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Association between prenatal exposure to multiple insecticides and child body weight and body composition in the VHEMBE South African birth cohort

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ABSTRACT

Background: Pregnant women may be co-exposed to multiple insecticides in regions where both pyrethroids and dichlorodiphenyltrichloroethane (DDT) are used for indoor residual spraying (IRS) for malaria control. Despite the potential for adverse effects on offspring, there are few studies in areas where IRS is currently used and little is known about the effects of pyrethroids on children's health.

Methods: We investigated the relationship between concentrations of four urinary pyrethroid metabolites in urine and organochlorine pesticide concentrations in maternal blood collected near delivery on body weight and body composition among children ≤2 years old participating in the prospective South Africa VHEMBE birth cohort (N = 708). We used measurements of length/height and weight collected at 1 and 2 years of age to calculate body mass index (BMI)-for-age, weight-for-age, and weight-for-height z-scores based on World Health Organization standards. We fit separate single-pollutant mixed effects models for each exposure of interest and also stratified by sex. We also fit all analyte concentrations jointly by using a Bayesian kernel machine regression (BKMR) statistical method to assess variable importance of each analyte and to explore the potential for joint effects of the multiple exposures.

Results: Single-pollutant linear mixed effects models showed that, among girls only, *p,p′*-DDT was associated with higher BMI-for-age (adjusted [a]β = 0.22 [95% CI: 0.10, 0.35]; sex interaction p-value = 0.001), weight-for-height (aβ = 0.22 [95% CI: 0.09, 0.34]; sex interaction p-value = 0.002), and weight-for-age (aβ = 0.17 [95% CI: 0.05, 0.29], sex interaction p-value = 0.01). Although single-pollutant models suggested that *p,p′*-DDT and dichlorodiphenyldichloroethylene (*p,p′*-DDE) were also associated with these outcomes in girls, *p,p′*-DDE was no longer associated in multi-pollutant models with BKMR. The pyrethroid metabolites *cis*-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylicacid (*cis*-DBCA) and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*trans*-DCCA) were inversely related to BMI-for-age and weight-for-height overall; however, results suggested that weight-for-age and weight-for-height associations for *trans*-DCCA (sex interaction $\text{p-value}_{\text{weight-for-age}} = 0.02$; $\text{p-value}_{\text{weight-for-height}} = 0.13$) and *cis*-DCCA (sex interaction $\text{p-value}_{\text{weight-for-age}} = 0.02$; $\text{p-value}_{\text{weight-for-height}} = 0.08$) were strongest and most consistent in boys relative to girls. BKMR also revealed joint effects from the chemical mixture. For instance, with increased concentrations of *p,p′*-DDE, the negative exposure-response relationship for *cis*-DBCA on BMI-for-age became steeper.

Conclusions: Our single-pollutant and multi-pollutant model results show that maternal serum *p,p′*-DDT concentration was consistently and positively associated with body composition and body weight in young girls and that maternal urinary pyrethroid metabolite concentrations (particularly *cis*-DBCA and *trans*-DCCA) were negatively associated with body weight and body composition in young boys. Joint effects of the insecticide exposure mixture were also apparent, underscoring the importance of using advanced statistical methods to examine the health effects of chemical mixtures.

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1. Introduction

Low- and middle-income countries in sub-Saharan Africa are undergoing rapid development and urbanization. This rapid transition is bringing with it a 'double burden' of co-existing malnutrition (defined by stunting/underweight) and overweight/obesity epidemics, which according to the World Health Organization (WHO), represent a growing public health threat to the African sub-continent (WHO, 2016a). Children under 5 years of age from the southern Africa sub-region have a higher prevalence of overweight (weight-for-height + 2 standard deviations (SD) of WHO growth standards (WHO, 2012)) than all other sub-regions in the world in this age group (WHO, 2016b), with prevalence being particularly high among girls (Pienaar, 2015; Sartorius et al., 2015). The prevalence of underweight (weight-for-height − 2SD of WHO growth standards (WHO, 2012)), at 10% (WHO, 2016b), is high as well and is higher in South African boys compared to girls (Kimani-Murage et al., 2010; Kruger, 2014).

Early-life exposure to endocrine disrupting chemicals (EDCs) has been hypothesized to play a role in the increasing rates of overweight and obesity globally (Braun, 2016; Chevalier and Fénichel, 2016). Indoor residual spraying (IRS), which involves the application of insecticides, such as dichlorodiphenyltrichloroethane (*p,p′*-DDT) or pyrethroids, on walls, ceilings and eaves of residences, is currently used for mosquito control in most malaria-endemic areas, including South Africa (Maharaj et al., 2016; van den Berg, 2009). In vitro studies show that both *p,p′*-DDT and its breakdown product, dichlorodiphenyldichloroethylene (*p,p′*-DDE), promote adipocyte cell growth, differentiation and/or dysfunction (Howell and Mangum, 2011; Kim et al., 2016; Moreno-Aliaga and Matsumura, 2002). *p,p′*-DDT is a strong agonist of estrogen (Shekhar et al., 1997), which is known to be involved in deposition, differentiation, and metabolism of adipose tissue (Pallottini et al., 2008), and *p,p′*-DDE demonstrates both anti-androgen and estrogenic activity (Kelce et al., 1995; Sohoni, 1998). Emerging evidence from in vitro and in vivo studies also show that IRS pyrethroids and their metabolites may be EDCs (Brander et al., 2016), suggesting that pyrethroids may also play a role in impacting child body composition.

Several epidemiologic studies have shown that prenatal measures of exposure to DDE is associated with higher body weight and body mass index (BMI) in children, and that these positive associations may be sex-specific (Agay-Shay et al., 2015; Delvaux et al., 2014; Heggeseth et al., 2015; Iszatt et al., 2015; La Merrill and Birnbaum, 2011; Lee et al., 2011; Tang-Peronard et al., 2014; Vafeiadi et al., 2015; Valvi et al., 2011, 2015; Verhulst et al., 2009; Warner et al., 2014). However, other studies did not observe an association (Cupul-Uicab et al., 2010, 2013; Garced et al., 2012; Gladen et al., 2004; Høyer et al., 2014; Karlsen et al., 2016; Tang-Peronard et al., 2014; Warner et al., 2013) or have observed a sex-specific inverse association (de Cock et al., 2014). Most studies have occurred in middle- or high-income countries usually when DDT was no longer in use. In addition, no published epidemiologic studies have investigated associations between prenatal pyrethroid exposure and body weight or body composition in childhood nor investigated associations between joint prenatal exposure to DDT/E *and* pyrethroids, which is especially relevant in the IRS context where co-exposures to these insecticides are likely to occur (Bouwman et al., 2006).

In the present study, we investigated associations between biomarker concentrations of DDT and DDE and pyrethroid metabolites in mothers near delivery in relation to body weight and body composition in their children at 1- and 2-years, in a longitudinal birth cohort in Limpopo, South Africa. We also explored the joint effects of exposure to both classes of insecticides using a multipollutant Bayesian statistical method (Bobb et al., 2015; Coker et al., 2017; Valeri et al., 2017). We have previously shown in this cohort that IRS-treated homes have higher dust contamination of DDT and DDE which are related to higher maternal serum levels (Gaspar et al., 2015).

2. Methods

2.1. Study participants and data collection

Data came from the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE) study, a longitudinal birth cohort of mother-child pairs living in the Vhembe district of South Africa's Limpopo Province. We recruited pregnant women presenting with signs of labor at Tshilidzini hospital, in the city of Thohoyandou between 2012 and 2013. Women were eligible if they were ≥18 years of age, lived in a home where the primary spoken language was Tshivenda, lived < 20 km from the hospital, had no intention of moving away from the area during the following 2 years, had no malaria diagnosis during pregnancy, had contractions more than 5 min apart, and delivered a live singleton infant. Of the 1649 women approached for participation in the study, 920 were eligible and 752 were enrolled. Of the children enrolled, 3.2% (n = 24) died by the 2nd year follow up (4 died within the first week of life, 13 died between delivery and 1 year, and 7 died between 1 and 2 years). Finally, a total of 708 children had anthropometric measures taken during at least one or both follow-up visits conducted around ages 1- and 2-years. The sample that did not complete anthropometric measurements at both visits (N = 44) were similar to the final study population on socio-demographic factors. Maternal written consent was obtained before participant enrollment and human subject research was approved by the Institutional Review Boards at the University of California, Berkeley, McGill University, the University of Pretoria, the Limpopo Department of Health and Social Development, and the Ethics Committee of Tshilidzini Hospital.

Shortly after delivery and at each follow-up visit, the mother or primary caretaker was interviewed using a structured questionnaire administered in Tshivenda (the local language) by bilingual interviewers. We collected information on household and maternal socio-demographic characteristics, and maternal and child health. Maternal and pediatric medical records were also abstracted for important indicators of maternal and child health (e.g., prescription of anti-retroviral therapy for HIV). At the initial interview, the mother's height and weight were measured, and the mother's weight was obtained at each subsequent visit. Birthweight was measured in the hospital using a digital neonatal scale (Tanita BD-815U scale, Arlington Heights, Il, USA) and weight measures were made at the 1- and 2-year visits using a pediatric digital scale (Tanita BD-590 Pediatric Scale). Infant length was measured in the hospital soon after birth and at the 1-year visit using a portable infantometer (Seca 417 Measuring Board, Chino, CA, USA) and height at the 2-year visit using a stadiometer (Seca 213 Measuring Board). Triplicate height measures were averaged for each time point. Weight-for-age z-scores, weight-for-height z-scores, and BMI-for-age z-scores were calculated for 1- and 2-year visits using the WHO reference weight growth curves by age (in days) and sex (WHO, 2011). BMI was calculated by dividing each child's weight measurement by the square of the length or height measurement (kg/m^2).

2.2. Exposure assessment of DDT/E and pyrethroids

Blood samples were collected from mothers by study nurses either just before (N = 595) or soon after delivery (N = 157). Each blood sample was divided into clot and serum and stored at −80 °C in the study's field office freezer on hospital grounds. Serum aliquots of 2 mL each were placed on dry ice and shipped to Emory University (Atlanta, GA) for analysis of *p,p′*-DDT/E and *o,p′*-DDT/E by high resolution gas chromatography-isotope dilution mass spectrometry (GC–MS) (Barr et al., 2003). DDT and DDE concentrations were expressed on a lipid basis (ng/g lipid) for statistical analysis purposes. DDT/E analytes required a lipid-adjustment to account for differences in partitioning in tissue of these analytes based on variation in lipid levels (Meeker et al., 2007). Triglycerides and cholesterol concentrations were measured in serum samples using standard enzymatic techniques (Roche Chemicals,