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Onset and tempo of sexual maturation is differentially associated with gestational phthalate exposure between boys and girls in a Mexico City birth cohort

Amber Cathey[a], Deborah J. Watkins[a], Brisa N. Sánchez[b], Marcela Tamayo-Ortiz[c,e], Maritsa Solano-Gonzalez[c], Libni Torres-Olascoaga[c], Martha Maria Téllez-Rojo[c], Karen E. Peterson[d], John D. Meeker[a,*]

[a] Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA
[b] Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI, USA
[c] Center for Nutrition and Health Research, Instituto Nacional de Salud Pública, Cuernavaca, MOR, Mexico
[d] Department of Nutritional Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA
[e] Mexican Council of Science and Technology, Mexico City, Mexico

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ABSTRACT

Phthalates are endocrine disrupting compounds commonly found in consumer products, exposure to which may influence reproductive maturation. Effects from exposure in utero on the onset and progression of sexual development are understudied. We examined longitudinal associations between gestational phthalate exposure and sexual maturation at two points in adolescence (8–14, 9–18 years). Gestational exposure was quantified using the geometric mean of 3 trimester-specific urinary phthalate metabolite measurements. Sexual maturation was assessed using Tanner stages and menarche onset for girls and Tanner stages and testicular volume for boys. Generalized estimating equations for correlated ordinal multinomial responses were used to model relationships between phthalates and odds of transitioning to the next Tanner stage, while generalized additive (GA) mixed models were used to assess the odds of menarche. All models were adjusted for child age (centered around the mean), BMI z-score, change in BMI between visits, time (years) between visits (ΔT), and interactions between ΔT and mean-centered child age and the natural log of exposure metabolite concentration. Among girls, a doubling of gestational MBzP concentrations was associated with increased odds of being at a higher Tanner stage for breast development at 8–14 years (OR = 4.62; 95% CI: 1.38, 15.5), but with slower progression of breast development over the follow-up period (OR = 0.65 per year; 95% CI: 0.46, 0.92) after adjustment for child age and BMI z-score. Similar results were found for ΣDEHP levels and breast development. In boys, a doubling of gestational MBP concentrations was associated with lower odds of being at a higher Tanner stage for pubic hair growth at 8–14 years (OR = 0.37; 95% CI: 0.14, 0.95) but with faster progression (OR: 1.28; 95% CI: 0.97, 1.69). These results indicate that gestational phthalate exposures may impact the onset and progression of sexual development, and that these relationships differ between boys and girls.

1. Introduction

Decreasing age at pubertal onset has become an increasingly common global problem in the last decade (Aksglaede et al., 2008; Biro and Greenspan, 2013; Herman-Giddens et al., 2012). Several different mechanisms have been proposed as influencing this trend including genetic factors (Elks et al., 2010; Ong et al., 2009; Perry et al., 2014), increasing trends in BMI (Aksglaede et al., 2009; Boyne et al., 2010; Buyken et al., 2008; Kleber et al., 2011; Lee et al., 2010, 2007; Sørensen et al., 2010), and endocrine disruption (Buck Louis et al., 2008), but true underlying factors are still poorly understood.

Phthalates are a class of endocrine disrupting compounds commonly used in the manufacture of consumer products including food storage containers, medical tubing, and personal care products. Exposure to phthalates is widespread in the population (A.M. Calafat et al., 2015) and has been linked to numerous adverse health outcomes including altered reproductive function throughout the life cycle (Hauser and Calafat, 2005). Exposure among pregnant women specifically has been

* Corresponding author at: 1415 Washington Heights, Rm 1835 SPHI, Ann Arbor, MI 48109, USA.
E-mail address: meekerj@umich.edu (J.D. Meeker).

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investigated (Arbuckle et al., 2014; Cantonwine et al., 2014; Valvi et al., 2015; Zeman et al., 2013) and found to be linked to adverse birth outcomes including low birth weight, birth length, head circumference, gestational age, and risk of spontaneous abortion and preterm birth (Casas et al., 2016; Dereumeaux et al., 2016; Ferguson et al., 2014a, 2016; Ko et al., 2013; Meeker et al., 2009; Mu et al., 2015; Peng et al., 2016; Smarr et al., 2015; Toft et al., 2012; Watkins et al., 2016).

Previous research has demonstrated significant associations between sexual maturation outcomes and phthalate exposures measured during childhood (Binder et al., 2018; Kasper-Sonnenberg et al., 2017; Mouritsen et al., 2013b; Wolff et al., 2014; Zhang et al., 2015) and adolescence (Frederiksen et al., 2012; Srilanchakon et al., 2017; Wolff et al., 2010). Animal studies have demonstrated that in utero phthalate exposure may lead to a myriad of adverse reproductive outcomes, particularly inhibition of testosterone synthesis in the testes among males and reduced fertility among females (X. Chen et al., 2017; Howdeshell et al., 2008; Hu et al., 2013; Kay et al., 2014; Wang et al., 2016; Zhou et al., 2017), but human studies are still lacking. Furthermore, studies that do utilize gestational phthalate exposure do not use multiple adolescent follow-up visits to assess influence on the rate of progression of sexual development. Previous research coming from the ELEMENT cohort utilized gestational phthalate concentrations to assess relationships with odds of onset of sexual maturation at 8–14 years, but we now have additional data at a second adolescent follow-up visit (ages 9–18 years) that was not available previously (Watkins et al., 2017a, 2017b). Therefore, the goal of this analysis was to build on previous ELEMENT work by utilizing multiple gestational measures of urinary phthalate biomarkers to test for associations with initiation and progression of sexual maturation at two different adolescent follow-up visits.

2. Methods

2.1. Study population

The present study was conducted as part of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) project, a longitudinal pregnancy cohort in Mexico City. Women were recruited from 1997 to 2004 during their first trimester from maternity hospitals (Lewis et al., 2013). Urine samples were collected and interview-based questionnaires were completed by mothers at up to three time points during pregnancy. Mean gestational ages, which were estimated based on the self-reported date of last menstrual period, were 13.5 weeks (range 9–24 weeks), 25.1 weeks (range 19–37 weeks) and 34.4 weeks (range 28–43 weeks) at each visit. A subset of adolescent children from these mothers were followed-up over two adolescent study visits, one beginning in 2011 and one in 2015, where they provided anthropometry and demographic information. Ages of children ranged from 8 to 14 years at the first adolescent visit and 9 to 18 years at the second visit (there was not a fixed number of years between study visits). The World Health Organization child reference curves for age and sex were used to calculate age-specific BMI z-scores (World Health Organization, 2007). The present analysis included children with data at both adolescent follow-up visits for at least one pubertal outcome, and whose mothers provided at least one urinary phthalate measurement during pregnancy, resulting in a final sample size of 103 girls and 91 boys. Among those 103 girls, a total of 2, 16, and 85 mothers provided urine samples at 1, 2, and 3 gestational visits, respectively. Among those 91 boys, a total of 9, 10, and 72 mothers provided urine samples at 1, 2, and 3 gestational visits, respectively. Supplementary Table 1 shows demographic characteristics of mothers included in the present analysis compared to all ELEMENT mothers who had children eligible for inclusion this study (N = 554). Research protocols were approved by the ethics and research committees of the Mexico National Institute of Public Health and the University of Michigan, and all participants provided informed consent prior to enrollment.

2.2. Urinary phthalate measurements

Spot urine samples were collected from participants. Samples were frozen, kept at −80 °C, and transported to the University of Michigan for analysis at NSF International (Ann Arbor, MI, USA). Nine phthalate metabolites were measured including monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP) using isotope dilution–liquid chromatography–tandem mass spectrometry (ID–LC–MS/MS), described elsewhere (Lewis et al., 2013). A summary measure of DEHP (ΣDEHP) exposure was calculated by dividing the concentrations of each metabolite by their molar mass and then summing the results. Specific gravity was measured at the time of sample analysis using a handheld digital refractometer (Atago Co., Ltd., Tokyo, Japan). All concentrations measured below the limit of detection (LOD) were replaced by the LOD/√2.

2.3. Sexual maturation outcome assessment

Tanner stages are measured on a standardized scale from 1 to 5 to indicate various stages of sexual maturation, with stage 1 indicating that an individual has not yet initiated development, stages 2–4 indicating progression through sexual development, and stage 5 indicating adulthood (Marshall and Tanner, 1970, 1969). In the present study, Tanner stages among all children were determined according to standard methods (Chavarro et al., 2017) by two trained physicians. Among girls, breast development was used as an indicator of puberty and pubic hair growth was used as an indicator of adrenarche. We utilized self-reported onset of menarche as an additional indicator of puberty. Among boys, genital development was used as an indicator of puberty and pubic hair growth was used as an indicator of adrenarche. We utilized testicular volume measurements as an additional indicator of puberty. Both right and left testicular volume were measured using an orchidometer and the larger of the two measurements was retained. Categories of testicular volume were set to ≤3 mL (prepubertal), > 3–20 mL (peripubertal), and > 20 mL (adulthood) (Mouritsen et al., 2013a).

2.4. Statistical methods

Arithmetic means and standard deviations were calculated for age and BMI at each adolescent follow up visit. Total N and percent of the population at each stage of sexual maturation, in addition to the mean age and standard deviation at each development stage, were determined at each study visit. Phthalate biomarker measurements were natural log transformed for subsequent individual analyses. Geometric means were calculated from all available phthalate metabolite measurements from multiple trimesters to represent overall gestational exposure for each participant. Additional analyses were conducted where we stratified results by trimester of phthalate exposure but no notable differences were observed (data not shown).

Because two visits were available per participant, methods for correlated outcome data were utilized to examine the association between phthalate exposure and sexual development. Generalized estimating equations (GEEs) for correlated ordinal multinomial responses with an independent correlation structure were used to model relationships between gestational phthalate exposure and odds of being at a higher Tanner stage or category of testicular volume at baseline (age 8–14 years). Generalized additive mixed models (GAMMs) were used to assess the relationship between exposures and the binary menarche outcome at baseline. The use of these models allows for examination of both baseline development stages and progression between study visits, and accommodation of intraindividual correlation of exposure and

Table 1
Outcome descriptive statistics among boys and girls at two adolescent follow-up visits.

	Girls (N = 103)					
	Visit 1			Visit 2		
	Mean (sd)	N (%)	Mean Age (sd)	Mean (sd)	N (%)	Mean Age (sd)
Age (years)	9.98 (1.52)			13.3 (1.63)		
ΔT (years)*	–			3.40 (0.400)		
BMI	19.4 (3.59)			21.8 (4.10)		
BMI - z Score	0.870 (1.25)			–		
ΔBMI	–			2.35 (1.93)		
Breast Development Tanner Stage						
1		74 (71.9%)	9.31 (0.960)		5 (4.90%)	11.5 (0.350)
2		16 (15.5%)	10.9 (1.36)		12 (11.8%)	12.2 (0.850)
3		11 (10.7%)	12.6 (0.470)		45 (44.1%)	12.7 (1.10)
4		2 (1.90%)	13.0 (0.500)		23 (22.5%)	13.8 (1.61)
5		0	–		17 (16.7%)	15.5 (1.11)
Pubic Hair Tanner Stage						
1		84 (81.6%)	9.42 (1.01)		9 (8.80%)	11.6 (0.490)
2		14 (13.5%)	12.2 (0.730)		38 (37.2%)	12.6 (1.05)
3		4 (3.90%)	13.0 (0.440)		26 (25.5%)	13.3 (1.43)
4		1 (1.00%)	13.3 (NA)		17 (16.7%)	14.3 (1.60)
5		0	–		12 (11.8%)	15.5 (1.16)
Menarche						
No		87 (84.5%)	9.51 (1.13)		23 (22.5%)	12.1 (0.850)
Yes		16 (15.5%)	12.5 (0.610)		79 (77.5%)	13.6 (1.60)
	Boys (N = 91)					
	Visit 1			Visit 2		
	Mean (sd)	**N (%)**	**Mean Age (sd)**	**Mean (sd)**	**N (%)**	**Mean Age (sd)**
Age (years)	10.2 (1.52)			13.5 (1.70)		
ΔT (years) *	–			3.32 (0.440)		
BMI	18.9 (3.08)			20.4 (3.85)		
BMI - z Score	0.880 (1.22)			–		
ΔBMI	–			1.53 (1.71)		
Genital Development Tanner Stage						
1		49 (53.8%)	9.41 (1.00)		7 (7.70%)	11.8 (0.390)
2		33 (36.3%)	10.5 (1.34)		17 (18.7%)	12.4 (0.820)
3		8 (8.80%)	12.9 (0.540)		22 (24.1%)	12.5 (1.10)
4		1 (1.10%)	13.2 (NA)		30 (33.0%)	14.0 (1.28)
5		0	–		15 (16.5%)	15.9 (1.13)
Pubic Hair Tanner Stage						
1		79 (86.8%)	9.80 (1.25)		27 (29.7%)	12.0 (0.79)
2		10 (11.0%)	12.6 (0.70)		15 (16.5%)	12.8 (1.01)
3		2 (2.20%)	12.6 (0.920)		25 (27.5%)	13.6 (1.19)
4		0	–		12 (13.2%)	15.0 (1.46)
5		0	–		12 (13.2%)	15.8 (1.23)
Testicular Volume						
[0, 3]		14 (15.4%)	9.29 (0.930)		0	–
(3, 20]		76 (83.5%)	10.3 (1.51)		59 (64.8%)	12.7 (1.20)
(20, 25]		1 (1.10%)	13.8 (NA)		32 (35.2%)	15.0 (1.51)

* Refers to the time, in years, between visits 1 and 2.

outcome variables. Models included time (in years) between first and second adolescent follow up visits (ΔT), the natural log of the phthalate metabolite concentration, and interaction between ΔT and the natural log of the phthalate metabolite concentration. Coefficients from these models were used to estimate (1) the odds of being at a higher versus a lower development stage (or menarche yes vs. no) at the initial adolescent follow up visit (age 8–14 years) per doubling in gestational phthalate concentration (the main effect of the metabolite), and (2) the effects of gestational phthalate exposure on the tempo at which individuals progressed through puberty and adrenarche (the interaction term between phthalate metabolite concentration and time between study visits). The following equations were used to calculate effects estimates and confidence intervals for a doubling in phthalate exposure:

$$\text{Effect Estimates: } \exp\ (\log(2) * \beta_{phthalate})$$

$$95\%\ \text{Confidence Intervals: } \exp\ (\log(2) * (\beta_{phthalate} \pm se_{phthalate}))$$

Tempo results are presented as the odds of being at a higher versus a lower development stage per year following the initial adolescent visit associated with a doubling in gestational phthalate exposure, among those with mean age at the initial adolescent visit. Tempo does not refer to the time it takes to progress from one preestablished maturation milestone to another, but rather the general amount of progression that occurs in one year. A tempo odds ratio greater than 1 indicates that higher phthalate concentrations are associated with a faster rate of development, while a tempo odds ratio less than 1 would indicate a slower rate of development.

Child age (centered around the mean) and BMI z-score at the first adolescent visit were included as covariates, in keeping with previous work published by our group (Watkins et al., 2017b) and from *a priori* knowledge of associations with phthalates (Harley et al., 2017; Yang et al., 2017) and sexual maturation (C. Chen et al., 2017; Kaplowitz, 2008; Rosenfield et al., 2009). Final models also adjusted for change in BMI between the first and second adolescent visits, interaction between

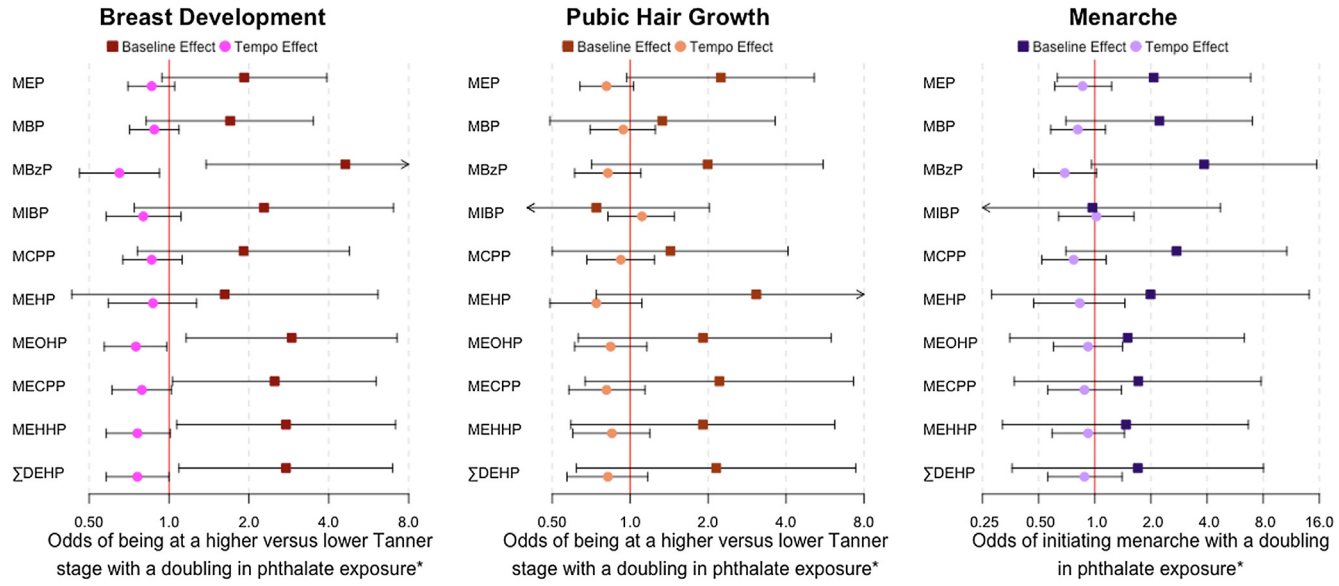

Fig. 1. Among girls, the odds of being at a higher tanner stage or menarche at the first adolescent study visit and the tempo of sexual maturation progression, with a doubling in gestational phthalate exposure (N = 103).* Baseline estimates correspond to effects at the first follow-up visit at 8–14 years of age. Tempo estimates correspond to effects per year following the initial study visit.

mean-centered age at first adolescent visit and ΔT, and interaction between ΔT and the natural log of the phthalate metabolite concentration. Other covariates that were explored for potential confounding effects included maternal age, education level, and socioeconomic status during pregnancy. None of these exploratory covariates were associated with both exposures and outcomes and were thus excluded from final models. All phthalate metabolites were adjusted for specific gravity before inclusion in the model to account for differences in urinary dilution. To address the issue of possible false discovery from conducting many comparisons, we calculated q values using the Benjamini and Hochberg method (Benjamini and Hochberg, 1995). Each sexual maturation outcome was treated as a family of tests (10 tests for each phthalate metabolite per outcome, run separately for main effect p-values and tempo p-values). High p-values were viewed as being at a higher risk of being false-positives, and q-values < 0.1 were interpreted with greater confidence.

3. Results

3.1. Phthalate concentrations through pregnancy

Detailed descriptions of prenatal phthalate exposure distributions among ELEMENT girls and boys are published elsewhere (Watkins et al., 2017b, 2017a) and are shown in Supplementary Table 2. Briefly, all metabolites except for MiBP were detected in at least 90% of samples. After adjustment for specific gravity, most median metabolite concentrations were higher among women expecting a female than a male child throughout gestation. Median concentrations of phthalate metabolites were at their highest in the third trimester among girls (except MEP and MECPP) and boys. Intraclass correlation coefficients (ICCs) were the highest for MEP and the lowest for MCPP among girls and MBzP among boys.

3.2. Sexual progression of the study population

Sexual maturation descriptive statistics over the study duration are shown in Table 1. On average, both girls and boys were 10 years old at the first adolescent study visit and just under 14 years old at the second visit. Both girls and boys had, on average, slightly lower BMI at baseline than age-matched children in other populations (BMI z-scores of 0.87 and 0.88 among girls and boys, respectively).

Among girls, initiation of breast development occurred earlier than menarche and adrenarche, with 28.1% of girls having initiated breast development at the first study visit compared to only 18.4% and 15.5% of girls having initiated pubic hair growth and menarche, respectively. Similarly, a larger portion of girls had reached sexual maturity (Tanner Stage = 5) by the second study visit with respect to breast development (16.7%) compared to pubic hair growth (11.8%). The majority of girls progressed 2 stages (N = 46) for breast development [median(IQR): 2(1)] and 1 stage (N = 41) for pubic hair growth [median(IQR): 1(1)].

Among boys, the patterns for puberty and adrenarche were more discordant. Adrenarche occurred much later than puberty, with only 13.2% of boys having initiated pubic hair development by the first study visit, compared to 46.2% of boys having initiated genital development and 84.6% of boys having a testicular volume greater than 3 mL. In contrast, a larger portion of boys had reached stage 5 by the second study visit with respect to genital development (16.5%) compared to pubic hair growth (13.2%). Furthermore, only 70.3% of the male population had initiated pubic hair growth by the second study visit. The majority of boys progressed 2 stages (N = 35) for genital development [median(IQR): 2(1)], 0 or 2 stages (N = 27 and 26, respectively) for pubic hair growth [median(IQR): 2(2)], and 0 or 1 category (N = 47 and 43, resepectively) for testicular volume [median (IQR): 0(1)].

3.3. Phthalate associations with sexual maturation among girls

Associations between gestational phthalate biomarker concentrations and sexual development outcomes among girls are shown in Fig. 1 and Supplementary Table 3. A doubling of ΣDEHP metabolites was associated with increased odds of being at a higher breast development Tanner Stage at the initial study visit (OR: 2.76, 95%CI: 1.09, 6.96), and also with reduced tempo of breast development over the study period (OR: 0.76, 95%CI: 0.58, 1.00). Similar results were found among DEHP metabolites at the initial study visit [MECPP (OR: 2.50, 95%CI: 1.03, 6.03), MEHHP (OR: 2.76, 95%CI: 1.07, 7.14), MEOHP (OR: 2.90, 95%CI: 1.16, 7.23)], and with MBzP (OR: 4.62, 95%CI: 1.38, 15.5). The tempo of breast development over the study period was reduced per each doubling of MBzP, MEOHP, MEHHP and ΣDEHP (OR range: 0.62–0.76), though not all of these results reached statistical

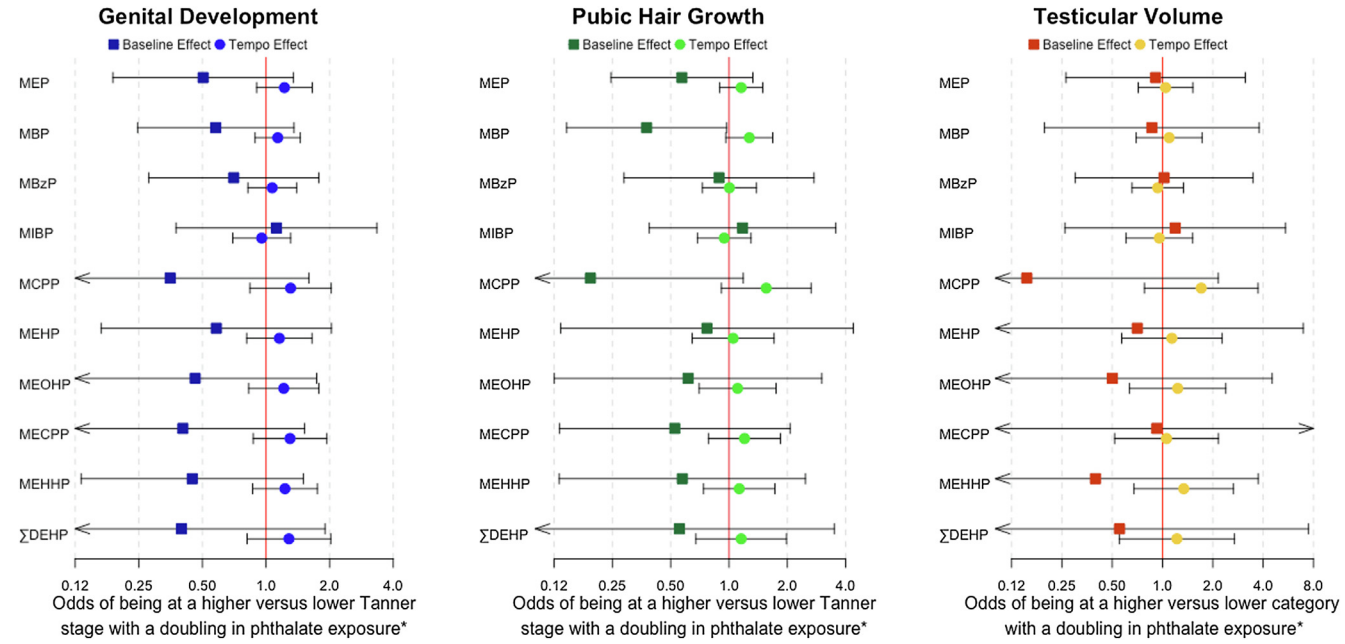

Fig. 2. Among boys, the odds of being at a higher tanner stage or testicular volume category at the first adolescent study visit and the tempo of sexual maturation progression, with a doubling in gestational phthalate exposure (N = 91).* Baseline estimates correspond to effects at the first follow-up visit at 8–14 years of age. Tempo estimates correspond to effects per year following the initial study visit.

significance.

Odds of being at a higher versus a lower Tanner Stage for pubic hair growth at baseline were marginally higher with a doubling of gestational MEP concentration (OR: 2.24, 95%CI: 0.97, 5.14). Odds of having reached menarche by the first study visit were marginally higher (OR: 3.86, 95%CI: 0.96, 15.5), and the tempo of progression to menarche was slower (OR: 0.69, 95%CI: 0.47, 1.02), with a doubling of gestational MBzP concentration.

3.4. Phthalate associations with sexual maturation among boys

Associations between gestational phthalate biomarker concentrations and sexual development outcomes among boys are shown in Fig. 2 and Supplementary Table 4. A doubling of gestational MBP concentration was associated with decreased odds of being at a higher Tanner Stage for pubic hair growth among boys at the first study visit (OR: 0.38, 95%CI: 0.15, 0.97), and with a marginally increased tempo of progression of pubic hair growth (OR: 1.27, 95%CI: 0.96, 1.68). Measures of gestational phthalate exposure were generally associated with decreased odds of being at a higher Tanner Stage for genital development at the first study visit and increased tempo of progression (except MIBP) through genital development over the study period, but none of these relationships were statistically significant. There were no clear patterns of association between gestational phthalate levels and testicular volume.

4. Discussion

We assessed relationships between geometric mean gestational phthalate metabolite concentrations, and onset and progression of sexual maturation outcomes among girls and boys over two adolescent follow-up visits. Our findings suggest that higher gestational exposure to phthalates among females was associated with earlier onset and slower progression of sexual development, while the opposite patterns were seen among males (i.e., later onset and faster progression). The most marked results were seen with high molecular weight phthalate metabolites (MBzP and DEHP metabolites) and breast development in girls, and low molecular weight phthalate metabolites (MBP) and pubic hair growth in boys.

This is one of the first studies to assess relationships between gestational phthalate exposure and the tempo of sexual maturation progression. Several previous studies have explored associations between onset of puberty and the rate of progression to sexual maturity, and most found that those with early onset of puberty progressed to adulthood significantly slower than those with late onset of puberty (German et al., 2018; Pantsiotou et al., 2008; Vizmanos et al., 2004). This apparent compensatory mechanism may function to ensure that age at sexual maturity remains within a normal range. In the present study, we found that onset and tempo of sexual maturation outcomes generally showed opposite relationships with increasing phthalate exposures, with onset being earlier and tempo being slower among girls, and onset being later and tempo being faster among boys. These associations suggest that the biological response to increasing phthalate exposures may exacerbate basal trends that are seen among individuals with early and late onset of puberty, or that innate physiology works to maintain homeostatic conditions by compensating for the effects of phthalate exposures.

Gestational urinary biomarkers of phthalate exposure have previously been assessed for relationships with sexual development later in life in numerous studies coming from two cohorts – ELEMENT and CHAMACOS. Early ELEMENT studies assessed relationships between third trimester phthalate measurements and sexual development at a single follow-up visit at age 8–14 years among girls (Watkins et al., 2014) and boys (Ferguson et al., 2014b), and found that odds of pubic hair growth were generally increased among girls and reduced among boys with greater gestational phthalate exposures. Subsequent ELEMENT studies examined measures of phthalate exposure across gestation in relation to odds of onset of sexual development in girls (Watkins et al., 2017b) and boys (Watkins et al., 2017a). Their results suggested that higher gestational exposure to MEP was associated with greater odds of initiation of menarche, higher gestational exposure to MEHP was associated with decreased odds of initiation of breast development, and higher gestational exposure to MBzP was inversely associated with odds of initiating pubic hair growth in boys. Except for MEHP and breast development, the direction of associations found in our study were consistent to those found previously, though not statistically

significant. The majority of our study population had initiated sexual development by the second follow-up visit and thus the stages of development were more evenly distributed across participants compared to the first visit. This allowed us to utilize a statistical model which takes advantage of the ordinal nature of Tanner Stage outcomes in the present work, while former studies were only able to assess odds of initiating development (Tanner Stage > 1) versus not (Tanner Stage = 1).

Multiple studies looking at gestational phthalate exposure relationships with sexual maturation outcomes have come from the CHAMACOS birth cohort in southern California (N = 179 girls and 159 boys). Urine samples were taken at two time points during pregnancy (mean 14 and 26.9 weeks) to measure metabolite concentrations of high (Berger et al., 2018) and low molecular weight (Harley et al., 2019) phthalates, and the geometric mean of these concentrations was used as an overall measure of gestational phthalate exposure. Children were followed to assess sexual development outcomes every 9 months between the ages of 9 and 13 years, and results were presented as the adjusted mean shift in age at onset of each sexual maturation outcome. Some results in the current study were consistent with those seen in the CHAMACOS cohort, including associations between gestational MEP exposure and earlier onset of pubic hair growth in girls, and between gestational MBzP and ΣDEHP metabolites and earlier onset of breast development in girls. However, various additional associations were found in the CHAMACOS studies that were not observed in our study. Sexual development stages were generally reached at a later age among ELEMENT girls compared to CHAMACOS girls, and distributions of some phthalate metabolite concentrations were different between ELEMENT and CHAMACOS, including those of several DEHP metabolites (median concentrations of MEHP, MEHHP, and MECPP were higher in ELEMENT), which may have contributed to differences in results. Additionally, the participants in the CHAMACOS cohort reside in a community where pesticide exposure is high (Castorina et al., 2003), reducing the generalizability of the results. Lastly, the CHAMACOS study utilized accelerated failure time models (AFTs) which accommodate data with outcomes occurring before or between follow-up visits, but do not allow for estimation of the rate of sexual maturation.

An additional study conducted in Australia looked at associations between maternal serum concentrations of phthalate metabolites during pregnancy and measures of reproductive development in female children of those mothers (Hart et al., 2014). They found marginally significant increased odds of onset of menarche with an increasing sum of MEHP and MECPP concentrations, results that were not seen in our study. Differences in methodology including their use of serum phthalate measurements instead of the preferred urinary measurements (A. Calafat et al., 2015; Johns et al., 2015), pooling of gestational serum samples rather than using repeated measures, and introduction of recall bias from asking participants to recall at what age they initiated menarche (Dorn et al., 2013), may have contributed to differing results between our studies. Lastly, a study conducted in Taiwan measured third trimester phthalate concentrations and tested for associations with various indicators of sexual development later in life (Su et al., 2015). Most outcomes assessed were not consistent with those measured in our study, and children were only followed until 11 years of age when most of them likely had not reached sexual maturity.

Although mechanisms of potential phthalate disruption on sexual development are poorly understood, female rodent studies have shown that exposure to DEHP at various times through the life cycle can alter estradiol concentrations, possibly via upstream deregulation of FSH synthesis or cholesterol transport (Brehm et al., 2017; Davis et al., 1994; Hirosawa et al., 2006; Ma et al., 2006; Moyer and Hixon, 2012; Svechnikova et al., 2007). An increase in estradiol concentration is necessary for initiation of enlargement of breast tissue (DiVall and Radovick, 2009), thus these animal studies point to the need to study estrogen disruption as being on the causal pathway from phthalate exposure to altered sexual development.

Our finding that MBP was inversely associated with onset of pubic hair growth in boys suggests that phthalates may have the capacity to disrupt adrenal function. In order for pubic hair growth to begin, DHEA-S from the adrenal gland must travel to target tissues where hair follicles and dermal exocrine glands possess the necessary enzymes to convert DHEA-S into dihydrotestosterone (Auchus and Rainey, 2004). Thus is it local synthesis of testosterone from upstream adrenal regulation, not circulating androgens, that are critical for the initiation of pubic hair growth. Previous animal studies have suggested that in utero phthalate exposure can alter expression of adrenal transcription factors (Lee et al., 2016), reduce serum aldosterone concentrations (Martinez-Arguelles et al., 2011), and down-regulate expression of genes required for cholesterol transport and steroid synthesis (Saillenfait et al., 2013), all possible mechanisms by which phthalates may interfere with adrenal regulation of pubic hair growth.

The present study had several limitations. Though we measured phthalate metabolite concentrations at up to three time points during pregnancy, phthalates are relatively short lived inside the body (Braun et al., 2012; Johns et al., 2015) and thus three measurements may not fully characterize overall gestational exposure. We also did not adjust for adolescent phthalate exposure which could have confounded our results. Additionally, phthalate exposure always occurs as a mixture of metabolites and we did not adjust for concurrent phthalate exposures. It is possible that BMI acts as a mediator on the causal pathway between prenatal phthalate exposure and sexual development, thus our adjustment for BMI at baseline and change in BMI between study visits may have introduced bias to our results. We were not able to begin follow-up before all children initiated puberty, nor were we able to conduct numerous visits thereafter, and thus the exact timing of initiation and progression of maturation from one stage to the next cannot be known. However, the majority of our population had initiated sexual maturation by the second follow-up visit which allowed us to more reliably measure onset and tempo of progression. This builds on previous work from the ELEMENT cohort because we have multiple measures of maturation outcomes. Lastly, our sample size was relatively small and thus our statistical power to detect true associations may be limited.

5. Conclusions

Our results suggest that gestational phthalate exposure is associated with earlier onset and slower progression of sexual maturation outcomes in girls, particularly breast development. Conversely, gestational phthalate exposure was associated with later onset and faster progression of sexual maturation outcomes in boys, though most associations did not reach statistical significance. Some of our results align with those of previous studies, but our study is methodologically unique. More studies looking at phthalate effects on tempo of sexual maturation among a larger sample of children with more frequent follow-up visits are needed to substantiate our results. Future research will also utilize longitudinal hormone measurements through adolescence to test for possible interactions between hormones and phthalates and the resulting impacts on sexual development.

CRediT authorship contribution statement

Amber Cathey: Writing - original draft, Methodology, Formal analysis, Visualization. **Deborah J. Watkins:** Supervision, Conceptualization, Writing - review & editing. **Brisa N. Sánchez:** Conceptualization, Methodology, Writing - review & editing. **Marcela Tamayo-Ortiz:** Conceptualization, Investigation, Project administration, Writing - review & editing. **Maritsa Solano-Gonzalez:** Methodology, Data curation. **Libni Torres-Olascoaga:** Methodology, Data curation, Investigation, Project administration. **Martha Maria Téllez-Rojo:** Funding acquisition, Conceptualization, Writing - review & editing. **Karen E. Peterson:** Funding acquisition, Conceptualization, Writing - review & editing. **John D. Meeker:** Supervision, Funding

acquisition, Conceptualization, Project administration, Writing - review & editing.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105469.

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