Peripubertal Weight Status and Growth: Associations with Preterm Birth and Exposures to Environmental Endocrine-Disrupting Compounds

by

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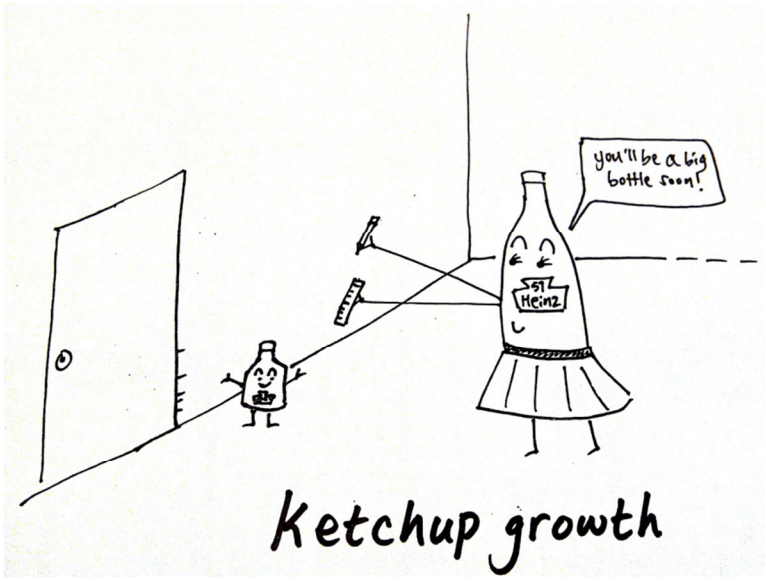

Ketchup growth

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List of Acronyms

AIC – Akaike information criterion

BIC – Bayesian information criterion

BMI – Body mass index

BPA – Bisphenol A

CUG – Catch-up growth

DEHP – Di(2-ethylhexyl) phthalate

EDC – Endocrine-disrupting compound

ER – Estrogen receptor

IOM – Institute of Medicine

MBP – Mono-*n*-butyl phthalate

MBzP – Monobenzyl phthalate

MCPP – Mono(3-carboxypropyl) phthalate

MECPP – Mono(2-ethyl-5-carboxypentyl) phthalate

MEHP – Mono(2-ethyl-5-oxohexyl) phthalate

MEHHP – Mono(2-ethyl-5-hydroxyhexyl) phthalate

MEOHP – Mono(20ethyl-5-oxohexyl) phthalate

MEP – Monoethyl phthalate

MiBP – Mono-isobutyl phthalate

NHANES – National Health and Nutrition Examination Survey

PPROM – Preterm Premature Rupture of the Membranes

SD – Standard deviation

TSH – Thyroid stimulating hormone

WHO – World Health Organization

Abstract

Childhood and adolescent obesity is a global public health issue, with increasing prevalence in developing and industrialized nations. Known to track into adulthood, it is a contributor to numerous adverse health indices including Type 2 Diabetes and cardiovascular disease. Increasing evidence suggests that environmental factors may be involved with weight dysregulation, including altering hormone balance and number, size, and distribution of adipocytes. Exposures or stimuli that occur at sensitive periods of development may alter the growth trajectory of an individual. Preterm birth and exposures to the environmental endocrine-disrupting compounds (EDC) Bisphenol A (BPA) and phthalates are suspected of disrupting numerous physiological processes. Preterm birth is hypothesized to be an adverse stimulus that puts the individual on accelerated growth trajectory. Whereas, exposures to EDCs have been associated with obesity and increased waist circumference.

The objectives of this dissertation were to determine whether preterm birth and exposures to BPA and phthalate metabolites in the third trimester of pregnancy and during adolescence were associated with adolescent weight status, fat distribution, and altered BMI and height trajectories. Using children from the Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) cohorts, we found that preterm birth was not associated with adolescent obesity, BMI, and waist circumference. BPA and phthalate metabolites were non-monotonically associated with adolescent BMI z-score, waist circumference, and triceps skinfold and differed in direction of association by sex as well as timing of exposure. Significant associations of these outcomes were mainly negative and observed in second and third quartile exposures with MECPP, MEHHP, MEOHP, MiBP, MEHP in pregnancy. In adolescence, second and third tertiles of BPA, MCPP, and MiBP were significantly negatively associated with adolescent outcomes. The third tertile of the phthalate metabolite MECPP was associated with the highest trajectory of BMI and height in females, whereas the first and second tertiles of MiBP, MBzP, MCPP, MEP, MEHHP, and MEOHP were associated with the highest BMI and height trajectories in males.

These results suggest that preterm birth is not associated with adolescent anthropometry, but that exposures to EDCs during a developmentally sensitive period may have consequences in growth and fat distribution in peripuberty.

CHAPTER 1

Introduction

Theme

Overweight and obesity continue to be a significant public health issue in adults as well as children (Malik et al. 2012). Increasing evidence suggests that genetics, diet, and physical activity behaviors may not be the only reasons for excess weight. A variety of potential influences may contribute to the increasing prevalence of obesity, including preterm birth and its associated rapid catch-up growth, as well as exposures to environmental compounds that may alter endogenous hormone balance or stimulate metabolic pathways that lead to increased adiposity and growth (Euser et al. 2008; Newbold et al. 2009; Uthaya et al. 2005).

Utilizing a series of sequentially-enrolled birth cohorts with repeated measures, the objectives of this dissertation were to examine the associations between preterm birth and exposures to the endocrine-disrupting compounds Bisphenol A (BPA) and phthalate metabolites on adolescent weight status andphysical growth. Archived biological specimens from pregnancy allowed for delineation of temporal events. We explored how exposures may impact weight status and growth trajectories from the perinatal to adolescent period, addressing

current gaps longitudinal analyses, particularly the role of exposures occurring during a critical period of development such as pregnancy.

Obesity

Worldwide, the prevalence of adult obesity has more than tripled from 1980 to over 900 million in 2008, resulting in over 34% of all adults classified as overweight or obese (Keats and Wiggins 2014). In addition, over 43 million children under the age of 5 are overweight or obese, with 92 million at risk for becoming overweight (de Onis et al. 2010). Among adults 20 years or older in the United States, 71.3% of males and 65.8% of females were classified as overweight (BMI≥25) while 33.5% of males and 36.1% of females were obese (BMI≥30) (Ogden et al. 2014). Among female adolescents aged 12-19, 34.2% were overweight (≥85th BMI-for-age percentile) and 20.4% were obese (≥95th BMI-for-age percentile), while 35.3% and 17.2% of males were overweight and obese, respectively (Skinner and Skelton 2014). Specifically, among Hispanics aged 12-19, 34.4% of females and 35.3% of males were overweight, and 19.7% of females and 21.4% of males were obese. In 2006 in Mexico, 26.2% of school-aged children 5-11 years old were overweight and obese, while 30.8% of female and 29.3% of male adolescents 12-18 years were classified as overweight or obese (Rivera et al. 2009).

Children with high BMI have an increased risk for insulin resistance, dyslipidemia, and cardiovascular health risks; of children who are in the ≥95th BMI-for-age percentile, over 50% have ≥1 cardiovascular risk (Flegal et al. 2010; Freedman and Sherry 2009; Guo et al. 1994; Lee et al. 2010; Ogden et al. 2012; de Onis et al. 2013; Sun et al. 2012). In addition to the myriad health

consequences that follow from being overweight or obese, there are a number of economic consequences. Being an overweight or obese adult in the United States increases total annual medical costs by 10% or 36%, respectively, compared to normal-weight individuals. As a whole, the annual United States medical cost of elevated BMI in childhood is estimated to be approximately $14.3 billion (Trasande and Chatterjee 2009). Indirect costs of obesity include productivity loss, transportation costs, and decrease in human capital accumulation (Hammond and Levine 2010). Productivity loss from obesity-related illness or disability results from a combination of absenteeism, presenteeism, increases in the number of disabled adults, and premature mortality (Frone 2007; Ricci and Chee 2005; Burkhauser and Cawley 2005; Fontaine et al. 2010). Increases in transportation costs result from the need to use more fuel and may, in effect, result in an increase in greenhouse gas emissions (Dannenberg et al. 2004; Jacobson and McLay 2006). Obesity also has been associated with a decrease in quantity as well as quality of educational attainment (Gortmaker et al. 1993; Sabia 2007). It has been suggested that total annual costs associated with obesity in the United States are in the excess of $215 billion; the impact of obesity is not strictly limited to the health of individuals (Hammond and Levine 2010).

Within the Nutrition Transition

Obesity prevalence differs within and between developed and developing countries. While obesity prevalence has seemingly plateaued or grown at a slower rate in industrialized countries, developing countries are still experiencing an increase in prevalence (Gupta et al. 2013; Moss et al. 2012; de Onis et al. 2010; Skinner and Skelton 2014). Our study population is situated in Mexico, which is

at an advanced stage of the nutrition transition, a phenomenon that occurs simultaneously with, or following, the epidemiological and demographic transition. Respectively, the epidemiological and demographic transitions are shifts in prevalence of communicable to non-communicable diseases and shifts from prevalence of high to low mortality and fertility (Popkin 2006; Shetty 2013).

The nutrition transition has been associated with a shift in behaviors such as increases in screen time, decreases in physical activity, and changes in dietary patterns—particularly fat, animal source foods, refined carbohydrates, and caloric sweetener consumption (Popkin 2011; Rivera et al. 2004). Trends in Mexico show increased fat, carbohydrate, as well as animal protein consumption which vary by region and socioeconomic class, with lower-income and rural areas consuming more than those in higher socioeconomic class or urban areas (Barquera et al. 2009). In addition to dietary changes, physical activity changes occur partly due to the shift in types of occupations and conveniences available due to urbanization. The high-energy expenditure activities such as farming and forestry gave way to service industries which are not as labor-intensive resulting in greater amounts of sedentary activity (Popkin and Gordon-Larsen 2004; Popkin 1999).

With these shifts in dietary and physical activity patterns, changes in types of disease also occur, with an increasing prevalence of obesity, cardiovascular disease, and other non-communicable diseases (Popkin 2006; Stevens et al. 2008). However, inequalities in income still exist and the pace of adaptation to changing lifestyle habits often result in a double burden of disease, with over- and under-nutrition existing within the same country or even households (Monteiro

et al. 2002; Popkin et al. 2012). This dual-burden of disease may occur as different regions within a country experience variation in stage of the nutritional, epidemiological, and demographic transitions (Popkin et al. 2012; Stevens et al. 2012). As a country develops, individuals affected by the transitions differ by regions and demographics; initial increase in overweight and obesity among those of higher socioeconomic brackets and urban areas shift to those of lower socioeconomic classes and rural areas (Kasper et al. 2014; McLaren 2007; Monteiro et al. 2002).

Due to the shifts in nutrition and lifestyle behaviors in countries undergoing the nutrition transition, the environment a fetus is conceived in may be drastically different from one that they experience as they grow and develop.

Developmental Origins of Health and Disease

The Developmental Origins of Health and Disease framework hypothesizes that early life influences may have long-term effects on later health and disease (Hales et al. 1991; Hanson and Gluckman 2008). Early life influences such as birth weight, mode of infant feeding, and exposures to environmental chemicals have been associated with later health consequences such as diabetes and obesity (Inadera 2013; Ravelli et al. 2000; Ross and Desai 2013; Thompson 2012). It is hypothesized that permanent structural or functional changes occur in the fetus or infant in response to exposures from environmental factors that would require the organism to adapt either immediately for short-term survival, or alter its physiological function for predictive long-term survival (Gluckman and Hanson 2004; Gluckman et al. 2005; Lucas 1991). This plasticity is a mechanism by which organisms adjust to variable environmental circumstances

in order to optimize its fitness, such as through inducing insulin resistance and storing fat if a poor nutritional environment is experienced or predicted, or accelerating sexual maturation postnatally if the environment is favorable (Cooper et al. 1996; Fall et al. 1995; Ibáñez et al. 2003).

The adaptations to match fetal environment with the predicted environment are maladaptive when the predicted environment is mismatched to that experienced. This "match-mismatch" theory is used to help explain the steep increase in prevalence of overweight and obesity in countries undergoing rapid nutrition transition (Hanson and Gluckman 2008; Popkin et al. 2012). In these settings, if maternal nutritional status indicates an environment of under-nutrition, the fetus may be set on a trajectory that would maximize their fitness in such an environment. However, if the environment is nutritionally-rich postnally, their physiology is mismatched and may contribute to the development of obesity (Hanson and Gluckman 2008). Matched scenarios are not necessarily protective for the fetus because fetal over-nutrition that may occur in children of obese mothers or to gestational diabetes is also a risk factor for the development of obesity (Paliy et al. 2014; Whitaker and Dietz 1998).

Applying this theory of adaptation to understanding obesity trends has suggested that the observed trends may be less likely related to genetic changes, as reflected from "natural experiments" such as the Dutch famine, and is more likely due to the interaction between genotype and environmental exposures which result in developmental adaptations that optimize the phenotype. These may occur through epigenetic changes, which are heritable changes in gene expression without an actual change in the sequence of the DNA (Gluckman and

Hanson 2008; Godfrey et al. 2011; Leimar et al. 2006; Painter et al. 2005). For example, children born to mothers exposed to restricted caloric intake during the first two trimesters of pregnancy during the Dutch Famine of 1944/1945, compared to their same-sex sibling, had a decrease in the methylation of insulin-like-growth factor 2 (IGF2) gene, an important regulator of human growth (Heijmans et al. 2008). This group of children also showed an increased prevalence of obesity at age 19 (Ravelli et al. 1976).

Sensitive and Critical Periods for Development

The Developmental Origins of Health and Disease framework focuses on prenatal and early life, but this period is only one of several critical and sensitive periods for development. A body of evidence suggests that there are sensitive periods of time for the development of adult chronic diseases, where risks are increased during, but decreased outside, these periods (Dietz 1994, 1997; Gillman 2008; Lawlor and Chaturvedi 2006).

Early life sensitive periods for obesity development are generally considered to include the pre- and perinatal period, the adiposity rebound, and adolescence (Dietz 1994, 1997). During these sensitive periods where there is rapid growth and development, perturbations of the trajectory of growth may positively or negatively affect risk outcomes. Fetal growth in the first and second trimesters is important for cellular differentiation and proliferation; with restriction of nutrients, the relegation of resources for growth of certain processes over others are hypothesized to adversely affect tissue function or formation, potentially leading to increased risk of obesity (Cole 2009; Gluckman et al. 2007).

The adiposity rebound, generally occurring between the ages of three and seven years, is a time of adipose hyperplasia and hypertrophy (Campbell et al. 2011; Dietz 1997; Knittle et al. 1979; Rolland-Cachera et al. 1984). An early adiposity rebound may lead to accelerated pubertal maturation, increased body mass, and increased adiposity in adolescence and adulthood (Cameron and Demerath 2002; Rolland-Cachera et al. 1984; Taylor et al. 2005; Williams and Dickson 2002; Williams and Goulding 2009).

Finally, adolescence is another period of rapid development, with alterations in insulin sensitivity and deviations in fat patterning by sex (Alberga et al. 2012; Dietz 1997; Mueller 1982; Smith et al. 1988). Adolescent overweight has been associated with adult overweight and obesity, increased risk of coronary heart disease, heart disease, and cancer, dependent and independent of adult BMI (Efrat et al. 2013; Must et al. 1992).

Preterm Birth

Preterm birth, defined as <37 weeks gestational age, is the second most common cause of death in children under 5 years of age; its associated complications account for the majority of neonatal deaths and over half of long-term morbidity (Clark and Fleischman 2011; Goldenberg et al. 2008; Liu et al. 2012; McCormick 1985). In 2010, 11.1% of all live births worldwide were preterm, with more than 60% of preterm births occurring in sub-Saharan Africa and south Asia (Blencowe et al. 2012; World Health Organization 2012). However, countries with high human development and economic indices are also affected; within the top 10 countries with the highest numbers of preterm births, the

United States of America ranks 6th worldwide, accounting for 3.5% of the global burden, and 12% of all live births within the United States (Blencowe et al. 2012).

Trends from 1990-2010 show that almost all countries have stable or increasing rates of preterm birth, but increases, especially in industrialized countries, may result from medical technologies such as surfactants or antenatal steroids enhancing the survival of individuals born at earlier and earlier gestational ages, rather than actual rate increases (Blencowe et al. 2012; Saigal and Doyle 2008; World Health Organization 2012). Certain countries may also be better prepared to manage and target risk factors, screen for and terminate congenital developmental anomalies, or do not report immediate neonatal deaths as live births, leading to differences in mortality (Mohangoo et al. 2011; World Health Organization 2012). Other factors that may influence preterm prevalence may be the method used to determine gestational age. Prevalence may differ depending on whether ultrasound or date of last menstrual period is used, as ultrasound measurements decrease the error that may result from use of recall of last menstrual date (Behrman and Butler 2007; Blondel et al. 2002; Kramer et al. 1988; Wingate et al. 2007).

The definition of "preterm" birth has been constantly evolving. In the first edition of *Williams Obstetrics*, Williams wrote "We possess no reliable means of estimating the exact date (of confinement) but are obliged to content ourselves with…the belief that labor occurs two hundred eighty days from the beginning of the last menstrual period." (Williams 1903). There appears to be continuum between gestational age and neonatal morbidity and mortality that reaches a

nadir at approximately 39 weeks' gestation (Clark and Fleischman 2011; Smith 2001).

While birth weight is intricately linked with gestational age, the two measures are not interchangeable since birth weight is a combination of not only time, but intrauterine growth (Behrman and Butler 2007; Kramer 1987). Therefore, prematurity is a consequence of inadequate gestational duration and has the added complexity of being additionally defined as appropriate-, small-, or large-for-gestational age (Kramer 1987). Low birth weight could result from a truncation of the 3rd trimester, where the most rapid fetal growth in weight occurs, leading to a small-for-gestational infant, or could occur due to intrauterine growth restriction, which could occur at any gestational age (Buckler 1997; Kramer 1987). Analyses linking these early life events need to distinguish between the two, as those born preterm may have different risks than those born with the same birth weight at term, but are small-for-gestational age.

Preterm birth can also be categorized as either spontaneous or indicated, where caesarean sections or labor inductions are carried out due to maternal or fetal indications (Behrman and Butler 2007; Goldenberg et al. 2008). Indicated preterm births are generally associated with acute or chronic fetal compromise such as intrauterine growth restriction, maternal hemorrhage, or hypertensive disorders (Behrman and Butler 2007; Goldenberg et al. 2008). Spontaneous preterm births can occur with intact membranes or due to premature rupture of the membranes (PPROM), which can arise from intrauterine infection and short cervical length, among others (Behrman and Butler 2007; Goldenberg et al. 2008; Mercer et al. 2000). In addition to dichotomization as indicated or

spontaneous preterm births, subdivisions based on length of gestational period are also used, separating extremely preterm (<28 weeks; ~5% of all preterm births), severely preterm (28-31 weeks; ~15% of all preterm births), moderate preterm (32-33 weeks; ~20% of all preterm births), and near term (34-36 weeks; ~60-70% of all preterm births) (Goldenberg et al. 2008).

Increases in singleton preterm births are thought to be due to a rise in medically indicated reasons from maternal complications like preeclampsia, or fetal compromise, such as intrauterine growth restriction (Ananth et al. 2005). The rise of in-vitro fertilization and other medically-assisted fertility programs are also associated with increased risks of preterm birth (Goldenberg et al. 2008; Jackson et al. 2004).

Risk Factors

While it is difficult to determine the exact mechanism, such as increased inflammation, placental hemorrhage, or stress, that initiates preterm labor, risk factors for preterm birth span a wide range of social and demographic characteristics (Behrman and Butler 2007; Goldenberg et al. 2008; Romero et al. 2006).

Maternal characteristics that have been associated with preterm birth include educational status, low socioeconomic status, low and high maternal ages, being a single mother, tobacco use, previous preterm birth, short interpregnancy interval, multiple gestations, medical disorders such as thyroid disease, diabetes, hypertension, and asthma, nutritional status such as low and high maternal BMI, and work-related stresses such as hard labor and long hours which may result in decreases in blood flow from the fetoplacental unit to the

active muscles (Andres and Day 2000; Behrman and Butler 2007; Cnattingius et al. 1998; Conde-Agudelo et al. 2006; Goldenberg et al. 2008; Launer et al. 1990; Mercer et al. 1999; Romero et al. 2006; Saurel-Cubizolles 2004; Smith et al. 2007, 2003; Thompson et al. 2006).

Low maternal pre-pregnancy BMI has been associated with an increased risk of spontaneous preterm birth. Low BMI may indicate nutritional malnourishment in total caloric or protein intake or micronutrient deficiencies, such as iron, folate, zinc, could increase risk of maternal infections or a decrease in blood volume or flow, resulting in reductions in uterine blood flow (Neggers and Goldenberg 2003; Ramakrishnan et al. 1999; Scholl 2005).

However, increasing maternal BMI is associated with an increase in indicated preterm birth (Hendler et al. 2005). Obese women are more likely to develop complications such as high blood pressure, diabetes, and preeclampsia and maternal obesity is associated with an increased pro-inflammatory biomarkers and endothelial dysregulation, which could further drive pregnancy complications (Cnattingius et al. 1998, 2013; Greer et al. 1994; Neggers and Goldenberg 2003; Ramsay et al. 2002).

The elevated risks of preterm birth in mothers with low socioeconomic status may be due to an increase in psychological or social stress (Copper et al. 1996; Farley 2012; Lobel et al. 1992). These stressors are hypothesized to affect preterm birth through increases in inflammatory markers or changes in vascular functions, such as hypertensive or cardiovascular disorders (Wadhwa et al. 2001).

Sub-optimal uteroplacental flow may also occur from women smoking during pregnancy; nicotine and carbon monoxide are known to be vasoconstrictors which could result in decreased blood flow and placental damage (Andres and Day 2000; Cnattingius 2004). The use of tobacco products is associated with an increase in inflammatory response and could contribute to spontaneous preterm birth and, in addition, maternal smoking during pregnancy is associated with later childhood overweight and obesity (Bermudez et al. 2002; Goldenberg et al. 2008; von Kries 2002).

Preterm birth is more common in males than in females. Approximately 55% of all preterm births occurring in males, who are also more highly associated with fetal and neonatal mortality and morbidity and long-term consequences, than their female counterparts (Hintz et al. 2006; Kent et al. 2012; Stevenson et al. 2000; Zeitlin et al. 2002).

Given that preterm birth typically results in birth weights that are lower than those normally observed at term birth, many studies use birth weight as an explanatory variable, rather than gestational age. Most studies have focused on indicators of intrauterine growth while limited studies exist for those born preterm, which is a risk factor for adverse later life events in adolescence (Euser et al. 2005; Hofman et al. 2004).

Consequences of Preterm Birth

Preterm babies face a host of complications both immediately post-delivery and long-term, including respiratory, cardiovascular, gastrointestinal, metabolic, neurocognitive impairments, and increased need for medical care (Behrman and Butler 2007; Bonner-Weir 2000; Boyle et al. 2012; Finken et al.

2006; Goldenberg et al. 2008; Hofman et al. 2004; McCormick et al. 2011; Mericq 2006; Pilgaard et al. 2010; Rowe et al. 2011; Saigal and Doyle 2008).

Though all organs are immature with preterm birth, the brain and lungs are particularly sensitive to long-term consequences, as they in critical periods for development in late pregnancy (Brown et al. 2013; Jobe and Bancalari 2001; Kugelman and Colin 2013; Rees and Inder 2005; Saigal and Doyle 2008; Teune et al. 2011). Neurological deficiencies include developmental and behavioral disabilities such as suboptimal control of motor function, decreased academic performance, hyperactivity, anxiety, as well as others (Aylward 2005; Chyi et al. 2008; Friedrich et al. 2007; Gray et al. 2004; Huddy et al. 2001; Pike et al. 2012; Rees and Inder 2005; Teune et al. 2011). Individuals born preterm are likely to develop respiratory distress syndrome due to restricted development and inability to make surfactant, preventing the lungs from remaining open to allow breathing; proper medical treatment with mechanical ventilation and oxygen therapy may still result in injury due to oxidant and ventilation-mediated stressors, leading to decreased lung function (Jobe and Bancalari 2001; Kugelman and Colin 2013; Teune et al. 2011).

Preterm birth has been associated with alterations in metabolism and growth, such as impaired glucose and insulin sensitivity, unfavorable body composition such as increased visceral fat deposition, and increased BMI in childhood and adulthood, (Doyle 2004; Euser et al. 2005; Finken et al. 2006; Hofman et al. 2004; Johnson et al. 2012; Pilgaard et al. 2010). While preterm babies are typically lighter compared to term babies, at 40 weeks past the last recalled menstrual period there were no differences in the amount of adipose

tissue present, and altered fat deposition, with increases in visceral, and decreases in subcutaneous, fat were observed (Euser et al. 2008; Uthaya et al. 2005). Even at 1 year of age, infants who were born preterm had greater fat mass normalized to weight than those born at term (Cooke et al. 1999). And, children who were born preterm had reduced insulin sensitivity, which may contribute to a future risk of Type 2 Diabetes, and other diseases related to insulin resistance, in adulthood (Hofman et al. 2004).

Growth trajectories differ by category of preterm and birth weight; those born very low birth weight (<1500 g; for reference, low-birth weight infants are defined as those with a birth weight ≤2,500 g) undergo growth failure during infancy and early childhood, notably in height, but sustained accelerated BMI *z*-scores from childhood through adulthood, resulting in a higher attained adult BMI z-score (Doyle 2004; Farooqi et al. 2006; Ford et al. 2000; Powls et al. 1996; Rowe et al. 2011; Saigal et al. 2006). This could place these individuals at increased risk for type 2 diabetes and cardiovascular diseases (Barker 1998; Pilgaard et al. 2010; Syddall et al. 2005).

In preterm infants, accelerated postnatal growth is a known phenomenon. This catch-up growth (CUG) occurs up to two years of age in infancy and CUG has been linked to an increased deposition of adipose tissue, increased waist circumference, greater risk of overweight and obesity and insulin resistance in adolescence (Belfort et al. 2013; Dulloo et al. 2006; Euser et al. 2005; Giannì et al. 2012; Kerkhof et al. 2012; Mericq 2006; Singhal 2010; Singhal et al. 2003; Tzoulaki et al. 2010). In infants born preterm, rapid CUG has been linked to higher insulin levels at 19 years of age as well as increased BMI, fat mass,

percentage body fat, and waist circumference (Euser et al. 2005; Finken et al. 2006). This compensatory acceleration of growth after shortened gestational length may serve as a method of adaptation for survival and the factors that may be involved in this growth may adversely program later adverse health effects. Being born preterm may be merely the stimulus needed to set the infant on a trajectory leading to future health risks.

We postulated that preterm birth was associated with adolescent obesity. Preterm birth was hypothesized to expose the fetus to an adverse environment which it is not developmentally prepared to encounter, resulting in such as through insulin resistance or increased fat deposition (Gluckman et al. 2007; Mericq 2006). One critical period for insulin sensitivity is hypothesized to occur during the early third trimester of pregnancy; disruption of this β-cell progression can lead to future complications (Bonner-Weir 2000; Hales and Barker 1992; Hofman et al. 2004; Tinnion et al. 2013).While structural and functional changes may be difficult to assess, it is thought that these adaptations take the form of CUG with preterm birth simply being the stimulus. CUG is a phase characterized by insulin resistance and growth that is primarily achieved thorough increases in body fat rather than lean tissue (Dulloo et al. 2006; Giannì et al. 2012). This demonstration of early insulin resistance and relative increase in body fat may be a mechanism by which increased risk in adulthood is conferred.

Environmental Endocrine-Disrupting Compounds

Environmental exposures have been increasingly scrutinized in recent years as possible factors involved in the rapid increase in overweight and obesity

that cannot be explained only by genetics or behavior (Baillie-Hamilton 2002). Bisphenol A (BPA) and phthalates are multi-functional materials used in everyday products; the prolific use of these products has resulted in widespread exposure to these compounds and their metabolites in humans of both genders and all age groups (Adibi et al. 2003; Calafat et al. 2008; Callan et al. 2012; Frederiksen et al. 2011; Pirard et al. 2012; Silva et al. 2004; Taskeen et al. 2012; Vandenberg et al. 2010).

BPA is one of the most highly manufactured chemicals in the world and is used in the production of polycarbonate plastics and epoxy resins; it is commonly found in food and beverage containers, medical equipment, toys, the linings of canned foods, thermal receipt paper, and dental sealants (Mendum et al. 2011; Shelby 2008; Vandenberg et al. 2007a).

Phthalates are also found in many consumer and industrialized products and are used in plastics for flexibility and also as a stabilizing and solubilizing material (David et al. 2012; Hauser and Calafat 2005; Meeker 2012). High molecular weight phthalates are used in manufacturing flexible vinyl plastics and are commonly found in food and beverage containers, medical equipment, and vinyl flooring. Low molecular weight phthalates are often found in solvents, paint thinners, medications and personal care products such as lotions, creams, and nail polish (David et al. 2012; Hernández-Díaz et al. 2009; Lewis et al. 2013).

Exposures and Metabolism

Exposure is widespread, with >92% of the U.S. population six years and older exhibiting detectable BPA and phthalate metabolites in their urine; metabolites have also been identified during pregnancy, with evidence of these

metabolites in the amniotic sac and cord blood (Calafat et al. 2008; Callan et al. 2012; Cantonwine et al. 2010; Chou et al. 2011; Huang et al. 2014; Meeker 2012; Silva et al. 2004; Vandenberg et al. 2010). Phthalates are not bound to the materials that they are used in, resulting in leaching and leading to human exposure via dermal absorption, inhalation, and ingestion (Meeker et al. 2009b). BPA exposure is also conducted through these pathways; BPA in the epoxy resin of food cans or polycarbonate plastic food and beverage containers can leach into the food material under high heat or pressure conditions, and through repeated use (Brede et al. 2003; Kang et al. 2003; Vandenberg et al. 2007a). BPA exposure also occurs through dermal absorption, such as from handling thermal receipt papers or through personal care products, as well as through inhalation through cigarette filters or dust particles (Biedermann et al. 2010; Dodson et al. 2012; Fu and Kawamura 2010; Rudel et al. 2003; Vandenberg et al. 2013).

Metabolism of BPA is dependent on mode of exposure and has a rapid half-life of approximately 6 hours (Völkel et al. 2002). When exposed orally, BPA enters the gastrointestinal tract and is absorbed and transported to the liver where “first-pass metabolism” occurs (Vandenberg et al. 2007a, 2013). This process rapidly conjugates BPA into BPA glucuronide or BPA sulfate, lowering the concentration of active unconjugated BPA from the blood. Alternate routes of exposure do not undergo “first-pass metabolism”, leaving BPA to circulate in the bloodstream in the unconjugated form.

Phthalates metabolism is also dependent on mode of exposure and has a half-life of fewer than 24 hours (Koch et al. 2005). The parent phthalate diester compound is hydrolyzed by esterases and lipases during phase I

biotransformation to form a hydrolytic monoester (reviewed in Hauser and Calafat 2005). High molecular weight parent diesters are additionally oxidized to form a more hydrophilic metabolite. These oxidized metabolites and monoesters could be excreted, or additionally undergo phase II biotransformation to produce glucuronide conjugates, which increases solubility in water and facilitates increased urinary excretion.

Both BPA and phthalate metabolites are measureable in urine and blood; urine is more commonly used due to several advantages: ability to obtain larger sample volumes, ease and non-invasive nature of collection, and reduced contamination during sample collection by the parent compounds (Koch and Calafat 2009). Total BPA (free+conjugated species) is generally measured due to the difficulty in identifying and quantifying conjugated forms, and phthalate monoester metabolites are generally used as biomarkers because they are largely considered the biologically active molecule (Hauser and Calafat 2005; Koch and Calafat 2009).

Epidemiological Studies

These environmental exposures have been increasingly examined in recent years because classic predictors of behaviors with regards to energy intake and expenditure, as well as genetics, do not fully explain the incredible rise in obesity (Baillie-Hamilton 2002). Endocrine-disrupting compounds such as BPA and phthalates mimic or interfere with the normal functioning of the endocrine system that regulates bodily functions such as growth, thyroid function, sexual development, insulin production and utilization, weight homeostasis, in addition to others (Elobeid and Allison 2008; Grün and Blumberg 2009; Hatch et al.

2010; Heindel 2003; Heindel and vom Saal 2009; Newbold 2010; Newbold et al. 2009).

Human epidemiological studies of BPA and phthalate exposurse on child and adolescent obesity and weight status have been mostly cross-sectional. Of the two long-term prospective studies, both center on associations of BPA concentrations *in utero* on child BMI, waist circumference, and overweight/obese status (Harley et al. 2013; Valvi et al. 2013).

For BPA, studies have found differences in significance and direction of association for males compared to females. Table 1.1 shows existing studies that span similar ages to our study population. While some studies found increasing concentrations of BPA to be associated with increases in outcome measures (BMI, obesity, waist circumference, etc.), others found evidence of non-monotonic associations.

Table 1.2, shows there are only cross-sectional studies of phthalate exposure with human BMI and metabolic endpoints, though a 1-year prospective study was conducted in children aged 6-8 years old but found no significant relationships (Teitelbaum et al. 2012). Increasing concentrations of phthalate metabolites were found to be associated with various body composition and metabolic endpoints including BMI, waist circumference, and insulin resistance, and were also marked by gender differences. One consistent finding was the association of increasing MEP concentrations with BMI and waist circumference in females (Hatch et al. 2010, 2008; Teitelbaum et al. 2012).

Animal and Cell Studies

in vitro studies have shown that BPA binds to both estrogen receptors (ER) α and β and can act as an estrogen mimicker, in addition to other mechanisms (Gould et al. 1998; Kuiper et al. 1998; Vandenberg et al. 2013). Though it was considered a weak estrogen due to its relatively low affinity for nuclear ERs compared with endogenous estradiol, it has been found to stimulate responses at concentrations well below those expected as necessary for binding to the nuclear ERs (Welshons et al. 2006). In addition, studies have shown that BPA has effects at levels less than the reference dose of 50μg/kg/day, showing that environmentally relevant exposures have human effects (Vandenberg et al. 2007a). Studies have also indicated that BPA may be anti-androgenic by interacting with the androgen receptor and preventing endogenous androgen activity (Wetherill et al. 2007).

The non-monotonic dose-response curves observed in human epidemiological studies have also been found in animal and cell studies and (Myers et al. 2009; Vandenberg et al. 2012; Watson et al. 2010). Hypothesized mechanisms include opposing signaling effects of different types of receptors (such as ERα and ERβ), decreased effects at higher doses due to cytotoxicity or receptor down-regulation or desensitization, up-regulation of gene expression at low doses, and opposing action responses in different sub-populations of cells. In addition, BPA has been found to be more potent in stimulating embryonic ERs than initially suspected, given its *in vitro* activity; this has implications for exposures that occur during pregnancy (Lemmen et al. 2004).

As BPA has been observed to cross the placental barrier, one question raised would be whether the fetus is able to metabolize the compound to the same degree as an adult. It is known that the human fetal liver does not express UDP-glucuronosyltransferase until after birth, leading to higher levels of circulating unconjugated BPA and, in primates, it has been shown that pregnancy alters BPA pharmacokinetics (Vom Saal et al. 2014). Fetal exposure and elimination of BPA in early pregnancy is thought to occur through passive diffusion through the placenta while, in late pregnancy, the fetus may dispose of BPA through the fetal kidney and via conjugation (Vom Saal et al. 2014). Pregnancy does not appear to affect first-pass metabolism of BPA in the liver after absorption from the gastrointestinal tract through oral exposures and that, at concentrations that humans are routinely exposed to, BPA exposure during pregnancy induced abnormal development in the mammary gland, brain, and ovaries. These findings are relevant for humans not only because primates are more similar compared to other models, but also because this study showed that non-oral routes of exposure may play a larger role than previously anticipated and fetal exposures to, and elimination of, BPA differ depending on the progression of pregnancy.

Studies from human adipocytes have shown that BPA inhibits adiponectin release (Hugo et al. 2008; Volberg et al. 2013). Adiponectin, secreted from adipocytes, is negatively correlated with fasting insulin, triglycerides, and glucose; higher concentrations are associated with lower risks of hypertension, dyslipidemia, and diabetes by increasing muscle and liver catabolism of fatty acids and glucose (Kadowaki and Yamauchi 2005; Kawada 2013). While, lower

levels are associated with type 2 diabetes and metabolic syndrome (Cruz et al. 2004; Shaibi et al. 2007). BPA has also been found to induce differentiation of preadipocytes to adipocytes, as well as increase lipid accumulation in these cells in both human explant cells from individuals of healthy BMI, as well as mouse fibroblast cells (Boucher et al. 2014; Masuno et al. 2002).

Using mouse models, perinatal and adult exposures to BPA have been observed to increase adipose tissue and body and alter glucose tolerance and insulin resistance; some studies observed differences in association by sex (Alonso-Magdalena et al. 2005b; Miyawaki et al. 2007; Ropero et al. 2008). *in vitro* studies have found altered glucose transport and increased differentiation of adipocytes (Masuno et al. 2002; Sakurai et al. 2004).

While BPA and phthalates have both been found to mimic or alter endogenous hormones, only phthalates are known to be PPAR activators in addition to being anti-andrognic and possible thyroid antagonists (Grün and Blumberg 2009; Meeker et al. 2007). PPARs are a family of lipid-sensors that are involved in energy homeostasis and can redirect metabolism when activated; PPAR-γ in particular has been shown to be a "master regulator" for the formation of adipocytes through differentiation and survival; forced expression of PPAR-γ in non-adipogenic cells can convert them into adipocytes (Evans et al. 2004; Feige et al. 2007; Tontonoz et al. 1994). Exposures during sensitive periods of development could result in permanent impacts on adipocyte development (Grün and Blumberg 2009; Hurst and Waxman 2003). Surprisingly, PPAR-γ is also involved in insulin sensitivity; thiazolidinediones, a class of medications used for controlling Type 2 diabetes through increasing insulin sensitivity, are PPAR-γ-

activating drugs (Berger et al. 2005; Lehrke and Lazar 2005). It is hypothesized that, as PPAR-γ activation largely affects adipose tissue by redirecting lipids away from liver and muscle, which are the tissues necessary for insulin-mediated glucose metabolism, PPAR-γ agonists prevent lipotoxicity-induced insulin resistance and prevent hyperglycemia (Bays et al. 2004; Mayerson et al. 2002).

Sex Differences in Findings

Differences in associations between exposures to BPA and phthalate metabolites for males and females are often observed and nimal studies have also indicated that the dose-response curves for females and males are different (Miyawaki et al. 2007). While the exact mechanism is not known, it is postulated to be related to BPA's estrogenic qualities, the sexually-dimorphic distribution of endogenous estrogen receptors, and its hypothesized ability to interfere with endogenous estrogen signaling (Alonso-Magdalena et al. 2005a, 2005b; Schneider et al. 2014). Males and females also differ in their energy-balancing characteristics behaviorally as well as morphologically and physiologically with regards to adipocyte differentiation and distribution (Schneider et al. 2014). It is hypothesized that males may be more sensitive than females to exposures to endocrine-disrupting compounds because the natural, default, evolution is towards the female phenotype whereas formation of the male phenotype necessitates hormonal influence from both testosterone and estradiol; alterations in these hormones may more negatively affect males (De Coster and van Larebeke 2012; Schneider et al. 2014). In addition, BPA may more adversely affect thyroid function of males rather than females (Chevrier et al. 2013; Sriphrapradang et al. 2013). Previous studies have found that low, circulating

levels of testosterone are associated with increased visceral and/or abdominal obesity in males; the anti-androgenic effects of phthalates may contribute to increased waist circumference and obesity in males but studies in females are inconclusive (Gapstur et al. 2002; Tchernof and Després 2013). Estrogen effects for females differ by menopausal status, with reduced estrogen levels post-menopause being associated with increased visceral adiposity (Lovejoy et al. 2008; Tchernof and Després 2013)

Estrogens are involved in the control of adipose distribution and metabolism and are known to be sexually dimorphic in deposition of subcutaneous or visceral fat (Cooke and Naaz 2004; Schneider et al. 2014). They are able to impact adipose tissue indirectly through other pathways other than through decreasing lipogenesis or increasing fatty acid β-oxidation; estrogen receptors are found within the brain in the hypothalamus, where energy balance is primarily regulated, and could impact appetite and metabolism (Cooke and Naaz 2004). The two estrogen receptors, ERα and ERβ, are nuclear receptors that are part of the steroid/thyroid hormone superfamily; binding of a ligand to the receptors triggers conformational changes that ultimately leads to changes in the rates of estrogen-regulated gene transcription (Nilsson et al. 2001). However, endocrine disrupting compounds can also act through classical nuclear receptors to initiate transcription, as well as through estrogen-related receptors, or through interactions with other targets that may activate pathways such as those involved in metabolism (De Coster and van Larebeke 2012; Wang et al. 2012b). Therefore, exposure to xenoestrogens, natural or man-made estrogens that mimic endogenous estrogen by binding to estrogen receptors, would be thought to

decrease the adipose stores. However, it has been shown that adipocyte numbers can be increased or decreased depending on the concentration of xenoestrogens (Cooke and Naaz 2004; Dang et al. 2003).

Given the observations from cell, animal, and human epidemiological studies, we hypothesized that exposures to BPA and phthalates would be associated with increased weight status and adiposity. In keeping with the Developmental Origins and critical period frameworks, exposures during early life, such as pregnancy, were hypothesized to have stronger associations with outcomes than those that occur in less sensitive periods of time. Additionally, it was hypothesized that associations would differ for males and females.

Study Population

The study population for this dissertation utilizes participants from the 19-year Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) research collaboration with Mexico's *Instituto Nacional de Salud Pública* that consists of three sequentially-enrolled birth cohorts.

The recruitments (starting in 1994, 1997, and 2001) occurred at family clinics serving low-to-moderate income populations in Mexico City: Mexican Social Security Institute, Manuel Gea González Hospital, and National Institute of Perinatology. Cohort 1 (N=616) was recruited between 1994-1995 and followed until 1997 as a randomized controlled trial on the effect of calcium supplementation during lactation on blood lead levels. Cohort 2 was comprised of two groups assessing bone lead, resorption, and fetal lead exposure; cohort 2A (N=327) was recruited during pre-pregnancy and followed between 1997-2000 and 2B (N=462) was recruited during pregnancy and followed between 1999-

2000. Cohort 3 (N=670) was recruited during pregnancy for a randomized controlled trial of calcium supplementation during pregnancy and lactation and recruited from 2001-2003. Study methods have been described previously (Ettinger et al. 2009; Gonzalez-Cossio et al. 1997; Hernandez-Avila et al. 2003; Hu et al. 2006; Téllez-Rojo et al. 2002, 2004).

In 2006, participants from all three cohorts were invited for a prospective follow-up after the child was at least 6 years old; 1,100 mother-child pairs were followed to assess the influence of fetal lead exposure on neurobehavioral outcomes. In 2012, recruitment of mother-child pairs (N=250) from cohorts 2 and 3 were initiated. Recruitment priority was based on existence of archived biological specimens and perinatal lead exposure data.

Similar exclusion criteria were applied to all three cohorts such as living outside of Mexico City, gestational diabetes, preeclampsia, or pregnancy-related hypertensive disorder, as well as other criteria described elsewhere (Ettinger et al. 2009; Gonzalez-Cossio et al. 1997; Téllez-Rojo et al. 2004). Common recruitment methods allow for pooling of the birth cohorts for analysis.

Thesis Overview

Chapter 2 investigated the association between preterm birth (gestational age<37 weeks) and BMI, waist circumference, and odds of obesity in youths aged 6-17 years, controlling for age, sex, and mother's BMI, smoking, years of education, and marital status.

Chapter 3 utilized archived maternal urine samples from the third trimester of pregnancy, as well as adolescent urine samples, to assess longitudinal and cross-sectional associations of BPA and 9 phthalate metabolites

with BMI z-score, waist circumference, and triceps skinfold in youths aged 8-14 years. Continuous and quartiles of metabolites were examined, controlling for specific gravity, child's age, and mother's years of schooling and BMI at 1 month postpartum, to explore the non-monotonic relationships noted in previous studies.

Chapter 4 explored a hypothesized relationship between exposures to BPA and 9 phthalate metabolites in the third trimester of pregnancy with the growth of children. Using repeated measures, this aim examined the predicted BMI and height trajectories of tertiles of specific gravity-adjusted metabolites in participants from 0.25 to 14 years of age, controlling for mother's years of schooling and BMI at 1 month postpartum. Estimated differences between tertiles in predicted trajectories were analyzed to determine ages where significant differences between tertiles of occurred.

Chapter 5 summarizes the work of this dissertation and offers suggested recommendations and future directions.

Table 1.1. Human epidemiological studies of exposures to BPA with weight status outcomes.

Authors	Study Design	Ages	Data Source	Exposure	Analysis	Outcome	Result
Wolff et al 207	Cross-sectional	6-80	U.S.	BPA, phthalates	N/A	N/A; characterizing pilot study	Higher BPA levels in girls <85th%ile compared to those >85%ile. phthalates differed by race/ethnicity in distributions
Eng et al 2013	Cross-sectional	6-18; subset 12-18	NHANES	BPA, phthalates	Quartiles	Adiposity, cholesterol, insulin, glucose	Higher odds obesity with non-monotonic BPA quartiles (2nd and 4th higher than 3rd), higher odds abnormal WC to height ratio
Wang et al. 2012	Cross-sectional	8-15	China	BPA	Continuous and quartiles	BMI	Associated with increasing BMI; after stratification by age or sex, remained significant in females and in those age 8-11 after stratification. Also observed non-monotonic associations of BMI with quartiles 2,3,4 compared to 1.
Trasande et al. 2012	Cross-sectional	6-19	NHANES	BPA	Continuous and quartiles	Obesity, BMI z-score	Increasing quartiles associated with increases in BMI z-score and non-monotonic odds of obesity; stronger association in males
Wells et al. 2013	Cross-sectional	6-18; subset 12-18	NHANES	BPA	Quartiles	Waist-to-height ratio	Increased WHR associated with greater BPA ;when stratified by sex, found significant increase in boys but not girls
Bhandari et al. 2013	Cross-sectional	6-18; subset 12-18	NHANES	BPA	Quartiles	Obesity	Increasing quartiles associated with odds of obesity; predominantly present in boys (note: though test for trend significant, 2Q had stronger effect than 3Q compared to 1Q reference)
Harley et al. 2013	Longitudinal and cross-sectional	Pregnancy-9 years	CHAMACOS; USA	BPA	Tertiles	BMI, fat mass, WC, overweight, obese	Prenatal associated with decreased BMI at 9 in girls but not boys; results strongest in pre-pubertal girls. Cross-sectional BPA concentrations at 9 for both boys and girls positively associated with BMI, WC, fat mass, and overweight/obese
Li et al. 2013	Cross-sectional	9-12	China	BPA	High vs low; trend test using <50th, 50-75, 75-90, >90th%ile	High weight percentile, WHR, BMI, skinfold, WC	High, and increasing, levels associated with overweight and hip circumference for girls 9-12; not observed in boys
Lee et al. 2013	1 year longitudinal	7-8 at baseline	Ewha Birth and Growth Cohort; Korea	BPA	Tertiles	Testosterone, estradiol, insulin, HOMA-IR, BMI	Girls in the high BPA exposure group had higher levels of testosterone, estradiol at 1 year compared to baseline. Cross-sectionally, relationship between BPA and BMI U-shaped, but not significant, increase in estradiol, testosterone, HOMA-IR with increasing tertiles
Valvi et al. 2013	Longitudinal and cross-sectional	Pregnancy-4 years	INMA, Spain	BPA	Continuous	BMI, WC	At 4 years, BPA associated with increased waist circumference, weakly associated (non-significant) with BMI

Table 1.2. Human epidemiological studies of exposures to phthalates with weight status outcomes.

Authors	Study Design	Ages	Data Source	Exposure	Analysis	Outcome	Result
Stahlhut et al 2007	Cross-sectional	> 18	NHANES males	MBP, MEP, MEHP, MBZP, MEHHP, MEOHP	Continuous, quintiles	Waist circumference, insulin resistance	MBZP, MEHHP, MEOHP, MEP associated with increased WC,. MBP, MBZP, MEP associated with insulin resistance
Hatch et al 2008	Cross-sectional	6-8	NHANES	MEP, MEHP, MBP, MBZP, MEHHP, MEOHP	Quartiles	BMI, WC	Consistent association in males age 20-59: BMI and WC increased across quartiles of MBZP, and positive association also found for MEOHP, MEHHP, MEP, MBP. In females, BMI & WC increased with MEP in girls while MEHP was inverse associated with BMI in adolescent girls
Hatch et al 2010	Cross-sectional	6-80	NHANES	MEP, MEHP, MBP, MBZP, MEHHP, MEOHP	Quartiles	BMI, WC	Associations marked by gender; MBZP strong positive relationship with BMI, WC with adult males 20-59 but no trend for females. MBP; positive suggestion trend for males for BMI and WC, but inverse trends for females. MEHP inversely related to BMI and WC in adolescent and adult females, but no trends for males. MEHHP, MEOHP similar. although MEP and BMI seen for adult males and for adolescent and adult females
Teitelbaum et al 2012	Prospective; 1 year	6-8	Hispanic and Black NYC children	MEP, MBP, MCPP, MBZP, MIBP, MEHP, MEOHP, MECPP, MEHHP, DEHP	Continuous, quartiles	BMI, WC	No significant relationships among boys or girls. dose-response seen with MEP and a sum of LMP and BMI and WC among overweight children. For increasing MEP quartiles among girls, associated with BMI and WC
Trasande et al 2013	Cross-sectional	6-19	NHANES	low MW, high MW, DEHP	Continuous	Blood pressure, lipid levels	DEHP associated with higher BP. no other association with other outcomes or other exposures
Trasande et al. 2013	Cross-sectional	12-19	NHANES	DEHP	Tertiles	Insulin resistance (HOMA-IR)	Each log increase (~3 fold) in DEHP metabolites increases 0.19 in HOMA-IR; Third tertile had 21.6% prevalence of insulin resistance compared to 14.5% in 1st

CHAPTER 2

Association of preterm birth with weight status and waist circumference in Mexico City youth

Abstract

Background**:** Preterm birth has been associated with adverse health profiles including impaired insulin sensitivity and increased truncal fat patterning in adolescence. In developing countries such as Mexico, changing environments coupled with preterm birth may deleteriously impact the development of health risks.

Objective: This study examines the association of preterm birth with adolescent obesity and markers of weight status and fat distribution among Mexico City adolescents.

Methods: Among 722 youths aged 6-17, we estimated differences in BMI and waist circumference by categories of premature birth (gestational age<37 weeks;N= 41;5.7%) using linear regression. In addition, we estimated odds ratios and 95% confidence intervals for obesity during adolescence according to preterm birth using logistic regression models adjusted for adolescent age, sex, and mother's age, education, marital status, smoking during pregnancy, and obesity.

Results: Premature birth was not associated with obesity (OR=1.03; 95%CI:0.43, 2.39), but sex-stratified models show possible differences by sex, with a suggestive increase in odds of obesity for females (OR=1.33; 95%CI:0.33, 5.24) but decrease for

males (OR=0.89; 95%CI:0.30, 2.64). There were non-significant negative associations between preterm birth with adolescent BMI (β=0.03; 95%CI:-1.09, 1.15) and waist circumference (β=-0.43; 95%CI:-3.33, 2.48) in adjusted models. Odds of obesity (OR=4.54, 95%CI:2.78, 7.42), BMI (β=2.63; 95%CI:1.85, 3.40), and waist circumference (β=5.88; 95%CI:3.87, 7.88), were significantly increased if mothers were obese.

Conclusions: Preterm birth does not indicate an increase in later adolescent BMI, waist circumference, or obesity in Mexico City youth, but there are suggestive differences by sex. The direction of association for increased BMI and waist circumference suggests a need for further research in a larger sample size. Efforts to reduce obesity in this context should consider the child's sex, socioeconomic status, and weight status of the mother.

Background

Trends in child and adolescent obesity are of immense public health concern because early obesity tends to track into adulthood; children with a high body mass index (BMI) have similar health hazards as obese adults including insulin resistance, dyslipidemia, and other cardiovascular disease risks (Freedman and Sherry 2009; Guo et al. 1994; Ogden et al. 2012; Sun et al. 2012). In countries such as Mexico undergoing a nutrition transition, shifts in environments and available resources may alter dietary and physical activity behaviors that lead to an increased risk of obesity (Popkin and Gordon-Larsen 2004; Popkin 2006). However, these social and behavioral changes may not fully explain the rapid rise in childhood and adolescent obesity seen in the past few decades.

Evidence suggests that the events and environments experienced in early life are associated with later adverse health outcomes; exposure to an adverse intrauterine environment is thought to stimulate the fetus to adapt for survival (Gluckman et al. 2007). If the fetus optimizes its predicted future survival based on the environment experienced *in utero* but the experienced environment is mismatched, the fetus may be maladapted, leading to future risk.

Most studies regarding birth weight or birth size with adult disease have focused on indicators of intrauterine growth while limited studies exist for those born preterm, which is itself a risk factor for adverse later life events in adolescence (Euser et al. 2005; Hofman et al. 2004). Prematurity is associated with catch-up growth (CUG) up to two years of age in infancy and CUG has been linked to an increased risk of obesity and insulin resistance in adolescence (Dulloo et al. 2006; Mericq 2006; Singhal et al. 2003). This compensatory acceleration of growth after

truncated prenatal growth may serve as a method of adaptation for survival; being born preterm may be merely the stimulus needed to set the infant on a trajectory leading to future health risks. Therefore, preterm birth may be a novel stimulus that results in future health consequences and warrants further assessment.

The purpose of this paper is to determine the association of preterm birth and adolescent weight status, waist circumference, and obesity among Mexico City youth aged 6-17 years in a developing country where the shifting burden of obesity lends an additional complexity in assessing the development of obesity and health effects.

Methods

Subjects and Settings

The study population consists of participants from the 19-year Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) research collaboration with Mexico's *Instituto Nacional de Salud Pública* (INSP) that involves three pre-birth cohorts. The recruitments (starting in 1994, 1997, and 2000) occurred at family clinics serving low-to-moderate income populations in Mexico City: Mexican Social Security Institute, Manuel Gea González Hospital, and National Institute of Perinatology. Cohort 1 was a randomized trial of the effect of calcium supplementation on blood lead levels during lactation, cohort 2 assessed effects of maternal lead burden, and cohort 3 mothers were enrolled in a randomized trial of calcium supplementation during pregnancy. Similar exclusion criteria were applied to all three cohorts such as living outside of Mexico City, gestational diabetes, preeclampsia, or pregnancy-related hypertensive disorder, as well as other criteria described elsewhere (Ettinger et al. 2009; Gonzalez-Cossio et al. 1997; Téllez-Rojo et al. 2004). Common recruitment methods allow for pooling of the birth cohorts for

analysis. Follow-up of the three cohorts were maintained and the children now span pre-adolescence and adolescence.

Mothers were given detailed information regarding study procedures and signed a letter of informed consent at the time of initial and follow-up recruitment. The research protocols were approved by the Ethics and Research Committees of the National Institute of Public Health in Mexico, the University of Michigan School of Public Health, and other participating institutions.

Anthropometric Measures

At one-month postpartum, maternal height was obtained using professional scales (BAME Mod 420) read to the nearest 0.1 centimeter (cm) and maternal weight was recorded to the nearest 0.1 kilogram (kg). Current adolescent anthropometry at ages 6-17 years were taken by study personnel using established research protocols (Lohman et al. 1988). Weight (BAME Mod 420) was measured to the nearest 0.1 kg; height (BAME Mod 420) was measured to the nearest 0.1 cm; waist circumference was measured with a non-stretchable tape (QuickMedical Model QM2000) to the nearest 0.1 cm. Duplicate measures were taken of weight and height while triplicate measures were taken of waist circumference; the observed values were then averaged. An additional measurement was taken if intra-personal variability exceeded the measurement tolerance of 0.5 cm.

Questionnaires

A questionnaire assessing social and demographic characteristics such as education, reproductive history, and marital status was administered by study personnel to the mother at the baseline visit.

Outcome Measures

Outcome measures were adolescent weight status, obesity, and waist circumference. Weight status is represented as body mass index (BMI), defined as weight divided by height squared ($\frac{kg}{m^2}$), and obesity is defined using the World Health Organization (WHO) classifications with the child exceeding a standard deviation score of +2 (de Onis 2007). BMI and waist circumference were analyzed as continuous variables.

The WHO growth curves were used to classify obese status because these references are used as a standard reflecting how children grow under optimal feeding (Garza and de Onis 2004). In contrast, the CDC growth charts are a reference of how a particular population of children did grow during a specific time period in a specific location while the International Obesity Task Force (IOTF) cut-offs are calculated from six diverse nations, using the adult BMI cut-offs for overweight (25 kg/m^2) and obese (30 kg/m^2) (Cole et al. 2000; de Onis and Yip 1996). We elected to use the WHO growth charts to categorize the weight status of the adolescent, which are in keeping with current and future studies.

A sensitivity analysis was also conducted for cohort effect, with the cohort variable included in the final models. Major findings did not change after adjustment (results not shown).

Predictor and Covariate Measures

Preterm birth (<37 weeks gestational age) was the primary exposure variable. Gestational age was estimated from the date of last recalled menstrual period by the mother. Covariates were chosen *a priori* based on biological and social relevance in

predicting the outcome measures or as potential confounders of the association between preterm birth and adolescent outcomes. They included baseline mother's age, years of education, marital status (married/not married), mother's smoking status during pregnancy (yes/no), obese status (BMI ≥ 30) at 1 month postpartum, and child's current age and sex.

Statistical Analysis

Descriptive statistics and distributions were examined and extreme outliers were identified and removed using the generalized extreme studentized deviation method (Rosner 1983). Differences in characteristics of children who were followed-up to adolescence versus those not followed-up were examined using the t-test for continuous and chi-square test for categorical measures (results not shown). For individuals followed-up and included in this study, the characteristics were stratified by sex and examined. Bivariate and multivariable analyses using linear and logistic regression models were conducted to assess the association between preterm birth and covariates with each outcome. Results were further stratified by sex to explore differences in associations.

Results

Table 2.1 shows the descriptive statistics for adolescents by sex. There were 41 preterm births, with slightly more occurring in males. Children were on average 11.3 years old and 51.8% male. Most (72.3%) had married mothers who were 25.6 years of age at baseline, mostly non-obese (86.6%), and averaged 10.5 years of total schooling. There were no differences in number of preterm births, child's age, BMI, and mother's marital status, smoking during pregnancy, age, obesity, and years of schooling between males and females. Males had significantly higher waist

circumference (69.1 cm) and were more obese (21.2%) compared to females (65.8 cm; 12.9%).

Bivariate linear and logistic regression models are shown in Table 2.2. For combined sex, marital status was significantly negatively associated with adolescent BMI (β=-0.83; 95%CI:-1.50, -0.15) and waist circumference (β=-1.91; 95%CI:-3.68, -0.13). This was also observed for males for BMI (β=-1.25; 95%CI: -2.23, -0.27) and waist circumference (β=-3.06; 95%CI:-5.67, -0.44). Mother's obesity was significantly positively associated with adolescent BMI, waist circumference, and obesity for males (respectively, β=2.47; 95%CI:1.22, 3.71, β=5.00; 95%CI:1.63, 8.35, β=5.00; 95%CI:2.67, 9.35), females (respectively, β=1.87; 95%CI:0.63, 3.10, β=4.37; 95%CI:1.22, 7.50, β=3.70; 95%CI:1.78, 7.64), and combined sex (respectively, β=2.18; 95%CI: 1.30, 3.05, β=4.68; 95%CI:2.37, 6.99, β=4.27; 95%CI:2.68, 6.80),.

Multivariable adjusted linear and logistic regression models are shown in Table 2.3. Preterm birth was not associated with odds of adolescent obesity (OR=1.03; 95%CI:0.43, 2.39) with the fully-adjusted model, but sex-stratified models show possible differences by sex, with a suggestive increase in odds of obesity for females (OR=1.33; 95%CI:0.33, 5.24) but decrease for males (OR=0.89; 95%CI:0.30, 2.64). In fully-adjusted models when stratified by sex, males were observed to have a decreased association with adolescent waist circumference (β=-0.79; 95%CI:-4.75, 3.16) and reduced odds of obesity (OR=0.89; 95%CI:0.30, 2.64) while females were observed to have an increased association with adolescent waist circumference (β=0.37; 95%CI:-4.01, 4.75) and increased odds of obesity (OR=1.33; 95%CI:0.33, 5.24).

Mother's obesity was significantly associated with odds of adolescent obesity and increases in BMI and waist circumference for all combined and sex-stratified models. Mother's years of schooling was also significantly associated with increases with adolescent BMI (β=0.13; 95%CI:0.03, 0.21) and waist circumference (β=0.29; 95%CI:0.05, 0.52), which was observed in sex-stratified models with only males (BMI β=0.15; 95%CI:0.02, 0.27, waist circumference β=0.36; 95%CI:0.03, 0.67).

Discussion

Our results showed no association in Mexico City youth between preterm birth and adolescent obesity, BMI, or waist circumference. However, several other studies have observed associations between infants born preterm with obesity and related complications such as insulin imbalance and metabolic syndrome (Euser et al. 2005; Finken et al. 2006; Hofman et al. 2004). Low birth weight, like preterm birth, is an early life event that is a risk factor for later adverse health effects; in a study of young Mexican-Americans, it was found that birth weight was significantly and inversely related to truncal fat deposition and higher fasting insulin levels (Barker 1998; Hales and Barker 1992; Valdez et al. 1994). These studies were carried out in industrialized countries, so our lack of significance may also be due to the nature of the study setting.

Our significant findings that associate maternal obesity with later adolescent BMI, waist circumference, and obesity is not surprising, as maternal obesity is known to be a risk factor for later obesity in children (Symonds et al. 2013). Additionally, maternal obesity is associated with risk of preterm birth, heightening the detrimental effects that maternal body fatness may have on not only birth outcomes, but later health indices (Cnattingius et al. 2013).

We posited that preterm birth exposes the fetus to an adverse environment which it is not developmentally prepared to encounter. In order to optimize survival in the short-term, the fetus undergoes adaptation in structure or function such as through insulin resistance or increased fat deposition (Gluckman et al. 2007; Mericq 2006). While this plasticity is advantageous for immediate survival, metabolic programming during critical periods of development may permanently alter the physiology of the infant (Finken et al. 2006; Hofman et al. 2004). For instance, one critical period for insulin sensitivity is hypothesized to occur during the early third trimester of pregnancy; disruption of this β-cell progression can lead to future insulin sensitivity (Bonner-Weir 2000; Hales and Barker 1992; Hofman et al. 2004).

While structural and functional changes in physiology may be difficult to assess, it is hypothesized that these adaptations take the form of CUG with preterm birth simply being the stimulus. Evidence suggests that CUG is a phase characterized by insulin resistance and that growth is primarily achieved thorough increases in body fat rather than lean tissue (Dulloo et al. 2006). This demonstration of early insulin resistance and relative increase in body fat may be the mechanism by which increased risk in adulthood is conferred.

Limitations of our study include possible misclassification of gestational age due to the reliance on using mother's recall of last menstrual period, broad range of ages for defining adolescence, and small sample size of preterm births. Selection bias was a possible concern, but the cohorts were observational in nature and analysis of differences between adolescents who were followed-up and analyzed with those who were not were not statistically significant. The strengths of our study include the

ability to control for multiple confounding factors and the use of multiple endpoints that relate to weight status and adiposity.

Disentangling the complexities surrounding the etiology of obesity would benefit public health interventions aimed at reducing the numbers of obese individuals. While the causes of preterm birth remain mostly unexplained (Behrman and Butler 2007; Kramer 1987), intervention measures can be directed towards those that may be more modifiable such as maternal obesity. Given our hypothesis that rapid CUG is the physiologic adaptation, interventions could be aimed at preventing overfeeding of preterm infants in a misguided attempt to hasten their growth. In addition, knowledge that individuals who were born preterm have been found to be at increased risk for later obese weight status could enhance targeted intervention strategies for these groups. Future work in this area could be enhanced with a larger sample size and the use of repeated measures to determine the extent of CUG preterm infants experience and their relation with later weight status and adiposity.

Table 2.1. Distribution of characteristics by sex.

	Male		Female		
	N	Mean(SD)/%	N	Mean(SD)/%	*p*-value*
Child premature					0.37
Yes	24	6.4	17	4.9	
No	350	93.6	331	95.1	
Child's age (yrs)	374	11.4 (2.9)	348	11.3 (2.9)	0.41
Child's BMI	374	20.4 (4.3)	348	20.2 (4.1)	0.43
Child's waist circumference (cm)	374	69.1 (11.4)	348	67.0 (10.3)	<0.01
Child obese					<0.01
Yes	79	21.2	45	12.9	
No	295	78.8	303	87.1	
Mother married					0.35
Yes	276	73.8	246	70.7	
No	98	26.2	102	29.3	
Mother smoked during pregnancy					0.16
Yes	11	1.5	17	2.4	
No	362	50.5	327	45.6	
Mother's age (yrs)	374	25.6 (5.1)	348	25.8 (5.5)	0.60
Mother's BMI[a]					0.96
≥30	50	13.4	47	13.5	
<30	324	86.6	301	86.5	
Mother's education (yrs)	373	10.7 (3.0)	347	10.5 (2.8)	0.50

*p-value t-test for continuous, chi-sq for categorical
[a]1 month postpartum

Table 2.2. Bivariate linear and logistic regressions estimating associations with adolescent BMI, waist circumference, and obesity.

			BMI		Waist circumference		Obese	
	Sex	N	β	95% CI	β	95% CI	OR	95% CI
Preterm birth	All	722	-0.44	(-1.75, 0.86)	-1.58	(-5.02, 1.85)	1.18	(0.53, 2.62)
	Male	374	-0.60	(-2.36, 1.16)	-2.91	(-7.62, 1.80)	0.98	(0.35, 2.71)
	Female	348	-0.27	(-2.25, 1.71)	-0.10	(-5.13, 4.92)	0.39	(0.40, 5.34)
Mother married	All	722	-0.83	(-1.50, -0.15)	-1.91	(-3.68, -0.13)	0.73	(0.48, 1.11)
	Male	374	-1.25	(-2.23, -0.27)	-3.06	(-5.67, -0.44)	0.61	(0.35, 1.04)
	Female	348	-0.43	(-1.36, 0.51)	-0.93	(-3.30, 1.44)	0.91	(0.46, 1.78)
Mother smoked	All	717	-0.01	(-1.58, 1.56)	-0.07	(-4.19, 4.06)	0.95	(0.35, 2.54)
	Male	373	-1.19	(-3.75, 1.36)	-0.96	(-7.79, 5.88)	0.46	(0.13, 1.60)
	Female	344	0.71	(-1.27, 2.68)	0.04	(-5.00, 5.07)	2.42	(0.31, 18.72)
Mother's age	All	722	-0.01	(-0.06, 0.04)	0.01	(-0.14, 0.15)	1.01	(0.97, 1.05)
	Male	374	0.02	(-0.06, 0.10)	0.09	(-0.13, 0.32)	1.02	(0.96, 1.06)
	Female	348	-0.04	(-0.11, 0.03)	-0.06	(-0.25, 0.13)	1.01	(0.95, 1.07)
Mother's BMI≥30	All	722	2.18	(1.30, 3.05)	4.68	(2.37, 6.99)	4.27	(2.68, 6.80)
	Male	374	2.47	(1.22, 3.71)	5.00	(1.63, 8.35)	5.00	(2.67, 9.35)
	Female	348	1.87	(0.63, 3.10)	4.37	(1.22, 7.50)	3.70	(1.78, 7.64)
Mother's education	All	720	0.004	(-0.10, 0.10)	-0.02	(-0.29, 0.25)	1.07	(0.99, 1.13)
	Male	373	0.06	(-0.08, 0.19)	0.08	(-0.30, 0.46)	1.08	(0.99, 1.17)
	Female	347	-0.06	(-.21, 0.08)	-0.17	(-0.55, 0.21)	1.03	(0.92, 1.15)

Table 2.3. Multivariable linear and logistic regressions estimating adjusted models of adolescent BMI, waist circumference, and obesity.

			BMI				Waist circumference				Obese			
			Adjusted model 1[a]		Adjusted model 2[b]*		Adjusted model 1[a]		Adjusted model 2[b]*		Adjusted model 1[a]		Adjusted model 2[b]*	
	Sex	N	β	95% CI	β	95% CI	β	95% CI	β	95% CI	OR	95% CI	OR	95% CI
Preterm birth	All	722	0.001	(-1.15, 1.15)	0.03	(-1.09, 1.15)	-0.46	(-3.42, 2.49)	-0.43	(-3.33, 2.48)	1.07	(0.47, 2.39)	1.03	(0.43, 2.39)
	Male	374	0.02	(-1.54, 1.58)	0.06	(-1.46, 1.58)	-1.06	(-5.07, 2.95)	-0.79	(-4.75, 3.16)	0.93	(0.33,2.58)	0.89	(0.30, 2.64)
	Female	348	-0.02	(-1.74, 1.70)	0.002	(-1.69, 1.69)	0.52	(-3.88, 4.92)	0.37	(-4.01, 4.75)	1.42	(0.38, 5.19)	1.33	(0.33, 5.24)
Mother married	All	722	-0.49	(-1.08, 0.10)	-0.50	(-1.09, 0.08)	-1.04	(-2.56, 0.49)	-1.13	(-2.65, 0.39)	0.67	(0.44, 1.02)	0.66	(0.42, 1.04)
	Male	374	-0.63	(-1.50, 0.24)	-0.51	(-1.36, 0.35)	-1.17	(-3.42, 1.07)	-0.95	(-3.18, 1.27)	0.57	(0.32, 0.97)	0.60	(0.33, 1.07)
	Female	348	-0.36	(-1.17, 0.45)	-0.43	(-1.26, 0.39)	-0.76	(-2.84, 1.32)	-1.12	(-3.25, 1.02)	0.90	(0.45, 1.77)	0.85	(0.40, 1.78)
Mother smoked	All	717	0.71	(-0.67, 2.09)	0.51	(-0.83, 1.85)	1.74	(-1.81, 5.29)	1.17	(-2.32, 4.66)	0.79	(0.28, 2.14)	0.65	(0.23, 1.83)
	Male	373	-0.47	(-2.73, 1.79)	-0.63	(-2.84, 1.57)	1.23	(-4.58, 7.05)	0.62	(-5.11, 6.35)	0.42	(0.11, 1.49)	0.35	(0.09, 1.28)
	Female	344	1.50	(-0.22, 3.21)	1.26	(-0.44, 2.95)	1.98	(-2.44, 6.40)	1.40	(-2.98, 5.79)	2.08	(0.26, 16.23)	1.91	(0.23, 15.69)
Mother's age	All	722	0.02	(-0.03, 0.06)	-0.01	(-0.05, 0.04)	0.09	(-0.04, 0.21)	0.04	(-0.08, 0.17)	1.01	(0.97, 1.05)	1.00	(0.96, 1.04)
	Male	374	0.03	(-0.04, 0.10)	0.01	(-0.06, 0.08)	0.12	(-0.06, 0.31)	0.08	(-0.10, 0.27)	1.02	(0.96, 1.06)	1.01	(0.95, 1.06)
	Female	348	0.01	(-0.06, 0.07)	-0.02	(-0.08, 0.05)	0.05	(-0.12, 0.21)	0.00	(-0.17, 0.17)	1.01	(0.95, 1.06)	1.00	(0.93, 1.05)
Mother's BMI≥30	All	722	2.62	(1.85, 3.37)	2.63	(1.85, 3.40)	5.90	(3.93, 7.85)	5.88	(3.87, 7.88)	4.24	(2.64, 6.82)	4.54	(2.78, 7.42)
	Male	374	2.77	(1.67, 3.85)	2.73	(1.62, 3.84)	5.88	(3.05, 8.70)	5.76	(2.87, 8.64)	4.93	(2.62, 9.23)	5.00	(2.60, 9.60)
	Female	348	2.46	(1.40, 3.52)	2.49	(1.39, 3.58)	5.84	(3.11, 8.56)	5.91	(3.07, 8.73)	3.42	(1.63, 7.14)	3.74	(1.74, 7.99)
Mother's education	All	720	0.11	(0.01, 0.20)	0.13	(0.03, 0.21)	0.27	(0.03, 0.50)	0.29	(0.05, 0.52)	1.05	(0.98, 1.12)	1.07	(0.99, 1.14)
	Male	373	0.15	(0.02, 0.27)	0.15	(0.02, 0.27)	0.37	(0.04, 0.69)	0.36	(0.03, 0.67)	1.08	(0.98, 1.16)	1.08	(0.99, 1.18)
	Female	347	0.06	(-0.07, 0.19)	0.09	(-0.04, 0.22)	0.14	(-0.20, 0.48)	0.21	(-0.14, 0.55)	1.01	(0.90, 1.12)	1.03	(0.91, 1.16)

[a]Adjusted for chid's age, child's sex
[b]Additionally adjusted for preterm birth, mother's age, smoking status during pregnancy, marital status, obesity, education
*N=715 for combined sex, N=372 for males, N=343 for females

CHAPTER 3

Bisphenol A and Phthalates Urinary Concentrations *in utero* and in Adolescence: Associations with Weight Status and Adiposity Differ by Sex

Abstract

Background**:** Childhood and adolescent obesity is known to track into adulthood, exacerbating future obesity burden. Environmental exposures to endocrine-disrupting compounds may contribute to dysregulation of weight gain and distribution, especially if exposures occur during critical periods of development.

Objectives**:** Assess the relationship between *in utero* and concurrent adolescent Bisphenol A (BPA) and phthalate metabolite exposures on adolescent BMI z-score, waist circumference, and triceps skinfolds.

Methods**:** This study utilizes participants from the Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT). BPA and phthalate metabolite urinary concentrations were assessed using linear regression with continuous measures of adolescent BMI z-score, waist circumference, and triceps skinfolds. Quartiles of exposures were also examined following observations of non-monotonicity from GAM modeling.

Results**:** I*n utero* exposures to continuous BPA and MBzP in females were significantly negatively associated with adolescent BMI z-score. Second and third quartiles of MEOHP, MEHHP, and MIBP in males, and MEHP, MECPP, MEHHP,

and MEOHP in females were significantly associated with adolescent outcomes. Concurrent second and third quartiles of exposures were significantly negatively associated with adolescent measures of BPA in males and for MCPP and MiBP in females. Significantly negative associations between concurrent continuous male concentrations of MEHP, and female concentrations of MBP, were observed with adolescent outcomes. Non-significant positive associations between female urinary concentrations of adolescent MEP and BPA and outcomes were observed.

Discussion**:** Significant non-monotonic associations of BPA and phthalates exposures in *in utero* and in adolescence with adolescent BMI z-score, waist circumference, and triceps skinfold were observed, with differences by sex. Our results suggest that fat distribution for males, but not females, is influenced by pregnancy exposures.

Background

Bisphenol A (BPA) and phthalates are multi-functional materials used in everyday products, resulting in widespread exposure to these compounds and their metabolites in humans of both genders and all age groups (Adibi et al. 2003; Calafat et al. 2008; Callan et al. 2012; Frederiksen et al. 2011; Pirard et al. 2012; Silva et al. 2004; Taskeen et al. 2012). Notably, metabolites have been detected during pregnancy, with evidence of these metabolites in the amniotic sac and cord blood (Calafat et al. 2008; Callan et al. 2012; Cantonwine et al. 2010; Chou et al. 2011; Meeker 2012; Silva et al. 2004; Vandenberg et al. 2007a).

The Developmental Origins of Health and Disease (DOHaD) framework considers early life exposures crucial to later health indices. Fat cell mass and number increase substantially in late pregnancy and exposures during this critical period, during which the organism undergoes rapid growth, could disrupt and alter physiological structure and function (Dietz 1994; Gluckman et al. 2008; Heindel and vom Saal 2009; Poissonnet et al. 1984). This increases risk of development of chronic diseases, including altered weight status, which could start in childhood. Accumulating evidence suggest these chemicals play a role in influencing physiology from the perinatal period, with animal studies showing environmentally-relevant effects on weight gain, adiposity, and alterations in satiety hormones (Angle et al. 2013; Wei et al. 2011; Xu et al. 2011).

Therefore, exposures have implications for development of childhood and adolescent overweight, which has been shown to track into adulthood. Overweight and obese children have many of the same health hazards as overweight and obese adults including insulin resistance, dyslipidemia, and cardiovascular health risks

(Flegal et al. 2010; Freedman and Sherry 2009; Guo et al. 1994; Lee et al. 2010; Ogden et al. 2012; de Onis et al. 2013; Sun et al. 2012). Studies have implicated these compounds to obesity, increased waist circumference and fat mass, alterations in adipogenesis, lipogenesis, and metabolic imbalance such as impaired glucose and insulin response (Alonso-Magdalena et al. 2005a; Carwile and Michels 2011; Hao et al. 2012; Harley et al. 2013; Hatch et al. 2008; Hauser and Calafat 2005; Hugo et al. 2008; Lang et al. 2008; Lind et al. 2012a, 2012b; Masuno et al. 2002; Newbold 2010; Ropero et al. 2008; Ryan et al. 2010; Sakurai et al. 2004; Shankar and Teppala 2011; Stahlhut et al. 2007; Teitelbaum et al. 2012; Trasande et al. 2012; Wang et al. 2012a, 2012b, 2012c; Wei et al. 2011). In addition, many cell and animal studies show effects at concentrations below calculated safe doses, making environmentally relevant levels a cause for concern (Alonso-Magdalena et al. 2005a; Hao et al. 2012; Marmugi et al. 2012; Vandenberg et al. 2007b).

Few human studies examine the associations between exposures to BPA and phthalates with weight status; of these, most are cross-sectional or are unable to assess the implications of early life exposure. Adult cross-sectional data suggest a positive association between exposures to BPA and phthalates with increasing BMI, waist circumference, fat mass, and diabetes (Carwile and Michels 2011; Hatch et al. 2010, 2008; Shankar and Teppala 2011; Stahlhut et al. 2007; Wang et al. 2012d). Of human studies examining prenatal exposures, only BPA has been assessed, and only up to 9 years of age: prenatal urinary BPA concentration were found to be associated with lower odds of overweight in males and females, as well as decreased BMI *z*-score and percent body fat among females at 9 years of age. Another study observed that prenatal BPA exposure resulted in marginal increases in BMI and waist

circumference in children at 4 years of age (Harley et al. 2013; Valvi et al. 2013). Among females 6-8 years old, a one-year prospective study showed increasing MEP quartiles were associated with BMI and waist circumference (Teitelbaum et al. 2012). Other cross-sectional studies in youth show positive associations between BPA and phthalates with odds of obesity, insulin resistance, central adiposity, and diabetes (Bhandari et al. 2013; Eng et al. 2013; Li et al. 2013; Trasande et al. 2012, 2013b, 2013c; Wang et al. 2012a; Wells et al. 2013). Studies report some differences in association by sex though results have not been conclusive.

Given the evidence that development of adiposity occurs early in life and can be influenced by exposures to endocrine-disrupting compounds, this study seeks to assess the impact in children older than previously reported. We examined the association of BPA and phthalate metabolite concentrations in maternal third trimester and adolescent urine samples with BMI z-score, waist circumference, and triceps skinfold in a cohort of Mexican adolescents aged 8-14.

Materials and Methods

Subjects and Settings

The study population involved participants from the 19-year Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) research collaboration with Mexico's *Instituto Nacional de Salud Pública* (INSP) that consists of three birth cohorts. Similar exclusion criteria were applied to all cohorts, as described elsewhere(Ettinger et al. 2009; Gonzalez-Cossio et al. 1997; Téllez-Rojo et al. 2004). Common recruitment methods allow for pooling of the cohorts for analysis and follow-up was continuously maintained.

Mothers were given detailed information regarding study procedures and signed a letter of informed consent at the time of initial recruitment and follow-up. The research protocols were approved by the Ethics and Research Committees of the National Institute of Public Health in Mexico, Harvard University and the University of Michigan Schools of Public Health.

Anthropometric Measures

At one-month postpartum, maternal height was obtained using professional scales (BAME Mod 420; Catálogo Médico) read to the nearest 0.1 centimeter (cm) and maternal weight was recorded to the nearest 0.1 kilogram (kg). Children's anthropometry were taken by study personnel using established research protocol(Lohman et al. 1988). Weight (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 kg; height (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 cm; waist circumference was measured with a non-stretchable tape (QM2000; QuickMedical) to the nearest 0.1 cm. Triceps and subscapular skinfold thickness were measured using a Lange skinfold caliper (Lange; Beta Technology) to the nearest 0.1 mm. Duplicate measures were taken of weight and height and triplicate measures were taken of waist circumference and triceps skinfold thickness; the observed values were averaged. An additional measurement was taken if intra-personal variability exceeded the measurement tolerance of 0.5 cm. BMI was calculated as kg/m^2. Age-specific Body Mass Index (BMI) z-score was calculated using the 2007 World Health Organization (WHO) data.

Questionnaires

A questionnaire assessing social and demographic characteristics was administered by study personnel to the mother at the baseline and follow-up visit when the children were 8-14 years old.

Urinary BPA and Phthalate Metabolites

A spot (second morning void) urine sample was collected from each woman during her third-trimester visit to the project's research center and frozen at – 80 °C; these were matched to urines from adolescents at follow-up. Samples were analyzed for total (free + glucuronidated) BPA and nine phthalate metabolites by NSF International (Ann Arbor, MI, USA) using validated modification of the Centers for Disease Control and Prevention (CDC) methods described elsewhere (Calafat et al. 2008; Lewis et al. 2013; Silva et al. 2007). The nine phthalate metabolites: monoethyl phthalate (MEP), metabolite of diethyl phthalate (DEP); mono-*n*-butyl phthalate (MBP), metabolite of di-*n*-butyl phthalate (DBP); mono-isobutyl phthalate (MiBP), metabolite of di-isobutyl-phthalate (DiBP); mono(3-carboxypropyl) phthalate (MCPP), metabolite of DBP and di-*n*-octyl phthalate (DOP); monobenzyl phthalate (MBzP), metabolite of butylbenzyl phthalate (BBzP); and mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), metabolites of di(2-ethylhexyl) phthalate (DEHP). Specific gravity (SG) of the urine samples was measured using a handheld digital refractometer (ATAGO Company Ltd., Tokyo, Japan).

BPA and phthalate metabolite concentrations below the limit of quantitation (LOQ) were assigned a value of LOQ/sqrt(2). Urinary concentrations were

statistically adjusted for specific gravity to adjust for variability in urine output (Mahalingaiah et al. 2008; Pearson et al. 2009).

Statistical Analysis

Data analysis was completed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). We used multivariable linear regression to assess the association of BPA and individual phthalates metabolites with continuous outcome measures (BMI z-score, waist circumference, and triceps skinfold), stratified by sex. Sensitivity analyses were also assessed for the outcomes of BMI and a sum score of triceps and subscapular skinfold, as it has been suggested that a sum score would be a better measure of adiposity in childhood and adolescence (Boeke et al. 2013). Results did not significantly differ; therefore, outcomes for BMI z-score and triceps skinfold are shown. Tables and Figures pertaining to BMI and triceps and subscapular skinfold results are found in the Appendix. Generalized additive models (GAMS) were utilized to visualize the relationship between BPA and phthalates metabolites with outcome measures; visual inspection and significant Analysis of Deviance *p*-values confirmed departure from linearity for certain metabolites (Figure 3.1). Therefore, results are shown with continuous and quartile exposure variables, with first quartile as reference.

Distributions of BPA and phthalate metabolite concentrations, uncorrected for SG, were analyzed at third trimester of pregnancy and at 8-14 years of age for males and females; comparisons were determined using Wilcoxon rank-sum tests. Spearman's partial-rank correlation coefficients and *p*-values for SG-corrected BPA and phthalates metabolites were calculated for males and females between the two time periods.

Potential confounding factors identified *a priori* and retained in the final adjusted model included maternal BMI at 1 month postpartum and years of education. Descriptive statistics and distributions were performed and extreme outliers were identified using the generalized extreme studentized deviation method (Rosner 1983).

Results

Table 3.1 shows the sample characteristics. Mean age of males and females was 10.3 years. Females had significantly higher measure of triceps skinfolds (17.3mm compared to 14.4mm; $p<0.0001$). Mothers had a mean BMI of 27 at 1 month postpartum and averaged 11 years of total schooling.

Tables 3.2 and 3.3 show the distribution of BPA and phthalates metabolite concentrations uncorrected for urinary dilution for samples collected from mothers during the third trimester of pregnancy, and in adolescence, respectively. The majority of all pregnancy samples had detectable concentrations of BPA (26-36%<LOQ) and phthalate metabolites (0-11%<LOQ). Only BPA showed marginal differences between males and females (GM=0.9ng/mL females; 0.7ng/ml males; p=0.05). Compared to maternal third trimester urine samples, there were fewer adolescent samples below the LOQ for BPA (14-15%<LOQ) and phthalates metabolites (0-6%<LOQ). Geometric means were higher in the adolescent samples with the exception of MEP (108.9ng/mL in males; 114.5ng/mL in females in maternal third trimester; 66ng/mL in males; 97.5ng/ml in females in adolescence), and females had significantly (p=0.03) higher concentrations compared to males. Spearman's partial-rank correlation coefficients comparing SG-corrected BPA and

phthalates metabolites concentrations between the two time periods did not show statistically significant correlations (data not shown).

The associations between sex-stratified continuous measures of maternal third trimester urinary BPA and phthalate metabolites with adolescent BMI z-score, waist circumference, and triceps skinfolds are shown in Table 3.4. Mothers of females had adjusted urinary BPA and MBzP concentrations that were significantly ($p<0.05$) negatively associated with adolescent BMI z-score and were suggestively negatively associated with adolescent waist circumference. Additionally, the high molecular weight phthalate metabolites MEHP, MECPP, MEHHP, and MEOHP were non-significantly positively associated with adolescent waist circumference. Males exposed *in* utero to MBP, MiBP, MBzP, MCPP, MEP, and the high molecular weight phthalates metabolites MECPP, MEHHP, and MEOHP were non-significantly associated with increases in adolescent triceps skinfold.

Figure 3.1 gives evidence for non-monotonic associations between the sex-stratified quartiles with adolescent outcomes; test for trend is non-significant for all metabolites except female BPA. All metabolites exhibited similar patterns across all outcome measures except for female BPA, MEP, MCPP and MBzP. Table 3.5 shows the associations between each quartile exposure compared to the reference quartile. Significant associations were observed for second and third quartile concentrations; in males, this occurred with MEHHP (2^{nd} quartile $\beta=3.70$; 95%CI: 0.81, 6.59) and MEOHP (2^{nd} quartile $\beta=4.87$; 95%CI:1.98, 7.76),with triceps skinfold, and MIBP with waist circumference (3^{rd} quartile $\beta=-6.07$; 95%CI:-11.54, -0.60). Females had significant associations between MECPP (2^{nd} quartile $\beta=-1.21$; 95%CI:-1.90, -0.51), MEHHP (2^{nd} quartile $\beta=-0.77$ 95%CI:-1.48, -0.06), and MEOHP (2^{nd} quartile $\beta=-$

0.79; 95%CI:-1.49, -0.09) with BMI z-score. MECPP (2nd quartile β=-4.92; 95%CI:-7.96, -1.88), MEHHP (2nd quartile β=-3.99; 95%CI:-7.05, -0.92), and MEOHP (2nd quartile β=-4.22; 95%CI:-7.28, -1.15) were also significantly associated with triceps skinfold. MEHP was negatively associated with triceps skinfold (3rd quartile β=-3.92; 95%CI: -7.01, -0.83) and MECPP with waist circumference (2nd quartile β=-7.66; 95%CI:-13.57, -1.76).

Table 3.6 shows the associations between continuous measures of adolescent urinary BPA and phthalate metabolites stratified by sex with BMI z-score, waist circumference, and triceps skinfolds at ages 8-14. Significant negative associations of male adolescent urine concentrations were found between adjusted MEHP with waist circumference (β=-1.95; 95%CI:-3.74, -0.15) and triceps skinfold (β=-1.17; 95%CI:-2.21, -0.12). Suggestive adjusted associations (p<0.1) were observed between MEHP with BMI z-score, and MCPP, MEOHP, and MEHHP with waist circumference. For females, significant negative associations between crude MBP with BMI z-score (β=-0.30; 95%CI:-0.54, -0.05) and waist circumference (β=-2.19; 95%CI:-2.19, -0.11) were observed. Suggestive negative associations were seen with MCPP and MiBP with waist circumference and MBP with triceps skinfold.

Comparing across the two time points show that the suggestive and significant findings in one time period was not found in the other. However, across time periods for males, all metabolites but MBP and MEHP were consistently negatively associated with BMI z-score and waist circumference. The positive suggestive associations seen for male MBzP, MCPP, MEP, MECPP, and MEHHP with triceps skinfold in the third trimester urines were reversed in adolescence. Female MBP, MCPP, MiBP, were consistently suggestively negatively associated with

all outcomes in both time periods; reversal in direction of association from negative in third trimester to positive in adolescence was observed for BPA and MEP for all outcomes.

Adolescent sex-stratified urinary quartiles of urinary biomarkers and outcome measures are shown in Figure 3.3. Tests for linear trend were non-significant for all metabolites and outcome measures. Similar to quartiles of maternal third trimester biomarker concentrations, adolescent urine concentrations of metabolites exhibit similar non-monotonic patterns across outcome measures with increasing quartiles. Table 3.7 shows the associations between quartiles of exposure with adolescent outcomes, compared to the reference quartile. Significant adjusted associations for males were observed between BPA (2^{nd} quartile β=-0.82; 95%CI:-1.51, -0.13) with BMI z-score, waist circumference (2^{nd} quartile β=-6.45; 95%CI:-11.85, -1.04), and triceps skinfold (2^{nd} quartile β=-3.26; 95%CI:-6.46, -0.06). For females, significant findings were observed for MCPP with BMI z-score (3^{rd} quartile β=-1.17; 95%CI:-1.82, -0.53), waist circumference (3^{rd} quartile β=-10.15; 95%CI:-15.76, -4.54), and triceps skinfold (3^{rd} quartile β=-3.54; 95%CI:-6.63, -0.44), and MiBP with BMI z-score (2^{nd} quartile β=-0.91; 95%CI:-1.56, -0.24) and waist circumference (2^{nd} quartile β=-7.61; 95%CI:-13.15, -2.08; 4^{th} quartile β=-6.44; 95%CI:-12.68, -0.20).

Discussion

Principal findings suggest that prenatal and adolescent exposures to BPA and phthalates are differentially associated with adolescent BMI z-score, waist circumference, and triceps skinfold by sex, which has been observed in other studies (Bhandari et al. 2013; Harley et al. 2013; Hatch et al. 2010, 2008; Teitelbaum et al. 2012; Wang et al. 2012a; Wells et al. 2013). Contrary to our hypothesized positive

association between urinary metabolites and outcome measures, significant results were mostly negative. Suggestive associations between continuous urinary metabolites and outcome measures were different between the two time periods and our findings also showed that, while some BPA and phthalate metabolites may be linear in their associations, division into quartile measures demonstrated that that is not true for all metabolites.

Quartile analyses revealed significant associations that occurred with second or third quartile exposures rather than the highest exposure quartile, compared to the lowest quartile. In the third trimester urinary concentrations, these significant findings were observed in both males and females with the high molecular weight phthalates MEHHP, MECCP, and MEOHP whereas, in adolescence, significant findings were different from those in the third trimester, as well as for males and females. In addition, continuous models of males and females were observed to be influenced by different metabolites in different time periods; the marginal increases in fat mass and distribution for females seen from adolescent urines were not observed from pregnancy urines while males only saw increases in triceps skinfold in relation to third trimester exposures.

Our cross-sectional findings of increases in fat mass and distribution from continuous measures of BPA and MEP exposures in females are consistent with other cross-sectional studies (Bhandari et al. 2013; Carwile and Michels 2011; Eng et al. 2013; Harley et al. 2013; Hatch et al. 2010, 2008; Li et al. 2013; Shankar and Teppala 2011; Stahlhut et al. 2007; Teitelbaum et al. 2012; Wang et al. 2012a, 2012d). For males, contrary to findings from Stahlhut et al. (2007) and Hatch et al. (2008), cross-sectional associations between increasing quartiles of male MBP,

MBzP, MEHHP, MEOHP, and MEP in our population were not shown to increase waist circumference and, in fact, increasing quartiles of MBzP were observed to decrease BMI z-score, waist circumference, and triceps skinfolds (Hatch et al. 2010, 2008; Stahlhut et al. 2007). In addition, our results contrast those found by Trasande et al. (2012) and Harley et al (2013), the latter of whom utilizes a Mexican-American birth cohort with participants now at 9 years of age; in males from that study, increasing tertiles of prenatal BPA exposure were found to non-significantly increase fat mass and distribution measures while we observed a significant decrease in outcome measures with the second exposure quartile, with increasing quartiles attenuating those negative associations (Harley et al. 2013; Trasande et al. 2012). It may be that our results are tempered by study participants entering the pubertal transition; associations may change depending on whether participants are pre- or post-transition, and may account for some differences in our results from other cross-sectional studies.

Prenatal (GM=0.8ng/mL) and adolescent (GM=1.3ng/mL) distributions of BPA in our study population are lower than that reported from the United States National Health and Nutrition Examination Survey (NHANES) for females (GM=2.9ng/mL) and Mexican-Americans (GM=2.9ng/mL) (Calafat et al. 2008). Pregnancy urinary BPA levels are also lower than concentrations found in other American and European populations (Braun et al. 2009; Callan et al. 2012; Harley et al. 2013; Philippat et al. 2012; Ye et al. 2008). Concentrations of MCPP were also lower in our population for the two time periods (GM=1.1ng/mL; 2.2ng/mL, respectively) compared to NHANES data (3.02ng/mL for all ages and sex; 4.54ng/mL for ages 6-11 years; 3.65ng/mL for ages 12-19; 2.31 for Mexican-

Americans) (CDC 2013). Higher concentrations of MBP (GM=53.8ng/mL prenatal; 103.5ng/mL adolescent), MEHP (GM=5.1ng/mL prenatal; 6.0ng/mL adolescent), MEHHP (GM=19.2ng/mL prenatal; 46.6ng/mL adolescent), and MEOHP (GM=11.6ng/mL prenatal; 46.6ng/mL adolescent) were higher than concentrations in NHANES for MBP (14.6ng/mL for all ages and sex; 21.7ng/mL for ages 6-11 years; 18.9ng/mL for ages 12-19; 17.2ng/mL for Mexican-Americans), MEHP (1.59ng/mL for all ages and sex; 1.64ng/mL for ages 6-11 years; 1.82ng/mL for ages 12-19; 2.08ng/mL for Mexican-Americans), MEHHP (12.9ng/mL for all ages and sex; 15.0ng/mL for ages 6-11 years; 15.3ng/mL for ages 12-19; 15.3ng/mL for Mexican-Americans), and MEOHP (8.02ng/mL for all ages and sex; 9.78ng/mL for ages 6-11 years; 15.3ng/mL for ages 12-19; 9.57ng/mL for Mexican-Americans). Compared to other study populations, phthalates metabolites in our study sample are lower, with the exception of MBP, MCPP, MEP, MEHHP, and MECPP, though these are not consistent across comparisons to all populations (Kasper-Sonnenberg et al. 2012; Philippat et al. 2012; Ye et al. 2008).

One limitation of our study is the use of a single spot-urine during pregnancy and in childhood. BPA and phthalates also have short metabolite half-lives, with <5-6 hours for BPA and <24 hours for phthalates (Koch et al. 2005; Völkel et al. 2002). Studies with repeated measurements find very low reproducibility (Braun et al. 2012a; Teitelbaum et al. 2008; Valvi et al. 2013). The distributions of urine metabolites in the third trimester of pregnancy and adolescence reported here are similar to those reported by our group earlier among a smaller subset of this study population (Lewis et al. 2013). The concentrations of metabolites may vary widely throughout the day and are influenced by a variety of factors. However, previous

studies have shown that a single measure may be a relatively good measure of exposure due to the consistency of behaviors (Braun et al. 2012b; Mahalingaiah et al. 2008; Teitelbaum et al. 2008). Another limitation was our relatively small sample size, but this study supplied evidence of significant non-monotonicity of BPA and phthalate urinary metabolites with adolescent anthropometric endpoints and provided a baseline for future work utilizing a larger sample size. As with all cross-sectional studies, it is difficult to assess temporality and results should be interpreted with caution. Individuals who are overweight may metabolize BPA and phthalates different than lean individuals, possibly leading to the observed positive associations in many studies. Overweight individuals may also consume more calories, or eat more foods packaged in materials utilizing BPA and phthalates, resulting in a higher exposure to these chemicals. Therefore, confidence in results from longitudinal studies is higher, where the issue of temporality is already established.

However, our study has several strengths. It is a prospective design establishing temporality, and the importance of early life exposures is well-known. The third trimester urine samples allowed us to assess the importance of exposure at a time of rapid development, and we had extensive follow-up of participants, permitting us to estimate associations at time points later than previously reported in the literature. Our findings show no correlations between maternal third trimester and adolescent urines, which may reflect differential sources of BPA and phthalates as well as differences in metabolism. For instance, it has been shown in our population that the use of personal care products by males and females in the previous 48-hours contributes to urinary phthalate metabolite concentrations (Lewis et al. 2013)

In conclusion, we found that there are differences in association with adolescent BMI z-score, waist circumference, and triceps skinfold between exposures to BPA and phthalates metabolites in the third trimester of pregnancy and cross-sectionally in adolescence. Increases in fat mass and distribution with continuous measures of BPA and MEP concentrations in adolescent female urines were consistent with other findings, while these associations were reversed with maternal third trimester urines. Many of the metabolites exhibit non-monotonic relationships with the outcome measures and suggest caution in interpretation of linear associations. Our results suggest that fat distribution for males may be influenced by pregnancy exposures. Further work utilizing a larger sample size will allow for more in-depth longitudinal analyses.

Table 3.1. Characteristics of mothers and adolescents in sample population.

Characteristic	Combined Sex		Males		Females		
	N	Mean±SD	N	Mean±SD	N	Mean±SD	*p*-value
Youth's age (yr)	249	10.3±1.6	117	10.3±1.5	132	10.3±1.7	0.95
weight (kg)	249	38.0±11.0	117	37.2 ±9.7	132	38.7±12.0	0.30
height (cm)	249	138.4±10.7	117	138.6±10.5	132	138.33±10.9	0.87
waist circumference (cm)	249	70.7±10.6	117	69.5 ±9.7	132	71.7±11.3	0.10
triceps skinfold (mm)	249	16.0±5.7	117	14.4±5.3	132	17.3± 5.7	<0.001
BMI z-score	249	0.89±1.2	117	0.91±1.1	132	0.88±1.2	0.85
Mother's BMI 1 month postpartum	240	27.0±3.9	114	26.7±4.2	126	27.2±3.6	0.31
years of education	245	11.0±2.8	115	11.3±2.8	130	10.8±2.8	0.25

Table 3.2. Distribution of total (free+glucuronidated) BPA and phthalate metabolites in third trimester maternal urine (ng/mL uncorrected for dilution).

						Percentiles							
Analyte	**LOQ[a]**	**Sex**	**N**	**%>LOQ**	**GM (SE)[b]**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**Max[c]**	***p*-value**
BPA	0.4	Male	107	64	0.7 (2.0)	<LOQ	<LOQ	0.6	1.1	1.8	2.7	9.0	0.05[a]
		Female	116	74	0.9 (2.1)	<LOQ	<LOQ	0.7	1.4	2.3	4.1	18.7	
MBP	0.5	Male	107	100	53.3 (3.1)	11.8	25.5	58.0	112.0	204.0	318.0	1000.0	1.00
		Female	116	100	54.3 (3.5)	12.7	26.4	54.2	119.0	206.0	606.0	1190.0	
MBzP	0.2	Male	107	99	4.3 (2.5)	1.4	2.6	5.2	7.7	13.4	15.9	32.5	0.18
		Female	116	100	4.1 (2.7)	1.3	2.2	3.7	7.0	12.8	29.6	109.0	
MCPP	0.2	Male	107	94	1.2 (2.5)	0.3	0.6	1.3	2.3	3.4	4.0	12.1	0.36
		Female	116	94	1.1 (2.7)	0.2	0.5	1.1	1.9	4.0	6.6	11.1	
MEP	1.0	Male	107	100	108.9 (2.4)	23.2	44.6	111.0	222.0	594.0	1130.0	7950.0	0.80
		Female	116	99	114.5 (2.8)	20.2	40.8	115.5	241.0	762.0	1900.0	9810.0	
MiBP	0.2	Male	107	98	1.8 (2.7)	0.4	0.9	1.7	3.6	6.4	8.4	40.1	0.33
		Female	116	98	2.0 (2.9)	0.5	1.0	2.0	3.6	8.6	12.6	33.9	
MEHP	1.0	Male	107	89	5.0 (3.5)	1.0	2.5	6.1	10.0	16.6	18.8	62.0	1.00
		Female	116	91	5.2 (2.6)	1.0	2.5	5.6	9.5	16.8	30.1	54.7	
MECPP	0.2	Male	107	100	31.9 (2.6)	8.6	19.4	33.7	58.3	107.0	125.0	193.0	0.99
		Female	116	100	30.9 (2.9)	9.7	15.1	35.4	58.1	107.0	138.0	251.0	
MEHHP	0.1	Male	107	100	19.4 (3.6)	4.7	10.6	16.9	42.7	76.4	95.2	167.0	0.83
		Female	116	100	19.1 (4.7)	4.9	9.1	22.7	37.5	67.8	96.7	161.0	
MEOHP	0.1	Male	107	100	11.6 (2.7)	3.1	6.0	11.2	25.2	46.0	49.9	85.8	0.83
		Female	116	100	11.6 (2.9)	3.2	5.8	13.3	24.7	42.7	56.1	133.0	

[a]LOQ: limit of quantification
[b]GM: geometric mean(standard error)
[c]Max: maximum
*p-value from Wilcoxon-Mann-Whitney test for differences between males and females

Table 3.3. Distribution of total (free+glucuronidated) BPA and phthalate metabolites in adolescent urine (ng/mL uncorrected for dilution).

						Percentiles							
Analyte	**LOQ[a]**	**Sex**	**N**	**%>LOQ**	**GM (SE)[b]**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**Max[c]**	***p*-value***
BPA	0.4	Male	113	86	1.2 (2.3)	<LOQ	0.7	1.2	1.8	3.1	4.9	33.2	0.62
		Female	129	85	1.3 (2.4)	<LOQ	0.6	1.3	2.6	5.0	5.8	20.1	
MBP	0.5	Male	113	100	98.3 (2.3)	31.9	55.2	97.5	163.0	288.0	398.0	1150.0	0.46
		Female	129	100	108.3 (2.8)	30.9	59.4	109.0	224.0	373.0	615.0	6690.0	
MBzP	0.2	Male	113	100	5.5 (2.2)	1.9	3.0	5.5	10.0	15.3	18.4	28.9	0.62
		Female	129	100	5.8 (2.5)	1.7	3.4	5.8	10.8	17.7	23.5	177.0	
MCPP	0.2	Male	113	100	2.1 (2.1)	0.8	1.3	2.1	3.1	5.7	8.0	18.5	0.34
		Female	129	98	2.3 (2.8)	0.7	1.1	2.5	3.9	6.6	13.7	140.0	
MECPP	0.2	Male	113	100	65.6 (2.4)	27.0	39.0	62.5	101.0	166.0	219.0	12900.0	0.73
		Female	129	100	61.8 (2.3)	21.0	36.0	67.1	111.0	149.0	213.0	762.0	
MEHHP	0.1	Male	113	100	48.0 (2.6)	18.9	27.7	43.6	78.7	121.0	155.0	13700.0	0.77
		Female	129	100	45.4 (2.4)	15.7	23.9	46.1	86.6	133.0	189.0	543.0	
MEHP	1.0	Male	113	95	6.1 (2.8)	2.2	3.4	5.1	11.1	16.7	24.2	1910.0	0.60
		Female	129	94	5.9 (2.3)	1.9	3.6	5.5	11.4	17.4	19.4	77.3	
MEOHP	0.1	Male	113	100	21.3 (2.5)	8.4	12.5	20.4	34.4	51.9	74.5	6000.0	0.84
		Female	129	100	20.0 (2.4)	6.7	11.6	20.3	39.0	57.1	84.5	186.0	
MEP	1.0	Male	113	100	66.0 (3.5)	16.2	25.8	59.1	134.0	319.0	1120.0	2230.0	0.03
		Female	129	100	97.5 (4.2)	19.4	32.2	82.9	243.0	855.0	1230.0	4970.0	
MIBP	0.2	Male	113	100	9.5 (2.1)	3.4	5.7	10.0	15.6	23.9	36.5	100.0	0.24
		Female	129	100	10.9 (2.3)	3.6	5.9	11.7	19.1	34.3	45.0	121.0	

[a]LOQ: limit of quantification
[b]GM: geometric mean(standard error)
[c]Max: maximum
*p-value from Wilcoxon-Mann-Whitney test for differences between males and females

Table 3.4. Association of BPA and phthalates metabolites concentrations in maternal third trimester urines with adolescent BMI z-score, waist circumference, and triceps skinfolds at ages 8-14.

		BMI z-score		Waist circumference		Triceps skinfold	
Analyte	**Sex**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**
BPA							
	Male	-0.18 (-0.54, 0.18)	-0.19 (-0.58, 0.20)	-1.15 (-3.95, 1.65)	-0.89 (-4.13, 2.35)	-0.88 (-2.51, 0.75)	-0.57 (-2.47, 1.34)
	Female	-0.27 (-0.63, 0.09)	-0.36 (-0.71, -0.01)*	-1.96 (-5.03, 1.11)	-2.54 (-5.68, 0.61)	-0.05 (-1.65, 1.54)	-0.15 (-1.85, 1.55)
MBP							
	Male	0.03 (-0.20, 0.27)	0.02 (-0.22, 0.25)	0.01 (-1.81, 1.83)	-0.31 (-2.28, 1.66)	0.54 (-0.52, 1.60)	0.5 7(-0.58, 1.73)
	Female	-0.15 (-0.37, 0.07)	-0.1 (-0.32, 0.12)	-1.22 (-3.11, 0.66)	-0.93 (-3.02, 1.15)	-0.14 (-1.12, 0.84)	-0.25 (-1.37, 0.86)
MBzP							
	Male	-0.10 (-0.36, 0.16)	-0.17 (-0.43, 0.10)	-0.04 (-2.08, 2.00)	-0.64 (-2.82, 1.54)	0.62 (-0.57, 1.81)	0.41 (-0.87, 1.70)
	Female	-0.28 (-0.54, -0.02)*	-0.25 (-0.53, 0.02)	-1.84 (-4.01, 0.34)	-1.94 (-4.37, 0.50)	-0.01 (-1.15, 1.12)	-0.05 (-1.37, 1.26)
MCPP							
	Male	-0.02 (-0.30, 0.27)	-0.06 (-0.36, 0.23)	-0.13 (-2.35, 2.10)	-0.54 (-2.99, 1.90)	0.47 (-0.82, 1.77)	0.58 (-0.86, 2.01)
	Female	-0.19 (-0.48, 0.10)	-0.10 (-0.39, 0.19)	-1.46 (-3.94, 1.02)	-1.16 (-4.07, 1.75)	-0.35 (-1.64, 0.94)	-0.37 (-1.92, 1.19)
MEP							
	Male	-0.04 (-0.23, 0.14)	-0.04 (-0.23, 0.14)	-0.42 (-1.86, 1.01)	-0.45 (-2.01, 1.12)	0.26 (-0.58, 1.10)	0.39 (-0.53, 1.31)
	Female	-0.09 (-0.25, 0.07)	-0.12 (-0.28, 0.04)	-0.45 (-1.85, 0.96)	-0.3 (-1.80, 1.21)	-0.03 (-0.76, 0.70)	-0.18 (-0.98, 0.62)
MiBP							
	Male	-0.09 (-0.34, 0.17)	-0.12 (-0.39, 0.15)	-1.11 (-3.07, 0.85)	-1.32 (-3.52, 0.87)	-0.19 (-1.34, 0.96)	0.12 (-1.18, 1.42)
	Female	-0.08 (-0.34, 0.19)	-0.09 (-0.36, 0.17)	-0.55 (-2.85, 1.74)	-0.7 (-3.02, 1.61)	-0.25 (-1.44, 0.93)	-0.51 (-1.74, 0.72)
MEHP							
	Male	0.04 (-0.23, 0.31)	0.03 (-0.24, 0.30)	-0.49 (-2.57, 1.58)	-0.83 (-3.15, 1.49)	-0.2 (-1.41, 1.02)	-0.32 (-1.69, 1.04)
	Female	-0.12 (-0.41, 0.16)	-0.08 (-0.36, 0.21)	-0.33 (-2.78, 2.12)	0.26 (-2.27, 2.79)	-0.8 (-2.06, 0.46)	-0.69 (-2.04, 0.65)
MECPP							
	Male	-0.14 (-0.46, 0.18)	-0.18 (-0.49, 0.14)	-1.17 (-3.65, 1.31)	-1.29 (-3.90, 1.31)	0.34 (-1.12, 1.79)	0.41 (-1.12, 1.95)
	Female	-0.04 (-0.31, 0.24)	-0.04 (-0.31, 0.24)	0.36 (-2.00, 2.72)	0.05 (-2.38, 2.48)	-0.56 (-1.77, 0.65)	-0.9 (-2.18, 0.38)
MEHHP							
	Male	-0.09 (-0.37, 0.18)	-0.1 (-0.37, 0.17)	-0.85 (-2.97, 1.27)	-0.69 (-2.96, 1.58)	-0.06 (-1.30, 1.18)	0.12 (-1.22, 1.46)
	Female	-0.04 (-0.29, 0.22)	-0.02 (-0.27, 0.23)	0.34 (-1.84, 2.52)	0.25 (-1.99, 2.49)	-0.33 (-1.46, 0.80)	-0.58 (-1.77, 0.61)
MEOHP							
	Male	-0.12 (-0.40, 0.16)	-0.12 (-0.39, 0.16)	-0.97 (-3.15, 1.20)	-0.89 (-3.24, 1.45)	0.17 (-1.10, 1.45)	0.35 (-1.03, 1.73)
	Female	-0.04 (-0.30, 0.21)	-0.03 (-0.28, 0.23)	0.2 (-2.01, 2.42)	0.04 (-2.26, 2.34)	-0.37 (-1.51, 0.77)	-0.61 (-1.83, 0.61)

[a]N=107 for males; 116 for females. Adjusted for age, sex, specific gravity
[b]N=94 for males; 98 for females. Additionally adjusted for mother's BMI 1 month postpartum, years of education.
*p<0.05

Table 3.5. Multivariable linear regression of associations of adolescent BMI z-score, waist circumference, and triceps skinfold with quartiles of maternal third trimester urine metabolites compared to the reference first quartile.

				BMI z-score			**Waist circumference**			**Triceps skinfold**		
Analyte	Model	Sex	N	β	95% CI		β	95% CI		β	95% CI	
BPA	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.10	-0.56	0.76	1.43	-3.78	6.63	1.63	-1.39	4.65
	Quartile 3			0.21	-0.40	0.83	0.85	-3.98	5.68	1.54	-1.26	4.35
	Quartile 4			-0.52	-1.24	0.20	-2.42	-8.05	3.22	-1.43	-4.70	1.84
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			0.40	-0.33	1.13	3.91	-2.23	10.04	-0.81	-4.09	2.47
	Quartile 3			-0.01	-0.71	0.70	2.09	-3.81	7.99	0.12	-3.03	3.27
	Quartile 4			-0.75	-1.52	0.02	-4.26	-10.72	2.19	-2.12	-5.57	1.33
MBP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.19	-0.49	0.87	1.71	-3.52	6.94	2.66	-0.41	5.73
	Quartile 3			-0.15	-0.80	0.50	-2.10	-7.12	2.93	1.67	-1.28	4.62
	Quartile 4			0.05	-0.72	0.83	-1.37	-7.37	4.63	1.31	-2.21	4.83
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			0.03	-0.66	0.71	-0.46	-6.16	5.23	-1.43	-4.33	1.48
	Quartile 3			-0.35	-1.10	0.41	-2.83	-9.14	3.48	-2.75	-5.97	0.47
	Quartile 4			-0.35	-1.12	0.41	-2.59	-8.98	3.80	0.05	-3.21	3.31
MBzP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.25	-0.95	0.45	-0.53	-6.02	4.96	-1.33	-4.57	1.91
	Quartile 3			-0.64	-1.35	0.08	-2.37	-7.95	3.20	-0.63	-3.92	2.66
	Quartile 4			-0.44	-1.16	0.28	-2.49	-8.12	3.13	-0.48	-3.80	2.84
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.24	-0.88	0.39	-2.60	-7.88	2.69	0.06	-2.67	2.80
	Quartile 3			-0.33	-0.99	0.32	-1.24	-6.68	4.21	-0.27	-3.09	2.55
	Quartile 4			-0.39	-1.13	0.34	-1.79	-7.91	4.33	1.88	-1.29	5.04
MCPP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.03	-0.72	0.67	-0.22	-5.64	5.20	2.14	-1.02	5.31
	Quartile 3			-0.18	-0.92	0.55	-1.06	-6.78	4.66	1.50	-1.84	4.84
	Quartile 4			-0.03	-0.79	0.73	0.37	-5.52	6.25	1.65	-1.79	5.08
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.11	-0.80	0.59	-2.44	-8.18	3.30	-1.93	-4.89	1.02
	Quartile 3			-0.07	-0.78	0.64	0.30	-5.59	6.20	-1.87	-4.90	1.17
	Quartile 4			-0.21	-1.06	0.63	-1.61	-8.56	5.34	-0.20	-3.78	3.38
MECPP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.23	-0.41	0.86	1.29	-3.65	6.22	2.02	-0.94	4.99
	Quartile 3			0.31	-0.40	1.03	3.00	-2.51	8.52	2.39	-0.92	5.71
	Quartile 4			-0.67	-1.47	0.14	-5.25	-11.48	0.98	-0.76	-4.50	2.98
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-1.19	-1.89	-0.50	-7.66	-13.57	-1.76	-4.92	-7.96	-1.88
	Quartile 3			-0.15	-0.83	0.54	-0.45	-6.25	5.35	-1.94	-4.93	1.05
	Quartile 4			-0.25	-1.01	0.52	-0.02	-6.51	6.47	-1.31	-4.65	2.04
MEHHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.49	-0.16	1.13	3.06	-1.90	8.03	3.70	0.81	6.59
	Quartile 3			0.21	-0.51	0.93	2.72	-2.80	8.25	1.85	-1.37	5.06
	Quartile 4			-0.32	-1.09	0.44	-3.69	-9.55	2.18	-0.48	-3.89	2.93
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.75	-1.47	-0.03	-5.29	-11.29	0.70	-3.99	-7.05	-0.92
	Quartile 3			-0.21	-0.88	0.47	-1.08	-6.74	4.58	-2.27	-5.16	0.63
	Quartile 4			-0.06	-0.94	0.81	0.42	-6.91	7.74	-1.02	-4.77	2.72
MEHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.01	-0.65	0.67	-1.42	-6.52	3.68	-0.05	-3.03	2.93
	Quartile 3			0.29	-0.39	0.96	0.83	-4.37	6.03	1.66	-1.38	4.69
	Quartile 4			-0.05	-0.77	0.66	-3.01	-8.52	2.51	-1.34	-4.56	1.88
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.17	-0.85	0.52	-0.13	-5.86	5.60	-1.87	-4.81	1.07
	Quartile 3			-0.66	-1.38	0.07	-4.14	-10.16	1.89	-3.92	-7.01	-0.83
	Quartile 4			-0.09	-0.88	0.70	0.71	-5.89	7.31	-1.96	-5.35	1.42
MEOHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.62	-0.04	1.28	3.65	-1.44	8.74	4.87	1.98	7.76
	Quartile 3			0.18	-0.50	0.87	2.08	-3.23	7.40	2.54	-0.47	5.56

	Quartile 4			-0.29	-1.07	0.49	-3.68	-9.71	2.35	0.00	-3.43	3.42
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.77	-1.48	-0.06	-5.34	-11.32	0.65	-4.22	-7.28	-1.15
	Quartile 3			0.02	-0.68	0.72	0.00	-5.85	5.86	-1.49	-4.49	1.51
	Quartile 4			-0.39	-1.25	0.46	-1.89	-9.10	5.32	-2.01	-5.70	1.68
MEP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.20	-0.85	0.46	-0.05	-5.11	5.02	0.61	-2.42	3.63
	Quartile 3			-0.50	-1.17	0.17	-3.83	-9.01	1.34	0.39	-2.70	3.48
	Quartile 4			-0.44	-1.20	0.31	-3.19	-8.98	2.60	-0.54	-4.00	2.92
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			0.49	-0.19	1.17	3.66	-2.01	9.34	0.47	-2.50	3.45
	Quartile 3			0.18	-0.52	0.88	1.81	-4.04	7.66	0.51	-2.55	3.58
	Quartile 4			-0.06	-0.75	0.62	1.07	-4.68	6.82	0.58	-2.43	3.59
MIBP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.01	-0.65	0.66	-0.61	-5.64	4.42	-0.16	-3.18	2.86
	Quartile 3			-0.61	-0.65	0.66	-6.07	-11.54	-0.60	-2.09	-5.37	1.19
	Quartile 4			-0.26	-1.00	0.49	-2.92	-8.64	2.81	-0.46	-3.90	2.97
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.44	-1.15	0.27	-3.64	-9.51	2.23	-1.68	-4.76	1.39
	Quartile 3			-0.09	-0.81	0.63	-0.77	-6.71	5.17	-0.42	-3.53	2.69
	Quartile 4			-0.51	-1.31	0.30	-4.64	-11.30	2.01	-1.23	-4.72	2.25

Adjusted for age, specific gravity, mother's BMI 1 month postpartum, years of education

Table 3.6. Association of BPA and phthalates metabolites concentrations adolescent urines with adolescent BMI z-score, waist circumference, and sum of triceps skinfolds at ages 8-14.

		BMI z-score		Waist circumference		Triceps skinfold	
Analyte	**Sex**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**
BPA							
	Male	-0.13 (-0.42, 0.16)	-0.15 (-0.44, 0.14)	-0.34 (-2.65, 1.96)	-0.50 (-2.89, 1.89)	-0.45 (-1.79, 0.90)	-0.59 (-1.98, 0.81)
	Female	0.09 (-0.22, 0.38)	0.12 (-0.17, 0.42)	0.55 (-1.99, 3.10)	1.02 (-1.51, 3.55)	0.40 (-0.98, 1.79)	0.79 (-0.55, 2.14)
MBP							
	Male	0.04 (-0.25, 0.33)	0.02 (-0.26, 0.31)	-0.27 (-2.58, 2.03)	-0.21 (-2.51, 2.09)	0.70 (-0.64, 2.03)	0.74 (-0.60, 2.08)
	Female	-0.30 (-0.54, -0.05)*	-0.20 (-0.45, 0.06)	-2.19 (-4.27, -0.11)*	-1.54 (-3.73, 0.64)	-0.95 (-2.09, 0.19)	-0.30 (-1.48, 0.88)
MBzP							
	Male	-0.10 (-0.40, 0.20)	-0.07 (-0.38, 0.24)	-1.62 (-3.99, 0.76)	-1.20 (-3.67, 1.29)	-0.79 (-2.18, 0.60)	-0.53 (-1.99, 0.92)
	Female	0.05 (-0.23, 0.34)	0.06 (-0.22, 0.35)	-0.17 (-2.62, 2.28)	-0.19 (-2.64, 2.26)	0.32 (-1.01, 1.65)	0.36 (-0.95, 1.67)
MCPP							
	Male	-0.18 (-0.50, 0.14)	-0.21 (-0.53, 0.12)	-2.05 (-4.64, 0.54)	-1.95 (-4.56, 0.66)	-0.70 (-2.22, 0.82)	-0.65 (-2.19, 0.89)
	Female	-0.25 (-0.51, 0.01)	-0.18 (-0.44, 0.09)	-1.73 (-3.93, 0.47)	-1.27 (-3.56, 1.03)	-0.49 (-1.70, 0.71)	-0.08 (-1.32, 1.15)
MEP							
	Male	-0.06 (-0.23, 0.12)	-0.05 (-0.23, 0.13)	-0.65 (-2.08, 0.78)	-0.55 (-2.02, 0.93)	-0.23 (-1.07, 0.60)	-0.19 (-1.06, 0.67)
	Female	0.07 (-0.09, 0.23)	0.06 (-0.11, 0.22)	0.40 (-1.00, 1.80)	0.22 (-1.21, 1.66)	0.30 (-0.46, 1.06)	0.34 (-0.43, 1.10)
MIBP							
	Male	-0.01 (-0.32, 0.29)	-0.06 (-0.37, 0.24)	-0.02 (-2.42, 2.38)	-0.24 (-2.67, 2.20)	0.24 (-1.16, 1.64)	0.18 (-1.25, 1.61)
	Female	-0.17 (-0.48, 0.12)	-0.16 (-0.47, 0.14)	-2.07 (-4.64, 0.50)	-1.94 (-4.56, 0.68)	-0.87 (-2.27, 0.53)	-0.58 (-1.99, 0.83)
MEHP							
	Male	-0.11 (-0.32, 0.10)	-0.21 (-0.43, 0.01)	-1.24 (-2.95, 0.47)	-1.95 (-3.74, -0.15)*	-0.76 (-1.75, 0.24)	-1.17 (-2.21, -0.12)*
	Female	-0.04 (-0.35, 0.27)	-0.09 (-0.41, 0.22)	-0.80 (-3.48, 1.87)	-1.14 (-3.83, 1.54)	-0.42 (-1.87, 1.03)	-0.56 (-1.99, 0.88)
MECPP							
	Male	-0.06 (-0.31, 0.18)	-0.19 (-0.45, 0.06)	-0.68 (-2.64, 1.27)	-1.48 (-3.54, 0.57)	-0.26 (-1.40, 0.88)	-0.69 (-1.89, 0.52)
	Female	0.09 (-0.24, 0.41)	0.05 (-0.27, 0.37)	0.17 (-2.64, 2.96)	-0.003 (-2.81, 2.80)	0.05 (-1.47, 1.57)	-0.06 (-1.57, 1.44)
MEHHP							
	Male	-0.05 (-0.28, 0.19)	-0.18 (-0.43, 0.06)	-0.68 (-2.54, 1.17)	-1.45 (-3.41, 0.51)	-0.11 (-1.20, 0.97)	-0.53 (-1.68, 0.63)
	Female	0.10 (-0.21, 0.40)	0.07 (-0.23, 0.37)	0.32 (-2.30, 2.93)	0.24 (-2.37, 2.86)	0.17 (-1.24, 1.59)	0.12 (-1.28, 1.52)
MEOHP							
	Male	-0.07 (-0.31, 0.17)	-0.21 (-0.46, 0.03)	-0.80 (-2.69, 1.09)	-1.63 (-3.62, 0.37)	-0.21 (-1.31, 0.90)	-0.65 (-1.82, 0.53)
	Female	0.04 (-0.27, 0.34)	0.03 (-0.28, 0.33)	-0.09 (-2.73, 2.55)	-0.03 (-2.68, 2.61)	0.08 (-1.36, 1.51)	0.07 (-1.35, 1.48)

[a]N=113for males; 129 for females. Adjusted for age, sex, specific gravity

[b]N=108 for males; 121 for females. Additionally adjusted for mother's BMI 1 month postpartum, years of education.

*p<0.05

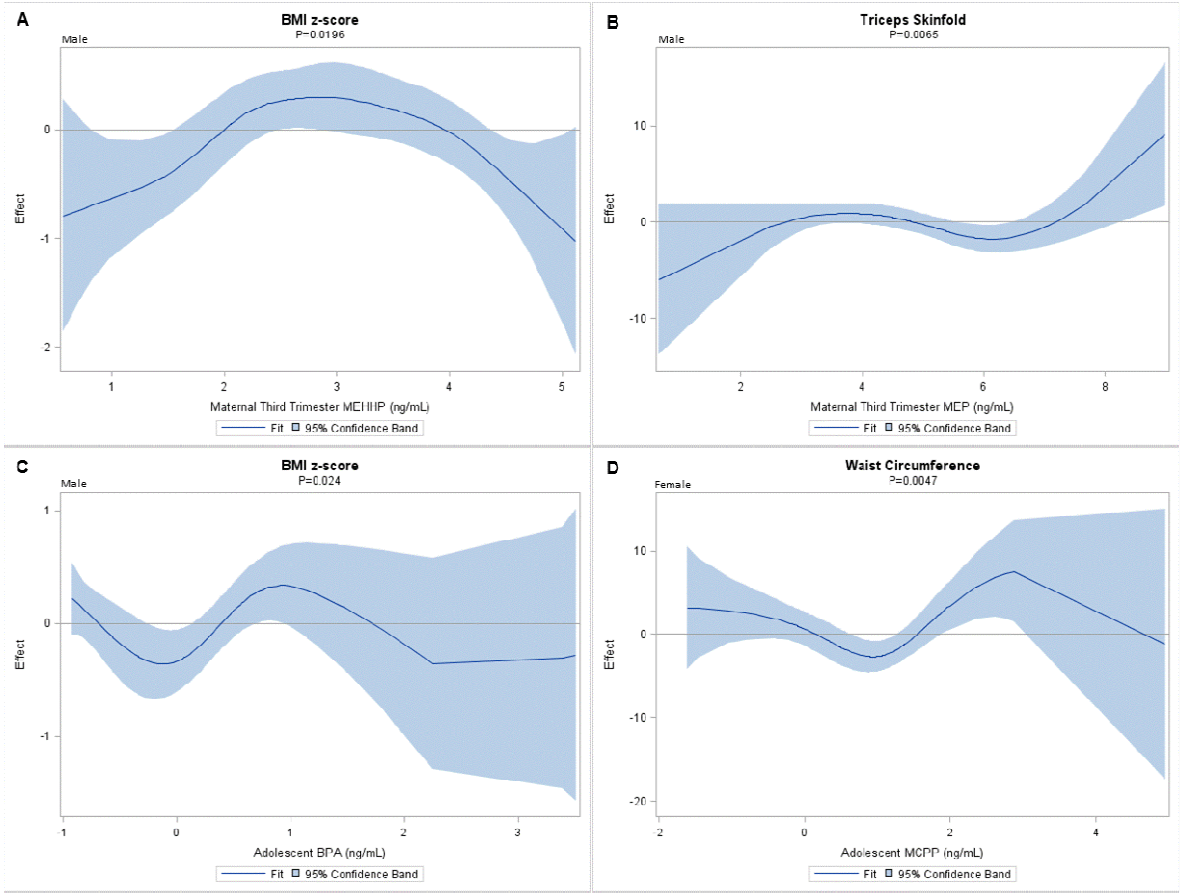
Table 3.7. Multivariable linear regression of associations of adolescent BMI z-score, waist circumference, and triceps skinfold with quartiles of adolescent urine metabolites compared to the reference first quartile.

				BMI z-score			Waist circumference			Tricep skinfold		
Analyte	Model	Sex	N	β	95% CI		β	95% CI		β	95% CI	
BPA	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.82	-1.51	-0.13	-6.45	-11.85	-1.04	-3.26	-6.46	-0.06
	Quartile 3			-0.29	-0.95	0.38	-2.15	-7.38	3.08	-1.10	-4.19	2.00
	Quartile 4			-0.34	-1.11	0.43	-1.98	-8.04	4.08	-2.01	-5.60	1.57
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			0.05	-0.62	0.72	-0.86	-6.47	4.75	-0.21	-3.21	2.79
	Quartile 3			0.14	-0.62	0.72	1.15	-5.13	7.42	1.84	-1.52	5.19
	Quartile 4			0.34	-0.40	1.08	3.01	-3.23	9.25	1.59	-1.75	4.92
MBP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.49	-1.15	0.16	-2.12	-7.34	3.10	-1.05	-4.11	2.01
	Quartile 3			-0.16	-0.83	0.52	-1.35	-6.72	4.03	-0.28	-3.43	2.87
	Quartile 4			-0.20	-0.89	0.50	-2.56	-8.09	2.98	-0.12	-3.37	3.13
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.50	-1.15	0.15	-2.07	-7.58	3.44	-1.15	-4.11	1.82
	Quartile 3			-0.68	-1.39	0.03	-5.16	-11.31	0.99	-1.89	-5.20	1.42
	Quartile 4			-0.33	-1.04	0.38	-1.42	-7.46	4.62	-0.02	-3.26	3.23
MBzP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			0.01	-0.61	0.62	-2.10	-6.99	2.80	-0.24	-3.11	2.64
	Quartile 3			-0.31	-0.94	0.33	-3.11	-8.11	1.90	-1.68	-4.61	1.26
	Quartile 4			-0.19	-0.89	0.50	-3.52	-8.96	1.93	-1.10	-4.29	2.10
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			0.05	-0.58	0.69	0.37	-5.07	5.81	1.71	-1.19	4.61
	Quartile 3			-0.02	-0.72	0.68	-1.39	-7.35	4.56	1.56	-1.61	4.73
	Quartile 4			0.20	-0.60	1.00	0.35	-6.41	7.11	2.01	-1.59	5.61
MCPP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.20	-0.87	0.46	-1.62	-6.86	3.63	-1.23	-4.30	1.84
	Quartile 3			-0.39	-1.12	0.34	-2.88	-8.63	2.86	-0.78	-4.15	2.59
	Quartile 4			-0.27	-1.02	0.48	-2.95	-8.96	3.06	-1.52	-5.04	2.00
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.35	-1.03	0.33	-3.67	-9.40	2.07	0.10	-3.06	3.26
	Quartile 3			-1.17	-1.82	-0.53	-10.15	-15.76	-4.54	-3.54	-6.63	-0.44
	Quartile 4			-0.27	-0.96	0.43	-1.85	-7.75	4.05	0.21	-3.04	3.46
MECPP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.21	-0.87	0.46	-2.97	-8.33	2.39	-0.20	-3.37	2.98
	Quartile 3			0.05	-0.67	0.77	-0.15	-5.95	5.64	0.63	-2.80	4.06
	Quartile 4			-0.41	-1.12	0.30	-3.70	-9.27	1.87	-0.82	-4.11	2.48
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.19	-0.86	0.48	-3.92	-9.49	1.65	-1.83	-4.84	1.17
	Quartile 3			0.20	-0.48	0.87	1.87	-3.77	7.51	0.41	-2.64	3.45
	Quartile 4			0.07	-0.65	0.80	-0.93	-7.02	5.16	-0.32	-3.61	2.96
MEHHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.57	-1.21	0.07	-4.58	-9.71	0.55	-1.80	-4.81	1.21
	Quartile 3			-0.37	-1.07	0.34	-1.87	-7.47	3.72	0.38	-2.90	3.67
	Quartile 4			-0.21	-0.90	0.49	-2.68	-8.17	2.80	-1.03	-4.25	2.19
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			0.12	-0.55	0.79	-0.44	-6.10	5.22	-0.38	-3.40	2.65
	Quartile 3			0.07	-0.61	0.76	1.18	-4.68	7.05	1.06	-2.07	4.19
	Quartile 4			0.35	-0.37	1.07	2.06	-4.10	8.22	1.39	-1.89	4.68
MEHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.04	-0.67	0.59	-1.02	-5.99	3.95	-0.13	-3.03	2.76
	Quartile 3			-0.32	-0.98	0.34	-2.49	-7.76	2.79	-1.13	-4.20	1.95
	Quartile 4			-0.38	-1.04	0.27	-3.80	-9.05	1.45	-2.50	-5.56	0.56
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.29	-0.93	0.34	-2.00	-7.37	3.37	0.31	-2.57	3.18
	Quartile 3			-0.38	-1.07	0.31	-3.42	-9.24	2.41	-1.29	-4.41	1.83
	Quartile 4			-0.13	-0.87	0.61	-1.74	-8.02	4.54	0.17	-3.19	3.53
MEOHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.59	-1.26	0.08	-3.98	-9.34	1.39	-1.26	-4.42	1.90
	Quartile 3			-0.45	-1.11	0.22	-2.24	-7.56	3.07	-0.21	-3.34	2.92
	Quartile 4			-0.37	-1.08	0.34	-3.29	-8.93	2.34	-1.05	-4.37	2.27
	Quartile 1	Female	121		Reference			Reference			Reference	

	Quartile 2			0.02	-0.64	0.67	-1.54	-7.06	3.97	-0.79	-3.75	2.17
	Quartile 3			-0.11	-0.84	0.62	-1.32	-7.50	4.86	0.57	-2.75	3.90
	Quartile 4			0.28	-0.46	1.01	2.06	-4.23	8.36	1.06	-2.32	4.44
MEP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.36	-0.97	0.25	-3.24	-8.05	1.57	-0.78	-3.62	2.06
	Quartile 3			-0.04	-0.65	0.56	-0.20	-4.97	4.57	-0.05	-2.87	2.77
	Quartile 4			-0.25	-0.93	0.44	-3.14	-8.56	2.29	-1.46	-4.66	1.75
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.23	-0.92	0.46	-3.04	-8.85	2.77	-0.52	-3.64	2.60
	Quartile 3			-0.31	-1.00	0.39	-2.57	-8.47	3.33	-0.60	-3.77	2.57
	Quartile 4			0.00	-0.68	0.69	-0.69	-6.49	5.10	0.58	-2.54	3.69
MIBP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.07	-0.75	0.60	-1.20	-6.61	4.20	0.02	-3.14	3.18
	Quartile 3			-0.05	-0.75	0.64	-0.91	-6.38	4.56	-0.16	-3.36	3.04
	Quartile 4			-0.25	-0.97	0.46	-1.46	-7.12	4.19	-1.05	-4.36	2.26
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.91	-1.56	-0.25	-7.61	-13.15	-2.08	-2.21	-5.24	0.83
	Quartile 3			-0.44	-1.14	0.26	-3.60	-9.52	2.31	-0.22	-3.46	3.02
	Quartile 4			-0.57	-1.30	0.17	-6.44	-12.68	-0.20	-1.47	-4.89	1.95

Adjusted for age, specific gravity, mother's BMI 1 month postpartum, years of education

Figure 3.1. Generalized additive model results for the association of maternal third trimester and adolescent urinary concentrations with adolescent outcomes measures.



(A) Maternal third trimester urinary concentrations of MEHHP (ng/mL) in males with adolescent BMI z-score, (B) Maternal third trimester MEP (ng/mL) in males with adolescent triceps skinfold, (C) Adolescent male BPA (ng/mL) with adolescent BMI z-score, and (D) Adolescent female MCPP and adolescent waist circumference.
Models are adjusted for specific gravity, child's age, and mother's BMI 1 month postpartum and total years of schooling.

Figure 3.2. Sex-stratified associations of maternal third trimester urinary concentrations of quartile BPA and phthalate metabolites with adolescent BMI z-score, waist circumference, and triceps skinfold measurements at ages 8-14. Point estimates and 95% confidence intervals are adjusted for specific gravity, child's age, and mother's 1 month postpartum BMI and total years of education.

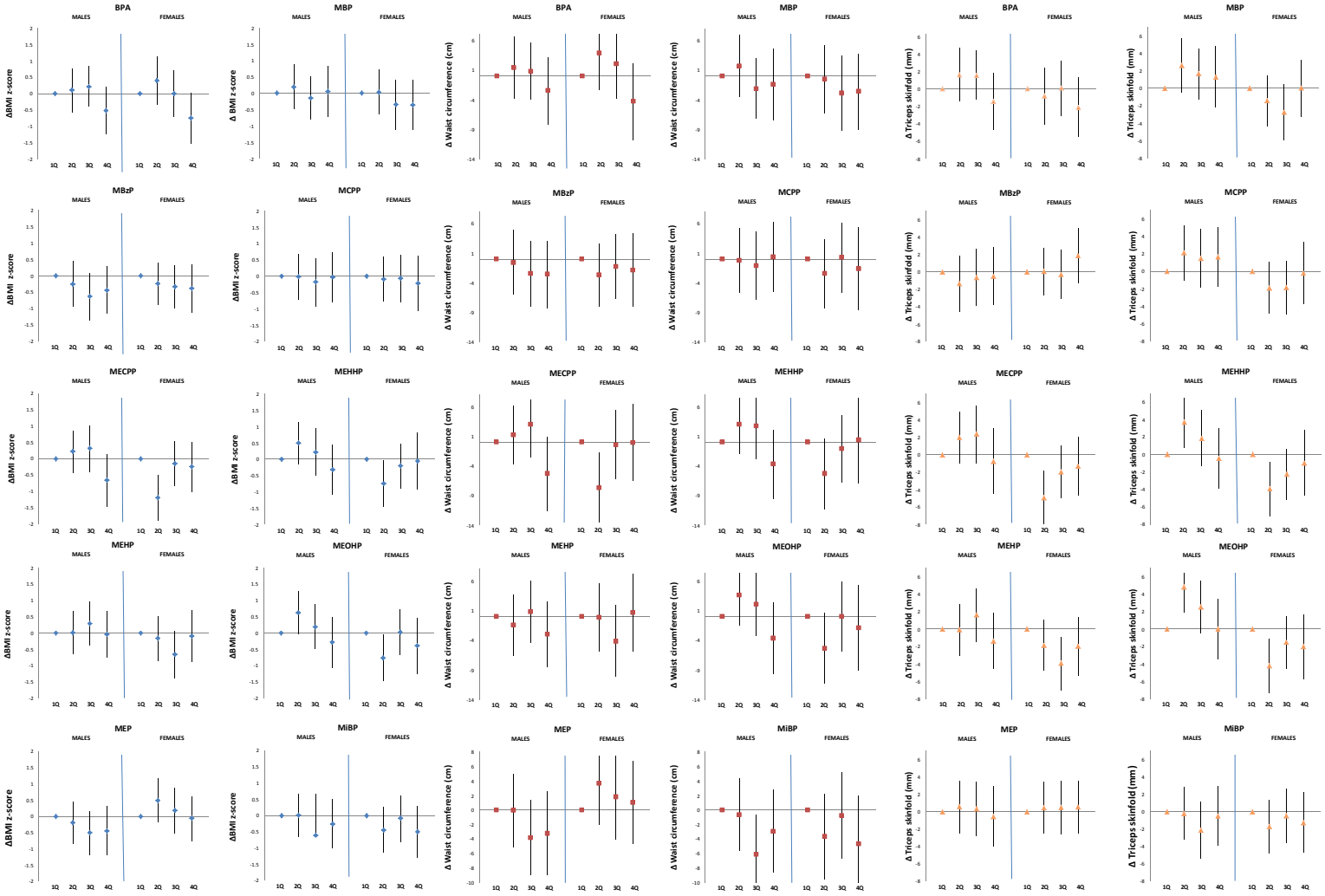
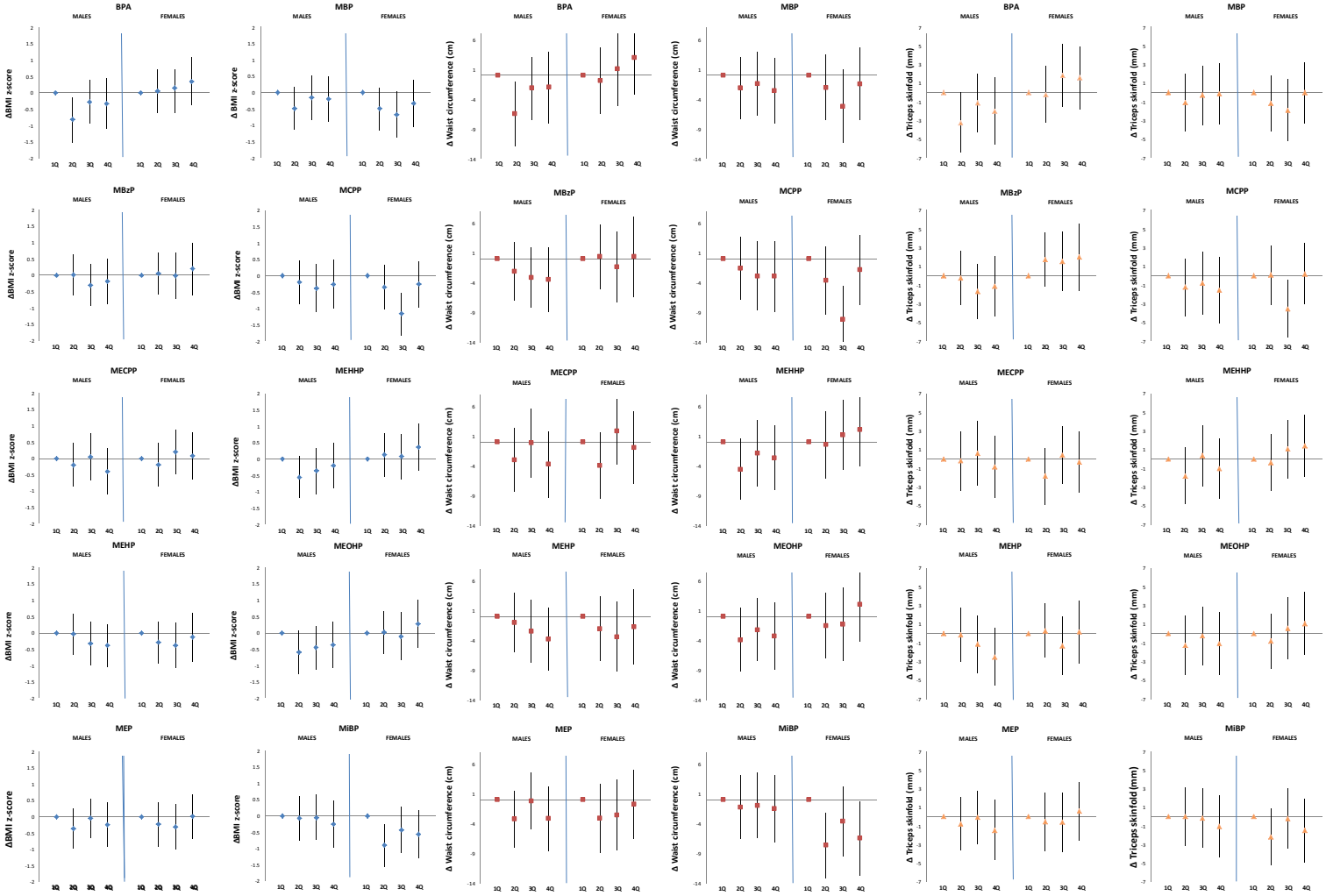


Figure 3.3. Sex-stratified associations of adolescent urinary concentrations of quartile BPA and phthalate metabolites with adolescent BMI z-score, waist circumference, and sum of triceps and subscapular skinfold measurements at ages 8-14.
Point estimates and 95% confidence intervals are adjusted for specific gravity, child's age, and mother's 1 month postpartum BMI and total years of education.



Appendix

Figure 3.4. Association of BPA and phthalates metabolites concentrations in maternal third trimester urines with adolescent BMI, waist circumference, and sum of triceps and subscapular skinfolds at ages 8-14.

		BMI		Waist circumference		Sum skinfold	
Analyte	**Sex**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**
BPA							
	Male	-0.55 (-1.50, 0.39)	-0.37 (-1.45, 0.71)	-1.15 (-3.95, 1.65)	-0.89 (-4.13, 2.35)	-2.18 (-5.50, 1.13)	-1.72 (-5.38, 1.95)
	Female	-0.57 (-1.68, 0.55)	-0.80 (-1.95, 0.34)	-1.96 (-5.03, 1.11)	-2.54 (-5.68, 0.61)	-1.96 (-4.45, 2.25)	-1.96 (-5.15,1.24)
MBP							
	Male	0.08 (-0.53, 0.69)	0.01 (-0.65, 0.67)	0.01 (-1.81, 1.83)	-0.31 (-2.28, 1.66)	0.25 (-1.91, 2.41)	0.35 (-1.88, 2.58)
	Female	-0.45 (-1.13, 0.24)	-0.35 (-1.11, 0.41)	-1.22 (-3.11, 0.66)	-0.93 (-3.02, 1.15)	-0.72 (-2.78, 1.33)	-0.21 (-2.20, 1.79)
MBzP							
	Male	-0.08 (-0.77, 0.60)	-0.28 (-1.01, 0.44)	-0.04 (-2.08, 2.00)	-0.64 (-2.82, 1.54)	0.62 (-1.80, 3.05)	0.21 (-2.30, 2.73)
	Female	-0.75 (-1.53, 0.04)	-0.75 (-1.63, 0.13)	-1.84 (-4.01, 0.34)	-1.94 (-4.37, 0.50)	-0.97 (-3.35, 1.41)	-0.31 (-2.79, 2.16)
MCPP							
	Male	0.01 (-0.74, 0.76)	-0.05 (-0.87, 0.76)	-0.13 (-2.35, 2.10)	-0.54 (-2.99, 1.90)	0.25 (-2.39, 2.90)	0.41 (-2.79, 3.19)
	Female	-0.56 (-1.45, 0.34)	-0.41 (-1.46, 0.65)	-1.46 (-3.94, 1.02)	-1.16 (-4.07, 1.75)	-1.41 (-4.11, 1.29)	-0.46 (-3.10, 2.19)
MEP							
	Male	-0.09 (-0.58, 0.39)	-0.14 (-0.69, 0.39)	-0.42 (-1.86, 1.01)	-0.45 (-2.01, 1.12)	-0.33 (-3.29, 2.62)	-0.53 (-3.51, 2.46)
	Female	-0.23 (-0.74, 0.28)	-0.25 (-0.79, 0.30)	-0.45 (-1.85, 0.96)	-0.3 (-1.80, 1.21)	-0.24 (-2.80, 2.32)	-0.34 (-2.83, 2.14)
MiBP							
	Male	-0.32 (-0.98, 0.34)	-0.29 (-1.03, 0.44)	-1.11 (-3.07, 0.85)	-1.32 (-3.52, 0.87)	-0.73 (-3.26, 1.79)	-0.73 (-3.28, 1.82)
	Female	-0.13 (-0.96, 0.70)	-0.11 (-0.95, 0.73)	-0.55 (-2.85, 1.74)	-0.7 (-3.02, 1.61)	0.02 (-2.35, 2.39)	0.08 (-2.21, 2.36)
MEHP							
	Male	0.02 (-0.68, 0.72)	-0.11 (-0.88, 0.67)	-0.49 (-2.57, 1.58)	-0.83 (-3.15, 1.49)	-0.83 (-3.30,1 .63)	-1.03 (-3.55, 1.49)
	Female	-0.26 (-1.15, 0.62)	-0.10 (-1.02, 0.82)	-0.33 (-2.78, 2.12)	0.26 (-2.27, 2.79)	-0.89 (-3.55, 1.77)	-0.33 (-2.92, 2.26)
MECPP							
	Male	-0.26 (-1.09, 0.58)	-0.31 (-1.18, 0.56)	-1.17 (-3.65, 1.31)	-1.29 (-3.90, 1.31)	-0.58 (-3.18, 2.01)	-0.53 (-3.16, 2.09)
	Female	-0.004 (-0.86, 0.85)	-0.11 (-0.99, 0.78)	0.36 (-2.00, 2.72)	0.05 (-2.38, 2.48)	0.06 (-2.35, 2.46)	0.12 (-2.22, 2.46)
MEHHP							
	Male	-0.19 (-0.91, 0.52)	-0.14 (-0.90, 0.62)	-0.85 (-2.97, 1.27)	-0.69 (-2.96, 1.58)	0.03 (-1.69, 1.74)	0.42 (-1.35, 2.20)
	Female	-0.01 (-0.80, 0.78)	-0.02 (-0.84, 0.79)	0.34 (-1.84, 2.52)	0.25 (-1.99, 2.49)	0.04 (-1.48, 1.57)	-0.22 (-1.70, 1.27)
MEOHP							
	Male	-0.24 (-0.97, 0.50)	-0.21 (-0.99, 0.57)	-0.97 (-3.15, 1.20)	-0.89 (-3.24, 1.45)	-1.40 (-3.72, 0.93)	-1.14 (-3.69, 1.42)
	Female	-0.02 (-0.82, 0.78)	-0.05 (-0.89, 0.78)	0.2 (-2.01, 2.42)	0.04 (-2.26, 2.34)	-0.44 (-2.93, 2.06)	-0.70 (-3.13, 1.72)

[a]N=107 for males; 116 for females. Adjusted for age, sex, specific gravity

[b]N=94 for males; 98 for females. Additionally adjusted for mother's BMI 1 month postpartum, years of education.

*p<0.05

Figure 3.5. Association of BPA and phthalates metabolites concentrations in adolescent urines with adolescent BMI, waist circumference, and sum of triceps and subscapular skinfolds at ages 8-14.

		BMI		Waist circumference		Sum skinfold	
Analyte	**Sex**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**	**Crude[a] β(95%CI)**	**Adjusted[b] β(95%CI)**
BPA							
	Male	-0.13 (-0.90, 0.64)	-0.23 (-1.01, 0.56)	-0.34 (-2.65, 1.96)	-0.50 (-2.89, 1.89)	-0.83 (-3.56, 1.90)	-1.11 (-3.94, 1.71)
	Female	0.25 (-0.68, 1.18)	0.39 (-0.52, 1.30)	0.55 (-1.99, 3.10)	1.02 (-1.51, 3.55)	1.09 (-1.76, 3.94)	1.64 (-1.12 4.40)
MBP							
	Male	0.07 (-0.70, 0.83)	0.05 (-0.70, 0.81)	-0.27 (-2.58, 2.03)	-0.21 (-2.51, 2.09)	0.74 (-1.98, 3.47)	0.83 (-1.89, 3.56)
	Female	-0.91 (-1.67, -0.16)*	-0.62 (-1.40, 0.16)	-2.19 (-4.27, -0.11)*	-1.54 (-3.73, 0.64)	-2.57 (-4.90, -0.23)*	-1.40 (-3.80, 0.99)
MBzP							
	Male	-0.30 (-1.09, 0.49)	-0.19 (-1.01, 0.62)	-1.62 (-3.99, 0.76)	-1.20 (-3.67, 1.29)	-1.55 (-4.38, 1.27)	-0.96 (-3.91, 2.00)
	Female	-0.04 (-0.93, 0.85)	0.004 (-0.88, 0.89)	-0.17 (-2.62, 2.28)	-0.19 (-2.64, 2.26)	0.52 (-2.22, 3.26)	0.57 (-2.12, 3.25)
MCPP							
	Male	-0.55 (-1.42, 0.31)	-0.58 (-1.42, 0.30)	-2.05 (-4.64, 0.54)	-1.95 (-4.56, 0.66)	-1.87 (-4.95, 1.21)	-1.75 (-4.87, 1.37)
	Female	-0.82 (-1.61, -0.02)*	-0.56 (-1.38, 0.26)	-1.73 (-3.93, 0.47)	-1.27 (-3.56, 1.03)	-1.57 (-4.04, 0.90)	-0.76 (-3.28, 1.76)
MEP							
	Male	-0.19 (-0.67, 0.29)	-0.17 (-0.65, 0.31)	-0.65 (-2.08, 0.78)	-0.55 (-2.02, 0.93)	-0.60 (-2.92, 1.71)	-1.46 (-3.91, 0.98)
	Female	0.24 (-0.27, 0.75)	0.14 (-0.37, 0.66)	0.40 (-1.00, 1.80)	0.22 (-1.21, 1.66)	0.03 (-3.11, 3.17)	-0.19 (-3.26, 2.88)
MIBP							
	Male	-0.003 (-0.80, 0.80)	-0.12 (-0.92, 0.68)	-0.02 (-2.42, 2.38)	-0.24 (-2.67, 2.20)	-0.40 (-2.60, 1.81)	-1.22 (-3.56, 1.12)
	Female	-0.61 (-1.55, 0.33)	-0.56 (-1.50, 0.39)	-2.07 (-4.64, 0.50)	-1.94 (-4.56, 0.68)	0.29 (-2.64, 3.22)	0.21 (-2.65, 3.07)
MEHP							
	Male	-0.25 (-0.82, 0.32)	-0.56 (-1.15, 0.03)	-1.24 (-2.95, 0.47)	-1.95 (-3.74, -0.15)*	-1.62 (-3.64, 0.40)	-2.46 (-4.58, -0.33)
	Female	-0.22 (-1.19, 0.76)	-0.38 (-1.35, 0.58)	-0.80 (-3.48, 1.87)	-1.14 (-3.83, 1.54)	-0.99 (-3.99, 1.99)	-1.41 (-4.35, 1.62)
MECPP							
	Male	-0.11 (-0.76, 0.54)	-0.44 (-1.11, 0.24)	-0.68 (-2.64, 1.27)	-1.48 (-3.54, 0.57)	-0.57 (-2.82, 1.67)	-1.46 (-3.85, 0.92)
	Female	0.11 (-0.92, 1.13)	0.04 (-0.97, 1.04)	0.17 (-2.64, 2.96)	-0.003 (-2.81, 2.80)	-0.14 (-3.10, 2.82)	-0.09 (-2.99, 2.80)
MEHHP							
	Male	-0.08 (-0.70, 0.54)	-0.41 (-1.06, 0.23)	-0.68 (-2.54, 1.17)	-1.45 (-3.41, 0.51)	-0.87 (-2.57, 0.82)	-0.77 (-2.52, 0.98)
	Female	0.09 (-0.87, 1.04)	0.06 (-0.88, 0.99)	0.32 (-2.30, 2.93)	0.24 (-2.37, 2.86)	0.40 (-1.17, 1.97)	0.19 (-1.38, 1.76)
MEOHP							
	Male	-0.13 (-0.76, 0.51)	-0.47 (-1.13, 0.18)	-0.80 (-2.69, 1.09)	-1.63 (-3.62, 0.37)	0.13 (-2.71, 2.98)	0.04 (-2.85, 2.94)
	Female	-0.10 (-1.06, 0.87)	-0.08 (-1.03, 0.87)	-0.09 (-2.73, 2.55)	-0.03 (-2.68, 2.61)	-2.06 (-4.94, 0.83)	-1.56 (-4.44, 1.31)

[a]N=113for males; 129 for females. Adjusted for age, sex, specific gravity

[b]N=108 for males; 121 for females. Additionally adjusted for mother's BMI 1 month postpartum, years of education.

*p<0.05

Figure 3.6. Multivariable linear regression of associations of adolescent BMI, waist circumference, and triceps skinfold with quartiles of maternal third trimester urine metabolites compared to the reference first quartile.

				BMI			**Waist circumference**			**Sum skinfold[a]**		
Analyte	Model	Sex	N	β	95% CI		β	95% CI		β	95% CI	
BPA	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.55	-1.17	2.26	1.43	-3.78	6.63	3.39	-2.76	9.54
	Quartile 3			0.35	-1.24	1.93	0.85	-3.98	5.68	2.26	-3.46	7.97
	Quartile 4			-1.24	-3.09	0.62	-2.42	-8.05	3.22	-3.51	-10.17	3.16
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			1.35	-0.83	3.54	3.91	-2.23	10.04	0.06	-6.63	6.74
	Quartile 3			0.88	-1.22	2.98	2.09	-3.81	7.99	0.27	-6.16	6.70
	Quartile 4			-1.63	-3.92	2.98	-4.26	-10.72	2.19	-5.36	-12.39	1.68
MBP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.71	-1.03	2.46	1.71	-3.52	6.94	4.16	-2.11	10.44
	Quartile 3			-0.34	-2.02	1.34	-2.10	-7.12	2.93	0.35	-5.68	6.37
	Quartile 4			0.03	-1.97	2.03	-1.37	-7.37	4.63	0.06	-7.13	7.24
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			0.17	-1.86	2.20	-0.46	-6.16	5.23	-1.01	-7.03	5.01
	Quartile 3			-0.61	-2.86	1.64	-2.83	-9.14	3.48	-5.25	-11.92	1.42
	Quartile 4			-1.05	-3.33	1.24	-2.59	-8.98	3.80	-0.60	-7.36	6.15
MBzP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.46	-2.27	1.35	-0.53	-6.02	4.96	-2.51	-9.10	4.09
	Quartile 3			-1.42	-3.26	0.42	-2.37	-7.95	3.20	-2.66	-9.35	4.04
	Quartile 4			-0.84	-2.70	1.02	-2.49	-8.12	3.13	-1.91	-8.67	4.84
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.72	-2.61	1.17	-2.60	-7.88	2.69	-1.79	-7.42	3.84
	Quartile 3			-0.76	-2.70	1.19	-1.24	-6.68	4.21	-1.21	-7.01	4.59
	Quartile 4			-1.01	-3.20	1.18	-1.79	-7.91	4.33	2.23	-4.29	8.75
MCPP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.09	-1.72	1.89	-0.22	-5.64	5.20	2.93	-3.54	9.41
	Quartile 3			0.08	-1.82	1.99	-1.06	-6.78	4.66	1.76	-5.08	8.60
	Quartile 4			0.02	-1.94	1.98	0.37	-5.52	6.25	1.85	-5.18	8.89
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.23	-2.30	1.83	-2.44	-8.18	3.30	-4.45	-10.55	1.64
	Quartile 3			0.04	-2.07	2.16	0.30	-5.59	6.20	-2.74	-8.99	3.52
	Quartile 4			-0.45	-2.95	2.05	-1.61	-8.56	5.34	-1.21	-8.59	6.18
MECPP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			0.84	-0.80	2.48	1.29	-3.65	6.22	3.60	-2.38	9.59
	Quartile 3			1.41	-0.43	3.24	3.00	-2.51	8.52	4.35	-2.34	11.04
	Quartile 4			-1.24	-3.31	0.83	-5.25	-11.48	0.98	-3.49	-11.04	4.06
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-3.29	-5.37	-1.20	-7.66	-13.57	-1.76	-9.11	-15.41	-2.81
	Quartile 3			-0.21	-2.25	1.84	-0.45	-6.25	5.35	-1.60	-7.78	4.58
	Quartile 4			-0.55	-2.84	1.73	-0.02	-6.51	6.47	-1.53	-8.45	5.38
MEHHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			1.62	-0.02	3.26	3.06	-1.90	8.03	6.51	0.64	12.37
	Quartile 3			0.98	-0.85	2.81	2.72	-2.80	8.25	2.94	-3.58	9.46
	Quartile 4			-0.72	-2.66	1.23	-3.69	-9.55	2.18	-3.15	-10.07	3.77
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-2.06	-4.20	0.09	-5.29	-11.29	0.70	-7.40	-13.74	-1.05
	Quartile 3			-0.54	-2.56	1.48	-1.08	-6.74	4.58	-2.20	-8.19	3.78
	Quartile 4			-0.20	-2.82	2.41	0.42	-6.91	7.74	-0.91	-8.66	6.84
MEHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.38	-2.08	1.32	-1.42	-6.52	3.68	-0.53	-6.59	5.53
	Quartile 3			0.65	-1.08	2.38	0.83	-4.37	6.03	2.56	-3.62	8.74
	Quartile 4			-0.44	-2.27	1.40	-3.01	-8.52	2.51	-3.78	-10.34	2.77
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-0.27	-2.32	1.79	-0.13	-5.86	5.60	-2.29	-8.36	3.78
	Quartile 3			-1.58	-3.74	0.57	-4.14	-10.16	1.89	-6.78	-13.17	-0.39
	Quartile 4			0.00	-2.36	2.37	0.71	-5.89	7.31	-1.51	-8.50	5.48
MEOHP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			1.86	0.16	3.54	3.65	-1.44	8.74	8.67	2.75	14.58
	Quartile 3			0.75	-1.01	2.50	2.08	-3.23	7.40	3.54	-2.63	9.70
	Quartile 4			-0.66	-2.65	1.33	-3.68	-9.71	2.35	-2.21	-9.20	4.79
	Quartile 1	Female	110		Reference			Reference			Reference	

	Quartile 2			-1.87	-4.02	0.27	-5.34	-11.32	0.65	-6.78	-13.14	-0.42
	Quartile 3			-0.02	-2.12	2.08	0.00	-5.85	5.86	-0.64	-6.85	5.58
	Quartile 4			-0.88	-3.46	1.70	-1.89	-9.10	5.32	-2.61	-10.27	5.04
MEP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.36	-2.05	1.34	-0.05	-5.11	5.02	0.25	-5.90	6.40
	Quartile 3			-0.97	-2.70	0.77	-3.83	-9.01	1.34	-0.68	-6.97	5.60
	Quartile 4			-1.07	-3.02	0.87	-3.19	-8.98	2.60	-2.79	-9.83	4.25
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			1.41	-0.61	3.43	3.66	-2.01	9.34	2.59	-3.50	8.69
	Quartile 3			0.73	-1.35	2.81	1.81	-4.04	7.66	2.23	-4.05	8.51
	Quartile 4			-0.19	-2.23	1.86	1.07	-4.68	6.82	1.78	-4.38	7.95
MIBP	Quartile 1	Male	102		Reference			Reference			Reference	
	Quartile 2			-0.03	-1.72	1.66	-0.61	-5.64	4.42	-1.44	-7.52	4.65
	Quartile 3			-1.53	-3.37	0.30	-6.07	-11.54	-0.60	-6.33	-12.94	0.29
	Quartile 4			-0.90	-2.83	1.02	-2.92	-8.64	2.81	-4.26	-11.18	2.67
	Quartile 1	Female	110		Reference			Reference			Reference	
	Quartile 2			-1.10	-3.20	1.91	-3.64	-9.51	2.23	-2.90	-9.22	3.42
	Quartile 3			0.13	-2.00	2.26	-0.77	-6.71	5.17	-0.32	-6.71	6.08
	Quartile 4			-1.14	-3.53	1.25	-4.64	-11.30	2.01	-3.11	-10.28	4.05

[a]Sum of triceps and subscapular skinfold measurements
Adjusted for age, specific gravity, mother's BMI 1 month postpartum, years of education

Figure 3.7. Multivariable linear regression of associations of adolescent BMI, waist circumference, and sum of triceps and subscapular skinfold with quartiles of adolescent urine metabolites compared to the reference first quartile.

				BMI			**Waist circumference**			**Sum skinfolds**[a]		
Analyte	Model	Sex	N	β	95% CI		β	95% CI		β	95% CI	
BPA	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-2.19	-3.95	-0.43	-6.45	-11.85	-1.04	-7.24	-13.69	-0.77
	Quartile 3			-0.54	-2.25	1.17	-2.15	-7.38	3.08	-1.91	-8.15	4.33
	Quartile 4			-0.68	-2.66	1.30	-1.98	-8.04	4.08	-3.61	-10.84	3.63
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			0.03	-1.99	2.05	-0.86	-6.47	4.75	-0.89	-7.05	5.27
	Quartile 3			0.24	-2.02	2.50	1.15	-5.13	7.42	1.23	-5.66	8.11
	Quartile 4			1.14	-1.11	3.38	3.01	-3.23	9.25	3.27	-3.58	10.12
MBP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-1.14	-2.84	0.57	-2.12	-7.34	3.10	-3.44	-9.63	2.75
	Quartile 3			-0.47	-2.23	1.28	-1.35	-6.72	4.03	-1.21	-7.59	5.16
	Quartile 4			-0.53	-2.33	1.28	-2.56	-8.09	2.98	-1.85	-8.42	4.72
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-1.04	-3.01	0.93	-2.07	-7.58	3.44	-2.99	-9.03	3.04
	Quartile 3			-2.28	-4.47	-0.08	-5.16	-11.31	0.99	-5.82	-12.55	0.91
	Quartile 4			-0.69	-2.85	1.47	-1.42	-7.46	4.62	-1.45	-8.06	5.16
MBzP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.07	-1.69	1.54	-2.10	-6.99	2.80	-2.34	-8.18	3.51
	Quartile 3			-0.72	-2.37	0.93	-3.11	-8.11	1.90	-3.23	-9.21	2.74
	Quartile 4			-0.64	-2.43	1.16	-3.52	-8.96	1.93	-2.93	-9.42	3.57
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			0.19	-1.77	2.15	0.37	-5.07	5.81	1.53	-4.43	7.49
	Quartile 3			-0.21	-2.35	1.93	-1.39	-7.35	4.56	1.48	-5.04	8.01
	Quartile 4			0.56	-1.87	2.99	0.35	-6.41	7.11	3.27	-4.13	10.67
MCPP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.81	-2.53	0.91	-1.62	-6.86	3.63	-2.45	-8.69	3.79
	Quartile 3			-0.90	-2.79	0.98	-2.88	-8.63	2.86	-2.78	-9.62	4.06
	Quartile 4			-0.91	-2.88	1.06	-2.95	-8.96	3.06	-3.29	-10.44	3.86
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.95	-3.00	1.09	-3.67	-9.40	2.07	-1.24	-7.57	5.10
	Quartile 3			-3.82	-5.82	-1.82	-10.15	-15.76	-4.54	-9.69	-15.89	-3.49
	Quartile 4			-0.71	-2.81	1.40	-1.85	-7.75	4.05	-0.59	-7.10	5.93
MECPP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.79	-2.57	0.98	-2.97	-8.33	2.39	-0.20	-3.37	2.97
	Quartile 3			-0.15	-2.07	1.76	-0.15	-5.95	5.64	0.63	-2.79	4.06
	Quartile 4			-0.87	-2.71	0.97	-3.70	-9.27	1.87	-0.82	-4.11	2.48
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-1.02	-3.04	0.99	-3.92	-9.49	1.65	-1.83	-4.84	1.17
	Quartile 3			0.74	-1.30	2.78	1.87	-3.77	7.51	0.41	-2.64	3.45
	Quartile 4			-0.12	-2.32	2.09	-0.93	-7.02	5.16	-0.32	-3.61	2.96
MEHHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-1.47	-3.15	0.21	-4.58	-9.71	0.55	-3.97	-10.10	2.17
	Quartile 3			-0.92	-2.75	0.91	-1.87	-7.47	3.72	-0.72	-7.41	5.98
	Quartile 4			-0.42	-2.22	1.38	-2.68	-8.17	2.80	-1.69	-8.25	4.87
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.07	-2.11	1.97	-0.44	-6.10	5.22	-2.49	-8.67	3.69
	Quartile 3			0.53	-1.58	2.64	1.18	-4.68	7.05	1.11	-5.29	7.51
	Quartile 4			0.56	-1.66	2.78	2.06	-4.10	8.22	1.65	-5.08	8.37
MEHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.46	-2.09	1.18	-1.02	-5.99	3.95	-0.59	-6.49	5.31
	Quartile 3			-0.79	-2.53	0.94	-2.49	-7.76	2.79	-2.54	-8.81	3.72
	Quartile 4			-0.90	-2.63	0.83	-3.80	-9.05	1.45	-4.53	-10.77	1.70
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.44	-2.38	1.49	-2.00	-7.37	3.37	-1.23	-7.13	4.66
	Quartile 3			-0.91	-3.01	1.19	-3.42	-9.24	2.41	-3.32	-9.72	3.07
	Quartile 4			-0.40	-2.66	1.87	-1.74	-8.02	4.54	-1.40	-8.29	5.49
MEOHP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-1.45	-3.20	0.31	-3.98	-9.34	1.39	-3.41	-9.82	3.00
	Quartile 3			-0.93	-2.67	0.81	-2.24	-7.56	3.07	-1.27	-7.63	5.08
	Quartile 4			-0.75	-2.60	1.09	-3.29	-8.93	2.34	-2.12	-8.85	4.62
	Quartile 1	Female	121		Reference			Reference			Reference	

	Quartile 2			-0.43	-2.42	1.57	-1.54	-7.06	3.97	-3.13	-9.17	2.91
	Quartile 3			-0.07	-2.31	2.17	-1.32	-7.50	4.86	-0.67	-7.44	6.11
	Quartile 4			0.45	-1.83	2.72	2.06	-4.23	8.36	1.33	-5.57	8.22
MEP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.77	-2.35	0.82	-3.24	-8.05	1.57	-2.38	-8.14	3.37
	Quartile 3			-0.11	-1.68	1.47	-0.20	-4.97	4.57	-1.63	-7.34	4.08
	Quartile 4			-0.83	-2.62	0.96	-3.14	-8.56	2.29	-4.04	-10.53	2.45
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-0.87	-2.95	1.22	-3.04	-8.85	2.77	-2.46	-8.85	3.92
	Quartile 3			-1.17	-3.29	0.95	-2.57	-8.47	3.33	-3.22	-9.70	3.26
	Quartile 4			0.01	-2.06	2.09	-0.69	-6.49	5.10	-0.88	-7.25	5.48
MIBP	Quartile 1	Male	108		Reference			Reference			Reference	
	Quartile 2			-0.49	-2.26	1.28	-1.20	-6.61	4.20	-0.83	-7.24	5.58
	Quartile 3			-0.36	-2.15	1.43	-0.91	-6.38	4.56	-1.51	-8.00	4.98
	Quartile 4			-0.65	-2.50	1.20	-1.46	-7.12	4.19	-2.67	-9.38	4.04
	Quartile 1	Female	121		Reference			Reference			Reference	
	Quartile 2			-2.54	-4.55	-0.54	-7.61	-13.15	-2.08	-6.48	-12.65	-0.30
	Quartile 3			-1.38	-3.53	0.76	-3.60	-9.52	2.31	-3.18	-9.77	3.42
	Quartile 4			-1.87	-4.13	0.39	-6.44	-12.68	-0.20	-4.71	-11.67	2.24

[a]Sum of triceps and subscapular skinfold measurements
Adjusted for age, specific gravity, mother's BMI 1 month postpartum, years of education

Figure 3.8. Sex-stratified associations of maternal third trimester urinary concentrations of quartile BPA and phthalate metabolites with adolescent BMI, waist circumference, and sum of triceps and subscapular skinfold measurements at ages 8-14.
Point estimates and 95% confidence intervals are adjusted for specific gravity, child's age, and mother's 1 month postpartum BMI and total years of education.

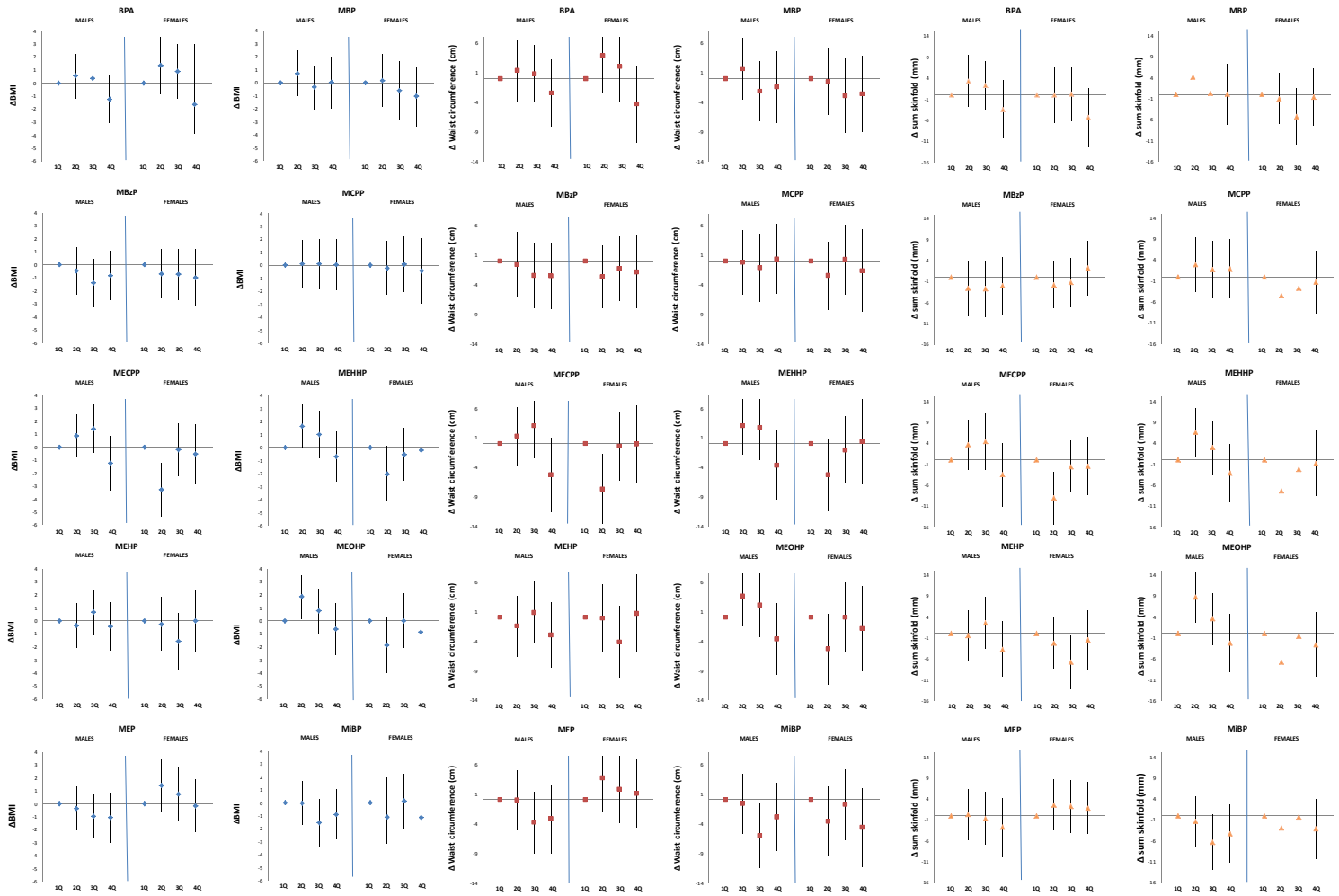
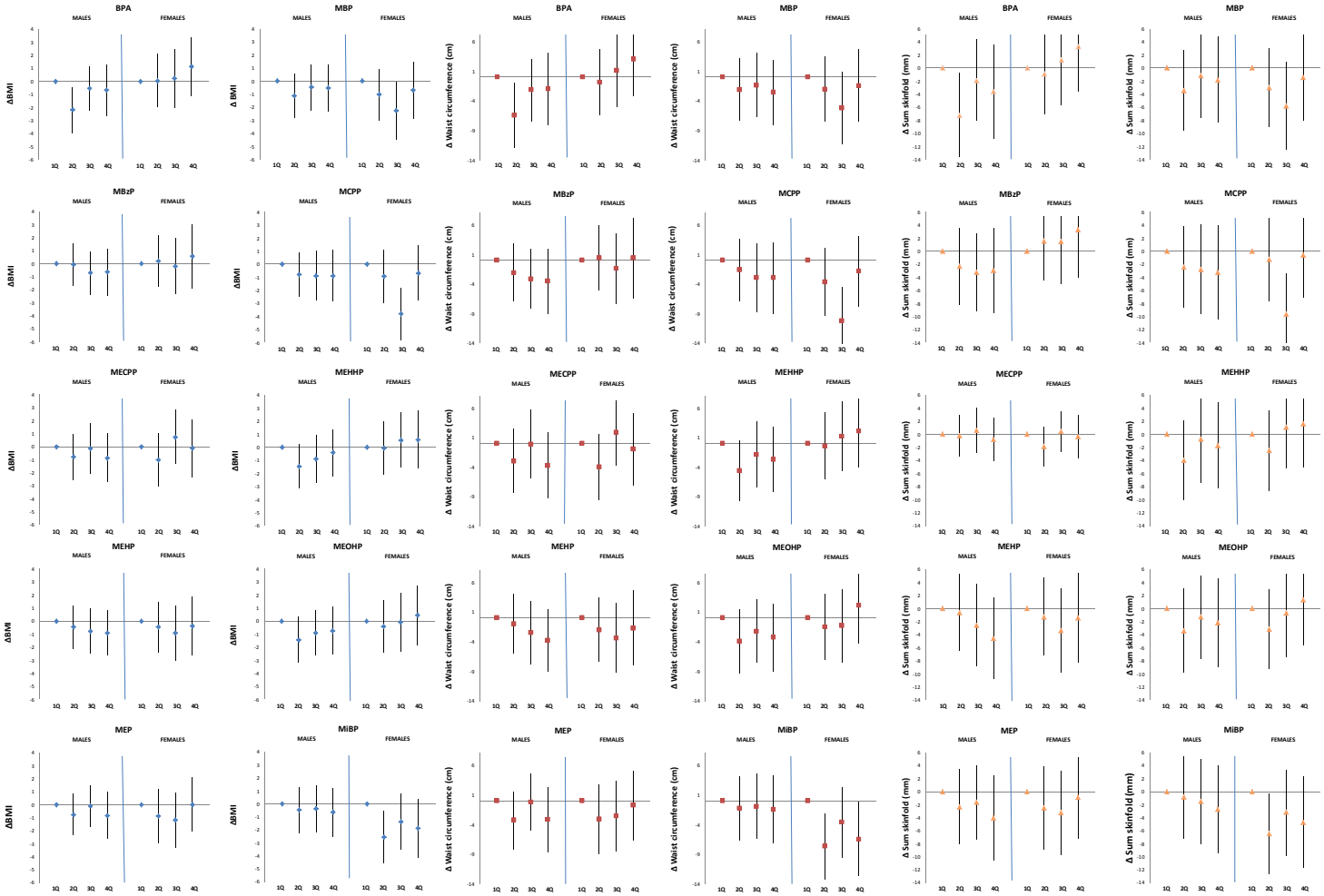


Figure 3.9. Sex-stratified associations of adolescent urinary concentrations of quartile BPA and phthalate metabolites with adolescent BMI, waist circumference, and sum of triceps and subscapular skinfold measurements at ages 8-14.
Point estimates and 95% confidence intervals are adjusted for specific gravity, child's age, and mother's 1 month postpartum BMI and total years of education.



CHAPTER 4

Differences in BMI and Height Trajectories of Males and Females Associated with *in utero* Urinary Concentrations of Bisphenol A and Phthalate Metabolites

Abstract

Background: Exposures to the environmental endocrine-disrupting compounds Bisphenol A and phthalates have been linked to a variety of adverse health effects including greater weight status and waist circumference. Cross-sectional studies have demonstrated non-monotonic relationships between exposure and outcomes, as well as sex differences in metabolites of interest and direction of association. However, associations from cross-sectional analyses have not been supported by the limited number of longitudinal studies. As children and adolescents do not grow with constant velocity, assessing outcomes at a single point in time may lead to inaccurate estimates of how these exposures may affect growth.

Objective: To assess the BMI and height trajectories of children from birth to 14 years of age using tertiles of third trimester maternal urinary concentrations of BPA and phthalate metabolites.

Methods: Fractional age polynomials and mixed effects models were fit separately for males and females for BMI and height trajectory models. Likelihood ratio tests were used to determine which models were better fit with the inclusion of tertiles of each metabolite, covariates, and interaction terms. Models were plotted with

covariates centered at average values for each tertile. Ages where salient differences between tertiles of predicted BMI and height were determined.

Results: Highest predicted BMI and height trajectories for females were observed for third tertiles of phthalate metabolites, while males with first and second tertiles of phthalate metabolites had highest predicted trajectories. The phthalate metabolites associated with trajectories for females (MECPP) were different than those for males (MiBP, MBzP, MEP, MCPP, MEHP, MEHHP, MEOHP). Findings for Bisphenol A and height trajectory were inverted compared to phthalate metabolites, with the highest predicted height trajectory occurring with first tertile for females and third tertile for males.

Discussion: Utilizing growth modeling of exposures to environmental endocrine-disrupting compounds, our results suggest that males and females are associated with different phthalate metabolites, suggesting differential sensitivity to exposures. Additionally, the BPA tertiles associated with height trajectory for males and females were reversed compared to their associations with phthalate metabolites and BMI trajectory.

Background

Childhood obesity is a globally persistent disease with multifactorial sources and a wide range of complications (Ebbeling et al. 2002). The balance between energy intake and expenditure cannot explain the increases in obesity prevalence observed in the past few decades; many contributing factors have been suggested, including exposures to environmental endocrine-disrupting compounds (Baillie-Hamilton 2002; Grün and Blumberg 2009; Institute of Medicine 2012; Zinn 2010).

Two compounds implicated with the rapid increase in childhood obesity are Bisphenol A (BPA) and phthalates. These multi-functional materials are used in everyday products; their prolific use has resulted in ubiquitous exposure to these compounds and their metabolites in humans of both genders and all age groups (Adibi et al. 2003; Calafat et al. 2008; Callan et al. 2012; Frederiksen et al. 2011; Pirard et al. 2012; Silva et al. 2004; Taskeen et al. 2012). BPA is used in the production of polycarbonate plastics and epoxy resins and is commonly found in food and beverage containers, medical equipment, toys, the linings of canned foods, thermal receipt paper, and dental sealants (Mendum et al. 2011; Shelby 2008; Vandenberg et al. 2007a). Phthalates are used as plasticizers in many consumer and industrialized products and as a stabilizing and solubilizing material (David et al. 2012; Hauser and Calafat 2005; Meeker 2012). High molecular weight phthalates are used in manufacturing flexible vinyl plastics and are commonly found in food and beverage containers, medical equipment, and vinyl flooring while low molecular weight phthalates are often found in solvents, paint thinners, medications and personal care products such as lotions, creams, and nail polish (David et al. 2012; Hernández-Díaz et al. 2009; Lewis et al. 2013).

Exposure is widespread, with >92% of the U.S. population six years and older with detectable metabolites in their urine; metabolites have also been detected during pregnancy, with evidence of these metabolites in the amniotic sac and cord blood (Calafat et al. 2008; Callan et al. 2012; Cantonwine et al. 2010; Chou et al. 2011; Meeker 2012; Silva et al. 2004; Vandenberg et al. 2007a). Exposures occur primarily from ingestion of food and beverages in contact with containers utilizing these plasticizers, but are also known to occur through inhalation and dermal contact (Adibi et al. 2003; Clark et al. 2011; Rudel et al. 2003; Wilson et al. 2003, 2007; Wormuth et al. 2006).

Exposures to these compounds have been implicated in obesity and increased waist circumference and fat mass and may be due to alterations in adipogenesis, lipogenesis, and metabolic imbalance such as impaired glucose and insulin response (Alonso-Magdalena et al. 2005a; Carwile and Michels 2011; Hao et al. 2012; Harley et al. 2013; Hatch et al. 2008; Hauser and Calafat 2005; Hugo et al. 2008; Lang et al. 2008; Lind et al. 2012a, 2012b; Masuno et al. 2002; Newbold 2010; Ropero et al. 2008; Ryan et al. 2010; Sakurai et al. 2004; Shankar and Teppala 2011; Stahlhut et al. 2007; Teitelbaum et al. 2012; Trasande et al. 2012; Wang et al. 2012a, 2012b, 2012c; Wei et al. 2011). Other health effects from exposures to BPA and phthalate metabolites have been noted: asthma, male reproductive development, timing of puberty, neurodevelopment, and shortened gestational length (Braun et al. 2011; Cantonwine et al. 2010; Colón et al. 2000; Frederiksen et al. 2012; Hsu et al. 2011; Kerkhof et al. 2012; Meeker et al. 2009a; Suzuki et al. 2012; Swan et al. 2005; Whyatt et al. 2012). Many cell and animal studies show effects at concentrations relevant to those encountered by humans, making current environmental levels a

cause for concern (Alonso-Magdalena et al. 2005a; Hao et al. 2012; Marmugi et al. 2012; Vandenberg et al. 2007b).

Few human studies examine the associations between exposures to BPA and phthalate metabolites with weight status; of these, most are cross-sectional and longitudinal studies are limited in age range. Cross-sectional data in youth and adult populations suggest a positive association between exposures to BPA and phthalates with BMI, waist circumference, fat mass, insulin resistance, and diabetes; many find differences in associations by sex as well as evidence of non-monotonic relations between exposure and outcomes (Bhandari et al. 2013; Carwile and Michels 2011; Eng et al. 2013; Hatch et al. 2010, 2008; Li et al. 2013; Shankar and Teppala 2011; Stahlhut et al. 2007; Trasande et al. 2013a, 2012, 2013b; Wang et al. 2012d; Wells et al. 2013).

Of human studies examining associations between prenatal exposures on weight status or adiposity, only BPA has been assessed and with inconsistent results. Among a primarily Latina community in the United States, a cross-sectional analysis at 9 years of age found positive associations with higher BPA concentrations and BMI, overweight and obesity, fat mass, and waist circumference (Harley et al. 2013). Prenatal urinary BPA concentrations from this population were found to be associated with lower odds of overweight and obesity, and lower BMI and percent body fat among girls at 9 years of age in the highest tertile of BPA concentrations. In contrast, Valvi et al (2013) observed that prenatal BPA exposure was weakly associated with waist circumference Z-score and BMI z-score in children at 4 years of age, though the latter was non-significant (Valvi et al. 2013).

Most epidemiological research on exposures to endocrine-disrupting compounds and their associated health effects have focused on assessing the impact of exposure on outcomes at one or several static points in time. This approach only allows a glimpse into the potential consequences of these exposures, particularly when the exposures occur at sensitive or critical periods of development where lifelong altered trajectories could be initiated (Inadera 2013; La Merrill and Birnbaum 2011). As many studies of BPA and phthalate metabolites find contradictory results, these may be due to the use of cross-sectional data as well as range of ages where outcomes are assessed. Therefore, assessing a conclusion at one point in time may not be optimal when determining the projected outcomes from these exposures, particularly as parameters of growth are influenced by the perinatal environment.

Growth patterns are often assessed by comparing how children grow with a standard or reference (de Onis et al. 2007). These patterns indicate the course of development for children and adolescents and can be used to assess an individual's growth through time as well as how they compare to peers of their age and sex. These trajectories allow estimation of milestones, such as infancy peak or the adiposity rebound, and could be used to link childhood growth with adult diseases like obesity (Dietz 1997; Rolland-Cachera et al. 1984). Derivation of velocity and acceleration of growth can also be used as early measures of later adverse outcomes (van Lenthe et al. 1996; Tzoulaki et al. 2010). One trait that growth patterns assess is adiposity; although BMI and other measures such as waist circumference and skinfolds are commonly used, height is also associated with adiposity in early life (Boeke et al. 2013; Freedman et al. 2002; Gibson 2005; WHO 1995).

Given the advantages of growth trajectories over singular measurements of gauges of adiposity, we utilized a birth cohort with children currently aged 8-14 years. We examined the possibility that exposures to endocrine-disrupting compounds in a sensitive period of development such as pregnancy may alter subsequent growth trajectories which could have implications for later health. By utilizing growth modeling, we fit and assessed the trajectories of BMI and height for males and females by tertiles of BPA and phthalate metabolites in a cohort of children from 0.25 years to their current ages of 8 to 14 years.

Methods

Study Population

This investigation utilized data from the Early Life in Mexico to ENvironmental Toxicants (ELEMENT) research collaboration with Mexico's *Instituto Nacional de Salud Pública* (INSP) that consists of three sequentially-enrolled birth cohorts from Mexico City. The recruitments started in 1994 at family clinics serving low-to-moderate income populations. Similar exclusion criteria were applied to all three cohorts including living outside of Mexico City, gestational diabetes, preeclampsia, or pregnancy-related hypertensive disorder, as well as other criteria described elsewhere (Ettinger et al. 2009; Gonzalez-Cossio et al. 1997; Téllez-Rojo et al. 2004). Common recruitment methods allow for pooling of the birth cohorts for analysis. Follow-up of the three cohorts were continuously maintained, with study visits at 3, 6, and 12 months of age and then every six months until 60 months; these children were then maintained in follow-up with 1-3 additional observations after the age of 5 years. Ages of the analytic sample range from 8-14 years. Trained personnel obtained biological samples, anthropometry, and

administered surveys to mothers to gather information on sociodemographic characteristics.

Anthropometric Measures

At one-month postpartum, maternal height was obtained using professional scales (BAME Mod 420; Catálogo Médico) read to the nearest 0.1 centimeter (cm) and maternal weight was recorded to the nearest 0.1 kilogram (kg). Children's anthropometry were taken by study personnel using established research protocol (Lohman et al. 1988). Weight (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 kg; height (BAME Mod 420; Catálogo Médico) was measured to the nearest 0.1 cm. Duplicate measures were taken of weight and height; the observed values were averaged. An additional measurement was taken if intra-personal variability exceeded the measurement tolerance of 0.5 cm. Body Mass Index (BMI) was calculated as weight divided by height squared (kg/m^2).

Urinary BPA and Phthalate Metabolites

A spot (second morning void) urine sample was collected from each woman during her third-trimester visit to the project's research center and frozen at – 80 °C; these were coordinated with urines from adolescents at follow-up. Samples were analyzed for total (free + glucuronidated) BPA and nine phthalate metabolites by NSF International (Ann Arbor, MI, USA) using validated modification of the Centers for Disease Control and Prevention (CDC) methods described elsewhere (Calafat et al. 2008; Lewis et al. 2013; Silva et al. 2007). The nine phthalate metabolites included: monoethyl phthalate (MEP), metabolite of diethyl phthalate (DEP); mono-*n*-butyl phthalate (MBP), metabolite of di-*n*-butyl phthalate (DBP); mono-isobutyl phthalate (MiBP), metabolite of di-isobutyl-phthalate (DiBP); mono(3-

carboxypropyl) phthalate (MCPP), metabolite of DBP and di-*n*-octyl phthalate (DOP); monobenzyl phthalate (MBzP), metabolite of butylbenzyl phthalate (BBzP); and mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), metabolites of di(2-ethylhexyl) phthalate (DEHP). Specific gravity (SG) of the urine samples was measured using a handheld digital refractometer (ATAGO Company Ltd., Tokyo, Japan).

BPA and phthalate metabolite concentrations below the limit of quantitation (LOQ) were assigned a value of LOQ/sqrt(2). Values were then corrected for SG using:

$$P_c = P\left[\frac{SG_p - 1}{SG_i - 1}\right]$$

where P_c is the *SG*-corrected BPA or phthalate metabolite concentration (ng/mL), P is the measured urinary BPA or phthalate metabolite concentration, SG_p is the median of the urinary specific gravities for the sample (SG_p for mothers = 1.013), and SG_i is the urinary specific gravity for the individual (Mahalingaiah et al. 2008). Specific gravity instead of creatinine was used because creatinine concentrations may be confounded by physical activity, time of day, diet, morbidity, and muscularity (Boeniger et al. 1993).

Statistical Analysis

Data analysis was completed using SAS (version 9.3; SAS Institute, Cary, NC, USA) for Windows. Descriptive statistics and distributions for all variables were assessed. Each child had 5 to 12 observations for BMI and height. BMI and height

values were checked for biological implausibility by visually assessing their growth trajectory. Three participants had one BMI observation that was atypical of their individual growth trajectory and three non-overlapping participants had heights that did not follow their trajectory; the questionable BMI and height value for each participant was removed from statistical analysis while retaining the other values.

Following an approach similar to published methods, BMI trajectories were constructed using a fractional polynomial age approach (Royston and Altman 1994; Wen et al. 2012). Whereas Wen et al. (2012) modeled BMI trajectories of individual children and used the fitted trajectory to determine the age and BMI at infancy and adiposity rebound, we fit sex-stratified models to assess the BMI and height trajectories resulting from exposures to tertiles of individual BPA and phthalate metabolites from the third trimester of pregnancy. The construction of the expected value of BMI was:

$$E(BMI) = b_0 + \sum_{j=1}^{m} b_j Age^{p_j}$$

where m is the model degree and the exponential p_j is selected from a set of 8 chosen values, including -2, -1, -0.5, log, 0.5, 1, 2, and 3. The minimum model degree was set at m = 3, since all children had 3 or more observations and the maximum degree was set at m = 8. Therefore, 219 candidate models were considered, with 1 model of the 8th degree, 8 models of the 7th degree, etc., and 56 models of the 3rd degree. The optimal number of fractional polynomial age terms from the 219 candidate models to include in the final models for males and females was selected based on smallest Akaike information criterion (AIC) and Bayesian information criterion (BIC). A

smaller AIC signifies a model that is thought be closer to the truth whereas a smaller BIC signifies that a model is thought to be more likely to be the truth. BIC more heavily penalizes model complexity, so both AIC and BIC are used in the model selection. The models were estimated separately by sex for the inclusion terms of each degree and assessed by goodness of fit tests. Models for each sex are shown in Table 4.1.

Mixed effects models using *proc mixed* were used to fit BMI trajectories within sex strata, with fixed effects for each fractional polynomial age term, which reflects the trend for the population-average, and random effects for intercept and linear age for each child, which reflects how each child deviates from the population-average. For each BPA and phthalate metabolite, tertiles of the metabolites and their interaction terms with the age variables were entered as fixed effects along with covariates centered at their mean. For example, the unadjusted model for BMI trajectory in females with the third tertile as the reference is:

$$\begin{aligned} BMI_{ti} = {} & \beta_0 + \beta_1 Age_{ti}^{-1} + \beta_2 Age_{ti}^{-0.5} + \beta_3 Age_{ti}^{0.5} + \beta_4 Age_{ti} + \beta_5 Age_{ti}^{3} + \beta_6 Tertile1_i \\ & + \beta_7 Tertile2_i + \beta_8 Tertile1_i \times Age_{ti}^{-1} + \beta_9 Tertile1_i \times Age_{ti}^{-0.5} \\ & + \beta_{10} Tertile1_i \times Age_{ti}^{0.5} + \beta_{11} Tertile1_i \times Age_{ti} + \beta_{12} Tertile1_i \times Age_{ti}^{3} \\ & + \beta_{13} Tertile2_i \times Age_{ti}^{-1} + \beta_{14} Tertile2_i \times Age_{ti}^{-0.5} + \beta_{15} Tertile2_i \\ & \times Age_{ti}^{0.5} + \beta_{16} Tertile2_i \times Age_{ti} + \beta_{17} Tertile2_i \times Age_{ti}^{3} + b_0 + b_1 Age_{ti} \\ & + \varepsilon_{ti} \end{aligned}$$

For each BPA and phthalate metabolite for males and females, the likelihood ratio test was conducted with the null model containing the age polynomials compared to the partially-adjusted model containing the age polynomials, the SG-

corrected metabolite, and their interaction terms. Predicted BMI trajectories for each tertile of EDC metabolite were plotted for the partially-adjusted models with significance at $p \leq 0.1$ (results not shown). Likelihood ratio tests were then conducted with the null model containing the age polynomials and the *a priori* identified covariates mother's years of schooling and BMI at 1 month postpartum centered at their means, against the fully-adjusted model additionally containing the SG-corrected metabolites and their interaction terms with the age polynomials. Plots of fully-adjusted predicted BMI trajectories for each tertile with covariate values that were centered at their means were plotted for models with significance at $p \leq 0.05$ from the likelihood ratio test. Accordingly, these plots demonstrate the estimated BMI trajectories for each tertile of the phthalate metabolite or BPA exposure for an individual with average characteristics. Estimated differences between tertiles were assessed using *estimate* statements in *proc mixed*. Results indicating ages at which significant differences ($p \leq 0.05$) between predicted tertiles occurred were plotted. As the likelihood ratio test takes all three tertiles into consideration and tests whether at least one group differs from another, the significance detected from the estimated differences between tertiles is used as a descriptor of which ages those differences occurred.

BMI velocity was plotted by taking the first derivative of the age polynomials. Estimates between tertiles of exposure were conducted using *estimate* statements in *proc mixed* to assess ages when significant differences ($p \leq 0.05$) between tertiles occurred (results not shown).

Height trajectory models were fitted using the same approach with BMI trajectory analysis. The optimum age terms were selected for males and females

from the 219 candidate models using smallest AIC and BIC. Selected age polynomials were different for males and females. The models, inclusion terms for each degree, goodness of fit tests, and chosen models for each sex are shown in Table 4.2. Likelihood ratio tests were conducted for partially- and fully-adjusted height trajectory models with the same approach using the same covariates, mother's years of schooling and BMI at 1 month postpartum centered at their means. Plots of fully-adjusted estimated height trajectories for each tertile were plotted for models with significance at $p \leq 0.05$ using covariate values centered at their means. Estimated differences between tertiles using the *estimate* statements in *proc mixed* were used to determine ages where significant differences ($p \leq 0.05$) between predicted tertiles occurred. Height velocity analysis was conducted using the same approach as for BMI velocity (results not shown).

Results

Table 4.3 shows the characteristics of the sample population. Among 249 children, 47% were male. Current mean age was 10.3 years for males and females, current height was 138.cm 6 for males and 138.3 cm for females, current BMI was 19.1 for males and 19.8 for females. Mothers at 1 month postpartum had an average BMI of 26.7 for male children and 27.2 for females, and mothers of male children averaged 11.3 years of education and 10.8 years for females. Among 2,162 total visits, 78% occurred at or under the age of 5 years old.

Distributions of BPA and phthalate metabolites in maternal third trimester urine are shown in Table 4.4. The majority of all pregnancy samples had detectable concentrations of BPA (26-36%<LOQ) and phthalates metabolites (0-11%<LOQ). Wilcoxon rank-sum tests comparing differences in concentrations between mothers

of males and females showed no significant differences except for BPA (GM=0.9ng/mL females; 0.7ng/ml males; p=0.05).

The results from the likelihood ratio test for BMI trajectory comparing the fully-adjusted model with SG-corrected metabolites, covariates, and age polynomial terms and their interactions with metabolites with the null model containing the age polynomials and covariates are shown in Table 4.5. Fully-adjusted models for female MECPP and male MiBP, MBzP, MCPP, MEHP, MEHHP, and MEOHP were a significantly better fit ($p \leq 0.05$) than the null models.

Figures 4.1-7 show the predicted BMI trajectories and the estimated differences between tertiles for an individual with average covariate values in each tertile of exposure. For female MECPP, the third tertile of exposure has the highest predicted BMI trajectory by the children's current age though, for most of the trajectory time period, the third tertile of exposure had the lowest predicted BMI trajectory (Figure 4.1).

For males, the first and second tertiles of exposure had the highest predicted BMI trajectory. The first and second tertiles for the low molecular weight phthalate metabolites MiBP (Figure 4.2), MBzP (Figure 4.3), and MCPP (Figure 4.4) were observed to decline in early childhood before crossing the trajectories of the second and third tertiles of exposure and become the highest predicted BMI trajectory. The first and second tertiles for the high molecular weight phthalates MEHP (Figure 4.5), MEHHP (Figure 4.6), and MEOHP (Figure 4.7) were consistently high throughout childhood. Figure 4.8 graphically shows where the ages and estimated significant BMI differences by tertiles of phthalate metabolites were observed. Figure 4.9 shows the ages where significant estimated BMI differences between tertiles occurred and

the color coding indicates whether those differences are positive (red) or negative (blue). For example, significant estimated differences between BMI trajectories were observed for female MECPP between tertiles 1 and 3 for the ages of 0.3 to 1.1 years and between tertiles 2 and 3 for ages 0.6 to 2.5 years (Figure 4.8 and 4.9). While fully-adjusted MCPP was significant in the likelihood ratio test, there were no significantly observed differences between tertiles (Figure 4.8 and 4.9).

For BMI trajectories, ages of significant differences between tertiles of metabolites followed different patterns for high and low molecular weight phthalates and between males and females (Figure 4.9). Male low molecular weight phthalate metabolites MiBP and MBzP had significant differences in the first few years of life, whereas the high molecular weight phthalate metabolites MEHHP and MEOHP were found to have significant differences in the mid-childhood years. This was in contrast to the female high molecular weight phthalate metabolite MECPP, where ages of significant estimated differences between tertiles occurred in early life.

Results from the likelihood ratio test for height trajectory comparing the fully-adjusted model with SG-corrected metabolites, covariates, and age polynomial terms and their interactions with the metabolites with the null model containing the age polynomials and covariates are shown in Table 4.6. Fully-adjusted models were significant ($p \leq 0.05$) for female MECPP and male MCPP, MEP, and MEOHP.

Figures 4.10-13 show the predicted height trajectories and the estimated differences between tertiles for an average individual in each tertile of exposure. For female MECPP, the third tertile of exposure had the highest predicted height trajectory (Figure 4.10).

For males, the first or second tertiles of exposure for MCPP (Figure 4.11), MEP (Figure 4.12), and MEOHP (Figure 4.13) had the highest predicted height trajectory. Figure 4.14 graphically shows where the ages and estimated significant height differences in growth by tertiles of phthalate metabolites were observed. Figure 4.15 shows the ages where significant estimated height differences between tertiles occurred and the color coding indicates whether those differences are positive or negative. For example, estimates between tertiles of female MECPP showed significant differences in height between tertiles 1 and 2 for ages 0.3 to 0.9 years. While the fully-adjusted model for MEP was significant with the likelihood ratio test, there were no significantly observed differences between tertiles of the metabolite (Figures 4.14 and 4.15).

Significant estimated differences between tertiles of metabolites for height trajectories occurred in early life for the high molecular weight phthalate metabolite MECPP in females in contrast to the high molecular weight phthalate MEOHP in males, where significant differences occurred in the peripubertal years. In males, the low molecular weight phthalate metabolite MCPP showed significant differences between tertiles for most of the study period.

Female (Figure 4.16) and male (Figure 4.17) BPA, while non-significant ($p=0.10$; $p=0.07$, respectively), had opposite findings than those for phthalate metabolites. For example, though the third tertile of the phthalate metabolite MECPP for females were found to have the highest trajectory, the first tertile of BPA had the highest trajectory.

Discussion

We observed that females with the highest tertile of phthalate metabolites had the highest predicted BMI and height trajectories whereas males with the first and second tertiles of phthalate metabolites were predicted to have the highest attained BMI and height trajectories. Additionally, females and males were influenced by different phthalate metabolites, which have been observed previously (Hatch et al. 2008). Ages of significant estimated differences between tertiles of phthalate metabolites differed between males and females, and between low and high molecular weight phthalate metabolites in males. Further exploration is needed to investigate the pattern behind this finding.

Harley et al. (2013) observed that prenatal exposure to the highest tertile of BPA was associated with a decrease in BMI z-score in females at 9 years of age, but an increase in males. As higher BMI values are correlated with increased height, our findings that the highest tertile of BPA is associated with the lowest predicted height trajectories for females while, in males, the highest tertile had the highest predicted height trajectory, suggestively mirror the observations by Harley et al. (2013). Together, these results are compatible within the context of overall growth, where height and weight are associated.

It has been recognized that tall males and females, compared to their shorter contemporaries, have a higher prevalence of overweight and obesity (van Dommelen et al. 2014). Taller children also tend to have higher skinfold thicknesses and BMI levels; additionally, they may experience an earlier adiposity rebound and some studies find that they have higher attained BMI as adults, independent of BMI in childhood (Freedman et al. 2002). It is hypothesized that excess gain in weight and

fat during childhood may be a driver in linear growth and additional energy remaining after the promotion of height would be stored as fat (Freedman et al. 2004; McCarthy 2014).

Numerous mechanisms for this relationship between height and weight have been proposed, including alterations in growth hormone, ghrelin, insulin-like growth factor, androgens, and the complex interplay among these hormonal systems (Fennoy 2013; Marcovecchio and Chiarelli 2013). Similar biological processes may control linear growth and the deposition of adipose, so infants who are heavy for their age may grow into tall adolescents, possibly because increased adiposity in childhood frequently occurs in before, or in tandem with, height (Garn et al. 1974; Johnston and Mack 1980). In addition, sexual maturation and height may be biologically linked. Maturation occurs in taller children at a younger age and adolescents who mature at younger ages tend to be heavier as adults (van Lenthe et al. 1996; Parsons et al. 1999).

Leptin is hypothesized to be a factor involved in skeletal growth by acting as a skeletal growth factor or via other regulatory systems (Maor et al. 2002). Overweight and obese children tend to have higher leptin levels and, as fat content and leptin levels are correlated and timing of sexual maturation is closely associated with body weight and, particularly, fat, leptin may potentially play a role in initiating an earlier onset of puberty (Frisch et al. 1973; Shalitin and Phillip 2003). Leptin may also influence the activity levels of enzymes necessary for adrenal androgen synthesis; obese children have an increase in adrenal androgen levels, which may impact rate of growth in the pubertal period (Genazzani et al. 1978; Shalitin and Phillip 2003). In addition, central leptin resistance, such as in the hypothalamus, is common among

obese individuals, and the differential sensitivity to leptin between these central sites and the skeletal growth sites in in the periphery may account for the increase in height in overweight and obese children (Shalitin and Phillip 2003).

Thyroid function is another proposed mechanism which could alter growth; thyroid hormone is required for skeletal development and may act through the stimulation of insulin-like growth factor 1 (IGF-1), growth hormone, or activation of target genes (Bassett and Williams 2003; Yakar and Adamo 2012; Yen 2001). It also plays a role in determining function and development of adipose tissue; similar to PPARγ, thyroid hormone can induce adipose differentiation and proliferation (Flores-Delgado et al. 1987; Tontonoz et al. 1994). Cross-sectional studies have found alterations in levels of thyroid stimulating hormone (TSH) and the thyroid hormones T3 and T4 associated with BPA and phthalates exposure (Boas et al. 2010; Meeker and Ferguson 2011; Meeker et al. 2007; Wu et al. 2013). Variation in thyroid hormones may be a mechanism by which these exposures influence waist circumference and metabolic imbalance in adults; reductions in thyroid hormones have been associated with increases in BMI and *in utero* concentrations of thyroid hormones are known to be involved in programming body weight (Grün and Blumberg 2009; Hatch et al. 2010; Knudsen et al. 2005; Lang et al. 2008; Zoeller 2007). BPA is known to bind to the thyroid hormone receptor, acting as an antagonist and resulting in reduced T3 (Ibhazehiebo and Koibuchi 2011; Moriyama et al. 2002; Wetherill et al. 2007; Zoeller 2007).

Limitations of this study include the relatively small sample size and the relatively fewer number of observations of BMI and height measures after the age of five, as follow-up was not systematic after that point in time. Extrapolations of

estimated values were conducted statistically and may not reflect actual trajectories of BMI and/or height. Another limitation is the use of a single spot urine. Concentrations of metabolites are known to vary widely throughout the course of a day and are influenced by a variety of factors such as diet, physical activity, and use of personal care products. However, previous studies have indicated that a single measure may be a moderately good measure of exposure due to the consistency of behaviors within an individual (Braun et al. 2012b; Mahalingaiah et al. 2008; Teitelbaum et al. 2008).

However, the extensive follow-up within this prospective study design allows temporality of events and is a strong component towards establishing causality. The use of an exposure sample from pregnancy, when development is occurring rapidly, also adds to the strength of this study. The Developmental Origins of Health and Disease (DOHaD) framework considers these early life events to be crucial towards the possible programming of later health indices (Hanson and Gluckman 2008; Heindel and vom Saal 2009). There is accumulating evidence that exposures to these chemicals play a role in altered physiology from the perinatal period and animal studies have found effects at doses relevant to those encountered by human populations on weight gain, adiposity, and numerous metabolic imbalances (Marmugi et al. 2012; Wei et al. 2011).

Some studies find that the association between tallness in overweight and obese children disappear after puberty. Pre puberty, obese children have a height advantage over their lean peers but they experience a reduced growth spurt in comparison, resulting in no difference in attained height (Denzer et al. 2007; He and

Karlberg 2001). Future work in disentangling the order of adiposity and linear growth as driving forces by modeling weight trajectory would be beneficial.

In conclusion, this study explored whether exposure to environmental endocrine-disrupting compounds differentially alters growth trajectories of BMI and height. We found that different metabolites were associated with growth trajectories for males and females. MECPP in females was the only metabolite that was associated with BMI and height trajectories while MEOHP and MCPP were both significantly associated with males in our study population. The third tertile of the phthalate metabolite MECPP was associated with the highest trajectory of BMI and height in females. For males, the first and second tertiles of the phthalate metabolites MiBP, MBzP, MCPP, MEHP, MEHHP, and MEOHP were associated with highest attained BMI trajectory and the first and second tertiles of MEP, MCPP, and MEOHP were associated with the highest attained height trajectories. The tertiles associated with the highest trajectory were reversed with BPA and height trajectory, where the highest estimated height trajectory for females was observed with the lowest tertile, but the highest tertile in males.

Table 4.1. Best fit fractional polynomial function for each model degree for BMI trajectory.

Model degree	Terms included in best fit model for each degree								Goodness of Fit[a]	
	$Age^{(-2)}$	$Age^{(-1)}$	$Age^{(-0.5)}$	log(Age)	$Age^{(0.5)}$	Age	$Age^{(2)}$	$Age^{(3)}$	AIC	BIC
Males (N=108)										
3rd				X	X	X			3484.8	3514.3
4th	X		X		X	X			3482.5	3525.4
5th	X	X		X	X	X			**2920.6**	**2074.3**
6th			X	X	X	X	X	X	3478.9	3554.0
7th	X	X	X	X	X	X	X		3478.9	3554.0
8th	X	X	X	X	X	X	X	X	3495.9	3592.4
Females (N=115)										
3rd				X	X	X			3982.6	4012.8
4th					X	X	X	X	3979.1	4020.3
5th		X	X		X	X		X	**1411.1**	**1463.2**
6th	X	X	X	X			X	X	3973.9	4050.8
7th	X	X	X	X	X	X	X		3981.6	4058.5
8th	X	X	X	X	X	X	X	X	3982.5	4081.3

[a]Final model selection based on smallest AIC and BIC are indicated in bold

Table 4.2. Best fit fractional polynomial function for each model degree for height trajectory.

Model degree	Terms included in best fit model for each degree								Goodness of Fit[a]	
	$Age^{(-2)}$	$Age^{(-1)}$	$Age^{(-0.5)}$	log(Age)	$Age^{(0.5)}$	Age	$Age^{(2)}$	$Age^{(3)}$	AIC	BIC
Males (N=108)										
3rd				X		X		X	**4513.0**	**4543.0**
4th				X	X	X		X	4514.1	4554.3
5th		XX	XX	XX		X	X	XX	4526.5	4582.8
6th		X	X	XX	XX	XX	XX	XX	4523.4	4598.5
7th	X	X	X	X	X	X	X		4523.4	4598.5
8th	X	X	X	X	X	X	X	X	4531.8	4652.5
Females (N=115)										
3rd					X		X	X	5073.4	5103.6
4th	XX	XX			XX	X	X		**3507.0**	**3546.0**
5th	X	X	X	X	X				5073.3	5114.5
6th	X	X	X	X	X	X			5077.4	5135
7th	X	X	X	X	X	X	X		5080.4	5157.3
8th	X	X	X	X	X	X	X	X	5080.4	5157.3

[a]Final model selection based on smallest AIC and BIC are indicated in bold
X = model terms selected with equal AIC and BIC values as X; not selected for final model

Table 4.3. Characteristics of mothers and children in sample population.

Characteristic	Males		Females	
	N	Mean±SD/%	N	Mean±SD/%
Youth's age (yr)	117	10.3±1.5	132	10.3±1.7
height (cm)	117	138.6±10.5	132	138.33±10.9
BMI (kg/m^2)	117	19.1±3.08	132	19.8±3.98
Total number of visits	1033		1129	
age ≤1 years old	243	25	263	24
age>1 and ≤3 years old	381	36	424	37
age>3 and ≤5 years old	182	17	201	18
age >5 years old	227	22	241	21
Mother's BMI 1 month postpartum	114	26.7±4.2	126	27.2±3.6
years of education	115	11.3±2.8	130	10.8±2.8

Table 4.4. . Distribution of total (free+glucuronidated) BPA and phthalate metabolites in third trimester maternal urine (ng/mL uncorrected for dilution).

						Percentiles							
Analyte	**LOQ[a]**	**Sex**	**N**	**%>LOQ**	**GM (SE)[b]**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**Max[c]**	***p*-value***
BPA	0.4	Male	107	64	0.7 (2.0)	<LOQ	<LOQ	0.6	1.1	1.8	2.7	9.0	0.05
		Female	116	74	0.9 (2.1)	<LOQ	<LOQ	0.7	1.4	2.3	4.1	18.7	
MBP	0.5	Male	107	100	53.3 (3.1)	11.8	25.5	58	112	204	318	1000	1.00
		Female	116	100	54.3 (3.5)	12.7	26.4	54.2	119	206	606	1190	
MBzP	0.2	Male	107	99	4.3 (2.5)	1.4	2.6	5.2	7.7	13.4	15.9	32.5	0.18
		Female	116	100	4.1 (2.7)	1.3	2.2	3.7	7.0	12.8	29.6	109	
MCPP	0.2	Male	107	94	1.2 (2.5)	0.3	0.6	1.3	2.3	3.4	4.0	12.1	0.36
		Female	116	94	1.1 (2.7)	0.2	0.5	1.1	1.9	4.0	6.6	11.1	
MEP	1	Male	107	100	108.9 (2.4)	23.2	44.6	111	222	594	1130	7950	0.80
		Female	116	99	114.5 (2.8)	20.2	40.8	115.5	241	762	1900	9810	
MiBP	0.2	Male	107	98	1.8 (2.7)	0.4	0.9	1.7	3.6	6.4	8.4	40.1	0.33
		Female	116	98	2.0 (2.9)	0.5	1.0	2.0	3.6	8.6	12.6	33.9	
MEHP	1	Male	107	89	5.0 (3.5)	1.0	2.5	6.1	10	16.6	18.8	62	1.00
		Female	116	91	5.2 (2.6)	1.0	2.5	5.6	9.5	16.8	30.1	54.7	
MECPP	0.2	Male	107	100	31.9 (2.6)	8.6	19.4	33.7	58.3	107	125	193	0.99
		Female	116	100	30.9 (2.9)	9.7	15.1	35.4	58.1	107	138	251	
MEHHP	0.1	Male	107	100	19.4 (3.6)	4.7	10.6	16.9	42.7	76.4	95.2	167	0.83
		Female	116	100	19.1 (4.7)	4.9	9.1	22.7	37.5	67.8	96.7	161	
MEOHP	0.1	Male	107	100	11.6 (2.7)	3.1	6.0	11.2	25.2	46.0	49.9	85.8	0.83
		Female	116	100	11.6 (2.9)	3.2	5.8	13.3	24.7	42.7	56.1	133	

[a]LOQ: limit of quantification
[b]GM: geometric mean(standard error)
[c]Max: maximum
*p-value from Wilcoxon-Mann-Whitney test for differences between males and females

Table 4.5. Likelihood ratio test for BMI trajectory with best fit models for females and males.

	Female				Male			
	-2LL null	-2LL full	DF	*p*-value	-2LL null	-2LL full	DF	*p*-value
BPA	3777.8	3767.3	12	0.57	3402.1	3394.8	12	0.84
MBP	3777.8	3762.6	12	0.23	3402.1	3383.9	12	0.11
MiBP	3777.8	3763.9	12	0.31	3402.1	3373.3	12	<0.01
MBzP	3777.8	3764.7	12	0.36	3402.1	3372.6	12	<0.01
MCPP	3777.8	3768.6	12	0.69	3402.1	3381.3	12	0.05
MEP	3777.8	3761.0	12	0.16	3402.1	3385.7	12	0.17
MEHP	3777.8	3766.4	12	0.49	3402.1	3370.5	12	<0.01
MEHHP	3777.8	3768.5	12	0.68	3402.1	3372.8	12	<0.01
MEOHP	3777.8	3769.0	12	0.72	3402.1	3381.3	12	0.05
MECPP	3777.8	3749.6	12	0.01	3402.1	3386.6	12	0.22

[a]null model contains age polynomials and covariates
[b]full model contains SG-corrected metabolites, covariates, age polynomials, and their interactions
[c]DF=degrees of freedom between null and full models
*p-value comparing null to full model; significance indicates full model has better fit.

Table 4.6. Likelihood ratio test for height trajectory with best fit models for females and males.

	Female				Male			
	-2LL null	-2LL full	DF	p-value	-2LL null	-2LL full	DF	*p*-value
BPA	4943.4	4927.3	10	0.10	4460.5	4446.2	8	0.07
MBP	4943.4	4927.5	10	0.10	4460.5	4451.1	8	0.31
MiBP	4943.4	4934.8	10	0.57	4460.5	4447.2	8	0.10
MBzP	4943.4	4935.5	10	0.64	4460.5	4456.6	8	0.87
MCPP	4943.4	4935.3	10	0.62	4460.5	4420.2	8	<0.01
MEP	4943.4	4929.9	10	0.20	4460.5	4444.6	8	0.04
MEHP	4943.4	4926.5	10	0.08	4460.5	4452.8	8	0.46
MEHHP	4943.4	4936.8	10	0.76	4460.5	4447.2	8	0.10
MEOHP	4943.4	4936.4	10	0.73	4460.5	4443.9	8	0.03
MECPP	4943.4	4925.2	10	0.05	4460.5	4446.3	8	0.08

[a]null model contains age polynomials and covariates
[b]full model contains SG-corrected metabolites, covariates, age polynomials, and their interactions
[c]DF=degrees of freedom between null and full models
*p-value comparing null to full model; significance indicates full model has better fit

Figure 4.1. Predicted BMI trajectories and estimated differences between tertiles of MECPP for a female with mean covariate values.

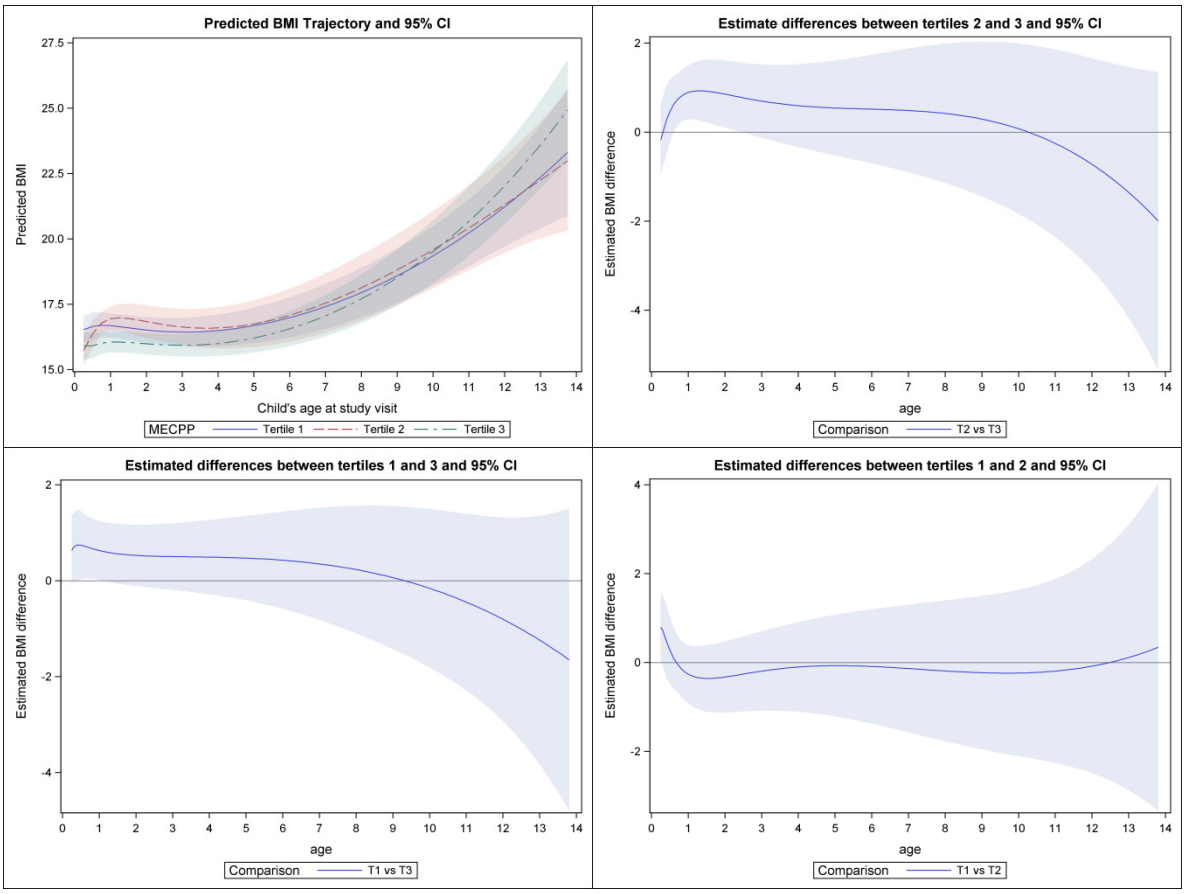


Figure 4.2. Predicted BMI trajectories and estimated differences between tertiles of MiBP for a male with mean covariate values.

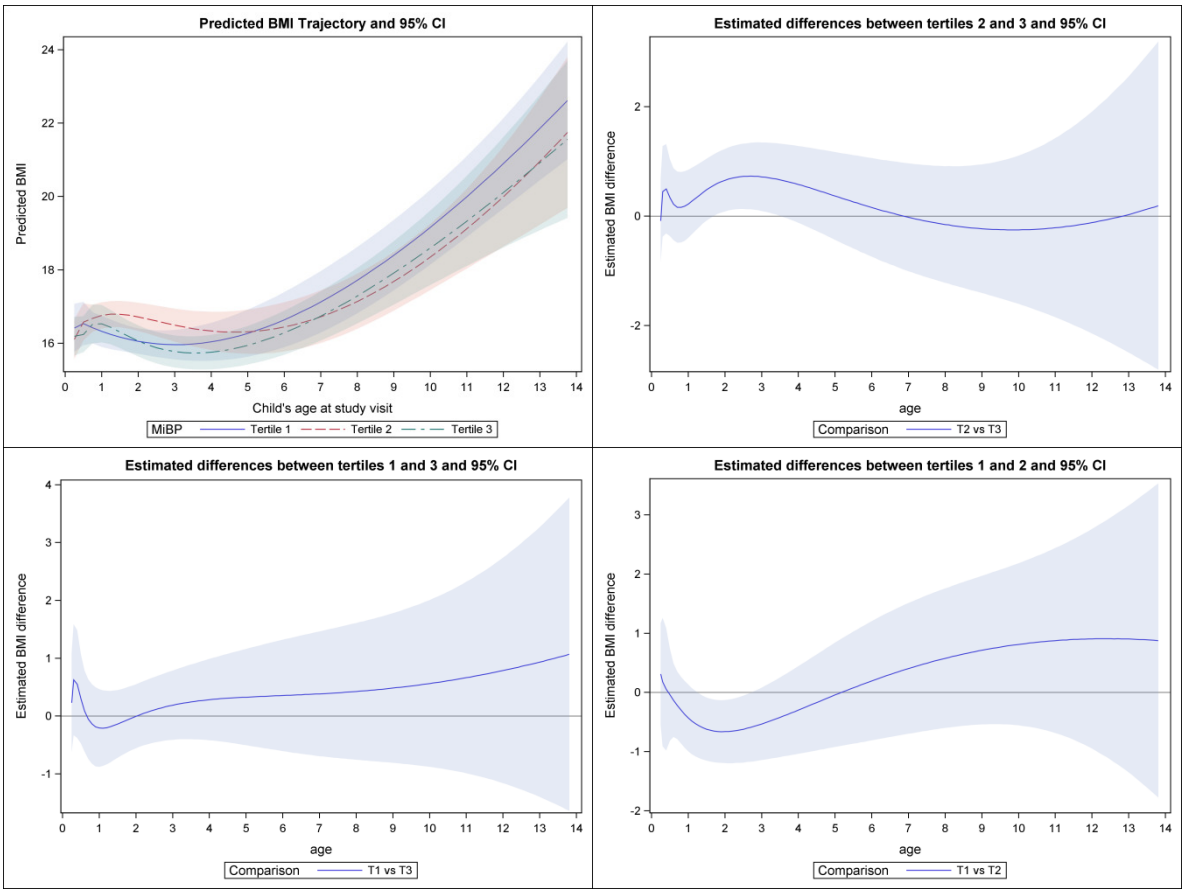


Figure 4.3. Predicted BMI trajectories and estimated differences between tertiles of MBzP for a male with mean covariate values.

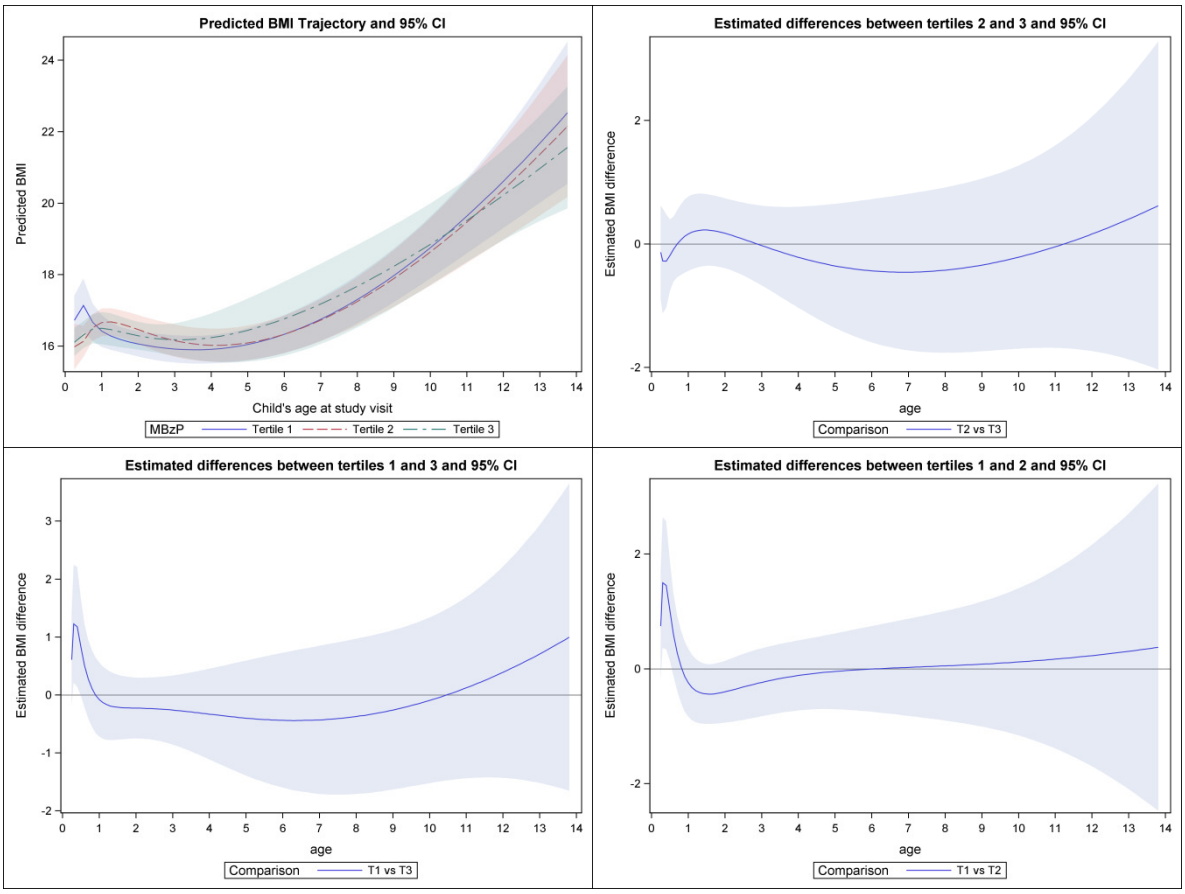


Figure 4.4. Predicted BMI trajectories and estimated differences between tertiles of MCPP for a male with mean covariate values.

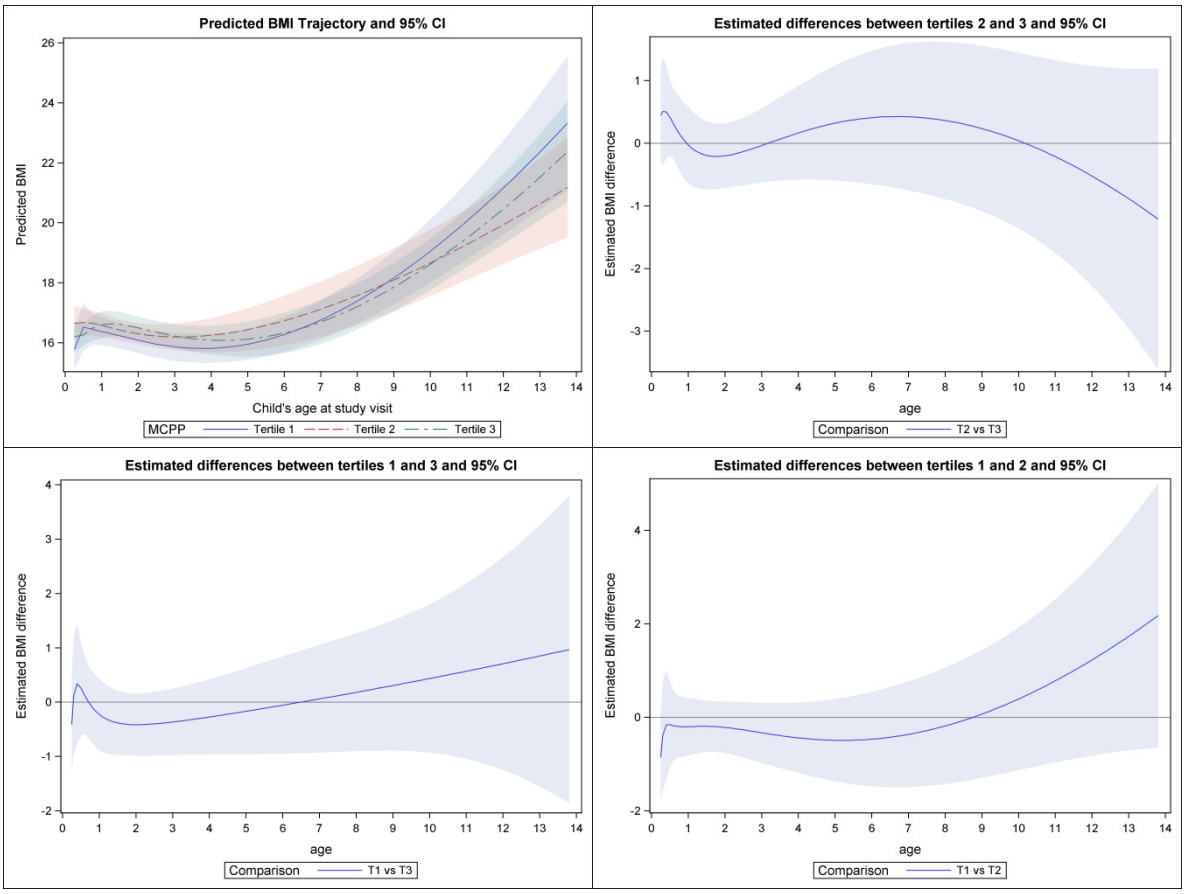


Figure 4.5. Predicted BMI trajectories and estimated differences between tertiles of MEHP for a male with mean covariate values.

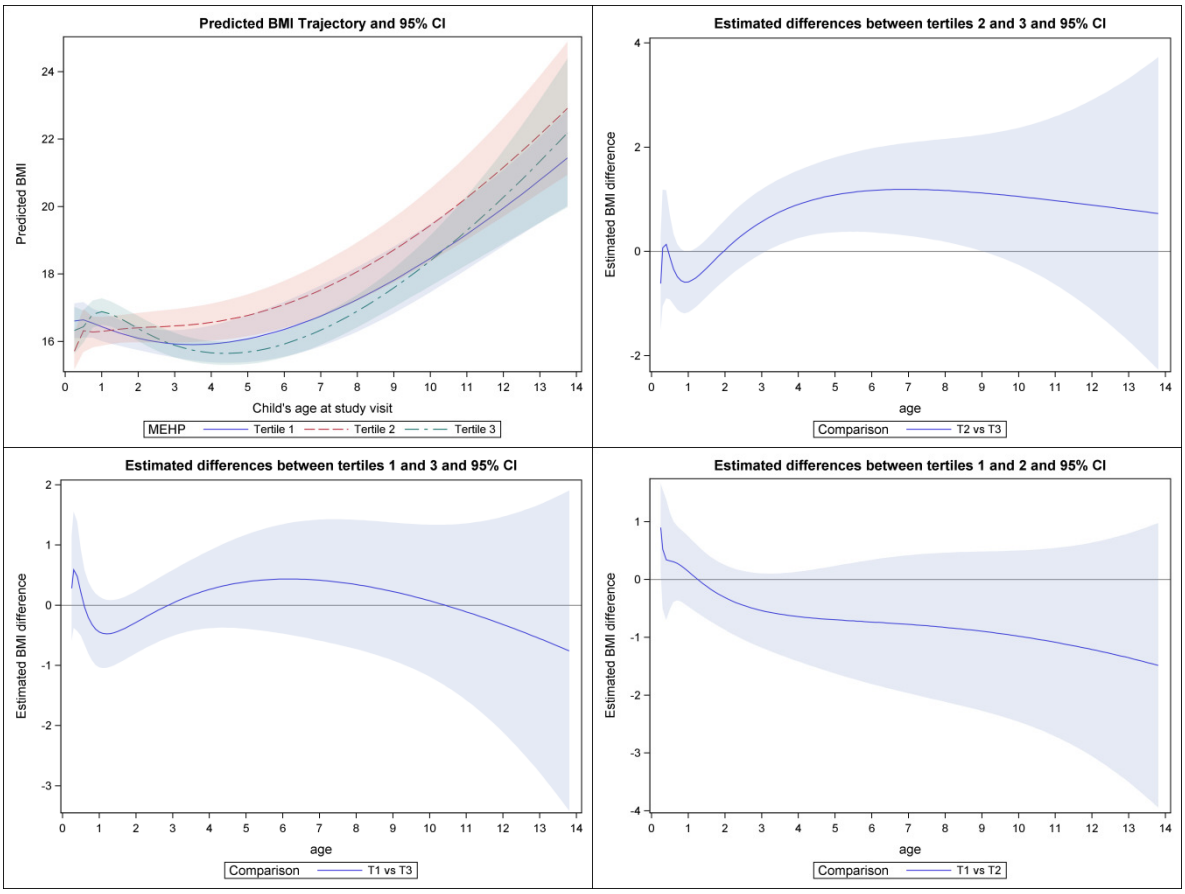


Figure 4.6. Predicted BMI trajectories and estimated differences between tertiles of MEHHP for a male with mean covariate values.

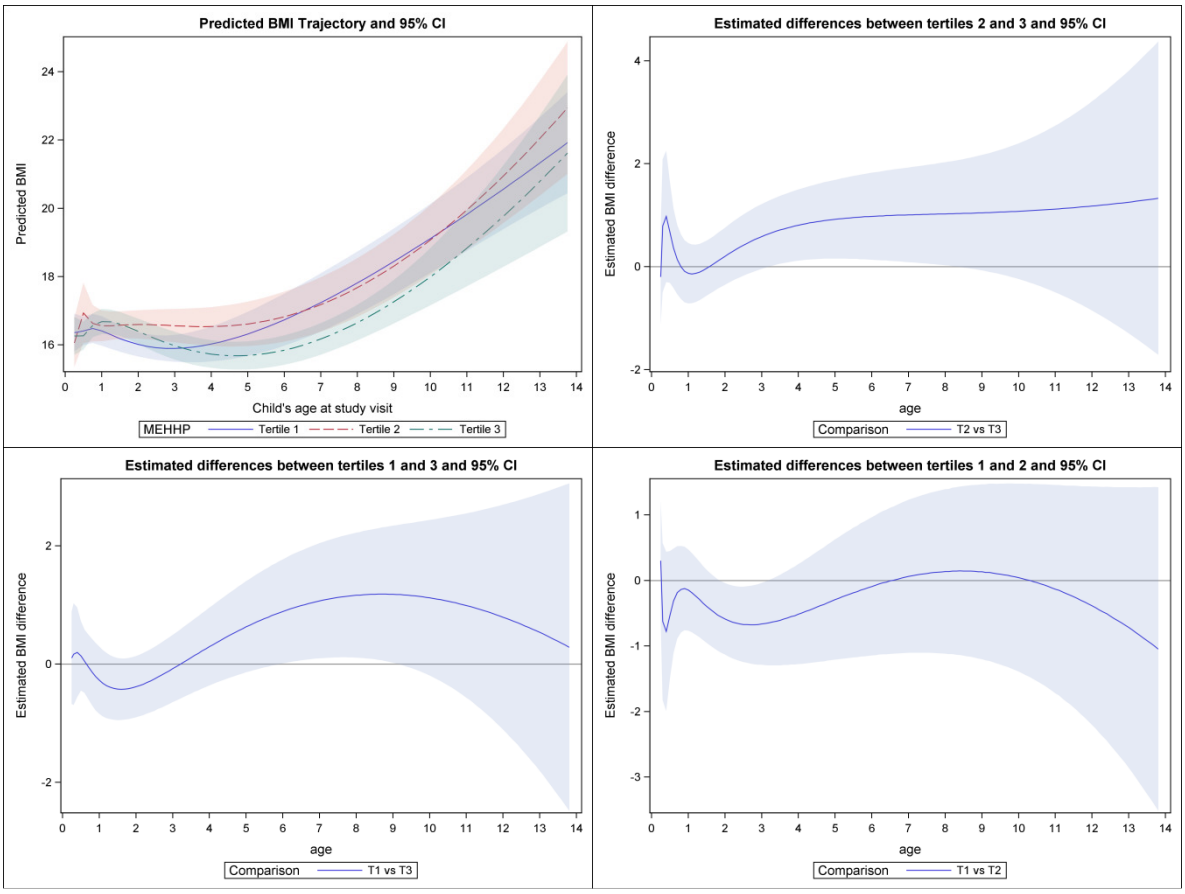


Figure 4.7. Predicted BMI trajectories and estimated differences between tertiles of MEOHP for a male with mean covariate values.

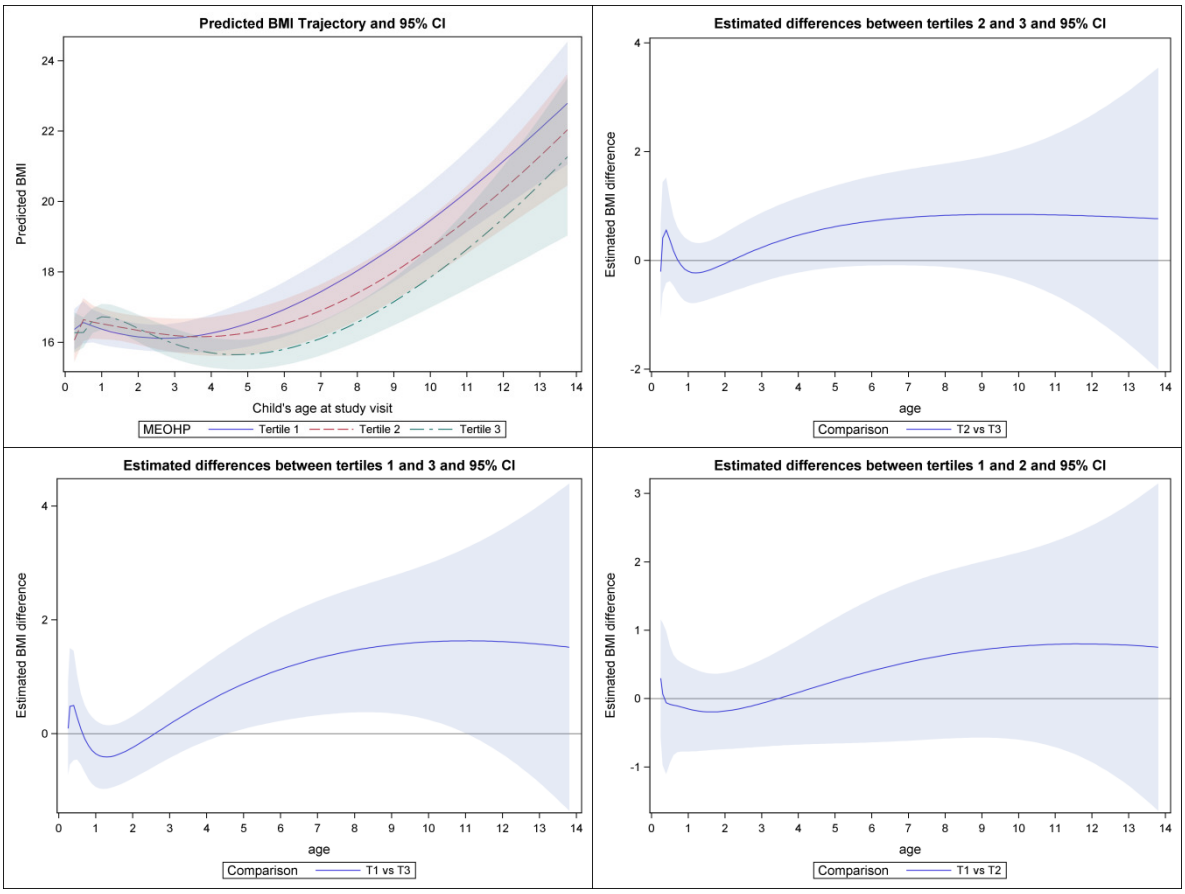


Figure 4.8. Ages and estimates of significant estimated BMI differences between tertiles of phthalate metabolites for males and females.

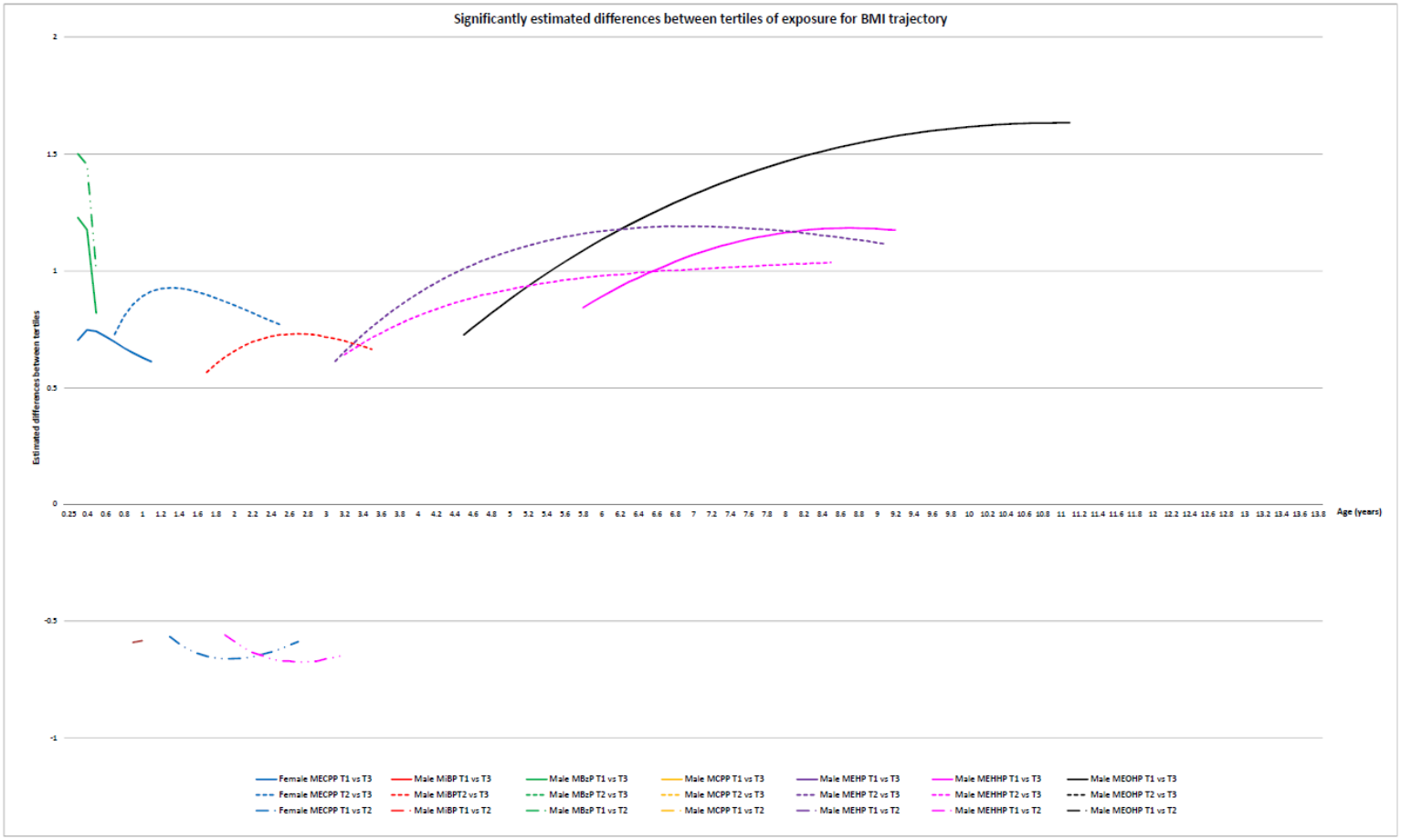


Figure 4.9. Ages of significant (p≤0.05) estimated differences between tertiles of phthalate metabolites that were significant from the likelihood ratio test for BMI trajectory. Red indicates positive estimated differences, blue indicates negative.

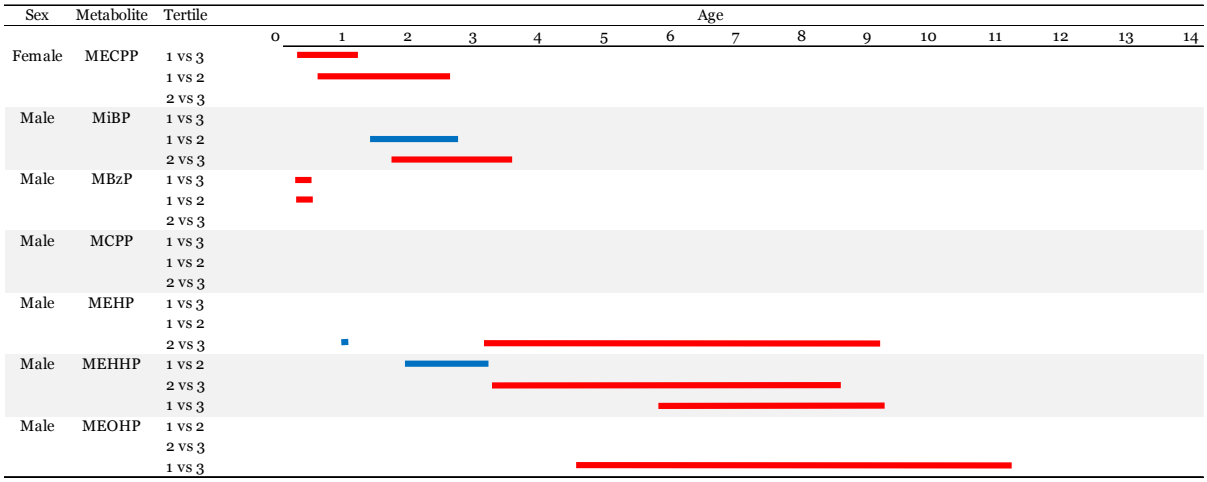


Figure 4.10. Predicted height trajectories and estimated differences between tertiles of MECPP for an average female.

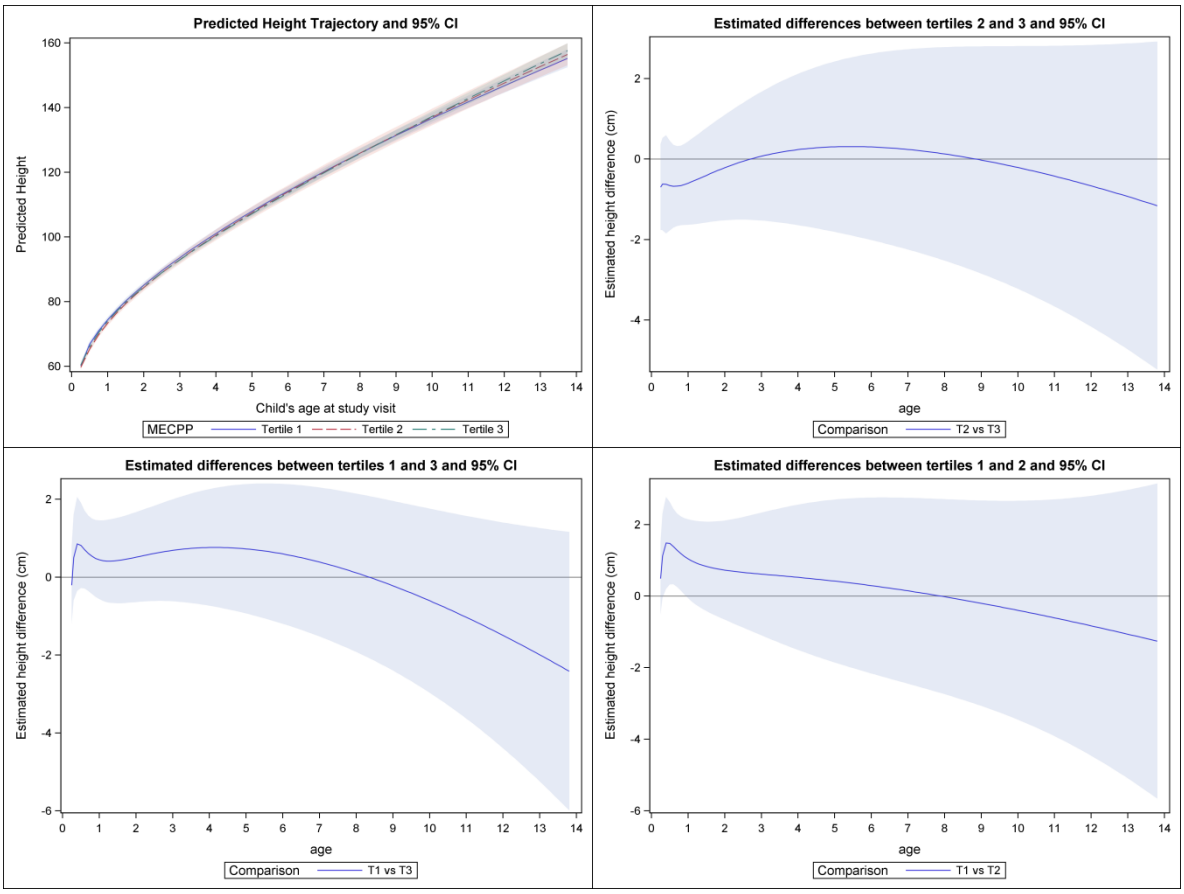


Figure 4.11. Predicted height trajectories and estimated differences between tertiles of MCPP for an average male.

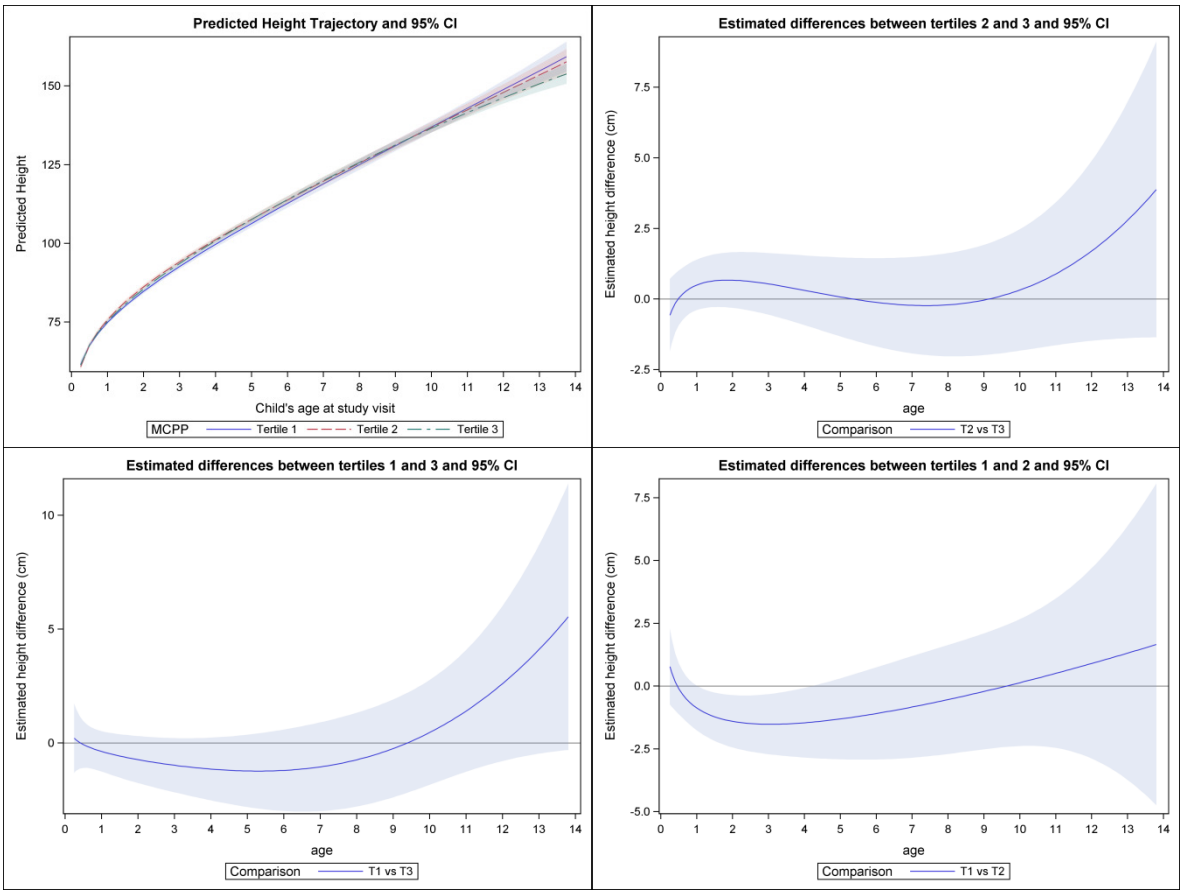


Figure 4.12. Predicted height trajectories and estimated differences between tertiles of MEP for an average male.

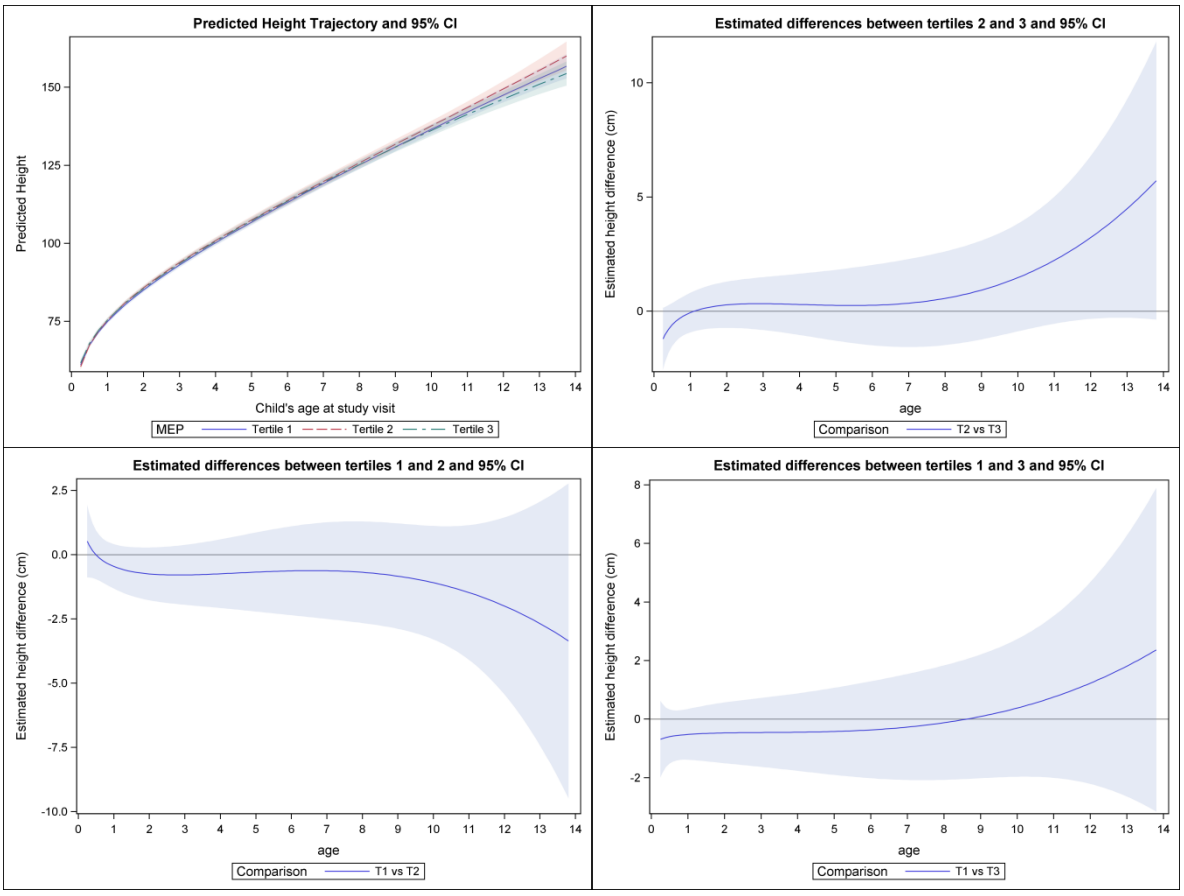


Figure 4.13. Predicted height trajectories and estimated differences between tertiles of MEOHP for an average male.

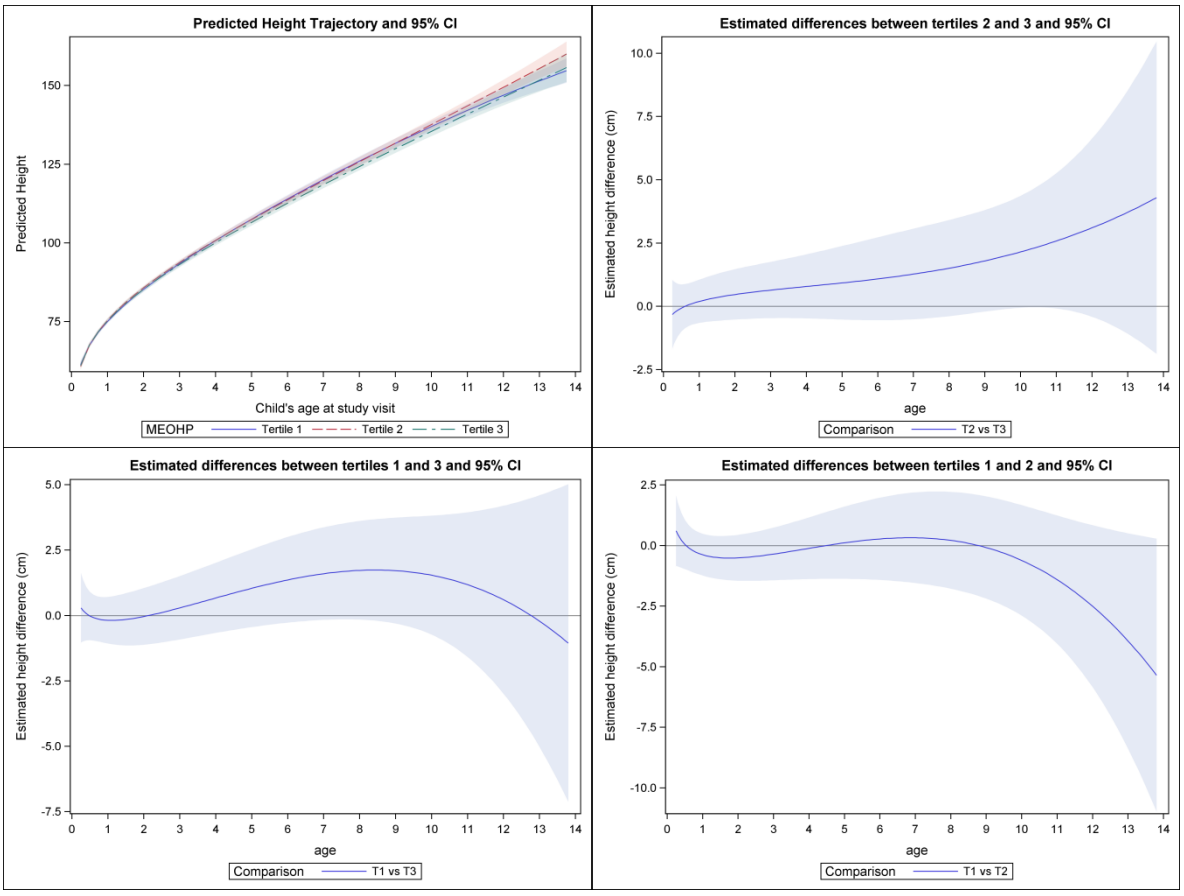


Figure 4.14. Ages and estimates of significant estimated height differences between tertiles of phthalate metabolites for males and females.

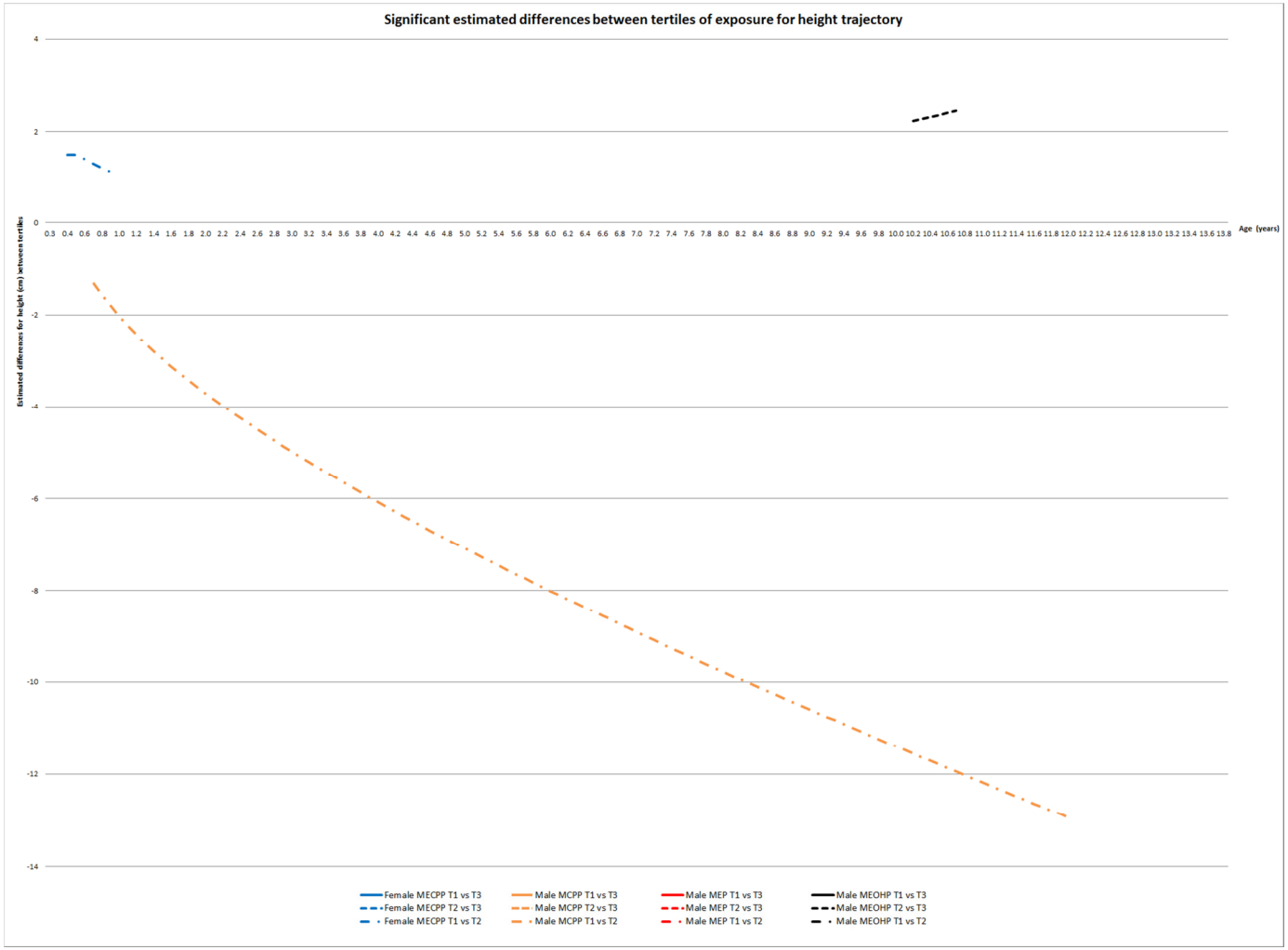


Figure 4.15. Ages of significant (p≤0.05) estimated differences between tertiles of phthalate metabolites that were significant from the likelihood ratio test for height trajectory. Red indicates positive estimated differences, blue indicates negative.

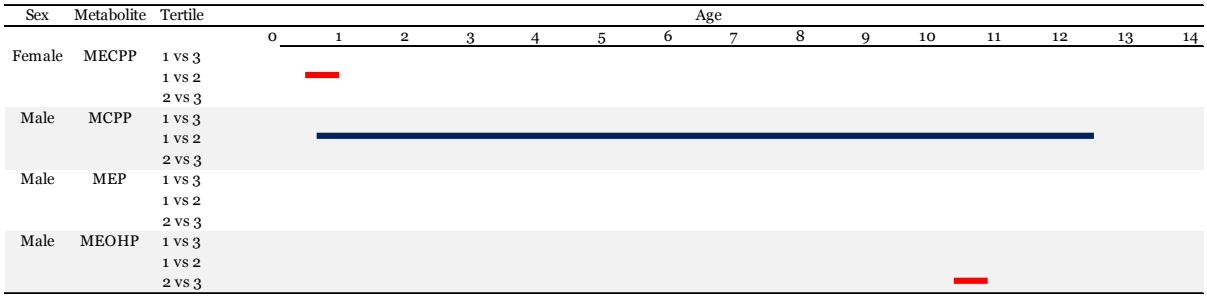


Figure 4.16. Predicted height trajectories and estimated differences between tertiles of BPA for an average female.

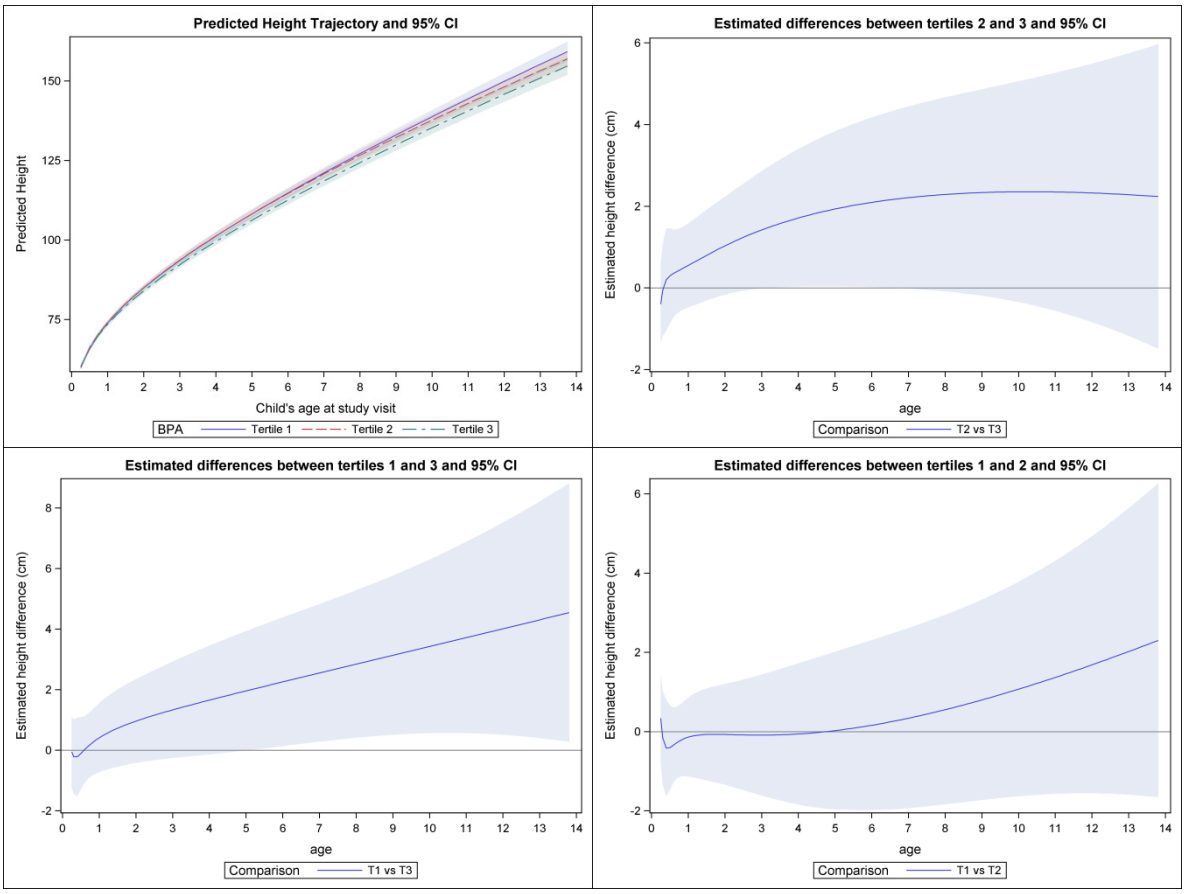
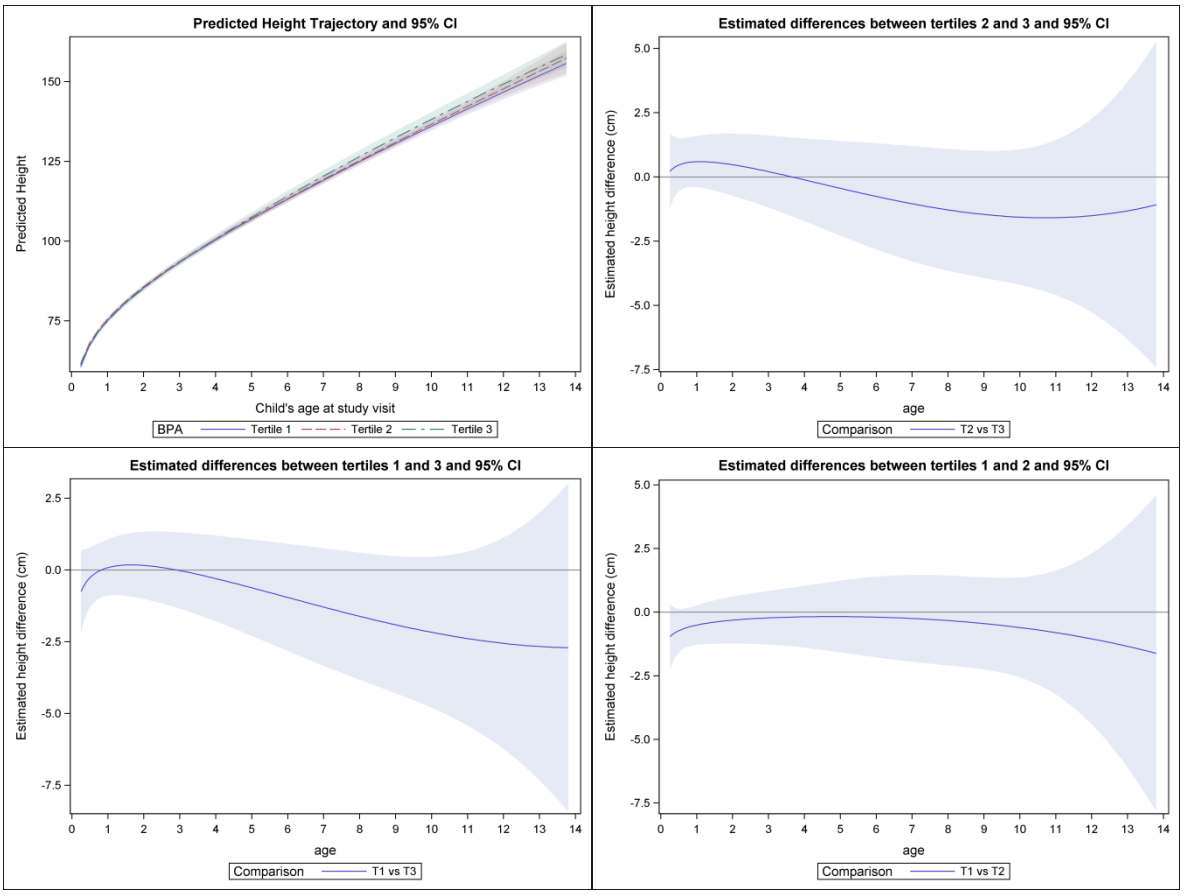


Figure 4.17. Predicted height trajectories and estimated differences between tertiles of BPA for an average male.



CHAPTER 5

Conclusions

This dissertation research sought to investigate potential contributing factors in the globally pervasive increases of overweight and obesity. Utilizing the frameworks of sensitive and critical periods for development and the Developmental Origin of Health and Disease, disruptions during these periods were hypothesized to be more detrimental than those occurring outside these periods. This research used a study population in Mexico, a country undergoing the nutrition transition, where shifting dietary and physical activity behaviors may increase the risks for later increased weight status, as fetuses may be exposed to environments that they are not physiologically adapted for (Hanson and Gluckman 2008; Popkin et al. 2012). This study population was rich resource, having recruited mothers from pregnancy and continuously following them and their children, who are now in adolescence. This provides an opportunity to temporality establish risk factors and their consequences and, given that childhood and adolescent obesity have been shown to track into adulthood, to suggest possible reasons for the increase in global obesity burden (Guo et al. 1994).

Chapter 2 focused on preterm birth as a stimulus for adverse catch-up growth and the relation with adolescent BMI, waist circumference, and obesity. Chapters 3 and 4 involved assessment of exposures to the endocrine-disrupting compounds

Bisphenol A and phthalate metabolites during pregnancy and adolescence. The objectives in chapter 3 were to assess the distributions of urinary metabolites in pregnancy and adolescent urines and to examine the continuous and quartile exposures in both time periods with adolescent BMI z-score, waist circumference, and triceps skinfold. Chapter 4 focused on the novel application of growth trajectory methods to examine whether tertiles of exposure to metabolites during pregnancy would differentially affect BMI and height trajectories

In chapter 2, we found no association between preterm birth and later odds of obesity or increases in BMI or waist circumference in either males or females. This study would greatly benefit from a larger sample size, as well as additional information regarding the type of preterm birth that occurred, such as spontaneous or medically indicated. However, our findings that maternal obesity was a significant risk factor for later child and adolescent obesity mirrored findings from other studies (Rooney and Ozanne 2011; Symonds et al. 2013). Possible future work could include the use of repeated measures to assess whether catch-up growth occurs for children born preterm, as well as whether the velocity of growth.

Preterm birth research would be greatly enhanced by improved quality and systematic reporting of all births in a globally-regulated format. Attaining consensus over definition and categories (spontaneous vs. medically-indicated vs. voluntary) of preterm birth would help monitor the changes in rates of preterm births reported. These practices would be informative to assess differences between low- and high-income countries particularly with voluntary induction of preterm birth, medical technologies, and structure of reporting stillbirths, where the interpretation of viability may be prone to misclassification. In developed countries, 5-10% of all

preterm births are stillbirths, with antepartum origins but occurring during the intrapartum period, which could lead to misclassification (Flenady et al. 2011). Availability of advanced early life medical care and technologies could facilitate early delivery of fetuses not growing optimally, reducing the number of stillbirths, but increasing the number of preterm births.

Implementation of various intervention strategies such as reducing the number of non-indicated caesarean deliveries and induction of labor, decreasing multiple embryo transfers during assisted reproductive technologies such as in-vitro fertilization, smoking cessation programs, and progesterone supplementation have only a projected conservative effect of decreasing the number of preterm birth rates by approximately 5% (Chang et al. 2013). However, the risk factors for preterm birth are diverse and elusive so it may be that focusing on modifiable behaviors, such as maternal over-nutrition, may be a realistic and positive modifier of a child's risk for later adverse weight status.

In chapter 3, we found that BPA and phthalate metabolites had primarily non-monotonic associations with adolescent BMI z-score, waist circumference, and triceps skinfold, and that direction and magnitude of association differed for males and females, similar to other studies (Bhandari et al. 2013; Harley et al. 2013; Hatch et al. 2010, 2008; Teitelbaum et al. 2012; Wang et al. 2012a; Wells et al. 2013). Additionally, significant findings were observed in lower levels of exposure (e.g. second quartile rather than fourth quartile, compared to the first, reference, quartile), which was observed in other studies; the non-monotonic relationship between these endocrine-disrupting compounds and outcomes may be an exception to the oft-quoted notion that, for toxins, "the dose makes the poison" (Marmugi et al.

2012; Vandenberg 2014; Welshons et al. 2006). Suggestive associations for continuous urinary metabolites and outcome measures were different between the two time periods and our adolescent cross-sectional findings of higher fat mass and distribution from continuous measures of BPA and MEP exposures in females are consistent with other cross-sectional studies (Bhandari et al. 2013; Carwile and Michels 2011; Eng et al. 2013; Harley et al. 2013; Hatch et al. 2010, 2008; Li et al. 2013; Shankar and Teppala 2011; Stahlhut et al. 2007; Teitelbaum et al. 2012; Wang et al. 2012a, 2012d).

Chapter 4 examined BPA and phthalate metabolite tertile exposures *in utero* and the resulting BMI and height trajectories and velocities for each tertile. The objective of this chapter was to use growth curve modeling for individuals with the novel approach of applying it to tertile levels of exposure during a sensitive period of development. Using mixed models and fractional polynomial age terms, models were created separately for males and females. The resulting trajectories indicated that males and females were influenced by different metabolites and that the highest trajectories for females by age 14 were due to the third tertile of exposure, whereas the lowest tertile of exposure produced the highest trajectories for males. These findings were reversed for males and females with BPA and height trajectories, where the lowest tertile in females and highest tertile in males were associated with the highest height trajectory.

Chapters 3 and 4 take advantage of repeated measures available in the study cohorts, as well as the archived biological samples from pregnancy, allowing us to examine a period of time where rapid development is occurring. The extensive follow-up time has also allowed us to examine outcome measures from biomarkers

in pregnancy at later ages than those previously reported in the literature. One limitation of this study is the use of a single spot urine during pregnancy and in adolescence, as BPA and phthalates are known to have short half-lives (Koch et al. 2005; Völkel et al. 2002). However, other studies have shown that a single measure may be a relatively good measure due to the consistency of everyday behaviors leading to exposure (Braun et al. 2012b; Mahalingaiah et al. 2008; Teitelbaum et al. 2008). Additionally, our confidence is stronger in the longitudinal results as reverse causality is not an issue. With cross-sectional studies, it is difficulty to establish temporality and results may be confounded by reverse causality; overweight individuals may consume more calories, or eat more foods packaged in materials with BPA and phthalates, resulting in a higher load of these chemicals.

Future research directions for chapters 3 and 4 would be to assess whether associations persist later into adolescence, beyond the pubertal stage, with additional follow-up of participants. Additionally, it would be interesting to investigate the "double hit" hypothesis, where exposures to EDCs during the perinatal period followed by exposures during the peripubertal period are thought to induce outcomes that were more severe than if exposures had only occurred at one point in time. Furthermore, assessing mixtures of EDCs, rather than individual metabolites, would be more representative of how individuals are commonly exposed.

Eliminating exposures to these compounds is likely impossible, given the pervasive nature of their use and multiple routes of exposure. However, several preventative strategies could be implemented by individuals to reduce their exposures, particularly during vulnerable periods of life such as pregnancy and early childhood. Limiting handling of thermal receipt paper, many of which contain BPA,

or choosing personal care products that do not contain phthalates could potentially reduce dermal exposure (Biedermann et al. 2010; Lewis et al. 2013). And, as oral contact is thought to be a major source of exposure, using glass or metal storage containers could decrease exposure; a dietary intervention involving the substitution of canned and packaged foods for "fresh foods" also found an average decrease of 66% for BPA and 53-56% for DEHP metabolites, showing a possibility for reduction in ingestion exposure (Rudel and Gray 2011; Wormuth et al. 2006).

Broadly, the results of this dissertation highlight that there may be factors outside an individual's control that may influence weight status and adiposity. Finding and understanding these potential factors are beneficial to public health and health care practitioners as they may contribute towards the design and implementation of more effective prevention or intervention strategies on child obesity.

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