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Marie-Véronique Poirier 4/19/2022
Date

Association of Prenatal Chlorpyrifos Exposure and Birth Weight in a Thai Birth Cohort Study

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in the Gangarosa Department of Environmental Health
2022

Abstract

Association of Prenatal Chlorpyrifos Exposure and Birth Weight
in a Thai Birth Cohort Study

By Marie-Véronique Poirier

Intro: Organophosphate (OP) pesticides are among the most commonly used insecticides worldwide. Though exposure is ubiquitous, developing fetuses and young children are known to be particularly vulnerable to toxic environmental exposures, with the potential for lifelong health consequences. Previous studies have identified agricultural regions in northern Thailand as particularly high risk for OP exposure. Accordingly, the Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE) was established in 2017 in the Chiang Mai province of northern Thailand, with the aim to evaluate prenatal insecticide exposures in relation to both birth outcomes and neurodevelopment in children. Using this dataset, this study specifically focuses on the association between maternal levels of TCPy (a urinary metabolite specific for the OP pesticide chlorpyriphos) and the primary outcome of birth weight, while evaluating the role of paroxonase 1 (PON1) phenotype as an effect modifier.

Methods: Participants were recruited between July 2017 and June 2019 in the Fang and Chom Thong districts of Chiang Mai province, Thailand. Women who met inclusion criteria were identified during routine antenatal care visits at hospitals or local health clinics, and 394 participants were ultimately enrolled (334 completed the study). Data collected included maternal questionnaire data, trimester-specific serum/urine analysis, and birth outcome measurements. Data analysis was conducted using SAS studio, using linear regression techniques to create trimester-specific and summary models describing the exposure-outcome relationship. Variable selection for the final model was determined using directed acyclic graphs (DAGs).

Results: Based on our DAG, several factors were identified as potential confounders between the exposure and outcome and were therefore controlled for in our linear regression models. Overall, we did not observe a statistically significant linear relationship between TCPy and birth weight.

Discussion: The strategy for variable selection used in this study avoids pitfalls associated with selecting variables based on statistical significance alone. While our study does not suggest a linear relationship, a non-linear relationship between TCPy and PON1 may be plausible. Further studies - perhaps evaluating a different DAG, and accounting for different covariate interactions - are needed to clarify the potential risks of chlorpyriphos exposure in this population.

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Acknowledgements

Thank you to my mentor, Dr. Dana Barr, as well as the countless people at Rollins School of Public Health and Emory School of Medicine (faculty and peers alike) who have taught me so much over the past few years. I am so thankful for what this institution has given me, and for the people I have met here – I look up to so many of you, both personally and professionally. This education has meant so much to me and will forever influence my career and future practice for the better.

A special thank you to my family (Maman, Papa, Jean-Samuel, Noah, and Pascal) and my partner in medicine, etc., Tanner McMahon, who helped me get through medical school and a (mostly) virtual global health degree during a global pandemic. I would not have made it through this strange and important time without your support.

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Introduction:

Organophosphate Pesticides and Impacts on Fetal Growth and Development

Organophosphate (OP) pesticides are some of the most used insecticides worldwide, despite a large body of evidence linking these compounds to serious adverse health impacts. Though exposure may be ubiquitous, impact is not equally distributed - developing infants and young children are known to be particularly vulnerable to environmental toxicants, with the potential for lifelong health consequences. Many studies conducted in a variety of settings have provided data for impaired fetal neurodevelopment and growth in cases of in-utero exposure to organophosphate compounds, with specific effects on birth weight, birth length, head circumference, gestational age at birth, and appropriate cognitive/behavioral development in childhood (Balalian et al., 2021; Beranger et al., 2020; Berkowitz et al., 2004; Bommarito et al., 2021; Cecchi et al., 2021; Ferguson et al., 2019; Fiedler et al., 2015; Fortenberry et al., 2014; Hoffman et al., 2018; Huang et al., 2017; Jaacks et al., 2019; Kalloo et al., 2020; Luo et al., 2020; Marsillach et al., 2016; Moreno-Banda et al., 2009; Naksen et al., 2015; Perera et al., 2003; Petit et al., 2010; Rauch et al., 2012; Rauh et al., 2011; Silver et al., 2018; Wang et al., 2012; Whyatt et al., 2004; Wolff et al., 2007). Contrary to these findings, however, several studies failed to find a significant or consistent association between OP pesticide exposure and these outcomes (Dalsager et al., 2018; Eskenazi et al., 2004; Eskenazi et al., 2007; Harley et al., 2016; Khoshhali et al., 2020; Kuiper et al., 2020; Wang et al., 2012). Thus, while the consensus remains that these substances pose a threat to human health and child development, the mechanisms underlying the connection between OP exposure and birth outcomes has yet to be clarified. Abnormalities in anthropomorphic birth measures are a major predictor of infant morbidity and mortality and may be predictive of health issues in childhood and beyond –

including the development of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), diabetes, renal disease, and cardiovascular disease (Eves et al., 2021; Franz et al., 2018; Widyawati et al., 2020). Given these and other potentially severe downstream effects, it is of utmost importance that associated risks are adequately characterized and mitigated.

PON1 Phenotype and Fetal Susceptibility

Inconsistencies across studies evaluating OPs and birth outcomes thus far may be related the ubiquity of pesticide residues and difficulty accounting for total exposure. Further, unique social, geographic, biologic, and metabolic factors may influence susceptibility in any given individual and may fluctuate over time. One such factor associated with differential vulnerability to toxic effects is activity of the paroxonase 1 (PON1) enzyme, which mediates the hydrolysis of some OP pesticides into their respective metabolites (Naksen et al., 2015). Several studies have shown a significant relationship between in-utero OP exposure and impaired fetal growth in the setting of slow-type maternal (or in some cases, infant) PON1phenotype (Harley et al., 2011; Marsillach et al., 2016; Moreno-Banda et al., 2009; Naksen et al., 2015; Rauch et al., 2012; Wolff et al., 2007). The modifying effect of PON1 polymorphisms therefore remains an active area of consideration in evaluating this complex exposure outcome relationship.

Chlorpyriphos and Regulatory Status

Briefly, the OP pesticide Chlorpyriphos has surfaced as an agent of particular concern due to its widespread use and accumulating data suggesting the potential for neurodevelopmental harm. Several studies have evaluated adverse birth effects associated with Chlorpyriphos, specifically (Balalian et al., 2021; Berkowitz et al., 2004; Chiu et al., 2021; Fortenberry et al., 2014; Marsillach et al., 2016; Perera et al., 2003; Rohitrattana, Siriwong, Tunsaringkarn, et al., 2014; Silver et al., 2018; Whyatt et al., 2004). Many nations have moved towards either strict

regulation or complete ban of this insecticide. Following years of failure to ban Chlorpyriphos, the United States Environmental Protection Agency (US EPA) released a final rule in August 2021 that it would revoke all tolerances for chlorpyriphos residues on food products (U.S.EPA, 2021). Related to this study, the Thai FDA established a maximum residue limit (MRL) of zero for the pesticides paraquat and chlorpyrifos on all imported food products starting on June 1, 2021, in compliance with the National Hazardous Substance Committee's vote to ban the two chemicals in November 2019 (Prasertsri, 2020).

Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE)

OP pesticide exposure is especially prevalent in developing countries where agriculture comprises a large fraction of national GDP, and previous studies have identified agricultural regions in northern Thailand as particularly high risk (Fiedler et al., 2015; Naksen et al., 2015; Panuwet, Prapamontol, Chantara, & Barr, 2009; Panuwet, Prapamontol, Chantara, Thavornyuthikarn, et al., 2009; Panuwet et al., 2008; Panuwet et al., 2012; Rohitrattana, Siriwong, Robson, et al., 2014; Rohitrattana, Siriwong, Tunsaringkarn, et al., 2014; Woskie et al., 2017). Concern regarding pesticide exposures in this region has increased over time; until recently, use of these substances has been poorly regulated, while the agricultural sector and demand for insecticide has expanded (Panuwet et al., 2012). The Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE) was established in 2017 in the Chiang Mai province of northern Thailand, with the aim to evaluate prenatal insecticide exposures in relation to both birth outcomes and neurodevelopment in children (Naksen et al., 2015). Using this cohort data, we aim to specifically assess the relationship between maternal levels of TCPy (a common biomarker for chlorpyriphos) and the primary

outcome of birth weight, while evaluating the role of paroxonase 1 (PON1) phenotype as an effect modifier. We hypothesize that TCPy levels will be inversely associated with birth weight, and that this relationship will be exacerbated in mothers with slow type PON1 metabolism.

Methods:

Study Location

Chiang Mai Province, Thailand, was selected as the study location for both its reliance on agriculture as a major contributor to the local economy and generalizability to other similarly agricultural low-middle income countries (LMIC) (Baumert, 2022). Two districts with distinct pesticide application scenarios, Fang and Chom Thong, were identified as recruitment sites for the purpose of comparison. Tangerines, requiring high intensity, short duration pesticide application, are the predominant crop in Fang. Contrarily, Thom Chong crops - including longans, cut-flowers, vegetables, and rice - require low intensity, longer duration pesticide application.

Study Participants

Details regarding the study population are published in Baumert et. al., 2022. Briefly, participants for the SAWASDEE longitudinal birth cohort study were recruited between July 2017 and June 2019 in the Fang and Chom Thong districts of Chiang Mai province, Thailand. All procedures were reviewed and approved by the Institutional Review Board at Emory University (with Rutgers reliance) and the Ethics Review Committee at the Research Institute for Health Sciences, Chiang Mai University (with Chulalongkorn reliance), and informed consent was obtained from all participants prior to enrollment in the study. A total of 1298 women were screened during routine antenatal care visits at hospitals or local health clinics, and 394 participants were ultimately enrolled based on eligibility criteria. There was sufficient data from

334 women-child pairs for this analysis evaluating the relationship between TCPy levels and birth weight. Concerning eligibility criteria, enrolled women "(1) were agricultural workers or lived within 50 m of an agricultural field; (2) had a Thai identification card permitting hospital and antenatal clinic access; (3) resided in their regional district for ≥6 months and planned residence at least three years after delivery, (4) spoke Thai language at home, (5) were in good general health (i.e., no major medical conditions such as hypertension, diabetes, thyroid disease, HIV), (6) consumed fewer than two alcoholic beverages (beer, wine, liquor) per day and did not use illegal drugs, (7) were <16 weeks of gestation, and (8) were 18–40 years of age" (Baumert, 2022). Expectant mothers with complicated pregnancies, including multiple gestation, were excluded at the time of diagnosis. Follow up of child neurocognitive outcomes is ongoing.

Of note, previous analyses of this dataset have elucidated significant differences between women in Fang and Chom Thong. Crops and associated agricultural tasks were dependent on location as described above. More women also endorsed being legally married (as opposed to living as married) in Chom Thong as compared to Fang. Finally, women in Chom Thong reported greater education and literacy rates, with approximately 95% of women reporting that they could read in Thai compared to 50% than those in Fang. Mean gestational age at birth and mean birth weight were similar between locations (Baumert et al., 2022).

Data Collection

Data collection and processing for this study – including maternal questionnaire data, maternal serum analysis, maternal urinalysis, cord blood analysis, enzyme assays, and birth outcome measurements - are discussed extensively elsewhere (Baumert, 2022). Of note, information including general demographic data (age, ethnicity, income, education), location, maternal height and weight, infant sex, previous birth history, maternal TCPy, maternal

creatinine, paraoxonase 1 phenotype, and birth outcome measurements were abstracted from the larger data set for the purposes of this analysis.

Measurement of TCPy, Creatinine, and PON1

Composite urine samples of equal volumes were collected in early, mid, and late pregnancy (roughly corresponding to trimester), and randomized prior to analysis using a Fisher-Yates shuffling algorithm (Fisher, 1948; Knuth, 1969). Samples were analyzed for 3,5,6-trichloro-2-pyridinol (TCPy), a metabolite specific for OP insecticides chlorpyrifos and chlorpyrifos methyl based on a previously validated method described by Olsson et. al. (Olsson et al., 2004). Creatinine was measured by diluting urine samples 1000-fold with water after spiking with its isotopically labeled analogue. Diluted samples were analyzed by liquid chromatography electrospray ionization coupled with tandem mass spectrometry using a previously validated method (Kwon et al., 2012).

In terms of PON1 phenotype, plasma from maternal venous blood was assayed for PONase and AREase activities using a method by Huen et. al. (Huen et al., 2009). Individual PON1 phenotype was determined using the ratio of salt-stimulated PONase activity to AREase activity from Eckerson et. al. (Eckerson et al., 1983). After averaging intra-person data for enzyme activity, the data was plotted and separated into three PON1 phenotypes of low (AA), middle (AB) and high (BB) activity - related to QQ, QR and RR genotypes, respectively, at codon192 of PON1 (Humbert et al., 1993).

Statistical Analysis

Data analysis was conducted with SAS studio, using linear regression techniques to create trimester-specific and summary models describing the exposure-outcome relationship. Variable selection was determined using directed acyclic graphs (DAGs), constructed with a

publicly available software ("DAGitty") for analyzing causal diagrams (Textor et al., 2016)**.** Using a DAG allows for clarification of how adjustment for a given covariate might impact bias, by providing visualize assumptions about the statistical relationships between the exposure, outcome, and covariates in question (Diemer et al., 2021). The structure and benefits of DAGs are discussed extensively elsewhere in the literature (Diemer et al., 2021; Textor et al., 2016; Williams et al., 2018). From an initial conceptual diagram showing all potential associations, the DAG was simplified to better facilitate analysis of causal relationships, based on data availability and the observed characteristics and/or relationships between variables within our specific dataset (figure 1). Variables were eliminated for any of the following reasons: 1) the effect of a particular variable (i.e. a mediator) was already accounted for by the presence of another measured factor in the model, 2) no significant variability was observed between responses for a given variable, 3) significant collinearity was observed between one or more variables, allowing one to act as a proxy for the others, 4) a proxy variable was used for an unmeasured variable, and 5) the information of interest was not available in the obtained dataset. Of note, creatinine and TCPy were analyzed as natural log transformed variables to ensure normal distribution. Where relevant, linear correlation tests (continuous vs continuous variable), T test/ANOVA (continuous vs categorical variable), and Chi Square Test of Association (categorical vs categorical variable) were used to explore relationships between variables and assist with exclusion vs inclusion in the simplified DAG.

Results:

Our simplified DAG highlighted several possible confounders creating biasing pathways between maternal chlorpyriphos exposure (urinary TCPy) and birth weight. Those factors identified as confounders were included in the linear regression model, while factors identified as possible mediators of the exposure outcome relationship (i.e. gestational age) based on available literature were excluded. Concerning the latter, it is thought that conditioning on a mediator closes one of the causal paths between the exposure and outcome, thus distorting the relationship

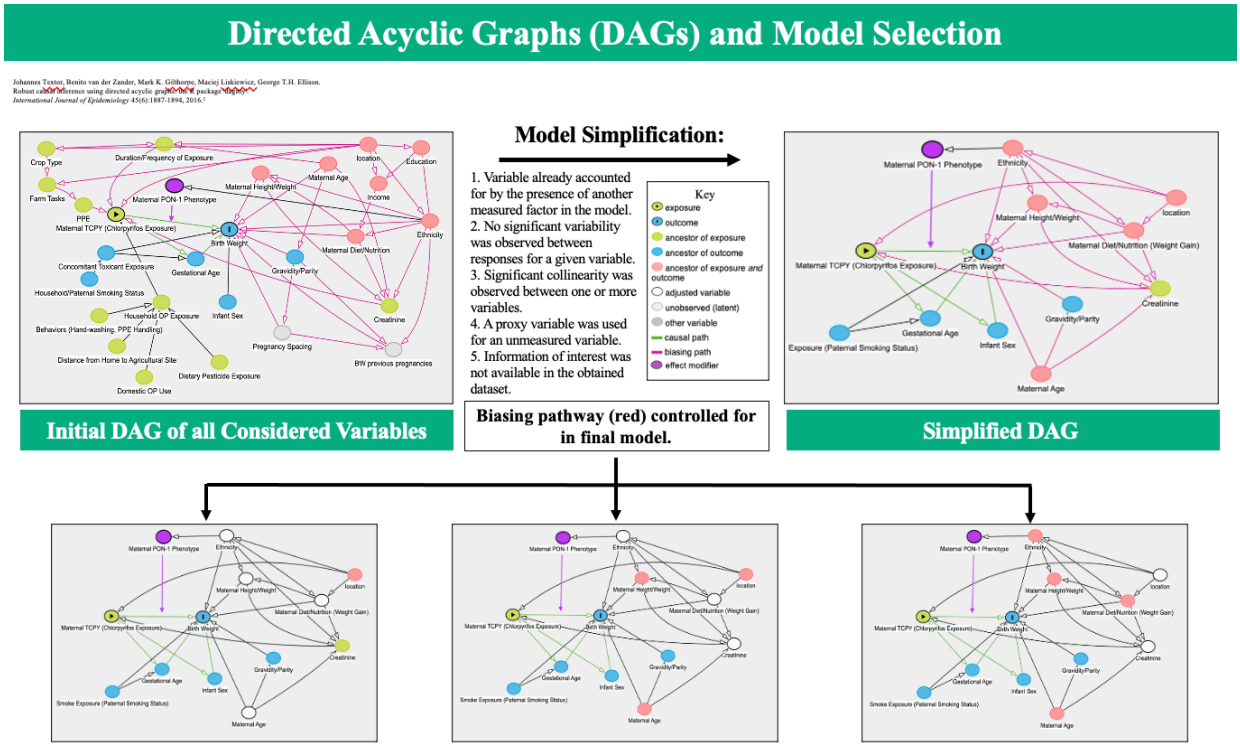

Figure 1, Directed acyclic graphs and the process of model selection: The figures above demonstrate the process from initial DAG construction to a simplified model for examining the relationship between maternal TCPy (exposure) and birth weight (outcome). This process is helpful for identifying potential confounders which open a "back door" or biasing pathway between the exposure and outcome of interest, so that they may be adjusted for in the regression model.

(Diemer et al., 2021; Williams et al., 2018). Based on our DAG, several covariates which may confound the exposure-outcome relationship may also be considered colliders of upstream

variables. While adjusting for colliders is generally considered unfavorable due to the risk of introducing collider bias, we did adjust for colliders in this model where there was a joint concern for confounding. While all identified confounders were included, use of additional covariates was limited to minimize overall variability and reduce the risk of overfitting in the final model. The following equation demonstrates the general model used, with an interaction term representing the modifying effects of PON1 on TCPy:

$$\underline{\textit{Birth Weight}} = \beta_0 + \beta_1 \textit{Ln TCPy} + \beta_2 \textit{TCPy*PON1} + \beta_3 \textit{Ethnicity} + \beta_4 \textit{Location} + \beta_5 \textit{Maternal Ht} + \beta_6 \textit{Maternal Wt} + \beta_7 \textit{Maternal Wt Gain} + \beta_8 \textit{Maternal Age} + \beta_9 \textit{Ln Creatinine}$$

Summary Model (n=292)	
Adjusted R-Sq	*0.01*
F Value	*1.18*
Pr > F	*0.29*
First Trimester (n=274)	
Adjusted R-Sq	*0.01*
F Value	*1.21*
Pr > F	*0.27*
Second Trimester (n=289)	
Adjusted R-Sq	*0.02*
F Value	*1.43*
Pr > F	*0.14*
Third Trimester (n=289)	
Adjusted R-Sq	*0.01*
F Value	*1.2*
Pr > F	*0.28*

Table 1, Summary Statistics: Adjusted R^2 values, F values, and Pr >F values for each of our four models (summary and trimester- specific). Statistical significance was established as $p < 0.05$ for all models. The adjusted R^2 values here approach zero, suggesting that essentially none of variance in the outcome can be predicted from the independent variables included in the model.

Overall, we did not observe a statistically significant (defined as $p < 0.05$) linear relationship between maternal TCPy and birth weight, and F values were similar across the summary and trimester-specific models (Table 1). Notably, the adjusted R^2 values all approach zero, suggesting that the independent variables included in the model do not predict the variance in the outcome. Holding all other covariates constant, maternal weight at first clinical visit was statistically significantly associated with birth weight, both in the summary and trimester-specific models; however, the parameter estimates (<0.01) suggest that the contribution is negligible (appendix 1). No other statistically significant relationships were observed (see appendix for parameter estimates and related p values).

Discussion:

This study has several unique strengths; mainly, that a conceptual approach to model building avoids pitfalls associated with relying on statistical significance for the purpose of variable selection (as in forward or backward selection, for example). Additionally, the overall response rate was relatively high given the circumstances of the study location (rural terrain with transportation challenges) and required level of participation (longitudinal study demanding multiple, time-intensive visits). Finally, the dataset utilized for this analysis is robust in terms of targeting both clinical and qualitative data. Many of the variables we identified as important in our DAG were directly or indirectly measured in this population.

This study also has several important limitations. While participant engagement was relatively high, not all data points could be collected for every participant; those without recorded TCPy or birth weight data (or with missing covariate data) were excluded from the analysis, introducing the possibility of information bias. For example, roughly twice as many patients were included from Chom Thong versus Fang (223 and 109, respectively) at the beginning of the analysis, and the results may have been skewed further as covariates were added to each model. In another example, fewer individuals with slow-type PON1 phenotype were captured in the data (n=29), perhaps underestimating the effect on TCPY and birth weight. Alternative handling of missing data could potentially reduce these biasing effects.

Additionally, while a robust dataset was available for use in this study, not all variables of interest could be measured. In some instances, proxy measurements (i.e. maternal weight gain as a proxy for nutrition) could be used, which may or may not have adequately captured the target covariate. While every attempt was made to account for the complex web of factors possibly contributing to the exposure, outcome, and/or exposure-outcome relationship in this

observational study, the influence of unmeasured confounders cannot be excluded. We favored a relatively simple statistical approach for this study, which did not account for all possible interactions between covariates; for example, infant sex has been described as an effect modifier in previous studies (Crawford et al., 2020). While the results do not suggest a linear relationship between these specific variables, a non-linear association may be plausible. There are limitations inherent to using DAGs, notably that they remain qualitative in nature and cannot describe the size of associations between variables (Williams et al., 2018). Finally, it is difficult to know whether an alternative DAG may ultimately be truer to the underlying relationships in this dataset.

Conclusion:

While substantial literature exists supporting the potential adverse effects of OP pesticide exposure on various birth outcomes, our linear models demonstrated no significant association between TCPy and birth weight, including with PON1 phenotype as an effect modifier. This study, however, offers a conceptual groundwork for future studies using this dataset (or similar exposure data), perhaps using an alternative DAG and/or analytical approach. Further studies characterizing the potential widespread harms of OP pesticides and other neurotoxic chemicals – especially in vulnerable populations – are crucial for supporting public health interventions and legislative action on a global scale.

Acknowledgements:

The SAWASDEE Birth Cohort Study was designed and assembled by Barr-Ryan Laboratory, in collaboration with researchers at Chulalongkorn University (CU) in central Thailand and Chiang Mai University (CMU) in northern Thailand. Numerous students and faculty at Rollins School of Public Health and abroad worked to collect, assemble, and analyze

the reference data on which this project is based. Finally, much is owed to the women and families of Northern Thailand who agreed to participate in this longitudinal cohort study. None of this would be possible without their continued enthusiasm and participation.

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Appendix:

Parameter	DF	Estimate	StandardError	t Value	Pr > |t|
Summary Model					
Intercept	1	2.333122	0.711983	3.28	0.0012
AvglnTCPY	1	0.021669	0.046038	0.47	0.6382
Mat_Age	1	-0.000545	0.004908	-0.11	0.9116
Mat_Height	1	-0.000255	0.004692	-0.05	0.9567
CRV1_Weight	1	0.008337	0.002552	3.27	0.0012
Wt_Gain	1	0.006143	0.005104	1.2	0.2298
LnAvgCr	1	0.023789	0.072176	0.33	0.7419
Location 1	1	0.06773	0.098102	0.69	0.4905
Location 2	0	0	.	.	.
Ethnicity 1	1	0.018298	0.160836	0.11	0.9095
Ethnicity 2	1	0.07799	0.158601	0.49	0.6233
Ethnicity 3	1	0.033012	0.139123	0.24	0.8126
Ethnicity 4	1	0.144943	0.237421	0.61	0.542
Ethnicity 5	0	0	.	.	.
AvglnTCPY*PON1 1	1	-0.06581	0.060494	-1.09	0.2776
AvglnTCPY*PON1 2	1	-0.030085	0.031473	-0.96	0.34
AvglnTCPY*PON1 3	0	0	.	.	.
First Trimester Model					
Intercept	1	2.229199	0.734724	3.03	0.0027
Mat_Age	1	-0.000052171	0.005179	-0.01	0.992
Mat_Height	1	-0.00084	0.004876	-0.17	0.8634
CRV1_Weight	1	0.008549	0.002705	3.16	0.0018
Wt_Gain	1	0.005754	0.005356	1.07	0.2837
Location 1	1	0.047298	0.101636	0.47	0.6421
Location 2	0	0	.	.	.
Ethnicity 1	1	0.03508	0.16517	0.21	0.832
Ethnicity 2	1	0.123345	0.163081	0.76	0.4501
Ethnicity 3	1	0.045964	0.140142	0.33	0.7432
Ethnicity 4	1	0.214063	0.241527	0.89	0.3763
Ethnicity 5	0	0	.	.	.
LnT1Cr	1	0.069916	0.049757	1.41	0.1612
LnTCPYT1	1	-0.008137	0.037856	-0.21	0.83
LnTCPYT1*PON1 1	1	-0.085204	0.064796	-1.31	0.1897
LnTCPYT1*PON1 2	1	-0.023121	0.029916	-0.77	0.4403
LnTCPYT1*PON1 3	0	0	.	.	.

Second Trimester Model					
Intercept	1	2.194737	0.707909	3.1	0.0021
Mat_Age	1	-0.000744	0.004808	-0.15	0.8772
Mat_Height	1	0.001772	0.004628	0.38	0.7022
CRV1_Weight	1	0.008756	0.002533	3.46	0.0006
Wt_Gain	1	0.006194	0.005065	1.22	0.2225
Location 1	1	0.081023	0.095626	0.85	0.3976
Location 2	0	0	.	.	.
Ethnicity 1	1	0.010988	0.158689	0.07	0.9448
Ethnicity 2	1	0.074903	0.155607	0.48	0.6306
Ethnicity 3	1	0.041101	0.137631	0.3	0.7654
Ethnicity 4	1	0.139614	0.232177	0.6	0.5481
Ethnicity 5	0	0	.	.	.
LnT2Cr	1	-0.022792	0.063773	-0.36	0.7211
LnTCPYT2	1	0.031555	0.040086	0.79	0.4319
LnTCPYT2*PON1 1	1	-0.075033	0.051013	-1.47	0.1425
LnTCPYT2*PON1 2	1	-0.043036	0.028975	-1.49	0.1386
LnTCPYT2*PON1 3	0	0	.	.	.
Third Trimester Model					
Intercept	1	2.272092	0.695317	3.27	0.0012
Mat_Age	1	-0.001143	0.004875	-0.23	0.8149
Mat_Height	1	0.001517	0.004671	0.32	0.7456
CRV1_Weight	1	0.007683	0.002546	3.02	0.0028
Wt_Gain	1	0.005679	0.005148	1.1	0.2709
Location 1	1	0.076114	0.095619	0.8	0.4267
Location 2	0	0	.	.	.
Ethnicity 1	1	0.021217	0.159207	0.13	0.8941
Ethnicity 2	1	0.059736	0.157217	0.38	0.7043
Ethnicity 3	1	0.031884	0.138184	0.23	0.8177
Ethnicity 4	1	0.123026	0.23129	0.53	0.5952
Ethnicity 5	0	0	.	.	.
LnT3Cr	1	-0.018043	0.056191	-0.32	0.7484
LnTCPYT3	1	0.040005	0.035962	1.11	0.2669
LnTCPYT3*PON1 1	1	-0.07852	0.061139	-1.28	0.2001
LnTCPYT3*PON1 2	1	-0.025549	0.031793	-0.8	0.4223
LnTCPYT3*PON1 3	0	0	.	.	.

Appendix 1, SAS output for parameter estimates: Above lists the parameter estimates and associated p values for the covariates included in each model. The variables are coded as follows: mat_age = maternal age, mat_height = maternal height, CRV1_weight = weight at first

clinical research visit (approximate “baseline” weight in early pregnancy), wt_gain = observed weight gain over pregnancy (weight at last – first clinical research visit), location 1 = Chom Thong, location 2 = Fang, Ethnicity 1 = Thai, Ethnicity 2 = Thai Yai, Ethnicity 3 = Hill Tribes (encompassing Hmong, Karen, Akha, Pa-Long, Yao/Mien, Lahu Na, Lahu Nyi, and Yunan), Ethnicity 4 = Burmese, Ethnicity 5 = Other, LnCr = natural log creatinine, LnTCPY = natural log TCPy, LnTCPY*PON1 = interaction term for TCPy by PON1 phenotype (1,2, and 3 denote phenotypes, with 1 being “slow type” and 3 being “fast type”). T1, T2, and T3 note first, second, and third trimester values, respectively.