal and paternal blood Hg in the 3rd tertiles were associated with longer GA (+1.1 and +1.3 days, respectively), with a linear trend for fathers ($P=0.02$). Maternal urine W was associated with shorter GA in the 2nd exposure tertile (−1.2 days). Paternal urine U was also associated with shorter GA in the 2nd and 3rd tertiles (−1.1 days). Gauging delivery using a Cox-proportional hazards model (Supplemental Table 4), the hazard ratio (HR) was lower than the null for the 2nd tertile of maternal urine Cr (HR=0.43). In contrast, HRs for delivery were higher than the null for the 2nd and 3rd tertiles of paternal urine Ba (HR=2.20 and 2.66, respectively) and W (HR=2.93 and 2.77, respectively). We also detected a positive linear trend for delivery with higher paternal U ($P=0.02$). Furthermore, we detected an interaction ($P=0.03$), adjusted for lipids only, in which maternal blood Pb was associated with higher delivery risk in boys (HR=1.49; 95% CI 1.06, 2.09), but not girls (HR=0.81; 95% CI 0.52, 1.27).

We also used linear regression to assess adjusted associations between BW and elements (Table 5), excluding one outlier. Women in the 3rd blood Cd tertile delivered babies 178.5 g heavier than for the 1st tertile, and with a linear trend ($P=0.03$). Men in the 3rd tertile for urine As fathered children 194.7 g heavier than men in the 1st tertile. In contrast, the children of men in the 3rd tertiles for urine Cs and Zn weighed 237.9 g and 209.1 g less than for 1st tertiles, with a linear trend for Cs ($P=0.03$). An inverse linear association was also indicated between BW and paternal urine Cr ($P=0.02$), and the children of men in the 2nd urine U tertile were 187.3 g lighter than for men in the 1st tertile.

In similar fashion, we used linear regression to assess BL and HC as outcomes, excluding two HC outliers, with confounder-adjusted elements as predictors (Table 6). Maternal blood Hg in the 3rd tertile was associated with 1.11 cm longer BL. The 2nd tertile of maternal urine W was associated with shorter BL by 1.22 cm. The 3rd tertile of paternal blood Hg was associated with 1.30 cm longer BL, and with a significant linear trend ($P=0.02$). In contrast, we detected 1.10 cm and 1.07 cm shorter BLs for fathers in the 2nd and 3rd urine U tertiles, respectively. Middle tertile paternal urine U was associated with 0.83 cm shorter HC. We also detected an interaction ($P=0.01$), adjusted for urine creatinine and lipids, in which higher paternal urine Mo was associated with lower HC in boys ($\beta=-0.57$ cm; 95% CI −1.11, −0.03) but not in girls ($\beta=0.10$ cm; 95% CI −0.42, 0.62). We did not detect associations between maternal or paternal elements and PI, using linear regression, or SSR, using log-binomial regression (Table 7). However, we observed negative, although non-significant, patterns for several elements in which PI tended towards lower values at higher levels of maternal exposure.

4. DISCUSSION

In this prospective couple-based cohort study we observed modest evidence for associations between exposure to select elements and birth outcomes. We detected no consistent pattern of diminished GA or birth size in association with preconception parental elements, yet paternal exposure tended to be more frequently related to decrements than maternal exposure. In adjusted models, maternal urine W and paternal urine U were associated with shorter GA, whereas blood Hg was associated with longer GA in both women and men. Higher maternal urine Cr was associated with lower delivery risk, although the risk was greater in association with higher paternal urine Ba, W, and U. Lower BW was associated with higher levels of paternal urine Cs, Cr, U, and Zn, even though paternal urine As and maternal blood Cd were linked to higher BW. BL was longer in conjunction with higher maternal and paternal blood Hg, yet BL was shorter for higher maternal urine W and paternal urine U. The latter was also linked to shorter HC. Of all analytes considered, the associations for urine W and U were most notable. Furthermore, boys appeared more vulnerable as maternal blood Pb was associated with a higher delivery risk and paternal urine Mo with shorter HC; yet we detected no effect for girls. Although no associations were detected for PI, lower values tended towards higher maternal exposure levels, potentially indicative of subtle yet undetected effects across pregnancy.

Elements in our sample (Tables 3 and 4) were low relative to U.S. population values for 2005 to 2010 (CDC, 2014a). U.S. women had modestly higher median blood Cd (0.273 µg/L) and Pb (0.73 µg/dL), as well as higher urine Sb (0.059 µg/L), Ba (1.56 µg/L), Cd (0.17 µg/L), Cs (4.65 µg/L), Co (0.45 µg/L), Pb (0.384 µg/L), Mo (48.48 µg/L), Tl (0.17 µg/L), W (0.08 µg/L), and U (0.006 µg/L) than study mothers. However, U.S. women had lower median total blood Hg (0.77 µg/L) and total urine As (7.60 µg/L). U.S. men had higher median blood Cd (0.23 µg/L) and Pb (1.17 µg/dL), as well as higher median urine Cd (0.153 µg/L), Co (0.364 µg/L), Pb (0.51 µg/L), Mo (54.3 µg/L), W (0.105 µg/L), and U (0.007 µg/L) compared to study fathers, although similar urine Sb (0.07 µg/L) and Cs (4.88 µg/L). Medians for U.S. men were also lower for total blood Hg (0.800 µg/L) and total urine As (8.93 µg/L).

Previous studies have reported associations between birth outcomes and maternal concentrations of metals and metalloids measured in blood or urine during pregnancy or at parturition, primarily among populations with exposures several-fold higher than we measured. Lower BW was reported in association with higher blood Pb in U.S. (Zhu et al., 2010) and Austrian (Gundacker et al., 2010) mothers, with higher maternal blood Cd in French smokers (Menai et al., 2012), and with higher blood Hg in *GST1* null genotype Korean mothers (Lee et al., 2010). Lower BW and shorter BL was also associated with higher cord blood Pb in Taiwan (Tian et al., 2009). Decreased BW and HC was reported in association with higher urine Cd collected from Bangladeshi mothers (Kippler et al., 2012a), but only among girls, and with a non-linear ‘inverted U-shaped’ dose-response for fetal size assessed by ultrasound (Kippler et al., 2012b). Other investigators reported increased odds for high blood Cd among Saudi mothers with smaller crown-rump length deliveries (Al-Saleh et al., 2014), and higher cord blood Cd was associated with shorter BL among infants in a highly contaminated area of China, although there was no association for maternal

blood Cd or for PD or BW (Zhang et al., 2004). Likewise, no associations were noted for GA or BL in a recent Polish study of maternal and cord blood Hg (Kozikowska et al., 2013). Whereas urine Cd was inversely associated with BW and urine Sn with HC among Japanese mothers, no associations were detected for BL or for levels of Sb, As, Be, Cu, Pb, Mo, Se, and Zn similar to ours (Shirai et al., 2010). A U.S. study more recently described a positive correlation between maternal blood Pb and PD among boys, also at levels similar to ours, although with no associations for BW, BL, or HC (Perkins et al., 2014).

Ours is the first report of effects on birth outcomes in association with background exposure to W and U. There exist very few experimental data to characterize the reproductive toxicity of W, and to our knowledge no observational studies have been conducted in humans (Keith et al., 2007). In contrast, U is well-recognized as a reproductive toxicant at high doses (Domingo, 2001). Recent animal evidence also suggests that U acts as an estrogen *in vivo* at low, environmentally relevant levels (Raymond-Whish et al., 2007). Early work in an occupational cohort indicated decreased SSR, although our data did not suggest an effect (Muller et al., 1967). No clinically significant reproductive effects were reported from a longitudinal study of n=74 depleted-U exposed U.S. Gulf War Veterans, although birth outcomes were not reported (Squibb and McDiarmid, 2006). If confirmed, our results merit further investigation to characterize the reproductive toxicity of W and U at background levels of exposure.

The positive associations we detected for GA and BL with maternal and paternal blood Hg, and BW and paternal urine As, were unexpected. However, the modestly elevated levels of blood Hg and urine As in our sample are likely to be indicative of seafood consumption (Marchiset-Ferlay et al., 2012; Mozaffarian and Rimm, 2006), and may thereby have served as markers for dietary exposure to long chain n-3 polyunsaturated fatty acids conferring benefits to fetal growth and development (Leventakou et al., 2014). We also detected a counterintuitive association for higher maternal blood Cd and increased BW. Increased fetal growth was likewise reported among Bangladeshi women with blood Cd below 1.5 µg/L (Kippler et al., 2012b). Still, this observation may reflect a chance occurrence given multiple comparisons and so we are circumspect in drawing conclusions. However, other results are consistent with the recent work assessing low dose gestational Pb (Perkins et al., 2014) and with long-recognized frailties among newborn males (Naeye et al., 1971).

Inconsistencies between our study results and those from prior studies are likely due to several factors, including differences in study design and in study populations. Exposure levels were generally lower than for prior reports and thus thresholds may not have been reached for previously reported birth outcome effects related to Cd, Pb, and Hg exposure. Thus, our findings may be useful to inform no observed adverse effect levels (NOAELs). Our multivariable models were also different from those used in prior studies as we adjusted for partner's exposure and confounders to more realistically represent the couple-driven nature of reproduction. Although prior reports incorporated maternal-level confounding variables, we were able to assess the impact of paternal effects using our approach. In fact, we detected paternal effects with greater frequency than maternal during multivariable analysis. The sparse concordance between effects for partners underscores the importance of capturing exposure at the couple level. Furthermore, we used a biomarker based date of

conception, whereas previous investigators employed bias-prone approaches relying on recall of the last menstrual period (Cooney et al., 2009).

Additional differences in data analysis strategies may account in part for discordance from prior study results. We included all births, without exclusion of PD or LBW, consistent with our *a priori* focus on ‘overall’ effects, although we may have missed subtle effects among clinical subgroups. Furthermore, we did not adjust for GA in assessing BW, BL, and HC, a common yet misdirected strategy likely to introduce bias when GA falls within causal pathways (Whitcomb et al., 2009). Finally, we collected biospecimens close to conception, although couples took up to 12 cycles for a pregnancy. The half-life for some elements is measured in hours-days (i.e., urine Sb, As, Ba, Cs, Co, Mo, Tl, W, and U) and is more vulnerable to exposure misclassification than those for which half-life is measured in weeks-months (i.e., blood Hg, blood and urine Cd and Pb) (CDC, 2009). However, prior studies indicate reasonable representation of As (intraclass correlation coefficient (ICC) = 0.49) (Kile et al., 2009) and Se (ICC = 0.77) (Longnecker et al., 1996) body burdens over time using single urine specimens. Furthermore, most of our participants (90%) conceived within six cycles of enrollment (Buck Louis et al., 2012). Still, exposure misclassification is possible, although very unlikely to have been differential according to outcomes given preconception biospecimen collection, and thus bias will have been towards the null hypothesis. Our *a priori* aim was to evaluate the impact of preconception couple-level exposures, the effects of which may differ from prenatal exposures.

The results of this exploratory study are limited by several factors. Despite a moderate sample size of 235 couples, we included a number of covariates in regression models which resulted in some sparse strata and imprecise estimates, in particular for interactions in which we detected small differences of questionable clinical relevance. For some elements (e.g. W), a substantial proportion of values fell below detection limits and so the results will require confirmation. For the essential elements, which are normally under homeostatic control in the body, serum and blood (i.e., Cu, Mn, Se, Zn), or plasma (i.e., Cr) measurements are considered preferable to urine, certainly for assessing nutritional status (Arnaud et al., 2008; CDC, 2009; Paustenbach et al., 1997; Sunderman, 1993). While other samples can be used to assess long term or historical exposure, they may be compromised by exogenous contamination (i.e., hair, nails) or they are difficult to obtain (i.e., bone). For these reasons, spot urine samples are widely used for exposure assessment studies, yet we would concede that they may not represent the best biomarker of exposure for all of the elements measured. Nonetheless, we used a highly sensitive multi-element ICP-MS method for urine that was optimized for biomonitoring studies as described previously (Pollack et al., 2013). Thus, we report a majority of detected values for Cu, Se, and Zn in urine, with the exception of Mn, which we did not consider further. We generated regression models based on individual elements to identify predictors of interest for future confirmation and thus unmitigated confounding by excluded elements might account in part for unexpected results. We were also unable to accommodate additional reproductive toxicants into the analysis that might have confounded associations. Still our limited sample size is likely to have reduced study power and so we may have missed subtle associations. Additionally, we conducted many independent statistical tests, without accommodating the likelihood for type-1 error

inflation. However, our intent was to maximize the sensitivity for detecting modest associations to inform future investigations (Goldberg and Silbergeld, 2011).

5. CONCLUSIONS

To the best of our knowledge, this is the first report to describe preconception parental element exposures and birth outcomes. Most consistently, we detected associations between maternal urine W and paternal urine U and birth outcomes, and also unique effects for maternal blood Pb and paternal urine U among boys. Though limited by several factors, ours is the largest multi-element investigation of prospective couple-level trace exposures and birth outcomes to date; the novel observations for W and U merit further investigation. It is critical to identify potentially modifiable risk factors to inform intervention strategies and to reduce risks for adverse birth outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING

This research was supported by the Intramural Research program of the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (Contracts #N01-HD-3-3355, N01-HD-3356, N01-HD-3-3358, HHSN27500001, and HHSN27500002).

We would like to thank Dr. Kathleen L. Caldwell at the U.S. Centers for Disease Control and Prevention for conducting the analysis of elements, cotinine, and lipids in blood.

References

- ACOG and ASRM. Committee opinion no. 575: Exposure to toxic environmental agents. *Obstet Gynecol.* 2013; 122:931–935. [PubMed: 24084567]
- Akins JR, Waldrep K, Bernert JT Jr. The estimation of total serum lipids by a completely enzymatic ‘summation’ method. *Clin Chim Acta.* 1989; 184:219–26. [PubMed: 2611996]
- Al-Saleh I, Shinwari N, Mashhour A, Rabah A. Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population. *Int J Hyg Environ Health.* 2014; 217:205–218. [PubMed: 23735463]
- Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science.* 2005; 308:1466–1469. [PubMed: 15933200]
- Arnaud J, Weber JP, Weykamp CW, Parsons PJ, Angerer J, Mairiaux E, Mazarrasa O, Valkonen S, Menditto A, Patriarca M, Taylor A. Quality specifications for the determination of copper, zinc, and selenium in human serum or plasma: Evaluation of an approach based on biological and analytical variation. *Clin Chem.* 2008; 54:1892–1899. [PubMed: 18719198]
- Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr.* 2009; 21:243–251. [PubMed: 19663042]
- Barker DJP. The developmental origins of adult disease. *J Am Coll Nutr.* 2004; 23:588S–595S. [PubMed: 15640511]
- Bergvall N, Iliadou A, Johansson S, Tuvemo T, Cnattingius S. Risks for low intellectual performance related to being born small for gestational age are modified by gestational age. *Pediatrics.* 2006; 117:E460–E467. [PubMed: 16510624]
- Bernert JT, Turner WE, Pirkle JL, Sosnoff CS, Akins JR, Waldrep MK, Ann Q, Covey TR, Whitfield WE, Gunter EW, Miller BB, Patterson DG, Needham LL, Hannon WH, Sampson EJ. Development

and validation of sensitive method for determination of serum cotinine in smokers and nonsmokers by liquid chromatography atmospheric pressure ionization tandem mass spectrometry. *Clin Chem.* 1997; 43:2281–2291. [PubMed: 9439445]

Boekelheide K, Blumberg B, Chapin RE, Cote I, Graziano JH, Janesick A, Lane R, Lillycrop K, Myatt L, States JC, Thayer KA, Waalkes MP, Rogers JM. Predicting later-life outcomes of early-life exposures. *Environ Health Perspect.* 2012; 120:1353–1361. [PubMed: 22672778]

Buck Louis GM, Schisterman EF, Sweeney AM, Wilcosky TC, Gore-Langton RE, Lynch CD, Boyd Barr D, Schrader SM, Kim S, Chen Z, Sundaram R. on behalf of the LS. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development – the LIFE Study. *Paediatr Perinat Epidemiol.* 2011; 25:413–424. [PubMed: 21819423]

Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Chen Z, Kim S, Caldwell KL, Barr DB. Heavy metals and couple fecundity, the LIFE Study. *Chemosphere.* 2012; 87:1201–1207. [PubMed: 22309709]

CDC. Fourth National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: 2009. p. 519

CDC. Continuous National Health and Nutrition Examination Survey, 2005–2010. Vol. 2014. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics; Hyattsville, MD: 2014a.

CDC. Fourth National Report on Human Exposure to Environmental Chemicals-Updated Tables, August 2014. U.S. Centers for Disease Control and Prevention; Atlanta, GA: 2014b. p. 1057

Cooney MA, Buck Louis GM, Sundaram R, McGuinness BM, Lynch CD. Validity of self-reported time to pregnancy. *Epidemiology.* 2009; 20:56–59. [PubMed: 19057382]

Crews D, McLachlan JA. Epigenetics, evolution, endocrine disruption, health, and disease. *Endocrinology.* 2006; 147:S4–S10. [PubMed: 16690812]

Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *J Amer Med Assoc.* 2011; 306:1233–1240.

Domingo JL. Metal-induced developmental toxicity in mammals - A review. *J Toxicol Environ Health.* 1994; 42:123–141. [PubMed: 8207750]

Domingo JL. Reproductive and developmental toxicity of natural and depleted uranium: a review. *Reprod Toxicol.* 2001; 15:603–609. [PubMed: 11738513]

Dyer, CA. Heavy metals as endocrine-disrupting chemicals. In: Gore, AC., editor. *Endocrine-disrupting Chemicals: From Basic Research to Clinical Practice.* Humana Press; Totowa, NJ: 2007. p. 111-133.

Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress part I: Mechanisms involved in metal-induced oxidative damage. *Curr Top Med Chem.* 2001; 1:529–539. [PubMed: 11895129]

Fairbrother A, Wenstel R, Sappington K, Wood W. Framework for metals risk assessment. *Ecotoxicol Environ Saf.* 2007; 68:145–227. [PubMed: 17889701]

Goldberg M, Silbergeld E. On multiple comparisons and on the design and interpretation of epidemiological studies of many associations. *Environ Res.* 2011; 111:1007–1009. [PubMed: 21906734]

Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, Chevrier C, Eggesbø M, Guxens M, Krämer U, Legler J, Martínez D, Palkovicova L, Patelarou E, Ranft U, Rautio A, Petersen MS, Slama R, Stigum H, Toft G, Trnovec T, Vandentorren S, Weihe P, Kuperus NW, Wilhelm M, Wittsiepe J, Bonde JP. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): A meta-analysis within 12 European birth cohorts. *Environ Health Perspect.* 2012; 120:162–170. [PubMed: 21997443]

Gundacker C, Frohlich S, Graf-Rohrmeister K, Eibenberger B, Jessenig V, Gicic D, Prinz S, Wittmann KJ, Zeisler H, Vallant B, Pollak A, Husslein P. Perinatal lead and mercury exposure in Austria. *Sci Total Environ.* 2010; 408:5744–5749. [PubMed: 20825977]

Guo Y, Harel O, Little RJ. How well quantified is the limit of quantification? *Epidemiology.* 2010; 21:S10–S16. [PubMed: 20526201]

- Ho SM, Johnson A, Tarapore P, Janakiram V, Zhang X, Leung YK. Environmental epigenetics and its implication on disease risk and health outcomes. *ILAR Journal*. 2012; 53:289–305. [PubMed: 23744968]
- Horton NJ, Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. *Am Stat*. 2007; 61:79–90. [PubMed: 17401454]
- Iavicoli I, Fontana L, Bergamaschi A. The effects of metals as endocrine disruptors. *J Toxicol Environ Health B Crit Rev*. 2009; 12:206–23. [PubMed: 19466673]
- Keith LS, Moffett DB, Rosemond ZA, Wohlers DW. ATSDR evaluation of health effects of tungsten and relevance to public health. *Toxicol Ind Health*. 2007; 23:347–387. [PubMed: 18386525]
- Kile ML, Hoffman E, Hsueh YM, Afroz S, Quamruzzaman Q, Rahman M, Mahiuddin G, Ryan L, Christiani DC. Variability in biomarkers of arsenic exposure and metabolism in adults over time. *Environ Health Perspect*. 2009; 117:455–460. [PubMed: 19337522]
- Kim K, Steuerwald AJ, Parsons PJ, Fujimoto VY, Browne RW, Bloom MS. Biomonitoring for exposure to multiple trace elements via analysis of urine from participants in the Study of Metals and Assisted Reproductive Technologies (SMART). *J Environ Monit*. 2011; 13:2413–2419. [PubMed: 21773592]
- Kippler M, Tofail F, Gardner R, Rahman A, Hamadani JD, Bottai M, Vahter M. Maternal cadmium exposure during pregnancy and size at birth: A prospective cohort study. *Environ Health Perspect*. 2012a; 120:284–289. [PubMed: 21862444]
- Kippler M, Wagatsuma Y, Rahman A, Nermell B, Persson L-Å, Raqib R, Vahter M. Environmental exposure to arsenic and cadmium during pregnancy and fetal size: A longitudinal study in rural Bangladesh. *Reprod Toxicol*. 2012b; 34:504–511. [PubMed: 22985739]
- Kozikowska I, Binkowski LJ, Szczepanska K, Slawska H, Miszczuk K, Sliwinska M, Laciak T, Stawarz R. Mercury concentrations in human placenta, umbilical cord, cord blood and amniotic fluid and their relations with body parameters of newborns. *Environ Pollut*. 2013; 182:256–262. [PubMed: 23938449]
- Landmann E, Reiss I, Misselwitz B, Gortner L. Ponderal index for discrimination between symmetric and asymmetric growth restriction: Percentiles for neonates from 30 weeks to 43 weeks of gestation. *J Matern Fetal Med*. 2006; 19:157–160.
- Lee BE, Hong YC, Park H, Ha M, Koo BS, Chang N, Roh YM, Kim BN, Kim YJ, Kim BM, Jo SJ, Ha EH. Interaction between GSTM1/GSTT1 polymorphism and blood mercury on birth weight. *Environ Health Perspect*. 2010; 118:437–442. [PubMed: 20194072]
- Leventakou V, Roumeliotaki T, Martinez D, Barros H, Brantsaeter AL, Casas M, Charles MA, Cordier S, Eggesbo M, van Eijsden M, Forastiere F, Gehring U, Govarts E, Halldorsson TI, Hanke W, Haugen M, Heppel DHM, Heude B, Inskip HM, Jaddoe VWV, Jansen M, Kelleher C, Meltzer HM, Merletti F, Molto-Puigmarti C, Mommers M, Murcia M, Oliveira A, Olsen SF, Pele F, Polanska K, Porta D, Richiardi L, Robinson SM, Stigum H, Strom M, Sunyer J, Thijs C, Viljoen K, Vrijkotte TGM, Wijga AH, Kogevinas M, Vrijheid M, Chatzi L. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. *Am J Clin Nutr*. 2014; 99:506–516. [PubMed: 24335057]
- Lin CM, Doyle P, Wang D, Hwang YH, Chen PC. Does prenatal cadmium exposure affect fetal and child growth? *Occup Environ Med*. 2011; 68:641–646. [PubMed: 21186202]
- Longnecker MP, Stram DO, Taylor PR, Levander OA, Howe M, Veillon C, McAdam PA, Patterson KY, Holden JM, Morris JS, Swanson CA, Willett WC. Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. *Epidemiology*. 1996; 7:384–390. [PubMed: 8793364]
- Marchiset-Ferlay N, Savanovitch C, Sauviant-Rochat MP. What is the best biomarker to assess arsenic exposure via drinking water? *Environ Int*. 2012; 39:150–171. [PubMed: 22208756]
- Mathews TJ, Hamilton BE. Trend analysis of the sex ratio at birth in the United States. National vital statistics reports from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2005; 53:1–17.
- Menai M, Heude B, Slama R, Forhan A, Sahuquillo J, Charles MA, Yazbeck C. Association between maternal blood cadmium during pregnancy and birth weight and the risk of fetal growth

restriction: The EDEN mother–child cohort study. *Reprod Toxicol.* 2012; 34:622–627. [PubMed: 23017269]

Minnich MG, Miller DC, Parsons PJ. Determination of As, Cd, Pb, and Hg in urine using inductively coupled plasma mass spectrometry with the direct injection high efficiency nebulizer. *Spectrochim Acta Part B At Spectrosc.* 2008; 63:389–395.

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *J Amer Med Assoc.* 2006; 296:1885–1899.

Muller C, Ruzicka L, Bakstein J. The sex ratio in the offsprings of uranium miners. *Acta Univ Carol [Med] (Praha).* 1967; 13:599–603.

Mwaniki MK, Atieno M, Lawn JE, Newton CRJC. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: A systematic review. *The Lancet.* 2012; 379:445–452.

Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. *Pediatrics.* 1971; 48:902–6. [PubMed: 5129451]

Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. *Carcinogenesis.* 1998; 19:1655–1663. [PubMed: 9771938]

Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. Proliferative lesions and reproductive tract tumors in male descendants of mice exposed developmentally to diethylstilbestrol. *Carcinogenesis.* 2000; 21:1355–1363. [PubMed: 10874014]

Paustenbach DJ, Panko JM, Fredrick MM, Finley BL, Proctor DM. Urinary chromium as a biological marker of environmental exposure: What are the limitations? *Regul Toxicol Pharmacol.* 1997; 26:S23–S34. [PubMed: 9380834]

Perkins M, Wright RO, Amarasiwardena CJ, Jayawardene I, Rifas-Shiman SL, Oken E. Very low maternal lead level in pregnancy and birth outcomes in an eastern Massachusetts population. *Ann Epidemiol.* 2014; 24:915–919. [PubMed: 25444892]

Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL. Chlorinated hydrocarbon levels in human serum: Effects of fasting and feeding. *Arch Environ Contam Toxicol.* 1989; 18:495–500. [PubMed: 2505694]

Pollack AZ, Louis GMB, Chen Z, Peterson CM, Sundaram R, Croughan MS, Sun L, Hediger ML, Stanford JB, Varner MW, Palmer CD, Steuerwald AJ, Parsons PJ. Trace elements and endometriosis: The ENDO Study. *Reprod Toxicol.* 2013; 42:41–48. [PubMed: 23892002]

Raymond-Whish S, Mayer LP, O'Neal T, Martinez A, Sellers MA, Christian PJ, Marion SL, Begay C, Proper CR, Hoyer PB, Dyer CA. Drinking water with uranium below the US EPA water standard causes estrogen receptor-dependent responses in female mice. *Environ Health Perspect.* 2007; 115:1711–1716. [PubMed: 18087588]

Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. *Science.* 2001; 293:1089–1093. [PubMed: 11498579]

Richardson DB, Ciampi A. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. *Am J Epidemiol.* 2003; 157:355–363. [PubMed: 12578806]

Robledo CA, Yeung E, Mendola P, Sundaram R, Maisog J, Sweeney AM, Barr DB, Buck Louis GM. Preconception maternal and paternal exposure to persistent organic pollutants and birth size: The LIFE Study. *Environ Health Perspect.* 2015; 123:88–94. [PubMed: 25095280]

Schisterman EF, Vexler A, Whitcomb BW, Liu A. The limitations due to exposure detection limits for regression models. *Am J Epidemiol.* 2006; 163:374–383. [PubMed: 16394206]

Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. *Environ Health Perspect.* 2000; 108:451–455. [PubMed: 10852844]

Shirai S, Suzuki Y, Yoshinaga J, Mizumoto Y. Maternal exposure to low-level heavy metals during pregnancy and birth size. *J Environ Sci Heal A.* 2010; 45:1468–1474.

Squibb KS, McDiarmid MA. Depleted uranium exposure and health effects in Gulf War veterans. *Philos Trans R Soc Lond B Biol Sci.* 2006; 361:639–648. [PubMed: 16687268]

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: A review of the science. *Reprod Sci.* 2008; 15:631–650. [PubMed: 18836129]

- Sunderman FW. Biological monitoring of nickel in humans. *Scand J Work Environ Health*. 1993; 19:34–38. [PubMed: 8159970]
- Sutton P, Giudice LC, Woodruff TJ. Reproductive environmental health. *Curr Opin Obstet Gynecol*. 2010; 22:517–524. [PubMed: 20978443]
- Tian LL, Zhao YC, Wang XC, Gu JL, Sun ZJ, Zhang YL, Wang JX. Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. *Biol Trace Elem Res*. 2009; 132:51–59. [PubMed: 19404590]
- Valko M, Morris H, Cronin MTD. Metals, toxicity and oxidative stress. *Curr Med Chem*. 2005; 12:1161–1208. [PubMed: 15892631]
- van Wijngaarden E, Harrington D, Kobrosly R, Thurston SW, O'Hara T, McSorley EM, Myers GJ, Watson GE, Shamlaye CF, Strain JJ, Davidson PW. Prenatal exposure to methylmercury and LCPUFA in relation to birth weight. *Ann Epidemiol*. 2014; 24:273–278. [PubMed: 24525104]
- Wall MA, Johnson J, Jacob P, Benowitz NL. Cotinine in the serum, saliva, and urine of nonsmokers, passive smokers, and active smokers. *Am J Public Health*. 1988; 78:699–701. [PubMed: 3369604]
- Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. *Paediatr Perinat Epidemiol*. 2009; 23:394–402. [PubMed: 19689488]
- WHO. World Health Organization: Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. *Acta Obstet Gynecol Scand*. 1977; 56:247–253. [PubMed: 560099]
- Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, Krewski D. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Environ Sci Heal B Crit Rev*. 2008; 11:373–517.
- Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect*. 2011; 119:878–885. [PubMed: 21233055]
- Zhang YL, Zhao YC, Wang JX, Zhu HD, Liu QF, Fan YG, Wang NF, Zhao JH, Liu HS, Li OY, Liu AP, Fan TQ. Effect of environmental exposure to cadmium on pregnancy outcome and fetal growth: A study on healthy pregnant women in China. *J Environ Sci Heal A*. 2004; 39:2507–2515.
- Zhu M, Fitzgerald EF, Gelberg KH, Lin S, Druschel CM. Maternal low-level lead exposure and fetal growth. *Environ Health Perspect*. 2010; 118:1471–1475. [PubMed: 20562053]

HIGHLIGHTS

- We assessed the impact of preconception parental trace elements on birth outcomes.
- We detected more effects for paternal exposure, than for maternal exposure.
- We most consistently detected effects for preconception levels of urine W and U.

Table 1

Description of mothers and fathers with singleton deliveries (n=235).

Characteristics ^a	Maternal Mean ± SD or n (%)	Paternal Mean ± SD or n (%)
Age (years)	29.75 ± 3.73	31.52 ± 4.57
BMI (kg/m ²)	26.45 ± 6.48	29.28 ± 5.34
Race/ethnicity		
non-Hispanic white	196 (83.4)	198 (83.9)
Hispanic	20 (8.5)	21 (8.9)
Other ^b	19 (8.1)	17 (7.2)
Education		
<College	9 (3.8)	7 (3.0)
College	226 (96.2)	228 (97.0)
Household income		
30,000–49,999	30 (13.0)	25 (10.7)
50,000–69,999	29 (12.6)	37 (15.8)
70,000	172 (74.5)	172 (73.5)
Health Insurance		
No	6 (2.6)	11 (4.7)
Yes	229 (97.5)	225 (95.3)
Urine creatinine (mg/dL) ^c	62.55 ± 2.40	116.78 ± 2.08
Serum lipids (ng/g serum) ^c	607.56 ± 1.19	699.94 ± 1.29
Serum cotinine (ng/mL):		
100 (Active exposure)	11 (4.7)	24 (10.3)
< 100 (Passive exposure)	220 (94.4)	207 (89.2)
Gravidity (# pregnancies)	1.06 ± 1.23	1.00 ± 1.09
Parity (# live births)	0.70 ± 0.81	0.69 ± 0.75
Prior preterm delivery		
No	120 (95.2)	-
Yes	6 (4.8)	-
Prior LBW delivery		
No	116 (92.1)	-
Yes	10 (7.9)	-

BMI, body mass index; LBW, low birth weight.

^a Categories may not add up to n=235 due to missing values for some variables, or may exceed 100% due to rounding error;^b 'Other' includes non-Hispanic black, multiracial, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander;^c Geometric values.

Table 2

Description of birth outcomes for singleton deliveries (n=235).

Birth outcomes	Mean $\pm$ SD or n (%)	Minimum	25 th %tile	Median	75 th %tile	Maximum
Sex						
Female	119 (50.6%)	-	-	-	-	-
Male	116 (49.4%)	-	-	-	-	-
2 nd sex ratio	0.97 $\pm$ 0.01	-	-	-	-	-
Gestation						
Gestational age at delivery (weeks)	36.66 $\pm$ 2.21	22	36	37	38	42
Preterm delivery ^a	23 (11.3%)	-	-	-	-	-
Delivery by medical intervention	151 (65.9%)	-	-	-	-	-
Birth size						
Weight (grams)	3,382.31 $\pm$ 487.52	2,012.81	3,061.75	3,387.77	3,713.78	5,017.86
Low birth weight	10 (4.3%)	-	-	-	-	-
Length (cm)	50.51 $\pm$ 2.73	43.18	48.26	50.8	53.34	55.88
Head circumference (cm)	34.80 $\pm$ 2.16	27.94	33.02	35.56	35.56	48.26
Ponderal index	2.62 $\pm$ 0.31	1.76	2.40	2.60	2.85	3.63

^a Defined as <35 weeks completed gestation from the date of ovulation.

Table 3

Distribution of select elements measured in blood and urine collected from mothers with singleton deliveries.

Elements	n (%)>LOD	Mean ± SD	Minimum	33 rd %tile	Median	67 th %tile	Maximum
Blood, µg/L (n=231)							
Cd	119 (51.5)	0.24 ± 0.14	<0.20	<0.20	0.21	0.26	0.91
Pb (µg/dL)	229 (99.1)	0.71 ± 0.30	<0.25	0.55	0.66	0.73	2.23
Hg	203 (87.9)	1.39 ± 1.36	<0.33	0.66	0.94	1.38	9.09
Urine, µg/L (n=215)							
Sb	192 (89.3)	0.06 ± 0.07	<0.01	0.02	0.04	0.06	0.52
As	196 (91.2)	17.13 ± 28.76	<2.00	5.18	7.78	13.48	262.31
Ba	183 (85.1)	2.14 ± 2.81	<0.40	0.78	1.47	2.24	32.17
Be	17 (7.9)	0.00 ± 0.15	<0.20	<0.20	<0.20	<0.20	0.47
Cd	205 (95.4)	0.14 ± 0.14	<0.02	0.07	0.10	0.15	0.99
Cs	215 (100.0)	3.61 ± 2.80	0.26	1.92	2.90	4.04	16.95
Cr	121 (56.3)	0.59 ± 0.62	<0.40	<0.40	0.47	0.72	3.42
Co	211 (98.1)	0.37 ± 0.38	<0.03	0.17	0.26	0.38	2.45
Cu	208 (96.7)	9.05 ± 5.94	<2.00	5.48	7.35	10.36	39.17
Pb	200 (93.0)	0.29 ± 0.31	<0.03	0.12	0.22	0.34	3.00
Mn	44 (20.5)	0.14 ± 0.38	<0.20	<0.20	<0.20	<0.20	4.61
Mo	215 (100.0)	46.11 ± 45.32	1.86	17.91	31.43	50.44	256.69
Ni	36 (16.7)	5.23 ± 4.97	<10.00	<10.00	<10.00	<10.00	24.28
Pt	0 (0.0)	-0.01 ± 0.01	<0.02	<0.02	<0.02	<0.02	<0.02
Se	169 (78.6)	30.13 ± 29.48	<7.00	11.21	21.87	36.58	143.29
Te	3 (1.4)	0.06 ± 0.20	<0.50	<0.50	<0.50	<0.50	0.94
Tl	207 (96.3)	0.12 ± 0.11	<0.01	0.06	0.10	0.14	0.68
Sn	172 (80.0)	0.74 ± 1.45	<0.09	0.16	0.31	0.62	12.49
W	103 (47.9)	0.11 ± 0.58	<0.04	<0.04	<0.04	0.08	8.35
U	180 (83.7)	0.006 ± 0.011	<0.001	0.002	0.003	0.006	0.124
Zn	214 (99.5)	200.1 ± 214.6	<5.0	77.6	129.4	218.1	1,699.5

LOD, limit of detection; "<" indicates quantities below the LOD value provided.

Table 4

Distribution of select elements measured in blood and urine collected from fathers with singleton deliveries.

Elements	n (%)>LOD	Mean ± SD	Minimum	33 rd %tile	Median	67 th %tile	Maximum
Blood, µg/L (n=234)							
Cd	81 (34.6)	0.22 ± 0.22	<0.20	<0.20	<0.20	0.21	1.87
Pb (µg/dL)	234 (100.0)	1.13 ± 0.63	0.34	0.84	0.98	1.16	6.43
Hg	214 (91.5)	1.85 ± 2.17	<0.33	0.76	1.11	1.76	16.06
Urine, µg/L (n=213)							
Sb	198 (93.0)	0.10 ± 0.13	<0.01	0.04	0.07	0.09	1.06
As	204 (95.8)	19.65 ± 23.60	<2.00	9.06	12.39	20.15	240.28
Ba	196 (96.0)	2.91 ± 3.89	<0.40	1.18	1.93	2.93	34.78
Be	18 (8.5)	0.02 ± 0.17	<0.20	<0.20	<0.20	<0.20	0.38
Cd	210 (98.6)	0.16 ± 0.14	<0.02	0.08	0.12	0.17	0.90
Cs	213 (100.0)	5.12 ± 3.11	0.55	3.43	4.90	6.10	17.08
Cr	150 (70.4)	0.72 ± 0.54	<0.40	0.46	0.64	0.88	2.98
Co	211 (99.1)	0.34 ± 0.27	<0.03	0.22	0.30	0.39	2.30
Cu	212 (99.5)	11.71 ± 10.05	<2.00	7.38	10.42	13.54	126.09
Pb	211 (99.1)	0.51 ± 0.47	<0.03	0.24	0.39	0.58	3.13
Mn	40 (18.8)	0.14 ± 0.30	<0.20	<0.20	<0.20	<0.20	3.55
Mo	213 (100.0)	62.54 ± 51.01	5.22	32.30	48.90	75.62	268.82
Ni	33 (15.5)	5.63 ± 5.31	<10.00	<10.00	<10.00	<10.00	45.69
Pt	0 (0.0)	-0.01 ± 0.01	<0.02	<0.02	<0.02	<0.02	<0.02
Se	194 (91.1)	48.17 ± 38.82	<7.00	24.85	41.85	57.72	200.14
Te	2 (0.9)	0.08 ± 0.20	<0.50	<0.50	<0.50	<0.50	0.60
Tl	213 (100.0)	0.17 ± 0.12	0.01	0.10	0.16	0.20	0.64
Sn	179 (84.0)	0.89 ± 3.07	<0.09	0.20	0.33	0.55	31.96
W	127 (59.6)	0.11 ± 0.19	<0.04	<0.04	0.06	0.11	2.02
U	185 (86.9)	0.007 ± 0.010	<0.001	0.003	0.004	0.007	0.110
Zn	213 (100.0)	320.7 ± 276.2	13.5	154.4	239.7	363.8	1,417.3

LOD, limit of detection; "<" indicates quantities below the LOD value provided.

Linear regression coefficients (95% confidence intervals) between gestational age, birth weight, and select elements ($\mu\text{g/L}$) measured in blood and urine collected from couples with singleton deliveries.

Table 5

Elements	Terfile ^a	Gestational age (n=231) ^b		Birth weight (n=232) ^c	
		Maternal exposure ^d	Paternal exposure ^e	Maternal exposure ^d	Paternal exposure ^e
Blood, $\mu\text{g/L}$					
Cd	2 nd	0.66 (−0.23, 1.55)	0.15 (−0.73, 1.03)	93.60 (−57.97, 245.17)	55.48 (−95.51, 206.47)
	3 rd	0.69 (−0.22, 1.60)	−0.25 (−1.18, 0.67)	178.52 (24.85, 332.18)	70.20 (−89.28, 229.67)
	P-trend	0.165	0.094	0.033	0.775
Pb ($\mu\text{g/dL}$)	2 nd	0.43 (−0.48, 1.35)	0.19 (−0.70, 1.08)	81.80 (−74.94, 238.55)	20.46 (−134.17, 175.09)
	3 rd	0.14 (−0.81, 1.09)	0.61 (−0.31, 1.53)	−34.85 (−197.76, 128.06)	62.91 (−94.73, 220.55)
	P-trend	0.671	0.416	0.202	0.882
Hg	2 nd	0.68 (−0.20, 1.56)	0.81 (−0.07, 1.69)	145.82 (−5.52, 297.15)	68.36 (−84.00, 220.73)
	3 rd	1.11 (0.18, 2.03)	1.30 (0.36, 2.24)	137.40 (−22.52, 297.32)	125.90 (−37.82, 289.62)
	P-trend	0.098	0.015	0.279	0.122
Urine, $\mu\text{g/L}$					
Sb	2 nd	0.28 (−0.92, 1.47)	−0.14 (−1.26, 0.97)	−68.56 (−264.26, 127.15)	−77.21 (−259.49, 105.07)
	3 rd	0.66 (−0.85, 2.16)	−0.66 (−1.88, 0.57)	−61.04 (−310.55, 188.47)	−140.33 (−339.64, 58.98)
	P-trend	0.262	0.831	0.615	0.268
As	2 nd	−0.40 (−1.43, 0.63)	0.42 (−0.54, 1.38)	−23.75 (−199.00, 151.50)	46.41 (−126.51, 219.33)
	3 rd	−0.02 (−1.17, 1.13)	0.79 (−0.24, 1.82)	38.59 (−152.02, 229.21)	194.71 (17.13, 372.30)
	P-trend	0.458	0.752	0.281	0.322
Ba	2 nd	−0.71 (−1.72, 0.29)	0.25 (−0.77, 1.28)	−103.00 (−275.89, 69.90)	−48.17 (−230.26, 133.91)
	3 rd	−0.50 (−1.66, 0.65)	−0.12 (−1.25, 1.02)	−82.10 (−279.01, 114.81)	25.82 (−162.06, 213.70)
	P-trend	0.673	0.725	0.243	0.967
Cd	2 nd	−0.04 (−1.19, 1.11)	−0.93 (−2.00, 0.15)	−35.76 (−226.69, 155.18)	−175.50 (−367.83, 16.83)
	3 rd	−0.27 (−1.72, 1.17)	−0.86 (−2.11, 0.39)	−99.22 (−337.44, 139.00)	−164.89 (−398.56, 68.77)
	P-trend	0.761	0.254	0.449	0.201

Elements	Terfile ^a	Gestational age (n=231) ^b		Birth weight (n=232) ^c	
		Maternal exposure ^d	Paternal exposure ^e	Maternal exposure ^d	Paternal exposure ^e
Cs	2 nd	-0.70 (-1.89, 0.49)	-0.74 (-1.91, 0.43)	-137.85 (-333.81, 58.10)	-156.25 (-342.15, 29.65)
	3 rd	-0.02 (-1.66, 1.62)	-1.18 (-2.50, 0.14)	-94.47 (-348.03, 159.08)	-237.85 (-463.04, -12.66)
	P-trend	0.936	0.061	0.558	0.032
Cr	2 nd	0.67 (-0.37, 1.71)	-0.11 (-1.21, 0.98)	73.31 (-107.24, 253.86)	-140.52 (-317.40, 36.35)
	3 rd	0.19 (-1.10, 1.48)	-0.13 (-1.30, 1.04)	-30.27 (-243.58, 183.03)	-144.33 (-343.28, 54.62)
	P-trend	0.949	0.095	0.859	0.021
Co	2 nd	0.56 (-0.62, 1.75)	-0.51 (-1.67, 0.65)	41.53 (-141.80, 224.87)	-86.72 (-284.19, 110.76)
	3 rd	0.76 (-0.75, 2.27)	-0.98 (-2.31, 0.35)	101.15 (-130.40, 332.70)	-203.47 (-437.45, 30.51)
	P-trend	0.417	0.824	0.614	0.876
Cu	2 nd	-0.04 (-1.27, 1.20)	-0.53 (-1.70, 0.64)	-64.91 (-263.39, 133.57)	-154.66 (-353.59, 44.27)
	3 rd	0.41 (-1.25, 2.06)	-0.47 (-1.85, 0.92)	-17.63 (-271.45, 236.20)	-144.12 (-385.53, 97.30)
	P-trend	0.744	0.135	0.952	0.455
Pb	2 nd	-0.56 (-1.57, 0.45)	0.20 (-0.84, 1.25)	-25.69 (-196.00, 144.61)	108.04 (-77.61, 293.69)
	3 rd	-0.18 (-1.46, 1.10)	0.04 (-1.11, 1.19)	-84.28 (-290.99, 122.43)	-8.71 (-205.40, 187.98)
	P-trend	0.954	0.737	0.637	0.604
Mo	2 nd	-0.09 (-1.19, 1.02)	0.01 (-1.01, 1.03)	-63.35 (-246.57, 119.88)	-45.05 (-220.12, 130.02)
	3 rd	0.61 (-0.84, 2.06)	-0.69 (-1.93, 0.55)	68.41 (-164.17, 300.99)	-137.05 (-361.17, 87.06)
	P-trend	0.922	0.877	0.947	0.354
Se	2 nd	0.44 (-0.68, 1.56)	-0.62 (-1.70, 0.47)	28.59 (-151.97, 209.15)	-99.33 (-277.40, 78.75)
	3 rd	0.26 (-1.20, 1.72)	-0.68 (-2.03, 0.66)	37.55 (-192.28, 267.38)	-34.03 (-257.16, 189.11)
	P-trend	0.607	0.812	0.536	0.211
Tl	2 nd	-0.18 (-1.33, 0.97)	-0.38 (-1.64, 0.88)	-70.04 (-259.24, 119.16)	-121.67 (-346.84, 103.50)
	3 rd	0.21 (-1.19, 1.62)	-0.68 (-2.11, 0.74)	-48.17 (-295.32, 198.98)	-169.81 (-446.45, 106.82)
	P-trend	0.223	0.651	0.939	0.529
Sn	2 nd	0.13 (-0.95, 1.22)	-0.16 (-1.21, 0.89)	-60.43 (-243.97, 123.11)	-16.88 (-190.85, 157.10)
	3 rd	0.72 (-0.58, 2.03)	-0.23 (-1.30, 0.85)	-24.86 (-238.61, 188.89)	-148.77 (-328.11, 30.57)
	P-trend	0.166	0.788	0.982	0.157

Elements	Terfile ^a	Gestational age (n=231) ^b		Birth weight (n=232) ^c	
		Maternal exposure ^d	Paternal exposure ^e	Maternal exposure ^d	Paternal exposure ^e
W	2 nd	-1.22 (-2.19, -0.25)	-0.13 (-1.08, 0.82)	-99.32 (-264.60, 65.96)	77.81 (-87.89, 243.51)
	3 rd	-0.60 (-1.72, 0.53)	-0.46 (-1.60, 0.68)	-12.23 (-202.23, 177.77)	-6.39 (-207.06, 194.27)
	P-trend	0.784	0.341	0.464	0.535
U	2 nd	-0.09 (-1.11, 0.93)	-1.10 (-2.09, -0.11)	-103.37 (-276.15, 69.41)	-187.34 (-366.34, -8.35)
	3 rd	-0.30 (-1.47, 0.86)	-1.07 (-2.07, -0.07)	-134.87 (-340.64, 70.90)	-142.14 (-319.80, 35.51)
	P-trend	0.494	0.260	0.146	0.133
Zn	2 nd	0.12 (-0.95, 1.19)	-0.89 (-1.92, 0.15)	-11.59 (-194.48, 171.29)	-153.92 (-329.25, 21.40)
	3 rd	0.22 (-1.09, 1.52)	-0.78 (-1.98, 0.43)	-76.51 (-295.15, 142.13)	-209.08 (-417.40, -0.77)
	P-trend	0.835	0.759	0.489	0.290

NOTE: Statistically significant associations (P<0.05) in bold typeface.

^a 1st tertile (not shown) is the reference category, P-trend test based on linear models using continuous exposure;

^b n=3 outliers excluded;

^c n=1 outlier excluded;

^d Effect of maternal exposure adjusted for paternal exposure, maternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL);

^e Effect of paternal exposure adjusted for maternal exposure, paternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL).

Table 6

Linear regression coefficients (95% confidence intervals) between birth length, head circumference, and select elements measured in blood and urine collected from couples with singleton deliveries.

Elements	Terile ^a	Birth length (n=231)		Head circumference (n=182) ^b	
		Maternal exposure ^c	Paternal exposure ^d	Maternal exposure ^c	Paternal exposure ^d
Blood, µg/L					
Cd	2 nd	0.66 (−0.23, 1.55)	0.15 (−0.73, 1.03)	−0.46 (−1.13, 0.21)	0.32 (−0.34, 0.98)
	3 rd	0.69 (−0.22, 1.60)	−0.25 (−1.18, 0.67)	−0.41 (−1.10, 0.28)	0.08 (−0.61, 0.77)
	P-trend	0.165	0.094	0.675	0.485
Pb (µg/dL)	2 nd	0.43 (−0.48, 1.35)	0.19 (−0.70, 1.08)	0.03 (−0.68, 0.74)	0.12 (−0.57, 0.80)
	3 rd	0.14 (−0.81, 1.09)	0.61 (−0.31, 1.53)	−0.33 (−1.07, 0.41)	−0.03 (−0.72, 0.67)
	P-trend	0.671	0.416	0.132	0.971
Hg	2 nd	0.68 (−0.20, 1.56)	0.81 (−0.07, 1.69)	−0.12 (−0.80, 0.57)	−0.04 (−0.71, 0.64)
	3 rd	1.11 (0.18, 2.03)	1.30 (0.36, 2.24)	0.11 (−0.61, 0.84)	0.58 (−0.14, 1.30)
	P-trend	0.098	0.015	0.569	0.067
Urine, µg/L					
Sb	2 nd	0.28 (−0.92, 1.47)	−0.14 (−1.26, 0.97)	0.06 (−0.79, 0.91)	−0.75 (−1.60, 0.11)
	3 rd	0.66 (−0.85, 2.16)	−0.66 (−1.88, 0.57)	0.02 (−1.07, 1.11)	−0.92 (−1.84, 0.01)
	P-trend	0.262	0.831	0.354	0.390
As	2 nd	−0.40 (−1.43, 0.63)	0.42 (−0.54, 1.38)	0.11 (−0.67, 0.89)	−0.57 (−1.30, 0.15)
	3 rd	−0.02 (−1.17, 1.13)	0.79 (−0.24, 1.82)	−0.33 (−1.18, 0.52)	−0.43 (−1.22, 0.36)
	P-trend	0.458	0.752	0.617	0.160
Ba	2 nd	−0.71 (−1.72, 0.29)	0.25 (−0.77, 1.28)	−0.40 (−1.19, 0.40)	−0.35 (−1.15, 0.44)
	3 rd	−0.50 (−1.66, 0.65)	−0.12 (−1.25, 1.02)	−0.22 (−1.08, 0.63)	0.13 (−0.73, 0.99)
	P-trend	0.673	0.725	0.357	0.911
Cd	2 nd	−0.04 (−1.19, 1.11)	−0.93 (−2.00, 0.15)	−0.29 (−1.13, 0.56)	−0.63 (−1.48, 0.22)
	3 rd	−0.27 (−1.72, 1.17)	−0.86 (−2.11, 0.39)	−0.75 (−1.78, 0.29)	−0.08 (−1.17, 1.00)
	P-trend	0.761	0.254	0.972	0.490

Elements	Tertile ^a	Birth length (n=231)		Head circumference (n=182) ^b	
		Maternal exposure ^c	Paternal exposure ^d	Maternal exposure ^c	Paternal exposure ^d
Cs	2 nd	-0.70 (-1.89, 0.49)	-0.74 (-1.91, 0.43)	0.11 (-0.78, 1.01)	-0.84 (-1.73, 0.05)
	3 rd	-0.02 (-1.66, 1.62)	-1.18 (-2.50, 0.14)	-0.57 (-1.79, 0.65)	-0.39 (-1.46, 0.69)
	P-trend	0.936	0.061	0.211	0.516
Cr	2 nd	0.67 (-0.37, 1.71)	-0.11 (-1.21, 0.98)	0.25 (-0.58, 1.07)	-0.73 (-1.52, 0.06)
	3 rd	0.19 (-1.10, 1.48)	-0.13 (-1.30, 1.04)	0.11 (-0.80, 1.03)	-0.74 (-1.62, 0.14)
	P-trend	0.949	0.095	0.820	0.116
Co	2 nd	0.56 (-0.62, 1.75)	-0.51 (-1.67, 0.65)	-0.02 (-0.87, 0.84)	-0.60 (-1.52, 0.32)
	3 rd	0.76 (-0.75, 2.27)	-0.98 (-2.31, 0.35)	0.30 (-0.81, 1.41)	-0.25 (-1.51, 1.02)
	P-trend	0.417	0.824	0.312	0.579
Cu	2 nd	-0.04 (-1.27, 1.20)	-0.53 (-1.70, 0.64)	-0.64 (-1.54, 0.27)	-0.52 (-1.39, 0.306)
	3 rd	0.41 (-1.25, 2.06)	-0.47 (-1.85, 0.92)	-0.58 (-1.71, 0.54)	-0.78 (-1.87, 0.30)
	P-trend	0.744	0.135	0.880	0.874
Pb	2 nd	-0.56 (-1.57, 0.45)	0.20 (-0.84, 1.25)	0.28 (-0.47, 1.03)	0.09 (-0.73, 0.92)
	3 rd	-0.18 (-1.46, 1.10)	0.04 (-1.11, 1.19)	-0.05 (-0.97, 0.87)	-0.31 (-1.20, 0.59)
	P-trend	0.954	0.737	0.387	0.958
Mo	2 nd	-0.09 (-1.19, 1.02)	0.01 (-1.01, 1.03)	0.19 (-0.66, 1.05)	-0.58 (-1.39, 0.23)
	3 rd	0.61 (-0.84, 2.06)	-0.69 (-1.93, 0.55)	0.44 (-0.60, 1.49)	-0.80 (-1.80, 0.19)
	P-trend	0.922	0.877	0.541	0.309
Se	2 nd	0.44 (-0.68, 1.56)	-0.62 (-1.70, 0.47)	0.02 (-0.78, 0.81)	-0.42 (-1.21, 0.36)
	3 rd	0.26 (-1.20, 1.72)	-0.68 (-2.03, 0.66)	-0.28 (-1.28, 0.73)	-0.10 (-1.09, 0.88)
	P-trend	0.607	0.812	0.612	0.369
Tl	2 nd	-0.18 (-1.33, 0.97)	-0.38 (-1.64, 0.88)	-0.32 (-1.14, 0.50)	-0.42 (-1.42, 0.58)
	3 rd	0.21 (-1.19, 1.62)	-0.68 (-2.11, 0.74)	-0.73 (-1.78, 0.33)	-0.78 (-2.04, 0.47)
	P-trend	0.223	0.651	0.325	0.589
Sn	2 nd	0.13 (-0.95, 1.22)	-0.16 (-1.21, 0.89)	0.43 (-0.38, 1.23)	0.17 (-0.64, 0.97)
	3 rd	0.72 (-0.58, 2.03)	-0.23 (-1.30, 0.85)	0.20 (-0.76, 1.15)	-0.02 (-0.88, 0.85)
	P-trend	0.166	0.788	0.593	0.678

Elements	Terile ^a	Birth length (n=231)		Head circumference (n=182) ^b	
		Maternal exposure ^c	Paternal exposure ^d	Maternal exposure ^c	Paternal exposure ^d
W	2 nd	-1.22 (-2.19, - 0.25)	-0.13 (-1.08, 0.82)	0.15 (-0.58, 0.87)	-0.20 (-0.94, 0.55)
	3 rd	-0.60 (-1.72, 0.53)	-0.46 (-1.60, 0.68)	-0.09 (-0.95, 0.77)	-0.12 (-0.99, 0.76)
	P-trend	0.784	0.341	0.815	0.476
U	2 nd	-0.09 (-1.11, 0.93)	-1.10 (-2.09, - 0.11)	-0.14 (-0.89, 0.61)	-0.83 (-1.60, - 0.05)
	3 rd	-0.30 (-1.47, 0.86)	-1.07 (-2.07, - 0.07)	-0.57 (-1.40, 0.25)	-0.81 (-1.64, 0.02)
	P-trend	0.494	0.260	0.116	0.443
Zn	2 nd	0.12 (-0.95, 1.19)	-0.89 (-1.92, 0.15)	-0.16 (-0.97, 0.65)	-0.80 (-1.60, 0.01)
	3 rd	0.22 (-1.09, 1.52)	-0.78 (-1.98, 0.43)	0.02 (-0.92, 0.97)	-0.71 (-1.70, 0.28)
	P-trend	0.835	0.759	0.850	0.412

NOTE: Statistically significant associations (P<0.05) in bold typeface.

^a 1st tertile (not shown) is the reference category, P-trend test based on linear models using continuous exposure;

^b n=2 outliers excluded;

^c Effect of maternal exposure adjusted for paternal exposure, maternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL);

^d Effect of paternal exposure adjusted for maternal exposure, paternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL).

Linear regression coefficients (95% confidence intervals (CI)) and relative risks (95% CI) between ponderal index and newborn sex, respectively, and elements measured in blood and urine collected from couples with singleton deliveries.

Table 7

Elements	Terile ^a	Ponderal index (n=231)		Newborn sex (n=233)	
		Maternal exposure ^b	Paternal exposure ^c	Maternal exposure ^b	Paternal exposure ^c
Blood, µg/L					
Cd	2 nd	-2.80 (-11.06, 5.45)	2.14 (-5.99, 10.26)	0.98 (0.76, 1.28)	0.97 (0.85, 1.10)
	3 rd	2.69 (-5.77, 11.16)	6.41 (-2.17, 14.99)	1.04 (0.80, 1.36)	1.07 (0.93, 1.23)
	P-trend	0.430	0.095	0.704	0.565
Pb (µg/dL)	2 nd	0.82 (-7.66, 9.31)	-0.22 (-8.50, 8.05)	0.97 (0.78, 1.22)	1.12 (0.89, 1.41)
	3 rd	-4.26 (-13.16, 4.64)	-5.19 (-13.71, 3.33)	1.00 (0.81, 1.24)	1.06 (0.84, 1.34)
	P-trend	0.321	0.150	0.884	0.854
Hg	2 nd	-0.03 (-8.30, 8.24)	-6.36 (-14.59, 1.87)	0.96 (0.77, 1.20)	0.97 (0.78, 1.19)
	3 rd	-4.32 (-13.02, 4.38)	-7.45 (-16.25, 1.35)	1.03 (0.81, 1.30)	1.00 (0.80, 1.26)
	P-trend	0.408	0.157	0.408	0.556
Urine, µg/L					
Sb	2 nd	-9.38 (-20.10, 1.35)	-3.96 (-15.72, 7.80)	1.01 (0.72, 1.41)	1.20 (0.87, 1.66)
	3 rd	-13.32 (-26.68, 0.03)	-0.26 (-12.73, 12.20)	1.00 (0.67, 1.49)	1.18 (0.84, 1.67)
	P-trend	0.328	0.445	0.825	0.905
As	2 nd	3.56 (-6.44, 13.56)	-3.16 (-12.85, 6.53)	0.84 (0.63, 1.11)	0.89 (0.70, 1.14)
	3 rd	4.24 (-6.82, 15.30)	2.67 (-6.94, 12.29)	1.05 (0.79, 1.40)	1.07 (0.82, 1.39)
	P-trend	0.628	0.416	0.534	0.851
Ba	2 nd	2.65 (-7.79, 13.10)	-6.11 (-16.34, 4.12)	1.12 (0.83, 1.51)	0.98 (0.74, 1.30)
	3 rd	0.85 (-10.30, 11.99)	1.98 (-9.78, 13.74)	1.03 (0.74, 1.42)	1.03 (0.74, 1.43)
	P-trend	0.470	0.706	0.730	0.944
Cd	2 nd	-0.14 (-10.98, 10.70)	-0.29 (-11.29, 10.71)	1.13 (0.78, 1.66)	1.06 (0.90, 1.26)
	3 rd	0.34 (-12.55, 13.22)	1.40 (-10.97, 13.76)	1.14 (0.74, 1.74)	1.12 (0.91, 1.38)
	P-trend	0.353	0.946	0.872	0.764
Cs	2 nd	-0.80 (-12.06, 10.46)	0.18 (-11.95, 12.32)	1.13 (0.94, 1.36)	0.93 (0.73, 1.18)

Elements	Terile ^a	Ponderal index (n=231)		Newborn sex (n=233)	
		Maternal exposure ^b	Paternal exposure ^c	Maternal exposure ^b	Paternal exposure ^c
	3 rd	-7.10 (-22.16, 7.97)	0.95 (-12.63, 14.54)	1.02 (0.80, 1.30)	0.82 (0.62, 1.09)
	P-trend	0.502	0.897	0.542	0.320
Cr	2 nd	-1.74 (-11.49, 8.01)	-6.81 (-16.39, 2.77)	0.91 (0.75, 1.09)	1.19 (0.84, 1.70)
	3 rd	-1.61 (-13.75, 10.52)	-6.24 (-17.67, 5.20)	0.99 (0.78, 1.25)	1.16 (0.78, 1.72)
	P-trend	0.826	0.709	0.647	0.384
Co	2 nd	-3.22 (-15.10, 8.66)	1.49 (-9.77, 12.74)	1.07 (0.82, 1.38)	1.12 (0.75, 1.66)
	3 rd	-0.07 (-15.06, 14.91)	-0.49 (-13.51, 12.53)	0.99 (0.70, 1.41)	0.96 (0.59, 1.55)
	P-trend	0.708	0.928	0.500	0.688
Cu	2 nd	-3.74 (-14.24, 6.75)	-2.20 (-13.49, 9.08)	1.02 (0.66, 1.57)	1.05 (0.81, 1.37)
	3 rd	-3.76 (-15.81, 8.29)	-1.73 (-12.59, 9.13)	1.22 (0.69, 2.17)	0.95 (0.68, 1.35)
	P-trend	0.787	0.222	0.261	0.903
Pb	2 nd	5.30 (-4.20, 14.80)	3.36 (-6.86, 13.58)	1.23 (0.89, 1.69)	0.97 (0.68, 1.38)
	3 rd	-5.78 (-20.06, 8.49)	-1.54 (-15.79, 12.71)	1.02 (0.68, 1.52)	1.02 (0.69, 1.51)
	P-trend	0.596	0.628	0.671	0.999
Mo	2 nd	-3.79 (-13.43, 5.85)	-3.04 (-14.09, 8.00)	1.13 (0.89, 1.44)	1.14 (0.82, 1.57)
	3 rd	-3.66 (-16.36, 9.04)	0.59 (-12.69, 13.87)	1.13 (0.84, 1.51)	1.09 (0.70, 1.70)
	P-trend	0.927	0.459	0.136	0.869
Se	2 nd	-3.12 (-13.24, 7.00)	1.92 (-8.31, 12.14)	1.12 (0.97, 1.29)	1.11 (0.84, 1.47)
	3 rd	-0.06 (-12.64, 12.52)	6.26 (-7.22, 19.74)	1.09 (0.91, 1.30)	0.96 (0.71, 1.31)
	P-trend	0.856	0.306	0.828	0.405
Tl	2 nd	-3.58 (-13.91, 6.75)	-2.12 (-13.74, 9.50)	1.13 (0.90, 1.41)	1.08 (0.78, 1.48)
	3 rd	-7.33 (-19.76, 5.10)	-0.66 (-14.82, 13.49)	1.06 (0.77, 1.47)	1.14 (0.78, 1.67)
	P-trend	0.112	0.951	0.629	0.937
Sn	2 nd	-4.67 (-14.90, 5.57)	1.37 (-8.83, 11.57)	1.20 (0.82, 1.74)	0.91 (0.61, 1.37)
	3 rd	-8.15 (-20.75, 4.45)	-6.74 (-17.37, 3.88)	1.15 (0.77, 1.71)	1.10 (0.71, 1.73)
	P-trend	0.162	0.208	0.710	0.194
W	2 nd	8.56 (-1.44, 18.57)	5.48 (-4.37, 15.33)	0.96 (0.79, 1.15)	0.96 (0.77, 1.20)

Elements	Tertile ^a	Ponderal index (n=231)		Newborn sex (n=233)	
		Maternal exposure ^b	Paternal exposure ^c	Maternal exposure ^b	Paternal exposure ^c
	3 rd	6.96 (−3.71, 17.62)	4.41 (−8.68, 17.50)	1.05 (0.85, 1.30)	0.89 (0.70, 1.14)
	P-trend	0.631	0.619	0.747	0.401
U	2 nd	−5.04 (−14.33, 4.26)	1.36 (−8.58, 11.30)	1.07 (0.78, 1.47)	1.17 (0.83, 1.63)
	3 rd	−3.23 (−14.51, 8.05)	4.40 (−5.58, 14.38)	1.11 (0.80, 1.54)	1.37 (0.92, 2.03)
	P-trend	0.469	0.803	0.950	0.788
Zn	2 nd	−3.44 (−13.04, 6.16)	2.15 (−7.80, 12.10)	1.17 (0.87, 1.57)	1.10 (0.86, 1.41)
	3 rd	−7.09 (−19.12, 4.94)	−2.72 (−13.93, 8.48)	1.16 (0.81, 1.64)	1.05 (0.83, 1.32)
	P-trend	0.394	0.520	0.478	0.529

NOTE: Statistically significant associations (P<0.05) in bold typeface.

^a 1st tertile (not shown) is the reference category, P-trend test based on linear models using continuous exposure;

^b Effect of maternal exposure adjusted for paternal exposure, maternal age, and difference in maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL);

^c Effect of paternal exposure adjusted for maternal exposure, paternal age, difference in maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL)