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A cohort study of the association between prenatal arsenic exposure and age at menarche in a rural area, Bangladesh

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ABSTRACT

Background: Millions of individuals worldwide, particularly in Bangladesh, are exposed to arsenic, mainly through drinking water from tube wells. Arsenic is a reproductive toxicant, but there is limited knowledge of whether it influences pubertal development.

Objectives: We evaluated the association between prenatal arsenic exposure and age at menarche.

Methods: This prospective study was based on data from two studies conducted in Matlab, Bangladesh—the Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial and the Health Consequences of Arsenic in Matlab (AsMat) study. We included 809 MINIMat girls who participated in assessing age at menarche from July 2016 to June 2017 and had prenatal arsenic exposure data through the AsMat study via measurements in tube well water used by the mothers during pregnancy. The exposure was categorized into <10, 10–49, 50–99, 100–199, and ≥200 μg/L. We used Kaplan-Meier and Cox proportional hazards analyses with adjustment for potential confounders to evaluate the association between arsenic exposure and age at menarche. The results were presented by adjusted hazards ratio (aHR) with a 95% confidence interval (CI).

Results: The median arsenic concentration in tube well water consumed by pregnant women was 80 μg/L (interquartile range 2–262 μg/L), and 55% drank water with concentrations above Bangladesh's acceptable value of 50 μg/L. The median age at menarche was 13.0 years. The unadjusted analysis revealed 3.2 months delay in menarche for girls exposed to arsenic concentrations ≥200 μg/L compared with the girl exposed to arsenic concentrations <10 μg/L. Girls exposed to the same higher arsenic concentrations were 23% (aHR 0.77, 95% CI: 0.63–0.95) less likely to have reached menarche than girls exposed to low arsenic concentrations.

Conclusions: Increased levels of prenatal arsenic exposure were associated with older age at menarche. This delay may indicate endocrine disruptions that could potentially result in adverse health consequences in later life. This finding, along with other severe adverse health reinforces the need for arsenic mitigation at the population level.

1. Introduction

Puberty is the transition from childhood to the attainment of mature reproductive functions. It is characterized by accelerated growth, development of secondary sexual characteristics, and psychological changes (Buck Louis et al. 2008). Menarche, the first menstrual period, is a prominent event in the sexual maturation of adolescent girls. The timing of onset of puberty, including age at menarche, is of public health interest due to its association with a wide range of adverse health outcomes in later life. The studies have reported various cancers, cardiometabolic, gynecological, and neurocognitive disease in later life (Day et al. 2015). Several factors are associated with the onset of puberty, such as nutrition, health conditions, genetics, and exposure to environmental toxicants (Canelon and Boland 2020; Morris et al. 2011; Villamor and Jansen 2016). Epidemiological studies have increasingly reported associations between exposure to certain naturally occurring

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metals and chemical compounds and several reproductive endpoints, including age at menarche (Chalupka and Chalupka 2010).

Arsenic contamination in groundwater exists in many parts of the world. Millions worldwide, particularly in Bangladesh, are exposed to arsenic mainly through drinking water from tube wells. The high content of arsenic in tube wells in Bangladesh probably originates from Ganges' delta fine alluvial sediments (Ahmad et al. 2018). Based on adverse health consequences of arsenic exposure, the World Health Organization (WHO) issued a provisional guideline value for arsenic drinking water less than 10 μg/L (National Research Council 2001; Smith et al. 2000; WHO 1993). However, Bangladesh continues to follow the previous WHO guideline value of 50 μg arsenic/L in drinking water as an acceptable level (WHO 1984). Studies have reported associations between arsenic exposure and increased risk of a wide range of diseases and conditions, including skin lesions (Rahman et al. 2006), cardiovascular (Moon et al. 2012; Rahman 2002) and respiratory diseases (Milton and Rahman 2002) and lung function (von Ehrenstein et al. 2005), type-2 diabetes (Navas-Acien et al. 2006), and malignancies of skin and internal organs (International Agency for Research on Cancer 2004).

Arsenic can easily pass through the placenta and poses a threat to early human development (Concha et al., 1998a). Previous studies have reported that prenatal arsenic exposure was associated with adverse pregnancy outcomes, including spontaneous abortion (Milton et al. 2005; Rahman et al. 2007), stillbirth (Milton et al. 2005; von Ehrenstein et al. 2006) and low birthweight (Rahman et al. 2009). Other studies have reported associations between prenatal arsenic exposure and children's neurocognitive development (Hamadani et al. 2011; Tolins et al. 2014; Vahter et al. 2020; von Ehrenstein et al. 2007), and in some studies, these associations have been reported to more pronounced in girls than in boys (Hamadani et al. 2011; Vahter et al. 2020).

Animal studies have indicated an association between arsenic exposure and endocrine disruption and altered sexual maturation (Davey et al. 2007; Davey et al. 2008; Davila-Esqueda et al. 2012; Kaltreider et al. 2001; Reilly et al. 2014). In contrast to the studies that reported delay in sexual maturation (Davila-Esqueda et al. 2012; Reilly et al. 2014), two studies conducted on female mice (Li et al. 2018; Rodriguez et al. 2016) reported early onset of puberty. While the possible roles of arsenic exposure on pubertal development in animal models have been increasingly published, the knowledge regarding the possible impact of arsenic exposure on the timing of pubertal development, including age at menarche, in girls in arsenic-affected areas is limited. So far, only two ecological studies have suggested that age at menarche was delayed when exposed to high arsenic levels (Sen and Chaudhuri 2007; Sengupta 2004). The first study evaluated 385 girls aged 15–20 years living in arsenic (>50 μg/L) and non-arsenic affected areas. The study observed that the mean age of menarche was 14.0 and 13.3 years in girls from areas of high (>50 μg/L) and low concentrations of arsenic in tube well water, respectively (Sengupta 2004). The second study evaluated 280 girls from four villages where water arsenic concentrations varied from 10 to 600 μg/L and 70 girls from a control village with arsenic concentrations in tube well water ranged from 10 to 300 μg/L. The study has reported the mean age at menarche 12.5 and 11.7 years in arsenic affected and control villages, respectively (Sen and Chaudhuri 2007). The studies had some limitations in exposure and outcome assessments.

No studies have previously addressed this research question based on prospectively collected information and individual arsenic exposure data. Therefore, we aimed to study the association between individual prenatal arsenic exposure and age at menarche in adolescent girls in a well-characterized cohort with a follow-up from birth to puberty in Matlab, Bangladesh.

2. Subjects and Methods

2.1. Study site

We conducted this study in Matlab Upazila, a sub-district under Chandpur, Bangladesh, located 55 km southeast of the capital Dhaka. This area is one of the most arsenic-affected regions in Bangladesh. About 70% of tube wells had arsenic concentrations exceeding the WHO guideline value of 10 μg/L (Rahman et al. 2006). The International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b) has been running a Health and Demographic Surveillance System (HDSS) in Matlab since 1966. In the HDSS area, Community Health Research Workers collect information on vital events such as marriage, birth, death, and migration by monthly home visits. The present study was conducted in half of the HDSS area, covering a population of about 110,000, in which icddr,b provides health services to women of reproductive age and their children up to five years of age. The study area is divided into four administrative blocks, and each block has a sub-center that provides primary obstetric and child health care through the paramedical staff. The sub-centers are linked to the Matlab Hospital, which provides maternal and child health services by nursing staff supervised by medical officers.

2.2. Study design and participants

The study was based on data from two research projects conducted in the HDSS area – the Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial (isrctn.org identifier: ISRCTN16581394) and the Health Consequences of Arsenic in Matlab (AsMat) study. The MINIMat trial enrolled pregnant women from November 2001 to October 2003 and randomly allocated them into different food and micronutrient supplementation groups to evaluate birth outcomes and child survival (Persson et al. 2012). The mother–child cohort of the MINIMat trial has been prospectively followed for a wide range of assessments. In the present study, we included the children who participated in the follow-up for evaluating growth and pubertal development, including information on the occurrence and age at menarche of participating girls from July 2016 to Jun 2017. In the cross-sectional AsMat study, conducted from January 2002 to August 2003, all household members were interviewed regarding lifetime drinking water sources used by the study participants, combined with the collection of tube well water samples to assess the individual arsenic exposure. The household is a unique structure within a 'bari' where all the members eat from the same cooking pot. A 'bari' is a cluster of households using a common courtyard. Each household usually installs a tube well for washing and drinking purposes. However, a household from a low socioeconomic group may not afford a tube well. In those instances, the members may use water from tube wells of neighboring households. The details of study procedures in the MINIMat (Arifeen et al. 2018) and the AsMat (Rahman et al. 2006) studies have been presented elsewhere. In the present analysis, girls in the MINIMat cohort who participated in assessing age at menarche and where information on their mothers' drinking water sources was available from the AsMat databases were eligible for analysis.

2.3. Exposure assessment

The individual prenatal arsenic exposure of MINIMat girls was based on arsenic concentration in the tube well water used by their mothers during pregnancy. Using the unique registration number from the HDSS, we extracted information on the tube well water used by the MINIMat women during their pregnancy from the AsMat databases. In the AsMat study, an independent team visited all households in the HDSS area to provide a unique identification number to all active tube wells. Teams of field workers collected information on lifetime drinking water sources and duration of uses of those sources for all inhabitants above the age of

four years in the study area by moving from household to household and interviewing the family members. A follow-up team subsequently visited already interviewed households to collect water samples from all functioning tube wells. All the above activities enabled the construction of chronological years of consumption of arsenic in the study participants' drinking water. The total arsenic concentration in water was measured by hydride generation atomic absorption spectrophotometry (model AA6800 spectrophotometer; Shimadzu Corporation, Kyoto, Japan) at the icddr,b laboratory (Vahter et al. 2006). The limit of detection (LOD) was 1 μg/L, and samples with values below LOD were assigned a value of LOD/2.

2.4. Outcome assessment

The outcome of the study was the age at menarche. Information on pubertal development was collected on two occasions, six months apart, to increase the validity of reported menarcheal age data collection. The first assessment was conducted from July 2016 to January 2017, and the second one from January 2017 to June 2017. All participants who took part in the first follow up were also invited for a second follow up visit after about six months. We used the age at menarche data collected in the second follow-up visit. However, for girls who did not participate in the second follow up, we used the information from the first follow up visit. If the information on age (date) at menarche differed between the first and the second follow-up, we used the information collected closer to the event (i.e., the first visit). Data on menarche were collected by asking the girls whether or not they had had their menstruation. If the girl had menstruation already, the exact day, month and year of the first menstruation were assessed by a recall. The interviewers used a local events calendar if needed. If the girl did not recall the exact day, the 15th of the month was imputed. Subsequently, the age at menarche was calculated by analyzing the exact time between the birth date from the MINIMat database and the first menstruation date. If the girl had not had her first menstruation, the follow-up was censored at the date of the second visit or the first visit when the girls did not reappear for the second assessment.

2.5. Covariates

Covariate information was obtained from the MINIMat databases that captured the mother's physical and socio-demographic data at pregnancy, delivery, and follow-up of the girls at 4.5 and 12–15 years of age. Maternal weight and height were assessed at first clinic visits in the sub-center during enrollment, usually around gestational week eight, using SECA, Uniscale, Hamburg, Germany (precision 100 g), and a locally made wooden scale (precision 0.1 cm). The mothers' body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Birthweight and birth length were collected using an electronic scale (SECA, Hamburg, Germany, precision 10 g) and a collapsible locally made length board (precision 0.1 cm), respectively. At birth, gestational age was calculated by subtracting the last menstrual period date, collected monthly by community health research workers, from the infant's delivery date. Information on maternal age, parity, and achieved educational level was obtained from the HDSS databases. Maternal education was expressed as the number of years in formal schooling. Socioeconomic status, defined as an asset score, was analyzed through principal component analysis based on the collected household asset ownership, including land possession and housing structures. We obtained children's height data from follow-up databases at 12–15 years of age to determine the height-for-age Z-score (HAZ) and subsequent categorization to stunted (<-2 Z-score) and not-stunted (≥-2 Z-score) children. Furthermore, we used the MINIMat intervention (different nutrition supplementations) as a covariate in the analysis. The MINIMat intervention groups were: supplementation of 30 mg iron and 400 μg of folic acid, 60 mg iron and 400 μg of folic acid or multiple micronutrients, including 30 mg iron and 400 μg of folic acid, combined with early (around nine gestation weeks) or late (around 20 gestation weeks) daily food supplementation (Arifeen et al. 2018; Persson et al. 2012).

2.6. Statistical analysis

Data were presented as means, medians, and proportions. Kaplan-Meier survival analysis was used to assess the median age at menarche. Associations between covariates (mother's age, BMI, parity, education, socioeconomic status, children's birthweight, height-for-age at 12–15 years, and supplementation group) and outcomes were assessed by log-rank test. Non-parametric tests determined associations between covariates and arsenic exposure. The covariates associated with arsenic exposure and outcome were identified as potential confounders and included in the final multivariable-adjusted model. The girls' prenatal arsenic exposure was expressed as water arsenic concentration measured in the tube well water used by the mothers during pregnancy. The exposure was categorized into levels <10, 10–49, 50–99, 100–199, and ≥200 μg/L. The categorization was done based on an earlier study in the same study area (Sohel et al. 2009) and easy interpretation of the problem's magnitude by policymakers. We also dichotomized the exposures according to Bangladesh's drinking water guidelines (<50 μg/L and ≥50 μg/L). Furthermore, due to a low number of girls in the categories between 10 and 200 μg/L, we assessed the risk by dividing the tube well arsenic concentrations into tertiles.

The association between arsenic exposure and age at menarche was evaluated by Cox proportional hazards model, including potential confounding factors. We used robust cluster errors in the regression analysis to estimate risks to account for multiple users of a tube well. We also performed the analysis limited to tube wells that were only used by one pregnant woman. The effect estimates were presented as adjusted hazards ratio (aHR) and 95% confidence intervals (CI). Date of birth was assigned as time = 0, and follow-up was censored if the outcome of interest (occurrence of menarche) had not happened at the interview date of the second follow up visit or at the first visit date of the girls who did not reappear for assessment. We used Stata version 13 for all statistical analyses (StataCorp, College Station, TX, USA).

3. Results

3.1. Participant selection

Out of the total of 4436 pregnant women enrolled in the MINIMat trial from February 2002 to January 2003, 3625 had live births, whereof 3560 were singletons. A total of 2307 children (1175 girls and 1132 boys) were followed up at 12–15 years of age. Out of the total girls who completed the pubertal follow-up, 809 had arsenic exposure information during the prenatal period and were included in the analysis (Fig. 1). All participants included in the analysis attended the first follow up, however, 770 girls reappeared in the second visit.

3.2. Characteristics of study girls and their mothers

The characteristics of pregnant women and their children enrolled in the MINIMat study are presented in Table 1. The mean (±SD) age of women at delivery was 26.7 (±6) years, and 37% were less than 25 years old. The mean weight and height of the women measured at 8 weeks of gestation were 45 (±6.7) kg and 150 (±5) cm, respectively, and 29% of women were underweight (BMI < 18.5 kg/m^2). The mean birthweight and gestational age at delivery of study girls were 2671 (±365) g and 39.5(±1.5) weeks, respectively. During the first and second pubertal follow-up, the mean and median (minimum, maximum) ages were 13.2 (±0.45), 13.2 (12.4, 14.2) and 13.8 (±0.46), 13.7(12.9, 14.7) years, respectively.

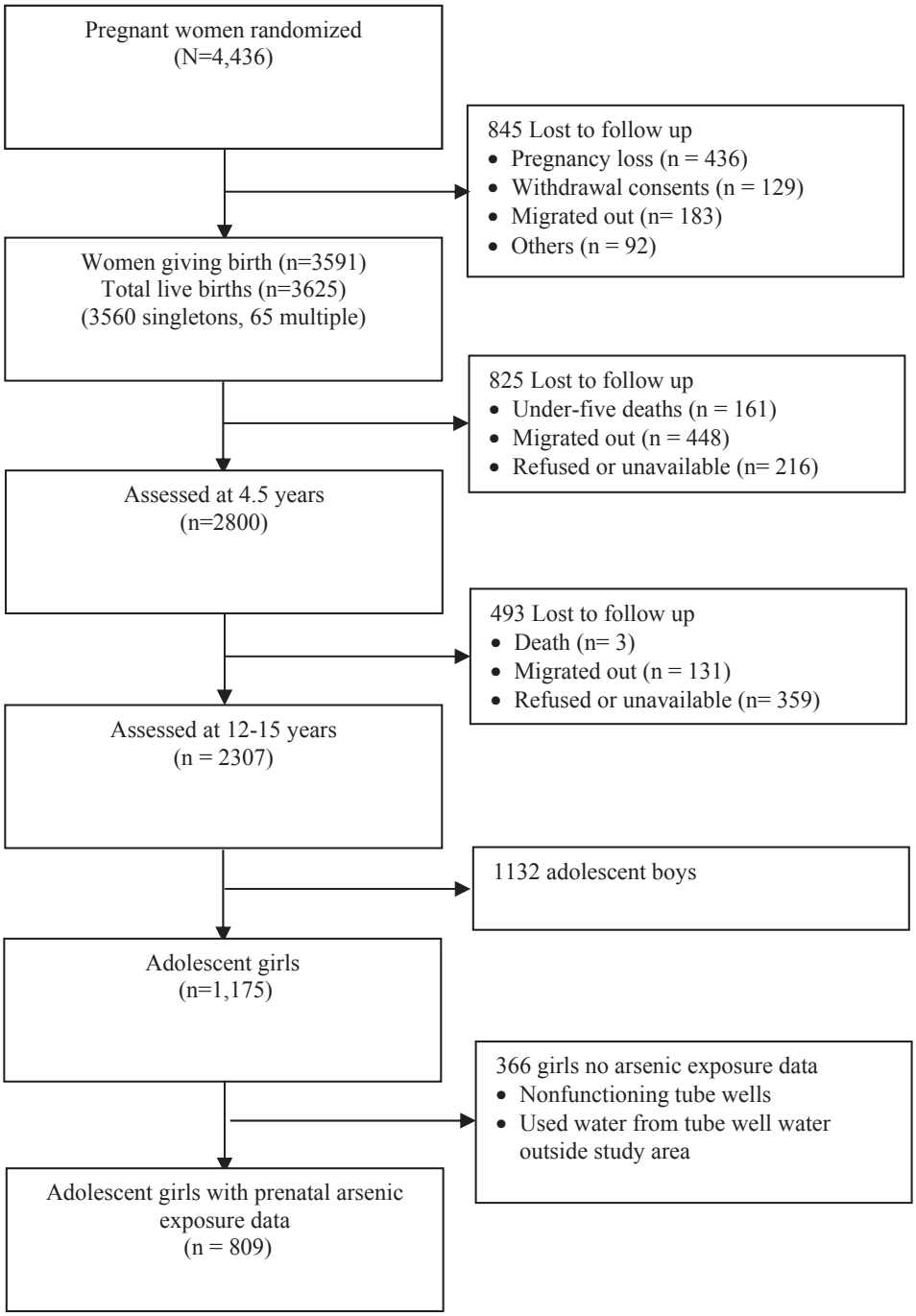

Fig. 1. Study profile.

3.3. Arsenic exposure and age at menarche, and their associations with covariates

The distributions of arsenic exposures are presented in Table 2. The median and mean arsenic concentrations in tube well water consumed by the pregnant women were 80 μg/L and 156 μg/L (±178), respectively. About 55% of the women were drinking tube well water with arsenic concentrations above Bangladesh's acceptable value of 50 μg/L. About 16.8% of tube wells were used by more than one mother, and 2% (n = 15) changed tube well during pregnancy.

Out of 809 girls, 39 (4.8%) did not appear in the second visit. Four girls did not report menarche occurrence at first visits and did not appear for the second assessment. All girls were able to report the year and month of menarche if it had happened. However, 245 (49%) girls could not report the exact day of the first menstruation. Table 3 presents the distribution of age at menarche of adolescent girls. The median age at menarche was 13.0 (95% CI: 12.9–13.1) years. About 61% and 76.4% of girls had reached menarche during the first and second follow-up visits, respectively. The median (minimum, maximum) recall period between menarche and data collection was 0.5 (0, 3.3) years.

Table 4 presents the associations of selected maternal and child characteristics with age at menarche and the corresponding median prenatal arsenic exposure. Maternal education, household asset scores, and maternal BMI were identified as potential confounders (Table 4) and thus adjusted for in the multivariable-adjusted model.

Table1
Characteristics of mothers and the adolescent girls participated in the follow up 2016–2017 in Matlab, Bangladesh.

	Included in analysis		Not included in analysis		
Maternal characteristics	No.	%	No.	%	P-value
Age at birth of infants(years)					
<25	300	37.1	199	54.4	<0.001
25–34	416	51.4	147	40.2	
≥35	93	11.5	20	5.5	
Parity					
0	166	20.5	149	40.7	<0.001
1–2	458	56.7	164	44.8	
≥3	184	22.8	53	14.5	
Body mass index(kg/m^2) at 8 weeks of gestation					
<18.5	234	29.0	111	30.5	0.0182
18.5–24.9	529	65.6	242	66.5	
≥25	44	5.4	11	3.0	
Mother's education (years)					
0	285	35.2	121	33.1	0.258
1–5	213	26.3	86	23.5	
>5	311	38.5	159	43.4	
Wealth scores in tertile					
1	290	35.8	142	38.8	0.431
2	274	33.9	126	34.4	
3	245	30.3	98	26.8	
Girls' characteristics					
Birthweight (g)					
<2500	257	31.8	146	39.9	0.007
≥2500	552	68.2	220	60.1	
Gestational age at birth (weeks)					
<37	43	5.3	26	7.1	0.227
≥37	766	94.7	340	92.9	
Education (years in school)					
<6	35	4.5		6.7	0.135
≥6	739	95.5	322	93.3	
Height-for-age Z –score at puberty					
Not stunted (≥−2)	667	82.5	276	76.2	0.011
Stunted (<−2)	141	17.5	687	23.8	

Table 2
The concentrations of arsenic in tube well water consumed by mothers of adolescent girls during pregnancy.

Arsenic level (μg/L)	Pregnancy		Arsenic concentration, group median ((μg/L)
	No.	%	
<10	280	34.6	0.5
10–49	86	10.6	23.0
50–99	46	5.7	68.1
100–199	106	13.1	158.3
≥200	291	36.0	327.6
Arsenic levels in μg/L by tertiles (minimum, maximum)			
1 (0.5, 7.8)	269	33.2	0.5
2 (7.9, 216)	270	33.4	76.9
3 (216.5,1014.7)	270	33.4	338.0

Table 3
Frequency distribution of reported age at menarche of adolescent girls in Matlab, Bangladesh (n = 809).

Age	Frequency of menarche	Percentage	Cumulative percentage
9.0–9.9	1	0.12	0.12
10.0–10.9	14	1.73	1.85
11.0–11.9	115	14.22	16.07
12.0–12.9	277	34.24	50.31
13.0–13.9	198	24.47	74.78
14.0–14.9	13	1.61	76.39

Table 4
Associations of selected maternal and girls' characteristics with age at menarche and prenatal arsenic exposure in Matlab, Bangladesh.

	Number	Age at menarche in years		Arsenic level in μg/L	
Maternal characteristics		Median	P-value[a]	Median	P-value[b]
Age at birth of infants (years)					
<25	300	13.3	<0.001	67	0.211
25–34	416	13.0		111	
≥35	93	12.7		53	
Parity					
0	166	12.8		46	0.681
1–2	458	13.0		103	
≥3	184	13.1		76	
Education (years)					
0	285	13.2	<0.001	157	0.002
1–5	213	13.1		53	
>5	311	12.7		49	
Wealth score in tertiles					
1 (poorer)	290	13.2	<0.001	185	<0.001
2 (medium)	274	13.1		68	
3 (richer)	245	12.6		26	
Body mass index (kg/m^2) at gestational week 8					
<18.5	234	13.1	<0.001	142	0.002
18.5–24.9	529	13.0		92	
≥25	44	12.5		15	
Prenatal supplementation groups[c]					
1	124	13.0	0.580	111	0.714
2	151	12.8		111	
3	138	12.9		68	
4	147	13.0		108	
5	122	13.0		70	
6	127	13.1		70	
Girls' characteristics					
Birthweight (g)					
<2500	257	13.0	0.826	102	0.860
>=2500	552	13.0		76	
Education at pubertal follow up (years in school)					
<6	35	12.9	0.387	102	1.0
≥6	739	13.0		88	
Height-for-age Z-score at 12–15 years					
Not stunted (≥−2)	667	12.8	<0.001	92	0.501
Stunted (<−2)	141	13.7		52	
Age at pubertal follow up (years)					
<14	759	13.0	0.097	83	0.683
≥14	51	13.1		105	

[a] by log-rank test.
[b] by median test.
[c] supplementation groups: 1 = early food + 30 mg iron and 400 μg of folic acid, 2 = early food + 30 mg iron and 400 μg of folic acid, 3 = early food + multiple micronutrient , 4 = late food + 30 mg iron and 400 μg of folic acid, 5 = late food + 60 mg iron and 400 μg of folic acid, 6 late food + multiple micronutrient.

3.4. Associations between arsenic exposure and age at menarche

The girls' prenatal arsenic exposure was associated with their age at menarche (Fig. 2). Age at menarche of girls with prenatal arsenic exposure ≥200 μg/L was delayed by 3.2 months compared to girls with prenatal arsenic exposure <10 μg/L in the unadjusted analysis (Fig. 2, Table 5). Girls exposed to the same high arsenic level in the prenatal period were 23% (aHR 0.77, 95% CI: 0.63–0.95) less likely to have

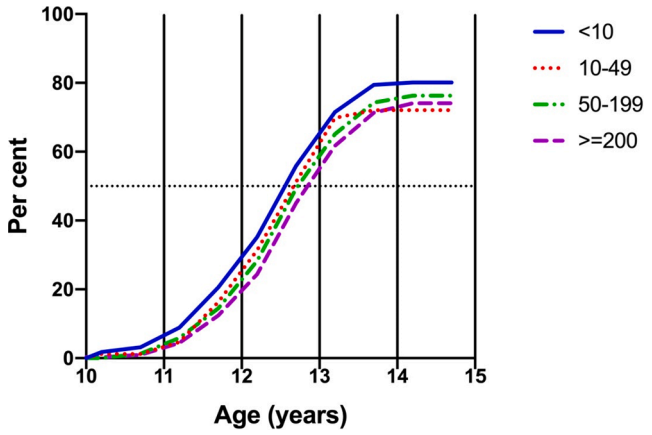

Fig. 2. Cumulative proportions of menarche by age for different prenatal arsenic exposure levels (μg arsenic/L in drinking water) in Matlab, Bangladesh.

reached menarche than girls exposed to low arsenic levels. When the analysis was limited to tube well users by single study participants, the likelihood of reaching menarche was similar (aHR 0.73, 95% CI: 0.59–0.89) in the high exposure group (≥200 μg/L) (Table 5). Exposure above Bangladesh's acceptable level of arsenic (≥50 μg/L) implied 2.8 months delay in the timing of menarche, and the aHR of 0.84 (95% CI: 0.70–0.99) compared with the girls who had exposure to arsenic below the accepted level (<50 μg/L) in drinking water.

Furthermore, when we included stunting of adolescent girls at first follow up visit as a covariate, the aHRs were 0.77 (95% CI: 0.57–1.06), 0.81 (95% CI: 0.53–1.25), 0.78 (95% CI 0.61–1.01),

and 0.74 (95% CI: 0.61–0.90) in the 10–49, 50–99, 100–199 and ≥200 μg/L arsenic concentration groups in drinking water, respectively, compared with the group in < 10 μg/L. Using the two water sources' averages for the 15 women who changed the tube well in pregnancy, we did not observe any change in the effect estimates (data not shown). The aHRs were 0.82 (95% CI: 0.66–0.1.03) and 0.75 (95% CI: 0.60–0.93) in the group second and third tertiles of arsenic exposures, respectively, compared with the group exposed in the first tertile.

4. Discussion

Pubertal development, including age at menarche, is a significant public health issue due to its implications for future health and well-being. In this prospective cohort study, we evaluated the associations of individual arsenic exposure in intrauterine life with age at menarche in the offspring for the first time. We report that early life arsenic exposure was associated with later age at menarche. Girls exposed to ≥200 μg arsenic/L were 23% less likely to have reached menarche at the time of follow-up than girls with arsenic concentrations below the WHO guideline value of 10 μg arsenic/L in water. A categorization according to Bangladesh's acceptable value of 50 μg arsenic/L in drinking water yielded similar results. Girls exposed to higher concentrations were 16% less likely to have reached menarche at the time of follow-up than those exposed to lower concentrations.

No previous epidemiological studies with individual exposure data have evaluated the association between early-life arsenic exposure and age at menarche. Two ecological studies from West Bengal, India, suggested such associations when comparing age at menarche in different villages with different arsenic levels in drinking water (Sen and Chaudhuri 2007; Sengupta 2004). Further, those studies lacked sufficient information on how the age at menarche was assessed. Although we measured individual water arsenic concentrations from tube wells, we observed that more than one woman used 16.8% of tube wells during pregnancy. We used robust clustered standard errors for estimating the risk in the regression model to address the issue of multiple users of a tube well. Furthermore, we did not find any change in effect estimation when the analysis was restricted to tube wells used by a single woman. For better exposure assessment, future studies should consider using urine arsenic concentrations or other biomarkers to capture individual exposure from drinking water and food (Hughes 2006).

The possible mechanisms of how arsenic may influence pubertal development in humans have so far not been studied. Experimental animal studies have documented that arsenic at low doses acts as an endocrine disruptor, possibly through an estrogenic mode of action (Bodwell et al. 2004; Davey et al. 2008; Jana et al. 2006; Kaltreider et al. 2001). Estrogen is a sex steroid, and menarche is mainly related to estrogen levels (Apter 1980; Apter and Vihko 1985). A study on rats showed that arsenic interacted with estrogenic receptors and suppressed estrogen synthesis (Chattopadhyay et al. 1999). In another study on rats with pre- and postnatal arsenic exposure, the estrogen levels were decreased, and like in the present study, pubertal development was delayed (Davila-Esqueda et al. 2012). Another study that exposed rats to arsenic during early development after births suggested that pubertal delay was linked to suppression of insulin-like growth factor-1 (IGF-1) (Reilly et al. 2014). In contrast to the studies mentioned above, two relatively new studies reported the early onset of puberty in mice exposed to arsenic during prenatal periods. (Li et al. 2018; Rodriguez et al. 2016). This early onset was suggested because of increased levels of luteinizing hormone or other factors, including mRNA and protein expression of the puberty related genes and glucose intolerance.

The present study has several strengths. The analyses were based on a well-characterized cohort of pregnant women with follow-up of the offspring on several occasions before assessing pubertal development on two occasions at 12–15 years of age. The loss to follow up was reasonably low, despite a long duration of cohort follow-up. Besides, compared to the background characteristics between the group included in the analysis and those not included due to missing arsenic exposure data, we did not observe any differences in potential confounders, including maternal education and socioeconomic status by asset tertiles and maternal body mass index. The fact that the assessment of the menarche outcome was performed without any prior knowledge of the arsenic-related research question decreased the risk of information bias.

The exposure in utero was assessed by the arsenic concentration in drinking water used by the adolescent girls' mothers during pregnancy. Arsenic in tube well water most likely captured the exposure levels efficiently as all women stayed in the study area during pregnancy and

Table 5
Association between prenatal arsenic exposure, assessed by arsenic concentrations in tube well water used by mothers, and age at menarche of girls in Matlab, Bangladesh.

Water arsenic concentration interval (median) in μg/L	No.	Events[a]	Median age at menarche in years	Unadjusted hazard ratio	95% confidence intervals	Adjusted hazard ratio[b]	95% confidence intervals
<10 (0.5)	281	224	12.8	1		1	
10–49 (22)	86	62	12.9	0.80	0.60–1.06	0.82	0.59–1.14
50–99 (68)	46	34	12.8	0.87	0.60 –1.24	0.89	0.58–1.36
100–199 (158)	106	82	13.1	0.79	0.61–1.01	0.82	0.64–1.05
200–1014 (328)	290	216	13.1	0.72	0.59–0.87	0.77	0.63–0.95

[a] Events indicate the menarche had taken place.
[b] Adjusted for maternal socioeconomic status, education, and body mass index.

used tube well water from the same source. In the present study, about two-thirds of participants fell into the lowest and the highest arsenic categories and the remaining one-third belonged to the three middle categories. This distribution was consistent with our previous studies in the same area (Rahman et al. 2007; Rahman et al. 2006). Very few of these women (2%) changed water sources during pregnancy. When checking the potential influence of this change, we did not observe any differences in effect estimates. The lack of information on water arsenic exposure during early childhood is a limitation. This implies that the observed association reflects the exposure of the mother-and-child dyad from pregnancy and onwards. The arsenic exposure through drinking water may continue when the child starts to drink tube well water. Thus, the relative strength of the association may have been influenced by this lack of information on the child's arsenic exposure. Earlier studies have reported that very small amounts of arsenic pass through breast milk (Concha et al. 1998b). Our study area findings confirmed this, showing that urinary arsenic concentrations measured at three months were substantially lower than the mother's urinary arsenic concentrations (Fangstrom et al. 2008), particularly in the exclusively breastfed group. It should be noted that exclusive breastfeeding practices among the MINIMat children were relatively high, with 50% of infants exclusively breastfed up to six months (Eneroth et al. 2009) and most continuing partial breastfeeding to two years and beyond (Saha et al. 2008). This population may also be exposed to arsenic from other sources, particularly from food (Kippler et al. 2016), and this additional exposure was probably most likely randomly distributed. We did not assess concurrent arsenic exposure in adolescent girls. However, the literature suggests that the critical windows of vulnerability to toxic exposures are during prenatal and early childhood (Braun 2017; Gluckman et al. 2008).

The reliability of reported age at menarche may be questioned. A menarche is a significant event in a young woman's life, which is not easily forgotten, also in the Bangladesh culture. Data on age at menarche were collected by recall using a local events calendar when needed. The recall period, i.e., the time between the interview and date of menarche, may influence the validity of the assessment. In our study, the median recall period was about 0.5 years, which is substantially lower than other studies. If the date of menarche differed between the first and the second follow-up, we used the information collected closer to the event (i.e., the first visit). In addition, we have the exact birth date information of the study participants.

The median age of menarche in the present study was 13 years, which is similar to estimates from many high-income countries (Harris et al. 2008; Parent et al. 2003). This similarity is surprising, considering the Bangladeshi girls' socioeconomic and nutritional background compared to those in affluent societies. However, our finding is also in concordance with other Bangladeshi studies conducted in 1996 and 2009 reporting a median age at menarche of 13.0 years and 12.8 years, respectively (Chowdhury et al. 2000; Rah et al. 2009). The distribution of menarche attainment by ages in our study was also found similar to Bangladesh's study (Chowdhury et al. 2000).

5. Conclusions

We have shown that an increased level of prenatal arsenic exposures was associated with a delay in age at menarche in adolescent girls in a rural area in Bangladesh. This delay may indicate endocrine disruption that potentially could impair reproductive health systems, including pubertal development. Endocrine-disruptive toxins may imply risk for other adverse health outcomes, including impaired neurodevelopment, thyroid function, and increases in hormone-sensitive cancers in later life (WHO 2013). Due to the lack of biomarker data we cannot link biological factors related to the observed delay in the present study. Future human studies are needed to study the role of arsenic exposures in perturbation of the neuroendocrine systems and impairment of other reproductive endpoints. The observed delay in age at menarche in this study, possibly through endocrine disruption, reinforces the need to mitigate arsenic contamination at the population level.

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CRediT authorship contribution statement

Anisur Rahman: Conceptualization, Methodology, Data curation, Project administration, Formal analysis, Writing - original draft. **Maria Kippler:** Writing - original draft, Formal analysis. **Jesmin Pervin:** Formal analysis, Supervision. **Chandan Tarafder:** Supervision. **Ishrat Javeen Lucy:** Supervision. **Pernilla Svefors:** Data curation, Writing - original draft. **Shams El Arifeen:** Writing - original draft. **Lars Åke Persson:** Conceptualization, Funding acquisition, Methodology, Formal analysis, Writing - original draft.

Declaration of Competing Interest

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

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