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Urinary Cadmium and Timing of Menarche and Pubertal Development in Girls

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Abstract

BACKGROUND: Cadmium (Cd) is a developmental toxicant that is released into the environment during industrial processes. Previous animal studies suggest that Cd may impact the onset of puberty.

OBJECTIVES: To determine whether Cd exposure, measured as urinary Cd concentration, was associated with ages at menarche and pubertal development.

METHODS: A cohort of 211 girls, ages 10 to 13 years at baseline, was followed for up to two years. Girls completed an interview and self-assessment of Tanner stages of breast development and pubic hair growth. They were followed monthly until menarche. Urinary Cd concentrations were measured in overnight urine specimens. Multivariable Cox regression was used to evaluate the association between urinary Cd and age at menarche and cumulative logit regression was used to evaluate the associations between Cd and breast development and pubic hair growth.

RESULTS: The baseline geometric mean creatinine-adjusted Cd concentration was 0.22 μg/g creatinine (geometric standard deviation = 1.6) and decreased with increasing age (p-trend =0.04). Cd levels were higher among Asian than White girls or girls of other/mixed race/ethnicity (p = 0.04). In multivariable analyses, girls with urinary Cd ≥ 0.4 μg/L were less likely to have attained menarche than girls with urinary Cd < 0.2 μg/L (hazard ratio = 0.42; 95% confidence interval, 0.23–0.78). Urinary Cd was negatively associated with pubic hair growth (p-trend = 0.01) but not with breast development (p-trend = 0.72) at baseline.

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Declaration of interests

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.

CONCLUSIONS: These findings suggest that a higher Cd body burden may delay some aspects of pubertal development among girls.

Keywords

Cadmium; puberty; menarche

1. BACKGROUND

Puberty, the transitional phase from immature to mature reproductive function, is marked by development of secondary sexual characteristics, behavioral changes, and accelerated growth. The onset of puberty is initiated by activation of the hypothalamic-pituitary-gonadal (HPG) axis, which triggers an elevated secretion in gonadotropin-releasing hormone (GnRH; Boswell et al. 2014). In girls, GnRH induces increased secretion of both estradiol, which initiates growth processes including secondary breast development (thelarche) and uterine growth and differentiation, and androgen, which leads to pubic hair growth (pubarche). The mean age of onset of thelarche is 10.5 years and is usually followed within a few months by pubarche, although this pattern is reversed in approximately 15% of girls (Tanner and Davies 1985). Increasing and fluctuating circulating levels of estradiol induce the onset of the first menstrual period (menarche).

An observed secular trend toward earlier onset of thelarche, pubarche, and menarche observed in multiple epidemiologic studies suggests that environmental factors including exposures to endocrine-disrupting environmental chemicals may interfere with the timing of pubertal development in girls (Mouritsen et al. 2010). Earlier development in girls has been linked to exposure chemicals such as polybrominated biphenyls (PBBs; Blanck et al. 2000) and dichlorodiphenyl trichloroethane (DDT; Ouyang et al. 2005) while lead (Pb) levels in blood have been associated with delayed pubertal outcomes in both girls (Selevan et al. 2003; Wu et al. 2003; Denham et al. 2005; Gollenberg et al. 2010; Naicker et al. 2010) and boys (Hauser et al. 2008; Williams et al., 2010).

Cadmium (Cd) is another environmental contaminant that may impact the timing of pubertal development. Cd is a trace metal released into the environment during mining operations and industrial processes and as a byproduct of petroleum combustion. Because Cd in contaminated soil can be absorbed by plants such as leafy green vegetables, cereal grains, and tobacco, Cd exposure in non-occupational settings occurs mainly via diet and tobacco smoking [Agency for Toxic Substances and Disease Registry (ATSDR) 2012]. Potential exposures among children, as a result of mouthing or accidentally ingesting toys, jewelry, and other consumer products contaminated with paint, have also emerged as a public concern (Weidenhamer et al. 2011; Guney et al. 2014). Cd exposure is associated with numerous adverse health effects (Åkesson et al. 2014) including cancer (Adams et al. 2012; Julin et al. 2012), kidney disease (Ferraro et al. 2010), cardiovascular disease (Peters et al. 2010), osteoporosis and fractures (Engström et al. 2012), and dental caries (Arora et al. 2008), as well as learning disabilities among children (Ciesielski et al. 2012). *In vivo* and *in vitro* studies suggest that Cd exhibits potent estrogenic activity, such as activation of the estrogen receptor (ER)-α (Stoica et al. 2000), malignant transformation of normal

breast cells (Benbrahim-Tallaa et al. 2009), and accelerated growth of malignant breast cells (Siewit et al. 2010). Animal studies of *in utero* Cd exposure on the onset of estrus have been inconsistent, with results observing either earlier (Johnson et al. 2003) or delayed onset in exposed female offspring (Salvatori et al. 2004; Samuel et al. 2011).

The objective of the present study was to determine whether Cd exposure, measured as urinary Cd concentration, was associated with pubertal development in girls participating in a two-year cohort study.

2. METHODS

2.1 Study population and data collection

The study population consisted of girls, aged 10-13 years at baseline, residing in the San Francisco Bay Area, California, who participated in the GRowth and LifeStyle (GRLS) Study, a prospective cohort study designed to examine the effects of isoflavones on pubertal development over a two-year follow-up period. Girls were recruited through schools and community groups in Alameda County and selected for study based on high- or low-estimated soy consumption from a screening interview (<4 mg/d of isoflavones vs. ≥15 mg/d of isoflavones), age, and race/ethnicity. A total of 228 eligible girls and their parents provided informed assent and consent, respectively, for collection and use of their personal information and biological samples (urine, blood and/or saliva) for research purposes and thus were enrolled in the cohort in 2005-06. The institutional review boards of the Cancer Prevention Institute of California and the University of Alabama, Birmingham approved this research. A total of 211 (93%) girls provided an overnight urine specimen at baseline; these girls form the basis of our analysis.

Each girl and a parent completed an in-person interview at baseline in 2005-06 and after 12 months of follow-up; in addition, 95 girls who were still pre-menarcheal at 12 months completed an additional interview at 24 months. The interviews assessed personal and family menstrual history, body size, physical activity, residential history, medical history, and diet and supplement use during the past year. Height, weight, and hip and waist circumference and percent body fat, via bioelectrical impedance, were measured by trained staff. Girls also were asked to indicate their stage of breast development and pubic hair growth using a self-administered confidential questionnaire that included standard pictures and descriptions following the Tanner staging model ranging from stage 1 (no pubertal development) to 5 (fully mature; Marshall and Tanner 1969).

Between the annual interviews, girls completed brief questionnaires mailed to them monthly that asked pre-menarcheal girls about the attainment of menarche and menstruating girls about the date of their period during the previous month. A total of 1,992 (87%) of 2,298 monthly questionnaires sent between the baseline and 12-month interviews were returned while 764 (81%) of 949 questionnaires sent between the 12- and 24-month interviews were returned.

2.2 Urine collection and analysis

At the time of the baseline interview, each girl received a urine collection kit and was instructed to collect urine before bedtime, throughout the night, and through the first morning void in a single polyethylene container. This overnight sample was refrigerated between collections and until retrieval by study staff the following morning. Within 6 hours of the end of collection, samples were filtered, centrifuged, aliquoted, and frozen at −70°C.

Urinary Cd concentrations (micrograms per liter) were measured using inductively-coupled plasma–mass spectrometry at a certified commercial laboratory (Pacific Toxicology Laboratories, Chatsworth, CA). Low- and high-Cd control standards were included in each batch to evaluate assay accuracy and precision. All specimens were equal to or above the limit of detection (LOD) of 0.1 μg/L. The within-batch coefficient of variation was < 10% and between-batch coefficient was < 15%. To correct for variations in urine dilution, creatinine (grams per liter) was measured using a modified-rate Jaffe method (Barr et al. 2005). We calculated the creatinine-adjusted urinary Cd levels (micrograms per gram creatinine) by dividing the urinary Cd concentrations (micrograms per liter) by the creatinine concentrations (grams per liter).

2.3 Statistical analysis

Initial analyses examined baseline bivariate associations of demographic and anthropometric characteristics with natural logarithm-transformed baseline urinary Cd concentrations (unadjusted and creatinine-adjusted) and Tanner stages of breast development and pubic hair growth categorized as ordinal variables using linear regression models adjusted for age. Associations between baseline demographic and anthropometric characteristics and the attainment of menarche were assessed using two-sided χ^2-tests. We also assessed potential selection bias by comparing demographic, anthropometric, attainment of menarche, and Tanner stages between the study sample and the 17 girls who were not included in the analyses.

We used Cox proportional hazards regression to estimate hazard rate ratios (HRs) and 95% confidence intervals (CIs) for the attainment of menarche at a given age and urinary Cd concentration. Unadjusted urinary Cd levels were modeled as either a categorical variable (<0.2, 0.2–0.3, 0.3–0.4, ≥0.4), or a continuous measure based on a natural logarithmic transformation to approximate a normal distribution. Models included covariates that could potentially confound the relation between menarche and Cd level: race/ethnicity (White, Asian, other/mixed), creatinine concentration (quartiles), percent body fat (continuous; standardized by age and race/ethnicity), and height (continuous; standardized by age and race/ethnicity). Age was used as the timescale in all models. Follow-up time was measured in days and started at birth and ended at the age of menarche for those girls who attained menarche (event; n=162) or at the end of follow-up for those who did not attain menarche prior to the end of follow-up (censored; n=49).

To evaluate whether unadjusted urinary Cd concentration was associated with Tanner stage of breast development or pubic hair growth at baseline, we employed cumulative logit regression to estimate ordinal odds ratios (ORs) representing the relative odds of reaching

a more advanced stage of development. Models included the covariates listed above. No violations of the proportional odds assumption were observed in any of the models. For both analyses of menarche and pubertal development, we evaluated stratified models as well as interaction terms to assess effect-measure modification by age, race/ethnicity, and other covariates of interest.

3. RESULTS

Compared with the 17 girls who did not provide a urine sample (of 228 eligible), the 211 girls included in the present analysis were less likely to have attained menarche at baseline (39% vs. 71%, p = 0.01) or by the end of the two-year follow-up (77% vs. 100%, p = 0.02). The distributions of race/ethnicity and age at baseline, Tanner stages of breast development and pubic hair growth, and standardized body fat percentage and height did not differ between these two groups (results not shown). Among all girls who had attained menarche by the end of the study period, those who were included in the present analysis also had an older mean age at menarche by 8 months (p = 0.008).

The distributions of urinary Cd concentration, attainment of menarche at baseline and by the end of the two-year follow-up, and average baseline Tanner stage of breast development and pubic hair growth across levels of demographic and anthropometric characteristics are listed in Table 1. The geometric means of unadjusted and creatinine-adjusted urinary Cd concentration were 0.26 μg/L and 0.22 μg/g creatinine, respectively. Creatinine-adjusted Cd levels decreased with increasing age (p-trend = 0.04) and standardized height (p-trend = 0.005); this negative association was marginally significant for standardized percent body fat (p-trend = 0.09). Asian girls (84% of whom were Chinese) had the highest geometric mean creatinine-adjusted Cd concentration (0.24 μg/g; p = 0.04).

At baseline, 82 (39%) of the girls had previously attained menarche; this number increased to 162 (77%) by the end of the two-year follow-up (Table 1). Menarcheal attainment at baseline and both 12- and 24-month time points by Tanner stages of breast development and pubic hair growth were all associated with increasing age, standardized body fat percentage and standardized height. Adjusting for age and race/ethnicity was not associated with attainment of menarche (p = 0.82 at baseline, p = 0.31 by the end of follow-up), was marginally associated with baseline breast development (p = 0.08), and was significantly associated with pubic hair growth (p < 0.0001). White girls had the highest mean (± SD) Tanner stage for pubic hair growth (3.00 ± 1.32), while Asian girls had the lowest (2.39 ± 0.98).

In bivariate comparisons (Table 2), increasing levels of unadjusted urinary Cd were not associated with menarcheal attainment at baseline (p-trend = 0.59) or by the end of the two-year follow-up period (p-trend = 0.19). For creatinine-adjusted Cd, attainment of menarche was somewhat less likely at higher Cd concentrations compared with the lowest category at both baseline (p-trend = 0.11) and by the end of follow-up (p-trend = 0.07). Among menarcheal girls at baseline, the mean age (± SD) of attainment was 11.78 ± 0.85 years; this increased to 12.21 ± 1.02 years for attainment through the end of the two-year follow-up period.

With adjustment for potential confounders, urinary Cd concentration was associated with later attainment of menarche (Figure 1; p-trend = 0.005). Girls with urinary Cd concentrations > 0.4 μg/L were 58% less likely to attain menarche at a given age than girls with Cd < 0.2 μg/L (HR = 0.42; 95% CI, 0.23–0.78). Additional stratified analyses did not reveal any heterogeneity by age or race/ethnicity (results not shown).

Ordinal ORs and 95% CIs from cumulative logit models for the association at baseline between Tanner stages of breast development and pubic hair growth and urinary Cd concentration are listed in Table 3. Adjusting for potential confounders, girls had a reduced odds of more advanced pubic hair growth with increasing urinary Cd level (p-trend = 0.01). Girls with a urinary Cd concentration ≥0.4 μg/L had 79% lower odds of a more advanced category of pubic hair growth than girls where urinary Cd <0.2 μg/L (OR = 0.21; 95% CI, 0.06–0.72). In contrast, Tanner stage of breast development was not associated with urinary Cd (p-trend = 0.72). Stratified analyses for these outcomes did not reveal any heterogeneity by age or race/ethnicity (results not shown).

4. DISCUSSION

To our knowledge, this is the first study to examine the relationship between Cd body burden and the timing of menarche and pubertal development in girls. We observed that girls with higher urinary Cd levels had less pubarcheal development at baseline and later menarcheal onset; no association, however, was observed for thelarcheal development at baseline. Late onset of pubertal development has been associated with increased risks of bone fragility and fractures (Chevalley et al. 2008) and endometriosis (Berube et al. 1998) and reduced breast cancer risk in adulthood (Collaborative Group on Hormonal Factors in Breast Cancer 2012).

Our findings for urinary Cd and delayed menarche are consistent with animal studies of *in utero* Cd exposures and the timing of estrous in rodents (Salvatori et al. 2004; Ishitobi and Watanabe 2005; Samuel et al. 2011). In one of these studies, female offspring of pregnant rats or mice treated with Cd in drinking water at concentrations of 50 or 200 ppm experienced statistically significant increases in the number of days between birth and vaginal opening compared with untreated controls (Samuel et al. 2011). These treated pups also had decreased body and ovary weight, extended estrous cycles, decreased antioxidant enzyme activity and increased lipid peroxidation and hydrogen peroxide (H_2O_2) levels in the ovaries and lower serum concentrations of circulating estradiol, progesterone, and testosterone, suggesting that Cd exposure may induce oxidative stress that impairs ovarian function and development. Delayed vaginal opening was also observed among pups of pregnant rats orally administered 20 mg/kg body weight per day (Salvatori et al. 2004), while a similar but not statistically significant difference was observed among pups of pregnant mice treated with 10 ppm Cd in drinking water (Ishitobi and Watanabe 2005). These animal studies of *in utero* exposures were conducted at levels substantially higher than expected in the general human population. In contrast, female pups of rats injected with “environmentally relevant” Cd doses of either 0.5 or 5.0 μg/kg had significantly earlier onset of vaginal opening and more terminal end buds (undifferentiated structures) of the mammary gland than pups from untreated controls, leading the study authors to conclude that Cd may have estrogenic effects at these lower doses (Johnson et al. 2003).

Aside from a recent ecologic study noting earlier menarche among girls living in an area of China heavily polluted with Cd (Chen et al. 2018), only one other epidemiologic study has examined the effects of Cd exposure in young girls (Gollenberg et al. 2010). This study looked at the associations between urinary Cd and blood Pb concentrations and serum levels of inhibin B and luteinizing hormone (LH), markers of HPG axis activity that regulates sexual development, in pre-pubertal girls aged 6–11 years enrolled in the cross-sectional US National Health and Nutrition Examination Survey (NHANES). Blood Pb was negatively associated with inhibin B; the magnitude of this association increased among girls in the highest tertile of urinary Cd, suggesting that Pb may inhibit puberty-related hormones, especially in the presence of Cd. However, no independent associations were observed between urinary Cd and inhibin B and LH levels, despite evidence from animal studies that Cd exposure impairs LH (Paksy et al. 1989; Pillai et al. 2003; Han et al. 2006; Nampoothiri and Gupta 2006). The authors, however, did not adjust Cd concentrations for creatinine or include creatinine as a covariate in the model; thus, the observed null associations for Cd and hormone levels may have been attenuated by variations in urinary dilution (Barr et al. 2005). Previous studies of NHANES (Selevan et al. 2003; Wu et al. 2003) and other populations consistently observed associations between girls' blood Pb levels and delayed menarche (Denham et al. 2005; Naicker et al. 2010; Sławińska et a. 2012); this association was not observed for Pb concentrations from blood collected from girls' mothers during gestation (Maisonet et al. 2014). In studies that also looked at secondary sex characteristics, blood Pb was negatively associated with pubic hair growth while findings were inconsistent for breast development (Selevan et al. 2003; Wu et al. 2003; Naicker et al. 2010). In our GRLS study cohort (where environmental contaminant exposures were not a primary interest), whole blood was not collected in tubes appropriate for Pb measurement, thus precluding us from examining the association between serum Pb and pubertal outcomes.

Similar to our findings for girls, urinary Cd was associated with delayed pubertal onset in a cross-sectional study of boys 12-14 years of age from industrial and non-industrial regions in Italy (Interdonato et al. 2014). Testicular volume and concentrations of urinary testosterone and serum LH, but not serum inhibin B and follicle-stimulating hormone, were negatively associated with urinary Cd. The geometric mean urinary Cd level in this population was twice the concentration observed in our cohort of girls (0.58 vs. 0.26 μg/L).

The inverse associations between urinary Cd and standardized height and body fat percentage in our analysis are consistent with findings for Cd and body size from other studies of girls (Dhooge et al. 2010; Lin et al. 2011; Gardner et al. 2013; Riederer et al. 2013; Delvaux et al. 2014). Although the underlying biological explanation for this observation is not known, the pattern may be attributable to the effects of Cd on estrogen and other steroid hormones that may induce lipid mobilization and lipolysis (Faulds et al. 2012). The negative association with height may be related to increased bone resorption due to Cd exposure (Sughis et al. 2011).

The geometric mean urinary Cd concentration among children and adolescents participating in NHANES declined by approximately 28% between the 1999-2000 and 2007-2008 survey years, mirroring a reduction observed among adults (Riederer et al. 2013). The change among adults was largely attributed to the declining prevalence of cigarette smoking

and reduced exposure to secondhand smoke among never smokers (Tellez-Plaza et al. 2012). However, the observed decline among children and adolescents could not be attributed to any specific sources such as environmental tobacco smoke, dietary intake, and dietary supplement use (Riederer et al. 2013). Since 2010, contamination of children's consumer products has emerged as a topic of great public concern with the discoveries and recalls of toys and children's jewelry with high levels of Cd (Mead 2010). Mouthing or accidentally ingesting these toys presents a potential source of Cd exposure among children (Weidenhamer et al. 2011; Guney et al. 2014). However, we were unable to assess exposures from specific sources in this study.

Our analysis had other limitations. We used the Cd concentration from an overnight urine specimen collected concurrently with the Tanner stage assessments for breast development and pubic hair growth for all girls and after the attainment of menarche for 39% of the girls. While urinary Cd is considered a biological marker of long-term body burden, it is possible that the associations we observed may represent a consequence rather than an antecedent of some aspects of pubertal development; however, no known longitudinal studies support this possibility and toxicokinetic models of Cd have not been validated in children (Amzal et al. 2009). Furthermore, our urinary Cd measurement may not be representative of etiologically relevant time periods of exposure such as during gestation or early childhood for the outcomes in our analysis. Because urinary specimens were not collected specifically for the measurement of Cd, potential leaching of metals from containers that were not acid-washed or metals-free may contribute to measurement error (Cornelis et al. 1996). Since a number of girls included in this analysis had achieved menarche prior to study entry, we ran a sensitivity analysis to address potential concerns that their inclusion might influence reverse causation. Excluding the post menarcheal at baseline, we found that, although based on smaller numbers, the negative association remained for the highest category of Cd level, albeit no longer statistically significant. We did not have measures of exposures to factors related to Cd exposure such as environmental tobacco smoke (Richter et al. 2009; Gunier et al. 2013) and did not assess iron deficiency, which may increase gastrointestinal Cd uptake (Silver et al. 2013). The detection limit for urinary Cd in our analysis (0.1 μg/L) was higher than the limit used for NHANES (0.042 μg/L), which may partly explain why our observed geometric mean concentrations for unadjusted and creatinine-adjusted urinary Cd were slightly higher than those observed for children and adolescents in NHANES (CDC 2015). In addition, we were limited to baseline cross-sectional assessments of pubarcheal and thearcheal development and urinary Cd. Girls' self-assessed Tanner stages may also be prone to error as previous studies have reported inconsistent validity when compared with physicians' assessments (Brooks-Gunn et al. 1987; Hergenroeder et al. 1999; Wu et al. 2001). Girls tend to more accurately assess pubic hair growth than breast development (Desmangles et al. 2006; Rasmussen et al. 2015) thus the observed null association between breast development and urinary Cd may be an artifact of this misclassification error.

Strengths of this analysis include its prospective design, the ethnic diversity of the cohort, assessment of menarcheal onset on an ongoing monthly basis, and anthropometric measurements. In addition, we accounted for variations in hydration and urinary output by adjusting for creatinine (Barr et al. 2005). Because urinary creatinine also may vary by gender, age, body size, kidney function, and meat consumption (Suwazono et al. 2005;

Akerstrom et al. 2012), we included unadjusted urinary cadmium and adjusted for creatinine as a separate variable in our Cox and cumulative logit regression models.

5. CONCLUSIONS

We observed that a higher Cd body burden may delay pubarche and the attainment of menarche in girls, but does not appear to affect breast development. These results are compatible with delayed estrous associated with Cd exposure in animal studies. Whether our findings are due to ovotoxicity, as proposed for animals, is unknown at this time. These findings contribute to the growing body of knowledge of the impacts of endocrine-disrupting metals on sexual maturation.

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Highlights:

- Body burden of cadmium may influence the onset of puberty
- 211 girls aged 10-13 were enrolled in a study of pubertal development
- Levels of cadmium were measured in urine samples from the girls
- Girls with higher levels of urinary cadmium were less likely to attain menarche

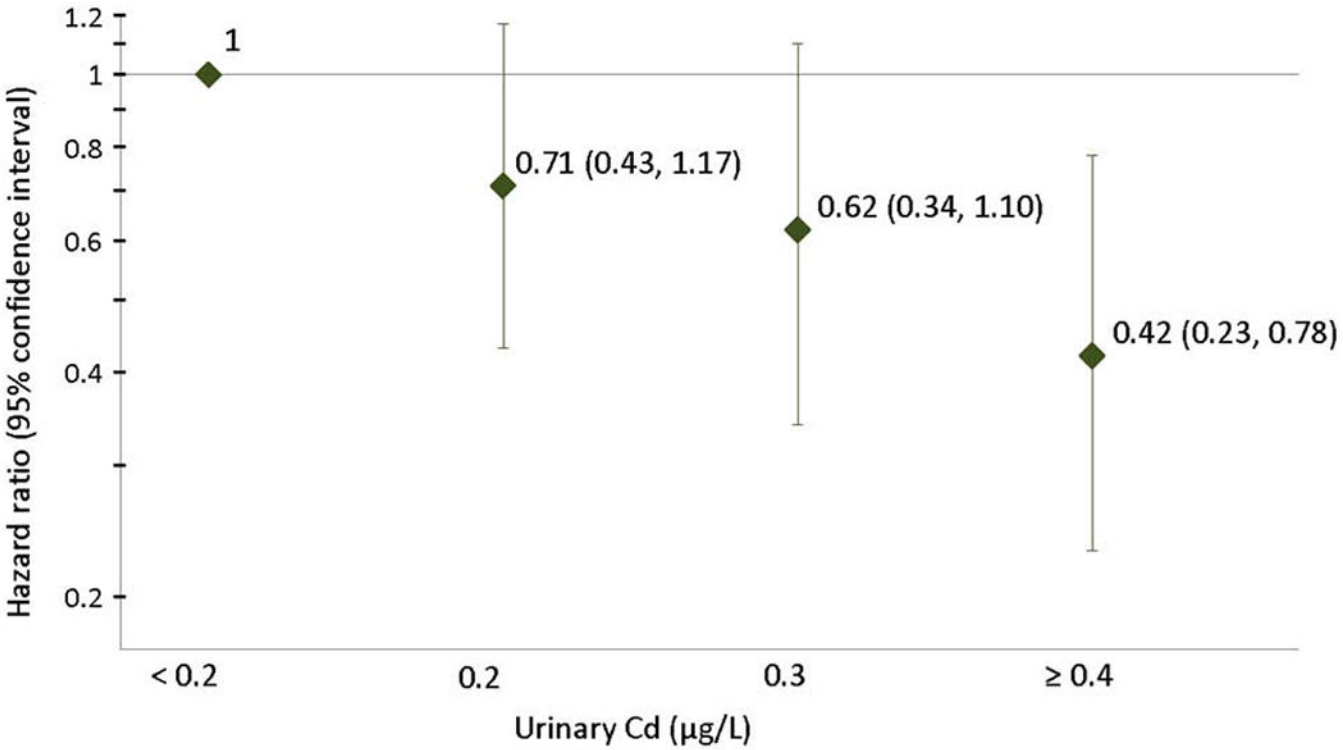

FIGURE 1.

Hazard ratios[a,b] and 95% confidence intervals for the attainment of menarche by urinary Cd concentration: GRLS cohort, 2005-08

[a] Based on Cox proportional hazards model adjusted for race/ethnicity (White, Asian, other/mixed), creatinine concentration (quartiles), body fat percentage (continuous; standardized by race/ethnicity and age), and height (continuous; standardized by race/ethnicity and age), with age (in days) as the timescale.

[b] p-value for trend = 0.005.

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TABLE 1.

Distributions of baseline demographic and anthropometric characteristics: GRLS cohort, 2005-08

		Baseline urinary Cd geometric mean (SD)		Attainment of menarche n (%)		Baseline Tanner stage[a] arithmetic mean ± SD	
Variable	**Total n (%)**	**Unadjusted (μg/L)**	**Adjusted (μg/g creatinine)**	**Baseline**	**By 2-year follow-up**	**Breast**	**Pubic Hair**
All girls	211 (100)	0.26 (1.7)	0.22 (1.6)	82 (39)	162 (77)	2.82 ± 1.03	2.79 ± 1.26
Baseline age (years)							
10	55 (26)	0.28 (1.5)	0.25 (1.3)	5 (9)	26 (47)	2.16 ± 0.97	1.85 ± 0.97
11	53 (25)	0.24 (1.3)	0.22 (1.2)	14 (26)	39 (74)	2.57 ± 0.82	2.47 ± 1.08
12	56 (27)	0.25 (1.4)	0.19 (1.2)	30 (54)	50 (89)	3.16 ± 0.96	3.25 ± 1.19
13	47 (22)	0.26 (1.3)	0.21 (1.2)	33 (70)	47 (100)	3.51 ± 0.80	3.70 ± 0.91
p-value (linear trend)		0.66[b]	0.04[b]	<0.0001[c]	<0.0001[c]	<0.0001[d]	<0.0001[d]
Race/ethnicity							
White	92 (44)	0.25 (1.4)	0.20 (1.2)	34 (37)	66 (72)	2.84 ± 1.12	3.00 ± 1.32
Asian	62 (29)	0.28 (1.5)	0.24 (1.3)	24 (39)	50 (81)	2.68 ± 0.97	2.39 ± 0.98
Other or mixed	57 (27)	0.25 (1.2)	0.21 (1.2)	24 (42)	46 (81)	2.98 ± 0.94	2.89 ± 1.35
p-value		0.41[e]	0.04[e]	0.82[c]	0.31[c]	0.08[f]	<0.0001[f]
Percent body fat (baseline; quartiles)							
< 17.1%	53 (25)	0.31 (1.7)	0.25 (1.5)	4 (8)	26 (49)	2.00 ± 0.81	2.02 ± 0.99
17.1 – < 21.9%	52 (25)	0.24 (1.7)	0.21 (1.6)	16 (31)	39 (75)	2.54 ± 0.83	2.63 ± 1.14
21.9 – < 27.6%	52 (25)	0.26 (1.9)	0.22 (1.6)	30 (58)	46 (88)	3.29 ± 0.89	3.17 ± 1.18
≥ 27.6	53 (25)	0.23 (1.6)	0.19 (1.6)	32 (60)	50 (94)	3.49 ± 0.87	3.35 ± 1.30
p-value (linear trend)		0.17[g]	0.09[g]	<0.0001[h]	0.0005[h]	<0.0001[i]	<0.0001[i]
Height (baseline; quartiles)							
< 57.5	53 (25)	0.27 (1.8)	0.26 (1.6)	4 (8)	22 (42)	1.87 ± 0.73	1.60 ± 0.79
57.5 – < 60.4	51 (24)	0.27 (1.8)	0.21 (1.6)	12 (24)	40 (78)	2.82 ± 0.91	2.55 ± 1.03
60.4 – < 62.5	53 (25)	0.25 (1.6)	0.22 (1.5)	27 (51)	49 (92)	3.23 ± 0.80	3.36 ± 1.11
≥ 62.5	53 (25)	0.24 (1.7)	0.19 (1.6)	39 (74)	50 (94)	3.40 ± 0.95	3.65 ± 0.97
p-value (linear trend)		0.15[g]	0.005[g]	<0.0001[h]	<0.0001[h]	<0.0001[i]	<0.0001[i]

[a]Tanner scale range = 1(least developed) – 5 (most developed).

[b] Regression model of natural logarithm-transformed Cd concentrations across age.

[c] χ^2-test indicating variation across age and race/ethnicity, respectively.

[d] Regression model of Tanner stage across age.

[e] Regression model of natural logarithm-transformed Cd concentrations across race/ethnicity, adjusted for age.

[f] Regression model of Tanner stage across race/ethnicity, adjusted for age.

[g] Regression model of standardized continuous variables for body fat percentage and height, respectively, and natural logarithm-transformed Cd concentrations adjusted for age.

[h] χ^2-test indicating variation across standardized continuous variables for body fat percentage and height, respectively.

[i] Regression model of Tanner stage across standardized continuous variables for body fat percentage and height, respectively, adjusted for age.

TABLE 2.

Attainment of menarche at baseline and by the end of 2-year follow-up by category of urinary Cd concentration: GRLS cohort, 2005-08

		Menarcheal at baseline		Menarcheal by 2-year follow-up	
	Total		Age at attainment [b]		Age at attainment [b]
	n	n (%)	mean ± SD	n (%)	mean ± SD
All girls	211	82 (39)	11.78 ± 0.85	162 (77)	12.21 ± 1.02
Unadjusted Cd (μ/L)					
<0.2	31	11 (35)	11.58 ± 0.74	26 (84)	12.06 ± 0.93
0.2 – <0.3	69	28 (41)	11.74 ± 0.85	54 (78)	12.20 ± 1.00
0.3 – <0.4	47	15 (32)	11.97 ± 0.64	36 (77)	12.35 ± 1.02
>0.4	64	28 (44)	11.80 ± 0.99	46 (72)	12.19 ± 1.10
p-value (trend) [a]		0.59		0.19	
Creatinine-adjusted Cd (μg/g creatinine)					
<0.2	37	17 (46)	11.55 ± 0.76	32 (86)	12.13 ± 1.09
0.2 – <0.3	97	42 (43)	12.03 ± 0.70	77 (79)	12.19 ± 0.83
0.3 – <0.4	49	13 (27)	11.60 ± 1.10	32 (65)	12.35 ± 1.17
≥0.4	28	10 (36)	11.33 ± 1.00	21 (75)	12.18 ± 1.34
p-value (trend) [a]		0.11		0.07	

[a] 2-sided Cochran-Armitage test for trend.

[b] Only among girls who attained menarche.

TABLE 3.

Association of urinary Cd with Tanner stages of breast development and pubic hair growth at baseline: GRLS cohort, 2005-08

			Tanner stage category (n)				
Outcome	**Urinary Cd (μg/L)**	**Tanner stage mean ± SD**	**1-2**	**3**	**4-5**	**OR (95% CI) [c]**	**p-trend**
Breast development (thelarche)	<0.2	2.7 ± 0.8	11	17	3	1.00	0.72
	0.2 – <0.3	3.0 ± 1.1	21	25	23	1.49 (0.59, 3.79)	
	0.3 – <0.4	2.7 ± 1.0	20	17	9	1.04 (0.36, 2.99)	
	≥0.4	2.8 ± 1.1	27	20	17	1.00 (0.33, 3.02)	
	Total		79	79	52		
Pubic hair growth (pubarche)	<0.2	2.7 ± 1.2	14	7	10	1.00	0.01
	0.2 – <0.3	3.0 ± 1.3	26	14	28	0.46 (0.16, 1.31)	
	0.3 – <0.4	2.7 ± 1.2	21	14	11	0.28 (0.08, 0.93)	
	≥0.4	2.8 ± 1.3	27	20	17	0.21 (0.06, 0.72)	
	Total		88	55	66		

[a]Ordinal odds ratios based on cumulative logit regression model under proportional odds assumption, adjusted for age at baseline (continuous), race/ethnicity (White, Asian, other/mixed), creatinine (quartiles), standardized body fat percentage and height (continuous).