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Sex and Poverty Modify Associations Between Maternal Peripartum Concentrations of DDT/E and Pyrethroid Metabolites and Thyroid Hormone Levels in Neonates Participating in the VHEMBE Study, South Africa

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Abstract

Indoor Residual Spraying (IRS), the application of insecticides on the inside walls of dwellings, is used by 84 countries for malaria control. Although effective in preventing malaria, this practice results in elevated insecticide exposure to more than 100 million people, most of whom are Africans. Pyrethroid insecticides and dichlorodiphenyl trichloroethane (DDT) are currently used for IRS. Animal and *in vitro* studies suggest that pyrethroids and DDT interfere with thyroid hormone homeostasis but human studies are inconsistent and no prior study has investigated this question in a population residing in an area where IRS is conducted. Our objective was thus to evaluate whether prenatal exposure to pyrethroids, DDT or DDT's breakdown product dichlorodiphenyl dichloroethylene (DDE) is associated with altered thyroid hormone levels among neonates from Limpopo, South Africa, an area where pyrethroids and DDT are used annually to control malaria. We measured serum DDT/E and urinary pyrethroid metabolite concentrations in maternal peripartum samples among 717 women participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), a birth cohort study conducted in Limpopo's Vhembe district. We measured total thyroxine (T4) and thyroid-stimulating hormone (TSH) in dried blood spots collected via heel stick. We found that all pyrethroid metabolites were positively associated with TSH; *trans*-DCCA and 3-PBA showed the strongest associations with a 12.3%

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CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

(95%CI=3.0, 22.3) and 14.0 % (95%CI=0.5, 30.2) change for each 10-fold increase in biomarker concentration, respectively. These associations were substantially stronger among children from households below the South African food poverty line. DDT and DDE were associated with lower total T4 among boys only (β=−0.27 μg/dL per 10-fold increase; 95%CI=−0.47, −0.04). Results suggest that prenatal exposure to DDT, DDE and pyrethroid insecticides is associated with changes in neonatal thyroid hormones consistent with hypothyroidism/hypothyroxinemia and that sex and poverty modify associations. Further research is needed to confirm these findings and examine whether they have implications for child development.

Keywords

DDT; Indoor Residual Spraying; Pyrethroid insecticides; Thyroid hormones; Thyroid-stimulating hormone; thyroxine

1. Introduction

According to the World Health Organization, 219 million people were infected by malaria in 2017, resulting in 430,000 deaths, primarily among African children under age 5 years.(1) Indoor residual spraying (IRS), the application of insecticides on the inside walls of residences, is used by 84 countries for malaria control.(1, 2) Although this practice appears effective in reducing infection, it results in elevated exposure to insecticides with incompletely understood health consequences.(3, 4) In South Africa, pyrethroid insecticides and dichlorodiphenyl trichloroethane (DDT) are used for IRS.

Animal and *in vitro* studies suggest that pyrethroids and DDT may alter thyroid hormones homeostasis, which play a critical role in child growth and brain development, particularly during pregnancy and the neonatal period.(5) Several pyrethroids including deltamethrin, permethrin, cypermethrin, and fenvalerate as well as the non-specific pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) interact with the thyroid receptor.(6, 7) No animal study has investigated the effect of prenatal exposure to pyrethroids on offspring thyroid function. However, postnatal intraperitoneal exposure to permethrin, deltamethrin, karate (a λ-cyhalothrin formulation) and talstar (a bifenthrin formulation) in rats and fenvalerate in mice was found to lower total triiodothyronine (T3) and total thyroxine (T4) and/or increase thyroid-stimulating hormone (TSH) blood concentrations.(8–11) In contrast, rats intraperitoneally exposed to fenvalerate showed elevated total T3 and/or total T4, and no change in total T3, total T4 or TSH following oral exposure to lower doses of deltamethrin.(12–14)

The only human study to investigate associations between prenatal exposure to pyrethroids and neonatal thyroid hormones found no associations between maternal urinary 3-PBA and TSH or free T4 concentrations in 147 mother-child pairs from Tokyo, Japan, but the moderate sample size may have limited statistical power.(15) Cross-sectional studies conducted in U.S. adults also found no associations between urinary 3-PBA concentrations and thyroid hormones (16, 17). However, an inverse relation was reported between urinary *cis*-3-(2,2-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DCCA) and total T3 blood concentrations among U.S. males recruited from an infertility clinic.(17)

DDT reduces total T4 blood concentration and induces the microsomal enzyme uridinediphosphate glucuronosyltransferase (UDP-GT) in rats (18). Since glururonidation by UDP-GT is the rate-limiting step in T4 metabolism, this mechanism may underlie the reported hypothyroidic (lower T4 and, in some cases, elevated TSH) effect of DDT in rodents.(18–21) While none of the three human studies investigating maternal blood concentrations of DDT, or DDT's breakdown product dichlorodiphenyl dichloroethylene (DDE), and neonatal thyroid hormones found associations (22–24), two studies reported inverse relations between cord DDT/E and cord free or total T4 concentrations.(25, 26) However, studies conducted in adolescents (27) and adults (23, 28–34) yielded conflicting results.

These prior studies were primarily conducted in high-income countries. However, vulnerable populations living in areas where IRS is conducted, and where poverty, malnutrition and poor health are prevalent, may be particularly susceptible to the adverse health effects of exposure to insecticides. Our objective was thus to evaluate whether prenatal exposure to pyrethroids, DDT or DDE is associated with altered thyroid hormone levels among neonates from Limpopo, South Africa, an area where pyrethroids and DDT are used annually to control malaria. We also aimed to identify whether child sex and household poverty modify these associations.

2. Methods

2.1. Study population

This analysis is based on data from the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), a birth cohort study that investigates the health effects of environmental exposures among women-child dyads from the Vhembe district of Limpopo Province, South Africa. Women were approached between August 2012 and December 2013 at Tshilidzini Hospital in the town of Thohoyandou, shortly before or after giving birth, and were invited to participate in the VHEMBE study if they were at least 18 years of age, had contractions > 5 minutes apart, spoke Tshivenda (the most common language in the region), lived within 20 km of the hospital, planned to live in the area for the following two years, were not diagnosed with malaria during pregnancy, and gave birth to a live singleton. Of 920 eligible women, 152 refused to participate, 3 did not provide sufficient blood for DDT analysis, and 14 did not complete a baseline questionnaire. One week postpartum, we visited 722 of these participants at home (4 children died before the visit, 6 could not be scheduled and 19 dropped out) to conduct a home inspection and collect a dry blood spot from neonates via heel stick for the measurement of thyroid hormone levels. We collected 720 blood spots and obtained valid total T4 and TSH measures for 717 neonates. Eight women did not provide urine and one 3-PBA measurement did not meet quality control standards, leaving samples sizes ranging between 708 and 717. We found no significant differences between participants enrolled and those included in analyses for any of the variables considered in this analysis. All mothers gave informed consent prior to participation. 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.

2.2. Data collection.

Trained, bilingual (Tshivenda and English) research staff originating from the study area conducted structured interviews with mothers shortly after delivery. The interview included questions on socioeconomic characteristics, household assets, lifestyle, diet (via a food-frequency questionnaire validated in the study area)(35), stress (using a stressful life event scale adapted for the local population)(36, 37) and health and pregnancy history. Gestational age at birth was determined based on date of last menstrual period and maternal HIV status was ascertained from self-report or use of anti-retroviral drugs based on medical records. Total energy and iodine intakes were estimated by a South African expert nutritionist using the FoodFinder3 software (South Africa Medical Research Council/WAMTechnology, Stellenbosch, South Africa). Low daily energy intake was defined based on Institute of Medicine Guidelines for pregnant women (38, 39) following methods described in Huang et al.(40) We defined poverty as income below 386 Rands/person/month (about 30 USD) based on Statistics South Africa guidelines (41) and high stress if more than two stressful life events occurred during pregnancy (the median in this sample). In addition, we generated a wealth index via principal component analysis based on Demographics and Health Survey methodology for South Africa.(42) We used data on asset ownership (15 items), livestock ownership (6 items), water source (8 items), number of household members, and cooking fuel (8 items) via maternal report; and toilet facilities (4 items), home floor and wall materials (20 items) via home inspections.(43) The questionnaire was developed in English, translated in Tshivenda and back-translated in English by native speakers in the translated language. Registered nurses abstracted medical records to obtain data on HIV status and delivery method (vaginal or cesarean section).

2.3. Measurement of insecticides.

Research staff collected maternal urine and blood samples before (NBlood=568; NUrine=444) or shortly after delivery (NBlood=152; NUrine=268) and immediately processed and stored them at −80°C until shipment to analytical laboratories. The Institut National de Santé Publique du Québec measured pyrethroid metabolite concentrations, including *cis*-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid (*cis*-DBCA), *cis*-DCCA, *trans*-DCCA, 3-phenoxybenzoic acid (3-PBA), and 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), in maternal urine by gas chromatography-mass spectrometry based on methods developed by Dewailly et al.(44) Limits of detection were 0.0025 μg/L for *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-F-3-PBA. Corresponding limits of quantification were 0.0082, 0.015, 0.013, 0.016 μg/L. Pyrethroid concentrations were corrected for dilution based on sample specific gravity, which was measured using a portable refractometer (Atago PAL-10S, Tokyo, Japan). Creatinine concentration was also measured via spectrophotometry (DRI Creatinine-Detect Test, Thermo Scientific, Waltham, MA).

The Emory University Environmental Health Laboratory measured the *p,p'* and *o,p'* isomers of DDT and DDE as well as polychlorinated biphenyls (PCBs) 118, 138, 153 and 180 using high resolution gas chromatography-isotope dilution mass spectrometry.(45) PCBs were considered as potential confounders due to prior reports of associations with neonatal thyroid hormones.(46) Limits of detection were 0.01 ng/mL serum for *p,p'*-DDT, *o,p'*-DDT

and *o,p'*-DDE, and 0.03 ng/mL serum for *p,p'*-DDE. Corresponding limits of quantification were 0.03 and 0.09 ng/mL serum. DDT/E and PCB concentrations were lipid-corrected and expressed in ng/g lipid. Total lipids were estimated based on triglycerides and total cholesterol concentrations (47) as measured using standard enzymatic methods (Roche Chemicals, Indianapolis, IN).

2.4. Thyroid hormone measurements.

TSH and T4 sharply increase at birth and then reduce gradually and stabilize over the next few days of life.(5) Capillary blood samples were thus taken from infants via heel stick at a median of 8 days postpartum (interquartile range: 7–10) and deposited on Whatman filter papers (GE Health Care Life Sciences, Maidstone, United Kingdom). Samples were air-dried at ambient temperature and stored at −30°C until shipped to the North-West University Newborn Screening Laboratory (Potchefstroom, South Africa) which measured total T4 and TSH using solid-phase, time-resolved sandwich fluoroimmunometric assays (DELFIA®, PerkinElmer Life and Analytical Sciences, Turku, Finland). The laboratory is certified by the U.S. Centers for Disease Control and Prevention (CDC) Newborn Screening Quality Assurance Program.(48) Limits of detection (LODs) and mean coefficients of variation are 1.5 μg/dL and 7.1% for total T4, and 2 μIU/mL and 7.9% for TSH, respectively. Reference intervals are 3.2–11.1 μg/dL for total T4 and 0.27–6.07 μIU/mL for TSH. Hormones were measured in duplicate and averaged.

2.5. Data analysis

Biomarkers of exposure were $\log_{10}$-transformed to reduce the influence of outliers and TSH was $\log_{10}$-transformed to normalize residuals. Reported associations thus represent mean (total T4) or percent (TSH) change in outcomes for each 10-fold increase in exposure biomarker concentration. Biomarker concentrations between the LOD and the limit of quantification were assigned machine-read values; concentrations below the LOD were imputed based on a log-normal probability distribution whose parameters were determined via maximum likelihood estimation.(49) We used analysis of variance and Pearson's correlations for bivariate analyses. We estimated the causal effect of exposure to IRS insecticides on neonatal thyroid hormone levels (expressed continuously or categorized based on reference ranges) based on marginal structural models with inverse probability-of-treatment weights. We applied stabilized weights which were estimated using the Super Learner algorithm, a loss-based supervised learning method that computes a weighted combination of prediction algorithms to return a function that minimizes cross-validated risk.(50)

Potential confounders were identified via Directed Acyclic Graphs and included maternal age (continuous), education (<12th grade, 12th grade, >12th grade), marital status (married or living as married, not married) and total polychlorinated serum concentration (continuous); alcohol and drug consumption (any, none), smoking (ever, never), exposure to environmental tobacco smoke (ever, never), iodine intake (continuous) and HIV status (positive, negative) during pregnancy; household income per capita and wealth index (continuous); and child sex and age in days at the time of heel stick (continuous). Variables such as birth weight, gestational age at birth and delivery method were not considered because they may be

situated on the causal pathway between exposures and thyroid hormones. Missing covariate values (<1.8%) were randomly imputed based on observed probability distributions.

We ran several sensitivity analyses to evaluate the robustness of our results. First, we evaluated the linearity assumption by running Generalized Additive Models with a 3-degree of freedom cubic spline. Second, we ran models correcting pyrethroid metabolites for creatinine concentration (expressed in μg/g creatinine). Third, we re-ran all models by expressing biomarkers of exposure on a sample volume weight and including cholesterol and triglycerides (for DDT/E models) or specific gravity/creatinine (for pyrethroid models) as covariates in models. Fourth, we ran all models excluding possible outliers identified using the generalized extreme studentized deviate many-outlier procedure.(51) Fifth, because pyrethroid metabolite concentrations may represent in part exposure in the hospital, we re-ran analyses stratified on whether urine samples were collected before or after delivery. Sixth, we applied a Generalized Propensity Score (GPS) method for continuous exposure by estimating the conditional density of exposure given covariates and included the propensity score variable in models.(52) The GPS was estimated using the Super Learner algorithm and a cubic spline was applied to the propensity score. Finally, we built models using a more traditional approach by adjusting only for variables that were associated with any of the exposure and outcomes at $p<0.20$. These models included maternal education; alcohol consumption and HIV status during pregnancy; household income per capita; and child sex. Results were not substantially affected by any of these different specifications. We show results based on marginal structural models with exposure biomarkers expressed linearly, corrected for lipids for DDT and DDE or specific gravity for pyrethroids, and including outliers.

We also investigated effect modification by child's sex and household poverty by running separate models including one of these binary cross-product terms. Although prior research in this and other populations suggests that poverty may affect susceptibility to the adverse effects of insecticides and other environmental exposures,(40, 53–64) the mechanisms for this effect modification have not been identified. Thus, as a secondary analysis we also examined whether maternal stress and low energy intake during pregnancy modified associations. All analyses were conducted using STATA, version 15 (StataCorp LP, College Station, TX, USA) or R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Population characteristics

Women included in this study were all Black/of African descent, and mostly young (mean age = 26.4 years), poor (61% < South African food poverty level) with low levels of education (86% ≤12th grade education) and low energy intake (68% < Institute of Medicine guidelines) during pregnancy (Table 1). About 14% were HIV-positive, and few reported consumption of alcohol (6%) or smoking (0.3%) during pregnancy. About half (49%) of infants were girls, 13% were born preterm (< 37 weeks gestation), 8% had a low birth weight (< 2,500 g), and 25% were small-for-gestational age (< 10th percentile of weight-for-gestational age).

3.2 Concentrations of DDT/E, pyrethroid metabolites, and thyroid hormone

Table 2 shows the distribution of biomarkers of exposure to insecticides as well as their detection and quantification frequencies. *o,p'*-DDE and 4-F-3-PBA were quantified in only 16% and 8% of samples, respectively, and were excluded from data analysis. Except for *p,p'*-DDT (98% detection) and *o,p'*-DDT (90% detection), the concentration of all other biomarkers of exposure were above the LOD. DDT/E (r=0.69 to 0.85, p<0.05) and pyrethroids (r=0.31 to 0.88, p<0.05) were intercorrelated within but not between (r=−0.03 to 0.04, p>0.05) chemical class. Maternal age and parity were positively associated with *cis*-DCCA, *trans*-DCCA and 3-PBA but not *cis*-DBCA. Male sex was associated with lower *p,p'*-DDT and *o,p'*-DDT, age at heel stick was associated with lower *o,p'*-DDT, and vaginal delivery was associated with higher *cis*-DBCA (data not shown). T4 and TSH were detected in all neonates. Mean T4 was 5.2 μg/dL (standard deviation=1.5) and the geometric mean of TSH was 1.2 μIU/mL (geometric standard deviation=1.9). Per capita household income was positively associated with lower TSH, and child age at heel stick and maternal HIV seropositivity were associated with lower T4. Forty-seven (6.6%) children had low T4, two (0.3%) had high T4, none had low TSH, and one (0.1%) had high TSH blood concentrations. We examined associations with low T4 but not with other categories due to insufficient number of cases.

3.3 Associations between pyrethroids and thyroid hormone concentrations

All pyrethroid metabolites were positively associated with TSH; *trans*-DCCA and 3-PBA showed the strongest associations with a 12.3% (95%CI=3.0, 23.3) and 14.0 % (95%CI=0.5, 30.2) change for each 10-fold increase in biomarker concentration, respectively (Table 3). Associations between pyrethroid metabolites and T4 were generally negative but weak and imprecise. However, as shown in Figure 1 and Table S1, associations with T4 were substantially stronger among children from poor households for all pyrethroid metabolites, and most particularly for *cis*-DCCA (β=−0.39; 95%CI=−0.74, −0.06), *trans*-DCCA (β=−0.28; 95%CI=−0.50, 0.00) and 3-PBA (β=−0.33; 95%CI=−0.70, 0.05) with interaction p-values below 0.04. In addition, odds of low T4 were elevated in relation to pyrethroid metabolites among children from poor households, with odds ratios (ORs) ranging between 1.5 (95%CI=0.6, 3.8) for *cis*-DBCA and 5.2 (95%CI=1.5, 17.3) for 3-PBA, and evidence of interaction (p_{int} 0.02 to 0.08) for *cis*-DCCA, and 3-PBA (Table 4).

3.4 Associations between DDT/E and thyroid hormone concentrations

DDT/E were not associated with TSH (Table 3). Associations with T4 were also weak overall and varied between −0.11 μg/dL (95%CI=−0.24, 0.03) and −0.08 μg/dL (95%CI=−0.24, 0.08) per 10-fold increase in *p,p'*-DDT and *p,p'*-DDE, respectively. However, investigation of effect modification by sex revealed that *o,p'*-DDT was associated with reduced T4 among boys (β=−0.27; 95%CI=−0.47, −0.04) but not among girls (β=0.10; 95%CI=−0.13, 0.32) (p_{int} = 0.02). *p,p'*-DDT was also inversely associated with T4 among boys (β=−0.20; 95%CI=−0.38, −0.03) but statistical evidence for effect modification was more limited (p_{int} = 0.15). In addition, we observed a positive association between the odds of low T4 and *p,p'*-DDT (OR=1.4; 95%CI=0.9, 2.3) and *o,p'*-DDT (OR=1.6; 95%CI=0.9,

2.8) among boys (p_{int} = 0.04 and 0.03, respectively) but confidence intervals crossed the null (Table S2).

Results for DDT/E and pyrethroids did not change markedly using either standard regressions (Tables S3–S6) or propensity score models (Tables S7–S10), or in other sensitivity analyses (not shown). We found no substantial evidence of effect modification by stress or energy intake during pregnancy (data not shown).

4. Discussion

We report associations between maternal peripartum pyrethroid metabolite concentrations and neonatal TSH overall and inverse associations with T4 levels among neonates from poor households. We also found inverse associations between maternal DDT concentrations and T4 among boys, particularly for *o,p'*-DDT. Studies conducted in Spain (n=387–453) and Sweden (n=198) found no association between maternal or cord DDT/E and neonatal TSH, free T4 or total T3 while inverse associations were reported between cord DDT/E and cord free or total T4 in Thailand (n=39) and Belgium (n=198). The only study examining exposure to pyrethroids found no association between maternal urinary 3-PBA during pregnancy and TSH or free T4 among 147 Japanese infants. Prior studies had smaller sample sizes than the current study and most were conducted in high-income countries.

Our results suggest that boys may be more susceptible to thyroid hormone disruption by DDT. Although the precise mechanism for this effect is unclear, DDT has been shown to differentially induce liver enzymes in male and female rats(65) and sexual dimorphism is commonly reported in studies of endocrine disruptors such as DDT.(66) While prior studies of prenatal exposure to DDT/E and thyroid hormones did not investigate effect modification by sex, a moderately-sized cross-sectional study conducted in adults found results that contrasted with ours in that the sum of DDT and DDE concentrations was positively related to both T4 and T3 among 48 women, but not among 66 men.(67) However, effect modification was not formally tested.

Prior studies using VHEMBE data also suggest that insecticides may have sexually dimorphic effects. For instance, we found that prenatal exposure to DDT and DDE was associated with increased birth size and elevated body mass index (BMI)-for-age and weight-for-height at 1 and 2 years among girls only.(68, 69) In addition, maternal urinary pyrethroid metabolite concentrations were associated with poorer expressive communication and motor development among girls but better motor skills in boys at age 2 based on the Bayley Scales of Infant Development III.(70) We also found inverse associations between maternal urinary pyrethroid metabolites and measures of body composition among boys only between 1 and 3.5 years of age.(43, 68)

Results from the present study also suggest that associations between maternal peripartum pyrethroid metabolite concentrations and lower T4 levels are modified by poverty. Although several studies found evidence of increased vulnerability to environmental exposures such as air pollution and lead among individuals of low socioeconomic status,(53–64) few studies have investigated the potential for economic hardship to potentiate the adverse effects of

insecticides. However, we recently reported associations between maternal DDT/E serum concentrations and higher rates of persistent fever among VHEMBE children from poor households but not among those from households with higher incomes.(40) We also found associations between DDT/E and higher fever rates among children of mothers who had low energy intake during pregnancy but not among those with sufficient energy intake, suggesting that undernutrition may underlie the potentiating effect of poverty. Although fasting is known to downregulate the hypothalamus-pituitary-thyroid axis in humans by reducing TSH and/or T4, likely to lower basal metabolism and save energy,(71–76) we found no evidence that low energy intake during pregnancy modified associations in the present study.

Stress may represent another potential mechanism for the modifying effect of socioeconomic status. However, despite evidence that stress suppresses the hypothalamus-pituitary-thyroid axis in rodents(77) and prior human studies suggesting that stress and adversity potentiate the adverse health effects of contaminants such as lead,(78) $PM_{2.5}$(79) and organophosphate insecticides,(80) we found no evidence of effect modification in the VHEMBE population.

Our findings suggesting stronger associations among children from poorer households raise important questions of environmental justice. While discussion on this topic initially largely centered on the fact that vulnerable populations may experience higher exposure, our results contribute to a growing body of evidence that individuals of lower socioeconomic standing may be more susceptible to the harmful health effects of environmental exposures(53–64) and support the need for policies that seek to protect vulnerable subpopulations. While such provisions are specifically integrated in environmental law in the United States (e.g. as part of the National Environmental Policy Act)(81) and to some extent in Europe (e.g. the Aarhus Convention),(82) low- and middle-income countries (LMICs), including African countries, lag behind in terms of codifying environmental justice into law. This is of particular concern given that the vast majority of the global environmental burden of disease, including 92% of pollution-related deaths, occurs in LMIC populations.(83) It has been estimated that, on average, 26% of the burden of disease is due to modifiable environmental factors in sub-Saharan countries(84) but, due to a lack of empirical data in African populations, these figures are primarily based on expert opinion or data generated in high-income countries. Given the potential for poverty to potentiate the impact of environmental exposures and the higher prevalence and severity of poverty in Africa relative to high-income countries, the environmental burden of disease may be substantially higher than these estimates suggest. A number of additional factors including different exposure sources, levels, and mixtures, which occur in widely different social, cultural and economic contexts, may render African populations particularly vulnerable to toxic effects, highlighting the need to conduct research in Africa and other LMICs.

This study has several strengths. To our knowledge, this is the first study to investigate associations between prenatal exposure to DDT/E or pyrethroids and thyroid hormone levels among neonates from an area where IRS is conducted. This is also the first such study to investigate effect modification by sex, poverty, stress or maternal undernutrition. Although the possibility of residual confounding cannot be dismissed, we considered a large number

of potential confounders including multiple variables to account for socioeconomic status and adjusted for them in marginal structural models. Thyroid hormone levels increase sharply shortly after birth and decrease during the first few days of life.(5) In order to limit measurement error, we measured thyroid hormones in duplicate at a median of 8 days postpartum and no earlier than 3 days. The very low rate of missing data and our use of experienced laboratories to measure biomarkers of exposure and thyroid hormones also constitute strengths. On the other hand, although we used food frequency questionnaires validated in the study population to estimate energy intake during pregnancy, these instruments have inherent limitations as they fully rely on accurate recall. In addition, the measurement of cortisol in serum or saliva may have provided a better indication of maternal stress than the stressful life events scale that we used but women were recruited at the time of delivery and so no samples were available earlier during gestation.

5. Conclusion

In summary, our results suggest that prenatal exposure to DDT/E is associated with lower total T4 among male neonates. Thyroid hormones play an essential role in fetal brain development. Although we previously reported some evidence that maternal serum DDT concentrations were inversely associated with motor scores on the Bayley Scales of Infant Development III at ages 1 and 2 years, associations were detected among girls only.(70) The developmental impact of the DDT and T4 association that we identified here among males is thus unclear. We also found that maternal exposure to pyrethroids is associated with higher TSH overall and lower neonatal T4 among children from poor households. Associations were found with 3-PBA, *trans*-DCCA and *cis*-DCCA but relations with *cis*-DBCA were weaker and imprecise and evidence for effect modification was limited. Given that *cis*-DBCA is a metabolite specific to deltamethrin, results suggest that exposure to other pyrethroid insecticides may be of greater concern with regards to thyroid hormone disruption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

3-PBA	3-phenoxybenzoic acid
4-F-3-PBA	4-fluoro-3-phenoxybenzoic acid
***cis*-DBCA**	*cis*-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid

***cis*-DCCA**	*cis*-3-(2,2-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid
BMI	Body mass index
DDT	Dichlorodiphenyl trichloroethane
DDE	Dichlorodiphenyl dichloroethylene
GPS	Generalized propensity score
HIV	Human immunodeficiency virus
IRS	Indoor residual spraying
LMICs	Low- and middle-income countries
LOD	Limit of detection
OR	Odds ratio
PCBs	Polychlorinated biphenyls
T3	Triiodothyronine
T4	Thyroxine
***trans*-DCCA**	*trans*-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid
TSH	Thyroid-stimulating hormone
UDP-GT	Uridinediphosphate glucuronosyltransferase
VHEMBE	Venda Health Examination of Mothers, Babies and their Environment

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HIGHLIGHTS

- Indoor Residual Spraying (IRS) is used by 84 countries to control malaria
- There are limited data on the potential adverse health effects of IRS insecticides
- Maternal serum DDT and DDE were associated with lower T4 in male neonates
- Maternal urinary pyrethroid metabolites were related to higher TSH in neonates
- Associations with TSH were stronger among neonates from poor households

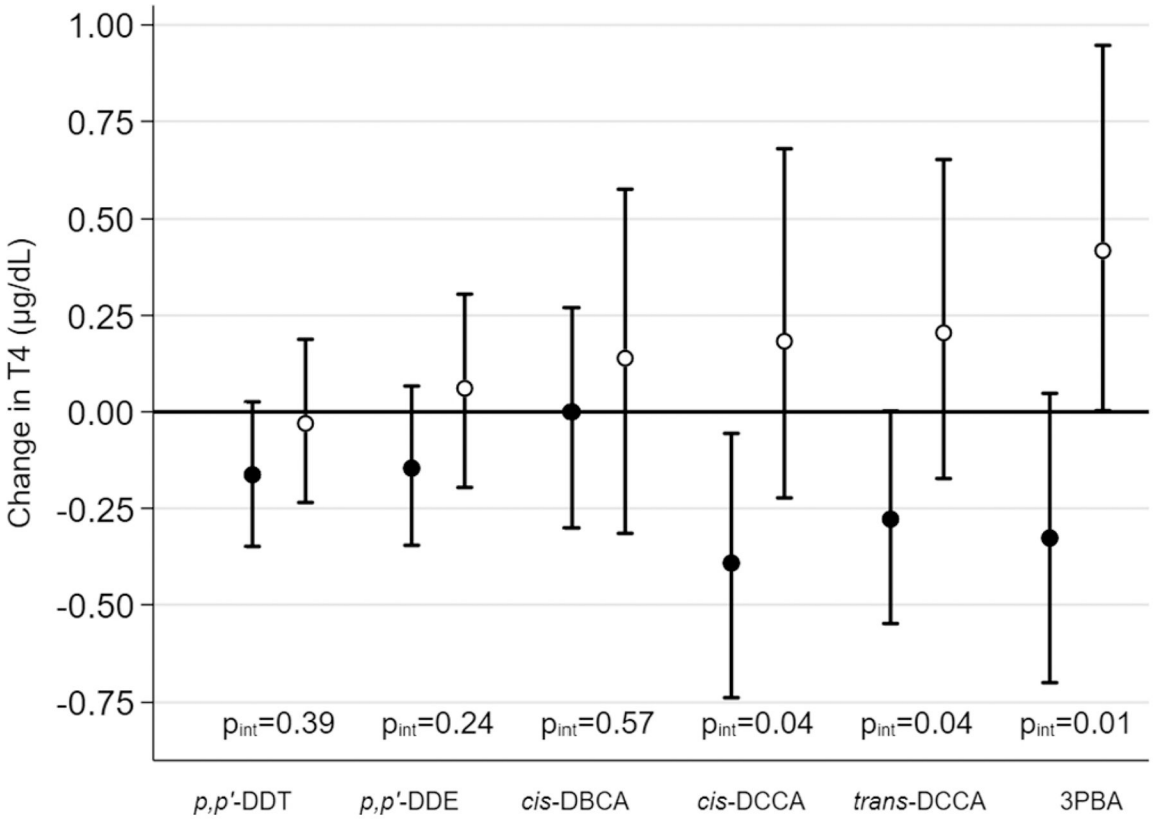

Figure 1.

Associations between T4 and DDT/E and pyrethroids by poverty status. Error bars represent 95% confidence intervals. Solid circles represent children from households with income below the South African food poverty level and hollow circles represent households with incomes above the poverty threshold. Marginal Structural Models are based on stabilized weights determined using the Super Learner algorithm. p_{int} represents the p-value associated with the interaction term.

Table 1.

Demographic characteristics of VHEMBE study participants who completed the 1-week follow-up visit, Limpopo, South Africa, 2012–2013 (n=720)

Maternal characteristics	
Maternal age, mean ± standard deviation	26.4 ± 6.2
Education, n (%)	
< 12th grade	399 (55.4)
Grade 12	217 (30.1)
> High school	104 (14.4)
Marital status, n (%)	
Married	342 (47.5)
Not married	378 (52.5)
Parity, n (%)	
0	312 (43.3)
1	192 (26.7)
2+	216 (30.0)
Alcohol consumption, n (%)	
Yes	41 (5.7)
No	679 (94.3)
Smoking, n (%)	
Yes	2 (0.3)
No	718 (99.7)
Environmental tobacco smoke exposure, n (%)	
Yes	276 (38.3)
No	444 (61.7)
HIV status, n (%)	
Positive	99 (13.8)
Negative	621 (86.2)
Low energy intake during pregnancy, n (%)	
Yes	490 (68.1)
No	230 (31.9)
Number of stressful live events, mean ± standard deviation	2 ± 1.7
Child characteristics	
Sex, n (%)	
Boy	371 (51.5)
Girl	349 (48.5)
Preterm (<37 weeks), n (%)	
Yes	96 (13.3)
No	624 (86.7)
Low birth weight (<2500g), n (%)	
Yes	61 (8.5)
No	659 (91.5)

Maternal characteristics	
Delivery method	
Vaginal birth	555 (77.1)
Cesarean	165 (22.9)
Small for gestational age, n (%)	
Yes	177 (24.6)
No	543 (75.4)
Household characteristics	
Below food poverty level (R386/month per capita)	
Yes	439 (61.0)
No	281 (39.0)
Food security	
High	411 (57.1)
Low or Very low	309 (42.9)

Totals may not add to 720 due to missing data.

Percentages may not add to 100% due to rounding

Table 2.

Maternal peripartum serum DDT/E (ng/g, lipid-adjusted) and urinary pyrethroid metabolite (ug/L, specific-gravity adjusted) concentrations among VHEMBE study participants, Limpopo, South Africa, 2012–2013.

						Percentile						
	n	**% Detected**[a]	**% Quantifiable**[b]	**GM**[c]	**± GSD**[d]	**Min**	**10**	**25**	**50**	**75**	**90**	**Max**
p,p'-DDT	720	98.1	90.6	69.3	± 6.7	<LOD	7.8	18.6	55.2	261.1	947.0	15027.6
p,p'-DDE	720	100.0	97.2	289.2	± 4.9	4.0	44.5	92.3	243.2	878.3	2612.1	26301.3
o,p'-DDT	720	90.4	43.3	9.0	± 4.7	<LOD	1.5	3.4	7.1	22.8	72.7	2029.3
o,p'-DDE	720	82.8	16.0	4.1	± 2.7	<LOD	<LOD	2.3	1.2	6.9	13.6	117.5
cis-DBCA	712	100	99.6	0.346	± 3.048	0.017	0.084	0.158	0.318	0.736	1.481	13.393
cis-DCCA	712	100	99.9	0.479	± 2.560	0.051	0.152	0.261	0.462	0.789	1.477	209.488
trans-DCCA	712	100	99.6	0.557	± 3.074	0.032	0.141	0.266	0.535	1.050	2.350	268.945
3-PBA	711	100	100	1.118	± 2.392	0.103	0.399	0.656	1.050	1.851	3.192	102.383
4-F-3-PBA	687	12.7	8.0	--[e]	--[e]	<LOD	<LOD	<LOD	<LOD	<LOD	0.017	0.517

[a] Limits of detection are 0.01 ng/g serum for *p,p'*-DDT, *o,p'*-DDT, and *o,p'*-DDE; 0.03 ng/g serum for *p,p'*-DDE; and 0.0025 ug/L for *cis*-DBCA, 0.0045 ug/L for *cis*-DCCA, 0.0038 ug/L for *trans*-DCCA, 0.0047 ug/L for 3-PBA, and 0.005 ug/L for 4-F-3 PBA.

[b] Limits of quantification are 0.05 ng/g serum for *p,p'*-DDT, *o,p'*-DDT, and *o,p'*-DDE; and 0.15 ng/g for *p,p'*-DDE; 0.0082 ug/L for *cis*-DBCA, 0.015 ug/L for *cis*-DCCA, 0.013 ug/L for *trans*-DCCA, 0.016 ug/L for 3-PBA, and 0.011ug/L for 4-F-3 PBA.

[c] Geometric mean.

[d] Geometric standard deviation.

[e] Geometric mean and standard deviation not computed due to the low detection frequency.

Table 3.

Associations between peripartum maternal serum DDT/E and urinary pyrethroid concentrations and neonatal thyroid hormone levels among VHEMBE study participants, Limpopo, South Africa, 2012–2013.[a]

	All	Boys	Girls	p_{int}[d]
TSH[b]				
p,p'-DDT	1.4% (−3.7, 6.4)	0.5% (−7.7, 9.1)	1.8% (−4.8, 9.0)	0.810
p,p'-DDE	−0.2% (−6.5, 6.3)	−0.2% (−8.8, 9.5)	−1.1% (−9.3, 7.4)	0.938
o,p'-DDT	3.0% (−3.2, 9.5)	1.9% (−7.0, 11.9)	3.2% (−5.1, 12.2)	0.812
cis-DBCA	10.6% (0.5, 20.9)*	4.5% (−9.2, 19.6)	18.2% (2.1, 36.0)*	0.228
cis-DCCA	11.7% (−0.4, 24.0)	6.4% (−9.4, 23.6)	17.8% (0.6, 37.8)*	0.338
trans-DCCA	12.3% (3.0, 23.3)*	9.5% (−2.7, 24.2)	16.0% (0.7, 33.7)*	0.55
3-PBA	14.0% (0.5, 30.2)*	8.5% (−8.3, 33.9)	22.2% (1.6, 44.6)*	0.376
T4[c]				
p,p'-DDT	−0.11 (−0.24, 0.03)	−0.20 (−0.38, −0.03)*	−0.01 (−0.21, 0.19)	0.152
p,p'-DDE	−0.08 (−0.24, 0.08)	−0.17 (−0.38, 0.07)	0.02 (−0.19, 0.24)	0.214
o,p'-DDT	−0.09 (−0.24, 0.07)	−0.27 (−0.47, −0.04)*	0.10 (−0.13, 0.32)	0.016†
cis-DBCA	0.05 (−0.20, 0.28)	0.06 (−0.30, 0.40)	0.07 (−0.28, 0.43)	0.922
cis-DCCA	−0.16 (−0.42, 0.12)	−0.16 (−0.52, 0.22)	−0.16 (−0.54, 0.25)	0.994
trans-DCCA	−0.10 (−0.32, 0.13)	−0.08 (−0.38, 0.24)	−0.12 (−0.46, 0.23)	0.852
3-PBA	−0.05 (−0.32, 0.24)	−0.03 (−0.40, 0.39)	−0.03 (−0.45, 0.39)	0.986

[a] Marginal Structural Models based on propensity scores determined using the Super Learner algorithm.

[b] Estimates show percent change in TSH for each 10-fold increase in maternal peripartum serum DDT/E or pyrethroid metabolite concentration calculated as $(10^{\beta} - 1)*100$.

[c] Estimates show change in mean total T4 (μg/dL) for each 10-fold increase in maternal peripartum serum DDT/E or pyrethroid metabolite concentration.

[d] p_{int} = p-value for interaction term.

* $p<0.05$

† $p_{int}<0.1$

Table 4.

Associations between peripartum maternal serum DDT/E and urinary pyrethroid concentrations and odds of low total T4 among neonates participating in the VHEMBE study, Limpopo, South Africa, 2012–2013[a]

	All	Boys	Girls	p_{int}[b]
p,p'-DDT	0.97 (0.63, 1.47)	1.43 (0.88, 2.32)	0.67 (0.34, 1.16)	0.038†
p,p'-DDE	1.28 (0.83, 1.92)	1.49 (0.82, 2.62)	1.08 (0.60, 1.88)	0.414
o,p'-DDT	1.10 (0.71, 1.63)	1.61 (0.88, 2.84)	0.69 (0.37, 1.10)	0.034†
cis-DBCA	1.20 (0.65, 2.25)	1.36 (0.56, 3.35)	1.06 (0.39, 2.53)	0.722
cis-DCCA	2.04 (0.81, 4.24)	1.65 (0.45, 4.02)	2.72 (0.71, 8.32)	0.532
trans-DCCA	1.84 (0.89, 3.48)	1.43 (0.51, 3.03)	2.63 (0.85, 7.10)	0.368
3-PBA	1.94 (0.82, 4.28)	1.34 (0.48, 3.31)	3.11 (0.75, 11.69)	0.352

[a] Marginal Structural Models based on propensity scores determined using the Super Learner algorithm. Estimates show relative changes in the odds of low T4 for a 10-fold increase in DDT/E or pyrethroids.

[b] p_{int} = p-value for interaction term.

* $p<0.05$

† $p_{int}<0.1$