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Authors
Huang, Jonathan Y
Eskenazi, Brenda
Bornman, Riana
et al.

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Maternal peripartum urinary pyrethroid metabolites are associated with thinner children at 3.5 years in the VHEMBE birth cohort (Limpopo, South Africa)

Jonathan Y. Huang[a], Brenda Eskenazi[b], Riana Bornman[c], Stephen Rauch[b], Jonathan Chevrier[a]

Background: Pyrethroids are the most widely used insecticides globally for domestic, agricultural, and malaria vector control. In 10 countries, dichlorodiphenyl trichloroethane (DDT) is also used for the latter. Thus, high exposure to pyrethroids and DDT have been reported among women and children from rural and/or malaria-endemic areas. Experimental studies suggest that fetal exposure to pyrethroids, particularly cypermethrin, and DDT may have sex-specific growth effects. However, epidemiologic investigations are scarce and inconsistent and have not considered postnatal environment or susceptibility factors.

Methods: In 665 mother–child dyads participating in the Venda Health Examination of Mothers, Babies, and their Environment (VHEMBE), a rural South African birth cohort with high insecticide exposure, we examined associations of maternal peripartum urinary pyrethroid metabolites and serum DDT concentrations with child anthropometrics at 3.5 years using multivariable linear regression. We investigated effect modification by child sex, maternal nutrition and HIV status, and household poverty.

Results: Pyrethroid metabolites *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DBCA), *cis*-3-(2,2,-dichlorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DCCA), *trans*-DCCA, and 3-phenoxybenzoic acid (3-PBA) were quantified in nearly all mothers. A 10-fold increase in *cis*-DCCA concentration was associated with 0.21 kg/m^2 lower body mass index (95% confidence interval = –0.41, –0.01), with similar estimates for other cypermethrin or permethrin metabolites (*trans*-DCCA and 3-phenoxybenzoic acid). In stratified analyses, stronger associations were observed with lower weight, body mass index, arm circumference, and weight-for-height among boys relative to girls. Associations with *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid, a metabolite specific to deltamethrin, were weaker or absent. No substantial associations were observed with DDT.

Discussion: In a population with ubiquitous pyrethroid exposure, maternal concentrations of metabolites of cypermethrin and permethrin were associated with thinness at 3.5 years.

Keywords: Pyrethroid; Cypermethrin; DDT/E; Child growth

In many low- and middle-income countries, poor child growth due to poverty, malnutrition, and chronic infections remains a major impediment to population health improvement.[1] Fetal exposure to environmental chemicals are increasingly suspected to play a role in child growth,[2] particularly in rural, agricultural communities where pregnant mothers may be highly exposed to insecticides.[3,4] In malaria-endemic regions, mothers may also be highly exposed to insecticides through indoor residual spraying (IRS). IRS involves the application of insecticides such as dichlorodiphenyl trichloroethane (DDT) or, more commonly, pyrethroids such as deltamethrin or cypermethrin to the interior walls of homes to repel and/or kill malaria-transmitting *Anopheles* mosquitoes.[5] Substantial animal and experimental evidence suggests pyrethroids may alter endocrine function.[6–9] Fetal exposure to cypermethrin, in particular, may alter androgen-mediated pathways.[6,7] Two recent human studies suggest that pyrethroids may accelerate puberty in boys[10] and delay puberty in girls.[11]

Epidemiologic studies of fetal pyrethroid exposure and child growth are sparse[2] and inconsistent. A few studies have found associations between urinary pyrethroid metabolite concentrations and lower birth weight[12,13] or thinness (body mass index [BMI] and weight-for-height) at 1 and 2 years.[14] One study by Zhang et al.[15] found associations between concentrations of the metabolite 3-phenoxybenzoic acid (3-PBA) and higher birth weight and head circumference. Others have found no associations with birth weight or other child anthropometrics at birth[15–18] or at 1 year.[19] Prior studies have been limited by small sample sizes, self-reported usage rather than the use of biomarkers, low detection frequencies, or limited durations of follow-up. Importantly, existing studies have generally not considered potential confounding by postnatal factors such as child diet or infections.

[a]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Quebec, Canada; [b]Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California at Berkeley, Berkeley, California; and [c]Institute for Sustainable Malaria Control, School of Health Systems and Public Health, University of Pretoria, Pretoria, South Africa.

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Data access and computing code: Access may be discussed by contacting Dr. Jonathan Chevrier (jonathan.chevrier@mcgill.ca). Stata code used for analyses can be obtained by contacting the corresponding author.

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Corresponding Author. Address: 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada. Tel.: 514-398-6989. E-mail address: jonathan.huang@mail.mcgill.ca (J. Huang).

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Our previous work in a rural South African birth cohort with high exposure to pyrethroids and DDT suggests associations between prenatal exposure to insecticides and early child size. We found that prenatal exposure to DDT and dichlorodiphenyl dichloroethylene (DDE, a DDT breakdown product) was associated with greater birth size (birth weight, length, and head circumference)[18] and larger weight-for-age at 1 and 2 years among girls.[14] In contrast, maternal urine concentrations of several pyrethroid metabolites were associated with lower weight-for-age at 1 and 2 years, especially among boys. In low- and middle-income countries such as South Africa, catch-up growth is observed after age 2 years in a substantial proportion of the population.[20] Thus, the aim of the present study is to evaluate whether observed associations between prenatal exposure to DDT and pyrethroids persist at age 3.5 years, while taking into account important postnatal determinants of child growth such as diet quality and infections.

Methods

Study population and recruitment

The current study was conducted in the context of the Venda Health Examination of Mothers, Babies, and their Environment (VHEMBE), a prospective birth cohort study of children born in the Vhembe district of Limpopo Province, South Africa, where individuals are exposed to pyrethroids such as deltamethrin and cypermethrin through IRS for malaria control, agriculture, and/or general domestic usage. Pyrethroid-treated bed nets are not provided by the Limpopo Malaria Control Program and are thus not commonly used in the study area. Individuals are also exposed to DDT/E through IRS. Between August 2012 and December 2013, women who presented for delivery at Tshilidzini Hospital in the city of Thohoyandou were screened for eligibility. Women were eligible if they were at least 18 years old, spoke Tshivenda at home, lived within 20 km of the hospital and planned to remain in the area for the next 2 years, were free from malaria during the index pregnancy, had contractions at least 5 minutes apart, and delivered a live, viable singleton. Informed consent was obtained prior to data collection. The study was approved by the Institutional Review Boards of the University of California, Berkeley; McGill University; the University of Pretoria; the Limpopo Department of Health and Social Development; and Tshilidzini Hospital.

Study staff screened 1,649 mothers, 920 of whom met eligibility criteria. Of eligible mothers, 752 provided informed consent, completed a baseline delivery questionnaire, and provided urine and a peripheral blood sample around the time of delivery for pyrethroid metabolite and DDT and DDE (DDT/E) quantification, respectively. Mothers and children were followed up at 1 week, 1 year, 2 years, and 3.5 years after delivery. The 1-week visit occurred in the mother's home where staff made observations on housing materials and other aspects of the living environment. The 665 children seen at 3.5 years (91% of those still alive) along with their mothers form the basis for this study (Table 1). Mother–child dyads included in this analysis were similar to those that were not followed up, except that study mothers were slightly less likely to be HIV positive.

Sample collection and analysis

Of the 665 dyads included in this study, 655 (98%) mothers provided a sufficient urine sample for pyrethroid metabolite quantification, of which 412 (62%) provided a urine sample before and 243 (38%) after delivery. Urinary-specific gravity was measured shortly after collection using a portable refractometer (Atago PAL-10S; Tokyo, Japan). Maternal peripheral blood (N = 665) was collected in red-top vacutainer tubes prior to, or immediately after, delivery. Urine and blood samples were immediately processed and stored at –80°C.

Table 1

Characteristics of Venda Health Examination of Mothers, Babies, and their Environment (VHEMBE) study participants (Venda District, Limpopo, South Africa; N = 665).

	%	N	Mean	Standard Deviation
Maternal characteristics at delivery				
Age (years)			26.3	6.2
Married or living as married	47%	312		
Nulliparous (no previous live births)	44%	291		
Grade 12 education or higher	44%	291		
Low energy intake in late pregnancy[a]	68%	450		
High blood pressure during pregnancy	11%	73		
HIV positive	12%	82		
Height (cm)			158.1	6.8
Postpartum BMI			27.6	5.4
Family/household characteristics at delivery				
Primary drinking water piped directly into home	55%	368		
Below food poverty level[b]	61%	403		
Household income/person/month (Rand)			508.3	640.4
Number of residents in household			5.2	2.8
Child characteristics (birth to 3.5 years)				
Female	49%	325		
Preterm (born at <37 weeks of gestation)	13%	84		
Birth weight (g)			3141	445
Length at birth (cm)			48.9	2.3
Months of exclusive breastfeeding			2.3	1.9
Frequent diarrhea at 1 year (weekly or more)	12%	81		
Any persistent fevers (4+ days), 0–1 year	15%	97		
Any persistent fevers (4+ days), 1–2 years	29%	190		
Child anthropometrics at 3.5 years visit				
Age at visit (years)			3.6	0.1
Standing height (cm)			96.0	3.7
Weight (kg)			14.4	1.7
BMI (kg/m^2)			15.6	1.3
Middle-upper arm circumference (cm)			16.5	1.2
Height-for-age Z score (HAZ)			–1.0	0.9
Low height-for-age (<–2 SD)	12%	82		
Weight-for-age Z score (WAZ)			–0.6	0.9
Low weight-for-age (<–2 SD)	4%	24		
Weight-for-height Z score			0.02	0.9
Low weight-for-height (<–2 SD)	2%	11		
BMI-for-age Z score			0.1	0.9

[a]If the individual's total energy intake falls below the Institute of Medicine (2009) recommended for women in late pregnancy based on age, height, weight, and activity level (Mean recommended intake in this population = 12,134 kJ; Range = 10,164–14,712 kJ).

[b]South African mid-2013 food poverty threshold: <386 Rand/person/month.

BMI indicates body mass index; SD, standard deviation.

Urine aliquots were shipped on dry ice to the *Centre de Toxicologie du Québec* of the *Institut National de Santé Publique du Québec* in Quebec City, Canada, for analyses. Gas chromatography-mass spectrometry was used to quantify the following five pyrethroid metabolites: 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DBCA), *cis*-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DCCA), *trans*-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*trans*-DCCA), and 3-PBA based on methodology adapted from Dewailly et al.[21] Blood aliquots were shipped to Emory University's Rollins School of Public Health Environmental Health Laboratory (Atlanta, GA) and analyzed by gas chromatography-tandem mass spectrometry with isotope dilution quantification[22] for *p,p′*-DDT, *p,p′*-DDE, *o,p′*-DDT, and *o,p′*-DDE.

Limits of detection (LOD) and quantification (LOQ) for pyrethroid metabolites and serum DDT/E are given in Table 2. Urinary concentrations of 4-F-3-PBA were only quantified in 7.7% (N = 51) of samples and were excluded from statistical analyses. The remaining four metabolites (*cis*-DBCA, *cis*-DCCA, *trans*-DCCA, and 3-PBA) were detected in all samples.

Table 2

Distribution of maternal-specific gravity-corrected urinary pyrethroid metabolite (μg/L) and lipid-corrected serum DDT (ng/g lipid) (N = 665).

	N	% ≥LOD[a]	% ≥LOQ[b]	Geometric Mean[c]	Geo. SD	Min	10th percentile	25th percentile	Median	75th percentile	90th percentile	Max
cis-DBCA	655	100%	99.5%	0.22	3.5	0.005	0.05	0.09	0.22	0.48	1.12	17.8
cis-DCCA	655	100%	99.8%	0.31	3.0	0.015	0.08	0.15	0.30	0.60	1.03	103.5
trans-DCCA	655	100%	99.5%	0.36	3.5	0.008	0.08	0.15	0.34	0.80	1.48	132.9
3-PBA	654	100%	100%	0.71	2.8	0.022	0.21	0.37	0.69	1.38	2.35	58.9
o,p′-DDT	665	90.5%	44.5%	9.1	4.6	<LOD	1.5	3.5	7.6	23.2	74.0	2,029.3
p,p′-DDE	665	100%	97.4%	292.6	4.8	4.0	46.1	93.7	252.4	858.1	2,688.1	22,613.4
p,p′-DDT	665	98.2%	90.7%	70.5	6.7	<LOD	8.1	19.1	58.3	262.2	966.6	15,027.6

[a]Limits of detection (LOD): 0.0025 (*cis*-DBCA), 0.0045 (*cis*-DCCA), 0.0038 (*trans*-DCCA), and 0.0047 (3-PBA) μg/L; 0.01 ng/mL (*o,p′*-DDT and *p,p′*-DDT) 0.03 ng/mL (*p,p′*-DDE); LOD for omitted measures: 4-F-3-PBA = 0.005 μg/L; *o,p′*-DDE = 0.01 ng/mL.

[b]Limits of quantification (LOQ): 0.0082 (*cis*-DBCA), 0.015 (*cis*-DCCA), 0.013 (*trans*-DCCA), to 0.016 (3-PBA) μg/L; 0.05 ng/mL (*o,p′*-DDT and *p,p′*-DDT) 0.15 ng/mL (*p,p′*-DDE); LOQ for omitted measures: 4-F-3-PBA = 0.011 μg/L; *o,p′*-DDE = 0.05 ng/mL.

[c]Geometric means for DDT/E include values below the LOD imputed by maximum likelihood estimation of log-normal distributions based on observed values.

DDE indicates dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; LOD, limits of detection; LOQ, limits of quantification.

Machine-read values were used for all analytes that were detected but below the LOQ. Concentrations for samples below the LOD were imputed at random from log-normal distributions whose parameters were estimated by maximum likelihood. Serum concentrations of *o,p′*-DDE were only quantified in 16% (N = 106) of samples and were excluded from analyses. Total serum lipid concentrations were estimated using the Phillips formula[23] from total triglyceride and cholesterol concentrations measured by standard enzymatic methods (Roche Chemicals, Indianapolis, IN).

Child anthropometrics

At the 3.5-year visit, study staff measured weight without clothes to the nearest 10 g using a digital scale (Tanita HD-351; Tokyo, Japan); standing height using a stadiometer (Charder HM200P; Taichung, Taiwan); and middle-upper arm circumference using a measuring tape following US National Health and Nutrition Examination Survey protocols.[24] All anthropometric measures were taken in triplicate and averaged. Age- and sex-standardized Z scores for height, weight, BMI, and arm circumference were calculated using WHO's *igrowup* Stata package which implements the 2006–2007 WHO child growth standards.[25,26]

Covariate data from maternal questionnaires

Study staff administered questionnaires in the local Tshivenda language to mothers prior to hospital discharge to collect information on maternal sociodemographics, nutrition, health, pregnancy history, and use of commercially available insecticides during pregnancy. We used maternal age, marital status, parity, food frequencies, family income, and pesticide usage recorded in the delivery questionnaire. Family income was classified as above or below the official South African mid-2013 food poverty level (386 Rand per person per month).[27] Maternal HIV status during pregnancy was ascertained from self-reported diagnosis or use of antiretroviral drugs based on medical records, which were abstracted by registered nurses. Maternal total energy intake in kilojoules (kJ) and percentage of daily energy intake from proteins were estimated by a South African expert nutritionist using the FoodFinder 3 software (South Africa Medical Research Council/WAMTechnology cc; Stellenbosch, South Africa) from a quantitative food frequency questionnaire designed and validated among residents from our study area.[28] Low energy intake was defined as having total daily caloric intake below that recommended by the Institute of Medicine (IOM) for late pregnancy.[29] Additionally, mother and infant drinking water source and number of months of exclusive breastfeeding were obtained from the 1-week and 1-year questionnaires, respectively.

A family wealth index was generated for each subject based on Demographic and Health Surveys methodology for South Africa using data from the 1-week home visit. Specifically, principal component analysis was used to construct a family wealth index based on dummy indicator variables for the following variables: asset ownership (15 items), livestock ownership (6 items), water sources (8 items), number of household members, and cooking fuels (8 item) by maternal self-report; and toilet facilities (4 items), household floor, and wall materials (20 items) by staff direct observation (complete list is given in eTable 1; http://links.lww.com/EE/A19). At the home visit, women were also asked about insecticide brands and usage frequency during pregnancy. Women were asked to identify the specific insecticide after being shown pictures of containers for the most common brands sold in the area. Finally, to consider potential postnatal confounding by child nutrition, we constructed a child diet diversity score by summing whether any of the 18 common food groups were eaten by the child (any versus none in the past month; median = 10; range = 2–18), as reported by the mother at the 2-year interview.

Statistical analyses

Urinary pyrethroid metabolite concentrations were corrected for dilution by dividing values by urine. Specific gravity (μg/L), and DDT/E were corrected for serum lipid content and expressed in ng/g lipid. Pyrethroid metabolite and DDT/E concentrations were $\log_{10}$-transformed to minimize the influence of outliers. Child anthropometric measures (*y* axis) were plotted against pyrethroid metabolites (*x* axis) with LOWESS smoothers for initial visual inspections for trends and outliers. Additionally, three-degree fractional polynomials were fit to visually investigate trends for multivariable (conditional) models. In all cases, exposure–response curves did not depart substantially from log-linearity.

To estimate the association between chemical concentrations and anthropometrics at 3.5 years, we fitted multivariable linear regression models. The following predictors of child growth were identified using a directed acyclic graph and included in all analyses: continuous maternal age (years), parity (live births excluding index child), height (cm), postdelivery weight (kg), and total number of household members at the time of delivery; categorical maternal educational attainment (<12 years, 12 years, some post-secondary; post-secondary diploma or degree); binary marital status (married or living-as-married versus single), household food poverty status, low energy intake, any alcohol use during pregnancy, and HIV status at the time of delivery of the index child; and child sex (male/female). Additionally, we adjusted for lipid-corrected serum concentrations (ng/g lipid) of hexachlorobenzene, β-hexachlorocyclohexane, dieldrin, and the sum of 4 polychlorinated biphenyl congeners (PCB 118, 138, 153, and 180),

which may be associated with both exposure and child size. Concentrations were also $\log_{10}$-transformed. Pyrethroid metabolite models were adjusted for *o,p′*-DDT, *p,p′*-DDT, and *p,p′*-DDE, and vice versa. Finally, the following potential confounders were included in addition to the above set: family wealth index, percentage of maternal daily energy intake from proteins, drinking water supply (municipal water piped into home versus public standpipe versus other), and duration of exclusive breastfeeding (in months) as a risk factor for chronic enteral infections and potential determinant of growth in this setting.[30] To account for potential selection bias due to differential follow-up, all analyses were weighted by inverse probability of inclusion in analyses. Logistic regression was used to predict the probability of inclusion in the sample using all pyrethroid and DDT/E measures and covariates listed above as independent variables. Associations between pyrethroid exposure and growth may be stronger among boys due to the putative role of the HPG axis and testosterone.[6] Additionally, maternal malnutrition HIV status, or poverty may also increase susceptibility to fetal pesticide exposure.[31] Consequently, effect measure modification was examined by separately including the product of $\log_{10}$-pyrethroid metabolite or -DDT/E and either child sex, maternal low energy intake, maternal HIV status, or family poverty indicator as interaction terms.

Postnatal factors including infections and nutrition may be important confounders of the relationship between fetal chemical exposures and child growth as they may be associated with fetal chemical concentrations and independently affect child growth. To evaluate whether such factors may confound observed relationships, additional analyses were conducted adjusting for child infections (number of diarrhea and persistent fever events drawn from maternal questionnaire at 1 and 2 years) and child diet diversity score.

Sensitivity analyses

To evaluate the impact of influential points on estimated associations, change in point estimates (*dfbetas*) from omitting each observation were calculated using jackknife estimation and models were re-fitted omitting the 10 most extreme *dfbeta* values. From scatter plots, it appeared that a single individual with a 3.5-year weight of 28.4 kg and arm circumference of 26.2 cm was an outlier (>8 standard deviations away from the sample mean/median for each). Models were refitted omitting this individual as well. While few observations were missing any covariate data (20 individuals), models were refitted using multiple imputation by chained equations to replace missing values probabilistically based on observed data on the same set of covariates used in the main regression models.

It is widely recognized that the use of urinary pyrethroid metabolites as measures of pyrethroid exposure may be limited due to the short half-life of parent compounds and rapid excretion of metabolites following exposure (i.e. near complete elimination in a few days). Consequently, a single measurement from a spot urine sample may not fully reflect longer-term exposure. To investigate whether any observed associations are consistent with longer-term exposure, we investigated associations between self-reports of personal pyrethroid insecticide usage during pregnancy as proxies for personal pyrethroid exposure on child anthropometrics, using identical multivariable adjustment models as the main analyses.

All analyses were conducted in Stata 12.1 (StataCorp, College Station, TX).

Results

Participant characteristics

All mothers were black South Africans, and their mean age at delivery of the index child was 24.7 years. Most women were unmarried (53%), had less than a 12th-grade education (56%), and lived below the South African food poverty line of 386 Rand (≈26 USD) per person per month (60%; Table 1). A substantial proportion (44%) did not have a direct water supply (piped directly into the home). Two-thirds of women (67%; N = 442) ate less than the IOM-recommended daily number of calories for late pregnancy, and 12% were HIV positive. Average birth weight of children was 3141 g, and 13% were preterm (gestational age <37 completed weeks). The median duration of exclusive breastfeeding was 2 months (any breastfeeding = 18 months). Thirty percent of children were stunted (height-for-age Z score <–2) at 2 years and 12% at the 3.5-year visit.

Maternal urinary pyrethroid metabolites and serum DDT/E

Concentrations of all four pyrethroid metabolites were above LOD in all maternal samples and above LOQ in all samples except for *cis*-DBCA and *trans*-DCCA in 3 samples and *cis*-DCCA in one. Specific gravity–adjusted geometric mean concentrations of *cis*-DBCA, *cis*-DCCA, *trans*-DCCA, and 3-PBA were 0.22, 0.31, 0.36, and 0.72 µg/L, respectively. Metabolites of permethrin and cypermethrin, *cis*-DCCA and *trans*-DCCA, were highly correlated with one another (Pearson's $r = 0.9$) and also with their common metabolite 3-PBA ($r = 0.87$–0.88) and moderately correlated with the deltamethrin-specific metabolite *cis*-DBCA ($r = 0.47$–0.48). Concentrations of *cis*-DCCA, *trans*-DCCA, and 3-PBA in this study (creatinine-corrected geometric means: 0.25, 0.29, and 0.57 µg/g, respectively) were generally higher than reported in US women (75%th percentile in 2001–2002: 0.27, 0.85, and 0.33 µg/g, respectively)[32] or European women (uncorrected median: 0.09, 0.14, and <0.008 µg/L, respectively; Brittany, France).[33] Detection rates were slightly higher, though average concentrations were slightly lower, than those for pregnant women from northern China (0.39, 0.49, and 0.57 µg/g, respectively).[13] A quarter of women (N = 166) reported usage of any commercially available insecticide in the peri-conception period and 19% (N = 129) use of a specific brand of permethrin during pregnancy. While peripartum urinary metabolite concentrations did not strongly differ by self-reported early pregnancy usage, they were markedly higher among those who reported using permethrin (median *cis*-DBCA, *cis*-DCCA, *trans*-DCCA, and 3-PBA: 0.21, 0.29, 0.32, and 0.65, respectively, among non-users versus 0.28, 0.34, 0.45, and 0.90, respectively, among users). Detection frequencies for serum *o,p′*-DDT, *p,p′*-DDT, and *p,p′*-DDE were 90.5%, 98.2%, and 100%, respectively (Table 2). Corresponding lipid-corrected, geometric mean concentrations were 9.1, 70.5, and 292.6 ng/g lipid, respectively. Correlations between DDT/E concentrations were 0.72 (*p,p′*-DDE/*o,p′*-DDT), 0.83 (*p,p′*-DDE/*p,p′*-DDT), and 0.92 (*o,p′*-DDT/*p,p′*-DDT).

Multivariable analyses

In main analyses, all four maternal pyrethroid urinary metabolites were associated with slightly increased height, lower weight, and therefore lower BMI (Table 3). The magnitude of association with lower BMI was consistent across metabolites, about –0.2 kg/m^2 per 10-fold increased concentration. Inverse associations were observed for BMI and weight-for-height Z scores as well. Results for age- and sex-standardized measures (height, weight, and BMI Z scores) show identical qualitative relationships (Table 3). All metabolites were associated with approximately a 0.2 cm reduction in arm circumference per 10-fold increase. Maternal DDT/E was not strongly associated with any measures of child size at 3.5 years (Table 4).

In interaction analyses, pyrethroid metabolites were more strongly associated with boys' than girls' size. For example, a 10-fold increase in *trans*-DCCA was associated with 0.3 kg/m^2 decrease among boys (95% confidence interval [CI] = –0.57, –0.11) versus a 0.06 kg/m^2 decrease (95% CI = –0.35, 0.22)

Table 3

Adjusted associations between log_{10}-transformed maternal urinary pyrethroid metabolite concentration and child anthropometrics.

	cis-DBCA		*cis*-DCCA		*trans*-DCCA		3-PBA	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)	0.07 [−0.48, 0.61]	0.82	0.43 [−0.17, 1.03]	0.16	0.36 [−0.17, 0.88]	0.19	0.31 [−0.33, 0.96]	0.34
Weight (kg)	−0.17 [−0.41, 0.07]	0.15	−0.09 [−0.34, 0.17]	0.51	−0.11 [−0.34, 0.11]	0.33	−0.14 [−0.41, 0.14]	0.34
BMI (kg/m^2)	−0.19 [−0.37, −0.01]	0.04[a]	−0.21 [−0.41, −0.01]	0.04[a]	−0.22 [−0.40, −0.04]	0.02[a]	−0.22 [−0.44, −0.01]	0.04[a]
Arm circumference (cm)	−0.15 [−0.31, 0.02]	0.09	−0.15 [−0.32, 0.03]	0.11	−0.18 [−0.33, −0.02]	0.03[a]	−0.19 [−0.38, 0.01]	0.06
WAZ (SD)	−0.08 [−0.21, 0.04]	0.20	−0.05 [−0.18, 0.08]	0.46	−0.07 [−0.19, 0.05]	0.23	−0.07 [−0.22, 0.07]	0.31
HAZ (SD)	0.02 [−0.12, 0.15]	0.81	0.08 [−0.06, 0.21]	0.26	0.06 [−0.06, 0.19]	0.30	0.05 [−0.10, 0.21]	0.49
BMI-for-age Z score (SD)	−0.14 [−0.28, −0.01]	0.04[a]	−0.15 [−0.30, −0.001]	0.05[a]	−0.17 [−0.30, −0.03]	0.01[a]	−0.16 [−0.32, −0.001]	0.05[a]
Weight-for-height Z score (SD)	−0.14 [−0.27, 0.001]	0.05	−0.14 [−0.28, 0.01]	0.07	−0.16 [−0.29, −0.03]	0.02[a]	−0.15 [−0.31, 0.01]	0.06

Estimated by multivariable linear regression adjusted for maternal age, educational attainment, marital status, parity, HIV status, any alcohol use during pregnancy, family wealth index, total number of household members, family poverty status (above or below poverty line), energy intake in late pregnancy (sufficient or not), percentage of calories from protein, height, post-delivery BMI, child sex, months of exclusive breastfeeding, source of drinking water, and maternal serum organochlorine concentrations (HCB, BHCCH, Dieldrin, PCBs 118, 138, 153, 180, *p,p′*-DDT, *p,p′*-DDE, *o,p′*-DDT). Observations were weighted by inverse probability of retention in the 3.5-year sample as predicted by exposure measures and the set of covariates including in the multivariable model.

[a]$P < 0.05$.

BMI indicates body mass index; CI, confidence interval; DDE, dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; HAZ, height-for-age Z score; HCB, hexachlorobenzene; BHCCH, β-hexachlorocyclohexane; PCB, polychlorinated biphenyl; SD, standard deviation; WAZ, weight-for-age Z score.

Table 4

Adjusted associations between log_{10}-transformed maternal serum DDT/E concentration and child anthropometrics.

	o,p′-DDT		*p,p′*-DDE		*p,p′*-DDT	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)	0.03 [−0.44, 0.49]	0.91	0.10 [−0.38, 0.58]	0.69	−0.05 [−0.43, 0.33]	0.80
Weight (kg)	0.06 [−0.13, 0.26]	0.53	0.11 [−0.08, 0.31]	0.26	0.11 [−0.05, 0.27]	0.17
BMI (kg/m^2)	0.07 [−0.09, 0.22]	0.38	0.09 [−0.08, 0.25]	0.32	0.12 [−0.002, 0.25]	0.05
Arm circumference (cm)	−0.03 [−0.17, 0.11]	0.70	0.002 [−0.15, 0.15]	0.98	0.04 [−0.08, 0.15]	0.53
WAZ (SD)	0.04 [−0.06, 0.15]	0.42	0.07 [−0.03, 0.18]	0.18	0.06 [−0.02, 0.15]	0.13
HAZ (SD)	0.02 [−0.09, 0.13]	0.71	0.04 [−0.08, 0.15]	0.51	0.0002 [−0.09, 0.09]	1.00
BMI-for-age Z score (SD)	0.05 [−0.07, 0.16]	0.41	0.08 [−0.05, 0.20]	0.23	0.09 [−0.0004, 0.19]	0.05
Weight-for-height Z score (SD)	0.05 [−0.06, 0.16]	0.41	0.08 [−0.05, 0.20]	0.22	0.09 [−0.002, 0.18]	0.06

Estimated by multivariable linear regression adjusted for: maternal age, educational attainment, marital status, parity, HIV status, any alcohol use during pregnancy, family wealth index, total household members, family poverty status (above or below poverty line), energy intake in late pregnancy (sufficient or not), percentage of calories from protein, height, post-delivery BMI, child sex, months of exclusive breastfeeding, source of drinking water, urinary pyrethroid metabolites, and maternal serum organochlorine concentrations (HCB, BHCCH, Dieldrin, PCBs 118, 138, 153, and 180). Observations were weighted by inverse probability of retention in the 3.5-year sample as predicted by exposure measures and the set of covariates including in the multivariable model.

BMI indicates body mass index; CI, confidence interval; DDE, dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; HAZ, height-for-age Z Score; PCB, polychlorinated biphenyl; SD, standard deviation; WAZ, weight-for-age Z score.

among girls, though there was limited statistical evidence of interaction ($P = 0.16$; Table 5). Additionally, these associations were more apparent among children with fewer susceptibility factors for poor growth. That is, associations were stronger in children born to mothers with sufficient antepartum energy intake in late pregnancy (Table 6) or who came from families with income above the South African poverty line (Table 7). For example, a 10-fold increase in *trans*-DCCA was associated with a 0.58 kg/m^2 decrease in BMI (95% CI = −0.90, −0.26) among children of mothers with sufficient energy intake versus −0.05 kg/m^2 (95% CI = −0.27, 0.16) among children with insufficient intake (interaction *P* value = 0.01). Stratification by poverty (β = −0.40 above vs. −0.11 below poverty line) show a similar relationship. Interaction results were consistent when using height, weight, and BMI Z scores (eTable 2–5; http://links.lww.com/EE/A19). For example, the corresponding associations between a 10-fold increase in *trans*-DCCA and BMI Z score in boys and girls was −0.23 SD (95% CI: −0.40, −0.06) and −0.08 SD (95% CI = −0.28, 0.12), respectively. There were no notable interactions by maternal HIV status (Table 8) or interactions between DDT/E concentrations and these factors.

Adjustments for postnatal child factors such as infections at 1 and 2 years and child dietary patterns at 3.5 years also had little influence on observed associations in main (eTable 6; http://links.lww.com/EE/A19) and interaction (Figure 1; eTable 7; http://links.lww.com/EE/A19) analyses. Sensitivity analyses excluding potential outliers and high leverage observations generally strengthened observed associations (eTable 8; http://links.lww.com/EE/A19). Due to the low number of missing observations, multiple imputation of missing values had limited influence on observed estimates. Importantly, associations between self-reported measures of personal pyrethroid insecticide use and child size showed similar associations to those found using maternal urinary metabolite concentrations (eTable 9; http://links.lww.com/EE/A19). For example, self-reported application of insecticides during pregnancy (N = 166; 25%) was associated with 0.34 kg/m^2 lower BMI (95% CI = −0.61, −0.06) among boys and no strong association among girls (β = 0.07 kg/m^2 [95% CI = −0.34, 0.48]).

Discussion

This study finds that fetal pyrethroid exposure may be related to child thinness at 3.5 years. Sensitivity analyses suggest that this association was not confounded by postnatal factors such as child diet or infections. Moreover, associations with proxies for perinatal pyrethroid usage showed similar associations with child size, supporting the etiologic relevance of observed associations with maternal urinary metabolite concentrations. Finally, we found these associations to be stronger among boys and among groups with lower overall susceptibility to poor growth (nonpoor, sufficient energy intake mothers).

Table 5

Maternal urinary pyrethroid metabolites and child anthropometrics, by child sex.[a]

	cis-DBCA		*cis*-DCCA		*trans*-DCCA		PBA	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)								
Boy	0.11 [−0.73, 0.95]	0.79	0.13 [−0.77, 1.02]	0.78	0.08 [−0.70, 0.86]	0.84	0.22 [−0.69, 1.14]	0.63
Girl	−0.02 [−0.74, 0.69]	0.95	0.73 [−0.10, 1.55]	0.09	0.65 [−0.08, 1.37]	0.08	0.37 [−0.54, 1.28]	0.42
P interaction		0.81		0.34		0.30		0.82
Weight (kg)								
Boy	−0.27 [−0.62, 0.07]	0.12	−0.32 [−0.66, 0.02]	0.07	−0.32 [−0.63, −0.02]	0.04[b]	−0.31 [−0.67, 0.06]	0.10
Girl	−0.08 [−0.43, 0.27]	0.64	0.16 [−0.24, 0.55]	0.44	0.14 [−0.21, 0.49]	0.43	0.06 [−0.37, 0.49]	0.78
P interaction		0.44		0.09		0.06		0.21
BMI (kg/m^2)								
Boy	−0.30 [−0.54, −0.07]	0.01[c]	−0.34 [−0.60, −0.08]	0.01[c]	−0.34 [−0.57, −0.11]	0.004[c]	−0.36 [−0.63, −0.09]	0.01[c]
Girl	−0.08 [−0.35, 0.19]	0.57	−0.07 [−0.38, 0.24]	0.67	−0.06 [−0.35, 0.22]	0.66	−0.05 [−0.38, 0.28]	0.76
P interaction		0.22		0.20		0.16		0.16
Arm circumference (cm)								
Boy	−0.18 [−0.41, 0.05]	0.13	−0.26 [−0.50, −0.03]	0.03[b]	−0.29 [−0.48, −0.09]	0.01[c]	−0.27 [−0.51, −0.03]	0.03[b]
Girl	−0.11 [−0.36, 0.14]	0.41	−0.02 [−0.30, 0.25]	0.86	−0.03 [−0.29, 0.23]	0.82	−0.08 [−0.38, 0.23]	0.63
P interaction		0.68		0.21		0.14		0.34
Weight-for-height (Z-score)								
Boy	−0.21 [−0.40, −0.03]	0.02[b]	−0.22 [−0.41, −0.03]	0.02[b]	−0.23 [−0.40, −0.07]	0.01[c]	−0.24 [−0.44, −0.04]	0.02[b]
Girl	−0.06 [−0.25, 0.14]	0.57	−0.06 [−0.27, 0.16]	0.61	−0.06 [−0.26, 0.14]	0.54	−0.05 [−0.28, 0.19]	0.70
P interaction		0.25		0.25		0.19		0.21

[a]Multivariable linear regression predicting anthropometric measures by log10-transformed pyrethroid metabolites, adjusted for the same set of covariates as the main model but adding a product term between pyrethroid metabolite concentration and child sex.

[b]$P < 0.05$.

[c]$P < 0.01$.

BMI indicates body mass index; CI, confidence interval; DBCA, 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid; DCCA, 3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid; PBA, phenoxybenzoic acid.

Table 6

Maternal urinary pyrethroid metabolites and child anthropometrics, by maternal late-pregnancy daily caloric intake sufficiency status.[a]

	cis-DBCA		*cis*-DCCA		*trans*-DCCA		PBA	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)								
Sufficient	0.09 [−0.80, 0.99]	0.84	1.10 [0.16, 2.03]	0.02[b]	1.22 [0.41, 2.02]	0.003[c]	1.01 [−0.04, 2.07]	0.06
Low	0.02 [−0.68, 0.73]	0.95	0.10 [−0.65, 0.84]	0.80	−0.03 [−0.67, 0.60]	0.915	−0.01 [−0.79, 0.77]	0.99
P interaction		0.91		0.10		0.02[b]		0.13
Weight (kg)								
Sufficient	−0.19 [−0.58, 0.20]	0.35	−0.26 [−0.65, 0.12]	0.18	−0.17 [−0.54, 0.20]	0.36	−0.21 [−0.62, 0.20]	0.31
Low	−0.18 [−0.49, 0.14]	0.27	−0.02 [−0.35, 0.31]	0.92	−0.08 [−0.37, 0.20]	0.57	−0.11 [−0.46, 0.24]	0.54
P interaction		0.96		0.35		0.72		0.72
BMI (kg/m^2)								
Sufficient	−0.22 [−0.53, 0.09]	0.17	−0.63 [−0.96, −0.30]	0.0002[c]	−0.58 [−0.90, −0.26]	0.0004[c]	−0.55 [−0.93, −0.17]	0.004[c]
Low	−0.18 [−0.41, 0.04]	0.12	−0.02 [−0.26, 0.22]	0.87	−0.05 [−0.27, 0.16]	0.61	−0.09 [−0.34, 0.17]	0.50
P interaction		0.86		0.004[c]		0.01[c]		0.05[b]
Arm circumference (cm)								
Sufficient	−0.17 [−0.46, 0.11]	0.24	−0.43 [−0.72, −0.13]	0.01[c]	−0.41 [−0.70, −0.11]	0.01[c]	−0.37 [−0.70, −0.04]	0.03[b]
Low	−0.13 [−0.34, 0.08]	0.23	−0.02 [−0.24, 0.19]	0.83	−0.07 [−0.26, 0.12]	0.49	−0.11 [−0.34, 0.13]	0.37
P interaction		0.79		0.04[b]		0.07		0.21
Weight-for-height (Z-score)								
Sufficient	−0.13 [−0.36, 0.10]	0.28	−0.41 [−0.64, −0.17]	0.001[c]	−0.38 [−0.61, −0.15]	0.03[b]	−0.36 [−0.63, −0.09]	0.01[c]
Low	−0.14 [−0.31, 0.03]	0.10	−0.02 [−0.20, 0.16]	0.82	−0.06 [−0.22, 0.09]	0.44	−0.07 [−0.26, 0.12]	0.48
P interaction		0.92		0.01[c]		0.01[c]		0.09

[a]Multivariable linear regression predicting anthropometric measures by log10-transformed pyrethroid metabolites, adjusted for the same set of covariates as the main model but adding a product term between pyrethroid metabolite concentration and caloric intake sufficiency status (equal to or above versus below recommended number of daily calories). Recommended caloric intake was calculated for each individual using Institute of Medicine (2009) formulae for women in late pregnancy based on age, height, weight, and activity level (mean recommended intake in this population = 12,134 kJ; range = 10,164 to 14,712 kJ).

[b]$P < 0.05$.

[c]$P < 0.01$.

BMI indicates body mass index; DBCA, 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid; DCCA, 3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid; PBA, phenoxybenzoic acid.

These findings extend our previous observations in this population. In earlier work from the VHEMBE study investigating associations between maternal DDT and pyrethroid metabolite associations and size in the first two years of life, Coker et al.[14] found evidence that higher *cis*-DBCA and *trans*-DCCA were associated with lower BMI-for-age (≈0.15 standard deviations per 10-fold increase), with a stronger association observed among boys for *trans*-DCCA models (−0.24 standard deviations (SD) per 10-fold increase [95% CI = −0.44, −0.04]). We found that associations with pyrethroid metabolites persist in the children 1.5 years

Table 7

Maternal urinary pyrethroid metabolites and child anthropometrics, by family poverty status.[a]

	cis-DBCA		*cis*-DCCA		*trans*-DCCA		3-PBA	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)								
Nonpoor	−0.16 [−1.12, 0.80]	0.74	0.38 [−0.67, 1.43]	0.48	0.57 [−0.38, 1.52]	0.24	0.39 [−0.74, 1.52]	0.50
Poor	0.17 [−0.51, 0.85]	0.62	0.43 [−0.30, 1.16]	0.25	0.22 [−0.40, 0.85]	0.48	0.24 [−0.54, 1.02]	0.55
P interaction		0.58		0.94		0.56		0.82
Weight (kg)								
Nonpoor	−0.29 [−0.68, 0.11]	0.15	−0.24 [−0.61, 0.12]	0.19	−0.19 [−0.54, 0.16]	0.28	−0.33 [−0.74, 0.08]	0.11
Poor	−0.12 [−0.43, 0.19]	0.46	−0.004 [−0.35, 0.34]	0.98	−0.07 [−0.37, 0.22]	0.64	−0.04 [−0.40, 0.32]	0.84
P interaction		0.50		0.36		0.62		0.29
BMI (kg/m^2)								
Nonpoor	−0.27 [−0.53, 0.0001]	0.05	−0.39 [−0.66, −0.11]	0.006[b]	−0.40 [−0.66, −0.15]	0.002[b]	−0.49 [−0.80, −0.19]	0.002[b]
Poor	−0.15 [−0.39, 0.09]	0.21	−0.10 [−0.37, 0.16]	0.44	−0.11 [−0.35, 0.12]	0.33	−0.08 [−0.34, 0.19]	0.58
P interaction		0.52		0.15		0.11		0.04[c]
Arm circumference (cm)								
Nonpoor	−0.23 [−0.48, 0.03]	0.08	−0.30 [−0.56, −0.05]	0.02[c]	−0.32 [−0.56, −0.08]	0.009[b]	−0.39 [−0.69, −0.10]	0.009[b]
Poor	−0.09 [−0.31, 0.13]	0.40	−0.06 [−0.29, 0.18]	0.64	−0.09 [−0.30, 0.11]	0.37	−0.07 [−0.31, 0.17]	0.57
P interaction		0.43		0.17		0.17		0.10
Weight-for-height (Z-score)								
Nonpoor	−0.22 [−0.42, −0.01]	0.04[c]	−0.28 [−0.47, −0.09]	0.005[b]	−0.30 [−0.48, −0.12]	0.001[b]	−0.36 [−0.59, −0.13]	0.002[b]
Poor	−0.09 [−0.27, 0.09]	0.32	−0.06 [−0.25, 0.14]	0.57	−0.08 [−0.26, 0.09]	0.34	−0.04 [−0.24, 0.16]	0.68
P interaction		0.35		0.11		0.10		0.04[c]

[a]Multivariable linear regression predicting anthropometric measures by log10-transformed pyrethroid metabolites, adjusted for the same set of covariates as the main model but adding a product term between pyrethroid metabolite concentration and family food poverty status (at or above versus below income limits for food poverty). The South African mid-2013 food poverty level was defined as 386 Rand/person/month.

[b]$P < 0.01$.

[c]$P < 0.05$.

BMI indicates body mass index; DBCA, 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid; DCCA, 3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid; PBA, phenoxybenzoic acid.

Table 8

Maternal urinary pyrethroid metabolites and child anthropometrics, by maternal HIV status.[a]

	cis-DBCA		*cis*-DCCA		*trans*-DCCA		PBA	
	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*	β [95% CI]	*P*
Height (cm)								
Negative	0.02 [−0.59, 0.63]	0.94	0.47 [−0.18, 1.13]	0.15	0.45 [−0.13, 1.03]	0.13	0.35 [−0.39, 1.08]	0.35
Positive	0.20 [−1.05, 1.46]	0.75	−0.002 [−1.46, 1.46]	1.00	−0.30 [−1.49, 0.89]	0.62	0.02 [−1.24, 1.28]	0.98
P interaction		0.80		0.56		0.26		0.66
Weight (kg)								
Negative	−0.22 [−0.49, 0.04]	0.10	−0.08 [−0.35, 0.20]	0.59	−0.08 [−0.33, 0.17]	0.55	−0.16 [−0.47, 0.15]	0.31
Positive	0.10 [−0.48, 0.69]	0.73	−0.22 [−0.77, 0.33]	0.44	−0.31 [−0.74, 0.11]	0.15	−0.06 [−0.65, 0.53]	0.84
P interaction		0.32		0.65		0.34		0.77
BMI (kg/m^2)								
Negative	−0.24 [−0.44, −0.04]	0.02[b]	−0.21 [−0.43, 0.009]	0.06	−0.21 [−0.41, −0.008]	0.04[b]	−0.26 [−0.50, −0.02]	0.03[b]
Positive	−0.11 [−0.40, 0.61]	0.68	−0.22 [−0.66, 0.23]	0.34	−0.23 [−0.57, 0.11]	0.18	−0.04 [−0.53, 0.46]	0.88
P interaction		0.21		0.98		0.90		0.42
Arm circumference (cm)								
Negative	−0.18 [−0.35, −0.005]	0.04[b]	−0.12 [−0.31, 0.07]	0.22	−0.13 [−0.31, 0.04]	0.13	−0.18 [−0.38, 0.03]	0.09
Positive	0.09 [−0.46, 0.63]	0.75	−0.36 [−0.83, 0.10]	0.13	−0.37 [−0.74, −0.005]	0.05[b]	−0.20 [−0.71, 0.30]	0.43
P interaction		0.36		0.34		0.25		0.93
Weight-for-height (Z-score)								
Negative	−0.17 [−0.32, −0.03]	0.02[b]	−0.14 [−0.30, 0.01]	0.07	−0.15 [−0.30, −0.008]	0.04[b]	−0.19 [−0.36, −0.01]	0.04[b]
Positive	0.10 [−0.29, 0.48]	0.62	−0.12 [−0.46, 0.21]	0.47	−0.16 [−0.42, 0.09]	0.20	−0.0005 [−0.39, 0.39]	1.00
P interaction		0.20		0.92		0.94		0.39

[a]Multivariable linear regression predicting anthropometric measures by log10-transformed pyrethroid metabolites, adjusted for the same set of covariates as the main model but adding a product term between pyrethroid metabolite concentration and maternal HIV status.

[b]$P < 0.05$.

BMI indicates body mass index; DBCA, 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid; DCCA, 3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid; PBA, phenoxybenzoic acid.

later (mean = 3.5 years; e.g. −0.23 SD per 10-fold higher *trans*-DCCA [95% CI = −0.41, −0.05], $P = 0.013$). However, findings at 3.5 years differed from those at 1 and 2 years, in that associations at 3.5 years were consistently stronger with both metabolites common to cypermethrin and permethrin (*cis*-DCCA, *trans*-DCCA, and 3-PBA) than with the deltamethrin-specific metabolite (*cis*-DBCA), particularly in sex-stratified analyses. Moreover, the current analyses extend our previous work by adjusting for factors relevant to growth in older children such as sources of drinking water, frequency of persistent fevers, family wealth, and child nutritional diversity. Nonetheless, it appears that some associations found in this population at younger ages persist into older ages, particularly among boys, and that these associations are consistent with some recent experimental and mechanistic studies.

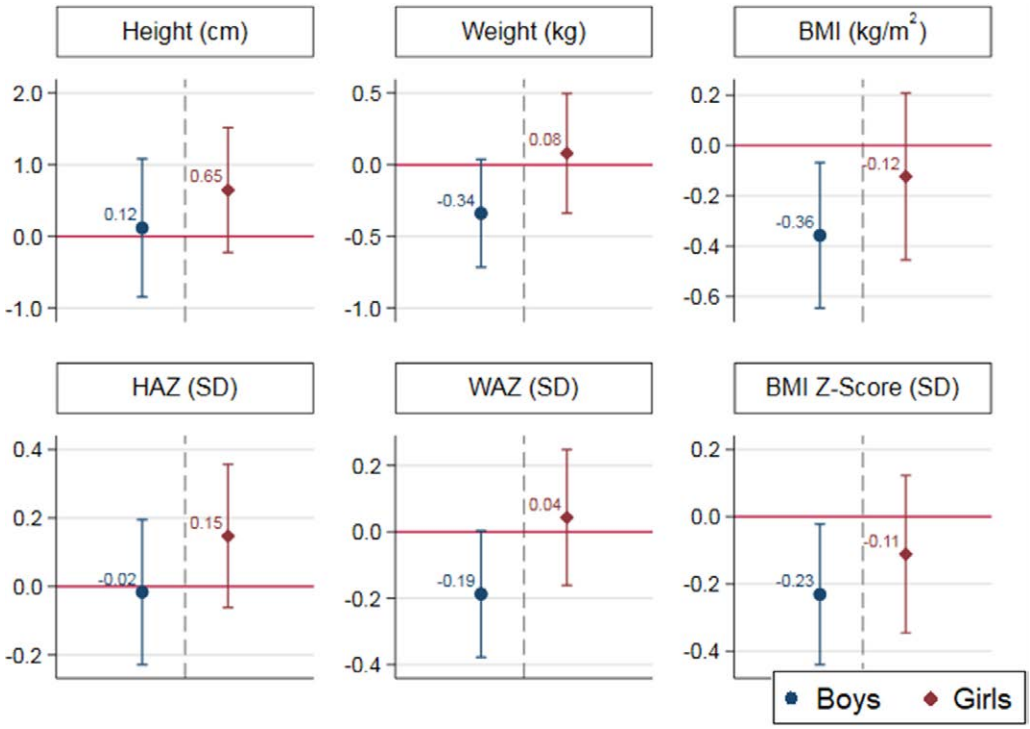

Figure 1. Associations between $\log_{10}$(*cis*-DCCA) and child anthropometrics adjusted for maternal and child characteristics, stratified by child sex. Estimated by multivariable linear regression stratified by child sex and adjusted for the same set of confounders as the sex-stratified model (Table 5) as well as the following child factors: frequency of diarrhea in the 1st and 2nd years of life; any persistent fevers lasting 4 days or more between 0 and 1 year; number of persistent fevers between 1 and 2 years; and a child food diversity score based on number of different food groups consumed (out of 18) as assessed at 2-year visit. Observations were weighted by inverse probability of inclusion in the sample as predicted by all exposure measures and covariates. DCCA, *cis*-3-(2,2,-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid; HAZ, height-for-age Z score; SD = standard deviation; WAZ, weight-for-age Z score; Units for *y* axis given in parentheses in the subheadings.

Recent work has drawn attention to the potential for fetal pyrethroid exposure to disrupt growth through androgen-mediated (agonist) pathways.[6] In a Chinese cohort, Ye et al.[10] found associations between 3-PBA and increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and accelerated puberty (Tanner stage) in 9- to 16-year-old Chinese boys. Moreover, in male mouse models, early postnatal dosing with cypermethrin caused a dose-dependent increase in LH, FSH, gonadotropin, and Leydig cell testosterone.[6] Findings from the United States Environmental Protection Agency's Endocrine Disruptor Screening Program also suggest that cypermethrin, but not deltamethrin, disrupts androgen-mediated pathways.[7] However, summary findings from the Endocrine Disruptor Screening Program implicate cypermethrin as an androgen antagonist.[7] We found that pyrethroid metabolites were associated with increased height and reduced weight particularly among boys, which is consistent with an androgenic effect of pyrethroids since androgens stimulate linear growth and are associated with lower fat mass in peripubertal boys[34] and may play a role in earlier child growth.[35] Although our study population is too young to investigate peripubertal effects, Ye et al.[6,10] reported that the concentration of urinary pyrethroid metabolites were associated with earlier puberty in boys, which is also consistent with an androgenic effect of pyrethroids. Additionally, we found association with metabolites common to cypermethrin and permethrin (*cis*-DCCA, *trans*-DBCA, 3-PBA) to be more strongly associated with anthropometrics than *cis*-DBCA, which is unique to deltamethrin.

Overall, despite the ubiquity of their use, few epidemiologic investigations have been conducted on the relation between fetal exposure to pyrethroids and growth in early childhood besides work conducted in this cohort.[14,18] Moreover, conflicting evidence for the influence of pyrethroids on birth characteristics[12,13,15–18] and child size[14,19] predominate. Studies in our cohort have several notable differences and advantages over past work including larger sample size, use of biomarkers of exposure (i.e., pyrethroid metabolite concentrations), and longer follow-up. For example, Hanke et al.[12] and Dabrowski et al.[16] found reductions in birth weight associated with self-reported synthetic pyrethroid usage in studies of 104 and 377 births. Berkowitz et al.[17] found no association with birth parameters (N = 404) but was only able to characterize 3-PBA as above or below the LOD. Two studies that quantified maternal urinary pyrethroids reported no associations with child size: Zhang et al.[15] (N = 147) measured 3-PBA in maternal urine at 10–12 weeks gestation but found no associations with birth size, and Xue et al.[19] (N = 497) quantified metabolites in postpartum urine but reported no quantitative findings with respect to 1-year-old height and weight. In a study among 454 rural, northern Chinese mothers, Ding et al.[13] quantified pyrethroid metabolites in antepartum urine samples and found a negative association between birth weight and urinary *cis*-DCCA but a positive association with *trans*-DCCA. In comparison, our study has followed over 660 mother and child pairs through 4 years with state-of-the-art quantification of urinary pyrethroid metabolites and completeness of follow-up (≈90%) and data collection (<3% with missing values). We previously demonstrated no associations between pyrethroid metabolite concentrations and birth size[18] and suggestive associations with lower BMI at 1 and 2 years among boys.[14] Moreover, for the current study, an extensive set of covariate data were collected for this study allowing us to account for a variety of environmental and nutritional factors including wealth, maternal and child diet, water sources, breastfeeding practices, and infection history.

An important limitation in extant pyrethroid studies is the low detection frequency and concentrations in most pregnant and nonpregnant adult women populations. However, in poor and rural settings like our own, domestic use, agriculture and

animal husbandry, as well as IRS for malaria control results in ubiquitous and frequent pyrethroid exposure, including among pregnant women. Detection frequencies and concentration quantiles in our study were higher than reported in the general US female population and in pregnant European women, comparable to regions in China, and lower than in an agriculturally intense regions elsewhere in South Africa.[36] Additionally, we were able to compare findings between urinary measures and self-reported usage of pyrethroids. We found that associations were consistent between these alternate measures, reducing the probability that our results may be due to chance.

Our study is the first to evaluate effect modification by susceptibility factors on the relationship between pyrethroid exposure and growth in preschool-aged children. We found associations to be consistently stronger among children from nonpoor families or mothers with sufficient antepartum caloric intake, both shown in our past work to modify the effect of fetal insecticide exposure on child health outcomes.[31] While these findings may seem counterintuitive, they may be understood in the context of component or competing causes: It is possible that children already susceptible to poor growth (i.e., due to family poverty and/or undernutrition) may be already stunted or otherwise less affected by fetal chemical exposures. In our study population, mean weight, BMI, and weight-for-height Z score are all lower among children of poor families than that of nonpoor families. Alternatively, if pyrethroid exposure has a true causal effect on child size, a plausible (nonchance) explanation is that these factors may be proxies for greater childhood exposure, for example, children from nonpoor families may consume foods with higher levels of pyrethroids. Despite our adjustment for child diet quality, residual confounding is still possible, and the presence of other postnatal confounders is possible.

As with most observational studies, the possibility that residual and unmeasured confounding may have affected these findings cannot be discounted. Including a large set of potential pre- and postnatal confounders as well as other correlated exposures in our models made little impact on our findings. Nonetheless, it is possible that a combination of other unmeasured confounders may explain our findings. In particular, correlated child dietary or chemical exposures may explain observed relationships. Relevant future investigations include evaluating the role of putative endocrine mediators and other child chemical exposures.

Conclusions

Early child growth has lifelong effects on health and well-being. A recent economic analysis of the United Nations' 2015–2030 Sustainable Developmental Goals suggests that programs to improve child growth can be very cost-effective: For every dollar invested, an average of $45 may be saved in health care costs and economic productivity. However, determinants of child growth differ widely by context. In low- and middle-income countries, child growth is commonly impeded by poverty, malnutrition, and chronic infections. In IRS-utilizing and agricultural regions, child growth may be uniquely challenged by exposure to higher concentrations of pyrethroid insecticides. Our findings suggest that fetal exposure to pyrethroid insecticides may be associated with thinness at 3–4 years independent of maternal or child nutritional exposures. Moreover, the magnitude of this association may be greater among boys: approximately 0.3 kg/m^2 reduction per 10-fold increase in metabolite. Such findings necessitate replication and elaboration in other agricultural and/or IRS-utilizing settings. Importantly, while pyrethroid-treated bed nets are not common in the study population, they may be relevant to other settings and their role, along with other common insecticides or repellents, should be considered in future studies.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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