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Early Life Environmental Exposure to Cadmium, Lead, and Arsenic and Age at Menarche: A Longitudinal Mother–Child Cohort Study in Bangladesh

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Background: Several metals act as endocrine disruptors, but there are few large longitudinal studies about associations with puberty onset.

Objectives: We evaluated whether early life cadmium, lead, and arsenic exposure was associated with timing of menarche.

Methods: In a mother–child cohort in rural Bangladesh ($n = 935$), the exposure was assessed by concentrations in maternal erythrocytes in early pregnancy and in girls' urine at 5 and 10 years of age using inductively coupled plasma mass spectrometry. The girls were interviewed twice, at average ages 13.3 [standard deviation (SD) = 0.43] and 13.8 (SD = 0.43) y, and the date of menarche, if present, was recorded. Associations were assessed using Kaplan–Meier analysis and multivariable-adjusted Cox regression.

Results: In total, 77% of the girls ($n = 717$) had reached menarche by the second follow-up. The median age of menarche among all girls was 13.0 y (25th–75th percentiles: 12.4–13.7 y). At 10 years of age, median urinary cadmium was 0.25 μg/L (5th–95th percentiles: 0.087–0.72 μg/L), lead 1.6 μg/L (0.70–4.2 μg/L), and arsenic 54 μg/L (19–395 μg/L). Given the same age, girls in the highest quartile of urinary cadmium at 5 and 10 years of age had a lower rate of menarche than girls in the lowest quartile, with an adjusted hazard ratio of (HR) 0.80 (95% CI: 0.62, 1.01) at 5 years of age, and 0.77 (95% CI: 0.60, 0.98) at 10 years of age. This implies that girls in the highest cadmium exposure quartile during childhood had a higher age at menarche. Comparing girls in the highest to the lowest quartile of urinary lead at 10 years of age, the former had a higher rate of menarche [adjusted HR = 1.23 (95% CI: 0.97, 1.56)], implying lower age at menarche, whereas there was no association with urinary lead at 5 years of age. Girls born to mothers in the highest quartile of erythrocyte arsenic during pregnancy were less likely to have attained menarche than girls born to mothers in the lowest quartile [adjusted HR = 0.79 (95% CI: 0.62, 0.99)]. No association was found with girls' urinary arsenic exposure.

Discussion: Long-term childhood cadmium exposure was associated with later menarche, whereas the associations with child lead exposure were inconclusive. Maternal exposure to arsenic, but not cadmium or lead, was associated with later menarche. https://doi.org/10.1289/EHP11121

Introduction

Puberty is the transitional phase between childhood and reproductive maturity. Besides being associated with fertility, puberty is also associated with development of secondary sexual characteristics, rapid growth, and behavioral changes.[1] Altered timing of puberty onset has been linked to various health conditions later in life.[2–5] Earlier menarche, the first menstruation, has been associated with increased risk of metabolic syndrome,[2] cardiovascular disease,[3] and cancer[4] later in life, whereas later menarche has been associated with lower peak bone mass and increased risk of osteoporosis.[5] Puberty starts with the activation of the hypothalamic–pituitary–gonadal (HPG) axis and the secretion of gonadotropin-releasing hormone (GnRH), triggering a hormonal cascade.[1] The timing of puberty depends on a variety of factors, such as genetics (which account for about half of the variability),[6] epigenetic regulation,[7] nutrition, growth trajectories, and exposure to endocrine disrupting chemicals.[8,9]

Emerging evidence indicates that metals, especially lead, commonly present in food, dust, drinking water, and various household items,[10] may alter pubertal development. Studies in Mexico have found that elevated maternal lead exposure during pregnancy, assessed via concentrations in blood[11] and bone,[12] was associated with later menarche in their daughters. In cross-sectional studies from the United States and South Africa, girls' blood lead concentrations were associated with later breast and pubic hair development or menarche[13–15] and with changes in hormonal markers consistent with later puberty.[16] Interestingly, one of these studies reported that a combination of elevated exposure to both lead and cadmium, another metal with endocrine disrupting properties[17] and a common dietary pollutant,[18] was associated with lower inhibin B in girls 6–11 years of age.[16] Inhibin B is a protein involved in the feedback regulation of the HPG axis, and lower concentrations are indicative of pubertal delay.[19] In addition, maternal gestational exposure to cadmium was associated with slower breast development in Mexican girls, and the girls' peripubertal urinary cadmium concentration was associated with later menarche.[20] Another study of girls in the United States reported that childhood exposure to cadmium was associated with later menarche and pubic hair growth.[21] In contrast, an ecological Chinese study reported that women in two heavily cadmium-polluted areas had undergone menarche earlier than women in a control area ($\sim$100–300 girls in each area).[22] Thus, there is a need for large prospective studies on the association between cadmium and puberty.

The aim of this study was to assess whether exposure to cadmium and lead during pregnancy and childhood was associated with age at menarche in a large longitudinal birth cohort in rural Bangladesh with documented low-to-moderate exposure to cadmium and lead.[23,24] In addition, this is a region where drinking water frequently contains elevated arsenic concentrations and we have previously reported that consumption of such water by mothers during pregnancy was associated with later menarche in this cohort.[25] Therefore, a secondary aim of this study was to investigate whether prenatal and childhood exposure to arsenic, assessed through individual exposure markers, was associated

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with age at menarche, and whether it modified the possible associations of cadmium and lead exposure.

Methods

Study Population

This study was conducted in Matlab, a region in Bangladesh located ~50 km southeast of the capital, Dhaka. Participants were children born to women in the Maternal and Infant Nutrition Interventions trial in Matlab (MINIMat, isrctn.org identifier: ISRCTN16581394). The MINIMat trial was a factorial randomized trial with the overarching objective to evaluate whether a combination of multiple micronutrients and food supplementations would improve pregnancy outcomes.[26] Pregnant women were randomly assigned to one of three different supplementations from gestational week (GW) 14; 30 mg iron and 400 µg folate, 60 mg iron and 400 µg folate, or a capsule of 15 recommended micronutrients that included 30 mg iron and 400 µg folate, in combination with food supplementation, which was either provided early (at around GW9) or at the usual timing (at around GW20).[26] From November 2001 to October 2003, community health research workers recruited 4,436 women during early pregnancy, and these pregnancies resulted in 3,625 live-born infants, of which 3,560 were singleton births.

Since birth, extensive follow-ups of the children have been conducted at ~4.5–5, 9–10, and at 12–15 years of age.[27] Of the 3,560 children, 2,307 participated (1,175 girls and 1,132 boys) in the puberty assessment, consisting of two follow-up visits, within the age interval of 12–15 y.[25,28] Reasons for loss to follow-up were outmigration, refusal to participate, and death (Figure S1). In children born in the MINIMat trial between October 2002 and November 2003, the exposure to metals has previously been assessed for the mothers during pregnancy and the children at 5 and 10 years of age ($n = 1{,}530$ at the 10-y follow-up) and thereafter related to outcomes such as anthropometry and neurodevelopment.[29–33] Furthermore, the exposure to metals has also been assessed at 4.5 and 9 years of age in a smaller subsample of the MINIMat children (born at the hospital in Matlab between June 2003 and June 2004; $n = 551$ at the 9-y follow-up) to evaluate the impact on immune function.[34,35] The girls and their mothers in this rural setting are primarily exposed to cadmium through their diet,[36] which is largely based on rice, known to easily take up cadmium from the soil.[18] Lead exposure occurs mainly through food and drinking water, dust, housing materials, and various utensils.[24] Elevated exposure to inorganic arsenic through drinking water and to some extent also via rice is prevalent.[37,38] In the present study, we included all girls who participated in the puberty assessment, had data on menarche, had complete covariate data for the primary analysis and for whom metal exposure had been previously assessed either for their mothers during pregnancy ($n = 771$) or for themselves at 5 ($n = 750$) or at 10 years of age ($n = 745$), resulting in a total of 935 girls (Figure S1).

Written and oral informed consent was obtained from the mothers at enrollment and from the girls, as well as the mother or other guardian, at the time of the puberty follow-ups. The study was conducted in concordance with the Helsinki Declaration, and approved by the Ethical Review Committee at the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) in Bangladesh and the ethical review board in Sweden.

Exposure Assessment

Exposure to cadmium, lead, and arsenic was assessed by the concentrations in the mothers' blood (erythrocyte fraction) during early pregnancy (GW14) and in the girls' urine at 5 and 10 years of age. Both blood and spot urine samples were collected at the health care facilities in Matlab. Erythrocytes were separated from plasma by centrifugation within a couple of hours. The collection and handling of blood samples and spot urine samples has been described in detail.[31,33,39]

Metal concentrations in erythrocytes reflect the exposure over the last few months, given that the erythrocytes' lifespan is about 3–4 months.[40] Cadmium concentration in urine is a measure of long-term exposure, because cadmium accumulates in the renal cortex with a half-life of decades.[41] Urinary lead and arsenic, on the other hand, are short-term exposure biomarkers because lead and arsenic are excreted in urine within a few days of exposure.[24] No blood samples were available from the children at these time points. However, because arsenic is present in the daily consumed water and food, the urinary concentrations reflect ongoing exposure quite well.[38] Arsenic in erythrocytes and urine was measured as total arsenic. We have previously reported that total arsenic in urine and the sum of arsenic metabolites, reflecting exposure to inorganic arsenic specifically, were in good agreement in this cohort, both in the mothers during pregnancy (linear regression coefficient $\beta = 0.93$, $p < 0.001$, and $R^2 = 0.96$)[42] and in the previously mentioned smaller subsample of children that participated in the follow-up at 9 years of age (Spearman's correlation rho = 0.98, $p < 0.001$).[43] In addition, there was a strong correlation between arsenic in erythrocytes and urine in the mothers during pregnancy (linear regression coefficient $\beta = 0.83$, $p < 0.001$, and $R^2 = 0.83$)[42] and in the children at 9 years of age (Spearman's correlation rho = 0.79, $p < 0.001$).[43]

The concentrations of cadmium (*m/z* 111), lead (*m/z* 208), and arsenic (*m/z* 75) were measured using inductively coupled plasma mass spectrometry (ICPMS; Agilent 7500ce or 7700ce; Agilent Technologies) at our laboratory at Karolinska Institutet, Stockholm, Sweden. Before analysis, the erythrocyte samples were diluted 1:25 in an alkali solution [2% (wt:vol) 1-butanol, 0.05% (wt:vol) ethylenediaminetetraacetic acid, 0.05% (wt:vol) Triton X-100, 1% (wt:vol) ammonium hydroxide, and 20 µg/L internal standard; Sigma-Aldrich]. Then they were vortex mixed, sonicated for 5 min, and centrifuged at $179 \times g$ for 2 min (MSE centrifuge, Super Minor; MSE Ltd.).[44] Urine samples were diluted 1:10 with 1% nitric acid (Scharlau, Scharlab, Sentmenat, Spain or Ultrapure Normatom; VWR Chemicals). The limit of detection was 0.006 µg/L, 0.015 µg/L, and 0.011 µg/L for erythrocyte cadmium, lead, and arsenic, respectively, and 0.005 µg/L, 0.007 µg/L, and 0.023 µg/L for urinary cadmium, lead, and arsenic, respectively. No samples were found to have metal concentrations below each respective limit of detection. The details of the quality control have been previously published,[30,34] and in general there was a good agreement between the expected values and our measurements.

A minor fraction of the maternal erythrocyte samples ($n = 269$ of total 771) was analyzed using acid digestion prior to the ICPMS analyses[39] instead of the alkali dilution described above. The results from the two methods were previously found to be strongly correlated when analyzing samples from another mother–child cohort in the Argentinean Andes ($R^2 > 0.96$ for cadmium, lead, and arsenic).[44] However, because the cadmium, lead, and arsenic concentrations were found to be consistently lower using the alkali method (by 9%, 10%, and 5% respectively),[44] the concentrations obtained with the acidic method were multiplied by 0.91 for cadmium, 0.90 for lead, and 0.95 for arsenic. To compensate for urine dilution, metal concentrations in urine were adjusted to the mean specific gravity (mean 1.012 in the children), which was measured with a digital refractometer (EUROMEX RD712 Clinical Refractometer; EUROMEX Holland).[45] Adjustment for specific gravity instead of creatinine has been shown to be more suitable, particularly in growing adolescents.[46]

Outcome Assessment

The assessment of puberty was conducted at health care facilities run by ICCDR,B in Matlab. Information about menstruation, breast, and pubic hair development was collected on two separate occasions, spaced 6 months apart, to optimize the validity of reported menarche.[25,28] Female nurses interviewed the girls about if they had had their first menstruation and its date. Mothers were asked to assist if needed, and a calendar with local events was used. Age at menarche was calculated using the date of birth and the recalled date of first menstruation. This study used menarche data obtained from the second puberty follow-up visit. Data from the first puberty follow-up visit were used for girls who did not participate in the second follow-up ($n = 43$). If two different dates of menarche were reported at the first and second puberty follow-up, we used data from the first, given that it was closer to the event. For girls who did not remember the month, but only the year of menarche ($n = 3$), the month June was imputed, and for girls who remembered the year and month but not the exact date ($n = 362$), the 15th of that month was imputed.

The girls also self-assessed their breast and pubic hair development according to Tanner, guided by pictures.[47] Available information on Tanner stages was primarily used to evaluate consistency with potential associations of the metals and age at menarche.

Covariates

Information concerning maternal and household characteristics was obtained either from the Health and Demographic Surveillance System (HDSS), which has been ongoing in Matlab since 1966 and is maintained by ICDDR,B, Dhaka, Bangladesh, or from the clinic visits and questionnaires administered during the MINIMat trial. The HDSS is continuously updated with data collected by community health research workers who visit the families on a monthly basis, and from here we obtained data to generate a household socioeconomic asset score. The household socioeconomic asset score was thereafter generated through principal component analysis using extensive information on household ownership of various assets, housing structure, and dwelling characteristics.[48] This asset score was categorized into tertiles. From the MINIMat trial we obtained data on maternal smoking during pregnancy (yes/no), maternal age, maternal education, and maternal anthropometry. In accordance with the social norms of the area, none of the women smoked. Maternal weight (in kilograms) was measured at the clinic visit at around GW8 with an electronic scale (Uniscale; SECA) with a precision of 0.1 kg, and maternal height (in centimeters) with a stadiometer to the nearest 0.1 cm. Maternal body mass index (BMI) was calculated as weight/(height in meters).[2] The children's weight and length or height were recorded at birth,[49] during the follow-up survey at 4.5 years of age, and two times during the puberty follow-up in the age interval of 12–15 y[28]; they were thereafter converted into weight- and height-for-age *Z*-scores.[50] Child stunting was defined as lower than (stunted) or above (not stunted) −2 *Z*-scores. The micronutrient supplementation during pregnancy had three categories (30 mg iron and 400 μg folate, 60 mg iron and 400 μg folate, or 15 recommended micronutrients), and the food supplementation during pregnancy had two categories (early or usual timing).

Statistical Analyses

All analyses were performed using Stata (version 16; StataCorp), and the statistical significance level was 0.05. To assess whether there were differences in characteristics between the mother–daughter pairs included ($n = 935$) and not included (owing to missing data on exposure, menarche, or covariates; $n = 240$) in this study, we compared these two groups using Mann-Whitney *U*-tests for continuous variables and Pearson's chi-square tests for categorical variables. We used Spearman's rank correlation to assess correlations between continuous variables.

Associations of gestational and childhood exposure to cadmium, lead, and arsenic with age at menarche were evaluated using so-called survival analysis. We calculated person-time for each girl from date of birth until date of menarche, or censored at second puberty assessment, if available, or first puberty assessment if the second was not available. Age was used as the timescale in all survival analyses. The Kaplan–Meier method was used to calculate the median age at menarche by the exposure biomarkers (maternal erythrocyte concentrations of cadmium, lead, and arsenic and girls' urinary concentrations of cadmium, lead, and arsenic) categorized into quartiles. Thereafter, we conducted Cox proportional hazards regression models to evaluate associations of the exposures (categorized into quartiles) with timing of menarche. The assumption of proportional hazards was evaluated by visually assessing the hazards plot and by testing that the Schoenfeld residuals were independent of time. The effect estimates were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Model 1 presents the crude association of exposure and age at menarche. Model 2 was adjusted for household socioeconomic asset score (in tertiles), maternal BMI at GW8 (in kilograms per meter squared; continuously), and maternal education (years; continuous variable). We selected these three covariates because they were identified as the minimal sufficient adjustment using a directed acyclic graph (DAG; R package dagitty; version 3.0).[51] The DAG indicated no need for adjustment for maternal age (Figure S2). Household socioeconomic asset score and maternal education were correlated (rho = 0.54, $p < 0.001$), but they were both included in the adjustment given that they do not reflect the same aspects. Moreover, these three variables were found to differ between girls who reached menarche earlier or later in this cohort.[28] Body composition or anthropometry at peripubertal age were not included in adjustments because puberty itself is a driver of growth.[52] Finally, we conducted a combined exposure model (model 3) including the time-specific exposure of cadmium, lead, and arsenic simultaneously.

In sensitivity analysis, we additionally adjusted for stunting at 4.5 years of age because childhood (1, 2, and 4.5 years of age) stunting has been associated with later menarche in this cohort[28] and exposure to cadmium and arsenic during the mother's pregnancy and during childhood (at 5 and 10 years of age) has been associated with decreased growth in these children from birth to 10 years of age.[23,29,30,49] Moreover, lead exposure has been associated with impaired growth in another Bangladeshi cohort.[53] Stunting was used as a binary variable, and it was categorized as having a height-for-age *Z*-score (calculated with the measured height at 4.5 years of age through the child growth international reference values developed by the World Health Organization[54]) lower than −2 (stunted) or above (not stunted). We also tested adjusting for the randomized micronutrient and food supplementation groups during pregnancy (three and two categories, respectively).

We used the Kruskal-Wallis *H*-test to assess differences in cadmium, lead, and arsenic exposure (as continuous variables) between the girls at different Tanner developmental stages. Ordered logistic regression models were used to calculate the odds ratios (ORs) representing the relative odds of reaching a more advanced Tanner stage at the second puberty follow-up. The models included the biomarkers of cadmium, lead, and arsenic exposure (categorized into quartiles using the lowest quartile as the reference category) during the mother's pregnancy, at

5 or at 10 years of age, and they were adjusted for household socioeconomic asset score (in tertiles), maternal BMI at GW8 (in kilograms per meter squared; continuously), and maternal education (years; continuous variable).

For the primary survival analysis, we conducted complete-subject analysis and included only mother–daughter pairs with complete covariate data. In the sensitivity analyses of Cox regression data, we again performed the main analyses (models 1–3), as well as models 4 and 5, including the mother–daughter pairs who had available data on stunting at 4.5 years of age, which was the limiting factor. For the analysis of associations between metal exposure and Tanner stages, we included the mother–daughter pairs who had complete covariate data and had participated in the second puberty follow-up.

Results

Participant Selection and Participant Characteristics

Among all girls who participated in at least one of the puberty follow-ups ($n = 1{,}175$), the girls who were included in the present study ($n = 935$) and those who were not (owing to lacking data on menarche or any metal exposure data either during their mother's pregnancy or at 5 or 10 years of age; $n = 240$) were comparable with respect to all measured background characteristics, such as age, weight, and height, as well as household socioeconomic asset score, and maternal BMI and education (Table S1). At enrollment in the MINIMat study, the pregnant women were all nonsmokers, had an average age of 26 y (min–max: 14–50 y) and 22% were considered underweight (BMI $< 18\ kg/m^2$) (Table 1). The mothers had on average attended 4.5 y of schooling (min–max: 0–16 y), and around one-third was illiterate, having never attended school.

The mean weight of girls at the first and second puberty assessment was 38.4 kg (min–max: 19.0–91.6 kg) and 40.6 kg (min–max: 22.7–93.0 kg), respectively, and their mean height was 148 cm (min–max: 121–167 cm) and 150 cm (min–max: 122–167 cm) at the first and the second follow-up. During the first puberty assessment, girls were on average 13.3 years of age [standard deviation (SD) = 0.43, min–max: 12.4–14.2 y] and 61% reported to have had menarche. At the second assessment the mean age was 13.8 y (SD = 0.43, min–max: 12.9–14.7 y) and the percentage who had reached menarche increased to 77%. The median age at menarche was 13.0 y (25th–75th percentiles: 12.4–13.7 y), and the mean recall time between menarche and data collection was 0.8 y (min–max: 0.0–3.6 y). Table S2 summarizes the frequency distribution of the reported age at menarche of the 717 girls who reached this milestone during this study, and the 218 girls who did not. None of the girls had reached menarche before their most recent metal exposure assessment at 10 years of age (min–max: 8.7–10.0 y), and the girl with the youngest age at menarche was 9.9 years old.

At the second puberty follow-up, more than two-thirds of the girls assessed themselves as belonging to Tanner stage 3 of breast development, and the other girls were quite evenly split between stage 2 and stage 4 (Table 1). Regarding pubic hair development, almost all girls were either stage 2 or 3, with only a few participants assessing themselves as stage 1 ($n = 3$) or 4 ($n = 20$) (Table 1).

The concentrations of the exposure biomarkers in this study are presented in Table 2. Median maternal erythrocyte concentrations at GW14 were 0.92 μg/kg (5th–95th percentiles: 0.27–2.3 μg/kg) for cadmium, 72 μg/kg (5th–95th percentiles: 22–150 μg/kg) for lead, and 4.8 μg/kg (5th–95th percentiles: 1.2–22 μg/kg) for arsenic. Maternal erythrocyte cadmium and lead concentrations were moderately correlated (rho = 0.38, $p < 0.001$), whereas maternal arsenic was not correlated with either maternal cadmium or lead. The girls' median urinary cadmium concentrations at 5 and 10 years of age were 0.23 μg/L (5th–95th percentiles: 0.083–0.73 μg/L) and 0.25 μg/L (5th–95th percentiles: 0.087–0.72 μg/L), respectively, and the exposure biomarkers at the two time points were moderately correlated (rho = 0.40, $p < 0.001$). The median urinary lead concentration was 3.4 μg/L (5th–95th percentiles: 1.4–9.8 μg/L) at 5 years of

Table 1. Characteristics of the girls and their mothers during early pregnancy, from a Bangladeshi mother–child cohort recruited between 2001 and 2003, who were included in the present study ($n = 935$).

Characteristics	*n* or *n* (%)	Missing data (*n*)	Mean ± SD or median (5th–95th percentiles)[a]
Mothers or household[b]			
Socioeconomic asset score (min–max)	935	0	—
Low (–5.93 to –0.81)	349 (37)	—	—
Medium (–0.80 to 1.46)	317 (34)	—	—
High (1.47 to 3.98)	269 (29)	—	—
Age (y)	935	0	26 ± 6.1
BMI at GW8 (kg/m^2)	935	0	20 ± 2.6
Education (y)	935	0	4.4 ± 3.9
Parity (no. of children)	935	0	1 (0–4)
Micronutrient supplementation	935	0	
30 mg iron and 400 μg folate	313 (33)	—	—
60 mg iron and 400 μg folate	313 (33)	—	—
15 recommended micronutrients	309 (33)	—	—
Food supplementation	935	0	—
Early timing (at around GW9)	478 (51)	—	—
Usual timing (at around GW20)	457 (49)	—	—
Girls			
Age			
1st follow-up (y)	935	0	13.3 ± 0.43
2nd follow-up (y)[c]	892	0	13.8 ± 0.43
Weight			
1st follow-up (kg)	932	3	38.4 ± 8.3
2nd follow-up (kg)[c]	891	1	40.6 ± 8.1
Height			
1st follow-up (cm)	933	2	148 ± 6.3
2nd follow-up (cm)[c]	891	1	150 ± 5.8
Breast development (Tanner stage)[c]	892	0	—
1	0 (0)	—	—
2	126 (14)	—	—
3	617 (69)	—	—
4	149 (17)	—	—
5	0 (0)	—	—
Pubic hair development (Tanner stage)[c]	892	0	—
1	3 (0.34)	—	—
2	413 (46)	—	—
3	456 (51)	—	—
4	20 (2.2)	—	—
5	0 (0)	—	—
Menarche by 1st follow-up	935	0	—
Yes	572 (61)	—	—
No	363 (39)	—	—
Menarche by 2nd follow-up	935	0	—
Yes	717 (77)	—	—
No	218 (23)	—	—
Age at menarche (y)[d]	717	0	12.66 ± 0.79
Birth weight (g)	935	0	2,647 ± 381
Stunting at 4.5 years of age	890	45	—
Yes	315 (35)	—	—
No	575 (65)	—	—

Note: —, not applicable; BMI, body mass index; GW, gestational week; max, maximum; min, minimum; SD, standard deviation.
[a]Median (5th–95th percentiles) reported for parity, mean ± SD reported for all other variables.
[b]At enrollment.
[c]At second puberty follow-up visit. Participants at second follow-up visit $n = 892$ girls.
[d]Menarche data available for all girls in this study ($n = 935$); 218 girls who had not reached menarche were censored.

age and 1.6 μg/L (5th–95th percentiles: 0.70–4.2 μg/L) at 10 years of age, and the correlation between them was weaker than for cadmium (rho = 0.24, $p < 0.001$). The girls' urinary lead concentrations at 5 and 10 years of age were weakly correlated with the maternal erythrocyte lead concentrations (rho = 0.082, $p < 0.050$). The median total urinary arsenic concentrations at 5 and 10 years of age were 56 μg/L (5th–95th percentiles: 17–353 μg/L) and 54 μg/L (5th–95th percentiles: 19–395 μg/L), respectively, and the arsenic urinary concentrations at the two time points were strongly correlated (rho = 0.57, $p < 0.001$). The girls' urinary arsenic concentrations were moderately correlated with the maternal erythrocyte arsenic concentrations (rho ~ 0.45) (Table S3).

Associations of Exposure to Cadmium, Lead, and Arsenic and Age at Menarche

Tables 3–5 show the median age at menarche for the quartiles of cadmium, lead, and arsenic exposure measured in maternal erythrocytes at GW14 and in the girls' urine at 5 and 10 years of age (unadjusted). A weak trend was observed between increasing concentrations of mothers' erythrocyte cadmium and higher median age at menarche (1.8 months difference between highest and lowest quartile). However, the trends between the girls' urinary cadmium at 5 years of age (2.9 months difference), and especially that at 10 years of age, with increasing age at menarche were more marked. Girls in the highest quartile of urinary cadmium at 10 years of age (>0.39 μg/L, median = 0.51 μg/L, 5th–95th percentiles: 0.40–1.1 μg/L) reached menarche 3.8 months later than girls in the lowest quartile (<0.17 μg/L; Table 3). Median age at menarche varied less consistently across quartiles of urinary lead (Table 4), but girls in the highest quartiles of urinary lead at 5 and 10 years of age reached menarche 2.2 and 3.0 months earlier, respectively, than girls in the lowest quartile (Table 4). We observed a trend of increasing age at menarche with increasing maternal erythrocyte arsenic concentrations, but not with increasing childhood urinary arsenic concentrations. Girls born to

Table 2. Concentrations of cadmium, lead, and arsenic in maternal erythrocytes during pregnancy and child urine at 5 and 10 years of age and range of concentration in each quartile of exposure.

						Percentile	
Exposure biomarker	*n*	Min	Max	Mean ± SD	Median	25th	75th
Erythrocyte Cd GW14 (μg/kg)	771	0.076	4.9	1.1 ± 0.72	0.92	0.61	1.4
Q1	193	0.076	0.61	—	—	—	—
Q2	193	0.61	0.92	—	—	—	—
Q3	193	0.93	1.4	—	—	—	—
Q4	192	1.4	4.9	—	—	—	—
Urinary Cd at 5 years of age (μg/L)[a]	750	0.20	3.8	0.31 ± 0.32	0.23	0.16	0.36
Q1	187	0.02	0.16	—	—	—	—
Q2	188	0.16	0.23	—	—	—	—
Q3	188	0.23	0.36	—	—	—	—
Q4	187	0.36	3.8	—	—	—	—
Urinary Cd at 10 years of age (μg/L)[a]	745	0.016	2.9	32 ± 0.25	0.25	0.17	0.39
Q1	187	0.016	0.17	—	—	—	—
Q2	186	0.17	0.25	—	—	—	—
Q3	186	0.26	0.39	—	—	—	—
Q4	186	0.39	2.9	—	—	—	—
Erythrocyte Pb GW14 (μg/kg)	771	7.0	607	78 ± 44	72	50	96
Q1	193	7	50	—	—	—	—
Q2	193	50	72	—	—	—	—
Q3	193	72	97	—	—	—	—
Q4	192	97	607	—	—	—	—
Urinary Pb at 5 years of age (μg/L)[a]	750	0.30	44	4.3 ± 3.4	3.4	2.4	5.2
Q1	187	0.3	2.4	—	—	—	—
Q2	188	2.4	3.4	—	—	—	—
Q3	188	3.4	5.2	—	—	—	—
Q4	187	5.3	44	—	—	—	—
Urinary Pb at 10 years of age (μg/L)[a]	745	0.059	12	1.9 ± 1.2	1.6	1.2	2.2
Q1	187	0.059	1.2	—	—	—	—
Q2	186	1.2	1.6	—	—	—	—
Q3	186	1.6	2.2	—	—	—	—
Q4	186	2.2	12	—	—	—	—
Erythrocyte As GW14 (μg/kg)	771	0.15	62	7.8 ± 7.6	4.8	2.4	11
Q1	193	0.15	2.4	—	—	—	—
Q2	193	2.4	4.8	—	—	—	—
Q3	193	4.8	11	—	—	—	—
Q4	192	11	62	—	—	—	—
Urinary As at 5 years of age (μg/L)[a]	750	6	1,152	104 ± 129	56	32	124
Q1	188	6	32	—	—	—	—
Q2	187	32	56	—	—	—	—
Q3	188	56	124	—	—	—	—
Q4	187	124	1,152	—	—	—	—
Urinary As at 10 years of age (μg/L)[a]	745	8.9	847	106 ± 126	54	33	121
Q1	187	8.9	33	—	—	—	—
Q2	186	33	54	—	—	—	—
Q3	186	54	121	—	—	—	—
Q4	186	121	847	—	—	—	—

Note: —, not shown; As, arsenic; Cd, cadmium; max, maximum; min, minimum; Pb, lead; Q, quartile; SD, standard deviation.
[a]Adjusted for urinary specific gravity.

Table 3. Cox regression models of girls' early life cadmium exposure (maternal erythrocyte concentrations at gestational week 14, urinary concentrations at 5 and 10 years of age), and age at menarche.

Exposure biomarker (median)	*n*	Time at risk (person-years)	Median age at menarche (y)[a]	Model 1		Model 2		Model 3	
				HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Erythrocyte Cd GW14 (μg/kg)	771	—	—	—	—	—	—	—	—
Q1 (0.44)	193	2,472	12.93	1.00	—	1.00	—	1.00	—
Q2 (0.77)	193	2,490	12.97	0.91 (0.73, 1.13)	0.39	0.94 (0.75, 1.18)	0.59	0.99 (0.78, 1.25)	0.91
Q3 (1.1)	193	2,499	13.11	0.86 (0.68, 1.07)	0.17	0.90 (0.72, 1.13)	0.36	0.94 (0.74, 1.19)	0.61
Q4 (1.8)	192	2,490	13.08	0.84 (0.67, 1.05)	0.13	0.91 (0.72, 1.14)	0.40	0.97 (0.76, 1.24)	0.83
Urinary Cd at 5 years of age (μg/L)	750	—	—	—	—	—	—	—	—
Q1 (0.12)	187	2,391	12.84	1.00	—	1.00	—	1.00	—
Q2 (0.19)	188	2,417	13.01	0.86 (0.68, 1.08)	0.20	0.88 (0.70, 1.10)	0.26	0.86 (0.68, 1.09)	0.22
Q3 (0.27)	188	2,415	13.11	0.87 (0.69, 1.10)	0.24	0.91 (0.72, 1.14)	0.41	0.89 (0.71, 1.13)	0.34
Q4 (0.50)	187	2,421	13.08	0.76 (0.60, 0.95)	0.018	0.81 (0.64, 1.02)	0.077	0.80 (0.62, 1.01)	0.065
Urinary Cd at 10 years of age (μg/L)	745	—	—	—	—	—	—	—	—
Q1 (0.12)	187	2,406	12.95	1.00	—	1.00	—	1.00	—
Q2 (0.21)	186	2,375	12.89	1.10 (0.88, 1.38)	0.42	1.11 (0.88, 1.40)	0.36	1.10 (0.87, 1.38)	0.43
Q3 (0.30)	186	2,383	12.89	1.07 (0.85, 1.35)	0.55	1.16 (0.92, 1.47)	0.21	1.15 (0.91, 1.45)	0.25
Q4 (0.51)	186	2,420	13.27	0.73 (0.57, 0.93)	0.010	0.77 (0.61, 0.99)	0.039	0.77 (0.60, 0.98)	0.035

Note: —, not applicable; Cd, cadmium; CI, confidence interval; GW, gestational week; HR, hazard ratio; Q, quartile.
[a]Unadjusted, calculated from Kaplan–Meier.
Model 1: adjusted for age of the child.
Model 2: additionally adjusted for household socioeconomic asset score at enrollment (tertiles), maternal body mass index at GW8 (kg/m^2), and maternal education at enrollment (y).
Model 3: additionally adjusted for lead and arsenic exposure in quartiles at the corresponding time points (maternal erythrocyte concentrations at GW14 and girls' urinary concentrations at 5 and 10 years of age).

mothers in the highest quartile of arsenic exposure reached menarche 5.5 months later than those born to mothers in the lowest quartile (Table 5). Figures S3–S5 show the cumulative incidence of menarche per quartile of cadmium, lead, and arsenic exposure at the three exposure time points.

In the Cox proportional hazard models (Tables 3–5), we did not find any consistent associations between maternal erythrocyte cadmium or lead concentration during pregnancy and the daughters' age at menarche. Instead, we found that girls born to mothers belonging to the highest quartile of erythrocyte arsenic had a 21% (HR = 0.79; 95% CI: 0.62, 0.99) lower rate of menarche than girls born to mothers in the lowest quartile of exposure. The HRs did not vary markedly with adjustments (Table 5). Regarding the relationship between metal exposure during childhood and age at menarche, we observed that girls in the highest quartile of urinary cadmium at 5 and 10 years of age had 20% (HR = 0.80; 95% CI: 0.62, 1.01) and 23% (HR = 0.77; 95% CI: 0.60, 0.98) lower rate of menarche at a given age than girls in the lowest quartile of exposure. The associations were very consistent regardless of adjustment (Table 3). For lead, we observed that the girls in the highest quartile of urinary lead at 10 years of age, but not at 5 years of age, obtained menarche earlier than those in the lowest quartile (Table 4), and after adjustments the HR remained similar but with a CI including 1.00 (HR = 1.23; 95% CI: 0.97, 1.56). No associations were found between urinary arsenic concentrations during childhood and age at menarche (Table 5).

In sensitivity analysis, the association between the girls' urinary cadmium concentrations at 5 years of age and later menarche was weakened following adjustment for stunting at 4.5 years of age (HR = 0.84; 95% CI: 0.66, 1.07), whereas that with urinary cadmium at 10 years of age remained the same (HR = 0.78; 95% CI: 0.61, 0.99) (Table S4, model 4). Adjustment for stunting at 4.5 years of age also weakened the association between urinary lead at 10 years of age and earlier menarche (Table S5, model 4). Instead, the association between maternal erythrocyte arsenic and later menarche was not affected by adjusting for stunting at 4.5 years of age (Table S6, model 4). Following additional adjustment for micronutrient and food supplementation groups during pregnancy, all the HRs remained unchanged (Tables S4–S6, model 5).

Associations of Exposure to Cadmium, Lead, and Arsenic and Tanner Developmental Stages

There was a statistically significant difference in urinary cadmium concentrations at 10 years of age between the girls at different stages of both breast and pubic hair development (Table S7). Girls assessing themselves to more advanced breast and pubic hair developmental Tanner stages had lower concentrations of urinary cadmium at 10 years of age. We also observed a significant difference in maternal erythrocyte lead concentrations by stages of breast development and in urinary lead concentrations at 5 years of age by stages of pubic hair development. Girls assessing themselves to more advanced breast developmental Tanner stages were born to mothers with higher erythrocyte lead concentrations during pregnancy, and girls assessing themselves to more advanced pubic hair developmental Tanner stages had higher concentrations of urinary lead at 5 years of age. No statistically significant difference in concentrations of urinary lead at 10 years of age could be observed between girls at different stages of either breast or pubic hair development. There was a statistically significant difference in concentrations of maternal erythrocyte arsenic between girls at different stages of breast development, as well as in concentrations of urinary arsenic at 10 years of age by stages of pubic hair development. The erythrocyte arsenic concentrations during pregnancy were lower in mothers of girls assessing themselves to more advanced breast developmental Tanner stages, and the urinary arsenic concentrations at 10 years of age were lower in girls with more advanced pubic hair development.

In ordered logistic regression models, neither gestational cadmium exposure, nor early childhood exposure (until 5 years of age) was associated with Tanner stages (Table S8). Girls belonging to the highest quartile of cadmium exposure at 10 years of age had lower odds of reaching an advanced stage of breast development (OR = 0.63; 95% CI: 0.40, 0.99) than the girls in the lowest quartile. Although maternal erythrocyte lead concentrations were not associated with Tanner stages in the daughters, the girls in the third and fourth quartiles of urinary lead concentrations at 5 years of age had higher odds of being at a more advanced stage of pubic hair development than the girls in the first quartile (Table S9). Moreover, girls belonging to the highest

Table 4. Cox regression models of girls' early life lead exposure (maternal erythrocyte concentrations at gestational week 14, urinary concentrations at 5 and 10 years of age), and age at menarche.

Exposure biomarker (median)	n	Time at risk (person-years)	Median age at menarche (y)[a]	Model 1		Model 2		Model 3	
				HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Erythrocyte Pb GW14 (μg/kg)	771	—	—	—	—	—	—	—	—
Q1 (36)	193	2,468	12.82	1.00	—	1.00	—	1.00	—
Q2 (61)	193	2,506	13.18	0.78 (0.62, 0.98)	0.030	0.78 (0.62, 0.98)	0.032	0.81 (0.64, 1.03)	0.086
Q3 (82)	193	2,501	13.06	0.87 (0.70, 1.09)	0.22	0.86 (0.69, 1.07)	0.18	0.89 (0.70, 1.12)	0.32
Q4 (118)	192	2,476	12.99	0.90 (0.72, 1.13)	0.37	0.85 (0.68, 1.06)	0.14	0.86 (0.68, 1.09)	0.20
Urinary Pb at 5 years of age (μg/L)	750	—	—	—	—	—	—	—	—
Q1 (1.8)	187	2,423	13.11	1.00	—	1.00	—	1.00	—
Q2 (2.9)	188	2,409	13.05	1.09 (0.85, 1.38)	0.50	1.08 (0.85, 1.37)	0.53	1.09 (0.86, 1.39)	0.49
Q3 (4.3)	188	2,409	12.99	1.15 (0.91, 1.46)	0.25	1.14 (0.90, 1.44)	0.29	1.17 (0.92, 1.49)	0.19
Q4 (7.1)	187	2,403	12.93	1.13 (0.89, 1.42)	0.33	1.09 (0.86, 1.38)	0.49	1.15 (0.90, 1.47)	0.25
Urinary Pb at 10 years of age (μg/L)	745	—	—	—	—	—	—	—	—
Q1 (0.89)	187	2,426	13.12	1.00	—	1.00	—	1.00	—
Q2 (1.4)	186	2,385	12.96	1.26 (0.99, 1.59)	0.054	1.27 (1.00, 1.60)	0.049	1.24 (0.98, 1.57)	0.076
Q3 (1.9)	186	2,394	13.14	1.04 (0.82, 1.32)	0.75	0.99 (0.78, 1.27)	0.97	0.99 (0.78, 1.27)	0.98
Q4 (2.8)	186	2,379	12.87	1.28 (1.01, 1.62)	0.039	1.21 (0.95, 1.53)	0.12	1.23 (0.97, 1.56)	0.094

Note: —, not applicable; CI, confidence interval; GW, gestational week; HR, hazard ratio; Pb, lead; Q, quartile.
[a]Unadjusted, calculated from Kaplan–Meier.
Model 1: adjusted for age of the child.
Model 2: additionally adjusted for household socioeconomic asset score at enrollment (tertiles), maternal body mass index at GW8 (kg/m^2), and maternal education at enrollment (y).
Model 3: additionally adjusted for cadmium and arsenic exposure in quartiles at the corresponding time points (maternal erythrocyte concentrations at GW14 and girls' urinary concentrations at 5 and 10 years of age).

quartile of urinary lead exposure at 10 years of age had higher odds of reaching a more advanced breast development stage (OR = 1.62; 95% CI: 1.03, 2.54) than girls in the lowest quartile of exposure. We found no statistically significant associations between maternal or childhood arsenic exposure and Tanner stages in ordered logistic regression models (Table S10). However, there was a statistically significant trend between erythrocyte arsenic concentrations and more advanced breast development.

Discussion

The first menstruation does not only change girls' lives during adolescence, but its timing also has the potential of influencing their health for decades to come.[2–5] In this large prospective cohort study of 935 girls, long-term elevated exposure to cadmium during childhood, determined as concentrations in urine at 5 and 10 years of age, was associated with a delay of menarche of ~3–4 months. There was a suggested association between ongoing lead exposure at 10 years of age, but not at 5 years of age or prenatally, and earlier menarche. Elevated maternal exposure to arsenic in early pregnancy was associated with later menarche in the daughters.

The finding of later menarche in girls with the highest long-term cadmium exposure during childhood (median urinary cadmium median ~ 0.5 μg/L in the highest quartile at both 5 and 10 years of age), which still implies low-level exposure, is consistent with the observation that urinary cadmium at 10 years of age was associated with later breast development at the second puberty follow-up. It is also in agreement with the results of two previous longitudinal studies. The first study[20] included 132 Mexican girls, who were 8–13 years of age at baseline and 14–18 years of age at the follow-up, and whose urinary cadmium concentration at baseline (median = 0.1 μg/L) was approximately one-half of that in the present study (median = 0.23 μg/L at 5 years of age and 0.25 μg/L at 10 years of age). Similar to our findings, they found that the girls' peripubertal urinary cadmium concentration was associated with later menarche, whereas maternal urinary cadmium during pregnancy showed no association.[20] The other study was conducted in the United States and included 211 girls, 11–13 years of age at baseline, who were followed for up to 2 y.[21] The reported urinary cadmium concentrations were similar (mean 0.26 μg/L) to those we observed, and elevated concentrations were associated with later menarche. However, while we compensated for the variation in urine dilution by adjusting for specific gravity, this U.S. study adjusted either the measured urinary concentrations or the Cox regression models for urinary creatinine. Creatinine adjustment may not be optimal for growing children and teenagers,[46] given that creatinine is associated with muscle mass, which is likely to increase during the peripubertal growth spurt.[55] Therefore, creatinine adjustment can lead to an underestimation of the exposure in more-developed children. Indeed, they found that the creatinine-adjusted urinary cadmium concentrations decreased with increasing age.[21] Because urinary cadmium reflects the accumulation in the renal cortex,[41] it usually increases with age, as found in the present study. The two previous studies also adjusted the models for the girls' body fat mass[21] or the BMI Z-score around puberty[20] although an increment in fat mass, like growth, is part of normal pubertal development.[52] We adjusted for stunting at 4.5 years of age in our sensitivity analyses to evaluate whether the association under study was mediated through a cadmium-related decrease in growth during early childhood.[23,29,30] Still, this adjustment did not alter the results. This suggests that cadmium may affect puberty onset through other modes of action, possibly through endocrine disruption, as discussed further below.

Animal studies on cadmium and reproductive maturity have yielded inconsistent results, probably due to differences in doses and mode of administration.[17,56–59] However, some of the experimental studies that administered cadmium orally have also reported later reproductive maturity in rats.[56–58] Later vaginal opening and an extended estrous cycle were observed in young females exposed after weaning[58] and in female offspring following exposure of the pregnant dams.[56,57] In contrast to the latter experimental studies, we did not observe any association between maternal erythrocyte cadmium during pregnancy and age at menarche. This could partly be due to the fact that cadmium accumulates in the human placenta with only little passing over to the fetus,[60] whereas it has been observed to readily pass through the rodent placenta, although it cannot be excluded that the difference is dose dependent.[61]

Table 5. Cox regression models of girls' early life arsenic exposure (maternal erythrocyte concentrations at gestational week 14, urinary concentrations at 5 and 10 years of age), and age at menarche.

Exposure biomarker (median)	n	Time at risk (person-years)	Median age at menarche (y)[a]	Model 1		Model 2		Model 3	
				HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Erythrocyte As GW14 (μg/kg)	771	—	—	—	—	—	—	—	—
Q1 (1.6)	193	2,464	12.82	1.00	—	1.00	—	1.00	—
Q2 (3.4)	193	2,498	13.06	0.89 (0.71, 1.11)	0.29	0.92 (0.74, 1.15)	0.46	0.93 (0.74, 1.17)	0.55
Q3 (7.6)	193	2,481	12.91	0.93 (0.74, 1.16)	0.51	0.95 (0.76, 1.19)	0.66	0.95 (0.76, 1.19)	0.66
Q4 (16)	192	2,508	13.28	0.73 (0.58, 0.91)	0.006	0.78 (0.62, 0.97)	0.029	0.79 (0.62, 0.99)	0.043
Urinary As at 5 years of age (μg/L)	750	—	—	—	—	—	—	—	—
Q1 (22)	188	2,399	12.85	1.00	—	1.00	—	1.00	—
Q2 (0.42)	187	2,405	13.01	0.91 (0.72, 1.14)	0.41	0.89 (0.70, 1.12)	0.33	0.89 (0.70, 1.13)	0.33
Q3 (77)	188	2,420	13.02	0.85 (0.67, 1.07)	0.17	0.85 (0.67, 1.08)	0.18	0.87 (0.68, 1.10)	0.23
Q4 (212)	187	2,420	13.05	0.86 (0.69, 1.09)	0.21	0.89 (0.71, 1.12)	0.33	0.89 (0.70, 1.12)	0.31
Urinary As at 10 years of age (μg/L)	745	—	—	—	—	—	—	—	—
Q1 (25)	187	2,399	12.97	1.00	—	1.00	—	1.00	—
Q2 (42)	186	2,391	13.02	1.02 (0.81, 1.29)	0.87	1.13 (0.89, 1.43)	0.31	1.14 (0.90, 1.44)	0.29
Q3 (73)	186	2,388	12.99	1.04 (0.82, 1.32)	0.73	1.12 (0.89, 1.42)	0.34	1.16 (0.91, 1.48)	0.22
Q4 (237)	186	2,407	13.02	0.93 (0.74, 1.18)	0.55	1.04 (0.82, 1.32)	0.76	1.07 (0.84, 1.36)	0.58

Note: —, not applicable; As, arsenic; CI, confidence interval; GW, gestational week; HR, hazard ratio; Q, quartile.
[a]Unadjusted, calculated from Kaplan–Meier.
Model 1: adjusted for age of the child.
Model 2: additionally adjusted for household socioeconomic asset score at enrollment (tertiles), maternal body mass index at GW8 (kg/m^2), and maternal education at enrollment (y).
Model 3: additionally adjusted for cadmium and lead exposure in quartiles at the corresponding time points (maternal erythrocyte concentrations at GW14 and girls' urinary concentrations at 5 and 10 years).

Cadmium has been reported to have estrogen-mimicking properties both *in vitro* and *in vivo*,[17,62–64] and could, therefore, be expected to result in earlier menarche. However, studies concerning the relationship between cadmium exposure and the hormones regulating puberty and menarche onset are scarce. The Mexican study mentioned above reported an association between peripubertal urinary cadmium and later menarche but did not find any associations between cadmium exposure and concentrations of pubertal hormones, including estradiol, although there was a tendency of inverse association with inhibin B, suggestive of pubertal delay.[20] A National Health and Nutrition Examination Survey (NHANES) III study also reported that girls with the combination of urinary cadmium and blood lead above the median values had lower inhibin B.[16] However, the girls included in that study were very young (6–11 years of age, $n = 260$) and a third of them had cadmium concentrations below the limit of detection. Some animal studies have found a decrease in serum testosterone, estradiol, and progesterone following cadmium exposure, as well as increased lipid peroxidation and decreased antioxidant enzymes in the ovaries.[57,58,65] Others have reported an activation of steroidogenesis and increased serum estradiol and progesterone concentrations in the female offspring of cadmium-treated pregnant dams.[66] These conflicting results emphasize the need for further research on cadmium exposure and hormonal levels before and during reproductive maturation in large epidemiological studies with girls in the right developmental window.

Exposure to lead prenatally and during childhood has repeatedly been reported to be associated with later menarche,[11,12,14,15] whereas a large ($n = 918$) longitudinal study in the UK found no association between prenatal lead exposure and timing of menarche.[67] Instead, we found indications that the girls in the highest quartile of lead exposure at 10 years of age reached menarche earlier than those in the lowest quartile. This was consistent with the association of more advanced breast development in the same girls. We observed an association between urinary lead at 5 years of age, but not at 10 years of age, and more advanced pubic hair development. However, because Tanner stages were self-assessed and less reliable than data on menarche, these findings should be interpreted with caution. Furthermore, we cannot exclude that the indicated association of urinary lead at 10 years of age and menarche might be due to reverse causality. During rapid pubertal growth, which may even precede menarche, the increased bone tissue turnover may release lead, which accumulates in bone,[10] thus leading to increased urinary lead concentrations. The lack of association between age at menarche and urinary lead at 5 years of age, that is, before the peripubertal growth spurt occurs, is consistent with this hypothesis. Furthermore, urinary lead, which was used to assess the girls' childhood exposure, is not an optimal biomarker for lead exposure. It is a short-time marker and can, therefore, be susceptible to day-to-day variation.[68] In addition, the urinary lead concentrations at 5 years of age were about twice those at 10 years of age, indicating changes in childhood exposure over time.

Our result of an association between elevated exposure to inorganic arsenic in early pregnancy and later menarche in the daughters is in accordance with the previous study in this cohort, showing an association between elevated arsenic concentrations in drinking water consumed in pregnancy and later menarche in the daughters.[25] In both studies, the association of later menarche was observed only in girls born to mothers belonging to the highest quartile of arsenic exposure (median erythrocyte arsenic $= 16$ μg/kg in this study). Besides the advantage that arsenic exposure was measured through biomarkers in the present study, it was also measured both during the mother's pregnancy and twice during childhood. Interestingly, we did not observe any association with the girls' own arsenic exposure in childhood. Although urinary arsenic is a short-term exposure biomarker, we found a fairly strong correlation between the concentrations at 5 and 10 years of age (median concentrations $= 56$ μg/L and 54 μg/L, rho $= 0.57$), indicating quite stable exposure over time on a group level, as shown previously.[38] However, at an individual level, the exposure may fluctuate because the children use different water sources at home and at school. It appears difficult to mitigate the elevated arsenic exposure through drinking water and there is additional exposure through rice, the main staple food.[38]

It can be speculated that the influence of arsenic exposure on menarche may be due to an epigenetic effect by arsenic during fetal life, previously documented in this cohort.[69,70] Animal studies have reported contradictory results. Studies in rats exposed to arsenic pre- and postnatally have reported later puberty and lower estrogen levels,[71–73] whereas studies of prenatal exposure to arsenic in mice have indicated an earlier puberty onset.[74,75]

Given the conflicting evidence, and the many millions of people exposed to arsenic worldwide, further research on arsenic-related effects on timing of puberty onset is warranted.

The strengths of this study include the large number of participating girls compared with prior studies on menarche and the longitudinal design with individual exposure assessment of all metals at two time points in childhood (each with narrow age span) and in the mothers during pregnancy. Furthermore, the timing of the two puberty follow-ups, one at 13.3 years of age and the other at 13.8 years of age, resulted in short periods between menarche and the data collection, on average only 0.8 y, minimizing recall bias. Menarche is a relatively late marker of sexual maturation, but an acknowledged and reliable indicator of the onset of puberty. It is a significant milestone for girls and highly correlated with age at thelarche (the time of first breast development), the first sign of female puberty.[52] Another strength is that the ranges of exposure to cadmium, lead, and arsenic were quite wide. The 5th–95th percentiles of urinary cadmium at 10 years of age were 0.09–0.72 μg/L, thus encompassing concentrations reported in children and pregnant women living in widely different settings around the world.[20,21,76,77] Cadmium exposure occurs predominantly through food, especially cereals and root vegetables because the plants easily take up cadmium from the soil,[18] and tobacco smoking.[18] Therefore, the observed associations regarding cadmium may be particularly relevant for the many millions of girls who consume a rice-based diet.

This study also has several limitations. Foremost, there were no measures of concentrations of lead in blood of the children. Another limitation is that data on age at menarche of the mothers was unavailable. Maternal menarche would have been an important factor to consider, given that it has been reported that genetics account for around half of the variability in age at menarche.[6] Moreover, although we knew that all the mothers were nonsmokers, we did not have data on other family members' smoking habits. Such exposure could result in unmeasured confounding, given that prenatal and childhood exposure to passive smoke has previously been associated with an earlier onset of puberty.[78,79] Although tobacco smoking is a source of cadmium and lead, exposure to passive smoking is not associated with higher cadmium exposure in children.[80] However, it may contribute to children's exposure to lead.[81] The role of air pollution due to indoor cooking, which is frequent in the study area, in puberty development is still largely unknown. Another limitation is that we were not able to adjust for other environmental pollutants such as polycyclic aromatic hydrocarbons (PAHs) and dichlorodiphenyltrichloroethane (DDT), which have previously been associated with altered pubertal timing,[82–84] and to which the participants may have been exposed to via indoor air pollution or food. We also did not have data on when the spot urine samples were collected during the day, although the possible exposure misclassification would bias our results toward the null hypothesis.

In conclusion, we found that exposure to cadmium during childhood, but not gestational exposure, was associated with later menarche. We could not ascertain an association between maternal or childhood exposure to lead and age at menarche. In addition, elevated arsenic exposure during pregnancy was associated with later menarche in the daughters. More research is needed to assess whether the found shift in menarche might play a role in the health effects of cadmium and arsenic exposure later in life.

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