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Original Contribution

Associations of Maternal Exposure to Dichlorodiphenyltrichloroethane and Pyrethroids With Birth Outcomes Among Participants in the Venda Health Examination of Mothers, Babies and Their Environment Residing in an Area Sprayed for Malaria Control

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Although effective in controlling malaria, indoor residual spraying results in elevated exposure to insecticides such as dichlorodiphenyltrichloroethane (DDT) and pyrethroids. These chemicals cross the placenta, but no studies have examined their associations with birth outcomes in populations residing in indoor residual spraying areas. We investigated this question in the Venda Health Examination of Mothers, Babies and Their Environment (VHEMBE), a birth cohort study of 751 South African children born between 2012 and 2013. We measured maternal peripartum serum DDT and urine pyrethroid metabolite concentrations and collected data on birth weight, length, head circumference, and duration of gestation. We analyzed the data using marginal structural models with inverse-probability-of-treatment weights, generalized propensity scores, and standard conditional linear regression. Using all 3 analytical methods, p,p'-DDT, o,p'-DDT, and to a lesser extent p,p'-dichlorodiphenyldichloroethylene were related to elevated birth weight, birth length, and head circumference among girls. Changes in gestational duration did not mediate this relationship, suggesting that these exposures accelerate fetal growth, which is consistent with the known estrogenic properties of o,p'-DDT and p,p'-DDT. No associations with pyrethroid metabolites were found. Results suggest that prenatal exposure to DDT is related to elevated birth size. Further studies are needed to elucidate the implications of these findings.

birth outcomes; birth weight; DDT; indoor residual spraying; insecticides; marginal structural models; pyrethroids; South Africa

Abbreviations: DCCA, (2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HIV, human immunodeficiency virus; ICC, intraclass correlation coefficient; IRS, indoor residual spraying; 3-PBA, 3-phenoxybenzoic acid; SD, standard deviation.

Indoor residual spraying (IRS), the use of insecticides on the interior walls of residences, is conducted by 83 countries to control malaria (1). The procedure protects 106 million people but potentially subjects them to elevated exposure to insecticides, with poorly understood health consequences (2, 3). Dichlorodiphenyltrichloroethane (DDT) and/or pyrethroid insecticides are commonly used for IRS in malaria-endemic areas.

DDT is a broad-spectrum organochlorine insecticide that was heavily used in agriculture and for public health purposes between the 1940s and the 1970s, when it was banned in most Western countries because of concerns about adverse health effects in humans and wildlife. In 2004, the Stockholm Convention on Persistent Organic Pollutants imposed an international ban on DDT, but an exemption was included for the control of insectborne diseases such as malaria. Pyrethroids are synthetic derivatives of pyrethrins, which are naturally produced by chrysanthemum flowers. These insecticides are commonly used in agriculture and commercial products; their use has increased substantially since the implementation of organophosphate pesticide bans in the early 2000s, making them the most commonly used retail insecticides in the United States (4–6).

DDT and pyrethroids readily cross the human placenta, which has led to hypotheses suggesting that exposure to these insecticides may be associated with adverse birth outcomes; but results from epidemiologic studies have been mixed. For instance, maternal and umbilical cord blood concentrations of p,p'-DDT have been found to be associated with decreased birth weight, birth length, and head circumference in Bolivia ($n = 200$) (7), decreased birth weight and birth length in California ($n = 385$) (8), and reduced birth weight but not birth length and head circumference in Valencia, Spain ($n = 494$) (9). In addition, analysis of 3 different subsamples of participants from the California-based Child Health and Development Study, conducted when DDT was still in use, produced conflicting results, with Jusko et al. (10) ($n = 399$) finding a positive association between exposure to p,p'-DDT and gestational age and no association with birth weight, Kezios et al. (11) ($n = 600$) reporting positive relationships with birth weight and null associations with gestational age, and Farhang et al. (12) ($n = 420$) finding no association with birth weight or gestational age. Studies of the association between p,p'-DDT's breakdown product, p,p'-dichlorodiphenyldichloroethylene (DDE), and birth weight or gestational duration have yielded similarly inconsistent results (7–40).

Few studies have examined associations between exposure to pyrethroids and birth outcomes, and, like studies of DDT/DDE, results have been mixed. Birth weight was not associated with third-trimester urinary concentrations of the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) in studies conducted in New York, New York (41) and Laizhou Bay, China (42), but a positive association was found with maternal first-trimester serum 3-PBA levels in Tokyo, Japan (43). In addition, no association was found between maternal urinary concentrations of the pyrethroid metabolites *cis*- and *trans*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DCCA) and birth weight in the Chinese study (42), but the researchers found positive associations between 3-PBA, *cis*-DCCA, and *trans*-DCCA and birth length and between *trans*-DCCA and gestational age at birth.

However, prior research has been almost exclusively conducted in high-income countries. It is unclear whether results may be applicable to populations residing in malaria-endemic areas, which have different genetic backgrounds and lifestyles, experience high exposure to insecticides due to IRS (2, 3), and may be uniquely susceptible to adverse effects due to poverty, malnutrition, and poor health. Our objective was thus to determine whether exposure to IRS insecticides was associated with adverse birth outcomes among children living in Limpopo Province, South Africa, a malaria-endemic area where spraying with DDT or the pyrethroid deltamethrin occurs annually.

METHODS

Participants

We used data from the Venda Health Examination of Mothers, Babies and Their Environment (VHEMBE), a birth cohort study taking place in the rural Vhembe district of Limpopo Province. Mothers were recruited between August 2012 and December 2013 when they presented to Tshilidzini Hospital in the town of Thohoyandou to give birth. Eligible women were at least 18 years of age, had contractions more than 5 minutes apart, spoke Tshivenda (the most commonly spoken language in Vhembe) at

home, lived within 20 km of the hospital, planned to remain in the area for at least 2 years, and had not been diagnosed with malaria during pregnancy (no otherwise-eligible woman was diagnosed with malaria). Of the 920 eligible women, 152 refused enrollment, 3 did not provide a sufficient blood sample for DDT analysis, and 14 did not complete a baseline questionnaire. Data on birth weight ($n = 1$), birth length ($n = 6$), and head circumference ($n = 6$) were missing for a few participants, leaving sample sizes ranging between 745 and 751, depending on the outcome, for DDT/DDE analyses. Thirteen participants did not provide urine samples and one 3-PBA measurement did not meet quality control standards, leaving sample sizes between 732 and 738 for pyrethroid analyses.

Written informed consent was obtained from all participants. Ethics approval was obtained from the University of California, Berkeley (Berkeley, California), the University of Pretoria (Pretoria, Gauteng, South Africa), the Limpopo Department of Health and Social Development (Polokwane, Limpopo, South Africa), and McGill University (Montreal, Quebec, Canada).

Data collection

Trained, bilingual (Tshivenda and English) staff originating from the study area conducted structured questionnaire-based interviews shortly after delivery. Staff collected data on demographic factors, household assets (based on the Demographic and Health Surveys) (44), nutrition (using a locally validated food frequency questionnaire) (45), food insecurity (based on the US National Center for Health Statistics' Household Food Security Survey) (46), stress (based on a scale developed for the Soweto-based Birth to Twenty Study) (47), lifestyle, and health and pregnancy history, including the date of the last menstrual period. We defined poverty as an income below 386 rands per person per month (about US$30) based on Statistics South Africa guidelines (48), and low energy intake (<11,000 kJ/day) was defined on the basis of US Institute of Medicine guidelines (49). Energy and fat intakes were estimated by a South African expert nutritionist using Food Finder 3 software (South Africa Medical Research Council/WAMTechnology, Stellenbosch, South Africa). In addition, because income may not fully represent socioeconomic status in our study area, we constructed a household asset index via principal components analysis. The questionnaire was developed in English, translated into Tshivenda, and back-translated into English by native speakers in the translated language.

Two registered nurses blinded to participants' exposure status abstracted information from maternal and child medical records in order to collect data on gestational age at birth, birth weight, and maternal human immunodeficiency virus (HIV) status. Birth weight was measured by hospital staff using a Tanita BD-815U neonatal scale (Tanita Corporation of America, Inc., Arlington Heights, Illinois) that we provided. For this study, gestational age at birth was based on the date of the last menstrual period as reported during the delivery interview. Some gestational age values were implausible, possibly because of incorrect recollection of the date of the last menstrual period. Unlikely values (above the first or below the 99th birth-weight-for-gestational-age percentile) were replaced with gestational ages indicated in medical records if the latter values were situated between the first and 99th birth-weight-for-gestational-age percentiles. We also generated a secondary variable based on gestational age values from medical

records as the reference value, with unlikely values being replaced with those based on delivery interviews (correlation between primary and secondary variables = 0.78; $P < 0.001$). Study nurses also measured birth length using a Seca 417 portable infantometer (Seca Corporation, Chino, California) and head circumference using measuring tapes, following protocols developed by the US Centers for Disease Control and Prevention for the National Health and Nutrition Examination Survey (50). Length and head circumference measures were taken in triplicate and averaged. Small (<10th percentile) and large (>10th percentile) size-for-gestational-age values were estimated on the basis of a revised version of the World Health Organization growth standards (51). Quality control data showed good agreement between nurses for birth length (intraclass correlation coefficient (ICC) = 0.98, $P < 0.001$; mean difference = 0.27 (standard deviation (SD), 0.41) cm) and head circumference (ICC = 0.98, $P < 0.001$; mean difference = 0.15 (SD, 0.16) cm).

Measurement of IRS insecticides

Urine and blood samples were collected from women either before ($n_{blood} = 590$; $n_{urine} = 455$) or shortly after ($n_{blood} = 161$; $n_{urine} = 283$) delivery, and they were immediately processed and stored at −80°C until shipment to analytical laboratories. The Emory University Environmental Health Laboratory (Atlanta, Georgia) measured concentrations of p,p'-DDT, p,p'-DDE, and o,p'-DDT in serum as well as levels of polychlorinated biphenyls 118, 138, 153, and 180 using high-resolution gas chromatography–isotope dilution mass spectrometry (52). The limits of detection for p,p'-DDT, p,p'-DDE, and o,p'-DDT were 0.01, 0.03, and 0.01 ng/mL serum, and the limits of quantification were 0.03, 0.09, and 0.03 ng/mL serum, respectively. DDT/DDE and polychlorinated biphenyl concentrations were lipid-adjusted and expressed in ng/g lipid. Total lipid levels were estimated on the basis of triglyceride and total cholesterol measurements using standard enzymatic methods (Roche Chemicals, Indianapolis, Indiana). The Institut National de Santé Publique du Québec measured pyrethroid metabolites in urine using gas chromatography–mass spectrometry. Limits of detection were 0.0025 µg/L for cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (cis-DBCA), 0.0045 µg/L for cis-DCCA, 0.0038 µg/L for trans-DCCA, 0.0047 µg/L for 3-PBA, and 0.005 µg/L for 4-fluoro-3-phenoxybenzoic acid. Metabolite concentrations (expressed in µg/L) were corrected for dilution by dividing values by urine specific gravity, which was measured using a portable refractometer (Atago PAL-10S; Atago Company Ltd., Tokyo, Japan) at the time of sample collection.

Statistical analysis

Data on biomarkers of exposure were log_{10}-transformed to reduce the influence of outliers. We used analysis of variance and Pearson's correlation coefficients to examine bivariate associations. We used marginal structural models with inverse-probability-of-treatment weights to estimate the causal effect of exposure to IRS insecticides on birth outcomes. We used stabilized weights which were estimated by means of the Super Learner algorithm, a loss-based supervised learning method that uses a weighted combination of prediction algorithms to return a function that minimizes cross-validated risk (53). Covariates considered included maternal age, education, marital status, postdelivery weight, postdelivery body mass index (weight (kg)/height (m)^2), parity, daily energy intake, fat intake, fruit and vegetable consumption, food security, HIV status, smoking, exposure to environmental tobacco smoke, total serum polychlorinated biphenyl levels, alcohol consumption, stress, household income, asset index, child's sex, season of birth, and mode of delivery (see Web Table 1, available at https://academic.oup.com/aje). We obtained percentile-based 95% confidence intervals and P values by bootstrapping the procedure 1,000 times. Based on observation of the propensity scores and of a reasonable range of weights (0.4–3.1), we concluded that the positivity assumption was not violated. We also examined effect modification by poverty, malnutrition, maternal HIV status, and child sex by including cross-product terms.

In order to evaluate the robustness of our results to different analysis strategies, we also reran all analyses applying 1) a generalized propensity score method for continuous exposure (54) and 2) standard conditional regression methods (i.e., multiple linear and logistic regression models). The generalized propensity score, which is equal to the conditional density of the exposure given the covariates, was estimated using the Super Learner algorithm including the above covariates and was included in models with a cubic spline to limit residual confounding; robust estimators were used to compute the variance. Variables included in standard regression models included those that were moderately ($P < 0.20$) associated with biomarkers of exposure and outcomes. We conducted generalized additive analyses with a cubic spline to evaluate the linearity assumption.

We also evaluated whether gestational age at birth mediated relationships between exposures and birth size using standard and counterfactual framework approaches. We first used the Baron and Kenny (55) method to estimate the indirect (mediated by gestational age) and direct (not mediated by gestational age) effects of exposures on birth size. As opposed to the Baron and Kenny method, the counterfactual approach (56) allows for exposure-mediator interactions and produces total effects that decompose into direct and indirect effects, thereby always generating mediation proportions between 0 and 1 (57). We thus used the latter approach to estimate the controlled direct effect by computing the average change in birth size due to a 10-fold increase in exposure when gestational age was set at the population average (39 weeks), the natural direct effect by estimating the change in birth size due to a 10-fold increase in exposure with gestational age values taking on their natural values when exposure was equal to the median, and the natural indirect effect by estimating the change in birth size due a change in gestational age in response to a 10-fold increase in exposure.

We also conducted sensitivity analysis to evaluate the robustness of our results. We repeated analyses by expressing DDT/DDE on a serum basis and included triglyceride and total cholesterol concentrations in the models. Similarly, we expressed concentrations of pyrethroid metabolites on a urine volume basis and conducted separate analyses by including urine specific gravity or creatinine concentration in models. We also fitted separate gestational age models using values based primarily on questionnaire (primary variable) or medical record (secondary variable) data, as described above. In addition, we reran the analyses using a variable representing pyrethroid exposure intensity (µg/hour), computed by multiplying metabolite concentrations by the volume of

Table 1. Characteristics of Participants in the Venda Health Examination of Mothers, Babies and Their Environment (n = 751), Limpopo Province, South Africa, 2012–2013

Characteristic	No. of Persons	%
Age, years		
<25	377	50.2
25–35	283	37.7
>35	91	12.1
Education		
<12th grade	412	54.9
12th grade	229	30.5
>12th grade	110	14.6
Household income[a]		
Above poverty level	291	38.7
At or below poverty level	460	61.3
Food security[b,c]		
High	421	56.1
Low	242	32.3
Very low	87	11.6
Energy intake,[d] kJ/day		
<11,000	453	60.3
≥11,000	298	39.7
Prestudy parity[e]		
0	325	43.3
1	201	26.8
≥2	225	30.0
HIV status[c]		
Negative	645	86.2
Positive	103	13.8
Smoking		
No	748	99.6
Yes	3	0.4
Alcohol consumption		
No	710	94.5
Yes	41	5.5
Child sex		
Male	387	51.5
Female	364	48.5
Birth weight, g[c]		
≥2,500	687	91.6
<2,500	63	8.4
Gestational age, weeks		
≥37	648	86.3
<37	103	13.7
Size for gestational age		
>10th percentile	41	5.5
10th–90th percentiles	528	70.3
<10th percentile	182	24.2

Table continues

Table 1. Continued

Characteristic	No. of Persons	%
Mode of delivery[c]		
Vaginal	569	77.3
Cesarean	167	22.7

Abbreviation: HIV, human immunodeficiency virus.

[a] Poverty was defined as a household income below 386 rands per person per month (about US$30) based on Statistics South Africa guidelines for mid-2013 (48).

[b] Food insecurity was defined on the basis of the US National Center for Health Statistics' Household Food Security Survey (46).

[c] Numbers do not add up to 751 because of missing data.

[d] Low energy intake (<11,000 kJ/day) was defined on the basis of US Institute of Medicine guidelines (49).

[e] Percentages do not add up to 100 because of rounding.

urine produced (participants were asked to empty their bladders) and dividing by time since the last void (58–60). Finally, we conducted analyses excluding potential outliers identified using the generalized extreme studentized deviate many-outlier procedure (61). Results were not substantially affected by these different specifications, and no substantial departure from linearity was observed. We present results with $\log_{10}$-transformed DDT/DDE and pyrethroid metabolites expressed linearly and corrected for lipid levels and specific gravity, respectively, and using the primary variable for gestational age.

Missing data for covariates (<2.1%) were imputed at random on the basis of observed univariate probability distributions. Machine-read values were used for DDT/DDE or pyrethroid concentrations between the limit of detection and the limit of quantification. Values below the limit of detection were imputed on the basis of a log-normal probability distribution whose parameters were estimated by maximum likelihood estimation (62). All analyses were conducted using STATA, version 13.1 (StataCorp LLC, College Station, Texas) or R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population characteristics

All participants were black/African and were born in South Africa. Women were aged 26.4 (SD, 6.3) years, on average, and most had a low level of education, with 54.9% not having completed high school and only 14.6% having pursued studies beyond high school (Table 1). Poverty and malnutrition are common in this population. Most of the women (61.3%) lived in households with incomes at or below the South African food poverty level, 43.9% were food-insecure, and 60.3% had a low energy intake during pregnancy. Most women (56.7%) were parous, and 13.8% were HIV-positive.

Birth outcomes

The average duration of gestation was 39.3 (SD, 2.3) weeks, with 13.7% of children being born preterm (<37 weeks). The

mean birth weight was 3,126 (SD, 452) g, and the prevalence of low birth weight (<2,500 g) was 8.4%. Almost one-quarter (24.2%) of the children were born small for gestational age (<10th percentile of weight for gestational age), and 5.5% were large for gestational age (>10th percentile of weight for gestational age). Mean birth length and head circumference were 48.9 (SD, 2.2) cm and 34.4 (SD, 1.5) cm, respectively.

Exposure to IRS insecticides

Table 2 shows the distribution of biomarkers of exposure to IRS insecticides, as well as their detection and quantification frequencies. Except for p,p'-DDT (98% detection) and o,p'-DDT (91% detection), the concentrations of all biomarkers of exposure were above the limit of detection. DDT/DDE ($r = 0.69–0.85$; $P < 0.001$) and pyrethroid ($r = 0.46–0.90$; $P < 0.001$) levels were intercorrelated within insecticide classes but not between insecticide classes ($r = 0.00–0.05$; $P = 0.19–0.85$) (Web Table 2).

Associations between exposure to IRS insecticides and birth outcomes

Marginal structural models, propensity score models, and standard conditional models yielded qualitatively similar results. We report results from marginal structural models here and in Tables 3 and 4; results derived from other models are shown in Web Tables 3–6. Maternal serum concentrations of p,p'-DDT, o,p'-DDT, and, to a lesser extent, p,p'-DDE were related to elevated birth weight ($\beta_{p,p'\text{-DDT}} = 70.7$ g (95% CI: 11.8, 130.8); $\beta_{o,p'\text{-DDT}} = 80.4$ g (95% CI: 10.2, 149.9); $\beta_{p,p'\text{-DDE}} = 58.4$ g (95% CI: 17.0, 129.4)), birth length ($\beta_{p,p'\text{-DDT}} = 0.41$ cm (95% CI: 0.11, 0.72); $\beta_{o,p'\text{-DDT}} = 0.48$ cm (95% CI: 0.12, 0.82); $\beta_{p,p'\text{-DDE}} = 0.40$ cm (95% CI: 0.07, 0.72)), and head circumference ($\beta_{p,p'\text{-DDT}} = 0.30$ cm (95% CI: 0.12, 0.46); $\beta_{o,p'\text{-DDT}} = 0.33$ cm (95% CI: 0.13, 0.52); $\beta_{p,p'\text{-DDE}} = 0.21$ cm (95% CI: 0.01, 0.41)) among girls but not among boys.

Associations between DDT/DDE and both gestational age and large size for gestational age among girls were positive but

imprecise, suggesting that increases in birth size may be due to a combination of increased gestation duration and intrauterine growth. However, mediation analysis using both the Baron and Kenny method (55) and the counterfactual framework showed small and imprecise indirect effects mediated by gestational age which ranged between 6.3 g (95% CI: −14.4, 29.0) and 12.8 g (95% CI: −6.3, 32.0) for associations between DDT/DDE and birth weight and approached zero for associations with birth length and head circumference (Figure 1; Web Tables 7 and 8). In contrast, controlled and natural direct effects (which were similar because exposures and gestational age did not interact) were large, and natural direct effects accounted for large portions (76%–97%) of total effects.

Associations between birth outcomes and pyrethroid metabolite concentrations were generally positive among girls and negative among boys, but evidence for effect modification by sex was limited, and estimates were imprecise. We found limited evidence of effect modification by household poverty, malnutrition, or maternal HIV status for DDT/DDE and pyrethroids, although associations between DDT/DDE and birth outcomes were generally more positive among children from poor households and children whose mothers were HIV-positive (Web Tables 9–20).

DISCUSSION

We found that maternal serum concentrations of p,p'-DDT, p,p'-DDE, and o,p'-DDT were associated with elevated birth weight, birth length, and head circumference among South African female infants from an area where IRS is used annually to control malaria, but not among males. Estimated associations with birth weight were notable, with a 10-fold elevation in DDT/DDE being related to increases of 58.4–80.4 g. However, we found limited evidence that maternal urinary concentrations of pyrethroid metabolites were associated with birth outcomes.

Positive associations between DDT/DDE and birth size may be regarded as a favorable outcome in study populations such as ours, which has a high prevalence of low birth weight. On the other hand, studies conducted in Western countries and Africa found that elevated birth weight is associated with higher risks

Table 2. Maternal Peripartum Serum Concentrations of Dichlorodiphenyltrichloroethane (ng/g Lipids) and Urinary Pyrethroid Metabolites (μg/L; Specific-Gravity–Corrected) Among Participants in the Venda Health Examination of Mothers, Babies and Their Environment, Limpopo Province, South Africa, 2012–2013

Compound	No. of Persons	Detection Frequency, %	Quantification Frequency, %	Geometric Mean (GSD)	Minimum	Percentile				Maximum
						25th	50th	75th	90th	
p,p'-DDT	751	98.0	90.7	69.6 (6.7)	<LOD	18.9	55.3	261.0	946.2	15,027.6
p,p'-DDE	751	100	97.2	287.9 (4.8)	4.0	91.8	242.2	878.9	2,577.7	26,301.3
o,p'-DDT	751	90.6	43.3	8.9 (4.6)	<LOD	3.4	7.1	22.7	72.0	2,029.3
cis-DBCA	738	100	99.6	0.23 (3.41)	<0.01	0.10	0.23	0.47	1.12	17.83
3-PBA	737	100	100	0.72 (2.80)	0.02	0.38	0.71	1.36	2.39	58.90
cis-DCCA	738	100	99.9	0.31 (2.94)	0.01	0.15	0.30	0.59	1.03	103.50
trans-DCCA	738	100	99.6	0.36 (3.43)	0.01	0.16	0.34	0.78	1.49	132.88

Abbreviations: DBCA, (2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DCCA, (2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; F3-PBA, 4-fluoro-3-phenoxybenzoic acid; GSD, geometric standard deviation; LOD, limit of detection; 3-PBA, 3-phenoxybenzoic acid.

Table 3.   Associations Between Maternal Peripartum Serum Concentrations of Dichlorodiphenyltrichloroethane and Dichlorodiphenyldichloroethylene and Birth Outcomes (Based on Marginal Structural Models), Venda Health Examination of Mothers, Babies and Their Environment, Limpopo Province, South Africa, 2012–2013[a]

Birth Outcome and Sex	No. of Persons	Compound					
		p,p′-DDT		p,p′-DDE		o,p′-DDT	
		β[b]	95% CI	β	95% CI	β	95% CI
Birth weight, g							
All children	750	12.2	−24.5, 49.7	10.5	−36.9, 58.1	11.4	−36.0, 60.6
Boys	387	−29.9	−77.0, 17.1	−28.0	−88.6, 32.1	−43.7	−105.8, 24.7
Girls	363	70.7[c]	11.8, 130.8	58.4	−17.0, 129.4	80.4[c]	10.2, 149.9
P for interaction		0.012		0.074		0.012	
Birth length, cm							
All children	745	0.16	−0.04, 0.36	0.20	−0.04, 0.44	0.20	−0.05, 0.45
Boys	383	0.01	−0.23, 0.27	0.06	−0.29, 0.38	0.01	−0.32, 0.36
Girls	362	0.41[c]	0.11, 0.72	0.40[c]	0.07, 0.72	0.48[c]	0.12, 0.82
P for interaction		0.036		0.138		0.072	
Head circumference, cm							
All children	745	0.07	−0.05, 0.19	0.02	−0.12, 0.16	0.09	−0.05, 0.24
Boys	383	−0.09	−0.24, 0.06	−0.13	−0.31, 0.07	−0.08	−0.31, 0.13
Girls	362	0.30[c]	0.12, 0.46	0.21[c]	0.01, 0.41	0.33[c]	0.13, 0.52
P for interaction		<0.001		0.012		0.004	
Gestational age, weeks							
All children	751	−0.02	−0.21, 0.18	−0.08	−0.34, 0.15	−0.04	−0.29, 0.20
Boys	387	−0.19	−0.46, 0.07	−0.25	−0.61, 0.08	−0.13	−0.50, 0.22
Girls	364	0.17	−0.10, 0.45	0.09	−0.25, 0.44	0.10	−0.25, 0.44
P for interaction		0.064		0.160		0.336	
		OR[d]	95% CI	OR	95% CI	OR	95% CI
Low birth weight							
All children	750	0.81	0.60, 1.08	0.78	0.53, 1.16	0.90	0.62, 1.32
Boys	387	1.09	0.73, 1.64	0.95	0.52, 1.69	1.03	0.53, 2.05
Girls	363	0.62[c]	0.39, 0.92	0.67	0.37, 1.13	0.74	0.47, 1.15
P for interaction		0.052		0.386		0.404	
Preterm birth							
All children	751	0.97	0.74, 1.27	1.04	0.75, 1.41	1.06	0.77, 1.48
Boys	387	1.18	0.83, 1.67	1.24	0.83, 1.94	1.22	0.75, 1.99
Girls	364	0.78	0.51, 1.16	0.86	0.54, 1.31	0.87	0.53, 1.34
P for interaction		0.138		0.220		0.266	
Small size for gestational age							
All children	750	0.92	0.73, 1.16	0.87	0.66, 1.10	0.89	0.68, 1.16
Boys	387	0.95	0.69, 1.29	0.93	0.66, 1.28	0.98	0.70, 1.36
Girls	363	0.91	0.66, 1.27	0.80	0.51, 1.18	0.85	0.54, 1.32
P for interaction		0.874		0.574		0.596	
Large size for gestational age							
All children	750	1.02	0.69, 1.51	1.13	0.72, 1.80	0.94	0.54, 1.57
Boys	387	0.91	0.57, 1.44	1.04	0.60, 1.75	0.59	0.26, 1.32
Girls	363	1.28	0.66, 2.44	1.29	0.63, 2.71	1.50	0.73, 2.83
P for interaction		0.364		0.600		0.084	

Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; OR, odds ratio.

[a] Propensity scores and inverse-probability-of-treatment weights were based on conditional probability density functions determined using the Super Learner algorithm ([53]).

[b] Change in mean outcome for each 10-fold increase in maternal peripartum serum DDT/DDE concentration.

[c] $P < 0.05$.

[d] OR for each 10-fold increase in maternal peripartum serum DDT/DDE concentration.

Table 4. Associations Between Maternal Peripartum Urinary Concentrations of Pyrethroid Metabolites and Birth Outcomes (Based on Marginal Structural Models), Venda Health Examination of Mothers, Babies and Their Environment, Limpopo Province, South Africa, 2012–2013[a]

| Birth Outcome and Sex	No. of Persons	Pyrethroid Metabolite							
		cis-DBCA		*cis*-DCCA		*trans*-DCCA		3-PBA	
		β[b]	95% CI	β	95% CI	β	95% CI	β	95% CI
Birth weight, g									
All children	738	4.8	−65.4, 79.8	15.8	−52.9, 83.4	5.2	−57.0, 65.1	7.5	−83.3, 99.8
Boys	383	−21.6	−106.5, 65.6	4.7	−81.5, 90.2	−16.7	−95.4, 58.5	−25.0	−127.2, 75.9
Girls	355	30.7	−84.2, 145.7	28.3	−71.8, 131.1	32.5	−52.3, 132.4	51.2	−108.4, 201.3
P for interaction		0.518		0.714		0.382		0.428	
Birth length, cm									
All children	733	0.03	−0.26, 0.33	0.11	−0.18, 0.37	0.02	−0.24, 0.26	0.12	−0.20, 0.45
Boys	379	−0.08	−0.48, 0.33	−0.07	−0.48, 0.28	−0.15	−0.48, 0.14	−0.03	−0.40, 0.37
Girls	354	0.12	−0.25, 0.58	0.31	−0.11, 0.70	0.23	−0.15, 0.60	0.31	−0.16, 0.78
P for interaction		0.474		0.156		0.088		0.274	
Head circumference, cm									
All children	733	0.04	−0.20, 0.27	0.06	−0.20, 0.28	−0.02	−0.25, 0.18	−0.01	−0.30, 0.27
Boys	379	−0.09	−0.41, 0.19	−0.02	−0.41, 0.28	−0.03	−0.35, 0.21	−0.09	−0.45, 0.27
Girls	354	0.17	−0.09, 0.46	0.15	−0.13, 0.45	−0.01	−0.29, 0.28	0.10	−0.28, 0.46
P for interaction		0.182		0.440		0.938		0.540	
Gestational age, weeks									
All children	738	−0.11	−0.49, 0.27	0.07	−0.26, 0.39	0.01	−0.27, 0.29	−0.11	−0.56, 0.29
Boys	383	−0.13	−0.57, 0.33	0.11	−0.34, 0.56	0.01	−0.38, 0.37	−0.11	−0.64, 0.34
Girls	355	−0.08	−0.70, 0.50	0.02	−0.48, 0.54	0.02	−0.40, 0.46	−0.10	−0.86, 0.62
P for interaction		0.820		0.784		0.910		0.962	
		OR[c]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low birth weight									
All children	738	0.97	0.45, 2.01	0.70	0.41, 1.12	0.81	0.51, 1.22	0.73	0.36, 1.56
Boys	383	0.75	0.32, 1.68	0.83	0.35, 1.67	1.00	0.51, 1.77	0.98	0.41, 2.24
Girls	355	1.09	0.37, 2.48	0.61	0.30, 1.13	0.68	0.35, 1.17	0.57	0.19, 1.90
P for interaction		0.638		0.554		0.334		0.444	
Preterm birth									
All children	738	1.11	0.69, 1.82	0.83	0.52, 1.27	0.98	0.67, 1.44	1.12	0.66, 1.99
Boys	383	1.22	0.72, 2.09	0.98	0.53, 1.64	1.15	0.71, 1.75	1.31	0.71, 2.60
Girls	355	0.99	0.43, 2.19	0.68	0.34, 1.33	0.80	0.43, 1.47	0.90	0.33, 2.21
P for interaction		0.622		0.440		0.362		0.524	
Small size for gestational age									
All children	738	0.97	0.70, 1.33	0.91	0.65, 1.32	0.99	0.72, 1.36	1.01	0.71, 1.49
Boys	383	1.23	0.82, 1.86	1.15	0.78, 1.84	1.16	0.81, 1.73	1.22	0.80, 2.00
Girls	355	0.69	0.38, 1.19	0.62	0.31, 1.19	0.73	0.41, 1.26	0.68	0.34, 1.43
P for interaction		0.088		0.082		0.140		0.186	
Large size for gestational age									
All children	738	0.78	0.47, 1.34	0.91	0.45, 1.70	0.91	0.49, 1.61	0.88	0.39, 1.84
Boys	383	0.86	0.40, 1.92	1.25	0.44, 2.91	1.12	0.42, 2.55	0.99	0.29, 2.99
Girls	355	0.71	0.32, 1.58	0.60	0.21, 1.60	0.69	0.28, 1.61	0.78	0.29, 2.02
P for interaction		0.730		0.300		0.448		0.750	

Abbreviations: CI, confidence interval; DBCA, (2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; DCCA, (2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; OR, odds ratio; 3-PBA, 3-phenoxybenzoic acid.

[a] Propensity scores and inverse-probability-of-treatment weights were based on conditional probability density functions determined using the Super Learner algorithm (53).

[b] Change in mean outcome for each 10-fold increase in maternal peripartum pyrethroid metabolite concentration.

[c] OR for each 10-fold increase in maternal peripartum pyrethroid metabolite concentration.
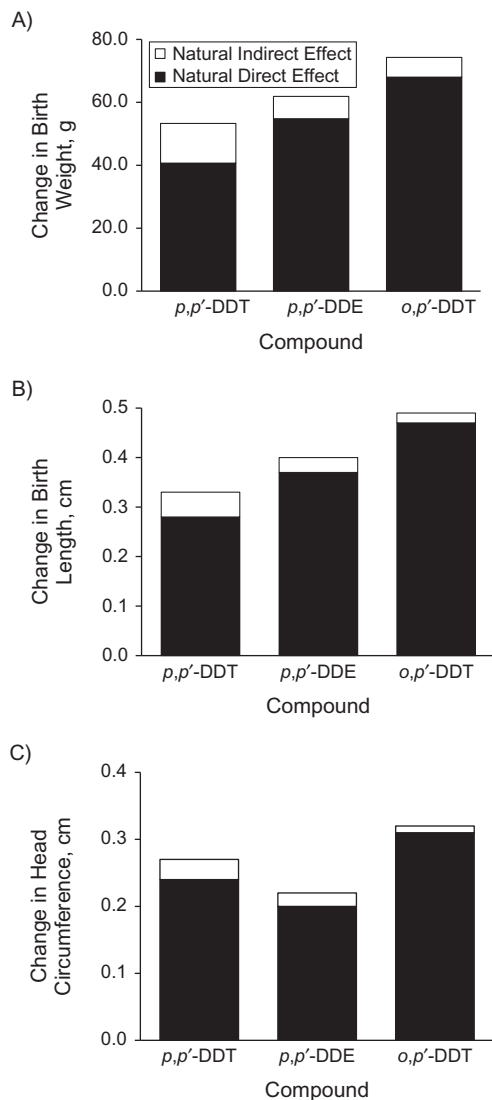
Figure 1. Direct, indirect (mediated by duration of gestation), and total effects of dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) on birth weight (A), birth length (B), and head circumference (C), based on the counterfactual framework approach, among girls ($n = 364$) participating in the Venda Health Examination of Mothers, Babies and Their Environment, Limpopo Province, South Africa, 2012–2013. Models adjusted for maternal age, education, marital status, smoking, alcohol use during pregnancy, postdelivery body mass index (weight (kg)/height (m)^2), human immunodeficiency virus status, household income per capita, assets, child's sex, parity, delivery method, and season of birth.

some cases be a marker for high in utero exposure to estrogen, which is related to adverse health effects later in life. In this context, it is noteworthy that we found that associations with birth size were strongest for o,p'-DDT, the most potently estrogenic DDT isomer, followed by p,p'-DDT, which is also estrogenic (p,p'-DDE is antiandrogenic but not estrogenic) (75). Similarly, maternal serum o,p'-DDT concentrations during pregnancy were more strongly associated with breast cancer risk than concentrations of p,p'-DDT or p,p'-DDE among women participating in the Child Health and Development Study, a birth cohort study that enrolled participants when DDT was still being used in the United States (76).

Elevated birth weight may occur through increased duration of gestation or accelerated intrauterine growth. The fact that we found little evidence that associations between DDT/DDE exposure and measures of birth size were mediated by longer gestation thus suggests that DDT/DDE may accelerate intrauterine growth. This is consistent with our finding of elevated, though imprecise, odds of large-for-gestational-age birth.

Our findings conflict with much of the previous literature, which primarily indicated inverse or null associations between birth size and exposure to DDT or pyrethroids. However, none of the prior studies were conducted in populations in which IRS is practiced. Poverty, malnutrition, and poor health, which are prevalent in these populations, may modify susceptibility to the adverse effects of insecticides. We found some evidence supporting this hypothesis within our study population in that associations between DDT/DDE and birth size variables were systematically stronger among children from poor households or who were exposed to HIV. Although statistical evidence for effect modification by these variables was limited within our study population, effects may differ more greatly between Western and IRS populations because of larger differences in income and health status between these populations than within IRS populations. An alternative explanation may be related to the different survival rates for low–birth-weight infants between Western populations and our study area. Because birth weight data are generally not available for stillbirths, prior studies (including ours) had to restrict their analysis to live infants. However, if elevated serum DDT/DDE levels and low birth weight adversely affected survival, restricting analysis to live infants could induce collider stratification (selection) bias by removing infants with this combination of exposure and birth weight from the study sample, which could result in a positive bias. Because, in our study population, people may be more susceptible to the adverse effects of DDT/DDE and low–birth-weight infants are less likely to survive than in Western populations, this bias may have been stronger in our study population.

This study had several strengths. To our knowledge, this was the first study to investigate associations between exposure to IRS insecticides and birth outcomes in a population living in a malaria-endemic area. Results were robust to a variety of sensitivity analyses and different modeling approaches such as marginal structural models, generalized propensity scores, and standard regression. Although residual confounding remains a possibility, we had data on numerous potential confounders and had complete data on virtually all variables.

This study also had a few limitations. Because women do not typically measure their weight in our study population, we did not have data on prepregnancy weight and thus on

of perinatal mortality (63–65), and authors of meta-analyses reported that higher birth weight and, to a lesser extent, birth length were associated with increased risks of breast cancer in women (66, 67). Elevated exposure to estrogens in utero has been proposed as the possible mechanism of action underlying these associations (67), since estrogens stimulate cell proliferation and numerous studies have found positive associations between exposure to estrogens and both birth size and breast cancer risk (68–74). In other words, elevated birth size may in

pregnancy weight gain, an important determinant of infant birth weight. However, it is unlikely that weight gain would have affected pyrethroid exposure. In addition, we previously showed that weight change was inversely associated with the serum concentration of DDT/DDE [77]. Weight gain would thus be expected to act as a negative confounder, so its omission from models should result in an underestimation of associations, which could not explain our results. Because of the short elimination half-life of pyrethroids (approximately 5–13 hours) [78, 79], metabolite concentrations in spot urine samples may not reflect long-term exposure. The literature is inconsistent on this topic, however. Although weak ($\leq$0.21) ICCs were reported for pyrethroid metabolite concentrations in spot urine samples among US adults [60], stronger reproducibility was found among Polish adults (ICC = 0.85) [80]. Finally, the possibility of chance findings cannot be excluded, given the large number of tests performed.

In summary, we found that prenatal exposure to the estrogenic DDT isomers o,p'-DDT and p,p'-DDT and, to a lesser extent, p,p'-DDE was related to elevated birth size among girls, including birth weight, birth length, and head circumference. Elevated birth size, particularly if due to exposure to estrogenic chemicals, may be associated with adverse health outcomes, including elevated perinatal mortality and breast cancer risk, but additional research is needed to fully elucidate the implications of our findings.

ACKNOWLEDGMENTS

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