Phthalates and Obesity:
Examining the Metabolism-disrupting Chemical Hypothesis in Midlife women

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2022

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Acknowledgements

I would like to thank each member of my dissertation committee, Dr. Park, Dr. Herman, Dr. Karvonen-Gutierrez, and Dr. Mukherjee. Without their mentorship, guidance, and support, this dissertation would not have been possible. I would also like to thank Dr. Siobán Harlow, who provided many of the resources needed for this dissertation. I have known Dr. Park, Dr. Karvonen-Gutierrez, and Dr. Harlow for much longer than the PhD program. Thank you all so much for introducing me to the field of epidemiology and your steadfast support throughout the years.

My sincere appreciation also goes to the staff and students at the Center for Midlife Science. Every research endeavor is a team sport, and you are the best team one can ask for. Special thanks go to Allie Leis and Robin Wiley for their friendship and encouragement during difficult moments.

I had the privilege of meeting scientists from outside of the University of Michigan during the PhD program. I would like to thank Dr. Michael Halpern for our monthly conversations about anything epidemiology and Dr. Elizabeth Radke-Farabaugh for helping me see the public health impact of environmental epidemiology research.

My deepest gratitude goes to my family and friends. Thank you, Mom and Dad, for always supporting me in my pursuits, even though you do not always understand what I do. Many thanks to Lisa, a fellow epidemiologist and friend who is always there to listen and to help. Justin, Alyssa, Jeremy, and John, thank you for reminding me to have fun outside of graduate school. Wallace, my best friend and life partner, thank you so much! None of this is possible without you.

I was fortunate to be funded by the Interdisciplinary Research Training on Health and Aging Grant (T32 AG-027708) for part of my studies. I would like to thank the National Institute on Aging (NIA), the University of Michigan, and the director of the training grant, Dr. Carlos Mendes de Leon for their support.

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720). The study was also supported by the SWAN Repository (U01AG017719). This publication was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131.

This study was also supported by grants from the National Institute of Environmental Health Sciences (NIEHS) R01-ES026578, R01-ES026964 and P30-ES017885, and by the Center for Disease Control and Prevention (CDC)/National Institute for Occupational Safety and Health (NIOSH) grant T42-OH008455.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

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1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; *Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI*; *University of California, Los Angeles – Gail Greendale, PI*; *Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004;* and the *University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.*

NIH Program Office: *National Institute on Aging, Bethesda, MD – Chhanda Dutta 2016-present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.*

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We thank the study staff at each site and all the women who participated in SWAN.

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Abstract

The prevalence of obesity and diabetes has increased dramatically in the past century. Because this period coincided with the increasing use of synthetic chemicals in industry and commerce, these chemicals are hypothesized to disrupt metabolism and contribute to the obesity-diabetes twin epidemic.

Phthalates, a class of synthetic chemicals added to numerous consumer and industrial products, are suspected to contribute to obesity, adverse adipokine profiles, and diabetes by interfering with energy and nutrient metabolism. Though supported by mechanistic studies, the epidemiologic evidence on phthalates, obesity, and its metabolic complications in adults is limited. Most studies are cross-sectional and conducted in largely homogeneous populations.

Using data from the Study of Women's Health Across the Nation, a racially/ethnically diverse group of women with urinary phthalate metabolite data in 1999/2000 and 2002/2003 and longitudinal metabolic outcomes, this dissertation examined the potential metabolic effects of phthalate exposure.

In Aim 1, we examined whether higher phthalate exposure in 1999/2000 was associated with more rapid increases in body weight (BW), fat mass (FM), and body fat percentage (BF%) over 18 years in 1369 women. After adjusting for demographic, lifestyle, and menopause-related factors, except for mono-carboxy-isononyl phthalate, higher urinary concentrations of all phthalate metabolites were associated with more rapid increases in FM and BF%. Per doubling of phthalate metabolite concentrations, differences in five-year BF% change ranged from 0.03 percentage point

(ppt) (95% confidence interval (CI): -0.03, 0.09) for mono-isobutyl phthalate to 0.09 ppt (95% CI: 0.02, 0.16) for mono(3-carboxypropyl) phthalate. Results were similar for FM change, but the associations with BW change were mostly null. Stratified analyses by baseline obesity status revealed stronger associations – at magnitudes comparable to some lifestyle risk factors of obesity – among normal/underweight women.

In Aim 2, we examined whether higher phthalate exposure was associated with adverse adipokine profiles characterized by higher leptin levels, lower high-molecular-weight (HMW) adiponectin levels, and a greater ratio between the two in 1250 women. We found that most phthalate metabolites were positively associated with leptin, but the associations were attenuated with adjustment for body mass index (BMI). Further, regardless of BMI adjustment, mono(2-ethylhexyl) phthalate (MEHP) was associated with higher HMW adiponectin levels, while most other phthalate metabolites were not associated with HMW adiponectin. None of the phthalates were positively associated with the leptin:HMW adiponectin ratio upon BMI adjustment, and MEHP was inversely associated with the ratio.

In Aim 3, we examined whether higher phthalate exposure was associated with a higher incidence of diabetes over six years in 1308 women. After adjusting for demographic, lifestyle, and health-related factors, several HMW phthalate metabolites were associated with a higher diabetes incidence, but none of the associations were statistically significant. There was effect modification by race/ethnicity. Among White women, each doubling of the concentrations of mono-isobutyl phthalate, monobenzyl phthalate, mono-carboxyoctyl phthalate, mono-carboxy-isononyl phthalate, and mono(3-carboxypropyl) phthalate was significantly associated with 30-63% higher diabetes incidence. In contrast, none of the phthalate metabolites were associated with diabetes incidence in Black or Asian women.

Overall, phthalate exposure was associated with more rapid body fat increases, but not adverse adipokine profiles independent of BMI. Some phthalates were associated with a higher incidence of diabetes in some women. These findings partially support a role of phthalates in the development of obesity and diabetes, suggesting that limiting phthalate exposure may help prevent obesity and its comorbidities.

Chapter 1 Introduction

1.1 Overview

Obesity, an excess of body fat, is a complex endocrine disorder with major consequences. Historically rare, the prevalence of obesity, as defined by an elevated body mass index (BMI), has increased dramatically around the world since the Second World War (1,2). In 2016, 13% of the world's adult population were obese, which was nearly triple the prevalence of obesity in 1975 (3). The prevalence of obesity in the United States is among the highest in the world. In 2017-2018, 42.4% of adults were obese (4), representing a substantial increase from a prevalence of less than 20% in the 1960s (5). Overweight and obesity are well-established risk factors of numerous chronic diseases, including cardiovascular disease, type 2 diabetes, and some cancers (6). Through these diseases, obesity was associated with the loss of over 70 million disability-adjusted life years in 2017 (7) and is estimated to cost up to 9.3% of a country's annual gross domestic product (8). The global prevalence of obesity is projected to continue increasing in the next decade, and so will its negative impacts (9). To address this ongoing epidemic, a thorough understanding the forces driving obesity and its comorbidities is urgently needed.

Type-2 diabetes (T2D), a metabolic disorder characterized by chronic hyperglycemia, is one of the leading metabolic complications of obesity. The global prevalence of diabetes rose in parallel to that of obesity in the past decades (10), reaching 9.3% in 2019 (11). Individuals with T2D are at increased risks of a range of micro- and macro-vascular complications, leading to increased disability and deaths (12,13). Since morbidity and mortality from T2D is a major

consequence of obesity, understanding the risk factors of T2D, particularly those shared with obesity, is important for further characterizing the obesity epidemic.

Obesity is closely linked to T2D partially because adipose tissue regulates whole-body energy and nutrient metabolism through secreting a plethora of bioactive compounds, including hormones named adipokines (14). Two major adipokines, leptin and adiponectin, are both implicated in the pathophysiology of T2D (Appendix). Leptin is a proinflammatory adipokine, higher levels of leptin are associated with adipose tissue inflammation (15), insulin resistance (16,17), and increased risks of diabetes (18). In contrast, adiponectin is an anti-inflammatory adipokine, higher levels of adiponectin are associated with increased insulin sensitivity (15,19) and reduced risk of diabetes (20). The high-molecular-weight (HMW) oligomer of adiponectin (HMW adiponectin) is the most biologically active form of adiponectin (15). Because adipose tissue secretes both adipokines at the same time, the ratio of leptin to adiponectin reflects the balance of pro- and anti-inflammatory processes and has been proposed as a marker of adipose tissue dysfunction (21,22). The connection between leptin and adiponectin and T2D highlights that adipose tissue is an endocrine organ important for metabolic health. Identifying factors that influence adipokines and thus adipose tissue's endocrine function will help us better understand the mechanisms behind obesity-related metabolic diseases.

Because the obesity epidemic is a recent phenomenon, research into the risk factors of obesity and its metabolic complications have rightfully focused on social and behavioral factors characteristic of modern societies. Car-centric urban design (23), reduced physical activity (24), increased consumption of energy-dense, processed foods (25), and sleep deprivation (26) are now widely recognized risk factors of obesity and T2D targeted by public health interventions. One aspect of modernity that emerged in tandem with the obesity epidemic but has received relatively

little attention is the increased production and use of synthetic chemicals. Juxtaposing the increasing volumes of synthetic chemical production and the increasing prevalence of overweight in the US between the 1960s and 2000s, Baillie-Hamilton first proposed in 2002 that synthetic chemicals such as pesticides, plasticizers, synthetic food flavorings, and solvents may promote body weight gain by disrupting the endocrine processes regulating appetite, satiety, metabolism, and growth (27). Four years later, Grün and Blumberg coined the term "environmental obesogen" (28) and postulated that these chemicals increased the risk of obesity by binding to metabolic sensors, steroid hormone receptors, and thyroid hormone receptors, thereby interfering with signaling pathways involved in adipogenesis and energy balance (29,30). Subsequently, Casals-Casas, Desvergne, Neel, and Sargis recognized that many of these signaling pathways are also involved in the metabolism of glucose and other nutrients, which led to the concepts of "environmental metabolic disruptors" (31) and "environmental diabetogens" (32). In the mid-2010s, Heindel and other experts unified existing concepts in the Parma Consensus Statement (33) and proposed the "metabolism disrupting chemical (MDC) hypothesis" (34). This hypothesis posits that environmental chemicals may act on adipose tissue and other organs during sensitive windows over the life course to adversely affect metabolism and increase the risk of obesity, diabetes, and other related metabolic disorders. Though supported by ecological and toxicological data, whether the MDC hypothesis explains the obesity epidemic has been tested in few longitudinal epidemiologic studies in adults (34). Such data will add valuable insights to the origin of the current epidemic of obesity and metabolic diseases and help identify additional targets for obesity prevention. In addition, understanding the health effects of synthetic chemicals to which the public is exposed is an integral part of health risk assessments and environmental regulations.

Quality epidemiologic data relevant to the MDC hypothesis will enhance the evidence base used for these purposes.

This dissertation examined whether higher exposure to phthalates, a group of synthetic chemicals added to numerous industrial and consumer products since the 1930s, was associated with more rapid increases in body fat, altered levels of leptin and adiponectin, and a higher incidence of diabetes in a racially/ethnically diverse group of midlife women. The two studies examining body fat and diabetes utilized longitudinal designs, while the study on adipokines provides data on phthalates' potential metabolism-disrupting mechanisms. This chapter describes phthalates, summarizes potential mechanisms of metabolic disruption, and reviews existing epidemiologic studies on phthalates and obesity, adipokines, and diabetes in adults. I will highlight major limitations in the current epidemiologic literature before presenting the dissertation's specific aims.

1.2 Phthalates

Phthalates are diesters of 1, 2-benzenedicarboxylic acid. Its generic structure is shown in **Figure 1.1**. The first commercially successful phthalate, di(2-ethylhexyl) phthalate (DEHP), was introduced to the market in the 1930s as a plasticizer for polyvinyl chloride (PVC) plastics (35). Since then the diversity and production volume of phthalates have increased rapidly with the growth of the plastic industry (36). By 2017, over 20 alcohols and their mixtures have been used to synthesize phthalates, and 18 billion pounds of phthalates were produced globally each year for use in the cosmetics, automotive, construction, home furnishing, electronics, apparel, food processing and packaging, outdoor and sporting goods, medical, and toy industries (37,38).

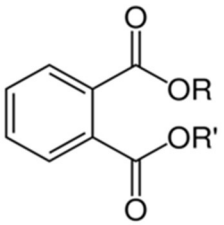

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Figure 1.1 The generic structure of phthalates

Based on the molecular structure of the alkoxy side chains, phthalates can be classified as low-molecular-weight (LMW) and high-molecular-weight (HMW) phthalates (39). LMW phthalates have no more than four carbons in each alkoxy side chain and are frequently added to personal care products as solvents and fixatives (40,41). HMW phthalates have five or more carbons in each alkoxy side chain and are frequently added to PVC plastic products as plasticizers (40,41). Common sources of LMW phthalates include fragrance, shampoo, and nail polish (40,42). Common sources of HMW phthalates include various PVC applications, such as vinyl tiles, upholstery, adhesives, automobile interior, electrical cable insulation, the plastic parts of electronic devices, food processing equipment, food packaging films, clothing, shoes, inflatable plastic toys, blood storage bags, and medical tubing (40,43–45). **Table 1.1** lists the most commonly used phthalates, their applications, and their metabolites, which are used as biomarkers of phthalate exposures. The metabolites of these phthalates have been the national biomonitoring priorities in the United States since 1999/2000, and they are the focus of this dissertation.

Table 1.1 List of phthalates and their metabolites examined in this dissertation

Group	Phthalates	Applications	Phthalate metabolites (biomarkers of phthalate exposure)
Low-molecular-weight phthalates	Di-ethyl phthalate (DEP)	Used as a solvent in personal care products, especially those containing fragrance (e.g., perfume, deodorant, soap, and lotion). Also used as a coating in some medications (40,41,46).	Mono-ethyl phthalate (MEP)
	Di-n-butyl phthalate (DnBP)	Used as an ingredient in caulk, adhesives, cosmetics such as nail polish (especially pre-2010s), and the coating of some medications. May also be used in some PVC applications as plasticizers (40,41,46).	Mono-n-butyl phthalate (MnBP)
	Di-isobutyl phthalate (DiBP)	Used as an ingredient in caulk, adhesives, and cosmetics such as nail polish (40,41).	Mono-isobutyl phthalate (MiBP)
DEHP (a HMW phthalate of particular public health interest)	Di(2-ethylhexyl) phthalate (DEHP)	Plasticizer for flexible PVC products, including food packaging. May be in medical devices such as blood bags. (40,47).	Mono(2-ethylhexyl) phthalate (MEHP)
			Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
			Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)
			Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)
Other high-molecular-weight phthalates	Butylbenzyl phthalate (BBzP)	Plasticizer for vinyl flooring, vinyl leather, and vinyl fabric (48). Also used as an ingredient in adhesives and sealants (41).	Monobenzyl phthalate (MBzP)
	Di-isononyl phthalate (DiNP)	Plasticizer for flexible PVC products, including flooring, electrical cords, and food packaging (40,41,44).	Mono-isononyl phthalate (MiNP)
			Mono-carboxyoctyl phthalate (MCOP)
	Di-isodecyl phthalate (DiDP)	Plasticizer for flexible PVC products, especially wires and cables (40,44).	Mono-carboxy-isononyl phthalate (MCNP)

Group	Phthalates	Applications	Phthalate metabolites (biomarkers of phthalate exposure)
	DnBP, Di-n-octyl phthalate (DnOP), and other HMW phthalates	DnOP is a plasticizer for PVC products, such as food packaging, flooring, and garden hoses (40,44).	Mono(3-carboxypropyl) phthalate (MCPP)

Because phthalates are not covalently bound to personal care products or the PVC polymer matrix, they readily migrate out of industrial or consumer goods, particularly in the presence of heat and hydrophobic substances such as fat (49). This property, as well as their high production volume and diverse applications, has resulted in nearly ubiquitous human exposure. The most important exposure pathway is ingesting food contaminated during processing, handling, and storage (50,51). Dermal absorption is an additional pathway particularly relevant for phthalates in personal care products (45). Inhaling and ingesting contaminated indoor dust can also result in exposure to phthalates in building materials (52,53). Upon exposure, phthalates are hydrolyzed into their monoesters, some of which may undergo further biotransformation to become secondary metabolites (54). Most primary and secondary metabolites are eventually excreted in urine within days of exposure (55,56). It is by measuring concentrations of urinary phthalate metabolites that human exposure to phthalates is assessed.

Biomonitoring studies from across the world in the past three decades showed that the metabolites of many phthalates were detected in over 90% of urine samples (57,58,40,59–61), confirming widespread phthalate exposure. The levels of urinary phthalate metabolites varied by location, socioeconomic status, race/ethnicity, age, gender, health behaviors, and over time, and the patterns of variations differed by phthalates. In the US, the urinary levels of MEP, MBzP, MCOP, MCNP, and MCPP were higher in the Northeast and the South than the West, potentially

reflecting differences in local product availability (62). Higher socioeconomic status was associated with lower exposure to MEP and MBzP but higher exposure to DEHP and some other HMW phthalate metabolites (63,64). The levels of LMW phthalate metabolites, especially MEP, were higher in non-Hispanic Black than non-Hispanic White (65), a pattern potentially attributable to racial/ethnic differences in personal care product use (66). In adults, older age was generally associated with lower exposure to phthalates (62,67). Compared to men, women had higher urinary levels of MEP, MnBP, and MBzP, but similar levels of DEHP metabolites (40,61). Recent use of personal care products, including shampoo, nail polish, bar soap, and perfume was associated with higher exposure to MEP (42,68), while frequent consumption of meat, dairy, processed foods, and foods prepared in restaurants including fast food establishments was associated with higher exposure to HMW phthalate metabolites such as DEHP metabolites, MCOP, MCNP, and MCPP (69,50,58,70–74). In the past 20 years, concerns about phthalates' reproductive and development toxicity have led to the restrictions of DnBP, DEHP, BBzP, DiNP, and other phthalates in toys and childcare articles in the US and changes in consumer preference (75). Consequently, the median concentrations of the metabolites of DEP, DnBP, DEHP, and BBzP decreased among Americans between 2001 and 2010, but the concentrations of the metabolites of other phthalates, such as DiBP, DnOP, and DiDP, increased during the same period as phthalates of public concerns were replaced with analogs with limited safety data (40). These exposure patterns highlight that exposure to phthalates and its associated health consequences truly is a public health problem, as exposure affects virtually everyone, including those who are vulnerable to chronic diseases due to their socioeconomic position and behaviors.

1.3 Mechanisms of metabolic disruption from toxicological studies

Given such pervasive exposure, it is concerning that some phthalates, such as DnBP, DEHP and BBzP have been found to cause body weight gain (76–78), increased leptin levels (76,77,79), reduced adiponectin levels (80), and elevated fasting glucose or glucose intolerance (80–82) in some rodents. Toxicological evidence suggests that phthalates may increase the risk of obesity by activating peroxisome proliferator-activated gamma (PPAR-γ). PPAR-γ are nuclear receptors abundantly expressed in adipose tissue, liver, skeletal muscle, and the hypothalamus (83). They modulate energy homeostasis, lipid and glucose metabolism, and inflammation by sensing fatty acids, hence their classification as "metabolic sensors" (30,83). PPAR-γ activation is essential for the maintenance and proliferation of adipose tissue because it is required for adipogenesis (84). Many phthalate metabolites, such as MEP, MEHP, MEOHP and MBzP, activate PPAR-γ (85–88). In mice preadipocytes (3T3-L1 cells), phthalate monoesters with PPAR-γ activity consistently induce adipogenesis (85,86,89–91), suggesting PPAR-γ activation in preadipocytes as a potential mechanism linking phthalates to obesity. Similarly, phthalate metabolites known to activate PPAR-γ, including MEHP, MBzP, monohydroxy isononyl phthalate (MHINP, a metabolite of DiNP), and MCNP, promote lipid accumulation in human SGBS preadipocytes, further supporting a role of PPAR-γ activation as a potential obesogenic mechanism of phthalates (88). In addition, DEHP has been shown to disrupt the hypothalamic-pituitary-thyroid axis (HPT) in rats, resulting in hypothyroidism, a lower basal metabolic rate, and hence less energy expenditure (77). Through this mechanism, phthalates may shift whole-body energy balance towards the positive, increasing the risk of obesity (92). Obesity may subsequently lead to increased leptin, reduced adiponectin, insulin resistance, and diabetes.

One intriguing aspect about the metabolism-disrupting mechanisms of phthalates is that PPAR-γ activation in adipose tissue by pharmacological agents typically increase adiponectin synthesis and insulin sensitivity (93,94). The anti-diabetic drugs, thiazolidinediones, are PPAR-γ agonists that improve insulin sensitivity at the expense of body weight gain (93). If phthalates simultaneously increase the risk of obesity, disrupt adipokines, and increase the risk of diabetes, multiple mechanisms may be present to counter the potentially beneficial effects of PPAR-γ activation. One study in differentiated murine adipocytes showed that repeated exposure to physiologically relevant levels of MEHP over several days increased the expression of pro-inflammatory cytokines and chemokines (95), which may increase the synthesis of leptin (96). Another study in mature human SGBS adipocytes showed that treatment with DiNP and MHINP at 10 nM for 8 days increased leptin secretion and decreased adiponectin secretion, potentially through mechanisms related to oxidative stress and disturbed lipid metabolism (88). As for glucose homeostasis, DEHP has been shown to disrupt glycolysis and gluconeogenesis in liver (97). DEHP and DEP may also hinder insulin signaling in liver cells (98,99), fat cells (99), and skeletal muscle cells (100) through oxidative stress and epigenetic mechanisms. Further, phthalates may increase insulin resistance indirectly by disrupting the signaling pathways of non-insulin hormones important for glucose homeostasis, such as the HPT and hypothalamic-pituitary-gonadal (HPG) axes, although the associations between phthalates and estradiol in women (101,102) and phthalates and testosterone in men (103,104) were not always consistent with phthalates' anti-estrogenic and anti-androgenic effects observed in *in vitro* studies (105,106). Limited *in vitro* evidence also suggests that certain phthalate metabolites, including MnBP, MiBP, and MEHP, may adversely affect pancreatic β-cell survival and glucose-stimulated insulin secretion, but the data were sometimes conflicting (107,108).

Overall, PPAR-γ activation, inflammation, oxidative stress, disruption of thyroid and sex steroid hormones, interference with glucose uptake or metabolism in liver, adipose tissue, and skeletal muscle, and potentially adverse effects on pancreatic β-cell viability and function are thought to be the major mechanisms linking phthalates to obesity, adverse adipokine profiles, and diabetes (**Figure *1.2***). It is important to note that these mechanisms are not exhaustive and may not be independent of each other. Given that the effects of phthalates in animal studies often varied by the species, genetic background, sex, and age of the exposed animals, as well as by the type of dose of phthalates, one may speculate that the relevance of each mechanistic pathway may change depending on the phthalate congener, the exposed organism's genetic background, and the exposed organism's developmental stages. In this regard, animal and *in vitro* data must be interpreted and extrapolated to humans cautiously. Ultimately, rigorous epidemiologic studies on phthalates and pertinent metabolic endpoints are needed to truly understand whether phthalates could disrupt metabolism and contribute to obesity and its complications.

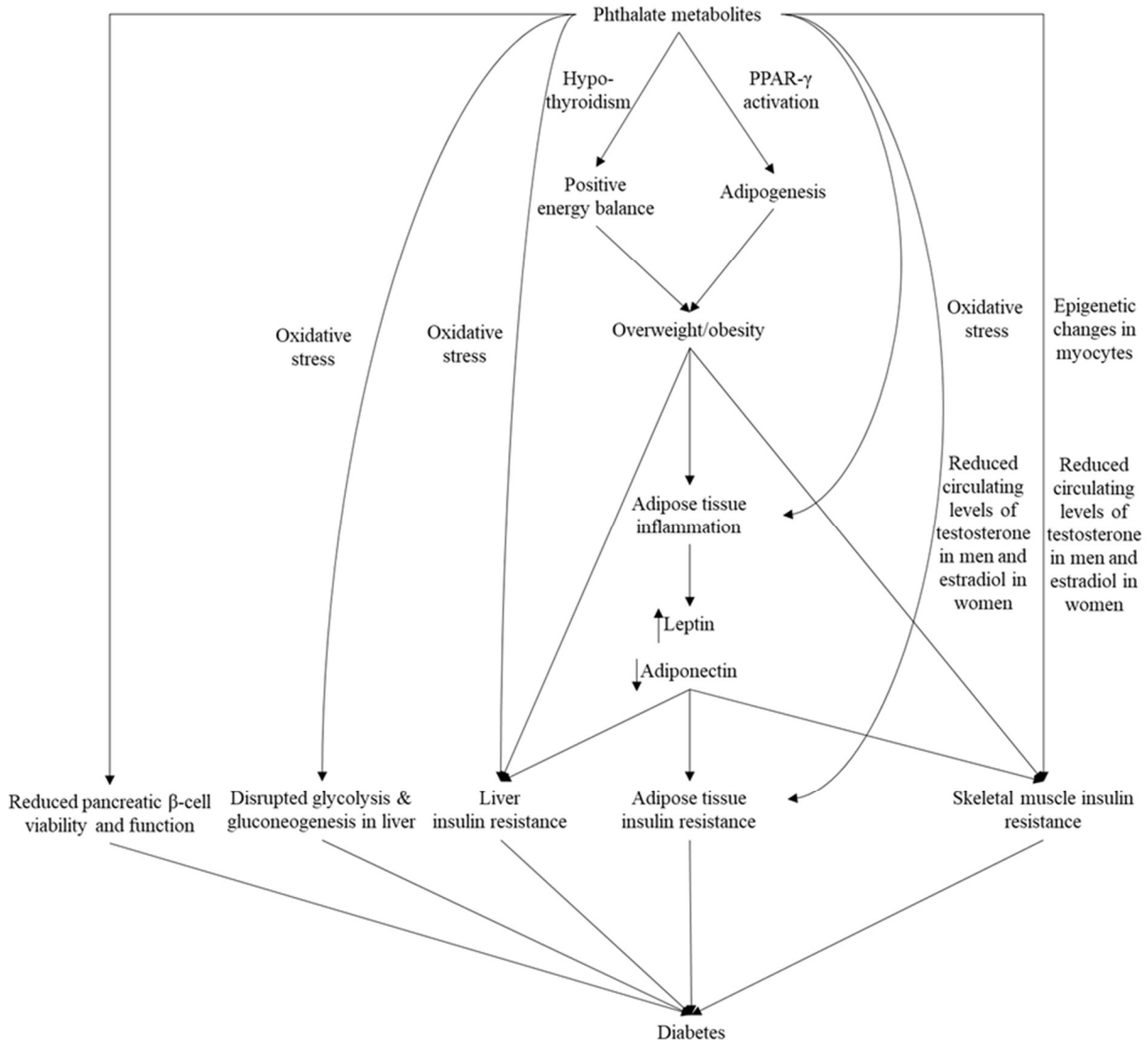

Figure 1.2 Major mechanisms linking phthalates to obesity, adverse adipokine profiles, and diabetes

1.4 Current epidemiologic evidence and its limitations

Relative to animal and *in vitro* data, the epidemiologic evidence on phthalates and obesity in human adults is limited. Most studies were cross-sectional and examined body mass index (BMI) or body weight as outcomes (109–117). In cross-sectional studies, few phthalate metabolites were robustly associated with increased body size or percent body fat (117). The

associations between phthalate metabolites and adiposity measures often varied by sex, age, and menopausal status, but there were no consistent patterns of effect modification. Regardless of the results, these studies ultimately provide limited evidence on the obesogenic potential of phthalates due to their temporal ambiguity.

Only seven studies have examined the associations between phthalates and longitudinal changes in adiposity in adults (118–124) (**Table 1.2**). All studies examined body weight or BMI as outcomes. One study also included body fat percentage as an outcome measure (119). In these studies, higher urinary concentrations of mono-ethyl phthalate (MEP, the primary metabolite of DEP), mono-n-butyl phthalate (MnBP, the primary metabolite of DnBP), mono-isobutyl phthalate (MiBP, the primary metabolite of DiBP), DEHP metabolites, monobenzyl phthalate (MBzP, a metabolite of BBzP), mono(3-carboxypropyl) phthalate (MCPP, a metabolite of DnBP, DnOP, and other HMW phthalates), and phthalic acid (a non-specific metabolite of phthalates) were associated with faster increases or slower declines in adiposity measures, but the results were highly heterogeneous both within and across studies (118–124). Few studies reported positive associations with changes in adiposity measures for all phthalate metabolites, and few phthalate metabolites were consistently associated with faster increases in adiposity measures across all studies. The analytic samples of these studies differed by age, reproductive status, obesity status, and other attributes, but it is unclear if these differences contributed to the inconsistent results across studies. A major limitation of most of these studies is the use of body weight to approximate body fat. Body weight is not an accurate measure of body fat. In an aging population, the simultaneous loss of lean muscle mass and increases in fat mass may result in a stable body weight, despite increases in body fat mass and body fat percentage (125). By using inaccurate measures of body fat, most previous studies may have underestimated the associations between phthalates and

changes in adiposity. The only study examining fat mass and body fat percentage provided some data on phthalates and changes in body fat, but the study was conducted among overweight and obese individuals undergoing extreme caloric restrictions to lose weight, so its generalizability is unknown (119). Overall, evidence linking phthalates directly to changes in fat mass or body fat percentage in a general population is still unavailable, which is a major obstacle to our understanding on phthalates' obesogenic potential.

Table 1.2 Longitudinal studies on phthalates and adiposity in adults

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
Exposures outside of pregnancy											
Haggerty, 2021 (118)	• Pre- and perimenopausal women in the "Mid-life Women's Health Study". • ~ 70% White and 30% Black • High socioeconomic status	Variable between 2006 and 2015, but predominantly between 2008 and 2010	Baltimore, Maryland	524	76% between 45 – 50 years	1 year	Change in BMI between follow-up and baseline	• 9 phthalate metabolites measured in pooled spot urine samples collected 2-4 times over four weeks at baseline • Specific-gravity adjusted	Age, race/ethnicity, education, alcohol use, smoking status, family income, marital status, diagnosis of depression	• Overall, phthalate metabolites NOT associated with BMI change. • Among those who transitioned from peri- to post-menopause, ∑DEHP, MiBP, MEP, and ∑LMW were positively associated with BMI change. • Among those who remained peri-menopausal, MnBP and MEP inversely associated with BMI change.	• Associations between some phthalates and BMI change strongest among those who transitioned from peri to post within one year • Suggests the menopausal transition may be a sensitive window for the obesogenic effects of phthalates

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
Van der Meer, 2020 (119)	• Overweight or obese subjects (BMI > 27 kg/m^2) enrolled in the "LOWER" RCT on diet-induced weight loss • ~ 15% male • Presumably majority White	2008-2010	The Netherlands	218	mean = 52 years	3 months	• Post-intervention BMI, body fat percentage (BF%), and waist circumference	• 8 phthalate metabolites measured in pooled 24-hr urine samples • Concentrations were multiplied by total 24-hr volume	Age, sex, diabetes, diet group, baseline value of outcome	• MEP, MiBP, MnBP, DEHP metabolites,and MBzP all positively associated with BMI, BF%, and waist circumference, but only two associations were statistically significant: MBzP and BF%; MBzP and waist circumference.	Some phthalate metabolites were associated with impaired fat loss during a calorie-restriction-induced weight loss program, consistent with hypothesized obesogenic effects
Diaz Santana, 2019 (120)	• Post-menopausal women in the "Women's Health Initiative" • Women were controls of a breast cancer case-control study • ~ 80% White	1993-1998	Birmingham, AL; Pittsburgh, PA; Tuscon, AZ	660	mean = ~ 62 years	3 years; 6 years	Body weight	• 13 phthalate metabolites measured in spot urine samples at baseline, categorized into quartiles	Urinary creatinine, age, race/ethnicity, education, income, smoking status, alcohol use, healthy eating index 2005, energy intake, physical activity, HT use, history of DM, CVD, HTN, and dyslipidemia	<u>At the end of 3 years</u> • Borderline ($0.05 \leq$p-value ≤ 0.10) or statistically significant (p-value < 0.05) positive association with BW change: MEP, mono-hydroxybutyl phthalate (a metabolite of DnBP), mono-hydroxyisobutyl phthalate (a metabolite of DiBP), MEOHP • Borderline significant inverse	Some phthalates may contribute to short-term weight gain in post-menopausal women

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
										association with BW change: MCOP <u>At the end of 6 years</u> Most associations were attenuated, and none were statistically significant or borderline significant.	
Song, 2014 (121)	• Nurses' Health Study (NHS) and NHS II • Women were controls of a T2D case-control study • ~ 100% White	• NHS: 2000 - 2001 • NHSII: 1995 - 2000	United States	977	• mean = 57.9 years at Quartile 1 of total phthalates • mean = 51.4 years at Quartile 4 of total phthalates	10 years	Self-reported body weight	• 9 phthalate metabolites measured in spot urine samples at baseline, categorized into quartiles	Urinary creatinine, cohort origin, age, menopausal status, smoking, physical activity, alcohol consumption, Alternative Healthy Eating Index, total energy intake, and baseline body weight	• Statistically significant or borderline significant positive association with body weight change: phthalic acid, MBzP, sum of MnBP and MiBP, and sum of all phthalate metabolites	Some phthalate metabolites were associated with modestly greater body weight gain

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
Exposures during pregnancy											
Philips, 2020 (122)	• Mothers in a population-based birth cohort	2004	Rotterdam, Netherlands	1192	37 years	6 years	• Maternal weight gain 6 years post-partum, calculated as "maternal weight 6 years postpartum – maternal pre-pregnancy weight"	• Average metabolite concentrations in early and mid-pregnancy urine samples; 13 phthalate metabolites were examined.	Early and mid-pregnancy creatinine concentrations, maternal age, parity, ethnicity, edu, dietary caloric intake during early pregnancy, pre-pregnancy BMI, maternal smoking during pregnancy, and maternal alcohol use during pregnancy	• All metabolite groups examined were associated with greater weight gain over 6 years postpartum, including LMW phthalate metabolites, HMW phthalate metabolites, DEHP metabolites, and DNOP metabolites, but only the associations for LMW phthalate metabolites and DNOP metabolites were statistically significant. • Results for HMW and DEHP slightly attenuated among those who did not have subsequent pregnancies • Effects stronger in overweight/obese	Early and mid-pregnancy phthalate exposures were associated with greater body weight gain 6 years postpartum.

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
Perng, 2020 (123)	• ELEMENT study • Mothers recruited in public maternity hospitals	1997 - 2004	Mexico City, Mexico	199	28 years	1 year	• Weight change from delivery to 1-year postpartum	• Geometric mean of urinary metabolites in urine samples collected at each trimester; 9 phthalate metabolites were examined.	Specific gravity, maternal age, parity, height, first trimester BMI, gestational age at enrollment, smoking during pregnancy, breastfeeding duration, offspring birth weight	• DBP metabolites, DEHP metabolites, MBzP, and MCPP were associated with slower body weight decrease between delivery and 1-year postpartum, but these metabolites were associated with lower body weight at delivery.	Prenatal exposure to certain phthalates was associated with lower body weight at delivery, but slower rate of body weight loss in the first year postpartum.
Rodriguez-Carmona, 2019 (124)	Pregnant women in the ELEMENT cohort	1997 - 2004	Mexico	178	mean = 27.3 years	mean = 7 years	• Change in BW per year after delivery	• Spot urine samples collected at each trimester of pregnancy; 9 phthalate metabolites were examined. • Log-transformed, specific-gravity adjusted, and geometric mean taken	Age, education, living with/without partner, parity, daily energy intake, breastfeeding duration	• Positive association with the rate of BW gain: MCPP • Inverse association with the rate of BW gain: MBzP	Exposure to some phthalates during pregnancy was positively associated with long-term body weight gain in women

The epidemiologic evidence on phthalates and adipokines is also limited. Only two studies have examined phthalates and leptin or adiponectin in adults and both were cross-sectional (126,127) (**Table 1.3**). In Lee et al. 2019, phthalate metabolites were not associated with leptin in a population of reproductive-aged women in Korea (126). The study did not adjust for body size, but most women had a normal BMI. This study also found that higher urinary concentrations of MnBP, MBzP, and the sum of DEHP metabolites were significantly associated with higher serum adiponectin (126). Consistent with these findings, the other study on phthalates and adiponectin found that almost all phthalate metabolites were positively associated with serum adiponectin independent of BMI (127), but it is unclear if these findings were generalizable because the study participants all had impaired glucose tolerance or diabetes. Neither study considered phthalates' associations with the ratio of leptin to adiponectin. In sum, little is known about the associations between phthalates and adipokine profiles in humans. Existing studies were both conducted in Asia, so studies on phthalates and leptin, adiponectin, and their ratio among populations in other social contexts will expand our knowledge on phthalates and adipokines.

Table 1.3 Studies on phthalates and leptin and adiponectin in adults

1st Author, year	Population	Location	Time period	N	Age	Outcomes	Exposure assessment	Covariates	Main results	Main conclusions
Lee, 2019 (126)	Women recruited from two sampling frames: 1) those who visited hospitals and public health centers for general health check-up and 2) those who participated in the Children's Health and Environmental Chemicals of Korea Study	Korea	2015-2016	459	between 20 and 48 years	Leptin in fasting blood samples Adiponectin in fasting blood samples.	17 phthalate metabolites in spot urine samples, corrected for hydration with creatinine.	Age, urinary nicotine metabolite, and current alcohol consumption	None of the phthalate metabolites were associated with leptin MnBP, ∑DEHP metabolites, and MBzP were positively associated with adiponectin.	Some phthalate metabolites were positively associated with adiponectin.
Duan, 2017 (127)	Volunteers from the outpatient clinic of Metabolic Diseases Hospital, Tianjin Medical University. • Over 98% of the participants had T2D. • 57% male	Tianjin, China	2016	329	between 29 to 93 years, with the majority between 55 to 69 years old.	Adiponectin in fasting blood samples	11 phthalate metabolites in spot urine samples	Age, sex, education, BMI, urinary creatinine, smoking status, alcohol consumption, physical activity, family history of diabetes, blood pressure, triglycerides, high-density lipoprotein cholesterol	Except for mono-methyl phthalate, higher levels of all phthalate metabolites were significantly associated with higher levels of adiponectin.	Exposures to phthalates were associated with higher levels of adiponectin.

Similar to studies on obesity and adipokines, most studies on phthalate exposure and diabetes are cross-sectional (128–135). This is a serious limitation because urinary phthalate metabolites reflect recent exposure (54), while diabetes is a chronic disease with a long latency period and a long disease duration. Phthalate exposure when diabetes is well-established may not correlate well with phthalate exposure before diabetes onset. Furthermore, if people become more health-conscious and reduce processed food consumption after diabetes diagnosis, phthalate exposure may be affected by diabetes status. All these concerns make cross-sectional studies on phthalates and diabetes less informative for causal inference purposes. To date, only one study has examined the associations between phthalates and incident diabetes (67) (**Table 1.4**). Using data from the Nurses' Health Study and Nurses' Health Study II cohorts, this study found that over approximately 10 years, higher urinary concentrations of butyl phthalate metabolites, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP, a secondary metabolite of DEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP, a secondary metabolite of DEHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP, a secondary metabolite of DEHP) were associated with a higher incidence of T2D in middle-aged, White, female nurses. Whether these findings are generalizable to non-White women from diverse socioeconomic backgrounds is unknown. Further, phthalate metabolites in only one spot urine sample at baseline were used to represent phthalate exposure over 10 years of follow-up. Given the short half-lives of phthalate metabolites in the body and the dynamic nature of phthalate exposure (54,68), the study's exposure measurement error may be relatively high, which may have attenuated the associations between phthalates and diabetes.

Table 1.4 The longitudinal study on phthalates and T2D in adults

1st Author, year	Population	Baseline year	Location	N	Age at baseline	Follow-up length	Outcome	Exposure assessment	Covariates	Main results	Main conclusions
Sun, 2014 (67)	• Women in the Nurses' Health Study (NHS) and NHS II • ~ 100% White • Subjects were selected based on a density case-control study design. T2D cases were identified from women who were free of T2D, cardiovascular diseases, and cancers at the time of phthalate exposure assessment (baseline). Controls were selected at the time of T2D case diagnosis, matched with cases on age at urine sample collection, date of urine sample collection, race/ethnicity, fasting status, menopausal status, and hormone therapy use at the time of urine sample collection.	• 2000 – 2002 for NHS • 1996 – 2001 for NHSII	United States	• 971 T2D cases • 970 controls	• Mean = 66 in NHS; mean = 46 in NHS II	Approximately 10 years	Self-reported physician's diagnosis of T2D. The accuracy of self-reported T2D in NHS and NHSII had been validated against medical records in a validation study.	9 phthalate metabolites in spot urine samples at baseline	Age at baseline, race/ethnicity, fasting status, time of urine sample collection, menopausal status, and hormone therapy use at urine sample collection, urinary creatinine, smoking status, post-menopausal hormone therapy use, oral contraceptive use, physical activity, alcohol consumption, family history of diabetes, history of hypercholesterolemia or hypertension, Alternative Healthy Eating Index, BMI	<u>NHS</u> • Positive association between the sum of DEHP metabolites and incident T2D, but the association was not statistically significant. <u>NHS II</u> • Positive associations between the sum of DEHP metabolites, butyl phthalate metabolites, and total phthalate metabolites with T2D, with the associations statistically significant for butyl phthalate metabolites and total phthalate metabolites. <u>Pooled analysis</u> • The highest quartiles of MEHHP, MECPP and phthalic acid were significantly associated with higher incidence of T2D. (Pooled analysis was not available for butyl phthalate metabolites because they were not measured in NHS)	Exposures to certain DEHP metabolites and butyl phthalate metabolites were associated with a higher T2D incidence. These associations were stronger in the younger women from NHS II.

1.5 Specific aims

This dissertation was designed to address the major limitations of the current epidemiologic literature on phthalates and obesity, adipokines, and diabetes. **Aim 1** examined whether higher phthalate exposure at baseline was associated with more rapid increases in body weight, fat mass, and body fat percentage over 18 years of follow-up. **Aim 2** examined whether higher phthalate exposure was associated with a more adverse adipokine profile characterized by higher levels leptin, lower levels of high-molecular-weight (HMW) adiponectin, and a greater ratio between the two. **Aim 3** examined whether higher phthalate exposure was associated with a higher incidence of diabetes over six years. Together, the three aims provided enhanced evidence for the metabolic impact of phthalates, which would contribute to the research examining the MDC hypothesis and inform risk assessments and environmental regulations of phthalates.

1.6 Appendix: Leptin, adiponectin, and their connection to diabetes

Leptin is a hormone secreted in direct proportion to body fat mass. Physiologic levels of leptin suppress appetite, increase energy expenditure, and sensitize skeletal muscle and liver to the action of insulin, thereby contributing to body weight maintenance and glucose homeostasis (14). However, chronically elevated levels of leptin, as is common in obesity, may induce leptin resistance (136). Leptin is also proinflammatory; it stimulates macrophage infiltration into adipose tissue and facilitates the production of other proinflammatory adipokines associated with impaired insulin sensitivity (137,138). In contrast, adiponectin is an anti-inflammatory adipokine with insulin-sensitizing effects. It inhibits the synthesis of proinflammatory cytokines, reduces adipose tissue inflammation, and thereby maintains the tissue's insulin sensitivity (139–141). Adiponectin

also acts on skeletal muscle and liver to increase insulin sensitivity (142). The circulating levels of adiponectin decrease with increasing body fat mass (137).

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Chapter 2 Phthalate Exposure is Associated with More Rapid Body Fat Gain in Midlife Women: The Study of Women's Health Across the Nation (SWAN) Multi-pollutant Study

2.1 Abstract

Background

Obesity is a major threat to health, but the etiology of obesity is incompletely understood. Phthalates, synthetic chemicals ubiquitous in the environment, are suspected to have obesogenic effects, but the relationship of phthalates and obesity in humans remains uncertain. We examined whether phthalate exposure was associated with body fat gain in midlife women.

Methods

We analyzed data from 1369 women in the Study of Women's Health Across the Nation Multi-Pollutant Study. Eleven phthalate metabolites measured in spot urine samples at baseline (1999/2000) were standardized with covariate-adjusted creatinine. Body weight (BW), fat mass (FM), and body fat percentage (BF%) were measured near-annually until 2016/2017. For each metabolite, linear mixed effects models with time and $\log_2$(metabolite) interactions were examined, adjusting for demographic, lifestyle, and menopause-related factors. Analyses were conducted overall and stratified by baseline obesity status. As sensitivity analyses, all analyses were repeated using a second set of metabolites measured in 2002/2003.

Results

Higher levels of all metabolites except mono-carboxy-isononyl phthalate were associated with faster increases in BF%. Per doubling of metabolite concentrations, differences in five-year BF% change ranged from 0.03 percentage point (ppt) (95% confidence interval (CI): -0.03, 0.09) for mono-isobutyl phthalate to 0.09 ppt (95% CI: 0.02, 0.16) for mono(3-carboxypropyl) phthalate. Results were similar for FM change, but associations with BW change were mostly null. In stratified analyses by baseline obesity status, positive associations were strongest in women who were normal/underweight at baseline. When metabolites from 2002/2003 were used as exposures, most associations were attenuated and not statistically significant, but they remained positive for normal/underweight women.

Conclusions

Phthalate metabolites were associated with more rapid body fat gain in midlife women. Phthalates may contribute to obesity, but our results need confirmation given attenuation of estimates in the sensitivity analyses.

2.2 Introduction

Obesity affects nearly 1 in 2 women in the United States (1) and is a major threat to health because it increases the risk of leading causes of death and disability (2). Preventing obesity requires a thorough understanding of its etiology, but the current understanding is incomplete (3). Some environmental chemicals are hypothesized to have obesogenic effects given the coinciding use of these chemicals in industry and commerce with increasing obesity prevalence in at least the past five decades (4,5). Investigating the relationship between chemical exposure and measures of obesity is critical to understanding the pathophysiology of obesity to appropriately identify targets for prevention.

Phthalates, diesters of 1, 2-benzenedicarboxylic acid, are among the chemicals suspected to promote body fat gain and contribute to obesity (6). Since the 1930s, phthalates have been added to numerous industrial and consumer products (7). Low-molecular-weight (LMW) phthalates are often added to personal care products as solvents and are frequently found in fragrance, shampoo, and cosmetics (8). High-molecular-weight (HMW) phthalates are often added to polyvinyl chloride plastics (PVC) as plasticizers and are found in many PVC applications, including flooring, cables, wires, clothing, food processing equipment, food packaging, and some medical devices (9). Human exposure to phthalates occurs mainly through ingesting food contaminated during handling, processing, and storage (10), dermal absorption by use of personal care products (11), and ingestion or inhalation of contaminated indoor dust (12,13). Exposure to phthalates is widespread; the metabolites of many were detected in over 90% of urine samples in biomonitoring studies in the US and elsewhere in the past 30 years (8,14–17).

Mechanistic support for the hypothesis of obesogenic effects of phthalates comes from observations that some phthalate metabolites, such as mono-ethyl phthalate (MEP), mono(2-

ethylhexyl) phthalate (MEHP), and monobenzyl phthalate (MBzP), activate peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor critical to the differentiation and survival of adipocytes, promoting adipogenesis *in vitro* (18–20). Furthermore, mice fed di(2-ethylhexyl) phthalate (DEHP) for 5-10 weeks gained more body weight than controls (21–23). To date, however, epidemiologic studies have yet to confirm whether phthalate exposure predicts excess body fat gain in humans. A recent systematic review on the metabolic effects of phthalates concludes that the current body of epidemiologic evidence is inadequate to determine whether phthalates are linked to obesity, mainly because most studies have been cross-sectional (24). Only seven studies have examined the associations between phthalates and longitudinal changes in adiposity in adults (25–31). In these studies, some phthalate metabolites, such as MEP, DEHP metabolites, and MBzP, have been associated with faster body weight gain, but not consistently. Further, insights from these studies are limited because most have used body weight or body mass index (BMI) as the primary outcomes, rather than specific measures of body fat. These proxies for body fat may not be sensitive and specific enough to detect associations between phthalate metabolites and body fat, especially in older individuals whose loss of muscle mass may mask gains in body fat (32).

In this study, we investigated whether urinary phthalate metabolites predicted faster increases in body weight (BW), fat mass (FM), and body fat percentage (BF%) in a group of midlife women followed for up to 18 years. Because previous studies suggest that obesity status may modify the associations between phthalates and changes in body weight (27,30), we additionally conducted stratified analyses by baseline obesity status.

2.3 Methods

2.3.1 Study population

Participants were drawn from the Study of Women's Health Across the Nation (SWAN), an ongoing cohort study of mid-life women's health. Since 1996/1997, women from seven study sites (Oakland, CA, Los Angeles, CA, Chicago, IL, Detroit-area, MI, Pittsburgh, PA, Boston, MA and Newark, NJ) have been followed near-annually through interviews and clinical examinations. Eligibility criteria at cohort inception included 1) self-identifying as White, Black, Chinese, Japanese, or Hispanic, 2) aged between 42 and 52 years, 3) having an intact uterus, at least one ovary, and at least one menstrual period in the past 3 months, and 4) not having used any exogenous reproductive hormone in the past 3 months. In total, 3302 women met these eligibility criteria and enrolled in SWAN. The study protocols of SWAN were approved by institutional review boards at each study site, and all participants provided informed consent to participate in the study at each study visit.

The SWAN Multi-pollutant Study (SWAN-MPS) is an ancillary study that selected SWAN participants for environmental chemical exposure assessments using banked biospecimens from the 1999/2000 and 2002/2003 study visits. Of the 2694 women who participated in the SWAN 1999/2000 study visit, the SWAN-MPS excluded all 646 women from the Chicago and Newark sites because neither site collected urine samples necessary for environmental chemical measurements. An additional 648 women were excluded because they had insufficient blood or urine samples for environmental chemical measurements. The SWAN-MPS thus included 1400 women; of those, all had phthalate metabolite measurements from 1999/2000 samples and 1,387 also had phthalate metabolite measurements from 2002/2003 samples.

We used phthalate metabolite data from 1999/2000 for our primary analyses. Of the 1400 SWAN-MPS women, we excluded 15 women with missing data on urinary creatinine or its predictors (age, race/ethnicity, BMI, height, and diabetes). We further excluded 16 women missing key covariates (education, calorie intake, menopausal status, hormone therapy (HT) use, physical activity, and smoking). The analytic sample thus included 1369 women. All of these women had at least one adiposity measure. Participants were followed for a maximum of 18 years including a maximum of 13 study visits. The median follow-up time was 16 years (IQR: 13, 17), and the median number of observations per woman was 11 for body weight (interquartile range (IQR): 9, 12) and 10 for fat mass and body fat percentage (IQR: 8, 12).

2.3.2 Phthalate metabolites

Women provided spot urine samples during in-person visits in 1999/2000 and 2002/2003. Urine was collected in polyethylene tubes and transferred to -80 °C freezers for long-term storage. In 2017/2018, urine samples were thawed, and phthalate metabolites were measured using on-line solid phase extraction (SPE) coupled to high-performance liquid chromatography-isotope dilution tandem mass spectroscopy (HPLC-MS). Twelve phthalate metabolites were measured, which can be grouped into three categories based on their parents' similarity in structure and sources (33): **1) LMW phthalate metabolites**: mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), and mono-isobutyl phthalate (MiBP); **2) DEHP metabolites**: 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); **3) Other HMW phthalate metabolites**: monobenzyl phthalate (MBzP), mono-isononyl phthalate (MiNP), mono-carboxyoctyl phthalate (MCOP), mono-carboxy-isononyl phthalate (MCNP), and mono(3-carboxypropyl) phthalate (MCPP). The coefficient of variation (CV, in %) of metabolite standards

for the HPLC-MS assay ranged from an average of 4% across a range of MEHP to an average of 19% for MCOP. We excluded mono-isononyl phthalate (MiNP) from all analyses because it was detected in less than 1% of urine samples.

2.3.3 Body weight, fat mass, and body fat percentage

Body weight and body composition were measured near-annually between 1999/2000 and 2016/2017 at the Michigan, Boston, and Los Angeles sites. For the Oakland site, body weight was measured until 2015/2016, and body composition was measured until 2012/2013. For the Pittsburgh site, body weight and body composition were measured until 2015/2016. We used all available data in our analyses.

Body weight was measured in light clothing and without shoes using a calibrated scale and recorded to the nearest 0.1 kg. Body composition measures were acquired using a Hologic dual-energy X-ray absorptiometry (DXA) instruments (Hologic Inc.). Different models of DXA were used throughout follow-up and across sites; calibration studies were conducted any time there was a change in DXA machinery. For this analysis, all body composition measures were calibrated to the Hologic QDR-4500 model under "NHANES" tissue-type calibration. All body composition measures excluded the head. Details of DXA instruments used, DXA measurement protocols, and calibration methods can be found in Greendale et al. (34). Body fat percentage was calculated as the ratio of fat mass and the sum of fat mass and the mass of lean soft tissues (i.e., body fat percentage = fat mass/ [fat mass + (total lean mass – bone mineral content)]. In the denominator, bone mineral content was subtracted from total lean mass because a large proportion of participants, especially Chinese participants, had metals in their body or wore jade jewelry, which affected the accuracy of bone mineral content measurements.

2.3.4 Other variables

Creatinine, used to account for hydration status, was measured in urine from the 1999/2000 and 2002/2003 visits with a Cobas Mira analyzer (Horiba ABX, Montpellier, France). Time was calculated as date of visit minus date of sample collection for phthalate assay. Age was calculated as date of visit minus date of birth. Race/ethnicity (White, Black, Chinese, Japanese) and educational attainment (high school or less, some college, college degree, postgraduate studies) was self-reported in 1996/1997. Height was measured with a stadiometer at each visit. BMI was calculated as body weight (kg)/height (m^2). Obesity was defined using race-specific BMI cut-points (35). For White and Black women, normal/underweight was defined as BMI < 25 kg/m^2; overweight, 25 $kg/m^2 \leq$ BMI < 30 kg/m^2; and obese, BMI $\geq$ 30 kg/m^2. For Chinese and Japanese women, normal/underweight was defined as BMI < 23 kg/m^2; overweight, 23 $kg/m^2 \leq$ BMI < 27 kg/m^2; and obese, BMI $\geq$ 27 kg/m^2. Dietary energy intake (kcal/day) was estimated with a modified Block Food Frequency Questionnaire (FFQ) in 1996/1997 and 2001/2002 (36). Dietary energy intake in 1996/1997 was used to approximate dietary energy intake in 1999/2000. Physical activity across three domains, including leisure-time sports, active living, and household activities, was quantified by an index derived from the Kaiser Physical Activity Survey (37). Physical activity was assessed six times over the 18 years of follow-up. For visits where physical activity data were not available, we set the physical activity index to its most recent value. Smoking status (never, former, or current) and current use of hormone therapy (HT) (yes, no) was self-reported at each visit. Menopausal status at each visit was determined based on self-reported bleeding frequency, history of oophorectomy and hysterectomy, and use of HT. Diabetes status at each visit was defined as self-reported anti-diabetic medication use, self-reported physician's diagnosis of

diabetes, or having a fasting glucose value at or above 126 mg/dL. Physician's diagnosis of cancer was self-reported at each visit.

2.3.5 Statistical methods

To facilitate $\log_2$-transformation, we replaced 7 negative observations of MiBP, 2 negative observations of MEHP, and 1 negative observation of MCPP with each metabolite's median concentration below its limit of detection. All other metabolite concentrations were used as output by the assay, including those that were below limits of detection. All urinary phthalate metabolite concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method (38). Each phthalate metabolite concentration was divided by the ratio of observed to predicted urinary creatinine. Predictors of creatinine were identified from the literature (39,40) and included age, race/ethnicity, BMI, height, and diabetes. We also calculated the molar sums of hydration-adjusted LMW phthalate metabolites ("∑LMW phthalates"), DEHP metabolites ("∑DEHP"), and other HMW metabolites ("∑HMW phthalates") to evaluate the impact of aggregate exposure.

Descriptive statistics (median (1^{st} quartile, 3^{rd} quartile) for continuous variables and count (proportion) for categorical variables) of the analytic sample in 1999/2000 were calculated. To understand the distributions and potential correlates of phthalates, median (1^{st} quartile, 3^{rd} quartile) values of phthalate metabolites were calculated overall, by baseline obesity status, and by covariates. Phthalate metabolite concentrations by baseline obesity status and covariate levels were compared using the Kruskal-Wallis test. To understand the correlation between metabolites, Spearman correlation coefficients were calculated between metabolites at baseline. To understand the within-person correlation of metabolites, we calculated the intraclass correlation coefficient

(ICC) of each metabolite. The ICCs were estimated using linear mixed effects models that predicted each $\log_2$-transformed metabolite with random intercepts and no fixed effects.

The trajectories of BW, FM, and BF% overall and by baseline obesity status were modeled with linear mixed effects models. Each model included time, age at baseline, race/ethnicity, site, educational attainment at baseline, baseline dietary energy intake, and time-varying menopausal status, HT use, smoking status, and physical activity as predictors. Time was modeled with a linear spline with a knot at time (T) = 6 years for BW and as a linear term for FM and BF%. These functional forms were selected based on smoothing plots from generalized additive mixed models (GAMM) (**Supplementary Figure 2.1, Supplementary Figure 2.2**). All models included random intercepts and random slopes for time to account for within-woman correlation of multiple observations.

To test whether phthalate exposure was associated with differences in the rates of change of each outcome, for each metabolite, we added to each outcome's trajectory model the main effect term of the metabolite and the interaction term between the metabolite and time. Phthalate metabolites were $\log_2$-transformed due to right-skewness. Models for the outcome of BW also included a time by race/ethnicity interaction, and models for FM and BF% also included a time by site interaction. We included these interaction terms because race/ethnicity- and site-specific smoothing plots from GAMMs showed that BW trajectories differed by race/ethnicity, while FM and BF% trajectories differed by site) (**Supplementary Figure 2.1, Supplementary Figure 2.2**). For each outcome, we obtained the main effect term of each phthalate metabolite and the interaction term between the phthalate metabolite and time. To facilitate interpretation, we scaled all phthalate metabolite by time interaction terms by five years. The scaled interaction terms can be interpreted as differences in the change in an adiposity outcome over five years per doubling of

phthalate metabolite concentrations. The main effect term of the phthalate metabolite can be interpreted as the difference in an adiposity measure at baseline per doubling of metabolite concentration. The main effect terms are of secondary interests and are reported in supplementary tables only.

To visualize adiposity trajectories associated with different levels of phthalate exposure, we plotted the least-squared means of BW, FM, and BF% at baseline, Year 6, and Year 10 for women at high (75^{th} percentile) vs. low (25^{th} percentile) levels of exposure to each phthalate metabolite. We calculated the adjusted differences in each outcome between exposure levels at each time point and the adjusted differences in the (annualized) changes in each outcome between exposure levels. All analyses were conducted overall and by baseline obesity status.

We conducted a series of sensitivity analyses to examine the robustness of our findings. First, all models were additionally adjusted for the total intake frequency (times/week) of food items previously reported to be associated with phthalate exposure. These food items included red meat, poultry, liver, processed meat, dairy, margarine, refined grains, salty snacks, desserts, meat substitutes, pizza, salad dressing, and salsa (41–43,17,44,45,40). Second, because the onset of cancer or diabetes may impact body weight and body composition, we re-ran all models after censoring data at the time of cancer or diabetes onset. Finally, because phthalate metabolites in spot urine samples may not accurately reflect habitual exposure, all analyses were repeated using phthalate metabolite data from 2002/2003. The baseline for these analyses was 2002/2003. Dietary energy intake from 2001/2002 was used to approximate energy intake in 2002/2003. For BW, the knot for the linear spline term for time was set at T = 3 years to be consistent with primary analyses.

All statistical analyses were performed in R version 4.0.3 using packages mgcv (version 1.8-33), nlme (version 3.1 – 151), and emmeans (version 1.5.5-1). Statistical significance was defined as two-sided p-value < 0.05.

2.4 Results

At baseline (1999/2000), women had a median age of 49.4 years (quartile (Q) 1 and Q3: 47.4, 51.5) (**Table 2.1**). Approximately half of the sample was non-White, and half did not have a college degree. Most women were pre- or peri- menopausal at baseline in 1999/2000 (71%) and approximately 30% and 34% of women were overweight and obese, respectively.

The detection frequency of phthalate metabolites ranged from 84.4% for MEHP to nearly 100% for the other metabolites (**Table 2.2**). The median concentrations of metabolites ranged from 2.61 ng/mL (Q1 and Q3: 1.55, 4.48) for MiBP to 81.8 ng/mL (Q1 and Q3: 36.42, 210.47) for MEP. The concentrations of most phthalate metabolites were higher in women who were younger, from Michigan, Black, or current smokers (**Supplementary Table 2.1**, **Supplementary Table 2.2**, **Supplementary Table 2.3**). Overweight and obesity were positively associated with the urinary concentrations of most phthalate metabolites (**Table 2.2**).

At baseline, the least-squared means of BW, FM, and BF% were 70.7 kg (95% confidence interval (CI): 69.3, 72.0), 26.3 kg (95% CI: 25.5, 27.1), and 39.7% (95% CI: 39.2, 40.2), respectively (**Table 2.3** and **Figure 2.1**). On average, BW increased by 0.17 kg/year (95% CI: 0.099, 0.24) in the first six years, followed by an average loss of 0.079 kg/year (95% CI: -0.13, -0.028) thereafter. FM and BF% increased at a rate of 0.015 kg/year (95% CI: -0.010, 0.041) and 0.030 percentage points (ppt)/year (95% CI: 0.011, 0.049), respectively. There was substantial heterogeneity in these growth rates by baseline obesity status (**Table 2.3** and **Figure 2.1**). Women

who were normal/underweight at baseline had the most rapid increases in BW prior to stabilization, FM, and BF%. In contrast, women who were obese at baseline primarily experienced decreases in BW, FM, and BF% over time.

Among all women, none of the phthalate metabolites were significantly associated with the changes in BW during follow-up (**Figure 2.2**; **Supplementary Table 2.5**). In contrast, all phthalate metabolites except MCNP were associated with faster increases in FM and BF% (**Figure 2.3**; **Supplementary Table 2.6**, **Supplementary Table 2.7**). Per doubling of phthalate metabolite concentrations, differences in the five-year change in FM ranged from 0.04 kg (95% CI: -0.05, 0.14) for MiBP to 0.11 kg (95% CI: 0.05, 0.18) for MEHP (**Figure 2.3**, Panel A; **Supplementary Table 2.6**); differences in the five-year change in BF% ranged from 0.03 ppt (95% CI: -0.03, 0.09) for MiBP to 0.09 ppt (95% CI: 0.02, 0.16) for MCPP (**Figure 2.3**, Panel B; **Supplementary Table 2.7**). The associations with BF% change were statistically significant for all DEHP metabolites, MBzP, MCOP, and MCPP, and were borderline significant for MEP (p-value = 0.09) and MnBP (p-value = 0.08) (**Supplementary Table 2.7**).

In analyses stratified by baseline obesity status, the associations between phthalate metabolites and changes in adiposity measures were strongest among women who were normal/underweight at baseline. In this group, all phthalate metabolites except MCNP were positively associated with the changes in all adiposity measures. Per doubling of phthalate metabolite concentrations, differences in the five-year change in BW during the period of BW increase ranged from 0.11 kg (95% CI: -0.10, 0.31) for MEHP to 0.40 kg (95% CI: 0.09, 0.70) for MCPP (**Figure 2.4**; **Supplementary Table 2.5**); differences in the five-year change in FM ranged from 0.08 kg (95% CI: -0.03, 0.18) for MiBP to 0.22 kg (95% CI: 0.10, 0.35) for ∑HMW phthalates (**Figure 2.5**; **Supplementary Table 2.6**); and differences in the five-year change in

BF% ranged from 0.06 ppt (95% CI: -0.04, 0.16) for MiBP to 0.19 ppt (95% CI: 0.07, 0.30) for ∑HMW phthalates (**Figure 2.6**; **Supplementary Table 2.7**). In contrast, the associations between phthalate metabolites and the five-year changes in adiposity measures were appreciably smaller in magnitude and largely not statistically significant among overweight and obese women (**Figures 2.4-2.6**).

Figure 2.7 visualizes adiposity trajectories for women who were normal/underweight at baseline and exposed to different levels of MEP, ∑DEHP, and MBzP. Women at the 75th percentile of each metabolite experienced steeper increases in all adiposity measures as compared to those at the 25th percentile. For example, during the phase of BW gain, the additional change in BW per year for those at the 75th versus those at the 25th percentile of MEP was 0.11 kg/year (95% CI: 0.16, 1.22) (**Supplementary Table 2.8**). This difference was equivalent to the impact of watching approximately 3 (0.11/0.035 = 3.1) more hours of TV per day in terms of expected weight gain (46). The diverging adiposity trajectories between women at high versus low levels of exposure were also evident for the other metabolites, except MCNP (**Supplementary Tables 2.8 – 2.10**).

Sensitivity analyses adjusting for dietary intake of food items or censoring data at the time of cancer or diabetes onset did not change estimates for the baseline or longitudinal associations between phthalate metabolites and all outcomes (data not shown). When metabolites from 2002/2003 were used as exposures, the associations between most metabolites and the five-year changes in adiposity measures were attenuated (**Supplementary Tables 2.11 – 2.13**). However, the degree of attenuation was smaller for women who were normal/underweight at baseline as compared to women who were overweight or obese. For normal or underweight women, positive associations in the primary analyses remained positive in the sensitivity analyses.

2.5 Discussion

In this study of a diverse group of midlife women followed for almost 20 years, we found that phthalate metabolites were associated with faster increases in fat mass and body fat percentage. The associations were strongest and most persistent in women who were normal/underweight at baseline. The associations between phthalate metabolites and body weight gain were less consistent, perhaps reflecting the fact that body weight is not an accurate measure of body fat in an aging cohort (32). Overall, this study suggests that phthalates contribute to body fat gain in mid-life women. However, our results were not replicated in sensitivity analyses with a second set of phthalate metabolites from a different time point, so our findings should be interpreted cautiously.

This study is the first piece of evidence directly linking phthalate exposure to body fat gain in women. Prior studies have linked MEP, MnBP, MiBP, DEHP metabolites, MBzP and MCPP to faster increases or slower declines in body weight or BMI, but results were highly heterogeneous both within and across studies (25–28,30,31). Few studies reported statistically significant, positive associations between body weight changes and all metabolites, and few metabolites have been consistently associated with faster body weight gain across studies. Consequently, whether phthalate exposure leads to body fat gain and obesity is still unclear. One critical limitation in most prior studies is the use of body weight to approximate body fat. Because changes in body fat do not always result in changes in body weight, many studies may have missed or underestimated the associations between phthalate exposure and increases in adiposity. Only one prior study examined percent body fat as the outcome (29). While that study found positive associations between some phthalate metabolites and greater retention of body fat, its generalizability is limited because participants were all overweight/obese and underwent intense caloric restriction in order to lose

weight. By examining the association of phthalates and fat mass and body fat percentage among a general population of midlife women, our findings provide stronger evidence for phthalates' obesogenic potential than has previously been reported. Whether our findings are generalizable to women at other life stages and men should be investigated in future studies, preferably with precise measures of adiposity rather than body weight alone.

The finding that some phthalate metabolites were associated with accelerated body fat gain in midlife women has important public health implications. Virtually all individuals are exposed to phthalates daily through using personal care products (47), ingesting food (43), or inhaling indoor dust (13) contaminated with phthalates. The near 100% detection rates of most phthalate metabolites in this and many other studies (48) despite the short half-lives of phthalates testify to the widespread and ongoing nature of phthalate exposure. Although some phthalates commonly used 20 years ago, such as di-n-butyl phthalate (the parent of MnBP), DEHP, and butyl benzyl phthalate (the parent of MBzP and MnBP), have been banned in children's toys and childcare articles since 2008 due to concerns about developmental toxicity (49), they are still used in other applications such as food packaging and food handling contact materials (50), and their metabolites continue to be found in recent urine samples (51). The finding that these widely used chemicals are predictive of more rapid changes in fat mass, a risk factor for numerous chronic diseases, is concerning. If phthalates are indeed causally related to obesity, it would be important to incorporate limiting phthalate exposures as part of a comprehensive obesity prevention strategy. Measures to limit phthalate exposures may include requiring the disclosure of phthalates in consumer products or further restricting their use in products. Currently, a bill to ban phthalates in food contact materials is pending in the United States Congress. This study provides evidence to support this ban.

One remarkable finding of this study was that phthalate metabolites were associated with faster increases in body fat primarily in women who were normal/underweight at baseline. This was somewhat unexpected, as previous studies did not always show stronger associations between phthalate metabolites and body weight gain in normal/underweight women (26,27). It is unclear why women who were normal/underweight at baseline in this study appeared more susceptible to phthalates' potential obesogenic effects. Since the adiposity trajectories differed substantially by baseline obesity status, we speculate that women's potential to gain additional body fat may modify the associations between phthalate metabolites and body fat gain. Those who are normal/underweight may be more susceptible to gain additional fat, whereas women who are already overweight or obese may have ceilinged out their body fat. Thus, this may result in normal/underweight women being more susceptible to phthalates' obesogenic effects. This is consistent with the observation that levels of PPAR-γ, a nuclear receptor through which phthalates promote adipogenesis, are reduced in the fat tissues of obese individuals (52).

PPAR-γ is essential for the growth and maintenance of body fat (53), and many phthalate metabolites activate PPAR-γ (18,19). Phthalates may also disrupt the hypothalamic-pituitary-thyroid axis (HPT), leading to a lower basal metabolic rate and hence less energy expenditure (22), although it is unclear if this mechanism is more prominent in normal/underweight individuals. Our findings underscore the existence of individuals with different susceptibility to phthalates in the population. Identifying these individuals and understanding the mechanisms behind different susceptibility is important for tailoring public health measures to specific populations.

Another notable result of this study was that the associations between phthalate metabolites and five-year changes in adiposity measures were attenuated when metabolites from 2002/2003 were used as exposures. This may be due to random exposure measurement error, as the degree of

attenuation generally increased when the intraclass correlation coefficient of a metabolite decreased. However, we note that the timing of exposure had also changed in sensitivity analyses. Given that women were three years older, and many had transitioned to post-menopause in 2002/2003, we cannot rule out that the effects of phthalates truly differ by the age or menopausal status at which women are exposed. There might exist a critical age window or life stage during which women are more sensitive to phthalates' obesogenic effects. Unfortunately, with only two sets of phthalate metabolites measured three years apart, we were not able to pinpoint the reason for the differences between primary and sensitivity analyses. Future studies should repeatedly measure phthalates at closer intervals within different life stages of interest.

This study has many important strengths and limitations. Unlike the majority of previous studies, our analysis considered fat mass and body fat percentage, measured precisely with DXA. This allowed us to minimize outcome measurement error and provide the first piece of evidence directly linking phthalate metabolites to changes in body fat in midlife women. Also unlike previous studies, we used a prospective study design with long-term follow-up, thereby reducing concerns about reverse causation. The SWAN-MPS cohort is diverse in terms of race/ethnicity, geographic location, and socioeconomic status. This diversity increases our confidence in the generalizability of our findings. Finally, many of the high-molecular-weight phthalate metabolites we examined were infrequently studied in previous investigations, so our work expands our understanding of a broad set of phthalate metabolites.

Despite these notable strengths, there are some key limitations to acknowledge. This study utilized a single spot urine per woman to measure phthalate exposure. Because the half-lives of phthalate metabolites in the body are relatively short (54), phthalate metabolites in a single urine sample may not reflect habitual exposure. Thus, the use of spot urine samples may result in non-

differential exposure measurement error, which would have attenuated the associations between phthalate metabolites and adiposity measures. Despite having limited dietary data to account for confounding by diet, we observed positive associations for low-molecular-weight phthalate metabolites, for which diet is not a major source of exposure (24,55). Thus, confounding by diet is unlikely to fully explain the positive associations between phthalate metabolites and body fat gain. Given the observational nature of this study, residual confounding by other factors is possible, including confounding by other phthalate metabolites and other environmental chemicals. Future analyses will explore multi-pollutant models to consider this limitation. While body fat distribution in addition to total body fat is an independent risk factor of cardiometabolic disease, we lacked imaging-based measures of body fat distribution. Finally, we did not adjust for multiple comparisons, so statistical significance should be interpreted cautiously.

2.6 Conclusions

In conclusion, in this longitudinal study on a diverse group of midlife women, we found that exposure to phthalates was associated with more rapid body fat gain, especially in women who were normal/underweight. These findings support the hypothesis that certain environmental chemicals may cause obesity. Limiting exposure to phthalates and potentially other synthetic chemicals may help prevent obesity and its comorbidities.

2.7 References

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Table 2.1 Participant characteristics in 1999/2000

	Median (Q1, Q3)[1]
Age (years)	49.4 (47.4, 51.5)
	N (%)
Site	
Detroit area, MI	247 (18%)
Boston, MA	227 (16.6%)
Oakland, CA	306 (22.4%)
Los Angeles, CA	359 (26.2%)
Pittsburgh, PA	230 (16.8%)
Race/ethnicity	
White	695 (50.8%)
Black	294 (21.5%)
Chinese	176 (12.9%)
Japanese	204 (14.9%)
Education	
High school or less	248 (18.1%)
Some college	438 (32%)
College degree	336 (24.5%)
Postgraduate	347 (25.3%)
Smoking	
Never	863 (63%)
Past	364 (26.6%)
Current	142 (10.4%)
Menopausal status	
Pre- or peri- menopausal	969 (70.8%)
Natural/surgical menopause	198 (14.5%)
Unknown due to hormone therapy	202 (14.8%)
Currently on hormone therapy	
No	1089 (79.5%)
Yes	280 (20.5%)
Obesity status	
Normal/underweight	502 (36.7%)
Overweight	407 (29.7%)
Obese	460 (33.6%)

[1] "Q1" stands for 1st quartile and "Q3" stands for 3rd quartile.

Table 2.2 Phthalate metabolite concentrations in 1999/2000, overall and by obesity status

		Overall (N = 1369)		Normal/under-weight (N = 502)	Overweight (N = 407)	Obese (N = 460)	p-value[2]
Group	**Phthalate metabolite[1]**	**N (%) detected**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	
Low-molecular-weight (LMW) phthalate metabolites	MEP (ng/mL)	1368 (99.9%)	81.8 (36.42, 210.47)	68.99 (33.16, 148.83)	72.63 (33.78, 185.69)	106.72 (47.89, 292.99)	<0.0001
	MnBP (ng/mL)	1369 (100%)	18.5 (11.69, 32.79)	17.32 (10.42, 27.61)	19.34 (11.74, 34.58)	19.27 (13.04, 36.36)	0.0003
	MiBP (ng/mL)	1342 (98%)	2.61 (1.55, 4.48)	2.53 (1.5, 4.26)	2.68 (1.5, 4.68)	2.64 (1.66, 4.5)	0.39
	∑LMW phthalates[3] (nmol/mL)	--	0.57 (0.29, 1.31)	0.50 (0.26, 0.94)	0.52 (0.27, 1.2)	0.72 (0.37, 1.77)	<0.0001
Di(2-ethylhexyl) phthalate (DEHP) metabolites	MEHP (ng/mL)	1156 (84.4%)	3.07 (1.59, 6.03)	2.98 (1.5, 6.04)	3.13 (1.71, 5.72)	3.11 (1.6, 6.41)	0.68
	MEHHP (ng/mL)	1368 (99.9%)	16.13 (8.5, 30.51)	13.08 (6.85, 26.6)	15.29 (7.85, 29.91)	19.48 (11.2, 38.06)	<0.0001
	MEOHP (ng/mL)	1367 (99.9%)	9.63 (5.17, 18.68)	8.05 (4.19, 16)	8.93 (4.7, 18.02)	11.36 (6.69, 21.87)	<0.0001
	MECPP (ng/mL)	1369 (100%)	16.85 (9.82, 31.33)	14.01 (8.43, 26.31)	15.70 (9.54, 29.48)	20.52 (12.75, 38.12)	<0.0001
	∑DEHP[4] (nmol/mL)	--	0.16 (0.09, 0.29)	0.13 (0.08, 0.26)	0.15 (0.08, 0.28)	0.19 (0.11, 0.38)	<0.0001
Other High-molecular-weight (HMW)	MBzP (ng/mL)	1366 (99.8%)	10.43 (5.8, 18.53)	8.78 (4.66, 15.64)	10.00 (5.87, 17.23)	12.28 (7.49, 21.7)	<0.0001
	MCOP (ng/mL)	1365 (99.7%)	4.41 (2.62, 7.88)	3.66 (2.37, 6.63)	4.40 (2.63, 6.93)	5.38 (3.22, 9.61)	<0.0001

		Overall (N = 1369)		Normal/under-weight (N = 502)	Overweight (N = 407)	Obese (N = 460)	p-value[2]
Group	**Phthalate metabolite[1]**	**N (%) detected**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	**Median (Q1, Q3)**	
phthalate metabolites	MCNP (ng/mL)	1365 (99.7%)	2.69 (1.52, 5.01)	2.19 (1.31, 4.07)	2.41 (1.41, 4.32)	3.66 (1.99, 6.16)	<0.0001
	MCPP (ng/mL)	1351 (98.7%)	2.65 (1.7, 4.27)	2.47 (1.55, 4.07)	2.57 (1.62, 3.95)	2.94 (2.01, 4.71)	<0.0001
	∑HMW phthalates[5] (nmol/mL)	--	0.08 (0.05, 0.14)	0.07 (0.04, 0.12)	0.08 (0.05, 0.13)	0.11 (0.07, 0.16)	<0.0001

[1] All phthalate metabolites were adjusted for hydration using the "covariate-adjusted creatinine standardization" method. Median and the 1st ("Q1") and 3rd ("Q3") quartiles are reported.
[2] p-values were obtained from Kruskal-Wallis tests.
[3] ∑LMW phthalates: molar sum of low-molecular-weight phthalate metabolites, including MEP, MnBP, and MiBP.
[4] ∑DEHP: molar sum of DEHP metabolites, including MEHP, MEHHP, MEOHP, and MECPP.
[5] ∑HMW phthalates: molar sum of all other high-molecular-weight phthalate metabolites, including MBzP, MCOP, MCNP, and MCPP.

Table 2.3 Baseline levels and rates of change in adiposity measures, overall and by obesity status

	Least-squared means of adiposity measures at baseline (95% CI)			
	All[1]	Normal/underweight	Overweight	Obese
Body weight (kg)	70.7 (69.3, 72.0)	56.2 (55.3, 57.0)	67.2 (66.2, 68.2)	87.4 (84.9, 89.9)
Fat mass (kg)	26.3 (25.5, 27.1)	17.9 (17.3, 18.5)	24.0 (23.4, 24.6)	36.6 (35.3, 38.0)
Body fat percentage (%)	39.7 (39.2, 40.2)	34.9 (34.2, 35.6)	39.1 (38.6, 39.7)	45.5 (44.9, 46.2)
	Rates of change in adiposity measures (95% CI)			
	All	Normal/underweight	Overweight	Obese
Body weight (kg/year)				
$T^2 \leq 6$ years	0.17 (0.099, 0.24)	0.30 (0.23, 0.38)	0.20 (0.090, 0.31)	-0.020 (-0.19, 0.15)
T > 6 years	-0.079 (-0.13, -0.028)	-0.00047 (-0.051, 0.050)	0.037 (-0.033, 0.11)	-0.28 (-0.41, -0.16)
Fat mass (kg/year)	0.015 (-0.010, 0.041)	0.094 (0.064, 0.13)	0.077 (0.037, 0.12)	-0.15 (-0.20, -0.086)
Body fat percentage (percentage point/year)	0.030 (0.011, 0.049)	0.096 (0.065, 0.13)	0.053 (0.022, 0.083)	-0.075 (-0.11, -0.041)

[1] Sample sizes varied by outcome. For body weight, the sample sizes for "all", "normal/underweight", "overweight", and "obese" were 1369, 502, 407, and 460, respectively. For fat mass and body fat percentage, the sample sizes for "all", "normal/underweight", "overweight", and "obese" were 1344, 499, 403, and 442, respectively.

[2] "T" stands for "time since baseline".

Figure 2.1 The average adiposity trajectories, overall and by obesity status

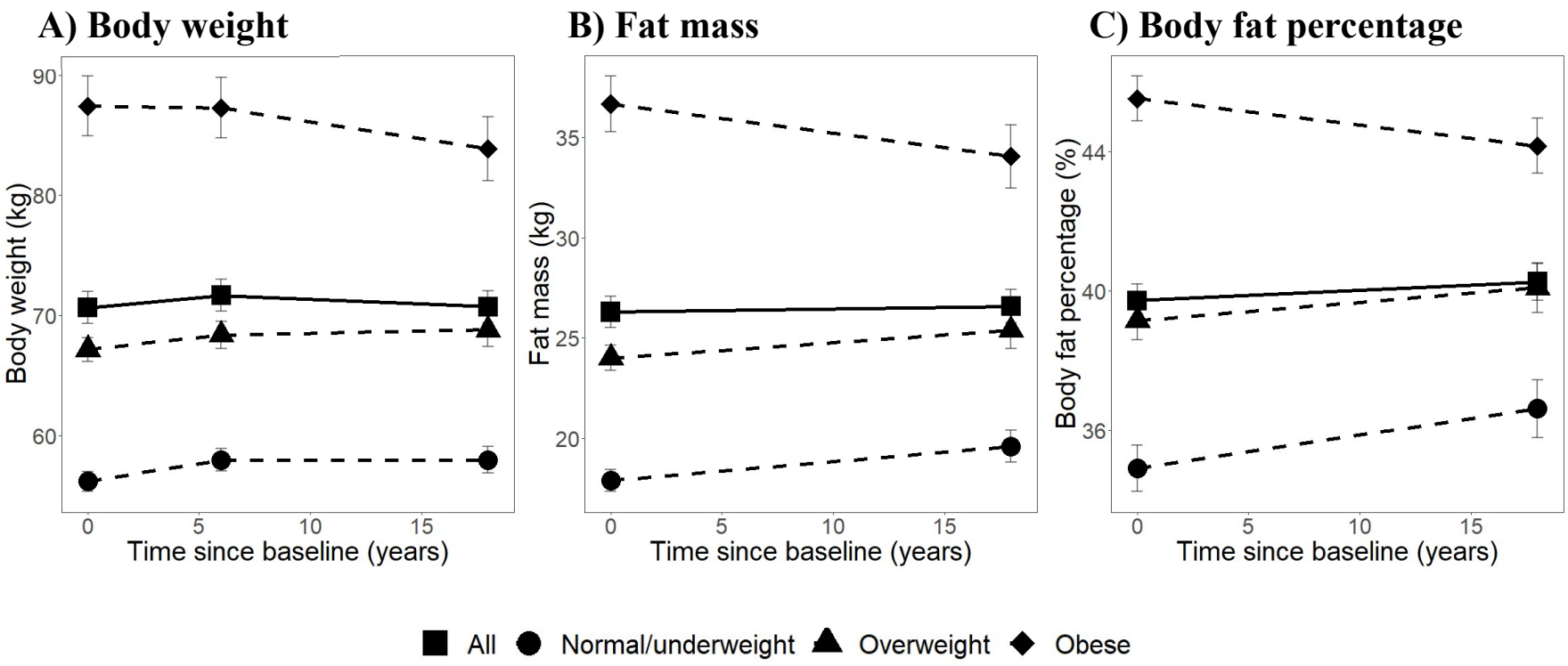
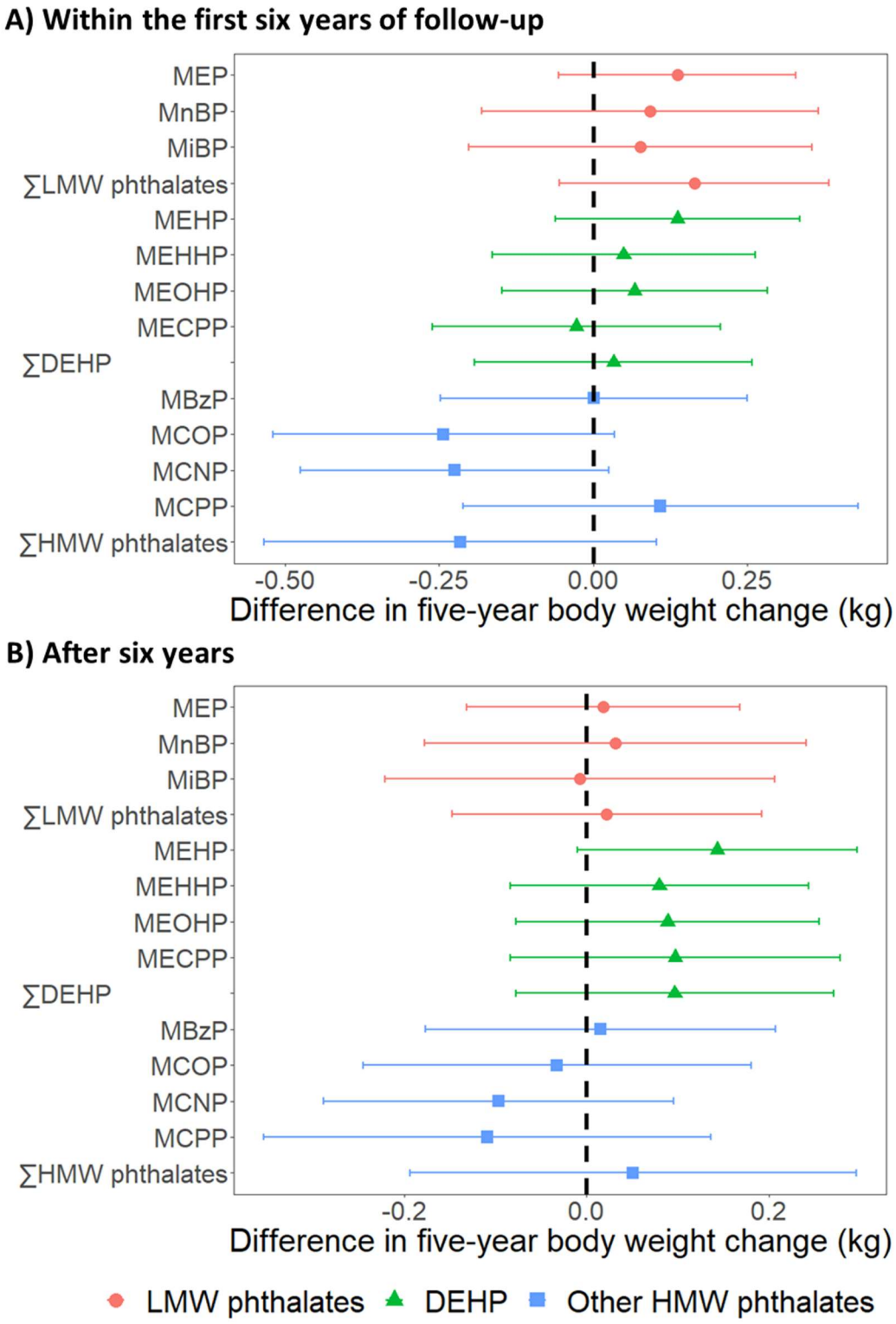
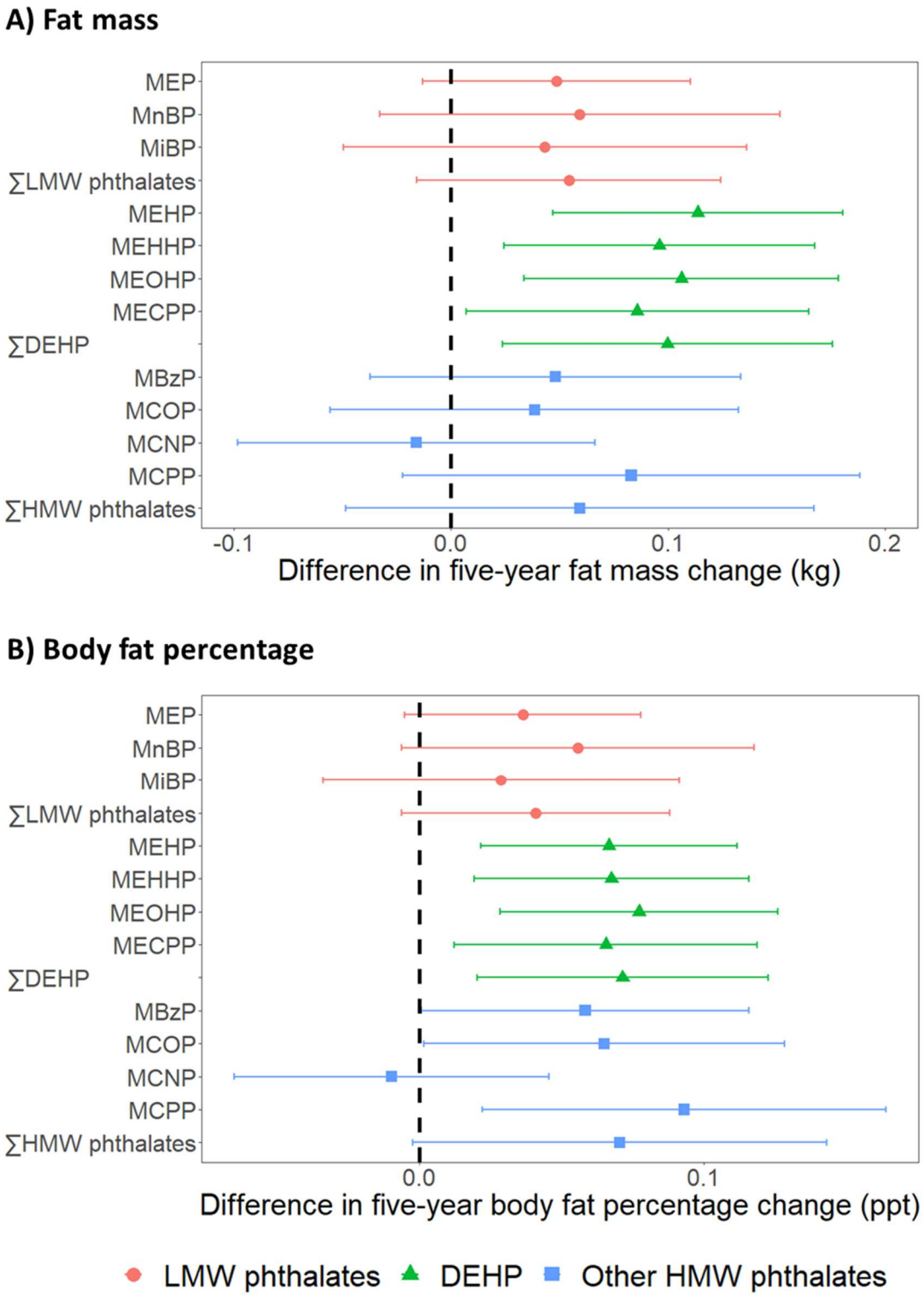


Figure 2.2 Differences in five-year body weight change per doubling of phthalate metabolite concentrations



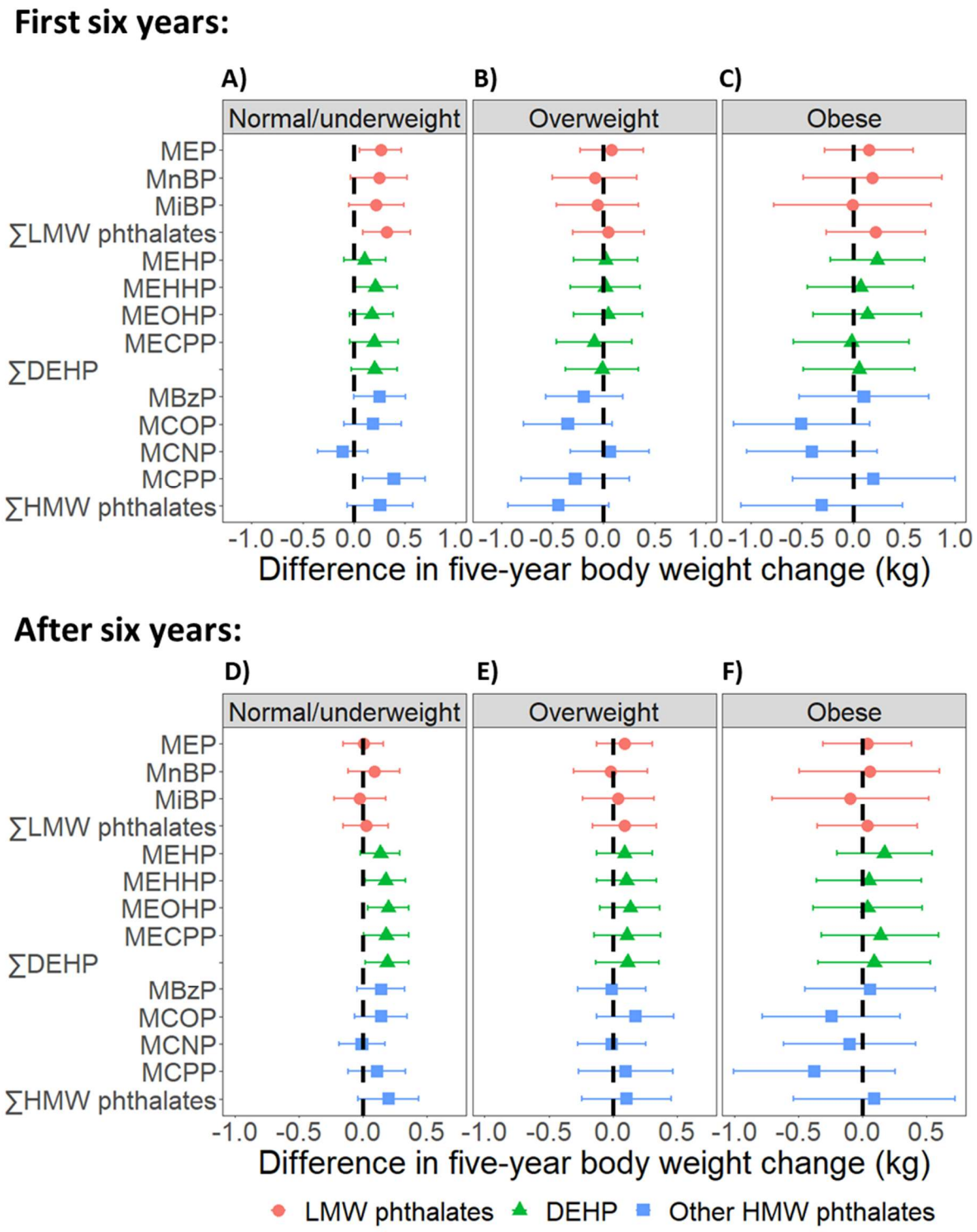
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 2.3 Differences in five-year changes in fat mass and body fat percentage per doubling of phthalate metabolite concentrations



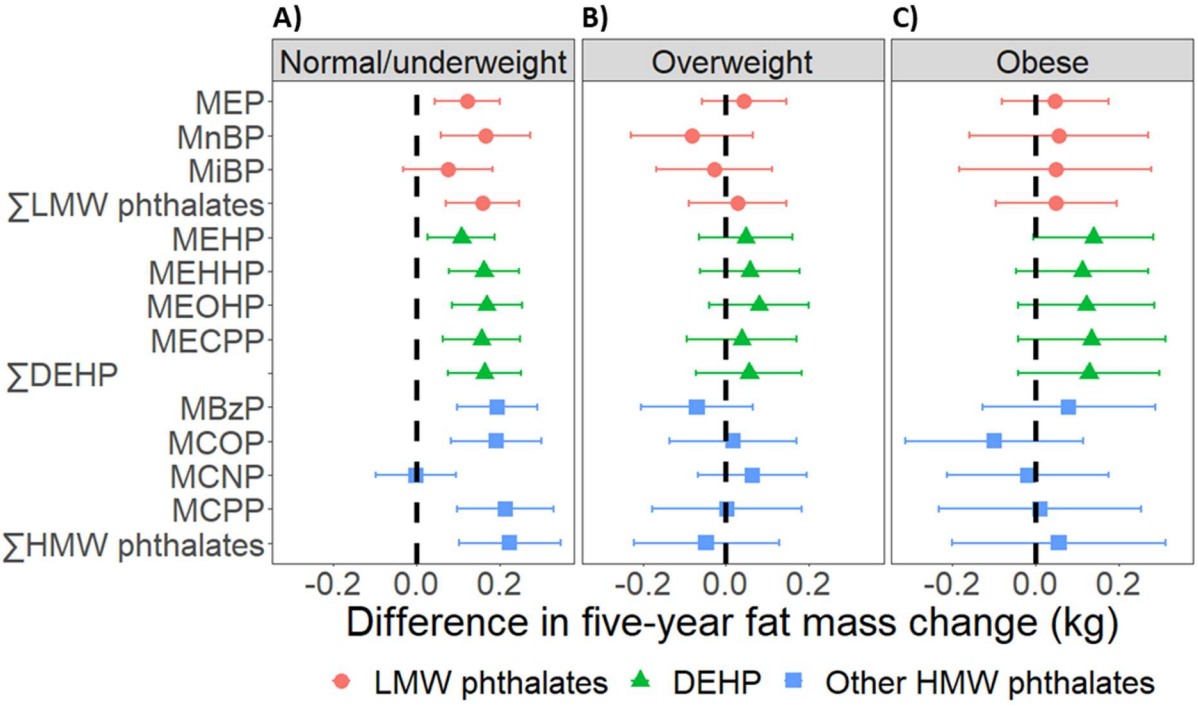
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 2.4 Differences in five-year body weight change per doubling of phthalate metabolite concentrations, by baseline obesity status



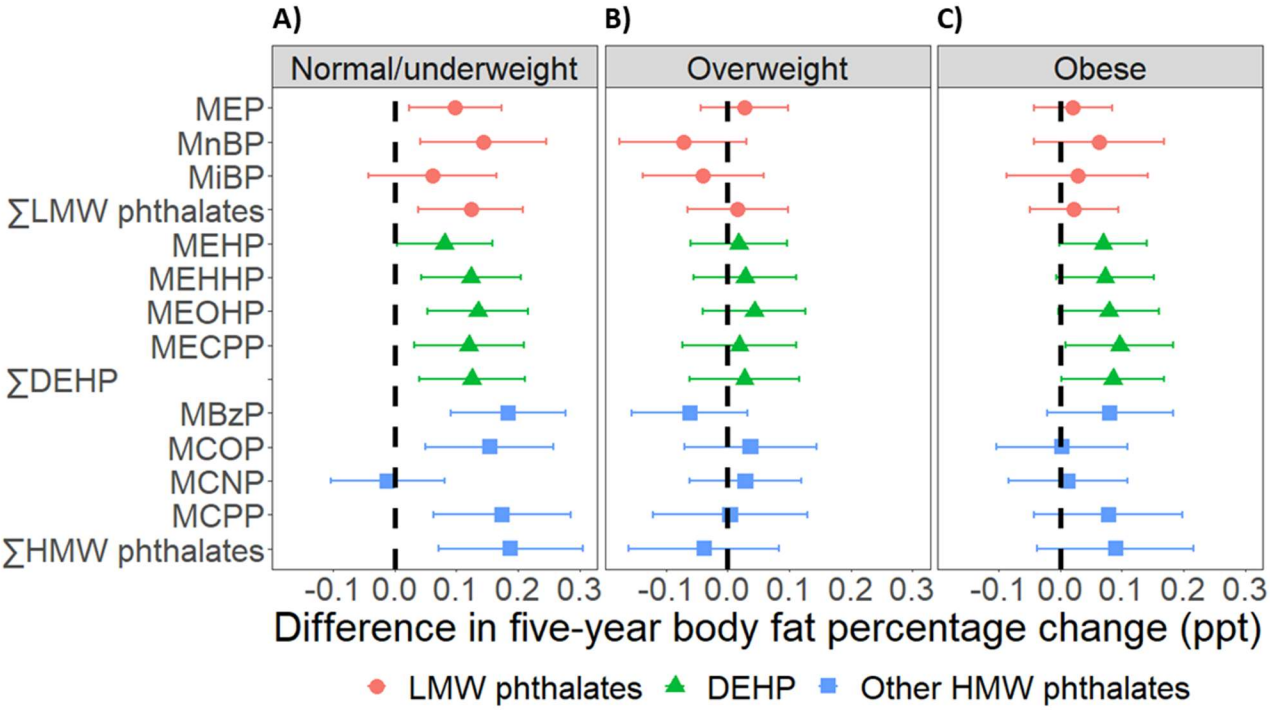
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 2.5 Differences in five-year fat mass change per doubling of phthalate metabolite concentrations, by baseline obesity status



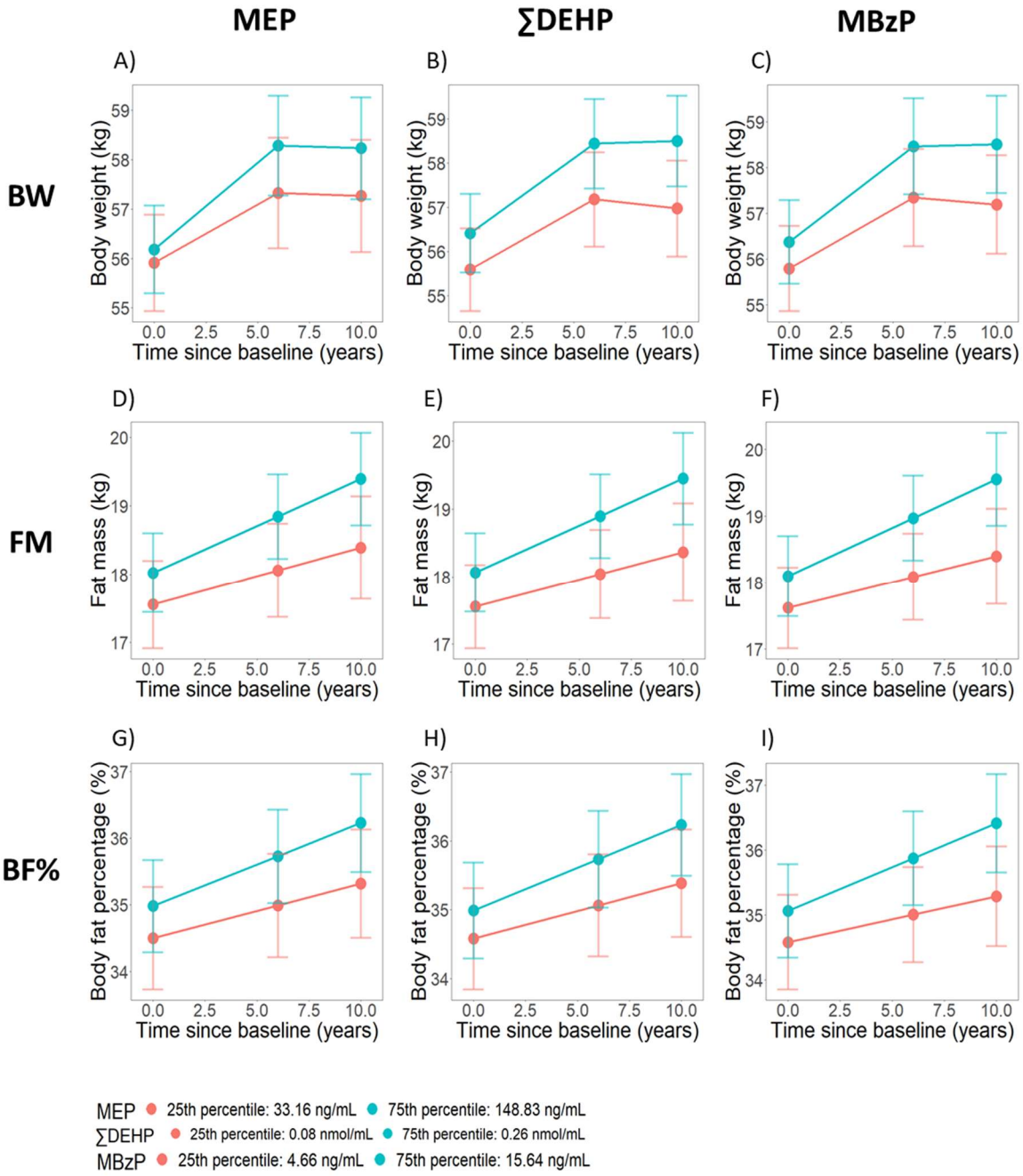
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 2.6 Differences in five-year body fat percentage change per doubling of phthalate metabolite concentrations, by baseline obesity status

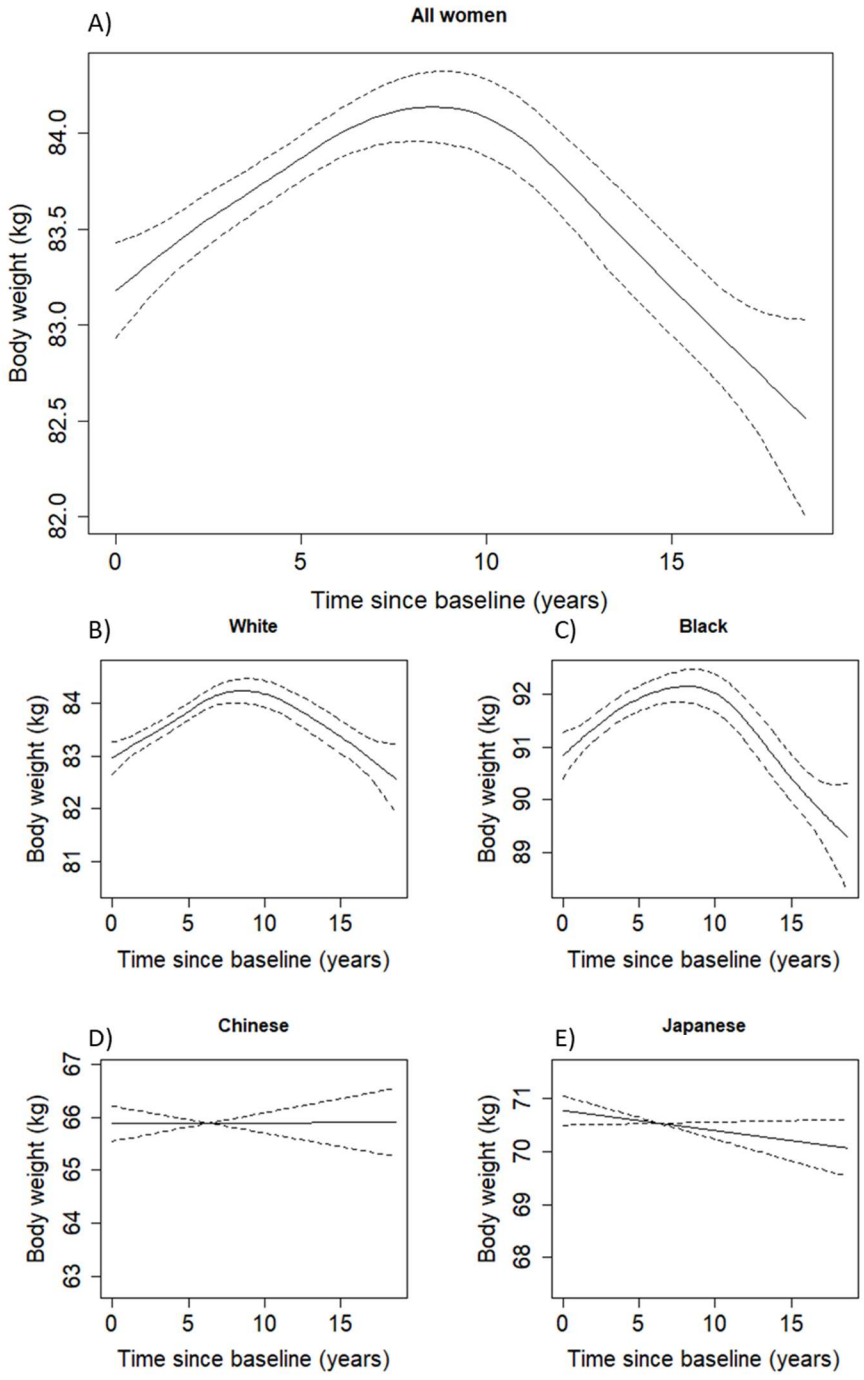


∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 2.7 Predicted adiposity trajectories at two levels of phthalate exposure among normal/underweight women

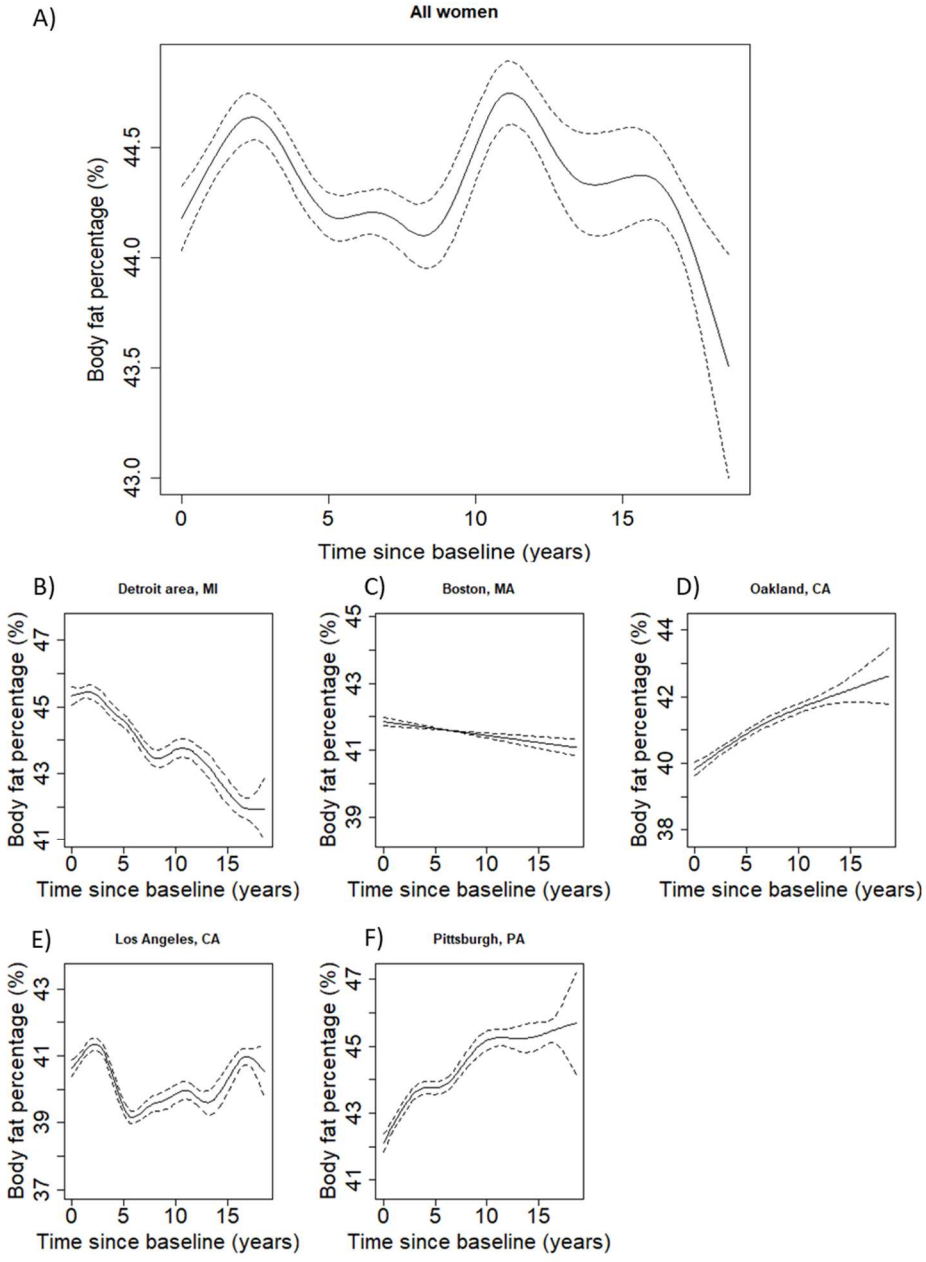


Supplementary Figure 2.1 Smoothed body weight trajectories for all women and by race/ethnicity



Smoothed trajectories were generated from generalized additive mixed models. Time was fitted with a penalized spline. Models were adjusted for all covariates. The smoothing plots suggest a change point for the slope of time between time (T) = 5 and T = 12. We selected T = 6 years as the knot for the linear spline in the parametric model for body weight because this knot produced the best model fit in terms of Akaike Information Criterion (AIC) among a series of models with knots at each year between T = 5 to 12 years.

Supplementary Figure 2.2 Smoothed body fat percentage trajectories for all women and by study site



Smoothed trajectories were generated from generalized additive mixed models. Time was fitted with a penalized spline. Models were adjusted for all covariates. Among all women (Panel A), there appeared to be a decrease in body fat percentage after 10 years, but this was an artefact. In the final visit in 2016/2017, 60% of participants were from the Detroit area and Boston as compared to approximately 35% in previous visits. Because women from these two sites lost body fat percentage over time, their over-representation in the final visit resulted in a downward shift in the overall body fat percentage trajectory for all women. Because the trajectory of body fat within each site was relatively linear (Panels B-F), we decided to model time with a linear term. In models used to test the association between phthalates and the rate of change in body fat percentage, we additionally included time by site interaction terms to capture site differences in body fat percentage trajectory. The smoothing plots of time for fat mass were similar to those for body fat percentage.

Supplementary Table 2.1 Low-molecular-weight phthalate metabolite concentrations by covariates

	N	MEP Median (Q1, Q3)[2] ng/mL	MnBP Median (Q1, Q3) ng/mL	MiBP Median (Q1, Q3) ng/mL	∑LMW phthalates[1] Median (Q1, Q3) nmol/mL
Age					
≤49	617	90.78 (37.47, 226.54)	19.62 (12.52, 35.45)	2.8 (1.63, 4.78)	0.6 (0.3, 1.44)
> 49	752	73.99 (35.97, 186.74)	17.71 (10.91, 29.52)	2.48 (1.49, 4.2)	0.54 (0.27, 1.21)
p-value[3]		0.01	0.01	0.01	0.01
Site					
Detroit area, MI	247	111.75 (61.58, 320.11)	23.57 (15.1, 48.94)	3.35 (1.86, 5.44)	0.84 (0.43, 2.03)
Boston, MA	227	118.05 (45.89, 322.24)	17.61 (11.79, 32.69)	2.76 (1.72, 4.67)	0.8 (0.36, 1.78)
Oakland, CA	306	43.09 (24.52, 114.84)	14.92 (9.42, 23.42)	2.19 (1.39, 4.32)	0.32 (0.2, 0.71)
Los Angeles, CA	359	65.34 (30.57, 141.91)	17.18 (10.85, 29.01)	2.17 (1.26, 3.66)	0.49 (0.26, 0.85)
Pittsburgh, PA	230	107.61 (47.91, 231.31)	23.07 (14.04, 41.5)	2.99 (1.83, 4.74)	0.72 (0.37, 1.37)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity					
White	659	82.15 (39.13, 181.54)	18.64 (11.63, 29.93)	2.32 (1.46, 4.01)	0.58 (0.31, 1.13)
Black	294	212.26 (95.42, 452.2)	27.04 (15.91, 50.43)	3.98 (2.53, 6.13)	1.31 (0.68, 2.66)
Chinese	176	35.38 (20.19, 69.46)	14.07 (8.13, 21.98)	2.21 (1.4, 4.36)	0.27 (0.18, 0.47)
Japanese	204	48.59 (24.94, 99.65)	14.67 (10.4, 24.25)	2.49 (1.24, 3.71)	0.39 (0.21, 0.68)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Education					
High school or less	248	85.41 (35.57, 232.42)	18.93 (12.06, 37.16)	2.95 (1.76, 5.14)	0.59 (0.29, 1.5)
Some college	438	90.1 (40.77, 246.05)	21.25 (13.16, 36)	2.68 (1.55, 4.78)	0.62 (0.34, 1.42)
College degree	336	71.72 (32.93, 187.41)	16.4 (10.9, 29.33)	2.46 (1.57, 4.2)	0.52 (0.26, 1.21)
Postgraduate	347	79.24 (35.09, 163.67)	16.68 (10.45, 27.04)	2.48 (1.48, 4.18)	0.52 (0.27, 0.99)
p-value		0.06	<0.0001	0.06	0.005
Smoking					
Never	863	69.18 (33.48, 180.96)	17.65 (11.23, 28.8)	2.48 (1.51, 4.34)	0.51 (0.26, 1.12)
Past	364	98.59 (43.9, 249.76)	18.97 (11.83, 32.67)	2.66 (1.56, 4.42)	0.64 (0.34, 1.48)
Current	142	131.21 (57.05, 278.77)	27.35 (13.87, 48.52)	3.11 (1.86, 5.62)	0.84 (0.44, 1.76)
p-value		<0.0001	<0.0001	0.001	<0.0001
Daily calorie intake					
1st quartile: < 1335 kcal/day	343	80.86 (37.44, 228.92)	19.61 (12.14, 35.19)	2.67 (1.57, 4.57)	0.57 (0.32, 1.35)

	N	MEP Median (Q1, Q3)[2] ng/mL	MnBP Median (Q1, Q3) ng/mL	MiBP Median (Q1, Q3) ng/mL	∑LMW phthalates[1] Median (Q1, Q3) nmol/mL
2nd quartile: 1335 – 1688 kcal/day	342	85.54 (36.19, 191.44)	18.08 (10.81, 28.82)	2.48 (1.5, 4.23)	0.56 (0.27, 1.25)
3rd quartile: 1688 – 2170 kcal/day	342	79.99 (37.32, 179.27)	16.63 (10.74, 31.75)	2.56 (1.5, 4.59)	0.55 (0.28, 1.12)
4th quartile: > 2170 kcal/day	342	86.88 (35.37, 226.03)	19.3 (12.54, 35.43)	2.79 (1.61, 4.64)	0.59 (0.29, 1.42)
p-value		0.93	0.04	0.23	0.73
Physical activity					
1st quartile: < 6.6	340	80.59 (36.71, 208.32)	18.76 (12.45, 30.7)	2.6 (1.55, 4.35)	0.56 (0.3, 1.3)
2nd quartile: 6.6 – 7.9	325	85.6 (38.64, 192.87)	18.34 (11.88, 34.87)	2.55 (1.48, 4.46)	0.59 (0.3, 1.31)
3rd quartile: 7.9 – 9.0	322	70.39 (34.67, 196.56)	20.62 (12.06, 36.1)	2.67 (1.61, 4.71)	0.52 (0.28, 1.31)
4th quartile: > 9.0	326	94.41 (36.37, 220.06)	15.85 (10.27, 29.71)	2.48 (1.53, 4.13)	0.6 (0.27, 1.3)
p-value		0.53	0.01	0.45	0.86
Menopausal status					
Pre- or peri-menopausal	969	82.84 (36.95, 205.25)	18.45 (11.88, 32.25)	2.67 (1.6, 4.48)	0.58 (0.29, 1.31)
Natural/surgical menopause	198	70.65 (37.14, 210.55)	15.79 (10.67, 29.28)	2.63 (1.5, 4.89)	0.52 (0.27, 1.33)
Unknown due to hormone therapy	202	81.92 (34.9, 217.13)	20.47 (11.37, 36.44)	2.37 (1.42, 4)	0.59 (0.28, 1.31)
p-value		0.64	0.11	0.33	0.67
Currently on hormone therapy					
No	1089	82.84 (36.42, 215.62)	18.31 (11.69, 31.48)	2.67 (1.6, 4.51)	0.57 (0.29, 1.33)
Yes	280	77.71 (36.51, 180.15)	19.38 (11.7, 35.94)	2.43 (1.43, 4.25)	0.56 (0.29, 1.17)
p-value		0.25	0.43	0.11	0.43

[1] ∑LMW phthalates was the sum of the molar concentrations of MEP, MnBP, and MiBP. All metabolite concentrations were adjusted for hydration using the "covariate-adjusted creatinine standardization" method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

Supplementary Table 2.2 DEHP metabolite concentrations by covariates

	N	MEHP Median (Q1, Q3)[2] ng/mL	MEHHP Median (Q1, Q3) ng/mL	MEOHP Median (Q1, Q3) ng/mL	MECPP Median (Q1, Q3) ng/mL	∑DEHP[1] Median (Q1, Q3) nmol/mL
Age						
≤49	617	3.65 (1.8, 7.02)	17.87 (9.28, 34.25)	10.83 (5.45, 21.04)	19.19 (10.75, 34.96)	0.18 (0.1, 0.33)
> 49	752	2.77 (1.45, 5.34)	14.85 (7.78, 27.89)	8.64 (4.86, 15.93)	15.61 (9.45, 27.73)	0.14 (0.08, 0.26)
p-value[3]		<0.0001	0.0008	0.0002	0.0002	0.0002
Site						
Detroit area, MI	247	3.53 (1.99, 6.91)	21.24 (11.18, 37.28)	12.5 (6.69, 22.69)	19.26 (12.06, 35.71)	0.19 (0.11, 0.36)
Boston, MA	227	3.88 (1.83, 7.6)	20.98 (10.99, 39.06)	11.66 (6.45, 20.79)	21.43 (12.22, 43.08)	0.19 (0.11, 0.39)
Oakland, CA	306	2.32 (1.39, 4.06)	10.29 (5.84, 18.83)	6.05 (3.41, 11.17)	12.16 (7.42, 21.72)	0.11 (0.06, 0.18)
Los Angeles, CA	359	2.64 (1.37, 5.42)	12.72 (6.61, 22.58)	7.6 (3.89, 14.25)	14.57 (8.34, 26.31)	0.13 (0.07, 0.23)
Pittsburgh, PA	230	4.25 (2.23, 8.77)	23.33 (13.24, 49.21)	13.85 (7.81, 27.68)	23.57 (13.1, 45.59)	0.22 (0.13, 0.44)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity						
White	659	3.12 (1.59, 5.84)	17.45 (9.6, 31.34)	10.7 (5.72, 19.11)	18.78 (10.82, 33.51)	0.17 (0.1, 0.3)
Black	294	4.25 (2.42, 9.41)	23.04 (13.57, 48.06)	12.84 (7.85, 26.63)	20.61 (13.21, 44.01)	0.21 (0.13, 0.42)
Chinese	176	2.17 (1.36, 3.91)	7.45 (4.69, 15.05)	4.95 (2.66, 8.57)	10.03 (6.29, 17.74)	0.08 (0.05, 0.15)
Japanese	204	2.47 (1.3, 5.34)	11.22 (5.75, 20.58)	6.73 (3.56, 11.94)	12.63 (7.95, 23.19)	0.11 (0.07, 0.21)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Education						
High school or less	248	2.94 (1.39, 5.65)	14.83 (7.22, 30.45)	8.73 (4.39, 17.05)	15.53 (9.52, 29.19)	0.14 (0.08, 0.28)
Some college	438	3.34 (1.7, 6.83)	17.54 (9.55, 31.99)	10.68 (5.73, 19.27)	18.37 (10.79, 32.02)	0.17 (0.1, 0.3)
College degree	336	3.2 (1.58, 5.97)	14.68 (7.76, 29.52)	8.84 (4.83, 18.46)	15.55 (9.13, 30.19)	0.15 (0.08, 0.29)
Postgraduate	347	2.86 (1.54, 5.73)	16.7 (8.86, 30.75)	9.65 (5.41, 18.21)	18.24 (10.3, 32.29)	0.16 (0.09, 0.3)
p-value		0.09	0.1	0.07	0.15	0.1
Smoking						
Never	863	2.97 (1.55, 6.2)	15.39 (7.48, 31.1)	9.26 (4.67, 19.25)	16.89 (9.44, 31.93)	0.15 (0.08, 0.3)
Past	364	3.06 (1.65, 5.52)	17.32 (10.11, 28.21)	10.14 (5.87, 16.6)	16.65 (11.01, 29.21)	0.16 (0.1, 0.26)
Current	142	3.67 (1.48, 6.95)	17.38 (8.92, 35.76)	9.81 (5.49, 21.18)	17.32 (10.57, 36.14)	0.16 (0.09, 0.35)
p-value		0.44	0.1	0.3	0.67	0.28
Daily calorie intake						
1st quartile: < 1335 kcal/day	343	3.04 (1.54, 6.01)	16.4 (8.75, 31.88)	9.92 (5.38, 18.46)	17.07 (10.23, 32.72)	0.16 (0.09, 0.3)

	N	MEHP Median (Q1, Q3)[2] ng/mL	MEHHP Median (Q1, Q3) ng/mL	MEOHP Median (Q1, Q3) ng/mL	MECPP Median (Q1, Q3) ng/mL	∑DEHP[1] Median (Q1, Q3) nmol/mL
2nd quartile: 1335 – 1688 kcal/day	342	2.94 (1.47, 5.62)	14.89 (7.43, 29.18)	8.76 (4.64, 18.18)	15.85 (8.95, 29.53)	0.15 (0.08, 0.28)
3rd quartile: 1688 – 2170 kcal/day	342	2.97 (1.61, 5.68)	15.69 (8.53, 30)	9.21 (4.98, 18.35)	16.59 (9.95, 30.84)	0.15 (0.09, 0.28)
4th quartile: > 2170 kcal/day	342	3.44 (1.85, 6.66)	17.56 (9.22, 34.11)	10.43 (5.31, 19.43)	18.27 (10.78, 33.28)	0.17 (0.09, 0.31)
p-value		0.2	0.18	0.31	0.2	0.17
Physical activity						
1st quartile: < 6.6	340	2.78 (1.42, 5.49)	15.26 (7.8, 30.03)	8.98 (4.85, 18.78)	15.39 (9.46, 29.21)	0.15 (0.08, 0.27)
2nd quartile: 6.6 – 7.9	325	2.86 (1.47, 5.49)	16.05 (8.22, 30.18)	9.62 (5, 18.08)	17.5 (9.63, 31.36)	0.16 (0.08, 0.29)
3rd quartile: 7.9 – 9.0	322	3.42 (1.84, 6.43)	16.78 (8.83, 29.57)	10.09 (5.27, 17.45)	17.18 (9.81, 32)	0.17 (0.09, 0.29)
4th quartile: > 9.0	326	3.3 (1.65, 7.04)	16.35 (9.44, 32.99)	9.71 (5.42, 18.88)	17.93 (11.02, 32.93)	0.16 (0.1, 0.31)
p-value		0.02	0.54	0.55	0.35	0.35
Menopausal status						
Pre- or peri-menopausal	969	3.08 (1.64, 5.97)	16.17 (8.36, 30.49)	9.62 (5.15, 18.81)	16.81 (10.07, 31.36)	0.16 (0.09, 0.29)
Natural/surgical menopause	198	2.73 (1.26, 5.74)	15.5 (7.42, 32.22)	9.14 (4.34, 18.63)	16.26 (8.99, 31.35)	0.15 (0.08, 0.3)
Unknown due to hormone therapy	202	3.42 (1.59, 6.84)	16.94 (9.41, 29.17)	11.14 (5.8, 17.91)	18.32 (10.22, 29.55)	0.17 (0.1, 0.28)
p-value		0.13	0.59	0.32	0.64	0.47
Currently on hormone therapy						
No	1089	3.07 (1.6, 5.93)	16.21 (8.22, 30.51)	9.52 (5.02, 18.78)	16.85 (9.91, 31.33)	0.16 (0.09, 0.29)
Yes	280	3.09 (1.55, 6.86)	15.8 (9.2, 30.27)	10.24 (5.43, 18.22)	16.63 (9.6, 30.97)	0.16 (0.09, 0.29)
p-value		0.79	0.52	0.48	0.65	0.72

[1] ∑DEHP was the sum of the molar concentrations of MEHP, MEHHP, MEOHP and MECPP. All metabolite concentrations were adjusted for hydration using the "covariate-adjusted creatinine standardization" method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

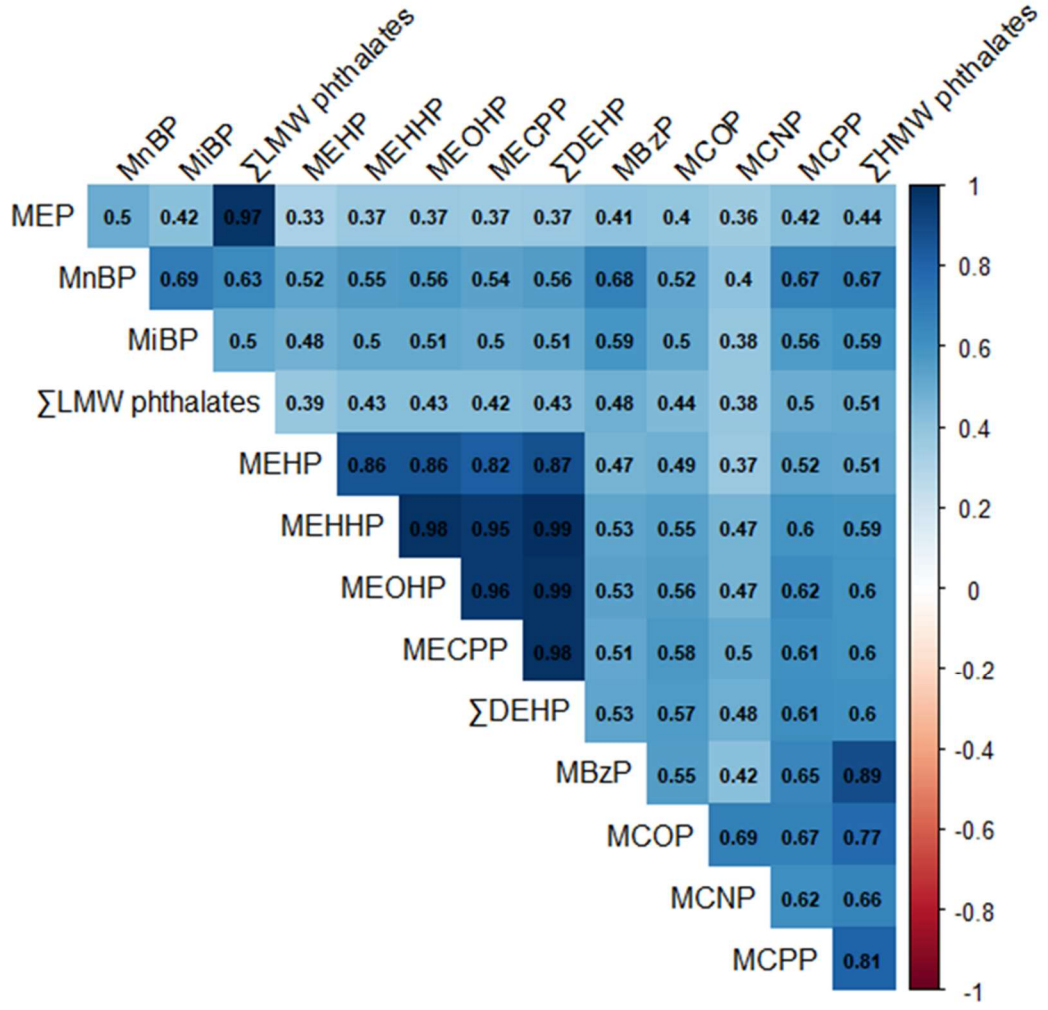
Supplementary Table 2.3 Other high-molecular-weight phthalate metabolite concentrations by covariates

	N	MBzP	MCOP	MCNP	MCPP	∑HMW phthalates[1]
		Median (Q1, Q3)[2] ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
Age						
≤49	617	11.43 (6.93, 20.21)	5.01 (3.01, 8.86)	3.02 (1.71, 5.81)	2.93 (1.91, 4.71)	0.09 (0.06, 0.15)
> 49	752	9.32 (5.18, 16.86)	3.97 (2.36, 6.8)	2.32 (1.4, 4.33)	2.41 (1.58, 3.9)	0.08 (0.05, 0.12)
p-value[3]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Site						
Detroit area, MI	247	14.02 (9, 23.88)	5.83 (3.71, 10.66)	3.71 (2.21, 6.65)	3.23 (2.38, 4.93)	0.12 (0.07, 0.17)
Boston, MA	227	10.59 (5.9, 18.57)	4.56 (2.86, 8.57)	3.44 (2.01, 6.92)	2.63 (1.8, 4.04)	0.09 (0.06, 0.13)
Oakland, CA	306	7.01 (4.04, 13.72)	2.91 (1.83, 5.18)	1.71 (1.06, 3.02)	2.12 (1.37, 3.33)	0.06 (0.04, 0.1)
Los Angeles, CA	359	8.83 (5.22, 14.95)	3.75 (2.34, 6.4)	1.97 (1.23, 3.72)	2.24 (1.45, 3.59)	0.07 (0.05, 0.12)
Pittsburgh, PA	230	13.4 (8.4, 22.83)	6.24 (3.77, 9.77)	3.55 (2.22, 5.73)	3.77 (2.42, 5.38)	0.12 (0.08, 0.17)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity						
White	659	11.21 (6.47, 19.42)	4.85 (3.02, 8.04)	3.02 (2, 5.48)	3.19 (2.13, 4.89)	0.09 (0.06, 0.14)
Black	294	13.58 (8.57, 22.35)	5.83 (3.52, 10.98)	3.84 (2.05, 6.81)	2.88 (1.91, 4.58)	0.11 (0.07, 0.16)
Chinese	176	5.83 (3.22, 10.37)	2.3 (1.5, 4.25)	1.24 (0.81, 1.93)	1.66 (0.94, 2.42)	0.04 (0.03, 0.07)
Japanese	204	8.1 (4.75, 13.83)	3.42 (2.14, 5.75)	1.51 (0.98, 2.88)	1.89 (1.24, 2.55)	0.06 (0.04, 0.09)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Education						
High school or less	248	9.48 (5.27, 17.07)	3.99 (2.38, 6.89)	2.29 (1.32, 4.56)	2.64 (1.55, 3.94)	0.08 (0.05, 0.13)
Some college	438	11.76 (6.48, 21.22)	4.54 (2.76, 8.01)	2.83 (1.5, 5.09)	2.59 (1.72, 4.33)	0.09 (0.06, 0.15)
College degree	336	10.34 (5.85, 17.96)	4.53 (2.56, 8.11)	2.57 (1.52, 4.87)	2.54 (1.62, 3.93)	0.08 (0.05, 0.13)
Postgraduate	347	9.76 (5.18, 18.43)	4.56 (2.81, 8.01)	2.85 (1.71, 5.43)	2.95 (1.92, 4.65)	0.09 (0.05, 0.13)
p-value		0.01	0.3	0.02	0.01	0.12
Smoking						
Never	863	9.59 (5.39, 17.86)	4.25 (2.49, 7.45)	2.51 (1.39, 4.86)	2.53 (1.58, 4.27)	0.08 (0.05, 0.13)
Past	364	11.37 (6.1, 19.2)	4.8 (2.82, 8.69)	2.96 (1.7, 5.28)	2.78 (1.99, 4.24)	0.09 (0.06, 0.14)
Current	142	11.99 (7.91, 19.8)	4.55 (2.89, 7.2)	2.7 (1.67, 5.17)	2.83 (1.66, 4.47)	0.09 (0.06, 0.15)
p-value		0.001	0.05	0.01	0.02	0.001
Daily calorie intake						

	N	MBzP	MCOP	MCNP	MCPP	∑HMW phthalates[1]
		Median (Q1, Q3)[2] ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
1st quartile: < 1335 kcal/day	343	10.56 (5.86, 18.46)	4.37 (2.71, 7.33)	2.56 (1.54, 4.74)	2.63 (1.73, 4.28)	0.09 (0.06, 0.14)
2nd quartile: 1335 – 1688 kcal/day	342	9.74 (5.42, 16.71)	4.15 (2.38, 7.21)	2.42 (1.41, 4.58)	2.5 (1.61, 3.79)	0.08 (0.05, 0.13)
3rd quartile: 1688 – 2170 kcal/day	342	10.23 (5.73, 17.93)	4.54 (2.6, 8.04)	2.8 (1.44, 5.25)	2.84 (1.71, 4.32)	0.08 (0.06, 0.13)
4th quartile: > 2170 kcal/day	342	11.27 (6.21, 19.69)	4.78 (2.87, 8.31)	2.94 (1.64, 5.69)	2.77 (1.77, 4.71)	0.09 (0.05, 0.14)
p-value		0.28	0.14	0.13	0.26	0.15
Physical activity						
1st quartile: < 6.6	340	10.48 (5.95, 18.63)	4.65 (2.81, 8.63)	2.66 (1.53, 5.07)	2.59 (1.57, 3.96)	0.09 (0.05, 0.15)
2nd quartile: 6.6 – 7.9	325	10.67 (6.08, 18.61)	4.35 (2.38, 7.01)	2.35 (1.42, 4.22)	2.69 (1.59, 4.29)	0.08 (0.05, 0.13)
3rd quartile: 7.9 – 9.0	322	10.66 (6.16, 18.76)	4.3 (2.6, 7.88)	2.79 (1.5, 5.1)	2.72 (1.9, 4.3)	0.09 (0.06, 0.13)
4th quartile: > 9.0	326	9.22 (4.76, 16.68)	4.44 (2.8, 7.85)	3 (1.71, 5.21)	2.74 (1.77, 4.64)	0.08 (0.05, 0.13)
p-value		0.13	0.29	0.01	0.11	0.55
Menopausal status						
Pre- or peri-menopausal	969	10.35 (5.95, 18.61)	4.54 (2.75, 7.91)	2.74 (1.54, 4.95)	2.64 (1.72, 4.23)	0.09 (0.05, 0.14)
Natural/surgical menopause	198	9.61 (4.65, 18.2)	4.31 (2.41, 6.94)	2.39 (1.33, 5.17)	2.13 (1.52, 4.23)	0.08 (0.04, 0.13)
Unknown due to hormone therapy	202	10.83 (6.58, 18.26)	4.27 (2.48, 8.18)	2.69 (1.49, 5.05)	3.01 (2.05, 4.48)	0.08 (0.06, 0.13)
p-value		0.21	0.28	0.68	0.01	0.27
Currently on hormone therapy						
No	1089	10.25 (5.78, 18.6)	4.45 (2.67, 7.88)	2.73 (1.52, 4.95)	2.59 (1.67, 4.2)	0.08 (0.05, 0.14)
Yes	280	10.79 (5.85, 18.12)	4.31 (2.5, 7.78)	2.59 (1.51, 5.16)	2.96 (1.8, 4.45)	0.08 (0.05, 0.13)
p-value		0.72	0.5	0.93	0.03	0.73

[1] ∑HMW phthalates was the sum of the molar concentrations of MBzP, MCOP, MCNP, and MCPP. All metabolite concentrations were adjusted for hydration using the "covariate-adjusted creatinine standardization" method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

Supplementary Figure 2.3 Spearman correlation coefficients between phthalate metabolites



Supplementary Table 2.4 Intraclass correlation coefficients of phthalate metabolites

Phthalate metabolite	Intraclass correlation coefficient[1]	
	Not adjusted for hydration	Adjusted for hydration[2]
MEP	0.40	0.45
MnBP	0.40	0.41
MiBP	0.35	0.35
∑LMW phthalates[3]	0.40	0.45
MEHP	0.37	0.33
MEHHP	0.33	0.27
MEOHP	0.35	0.29
MECPP	0.31	0.23
∑DEHP	0.32	0.26
MBzP	0.38	0.40
MCOP	0.25	0.21
MCNP	0.28	0.25
MCPP	0.28	0.20
∑HMW phthalates	0.32	0.31

[1] The intraclass correlation coefficient (ICC) of each phthalate metabolite was estimated from a linear mixed effects model that predicted the $\log_2$-transformed metabolite with random intercepts and no fixed effects.
[2] Hydration adjustment was made using the "covariate-adjusted creatinine standardization" method.
[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.5 Associations between phthalate metabolites and body weight

	For each doubling of metabolite concentration …		
	Difference in body weight at baseline[1] (95% CI) (kg)	**Difference in the five-year change in body weight** (95% CI) (kg)	
		T ≤ 6 years[2]	**T > 6 years**
All women (N = 1369)			
MEP	0.47 (-0.09, 1.03)	0.14 (-0.06, 0.33)	0.02 (-0.13, 0.17)
MnBP	0.31 (-0.49, 1.10)	0.09 (-0.18, 0.37)	0.03 (-0.18, 0.24)
MiBP	0.06 (-0.75, 0.86)	0.08 (-0.20, 0.35)	-0.01 (-0.22, 0.21)
∑LMW phthalates[3]	0.54 (-0.10, 1.17)	0.16 (-0.05, 0.38)	0.02 (-0.15, 0.19)
MEHP	-0.25 (-0.83, 0.33)	0.14 (-0.06, 0.34)	0.14 (-0.01, 0.30)
MEHHP	**1.27 (0.65, 1.89)**[4]	0.05 (-0.16, 0.26)	0.08 (-0.08, 0.24)
MEOHP	**1.20 (0.57, 1.82)**	0.07 (-0.15, 0.28)	0.09 (-0.08, 0.26)
MECPP	**1.63 (0.96, 2.30)**	-0.03 (-0.26, 0.21)	0.10 (-0.08, 0.28)
∑DEHP	**1.30 (0.65, 1.96)**	0.03 (-0.19, 0.26)	0.10 (-0.08, 0.27)
MBzP	**1.58 (0.85, 2.31)**	0.00 (-0.25, 0.25)	0.01 (-0.18, 0.21)
MCOP	**2.20 (1.38, 3.01)**	-0.24 (-0.52, 0.04)	-0.03 (-0.25, 0.18)
MCNP	**1.95 (1.22, 2.68)**	-0.23 (-0.48, 0.03)	-0.10 (-0.29, 0.10)
MCPP	**1.29 (0.35, 2.23)**	0.11 (-0.21, 0.43)	-0.11 (-0.35, 0.14)
∑HMW phthalates	**2.59 (1.66, 3.52)**	-0.22 (-0.53, 0.10)	0.05 (-0.19, 0.30)
Normal/underweight (N = 502)			
MEP	0.12 (-0.21, 0.46)	**0.27 (0.06, 0.47)**	0.00 (-0.15, 0.16)
MnBP	0.05 (-0.40, 0.50)	0.25 (-0.03, 0.52)	0.09 (-0.11, 0.29)
MiBP	0.08 (-0.36, 0.51)	0.22 (-0.05, 0.49)	-0.02 (-0.23, 0.18)
∑LMW phthalates	0.13 (-0.25, 0.52)	**0.32 (0.09, 0.56)**	0.02 (-0.15, 0.20)
MEHP	0.26 (-0.08, 0.59)	0.11 (-0.10, 0.31)	0.14 (-0.02, 0.29)
MEHHP	**0.45 (0.10, 0.80)**	0.21 (-0.00, 0.43)	**0.18 (0.02, 0.33)**
MEOHP	**0.46 (0.10, 0.81)**	0.17 (-0.04, 0.39)	**0.20 (0.04, 0.36)**
MECPP	**0.53 (0.14, 0.91)**	0.20 (-0.04, 0.43)	**0.18 (0.00, 0.36)**
∑DEHP	**0.47 (0.10, 0.84)**	0.20 (-0.02, 0.43)	**0.19 (0.02, 0.36)**
MBzP	0.33 (-0.08, 0.75)	**0.26 (0.01, 0.51)**	0.14 (-0.05, 0.33)
MCOP	**0.72 (0.26, 1.19)**	0.19 (-0.09, 0.47)	0.14 (-0.07, 0.35)
MCNP	0.21 (-0.21, 0.62)	-0.11 (-0.35, 0.14)	-0.01 (-0.19, 0.17)
MCPP	0.44 (-0.06, 0.94)	**0.40 (0.09, 0.70)**	0.11 (-0.12, 0.33)
∑HMW phthalates	0.49 (-0.04, 1.02)	0.26 (-0.06, 0.58)	0.20 (-0.04, 0.43)
Overweight (N = 407)			
MEP	-0.15 (-0.57, 0.28)	0.08 (-0.22, 0.39)	0.09 (-0.12, 0.31)
MnBP	0.13 (-0.46, 0.71)	-0.08 (-0.50, 0.33)	-0.02 (-0.30, 0.27)

	For each doubling of metabolite concentration …		
	Difference in body weight at baseline[1] (95% CI) (kg)	**Difference in the five-year change in body weight** (95% CI) (kg)	
		T ≤ 6 years[2]	**T > 6 years**
MiBP	0.55 (-0.02, 1.12)	-0.06 (-0.46, 0.34)	0.04 (-0.24, 0.32)
∑LMW phthalates	-0.17 (-0.66, 0.32)	0.05 (-0.30, 0.40)	0.09 (-0.16, 0.34)
MEHP	-0.05 (-0.50, 0.40)	0.02 (-0.29, 0.34)	0.09 (-0.13, 0.31)
MEHHP	-0.09 (-0.57, 0.40)	0.02 (-0.32, 0.36)	0.11 (-0.13, 0.34)
MEOHP	-0.11 (-0.59, 0.37)	0.05 (-0.29, 0.38)	0.14 (-0.10, 0.37)
MECPP	-0.07 (-0.60, 0.46)	-0.09 (-0.46, 0.28)	0.11 (-0.15, 0.37)
∑DEHP	-0.10 (-0.61, 0.42)	-0.01 (-0.37, 0.34)	0.11 (-0.13, 0.36)
MBzP	0.20 (-0.33, 0.74)	-0.19 (-0.56, 0.19)	-0.01 (-0.28, 0.26)
MCOP	0.48 (-0.14, 1.10)	-0.35 (-0.78, 0.09)	0.18 (-0.13, 0.48)
MCNP	**0.64 (0.10, 1.18)**	0.06 (-0.32, 0.45)	-0.01 (-0.27, 0.26)
MCPP	0.64 (-0.12, 1.39)	-0.27 (-0.81, 0.26)	0.10 (-0.27, 0.47)
∑HMW phthalates	0.46 (-0.24, 1.16)	-0.44 (-0.93, 0.06)	0.11 (-0.24, 0.46)
Obese (N = 460)			
MEP	-0.02 (-0.88, 0.85)	0.15 (-0.28, 0.58)	0.04 (-0.31, 0.38)
MnBP	0.01 (-1.35, 1.37)	0.19 (-0.49, 0.87)	0.06 (-0.49, 0.60)
MiBP	0.86 (-0.66, 2.38)	-0.01 (-0.78, 0.76)	-0.09 (-0.71, 0.52)
∑LMW phthalates	-0.11 (-1.08, 0.87)	0.22 (-0.26, 0.71)	0.03 (-0.36, 0.43)
MEHP	-0.17 (-1.10, 0.76)	0.24 (-0.22, 0.70)	0.17 (-0.20, 0.54)
MEHHP	0.87 (-0.15, 1.90)	0.07 (-0.44, 0.59)	0.05 (-0.36, 0.46)
MEOHP	0.70 (-0.36, 1.76)	0.14 (-0.39, 0.67)	0.04 (-0.39, 0.47)
MECPP	0.95 (-0.19, 2.08)	-0.02 (-0.59, 0.55)	0.14 (-0.32, 0.60)
∑DEHP	0.84 (-0.25, 1.93)	0.06 (-0.49, 0.61)	0.09 (-0.35, 0.53)
MBzP	0.89 (-0.39, 2.18)	0.11 (-0.53, 0.74)	0.06 (-0.45, 0.57)
MCOP	**2.03 (0.70, 3.36)**	-0.51 (-1.17, 0.16)	-0.24 (-0.78, 0.29)
MCNP	1.00 (-0.28, 2.28)	-0.40 (-1.04, 0.24)	-0.10 (-0.62, 0.42)
MCPP	0.63 (-1.00, 2.26)	0.20 (-0.59, 1.00)	-0.38 (-1.01, 0.26)
∑HMW phthalates	**1.69 (0.09, 3.30)**	-0.31 (-1.10, 0.48)	0.09 (-0.54, 0.72)

[1] For each phthalate metabolite, difference in body weight at baseline and differences in the rates of change in body weight associated with phthalate exposure were estimated from a mixed effects model that predicted body weight with the metabolite in 1999/2000 (log_2-transformed), linear spline for time, and the interaction between the metabolite and both terms for time. This model was additionally adjusted for age at baseline (1999/2000), race/ethnicity, the interaction between race/ethnicity and both terms for time, site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and both terms for time were also included. Models were run for all women and by baseline obesity status.

[2] "T ≤ 6 years" means "within the first six years of follow-up". "T > 6 years" means "after the first six years of follow-up".

[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

[4] Bold: p-value < 0.05.

Supplementary Table 2.6 Associations between phthalate metabolites and fat mass

	For each doubling of metabolite concentration…	
	Difference in fat mass at baseline[1] (95% CI) (kg)	**Difference in the five-year change in fat mass** (95% CI) (kg)
All women (N = 1344)		
MEP	**0.38 (0.06, 0.71)**[2]	0.05 (-0.01, 0.11)
MnBP	0.24 (-0.23, 0.70)	0.06 (-0.03, 0.15)
MiBP	0.15 (-0.32, 0.63)	0.04 (-0.05, 0.14)
∑LMW phthalates[3]	**0.45 (0.08, 0.82)**	0.05 (-0.02, 0.12)
MEHP	-0.03 (-0.37, 0.31)	**0.11 (0.05, 0.18)**
MEHHP	**0.77 (0.41, 1.13)**	**0.10 (0.02, 0.17)**
MEOHP	**0.73 (0.36, 1.09)**	**0.11 (0.03, 0.18)**
MECPP	**0.97 (0.57, 1.36)**	**0.09 (0.01, 0.16)**
∑DEHP	**0.78 (0.40, 1.17)**	**0.10 (0.02, 0.18)**
MBzP	**1.06 (0.63, 1.49)**	0.05 (-0.04, 0.13)
MCOP	**0.90 (0.43, 1.38)**	0.04 (-0.06, 0.13)
MCNP	**0.88 (0.45, 1.30)**	-0.02 (-0.10, 0.07)
MCPP	**0.70 (0.15, 1.25)**	0.08 (-0.02, 0.19)
∑HMW phthalates	**1.42 (0.87, 1.97)**	0.06 (-0.05, 0.17)
Normal/underweight (N = 499)		
MEP	0.22 (-0.00, 0.43)	**0.12 (0.05, 0.20)**
MnBP	0.07 (-0.23, 0.36)	**0.17 (0.06, 0.27)**
MiBP	0.10 (-0.19, 0.39)	0.08 (-0.03, 0.18)
∑LMW phthalates	0.23 (-0.01, 0.48)	**0.16 (0.07, 0.25)**
MEHP	0.15 (-0.07, 0.37)	**0.11 (0.03, 0.19)**
MEHHP	**0.29 (0.06, 0.52)**	**0.16 (0.08, 0.25)**
MEOHP	**0.26 (0.03, 0.49)**	**0.17 (0.08, 0.25)**
MECPP	**0.33 (0.08, 0.58)**	**0.16 (0.06, 0.25)**
∑DEHP	**0.29 (0.05, 0.53)**	**0.16 (0.08, 0.25)**
MBzP	**0.27 (0.00, 0.54)**	**0.19 (0.10, 0.29)**
MCOP	**0.38 (0.07, 0.68)**	**0.19 (0.08, 0.30)**
MCNP	0.07 (-0.20, 0.34)	-0.00 (-0.10, 0.09)
MCPP	**0.45 (0.12, 0.77)**	**0.21 (0.10, 0.33)**
∑HMW phthalates	**0.40 (0.06, 0.75)**	**0.22 (0.10, 0.35)**
Overweight (N = 403)		
MEP	-0.14 (-0.41, 0.13)	0.04 (-0.06, 0.14)

	For each doubling of metabolite concentration…	
	Difference in fat mass at baseline[1] (95% CI) (kg)	**Difference in the five-year change in fat mass** (95% CI) (kg)
MnBP	0.12 (-0.26, 0.49)	-0.08 (-0.23, 0.07)
MiBP	**0.38 (0.02, 0.74)**	-0.03 (-0.17, 0.11)
∑LMW phthalates	-0.18 (-0.49, 0.12)	0.03 (-0.09, 0.14)
MEHP	-0.01 (-0.30, 0.28)	0.05 (-0.07, 0.16)
MEHHP	0.01 (-0.30, 0.32)	0.06 (-0.06, 0.18)
MEOHP	0.00 (-0.30, 0.31)	0.08 (-0.04, 0.20)
MECPP	0.06 (-0.28, 0.39)	0.04 (-0.09, 0.17)
∑DEHP	0.02 (-0.31, 0.34)	0.06 (-0.07, 0.18)
MBzP	0.25 (-0.09, 0.59)	-0.07 (-0.20, 0.06)
MCOP	0.19 (-0.20, 0.58)	0.02 (-0.14, 0.17)
MCNP	**0.38 (0.03, 0.72)**	0.06 (-0.07, 0.19)
MCPP	0.30 (-0.17, 0.78)	0.00 (-0.18, 0.18)
∑HMW phthalates	0.32 (-0.13, 0.77)	-0.05 (-0.22, 0.13)
Obese (N = 442)		
MEP	0.18 (-0.28, 0.64)	0.05 (-0.08, 0.18)
MnBP	0.23 (-0.50, 0.96)	0.06 (-0.16, 0.27)
MiBP	**0.96 (0.16, 1.76)**	0.05 (-0.18, 0.28)
∑LMW phthalates	0.20 (-0.31, 0.72)	0.05 (-0.10, 0.19)
MEHP	0.22 (-0.27, 0.71)	0.14 (-0.00, 0.28)
MEHHP	**0.59 (0.05, 1.14)**	0.11 (-0.05, 0.27)
MEOHP	0.55 (-0.01, 1.11)	0.12 (-0.04, 0.29)
MECPP	**0.63 (0.03, 1.23)**	0.14 (-0.04, 0.31)
∑DEHP	**0.59 (0.01, 1.16)**	0.13 (-0.04, 0.30)
MBzP	**0.74 (0.04, 1.45)**	0.08 (-0.13, 0.29)
MCOP	0.56 (-0.16, 1.28)	-0.10 (-0.31, 0.11)
MCNP	0.09 (-0.60, 0.77)	-0.02 (-0.21, 0.18)
MCPP	0.34 (-0.52, 1.21)	0.01 (-0.23, 0.26)
∑HMW phthalates	0.70 (-0.18, 1.57)	0.06 (-0.20, 0.31)

[1] For each phthalate metabolite, difference at baseline and difference in rate of change were estimated from a mixed effects model that predicted fat mass with the metabolite in 1999/2000 (log_2-transformed), time, and their interaction. This model was additionally adjusted for age at baseline (1999/2000), race/ethnicity, site, the interaction between time and site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and time were also included. Models were run for all women and by baseline obesity status.

[2] Bold: p-value < 0.05.

[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.7 Associations between phthalate metabolites and body fat percentage

	For each doubling of metabolite concentration…	
	Difference in body fat percentage at baseline[1] (95% CI) (percentage point)	**Difference in the five-year change in body fat percentage** (95% CI) (percentage point)
All women (N = 1344)		
MEP	**0.23 (0.04, 0.42)**[2]	0.04 (-0.01, 0.08)
MnBP	0.20 (-0.08, 0.47)	0.06 (-0.01, 0.12)
MiBP	0.14 (-0.14, 0.42)	0.03 (-0.03, 0.09)
∑LMW phthalates[3]	**0.27 (0.05, 0.49)**	0.04 (-0.01, 0.09)
MEHP	0.05 (-0.15, 0.25)	**0.07 (0.02, 0.11)**
MEHHP	**0.43 (0.21, 0.64)**	**0.07 (0.02, 0.12)**
MEOHP	**0.40 (0.18, 0.62)**	**0.08 (0.03, 0.13)**
MECPP	**0.54 (0.30, 0.77)**	**0.07 (0.01, 0.12)**
∑DEHP	**0.44 (0.21, 0.66)**	**0.07 (0.02, 0.12)**
MBzP	**0.63 (0.38, 0.89)**	**0.06 (0.00, 0.12)**
MCOP	**0.48 (0.20, 0.77)**	**0.07 (0.00, 0.13)**
MCNP	**0.43 (0.18, 0.68)**	-0.01 (-0.07, 0.05)
MCPP	**0.47 (0.14, 0.80)**	**0.09 (0.02, 0.16)**
∑HMW phthalates	**0.85 (0.52, 1.18)**	0.07 (-0.00, 0.14)
Normal/underweight (N = 499)		
MEP	0.22 (-0.04, 0.49)	**0.10 (0.02, 0.17)**
MnBP	0.10 (-0.25, 0.46)	**0.14 (0.04, 0.25)**
MiBP	0.09 (-0.26, 0.43)	0.06 (-0.04, 0.16)
∑LMW phthalates	0.25 (-0.05, 0.55)	**0.12 (0.04, 0.21)**
MEHP	0.12 (-0.15, 0.39)	**0.08 (0.00, 0.16)**
MEHHP	0.24 (-0.03, 0.52)	**0.12 (0.04, 0.20)**
MEOHP	0.21 (-0.07, 0.49)	**0.13 (0.05, 0.22)**
MECPP	0.25 (-0.05, 0.55)	**0.12 (0.03, 0.21)**
∑DEHP	0.23 (-0.06, 0.52)	**0.12 (0.04, 0.21)**
MBzP	0.28 (-0.05, 0.60)	**0.18 (0.09, 0.28)**
MCOP	0.24 (-0.12, 0.61)	**0.15 (0.05, 0.26)**
MCNP	0.03 (-0.29, 0.35)	-0.01 (-0.10, 0.08)
MCPP	**0.46 (0.07, 0.85)**	**0.17 (0.06, 0.29)**
∑HMW phthalates	**0.42 (0.01, 0.84)**	**0.19 (0.07, 0.30)**
Overweight (N = 403)		
MEP	-0.12 (-0.35, 0.11)	0.03 (-0.04, 0.10)

	For each doubling of metabolite concentration…	
	Difference in body fat percentage at baseline[1] (95% CI) (percentage point)	**Difference in the five-year change in body fat percentage** (95% CI) (percentage point)
MnBP	0.07 (-0.25, 0.39)	-0.07 (-0.17, 0.03)
MiBP	0.27 (-0.04, 0.58)	-0.04 (-0.14, 0.06)
∑LMW phthalates	-0.17 (-0.44, 0.09)	0.02 (-0.06, 0.10)
MEHP	0.06 (-0.19, 0.30)	0.02 (-0.06, 0.10)
MEHHP	0.08 (-0.18, 0.35)	0.03 (-0.05, 0.11)
MEOHP	0.08 (-0.18, 0.34)	0.04 (-0.04, 0.13)
MECPP	0.14 (-0.15, 0.43)	0.02 (-0.07, 0.11)
∑DEHP	0.10 (-0.18, 0.38)	0.03 (-0.06, 0.12)
MBzP	0.23 (-0.06, 0.52)	-0.06 (-0.15, 0.03)
MCOP	0.13 (-0.20, 0.47)	0.04 (-0.07, 0.14)
MCNP	0.14 (-0.16, 0.43)	0.03 (-0.06, 0.12)
MCPP	0.18 (-0.23, 0.59)	0.00 (-0.12, 0.13)
∑HMW phthalates	0.27 (-0.11, 0.66)	-0.04 (-0.16, 0.08)
Obese (N = 442)		
MEP	0.12 (-0.09, 0.33)	0.02 (-0.04, 0.08)
MnBP	0.15 (-0.19, 0.48)	0.06 (-0.04, 0.17)
MiBP	**0.61 (0.25, 0.98)**	0.03 (-0.09, 0.14)
∑LMW phthalates	0.14 (-0.09, 0.38)	0.02 (-0.05, 0.09)
MEHP	0.16 (-0.07, 0.38)	0.07 (-0.00, 0.14)
MEHHP	0.18 (-0.07, 0.43)	0.07 (-0.01, 0.15)
MEOHP	0.18 (-0.07, 0.44)	0.08 (-0.00, 0.16)
MECPP	0.23 (-0.04, 0.51)	**0.10 (0.01, 0.18)**
∑DEHP	0.20 (-0.06, 0.47)	**0.09 (0.00, 0.17)**
MBzP	**0.33 (0.01, 0.65)**	0.08 (-0.02, 0.18)
MCOP	0.23 (-0.10, 0.56)	0.00 (-0.10, 0.11)
MCNP	0.10 (-0.21, 0.42)	0.01 (-0.08, 0.11)
MCPP	0.24 (-0.16, 0.64)	0.08 (-0.04, 0.20)
∑HMW phthalates	0.32 (-0.08, 0.72)	0.09 (-0.04, 0.22)

[1] For each phthalate metabolite, difference at baseline and difference in rate of change were estimated from a mixed effects model that predicted body fat percentage with the metabolite in 1999/2000 (log_2-transformed), time, and their interaction. This model was additionally adjusted for age at baseline (1999/2000), race/ethnicity, site, the interaction between time and site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and time were also included. Models were run for all women and by baseline obesity status.
[2] Bold: p-value < 0.05.
[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.8 Predicted 10-year body weight trajectories for normal/underweight women at the 25th and 75th percentiles of each phthalate metabolite

	Predicted BW			Changes in BW T ∈ [0, 6]		Changes in BW T ∈ (6, 10]	
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ per year** kg/year (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
MEP							
25th percentile: 33.16 ng/mL	55.9 (54.9, 56.9)	57.3 (56.2, 58.4)	57.3 (56.1, 58.4)	1.41 (0.8, 2.03)	0.24 (0.13, 0.34)	-0.06 (-0.35, 0.23)	-0.01 (-0.09, 0.06)
75th percentile: 148.83 ng/mL	56.2 (55.3, 57.1)	58.3 (57.3, 59.3)	58.2 (57.2, 59.3)	2.1 (1.54, 2.66)	0.35 (0.26, 0.44)	-0.05 (-0.32, 0.21)	-0.01 (-0.08, 0.05)
Δ (75th – 25th)	0.27 (-0.46, 1)	0.96 (0.08, 1.83)	0.96 (0.07, 1.85)	0.69 (0.16, 1.22)	0.11 (0.03, 0.2)	0 (-0.27, 0.27)	0 (-0.07, 0.07)
MnBP							
25th percentile: 10.42 ng/mL	56.1 (55.1, 57)	57.6 (56.6, 58.7)	57.5 (56.4, 58.6)	1.58 (1, 2.17)	0.26 (0.17, 0.36)	-0.11 (-0.39, 0.16)	-0.03 (-0.1, 0.04)
75th percentile: 27.61 ng/mL	56.1 (55.2, 57)	58.1 (57.1, 59.1)	58.1 (57.1, 59.1)	2 (1.45, 2.56)	0.33 (0.24, 0.43)	-0.02 (-0.28, 0.25)	0 (-0.07, 0.06)
Δ (75th – 25th)	0.07 (-0.56, 0.71)	0.49 (-0.27, 1.25)	0.59 (-0.18, 1.36)	0.42 (-0.05, 0.88)	0.07 (-0.01, 0.15)	0.1 (-0.13, 0.33)	0.02 (-0.03, 0.08)
MiBP							
25th percentile: 1.5 ng/mL	56 (55.1, 57)	57.6 (56.5, 58.7)	57.6 (56.5, 58.7)	1.6 (1, 2.19)	0.27 (0.17, 0.37)	-0.04 (-0.32, 0.24)	-0.01 (-0.08, 0.06)
75th percentile: 4.26 ng/mL	56.1 (55.3, 57)	58.1 (57.1, 59.2)	58.1 (57, 59.1)	2 (1.44, 2.56)	0.33 (0.24, 0.43)	-0.07 (-0.33, 0.2)	-0.02 (-0.08, 0.05)
Δ (75th – 25th)	0.12 (-0.54, 0.78)	0.52 (-0.28, 1.31)	0.49 (-0.32, 1.29)	0.4 (-0.09, 0.89)	0.07 (-0.01, 0.15)	-0.03 (-0.27, 0.21)	-0.01 (-0.07, 0.05)
∑LMW phthalates[1]							
25th percentile: 0.26 nmol/mL	55.9 (54.9, 56.9)	57.3 (56.2, 58.4)	57.2 (56.1, 58.4)	1.39 (0.78, 2)	0.23 (0.13, 0.33)	-0.08 (-0.37, 0.22)	-0.02 (-0.09, 0.05)
75th percentile: 0.94 nmol/mL	56.2 (55.3, 57.1)	58.3 (57.3, 59.3)	58.2 (57.2, 59.3)	2.1 (1.55, 2.65)	0.35 (0.26, 0.44)	-0.04 (-0.31, 0.22)	-0.01 (-0.08, 0.06)
Δ (75th – 25th)	0.25 (-0.46, 0.95)	0.96 (0.11, 1.8)	0.99 (0.13, 1.85)	0.71 (0.2, 1.22)	0.12 (0.03, 0.2)	0.03 (-0.23, 0.29)	0.01 (-0.06, 0.07)
MEHP							
25th percentile: 1.5 ng/mL	55.8 (54.8, 56.7)	57.4 (56.3, 58.5)	57.2 (56.1, 58.4)	1.67 (1.06, 2.28)	0.28 (0.18, 0.38)	-0.19 (-0.48, 0.1)	-0.05 (-0.12, 0.02)
75th percentile: 6.04 ng/mL	56.3 (55.4, 57.2)	58.2 (57.2, 59.2)	58.2 (57.2, 59.3)	1.93 (1.38, 2.48)	0.32 (0.23, 0.41)	0.03 (-0.24, 0.29)	0.01 (-0.06, 0.07)

	Predicted BW			Changes in BW T ∈ [0, 6]		Changes in BW T ∈ (6, 10]	
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ per year** kg/year (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
Δ (75th – 25th)	0.52 (-0.17, 1.2)	0.77 (-0.04, 1.59)	0.99 (0.16, 1.82)	0.26 (-0.23, 0.75)	0.04 (-0.04, 0.13)	0.22 (-0.03, 0.46)	0.05 (-0.01, 0.12)
MEHHP							
25th percentile: 6.85 ng/mL	55.5 (54.6, 56.5)	57.1 (56, 58.2)	56.9 (55.8, 58)	1.55 (0.95, 2.15)	0.26 (0.16, 0.36)	-0.21 (-0.49, 0.07)	-0.05 (-0.12, 0.02)
75th percentile: 26.6 ng/mL	56.4 (55.5, 57.3)	58.5 (57.5, 59.5)	58.5 (57.5, 59.6)	2.05 (1.49, 2.61)	0.34 (0.25, 0.44)	0.07 (-0.2, 0.33)	0.02 (-0.05, 0.08)
Δ (75th – 25th)	0.88 (0.19, 1.57)	1.38 (0.56, 2.2)	1.66 (0.82, 2.49)	0.5 (0, 1)	0.08 (0, 0.17)	0.27 (0.03, 0.52)	0.07 (0.01, 0.13)
MEOHP							
25th percentile: 4.19 ng/mL	55.6 (54.6, 56.5)	57.2 (56.1, 58.2)	57 (55.9, 58)	1.61 (1.01, 2.2)	0.27 (0.17, 0.37)	-0.22 (-0.5, 0.06)	-0.06 (-0.13, 0.01)
75th percentile: 16 ng/mL	56.5 (55.6, 57.3)	58.5 (57.4, 59.5)	58.5 (57.5, 59.6)	2.01 (1.45, 2.58)	0.34 (0.24, 0.43)	0.08 (-0.19, 0.35)	0.02 (-0.05, 0.09)
Δ (75th – 25th)	0.88 (0.2, 1.57)	1.29 (0.47, 2.11)	1.59 (0.76, 2.42)	0.41 (-0.09, 0.91)	0.07 (-0.02, 0.15)	0.3 (0.05, 0.55)	0.08 (0.01, 0.14)
MECPP							
25th percentile: 8.43 ng/mL	55.6 (54.6, 56.5)	57.2 (56.1, 58.2)	57 (55.9, 58.1)	1.6 (1.01, 2.2)	0.27 (0.17, 0.37)	-0.2 (-0.47, 0.08)	-0.05 (-0.12, 0.02)
75th percentile: 26.31 ng/mL	56.4 (55.6, 57.3)	58.4 (57.4, 59.4)	58.5 (57.5, 59.5)	2 (1.44, 2.55)	0.33 (0.24, 0.42)	0.04 (-0.22, 0.3)	0.01 (-0.05, 0.08)
Δ (75th – 25th)	0.86 (0.23, 1.49)	1.26 (0.5, 2.01)	1.49 (0.73, 2.26)	0.39 (-0.07, 0.85)	0.07 (-0.01, 0.14)	0.24 (0, 0.47)	0.06 (0, 0.12)
∑DEHP							
25th percentile: 0.08 nmol/mL	55.6 (54.7, 56.5)	57.2 (56.1, 58.2)	57 (55.9, 58.1)	1.59 (1, 2.18)	0.26 (0.17, 0.36)	-0.21 (-0.48, 0.07)	-0.05 (-0.12, 0.02)
75th percentile: 0.26 nmol/mL	56.4 (55.5, 57.3)	58.4 (57.4, 59.5)	58.5 (57.5, 59.5)	2.02 (1.46, 2.58)	0.34 (0.24, 0.43)	0.06 (-0.2, 0.32)	0.02 (-0.05, 0.08)
Δ (75th – 25th)	0.82 (0.17, 1.48)	1.26 (0.47, 2.04)	1.52 (0.73, 2.32)	0.43 (-0.05, 0.91)	0.07 (-0.01, 0.15)	0.27 (0.03, 0.51)	0.07 (0.01, 0.13)
MBzP							

	Predicted BW			Changes in BW T ∈ [0, 6]		Changes in BW T ∈ (6, 10]	
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ per year** kg/year (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
25th percentile: 4.66 ng/mL	55.8 (54.9, 56.7)	57.3 (56.3, 58.4)	57.2 (56.1, 58.3)	1.55 (0.96, 2.14)	0.26 (0.16, 0.36)	-0.15 (-0.43, 0.12)	-0.04 (-0.11, 0.03)
75th percentile: 15.64 ng/mL	56.4 (55.5, 57.3)	58.5 (57.4, 59.5)	58.5 (57.4, 59.6)	2.09 (1.51, 2.67)	0.35 (0.25, 0.44)	0.04 (-0.23, 0.32)	0.01 (-0.06, 0.08)
Δ (75th – 25th)	0.58 (-0.14, 1.3)	1.12 (0.26, 1.98)	1.32 (0.44, 2.19)	0.54 (0.01, 1.06)	0.09 (0, 0.18)	0.2 (-0.06, 0.46)	0.05 (-0.02, 0.11)
MCOP							
25th percentile: 2.37 ng/mL	55.5 (54.6, 56.4)	57.2 (56.1, 58.2)	57 (55.9, 58.1)	1.66 (1.08, 2.25)	0.28 (0.18, 0.37)	-0.14 (-0.42, 0.13)	-0.04 (-0.1, 0.03)
75th percentile: 6.63 ng/mL	56.6 (55.7, 57.5)	58.6 (57.5, 59.6)	58.6 (57.5, 59.6)	2 (1.42, 2.57)	0.33 (0.24, 0.43)	0.02 (-0.25, 0.29)	0.01 (-0.06, 0.07)
Δ (75th – 25th)	1.07 (0.38, 1.77)	1.41 (0.58, 2.24)	1.57 (0.73, 2.42)	0.33 (-0.16, 0.83)	0.06 (-0.03, 0.14)	0.17 (-0.08, 0.41)	0.04 (-0.02, 0.1)
MCNP							
25th percentile: 1.31 ng/mL	55.9 (55, 56.8)	57.8 (56.8, 58.9)	57.8 (56.7, 58.9)	1.94 (1.36, 2.52)	0.32 (0.23, 0.42)	-0.05 (-0.33, 0.22)	-0.01 (-0.08, 0.06)
75th percentile: 4.07 ng/mL	56.2 (55.3, 57.1)	58 (56.9, 59)	57.9 (56.9, 59)	1.73 (1.16, 2.31)	0.29 (0.19, 0.38)	-0.06 (-0.33, 0.21)	-0.02 (-0.08, 0.05)
Δ (75th – 25th)	0.34 (-0.34, 1.01)	0.13 (-0.68, 0.94)	0.12 (-0.71, 0.94)	-0.21 (-0.7, 0.28)	-0.03 (-0.12, 0.05)	-0.01 (-0.25, 0.23)	0 (-0.06, 0.06)
MCPP							
25th percentile: 1.55 ng/mL	55.8 (54.9, 56.7)	57.3 (56.3, 58.4)	57.2 (56.2, 58.3)	1.54 (0.97, 2.11)	0.26 (0.16, 0.35)	-0.11 (-0.38, 0.16)	-0.03 (-0.09, 0.04)
75th percentile: 4.07 ng/mL	56.4 (55.5, 57.3)	58.6 (57.6, 59.7)	58.6 (57.6, 59.7)	2.2 (1.61, 2.79)	0.37 (0.27, 0.47)	0.01 (-0.27, 0.29)	0 (-0.07, 0.07)
Δ (75th – 25th)	0.61 (-0.09, 1.31)	1.27 (0.44, 2.11)	1.4 (0.55, 2.24)	0.66 (0.15, 1.17)	0.11 (0.03, 0.19)	0.12 (-0.13, 0.37)	0.03 (-0.03, 0.09)
∑HMW phthalates							
25th percentile: 0.04 nmol/mL	55.7 (54.8, 56.7)	57.3 (56.2, 58.4)	57.1 (56.1, 58.2)	1.6 (1.01, 2.2)	0.27 (0.17, 0.37)	-0.17 (-0.45, 0.11)	-0.04 (-0.11, 0.03)
75th percentile: 0.12 nmol/mL	56.4 (55.5, 57.4)	58.5 (57.4, 59.5)	58.5 (57.5, 59.6)	2.05 (1.47, 2.64)	0.34 (0.24, 0.44)	0.06 (-0.22, 0.34)	0.01 (-0.05, 0.08)

	Predicted BW			Changes in BW T ∈ [0, 6]		Changes in BW T ∈ (6, 10]	
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ per year** kg/year (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
Δ (75th – 25th)	0.71 (-0.06, 1.49)	1.16 (0.24, 2.09)	1.39 (0.46, 2.33)	0.45 (-0.11, 1.01)	0.08 (-0.02, 0.17)	0.23 (-0.04, 0.5)	0.06 (-0.01, 0.13)

[1] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.9 Predicted 10-year fat mass trajectories for normal/underweight women at the 25th and 75th percentiles of each phthalate metabolite

	Predicted FM			Changes in FM		
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
MEP						
25th percentile: 33.16 ng/mL	17.6 (16.9, 18.2)	18.1 (17.4, 18.7)	18.4 (17.6, 19.1)	0.5 (0.27, 0.73)	0.33 (0.18, 0.49)	0.08 (0.05, 0.12)
75th percentile: 148.83 ng/mL	18 (17.4, 18.6)	18.8 (18.2, 19.5)	19.4 (18.7, 20.1)	0.82 (0.62, 1.03)	0.55 (0.41, 0.68)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.47 (-0.01, 0.94)	0.79 (0.27, 1.3)	1 (0.42, 1.58)	0.32 (0.12, 0.52)	0.21 (0.08, 0.35)	0.05 (0.02, 0.09)
MnBP						
25th percentile: 10.42 ng/mL	17.8 (17.2, 18.4)	18.3 (17.7, 19)	18.7 (18, 19.4)	0.53 (0.3, 0.75)	0.35 (0.2, 0.5)	0.09 (0.05, 0.12)
75th percentile: 27.61 ng/mL	17.9 (17.3, 18.5)	18.7 (18.1, 19.3)	19.3 (18.6, 19.9)	0.81 (0.61, 1.01)	0.54 (0.4, 0.67)	0.13 (0.1, 0.17)
Δ (75th – 25th)	0.09 (-0.32, 0.51)	0.38 (-0.08, 0.83)	0.56 (0.05, 1.08)	0.28 (0.1, 0.46)	0.19 (0.07, 0.31)	0.05 (0.02, 0.08)
MiBP						
25th percentile: 1.5 ng/mL	17.8 (17.2, 18.4)	18.4 (17.7, 19.1)	18.8 (18.1, 19.5)	0.63 (0.41, 0.85)	0.42 (0.27, 0.57)	0.1 (0.07, 0.14)
75th percentile: 4.26 ng/mL	17.9 (17.3, 18.5)	18.7 (18.1, 19.3)	19.2 (18.5, 19.9)	0.76 (0.55, 0.97)	0.51 (0.37, 0.65)	0.13 (0.09, 0.16)
Δ (75th – 25th)	0.15 (-0.28, 0.58)	0.29 (-0.19, 0.76)	0.38 (-0.16, 0.92)	0.14 (-0.06, 0.33)	0.09 (-0.04, 0.22)	0.02 (-0.01, 0.06)
∑LMW phthalates[1]						
25th percentile: 0.26 nmol/mL	17.6 (16.9, 18.2)	18.1 (17.4, 18.7)	18.4 (17.6, 19.1)	0.48 (0.25, 0.7)	0.32 (0.17, 0.47)	0.08 (0.04, 0.12)
75th percentile: 0.94 nmol/mL	18 (17.4, 18.6)	18.8 (18.2, 19.4)	19.4 (18.7, 20)	0.83 (0.62, 1.03)	0.55 (0.42, 0.68)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.43 (-0.03, 0.89)	0.78 (0.28, 1.28)	1.01 (0.45, 1.57)	0.35 (0.15, 0.54)	0.23 (0.1, 0.36)	0.06 (0.03, 0.09)
MEHP						
25th percentile: 1.5 ng/mL	17.7 (17, 18.3)	18.2 (17.5, 18.9)	18.6 (17.8, 19.3)	0.54 (0.31, 0.77)	0.36 (0.21, 0.51)	0.09 (0.05, 0.13)
75th percentile: 6.04 ng/mL	18 (17.4, 18.6)	18.8 (18.2, 19.4)	19.3 (18.6, 20)	0.8 (0.6, 1.01)	0.53 (0.4, 0.67)	0.13 (0.1, 0.17)

	Predicted FM			Changes in FM		
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
Δ (75th – 25th)	0.3 (-0.14, 0.75)	0.56 (0.08, 1.05)	0.74 (0.19, 1.29)	0.26 (0.07, 0.46)	0.17 (0.05, 0.3)	0.04 (0.01, 0.08)
MEHHP						
25th percentile: 6.85 ng/mL	17.5 (16.9, 18.1)	18 (17.3, 18.6)	18.3 (17.6, 19)	0.46 (0.23, 0.69)	0.31 (0.16, 0.46)	0.08 (0.04, 0.11)
75th percentile: 26.6 ng/mL	18.1 (17.5, 18.7)	18.9 (18.3, 19.5)	19.5 (18.8, 20.2)	0.84 (0.64, 1.04)	0.56 (0.43, 0.7)	0.14 (0.11, 0.17)
Δ (75th – 25th)	0.56 (0.11, 1.01)	0.94 (0.45, 1.43)	1.2 (0.64, 1.75)	0.38 (0.18, 0.58)	0.25 (0.12, 0.38)	0.06 (0.03, 0.1)
MEOHP						
25th percentile: 4.19 ng/mL	17.6 (16.9, 18.2)	18 (17.4, 18.7)	18.3 (17.6, 19)	0.45 (0.23, 0.68)	0.3 (0.15, 0.45)	0.08 (0.04, 0.11)
75th percentile: 16 ng/mL	18.1 (17.5, 18.7)	18.9 (18.3, 19.5)	19.5 (18.8, 20.2)	0.85 (0.64, 1.05)	0.56 (0.43, 0.7)	0.14 (0.11, 0.17)
Δ (75th – 25th)	0.51 (0.06, 0.95)	0.9 (0.41, 1.39)	1.16 (0.61, 1.71)	0.39 (0.2, 0.59)	0.26 (0.13, 0.39)	0.07 (0.03, 0.1)
MECPP						
25th percentile: 8.43 ng/mL	17.5 (16.9, 18.2)	18 (17.4, 18.7)	18.4 (17.7, 19.1)	0.51 (0.28, 0.73)	0.34 (0.19, 0.49)	0.08 (0.05, 0.12)
75th percentile: 26.31 ng/mL	18.1 (17.5, 18.7)	18.9 (18.3, 19.5)	19.4 (18.8, 20.1)	0.81 (0.61, 1.01)	0.54 (0.41, 0.68)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.54 (0.12, 0.95)	0.84 (0.39, 1.29)	1.05 (0.54, 1.55)	0.31 (0.13, 0.49)	0.2 (0.08, 0.33)	0.05 (0.02, 0.08)
∑DEHP						
25th percentile: 0.08 nmol/mL	17.6 (16.9, 18.2)	18 (17.4, 18.7)	18.4 (17.6, 19.1)	0.48 (0.26, 0.71)	0.32 (0.17, 0.47)	0.08 (0.04, 0.12)
75th percentile: 0.26 nmol/mL	18.1 (17.5, 18.6)	18.9 (18.3, 19.5)	19.5 (18.8, 20.1)	0.83 (0.63, 1.03)	0.55 (0.42, 0.69)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.51 (0.08, 0.94)	0.86 (0.39, 1.32)	1.09 (0.56, 1.62)	0.35 (0.16, 0.54)	0.23 (0.11, 0.36)	0.06 (0.03, 0.09)
MBzP						

	Predicted FM			Changes in FM		
	T = 0 kg (95% CI)	**T = 6** kg (95% CI)	**T = 10** kg (95% CI)	**Δ (T6 – T0)** kg (95% CI)	**Δ (T10 – T6)** kg (95% CI)	**Δ per year** kg/year (95% CI)
25th percentile: 4.66 ng/mL	17.6 (17, 18.2)	18.1 (17.4, 18.7)	18.4 (17.7, 19.1)	0.47 (0.24, 0.69)	0.31 (0.16, 0.46)	0.08 (0.04, 0.11)
75th percentile: 15.64 ng/mL	18.1 (17.5, 18.7)	19 (18.3, 19.6)	19.6 (18.9, 20.2)	0.87 (0.67, 1.08)	0.58 (0.44, 0.72)	0.15 (0.11, 0.18)
Δ (75th – 25th)	0.48 (0.01, 0.94)	0.88 (0.37, 1.39)	1.15 (0.58, 1.73)	0.41 (0.2, 0.61)	0.27 (0.14, 0.41)	0.07 (0.03, 0.1)
MCOP						
25th percentile: 2.37 ng/mL	17.6 (16.9, 18.2)	18 (17.4, 18.7)	18.4 (17.7, 19.1)	0.49 (0.27, 0.72)	0.33 (0.18, 0.48)	0.08 (0.04, 0.12)
75th percentile: 6.63 ng/mL	18.1 (17.5, 18.7)	18.9 (18.3, 19.6)	19.5 (18.8, 20.2)	0.83 (0.63, 1.03)	0.55 (0.42, 0.69)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.56 (0.1, 1.01)	0.9 (0.4, 1.39)	1.13 (0.57, 1.68)	0.34 (0.15, 0.53)	0.23 (0.1, 0.36)	0.06 (0.02, 0.09)
MCNP						
25th percentile: 1.31 ng/mL	17.8 (17.2, 18.4)	18.5 (17.9, 19.2)	19 (18.3, 19.7)	0.71 (0.47, 0.94)	0.47 (0.32, 0.63)	0.12 (0.08, 0.16)
75th percentile: 4.07 ng/mL	17.9 (17.3, 18.5)	18.6 (18, 19.2)	19.1 (18.4, 19.8)	0.7 (0.5, 0.9)	0.47 (0.33, 0.6)	0.12 (0.08, 0.15)
Δ (75th – 25th)	0.11 (-0.32, 0.55)	0.11 (-0.37, 0.59)	0.11 (-0.44, 0.65)	0 (-0.19, 0.19)	0 (-0.13, 0.12)	0 (-0.03, 0.03)
MCPP						
25th percentile: 1.55 ng/mL	17.6 (17, 18.2)	18.1 (17.4, 18.7)	18.4 (17.7, 19.1)	0.49 (0.26, 0.71)	0.32 (0.17, 0.47)	0.08 (0.04, 0.12)
75th percentile: 4.07 ng/mL	18.2 (17.6, 18.8)	19 (18.4, 19.7)	19.6 (18.9, 20.3)	0.84 (0.64, 1.05)	0.56 (0.43, 0.7)	0.14 (0.11, 0.17)
Δ (75th – 25th)	0.62 (0.17, 1.07)	0.98 (0.49, 1.47)	1.22 (0.66, 1.78)	0.36 (0.16, 0.55)	0.24 (0.11, 0.37)	0.06 (0.03, 0.09)
∑HMW phthalates						
25th percentile: 0.04 nmol/mL	17.6 (16.9, 18.2)	18 (17.4, 18.7)	18.3 (17.6, 19.1)	0.46 (0.23, 0.69)	0.31 (0.15, 0.46)	0.08 (0.04, 0.12)
75th percentile: 0.12 nmol/mL	18.1 (17.5, 18.7)	19 (18.4, 19.6)	19.6 (18.9, 20.3)	0.85 (0.65, 1.06)	0.57 (0.43, 0.7)	0.14 (0.11, 0.18)
Δ (75th – 25th)	0.58 (0.08, 1.08)	0.97 (0.43, 1.52)	1.24 (0.62, 1.85)	0.39 (0.18, 0.6)	0.26 (0.12, 0.4)	0.07 (0.03, 0.1)

[1] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.10 Predicted 10-year body fat percentage trajectories for normal/underweight women at the 25th and 75th percentiles of each phthalate metabolite

	Predicted BF%			Changes in BF%		
	T = 0 % or percentage point (95% CI)	**T = 6** % or percentage point (95% CI)	**T = 10** % or percentage point (95% CI)	**Δ (T6 – T0)** percentage point (95% CI)	**Δ (T10 – T6)** percentage point (95% CI)	**Δ per year** percentage point/year (95% CI)
MEP						
25th percentile: 33.16 ng/mL	34.5 (33.7, 35.3)	35 (34.2, 35.8)	35.3 (34.5, 36.1)	0.49 (0.27, 0.71)	0.33 (0.18, 0.48)	0.08 (0.05, 0.12)
75th percentile: 148.83 ng/mL	35 (34.3, 35.7)	35.7 (35, 36.4)	36.2 (35.5, 37)	0.75 (0.55, 0.95)	0.5 (0.36, 0.63)	0.12 (0.09, 0.16)
Δ (75th – 25th)	0.48 (-0.09, 1.05)	0.74 (0.16, 1.31)	0.91 (0.3, 1.52)	0.25 (0.06, 0.45)	0.17 (0.04, 0.3)	0.04 (0.01, 0.07)
MnBP						
25th percentile: 10.42 ng/mL	34.7 (34, 35.5)	35.2 (34.5, 36)	35.6 (34.8, 36.3)	0.5 (0.28, 0.71)	0.33 (0.19, 0.48)	0.08 (0.05, 0.12)
75th percentile: 27.61 ng/mL	34.9 (34.2, 35.6)	35.6 (34.9, 36.3)	36.1 (35.4, 36.8)	0.74 (0.54, 0.94)	0.49 (0.36, 0.62)	0.12 (0.09, 0.16)
Δ (75th – 25th)	0.15 (-0.35, 0.64)	0.39 (-0.11, 0.89)	0.55 (0.02, 1.08)	0.24 (0.07, 0.42)	0.16 (0.05, 0.28)	0.04 (0.01, 0.07)
MiBP						
25th percentile: 1.5 ng/mL	34.7 (34, 35.5)	35.3 (34.6, 36.1)	35.7 (34.9, 36.5)	0.59 (0.38, 0.8)	0.39 (0.25, 0.54)	0.1 (0.06, 0.13)
75th percentile: 4.26 ng/mL	34.9 (34.2, 35.6)	35.6 (34.9, 36.3)	36 (35.3, 36.8)	0.7 (0.5, 0.91)	0.47 (0.33, 0.6)	0.12 (0.08, 0.15)
Δ (75th – 25th)	0.13 (-0.39, 0.65)	0.24 (-0.28, 0.76)	0.31 (-0.25, 0.88)	0.11 (-0.08, 0.3)	0.07 (-0.05, 0.2)	0.02 (-0.01, 0.05)
∑LMW phthalates[1]						
25th percentile: 0.26 nmol/mL	34.5 (33.7, 35.3)	35 (34.2, 35.8)	35.3 (34.5, 36.1)	0.48 (0.26, 0.7)	0.32 (0.17, 0.46)	0.08 (0.04, 0.12)
75th percentile: 0.94 nmol/mL	35 (34.3, 35.7)	35.7 (35, 36.4)	36.2 (35.5, 36.9)	0.75 (0.55, 0.95)	0.5 (0.37, 0.63)	0.12 (0.09, 0.16)

	Predicted BF%			Changes in BF%		
	T = 0 % or percentage point (95% CI)	**T = 6** % or percentage point (95% CI)	**T = 10** % or percentage point (95% CI)	**Δ (T6 – T0)** percentage point (95% CI)	**Δ (T10 – T6)** percentage point (95% CI)	**Δ per year** percentage point/year (95% CI)
Δ (75th – 25th)	0.46 (-0.09, 1.01)	0.73 (0.18, 1.29)	0.91 (0.33, 1.5)	0.27 (0.09, 0.46)	0.18 (0.06, 0.31)	0.05 (0.01, 0.08)
MEHP						
25th percentile: 1.5 ng/mL	34.7 (33.9, 35.4)	35.2 (34.4, 36)	35.6 (34.8, 36.3)	0.53 (0.31, 0.75)	0.35 (0.21, 0.5)	0.09 (0.05, 0.13)
75th percentile: 6.04 ng/mL	34.9 (34.2, 35.6)	35.6 (34.9, 36.3)	36.1 (35.4, 36.8)	0.72 (0.52, 0.92)	0.48 (0.35, 0.62)	0.12 (0.09, 0.15)
Δ (75th – 25th)	0.24 (-0.3, 0.78)	0.43 (-0.11, 0.97)	0.56 (-0.01, 1.14)	0.19 (0.01, 0.38)	0.13 (0, 0.25)	0.03 (0, 0.06)
MEHHP						
25th percentile: 6.85 ng/mL	34.5 (33.8, 35.3)	35 (34.2, 35.7)	35.3 (34.5, 36.1)	0.47 (0.25, 0.69)	0.31 (0.16, 0.46)	0.08 (0.04, 0.11)
75th percentile: 26.6 ng/mL	35 (34.3, 35.7)	35.8 (35.1, 36.5)	36.3 (35.5, 37)	0.76 (0.56, 0.96)	0.5 (0.37, 0.64)	0.13 (0.09, 0.16)
Δ (75th – 25th)	0.48 (-0.06, 1.02)	0.77 (0.23, 1.31)	0.96 (0.38, 1.54)	0.29 (0.1, 0.48)	0.19 (0.07, 0.32)	0.05 (0.02, 0.08)
MEOHP						
25th percentile: 4.19 ng/mL	34.6 (33.9, 35.3)	35 (34.3, 35.8)	35.3 (34.6, 36.1)	0.45 (0.23, 0.67)	0.3 (0.15, 0.45)	0.08 (0.04, 0.11)
75th percentile: 16 ng/mL	35 (34.3, 35.7)	35.8 (35.1, 36.5)	36.3 (35.5, 37)	0.77 (0.57, 0.96)	0.51 (0.38, 0.64)	0.13 (0.09, 0.16)
Δ (75th – 25th)	0.4 (-0.13, 0.94)	0.72 (0.18, 1.26)	0.93 (0.35, 1.5)	0.31 (0.12, 0.5)	0.21 (0.08, 0.33)	0.05 (0.02, 0.08)
MECPP						
25th percentile: 8.43 ng/mL	34.6 (33.8, 35.3)	35.1 (34.3, 35.8)	35.4 (34.6, 36.2)	0.5 (0.28, 0.72)	0.33 (0.19, 0.48)	0.08 (0.05, 0.12)
75th percentile: 26.31 ng/mL	35 (34.3, 35.7)	35.7 (35, 36.4)	36.2 (35.5, 37)	0.74 (0.54, 0.93)	0.49 (0.36, 0.62)	0.12 (0.09, 0.16)
Δ (75th – 25th)	0.42 (-0.08, 0.91)	0.65 (0.16, 1.15)	0.81 (0.28, 1.34)	0.24 (0.06, 0.41)	0.16 (0.04, 0.27)	0.04 (0.01, 0.07)

	Predicted BF%			Changes in BF%		
	T = 0 % or percentage point (95% CI)	**T = 6** % or percentage point (95% CI)	**T = 10** % or percentage point (95% CI)	**Δ (T6 – T0)** percentage point (95% CI)	**Δ (T10 – T6)** percentage point (95% CI)	**Δ per year** percentage point/year (95% CI)
∑DEHP						
25th percentile: 0.08 nmol/mL	34.6 (33.8, 35.3)	35.1 (34.3, 35.8)	35.4 (34.6, 36.2)	0.48 (0.27, 0.7)	0.32 (0.18, 0.47)	0.08 (0.04, 0.12)
75th percentile: 0.26 nmol/mL	35 (34.3, 35.7)	35.7 (35, 36.4)	36.2 (35.5, 37)	0.75 (0.55, 0.95)	0.5 (0.37, 0.63)	0.12 (0.09, 0.16)
Δ (75th – 25th)	0.41 (-0.11, 0.93)	0.67 (0.16, 1.19)	0.85 (0.3, 1.4)	0.26 (0.08, 0.45)	0.18 (0.06, 0.3)	0.04 (0.01, 0.07)
MBzP						
25th percentile: 4.66 ng/mL	34.6 (33.9, 35.3)	35 (34.3, 35.7)	35.3 (34.5, 36.1)	0.42 (0.21, 0.64)	0.28 (0.14, 0.43)	0.07 (0.03, 0.11)
75th percentile: 15.64 ng/mL	35.1 (34.3, 35.8)	35.9 (35.2, 36.6)	36.4 (35.7, 37.2)	0.81 (0.61, 1.01)	0.54 (0.41, 0.68)	0.14 (0.1, 0.17)
Δ (75th – 25th)	0.48 (-0.08, 1.04)	0.87 (0.31, 1.43)	1.13 (0.53, 1.73)	0.39 (0.19, 0.58)	0.26 (0.13, 0.39)	0.06 (0.03, 0.1)
MCOP						
25th percentile: 2.37 ng/mL	34.6 (33.9, 35.4)	35.1 (34.4, 35.8)	35.4 (34.6, 36.2)	0.48 (0.26, 0.7)	0.32 (0.17, 0.47)	0.08 (0.04, 0.12)
75th percentile: 6.63 ng/mL	35 (34.3, 35.7)	35.7 (35, 36.5)	36.2 (35.5, 37)	0.75 (0.55, 0.95)	0.5 (0.37, 0.63)	0.13 (0.09, 0.16)
Δ (75th – 25th)	0.36 (-0.18, 0.91)	0.64 (0.09, 1.19)	0.82 (0.24, 1.4)	0.27 (0.09, 0.46)	0.18 (0.06, 0.31)	0.05 (0.01, 0.08)
MCNP						
25th percentile: 1.31 ng/mL	34.8 (34.1, 35.5)	35.5 (34.7, 36.2)	35.9 (35.1, 36.7)	0.67 (0.44, 0.89)	0.44 (0.29, 0.59)	0.11 (0.07, 0.15)
75th percentile: 4.07 ng/mL	34.8 (34.1, 35.6)	35.5 (34.8, 36.2)	35.9 (35.2, 36.7)	0.64 (0.45, 0.84)	0.43 (0.3, 0.56)	0.11 (0.07, 0.14)
Δ (75th – 25th)	0.05 (-0.47, 0.58)	0.03 (-0.5, 0.56)	0.02 (-0.55, 0.58)	-0.02 (-0.2, 0.16)	-0.01 (-0.13, 0.11)	0 (-0.03, 0.03)
MCPP						
25th percentile: 1.55 ng/mL	34.5 (33.8, 35.2)	35 (34.3, 35.7)	35.3 (34.6, 36.1)	0.47 (0.26, 0.69)	0.32 (0.17, 0.46)	0.08 (0.04, 0.12)

	Predicted BF%			Changes in BF%		
	T = 0 % or percentage point (95% CI)	**T = 6** % or percentage point (95% CI)	**T = 10** % or percentage point (95% CI)	**Δ (T6 – T0)** percentage point (95% CI)	**Δ (T10 – T6)** percentage point (95% CI)	**Δ per year** percentage point/year (95% CI)
75th percentile: 4.07 ng/mL	35.2 (34.5, 35.9)	35.9 (35.2, 36.7)	36.4 (35.7, 37.2)	0.77 (0.57, 0.97)	0.51 (0.38, 0.64)	0.13 (0.09, 0.16)
Δ (75th – 25th)	0.64 (0.1, 1.19)	0.94 (0.39, 1.48)	1.13 (0.55, 1.71)	0.29 (0.1, 0.48)	0.19 (0.07, 0.32)	0.05 (0.02, 0.08)
∑HMW phthalates						
25th percentile: 0.04 nmol/mL	34.5 (33.8, 35.2)	35 (34.2, 35.7)	35.3 (34.5, 36)	0.45 (0.22, 0.67)	0.3 (0.15, 0.45)	0.07 (0.04, 0.11)
75th percentile: 0.12 nmol/mL	35.1 (34.4, 35.8)	35.9 (35.2, 36.6)	36.4 (35.7, 37.2)	0.77 (0.57, 0.97)	0.52 (0.38, 0.65)	0.13 (0.1, 0.16)
Δ (75th – 25th)	0.61 (0.01, 1.22)	0.94 (0.34, 1.54)	1.16 (0.52, 1.8)	0.33 (0.12, 0.53)	0.22 (0.08, 0.35)	0.05 (0.02, 0.09)

[1] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.11 Associations between phthalate metabolites in 2002/2003 and body weight

	For each doubling of metabolite concentration …		
	Difference in body weight at baseline[1] (95% CI) (kg)	**Difference in the five-year change in body weight** (95% CI) (kg)	
		T ≤ 3 years[2]	**T > 3 years**
All women (N = 1290)			
MEP	0.44 (-0.11, 1.00)	0.04 (-0.26, 0.35)	-0.01 (-0.15, 0.13)
MnBP	0.21 (-0.65, 1.07)	0.46 (-0.01, 0.93)	-0.00 (-0.22, 0.21)
MiBP	**0.93 (0.07, 1.78)**[3]	0.15 (-0.33, 0.62)	-0.03 (-0.25, 0.19)
∑LMW phthalates[4]	0.48 (-0.18, 1.15)	0.11 (-0.26, 0.48)	-0.04 (-0.21, 0.13)
MEHP	-0.17 (-0.76, 0.41)	-0.06 (-0.38, 0.26)	-0.00 (-0.15, 0.15)
MEHHP	**1.18 (0.56, 1.80)**	-0.19 (-0.53, 0.15)	-0.07 (-0.23, 0.09)
MEOHP	**1.17 (0.54, 1.79)**	-0.20 (-0.54, 0.15)	-0.06 (-0.22, 0.10)
MECPP	**1.56 (0.90, 2.22)**	-0.29 (-0.65, 0.08)	-0.08 (-0.25, 0.09)
∑DEHP	**1.30 (0.65, 1.95)**	-0.24 (-0.59, 0.12)	-0.07 (-0.24, 0.09)
MBzP	**1.47 (0.72, 2.22)**	-0.30 (-0.71, 0.12)	-0.01 (-0.21, 0.18)
MCOP	**1.80 (1.07, 2.53)**	-0.37 (-0.78, 0.04)	-0.11 (-0.30, 0.08)
MCNP	**1.95 (1.26, 2.64)**	-0.07 (-0.45, 0.32)	-0.16 (-0.34, 0.02)
MCPP	**1.59 (0.64, 2.55)**	0.01 (-0.52, 0.55)	-0.20 (-0.45, 0.05)
∑HMW phthalates	**2.20 (1.31, 3.10)**	-0.20 (-0.70, 0.30)	-0.15 (-0.38, 0.09)
Normal/underweight (N = 471)			
MEP	0.13 (-0.18, 0.44)	0.25 (-0.08, 0.58)	0.05 (-0.10, 0.20)
MnBP	-0.10 (-0.56, 0.35)	0.43 (-0.04, 0.90)	-0.07 (-0.29, 0.14)
MiBP	-0.23 (-0.68, 0.23)	0.33 (-0.15, 0.81)	0.06 (-0.15, 0.28)
∑LMW phthalates	0.12 (-0.26, 0.50)	0.38 (-0.03, 0.78)	0.02 (-0.16, 0.20)
MEHP	0.19 (-0.12, 0.51)	0.11 (-0.23, 0.45)	-0.08 (-0.24, 0.07)
MEHHP	0.25 (-0.08, 0.59)	0.11 (-0.24, 0.47)	0.01 (-0.15, 0.17)
MEOHP	0.26 (-0.08, 0.60)	0.09 (-0.27, 0.45)	0.01 (-0.15, 0.18)
MECPP	0.32 (-0.04, 0.68)	0.19 (-0.19, 0.58)	-0.01 (-0.19, 0.16)
∑DEHP	0.29 (-0.07, 0.64)	0.13 (-0.24, 0.50)	-0.01 (-0.18, 0.16)
MBzP	0.08 (-0.32, 0.48)	0.06 (-0.37, 0.49)	0.04 (-0.15, 0.24)
MCOP	0.18 (-0.21, 0.56)	0.40 (-0.02, 0.81)	-0.11 (-0.29, 0.08)
MCNP	0.34 (-0.04, 0.73)	0.31 (-0.11, 0.72)	-0.07 (-0.26, 0.11)
MCPP	-0.15 (-0.66, 0.37)	0.43 (-0.11, 0.98)	-0.09 (-0.34, 0.15)
∑HMW phthalates	0.18 (-0.29, 0.66)	0.28 (-0.23, 0.80)	-0.09 (-0.32, 0.14)
Overweight (N = 373)			
MEP	-0.05 (-0.44, 0.33)	0.26 (-0.23, 0.75)	-0.01 (-0.23, 0.20)

	For each doubling of metabolite concentration …		
	Difference in body weight at baseline[1] (95% CI) (kg)	**Difference in the five-year change in body weight** (95% CI) (kg)	
		T ≤ 3 years[2]	**T > 3 years**
MnBP	-0.39 (-0.98, 0.20)	0.62 (-0.13, 1.36)	0.12 (-0.21, 0.44)
MiBP	0.08 (-0.50, 0.67)	0.12 (-0.63, 0.86)	-0.01 (-0.34, 0.32)
∑LMW phthalates	-0.19 (-0.65, 0.27)	0.37 (-0.22, 0.95)	-0.05 (-0.30, 0.21)
MEHP	-0.02 (-0.44, 0.40)	-0.18 (-0.69, 0.34)	0.08 (-0.14, 0.31)
MEHHP	0.04 (-0.41, 0.48)	-0.22 (-0.77, 0.34)	0.14 (-0.10, 0.39)
MEOHP	0.07 (-0.38, 0.51)	-0.18 (-0.73, 0.38)	0.12 (-0.12, 0.37)
MECPP	0.17 (-0.30, 0.64)	-0.21 (-0.80, 0.38)	0.18 (-0.08, 0.44)
∑DEHP	0.10 (-0.37, 0.56)	-0.21 (-0.78, 0.37)	0.16 (-0.10, 0.41)
MBzP	-0.51 (-1.01, -0.00)	-0.37 (-1.01, 0.27)	0.07 (-0.21, 0.35)
MCOP	**0.66 (0.13, 1.19)**	**-0.91 (-1.58, -0.24)**	0.23 (-0.06, 0.53)
MCNP	0.20 (-0.27, 0.68)	-0.19 (-0.78, 0.39)	**0.26 (0.00, 0.51)**
MCPP	0.27 (-0.43, 0.97)	-0.56 (-1.43, 0.31)	0.04 (-0.34, 0.42)
∑HMW phthalates	0.03 (-0.60, 0.67)	-0.64 (-1.42, 0.14)	0.26 (-0.08, 0.60)
Obese (N = 446)			
MEP	0.81 (-0.05, 1.67)	-0.26 (-0.94, 0.42)	-0.03 (-0.35, 0.30)
MnBP	0.35 (-1.10, 1.80)	0.44 (-0.69, 1.58)	0.05 (-0.49, 0.60)
MiBP	1.14 (-0.28, 2.56)	0.17 (-0.96, 1.30)	-0.09 (-0.63, 0.44)
∑LMW phthalates	0.98 (-0.04, 2.00)	-0.25 (-1.07, 0.56)	-0.06 (-0.45, 0.32)
MEHP	-0.25 (-1.17, 0.68)	-0.21 (-0.95, 0.52)	0.03 (-0.32, 0.38)
MEHHP	0.84 (-0.15, 1.84)	-0.39 (-1.18, 0.40)	-0.20 (-0.58, 0.18)
MEOHP	0.89 (-0.10, 1.89)	-0.41 (-1.19, 0.38)	-0.16 (-0.53, 0.22)
MECPP	**1.18 (0.12, 2.24)**	-0.73 (-1.57, 0.11)	-0.18 (-0.59, 0.22)
∑DEHP	0.97 (-0.07, 2.01)	-0.54 (-1.36, 0.29)	-0.18 (-0.58, 0.21)
MBzP	0.77 (-0.56, 2.10)	-0.30 (-1.33, 0.73)	0.04 (-0.46, 0.55)
MCOP	**1.56 (0.35, 2.77)**	-0.56 (-1.51, 0.38)	-0.23 (-0.68, 0.22)
MCNP	**2.43 (1.34, 3.53)**	-0.24 (-1.13, 0.64)	**-0.49 (-0.92, -0.07)**
MCPP	**1.98 (0.44, 3.52)**	0.20 (-1.02, 1.43)	-0.34 (-0.93, 0.26)
∑HMW phthalates	**2.10 (0.58, 3.62)**	-0.02 (-1.23, 1.18)	-0.37 (-0.96, 0.22)

[1] For each phthalate metabolite, difference in body weight at baseline and differences in the rates of change in body weight were estimated from a mixed effects model that predicted body weight with the metabolite in 2002/2003 (log_2-transformed), linear spline for time, and the interaction between the metabolite and both terms for time. This model was additionally adjusted for age at baseline (2002/2003), race/ethnicity, the interaction between race/ethnicity and both terms for time, site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and both terms for time were also included. Models were run for all women and by baseline obesity status.

[2] "T ≤ 3 years" means "within the first three years of follow-up". "T > 3 years" means "after the first three years of follow-up".

[3] Bold: p-value < 0.05.

[4] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.12 Associations between phthalate metabolites in 2002/2003 and fat mass

	For each doubling of metabolite concentration…	
	Difference in fat mass at baseline[1] (95% CI) (kg)	**Difference in the five-year change in fat mass** (95% CI) (kg)
All women (N = 1254)		
MEP	**0.35 (0.02, 0.68)**[2]	0.00 (-0.07, 0.08)
MnBP	0.29 (-0.23, 0.81)	0.05 (-0.07, 0.17)
MiBP	**0.56 (0.05, 1.08)**	0.02 (-0.11, 0.14)
∑LMW phthalates[3]	**0.42 (0.02, 0.82)**	-0.01 (-0.10, 0.08)
MEHP	-0.20 (-0.55, 0.16)	-0.00 (-0.08, 0.08)
MEHHP	**0.58 (0.21, 0.96)**	-0.05 (-0.14, 0.04)
MEOHP	**0.57 (0.20, 0.95)**	-0.05 (-0.13, 0.04)
MECPP	**0.79 (0.39, 1.19)**	-0.07 (-0.17, 0.02)
∑DEHP	**0.64 (0.24, 1.03)**	-0.06 (-0.15, 0.04)
MBzP	**1.03 (0.58, 1.48)**	-0.04 (-0.15, 0.06)
MCOP	**0.89 (0.45, 1.33)**	-0.06 (-0.17, 0.04)
MCNP	**0.97 (0.55, 1.38)**	-0.01 (-0.10, 0.09)
MCPP	**0.72 (0.15, 1.30)**	-0.02 (-0.15, 0.12)
∑HMW phthalates	**1.37 (0.83, 1.90)**	-0.06 (-0.19, 0.07)
Normal/underweight (N = 463)		
MEP	0.18 (-0.03, 0.39)	**0.11 (0.02, 0.20)**
MnBP	0.04 (-0.27, 0.34)	0.07 (-0.07, 0.21)
MiBP	-0.19 (-0.50, 0.12)	**0.16 (0.02, 0.30)**
∑LMW phthalates	0.20 (-0.06, 0.46)	**0.14 (0.02, 0.25)**
MEHP	0.03 (-0.19, 0.25)	0.05 (-0.05, 0.15)
MEHHP	0.08 (-0.15, 0.31)	0.10 (-0.01, 0.20)
MEOHP	0.06 (-0.17, 0.29)	0.10 (-0.01, 0.21)
MECPP	0.11 (-0.13, 0.36)	0.10 (-0.02, 0.21)
∑DEHP	0.09 (-0.15, 0.33)	0.10 (-0.01, 0.21)
MBzP	0.26 (-0.01, 0.53)	0.09 (-0.04, 0.21)
MCOP	0.18 (-0.09, 0.44)	0.05 (-0.07, 0.16)
MCNP	0.17 (-0.09, 0.44)	0.10 (-0.02, 0.22)
MCPP	0.03 (-0.32, 0.37)	0.11 (-0.05, 0.26)
∑HMW phthalates	0.29 (-0.03, 0.62)	0.08 (-0.07, 0.22)
Overweight (N = 364)		
MEP	0.12 (-0.14, 0.37)	0.02 (-0.10, 0.13)

	For each doubling of metabolite concentration…	
	Difference in fat mass at baseline[1] (95% CI) (kg)	**Difference in the five-year change in fat mass** (95% CI) (kg)
MnBP	-0.20 (-0.58, 0.19)	0.11 (-0.07, 0.30)
MiBP	-0.04 (-0.43, 0.34)	0.03 (-0.16, 0.22)
∑LMW phthalates	0.07 (-0.23, 0.38)	0.00 (-0.14, 0.14)
MEHP	-0.27 (-0.54, 0.00)	0.01 (-0.12, 0.13)
MEHHP	-0.26 (-0.55, 0.03)	0.05 (-0.08, 0.18)
MEOHP	-0.22 (-0.51, 0.07)	0.04 (-0.09, 0.18)
MECPP	-0.19 (-0.49, 0.12)	0.07 (-0.07, 0.21)
∑DEHP	-0.23 (-0.53, 0.07)	0.06 (-0.09, 0.20)
MBzP	-0.19 (-0.53, 0.15)	-0.03 (-0.19, 0.13)
MCOP	0.02 (-0.33, 0.38)	0.04 (-0.13, 0.21)
MCNP	0.03 (-0.29, 0.34)	**0.17 (0.03, 0.31)**
MCPP	0.00 (-0.45, 0.46)	0.02 (-0.20, 0.23)
∑HMW phthalates	-0.06 (-0.48, 0.36)	0.08 (-0.11, 0.27)
Obese (N = 427)		
MEP	**0.57 (0.08, 1.06)**	-0.06 (-0.22, 0.10)
MnBP	0.41 (-0.44, 1.26)	0.05 (-0.25, 0.35)
MiBP	0.81 (-0.02, 1.63)	-0.07 (-0.35, 0.22)
∑LMW phthalates	**0.70 (0.12, 1.29)**	-0.08 (-0.27, 0.12)
MEHP	-0.15 (-0.70, 0.40)	-0.02 (-0.21, 0.17)
MEHHP	0.47 (-0.12, 1.06)	-0.18 (-0.38, 0.03)
MEOHP	0.51 (-0.08, 1.10)	-0.17 (-0.37, 0.04)
MECPP	0.63 (-0.00, 1.25)	**-0.24 (-0.46, -0.02)**
∑DEHP	0.53 (-0.09, 1.15)	-0.20 (-0.41, 0.02)
MBzP	0.57 (-0.20, 1.34)	0.01 (-0.26, 0.28)
MCOP	0.52 (-0.18, 1.23)	-0.11 (-0.35, 0.14)
MCNP	**1.18 (0.55, 1.81)**	-0.19 (-0.41, 0.03)
MCPP	0.69 (-0.22, 1.60)	-0.04 (-0.36, 0.27)
∑HMW phthalates	**1.25 (0.38, 2.13)**	-0.11 (-0.42, 0.20)

[1] For each phthalate metabolite, difference at baseline and difference in rate of change were estimated from a mixed effects model that predicted fat mass with the metabolite in 2002/2003 (log_2-transformed), time, and their interaction. This model was additionally adjusted for age at baseline (2002/2003), race/ethnicity, site, the interaction between time and site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and time were also included. Models were run for all women and by baseline obesity status.

[2] Bold: p-value < 0.05.

[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 2.13 Associations between phthalate metabolites in 2002/2003 and body fat percentage

	For each doubling of metabolite concentration…	
	Difference in body fat percentage at baseline[1] (95% CI) (Percentage point)	**Difference in the five-year change in body fat percentage** (95% CI) (Percentage point)
All women (N = 1254)		
MEP	**0.28 (0.08, 0.48)**[2]	0.02 (-0.03, 0.07)
MnBP	0.29 (-0.03, 0.60)	0.03 (-0.06, 0.11)
MiBP	0.18 (-0.13, 0.49)	0.04 (-0.04, 0.12)
∑LMW phthalates[3]	**0.35 (0.11, 0.59)**	0.02 (-0.04, 0.08)
MEHP	-0.17 (-0.39, 0.04)	0.02 (-0.03, 0.08)
MEHHP	0.21 (-0.02, 0.44)	-0.01 (-0.07, 0.05)
MEOHP	0.20 (-0.03, 0.42)	-0.01 (-0.07, 0.05)
MECPP	**0.30 (0.06, 0.54)**	-0.02 (-0.09, 0.04)
∑DEHP	0.23 (-0.01, 0.46)	-0.02 (-0.08, 0.05)
MBzP	**0.65 (0.38, 0.92)**	-0.03 (-0.10, 0.04)
MCOP	**0.39 (0.12, 0.65)**	-0.02 (-0.09, 0.05)
MCNP	**0.34 (0.09, 0.59)**	0.04 (-0.03, 0.10)
MCPP	0.30 (-0.04, 0.65)	0.00 (-0.09, 0.09)
∑HMW phthalates	**0.69 (0.37, 1.01)**	-0.03 (-0.11, 0.06)
Normal/underweight (N = 463)		
MEP	0.23 (-0.04, 0.50)	0.09 (-0.00, 0.18)
MnBP	0.07 (-0.33, 0.46)	0.05 (-0.08, 0.18)
MiBP	-0.23 (-0.63, 0.16)	**0.16 (0.02, 0.30)**
∑LMW phthalates	0.27 (-0.06, 0.60)	0.11 (-0.00, 0.22)
MEHP	-0.08 (-0.36, 0.20)	0.05 (-0.05, 0.15)
MEHHP	0.00 (-0.29, 0.29)	0.07 (-0.03, 0.18)
MEOHP	-0.04 (-0.33, 0.26)	0.08 (-0.03, 0.18)
MECPP	-0.01 (-0.33, 0.31)	0.07 (-0.04, 0.18)
∑DEHP	-0.02 (-0.33, 0.29)	0.07 (-0.04, 0.18)
MBzP	**0.39 (0.05, 0.74)**	0.05 (-0.08, 0.17)
MCOP	0.14 (-0.20, 0.48)	0.02 (-0.09, 0.14)
MCNP	0.01 (-0.33, 0.34)	0.11 (-0.00, 0.22)
MCPP	0.03 (-0.41, 0.47)	0.07 (-0.08, 0.22)
∑HMW phthalates	0.35 (-0.06, 0.76)	0.03 (-0.11, 0.18)
Overweight (N = 364)		
MEP	0.16 (-0.07, 0.39)	0.01 (-0.08, 0.09)

	For each doubling of metabolite concentration…	
	Difference in body fat percentage at baseline[1] (95% CI) (Percentage point)	**Difference in the five-year change in body fat percentage** (95% CI) (Percentage point)
MnBP	-0.14 (-0.49, 0.22)	0.05 (-0.09, 0.18)
MiBP	-0.14 (-0.50, 0.21)	-0.01 (-0.15, 0.13)
∑LMW phthalates	0.15 (-0.13, 0.43)	-0.00 (-0.10, 0.10)
MEHP	**-0.37 (-0.61, -0.12)**	0.02 (-0.08, 0.11)
MEHHP	**-0.36 (-0.63, -0.10)**	0.03 (-0.07, 0.13)
MEOHP	**-0.32 (-0.59, -0.06)**	0.02 (-0.08, 0.12)
MECPP	**-0.31 (-0.59, -0.03)**	0.04 (-0.07, 0.14)
∑DEHP	**-0.35 (-0.63, -0.08)**	0.03 (-0.07, 0.13)
MBzP	-0.03 (-0.34, 0.28)	-0.04 (-0.16, 0.08)
MCOP	-0.19 (-0.51, 0.14)	0.02 (-0.10, 0.14)
MCNP	0.01 (-0.28, 0.29)	**0.13 (0.03, 0.23)**
MCPP	-0.06 (-0.48, 0.36)	0.04 (-0.12, 0.19)
∑HMW phthalates	-0.10 (-0.48, 0.29)	0.06 (-0.08, 0.20)
Obese (N = 427)		
MEP	**0.32 (0.09, 0.55)**	-0.02 (-0.09, 0.06)
MnBP	**0.53 (0.13, 0.93)**	0.01 (-0.13, 0.16)
MiBP	0.38 (-0.01, 0.77)	-0.01 (-0.15, 0.13)
∑LMW phthalates	**0.43 (0.15, 0.70)**	-0.02 (-0.11, 0.07)
MEHP	0.03 (-0.23, 0.30)	0.02 (-0.07, 0.11)
MEHHP	0.23 (-0.05, 0.51)	-0.08 (-0.18, 0.02)
MEOHP	0.26 (-0.02, 0.54)	-0.07 (-0.17, 0.02)
MECPP	**0.31 (0.01, 0.61)**	-0.10 (-0.21, 0.00)
∑DEHP	0.27 (-0.03, 0.56)	-0.09 (-0.19, 0.02)
MBzP	0.30 (-0.06, 0.67)	-0.00 (-0.13, 0.13)
MCOP	0.18 (-0.16, 0.51)	-0.01 (-0.13, 0.11)
MCNP	0.26 (-0.05, 0.56)	-0.08 (-0.19, 0.02)
MCPP	0.25 (-0.18, 0.69)	-0.05 (-0.21, 0.10)
∑HMW phthalates	**0.46 (0.04, 0.88)**	-0.05 (-0.20, 0.10)

[1] For each phthalate metabolite, difference at baseline and difference in rate of change were estimated from a mixed effects model that predicted percent body fat with the metabolite in 2002/2003 (log_2-transformed), time, and their interaction. This model was additionally adjusted for age at baseline (2002/2003), race/ethnicity, site, the interaction between time and site, education level, daily dietary energy intake at baseline, and time-varying physical activity, smoking status, menopausal status, and use of hormone therapy. Random effects for intercept and time were also included. Models were run for all women and by baseline obesity status.
[2] Bold: p-value < 0.05.
[3] ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Chapter 3 Phthalates and Adipokines in Midlife Women: A Cross-sectional Study in the Study of Women's Health Across the Nation (SWAN)

3.1 Abstract

Background

Phthalates are associated with obesity and its metabolic complications, but the mechanisms are not well-understood. We examined if phthalate exposure was associated with adverse adipokine profiles, a potential mechanism of metabolic disturbance.

Methods

In 1250 midlife women in the Study of Women's Health Across the Nation (SWAN), we measured 11 phthalate metabolites in spot urine samples and leptin and high-molecular-weight (HMW) adiponectin in fasting blood samples from 2002/2003. We used linear regression to examine the association between each hydration-adjusted metabolite and log-transformed leptin, HMW adiponectin, and the leptin:HMW adiponectin ratio, adjusting for demographic, lifestyle, and menopause-related factors. Additionally, we used Bayesian kernel machine regression (BKMR) to examine the joint associations between the phthalate metabolite mixture and adipokines.

Results

In single-pollutant models adjusted for all covariates except body mass index (BMI), most phthalate metabolites were positively associated with leptin. Mono(2-ethylhexyl) phthalate (MEHP) was positively associated with HMW adiponectin and inversely associated with the leptin:HMW adiponectin ratio. Adjustment for BMI attenuated all associations with leptin, with statistically significant linear trends remaining for mono(2-ethyl-5-oxohexyl) phthalate only. MEHP remained robustly associated with higher HMW adiponectin and a lower leptin:HMW adiponectin ratio after BMI adjustment. Compared to the 1st quartile, the 2nd to 4th quartiles of MEHP were associated with -16.9% (95% confidence interval (CI): -29.1, -2.6), -24.0% (-35.2, -10.8), and -17.7% (-30.2, -3.1) lower leptin:HMW adiponectin ratio. BKMR revealed a statistically significant, positive association between the phthalate metabolite mixture and HMW adiponectin and identified MEHP as the most important metabolite.

Conclusions

Phthalates were positively associated with leptin, but the associations were attenuated with BMI adjustment. MEHP was associated with higher HMW adiponectin and a lower leptin:HMW adiponectin ratio regardless of BMI adjustment, suggesting a more beneficial adipokine profile. The apparent difference between these findings and phthalates' associations with metabolic diseases calls for further investigations on phthalates' potential metabolism-disrupting mechanisms.

3.2 Introduction

Over the past century, the prevalence of obesity and its cardiometabolic complications has increased dramatically (1,2). This increase has coincided with the widespread use of many synthetic chemicals in industry and commerce, leading to the hypothesis that synthetic chemicals may cause obesity and related metabolic disorders (3,4).

Phthalates, di-esters of 1,2-benzenedicarboxylic acid, are among the chemicals hypothesized to cause obesity and metabolic diseases. Phthalates have been used as additives in numerous industrial and consumer products since the 1930s (5), including shampoo, fragrance, nail polish, and various polyvinyl chloride (PVC) plastic applications such as plastic food packaging, factory conveyor belts, building materials, wires and cables, and some medical devices (6). Widespread exposure to phthalates occurs through ingesting food contaminated during processing, handling, or storage (7,8). Dermal absorption is also an important route of exposure to phthalates in personal care products (9).

Multiple epidemiologic studies have linked phthalate exposure to obesity, metabolic syndrome, and diabetes (10,11), but the mechanisms by which phthalates may cause metabolic disturbance are not fully understood. One hypothesized mechanism is that phthalate exposure may alter levels of leptin and adiponectin, two major adipokines that regulate energy and nutrient metabolism (12). Leptin is proinflammatory, and higher levels of leptin are associated with adipose tissue inflammation (13), insulin resistance (14,15), and diabetes (16). Adiponectin is anti-inflammatory, and higher levels of adiponectin are associated with increased insulin sensitivity (13,17) and reduced risk of diabetes (18). High-molecular-weight (HMW) adiponectin is the most biologically active form of adiponectin (13). Because adipose tissue secretes both adipokines at

the same time, the ratio of leptin to adiponectin reflects the balance of proinflammatory and anti-inflammatory processes and has been suggested as a marker of adipose tissue dysfunction (19,20). In a Taiwanese cohort, the ratio of leptin to adiponectin predicts insulin resistance more accurately than either adipokine alone (21).

In rodents, ingestion of di(2-ethylhexyl) phthalate (DEHP) for 4-10 weeks resulted in non-monotonic increases in the expression of leptin mRNA in fat tissues (22,23), increases in leptin levels in blood (22,24), and decreases in adiponectin levels in blood (25). Data in humans are limited. Only two studies have examined phthalates and leptin or adiponectin in adults. These studies reported largely null findings (26) or results that contradicted those in animals (26,27). Both studies were conducted in Asia among either predominantly normal-weight women (26) or people with diabetes (27), so these studies' generalizability to adults under other social context and with other health status is unknown. In this study, we aimed to address these knowledge gaps by examining phthalates and leptin, HMW adiponectin, and their ratio in a multi-ethnic sample of women in the United States. We hypothesized that phthalate exposure would be associated with higher levels of leptin, lower levels of HMW adiponectin, and a higher ratio between the two.

3.3 Methods

3.3.1 Study population

Participants were identified from the Study of Women's Health Across the Nation (SWAN). SWAN is an ongoing longitudinal study of women's health in midlife. This cohort study was initiated in 1996/1997. Women from seven study sites (Oakland, CA, Los Angeles, CA, Chicago, IL, Detroit-area, MI, Pittsburgh, PA, Boston, MA and Newark, NJ) were recruited and

followed nearly annually ever since. At the time of cohort inception, eligibility criteria include 1) self-identifying as White, Black, Chinese, Japanese, or Hispanic, 2) aged between 42 and 52 years, 3) having an intact uterus, at least one ovary, and at least one menstrual period in the past 3 months, and 4) not having used any exogeneous reproductive hormone in the past 3 months. A total of 3302 women met those eligibility criteria and participated in SWAN.

The SWAN Multi-pollutant Study (SWAN-MPS) is an ancillary study that selected SWAN participants for environmental chemical exposure assessments using banked biospecimens from the 1999/2000 and 2002/2003 study visits. Of the 2694 women still active in SWAN in 1999/2000, SWAN-MPS excluded all women from Chicago and Newark (n = 646) because these sites did not collect urine samples necessary for environmental exposure assessments. Further, SWAN-MPS excluded 648 women because they did not have enough blood or urine samples for environmental exposure assessments. Thus, SWAN-MPS included 1400 women from Oakland, CA, Los Angeles, CA, Detroit-area, MI, Pittsburgh, PA, and Boston, MA with adequate biospecimen sample volumes.

This analysis was based on SWAN-MPS participants who had concurrent measures of phthalate metabolites and adipokines in the 2002/2003 visit. Of the 1400 women, we first excluded 13 women missing phthalate metabolite data in 2002/2003. Next, we excluded 30 women with missing data on urinary creatinine or its predictors (age, race/ethnicity, height, body mass index (BMI), and diabetes) which were used to account for hydration. Further, we excluded 20 women missing leptin and HMW adiponectin data. Finally, we excluded 87 women with missing data in key covariates including education, menopausal status, hormone therapy (HT) use, physical activity, smoking, and dietary energy intake. The final analytic sample included 1250 women who had complete data in phthalate metabolites, covariates, and at least one adipokine.

All SWAN and SWAN-MPS study protocols have been approved by institutional review boards. SWAN participants provided written informed consent to participate in the study.

3.3.2 Phthalate metabolites

In 2002/2003, women provided spot urine samples in polyethylene tubes at in-person visits. The samples were transferred to -80 °C freezers for long-term storage. In 2017/2018, urine samples were thawed, and phthalate metabolites were measured using on-line solid phase extraction (SPE) coupled to high-performance liquid chromatography-isotope dilution tandem mass spectroscopy (HPLC-MS). We measured 12 phthalate metabolites: mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), monobenzyl phthalate (MBzP), mono-isononyl phthalate (MiNP), mono-carboxyoctyl phthalate (MCOP), mono-carboxy-isononyl phthalate (MCNP), and mono(3-carboxypropyl) phthalate (MCPP). The parents of MEP, MnBP, and MiBP are frequently added to personal care products as solvents and fixatives (28,29). MEHP, MEHHP, MEOHP, and MECPP are all metabolites of DEHP, the first commercially successful phthalate and one of the most widely used phthalates in PVC products (5). The parents of the other phthalate metabolites are also commonly used as PVC plasticizers (7). All phthalate metabolites examined have been national biomonitoring priorities since the early 2000s (30). The coefficient of variation (CV) of metabolite standards ranged from an average of 4% for MEHP to 19% for MCOP. We excluded MiNP from all analyses because it was detected in less than 1% of urine samples.

3.3.3 Adipokines

Adipokines were measured for all SWAN participants only at the 2002/2003 visit. All blood samples were collected after an overnight fast. Commercially available colorimetric enzyme immunoassays were used to measure leptin and HMW adiponectin in blood samples (Millipore, St. Charles, MO). Each sample was measured in duplicate. The CV of each duplicate measurement, averaged across all women, was 4.0% for leptin and 8.1% for HMW adiponectin. For this analysis, the mean of each duplicate was used. The ratio of the two adipokines was calculated as "leptin:HMW adiponectin ratio = leptin / HMW adiponectin (ng/μg)".

3.3.4 Other variables

Urinary creatinine was measured with a Cobas Mira analyzer (Horiba ABX, Montpellier, France). Age was calculated based on follow-up visit date and date of birth. Race/ethnicity (White, Black, Chinese, Japanese) and education (high school or less, some college, college degree, and postgraduate studies) were self-reported at enrollment in SWAN in 1996/1997. Smoking status (never, past, current) in 2002/2003 was self-reported. Non-occupational physical activity was measured with an index derived from the Kaiser Physical Activity Survey (31). Dietary energy intake (kcal/day) was calculated from a modified Block Food Frequency Questionnaire (FFQ) administered in 2001/2002 (32). Current use of hormone therapy (HT) (Yes, No) was self-reported in 2002/2003. Menopausal status (pre- or peri- menopausal, natural/surgical menopause, unknown due to hormone therapy use) was determined based upon self-reported bleeding patterns, self-reported history of gynecological surgeries, and self-reported use of HT in 2002/2003. Body weight was measured with a scale, and height was measured with a stadiometer. BMI was calculated as body weight (kg)/height (m^2). Obesity was defined with BMI based on race/ethnic-specific cut-points (33). For White and Black women, normal/underweight was defined as BMI < 25 kg/m^2, overweight as 25 kg/m^2 $\leq$ BMI < 30 kg/m^2, and obese as BMI $\geq$ 30 kg/m^2. For Chinese

and Japanese women, normal/underweight was defined as BMI < 23 kg/m^2, overweight as 23 $kg/m^2 \leq$ BMI < 27 kg/m^2, and obese as BMI $\geq$ 27 kg/m^2. Diabetes was defined as self-reported doctor's diagnosis of diabetes, self-reported use of anti-diabetic medications, or having a fasting glucose value of 126 mg/dL or greater.

3.3.5 Statistical methods

To facilitate log_2-transformation, four MEHP, one MCOP, and three MCPP concentrations that were zero or negative were replaced by each metabolite's median concentration below its limit of detection. All other metabolite concentrations were used as output by the assay. All metabolite concentrations were then adjusted for hydration using the covariate-adjusted creatinine standardization method (34). Briefly, each metabolite concentration was divided by the ratio of observed to predicted urinary creatinine. Predictors of creatinine included age, race/ethnicity, height, BMI, and diabetes. We obtained descriptive statistics of the study population (median (1^{st} and 3^{rd} quartiles) for continuous variables; count (%) for categorical variables). We also obtained the median (1^{st} and 3^{rd} quartiles) of each hydration-adjusted phthalate metabolite and adipokine, overall and by covariates. The medians of each phthalate metabolite and adipokine across covariate levels were compared with Kruskal-Wallis tests. Correlation between phthalate metabolites was described with Spearman correlation coefficients.

In single-pollutant analyses, we fit two models for each adipokine and phthalate metabolite combination. Model 1 was adjusted for age, race/ethnicity, study site, education level, menopausal status, current use of HT, physical activity, smoking status, and dietary energy intake. Model 2 was additionally adjusted for BMI. We fit these two models to examine the impact of BMI adjustment on the associations between phthalates and adipokines. Because phthalates have been associated with higher BMI and body weight gain (35), and BMI is one of the most important

determinants of leptin and HMW adiponectin (13), adjusting for BMI may lead to underestimation of the associations between phthalates and adipokines. In these models, adipokines were log-transformed. Phthalate metabolites were fitted as quartiles because preliminary analyses with generalized additive models (GAM) indicated that the associations between some metabolites and log adipokines were not linear (**Supplementary Figure 3.1**). In Model 2, BMI was fitted with a natural spline with knots at the 25^{th} and 75^{th} percentiles to accommodate the non-linear associations between BMI and adipokines as discovered in preliminary analyses with GAMs (**Supplementary Figure 3.1**). For each model, we also obtained the p-value for linear trend for each metabolite by replacing the quartile indicator with each quartile's median and fitting that as a continuous variable.

In multi-pollutant analyses, we $\log_2$-transformed all phthalate metabolite concentrations. We then standardized all $\log_2$ phthalate metabolite concentrations and all continuous covariates. Bayesian kernel machine regression (BKMR) with hierarchical variable selection (36) was used to examine the joint association between all phthalate metabolites and each log-transformed adipokine. The BKMR models included the same set of covariates as Model 2 in single-pollutant analyses. We grouped the four DEHP metabolites together for hierarchical variable selection because they came from the same parent and were much more highly correlated with each other (Spearman correlation coefficient > 0.75) than with the other metabolites. All other metabolites were selected individually because they have different parents and were correlated with each other to approximately the same degree. To fit the BKMR models, we ran four parallel Markov Chain Monte Carlo (MCMC) chains with 125,000 iterations per chain for leptin and HMW adiponectin and 275,000 iterations per chain for the leptin:HMW adiponectin ratio. More iterations were run for the leptin:HMW adiponectin because more iterations were required to achieve model

convergence. Model convergence was assessed with Gelman's Rhat and trace plots. The first half of each chain was used for burn-in. Posterior inferences were based on all chains combined.

From the BKMR models, we obtained estimates for the joint associations between phthalate metabolites and each adipokine. The joint association was defined as the percent difference in the outcome comparing when all metabolites were at a particular percentile to when all of them were at their 50th percentile (37,38). In addition, we obtained the group and conditional posterior inclusion probabilities (PIP) of each metabolite. The PIPs are a measure of the importance of each metabolite in terms of its contribution to the mixture's joint association with an outcome (36). There were group and conditional PIPs because DEHP metabolites were first selected as a group. If the group was selected, metabolites within this group were then selected on an individual basis (36,37). For metabolites that were selected individually, each metabolite essentially constituted its own group, so that the group PIPs represented each metabolite's importance, and the conditional PIPs always equaled to 1. Finally, we obtained individual dose-response curves between each metabolite and each outcome from the BKMR models to see if they were consistent with results from single-pollutant analyses. Because all metabolites were considered simultaneously in the BKMR models, these dose-response curves were adjusted for confounding by the other metabolites.

We conducted four sensitivity analyses for the single-pollutant models. First, we additionally adjusted Model 2 for total intake frequency of food items potentially associated with phthalates to evaluate potential residual confounding by diet quality. These food items included red meat, poultry, liver, processed meat, dairy, margarine, refined grains, salty snacks, desserts, meat substitutes, pizza, salad dressing, and salsa (8,39–44). Second, we additionally adjusted Model 2 for methyl paraben to evaluate potential confounding by parabens. Parabens are

preservatives added to personal care products often at the same time as phthalates and may also have metabolic effects (45). Third, we conducted stratified analyses by race/ethnicity to explore potential effect modification by race/ethnicity. Lastly, because previous studies showed differences in the association between phthalate metabolites and leptin or adiponectin by obesity status (26,27), we stratified our analyses by obesity status. We did not repeat these analyses with BKMR because their results were similar to the main analyses (sensitivity analyses #1 and #2), or they were exploratory in nature (sensitivity analyses #3 and #4). Statistical analyses were conducted in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). The packages "bkmrhat" (46) and "bkmr" (47) were used to fit BKMR models. A two-sided p-value < 0.05 was considered statistically significant.

3.4 Results

Participants had a median age of 52.4 years (1st quartile (Q1), 3rd quartile (Q3): 50.4, 54.5) (**Table 3.1**). Approximately half of the participants were White, 19.4% Black, 12.3% Chinese, and 15.8% Japanese. Approximately half of the participants had a college degree or higher. Almost half of the participants (47.3%) were post-menopausal. The medians of leptin, HMW adiponectin, and the leptin:HMW adiponectin ratio were 19.30 ng/mL (Q1, Q3: 10.51, 34.32), 5.88 µg/mL (Q1, Q3: 3.26, 9.73), and 3.43 ng/µg (Q1, Q3: 1.28, 8.81), respectively.

The frequency of detection of phthalate metabolites ranged from 82.2% for MEHP to 100% for MEHHP, MEOHP, and MECPP (**Table 3.2**). The median concentrations of phthalate metabolites ranged from 1.54 ng/mL (Q1, Q3: 0.99, 2.32) for MCPP to 56.73 ng/mL (Q1, Q3: 24.49, 149.95) for MEP. Younger age, being black, having lower levels of education, past or

current smoking, and being overweight or obese were generally associated with higher urinary concentrations of phthalate metabolites (**Supplementary Tables S3.2-S3.4**).

3.4.1 Leptin

In single-pollutant models not adjusted for BMI, higher levels of 7 of the 11 phthalate metabolites including MEHHP, MEOHP, MECPP, MBzP, MCOP, MCNP, and MCPP were associated with significantly higher levels of leptin (p-values for linear trend <0.05) (Model 1, **Figure 3.1** and **Supplementary Table 3.5**). Some quartiles of three additional phthalate metabolites including MEP, MnBP, and MiBP were also associated with significantly higher levels of leptin, although there were no statistically significant linear trends. MEHP was not associated with leptin. Upon BMI adjustment, the overall shape of the association between each metabolite and leptin remained similar (Model 2, **Figure 3.1** and **Supplementary Table 3.5**). However, BMI adjustment substantially attenuated the associations between phthalate metabolites and leptin. Compared to the 1st quartile, the 2nd to 4th quartiles of each metabolite were associated with no more than 11% higher concentrations of leptin, with most differences being statistically non-significant. In fully-adjusted models, a statistically significant linear trend was observed for MEOHP only (p-value for linear trend = 0.025), while the p-values for linear trend were borderline significant for two other DEHP metabolites (p-value for trend = 0.073 for MEHHP and 0.062 for MECPP).BKMR revealed statistically non-significant increases in leptin with increasing phthalate metabolite mixture (**Figure 3.2**, Panel A) and identified MCPP as the main contributor to the mixture's effect (group PIP = 0.43) ((**Figure 3.2**, Panel B). The dose-response relationship between MCPP and leptin was potentially non-linear (**Supplementary Figure 3.3**).

3.4.2 HMW adiponectin

In single-pollutant models not adjusted for BMI, few phthalate metabolites were associated with HMW adiponectin (Model 1, **Figure 3.3** and **Supplementary Table 3.6**). One notable exception was MEHP, where the 2nd to 4th quartiles were associated with 20.0% (95% CI: 5.3, 36.6), 28.6% (95% CI: 12.9, 46.7), and 26.9 % (95% CI: 11.0, 45.1) higher concentrations of HMW adiponectin, respectively. These associations remained similar after BMI adjustment (Model 2, **Figure 3.3** and **Supplementary Table 3.6**). In final models, no metabolites were significantly associated with HMW adiponectin, except for MEHP. BKMR revealed significant increases in HMW adiponectin with increasing phthalate metabolite mixture (**Figure 3.4**, Panel A) and identified MEHP as the top contributor to the mixture's effect (group PIP for DEHP metabolites = 0.89; conditional PIP for MEHP = 0.99) (**Figure 3.4**, Panels B and C). Consistent with the single-pollutant model, MEHP was potentially non-linearly associated with HMW adiponectin (**Supplementary Figure 3.4**).

3.4.3 Leptin:HMW adiponectin ratio

In single-pollutant models not adjusted for BMI, MEHP was significantly, inversely associated with the leptin:HMW adiponectin ratio (Model 1, **Figure 3.5** and **Supplementary Table 3.7**). For the other phthalate metabolites, all associations were positive, but only a few were statistically significant. Statistically significant linear trends were found for MBzP, MCOP, and MCNP only (Model 1, **Figure 3.5** and **Supplementary Table 3.7**). All associations became attenuated upon BMI adjustment (Model 2, **Figure 3.5** and **Supplementary Table 3.7**). In final models, only MEHP remained significantly associated with a lower leptin:HMW adiponectin ratio. Compared to the 1st quartile, the 2nd to 4th quartiles of MEHP were associated with -16.9% (95% CI: -29.1, -2.6), -24.0% (95% CI: -35.2, -10.8), and -17.7% (95% CI: -30.2, -3.1) lower leptin:HMW adiponectin ratio, respectively. BKMR revealed a statistically non-significant,

inverse association between the phthalate metabolite mixture and the leptin:HMW adiponectin ratio (**Figure 3.6**, Panel A) and identified MEHP as the main contributor to the mixture's effect (group PIP of DEHP metabolites = 0.73; conditional PIP of MEHP = 0.99) (**Figure 3.6**, Panels B and C). The dose-response curve between MEHP and the lepin:HMW adiponectin ratio was potentially non-linear (**Supplementary Figure 3.5**).

The associations between phthalate metabolites and adipokines did not differ by race/ethnicity. Obesity status modified the associations between some phthalate metabolites and adipokines, but no consistent effect modification pattern was found (**Supplementary Figures S3.6-S3.8**).

3.5 Discussion

In this study on phthalates and adipokines in a diverse population, we found that 1) 7 of 11 phthalate metabolites were associated with higher levels of leptin, but these associations were largely attenuated by adjusting for body size as assessed by BMI; 2) most phthalate metabolites were not associated with HMW adiponectin regardless of adjustment for BMI; 3) higher concentrations of MEHP were associated with higher levels of HMW adiponectin regardless of adjustment for BMI ; and 4) phthalate metabolites were not associated with the leptin:HMW adiponectin ratio after adjustment for BMI, except for MEHP. Taken together, this study suggests that phthalates are not associated with an adverse adipokine profile independent of body size. MEHP may even be associated with a better profile. If phthalates truly cause metabolic conditions such as insulin resistance, metabolic syndrome, and diabetes, shifting the adipokine secretory

profile towards higher levels of leptin and lower levels of HMW adiponectin is likely not a major mechanism of action for this effect.

Our findings for leptin are largely consistent with the only other study on this topic. In a population of reproductive-aged women in Korea, Lee et al. found that phthalate metabolites were not associated with leptin levels (26). The study did not adjust for body size, but the reported associations are likely close to what would have been obtained with body size adjustment because most participants had normal BMIs. We extended Lee et al.'s findings in three important ways. First, by conducting analyses with and without BMI adjustment, we demonstrated that body size is an important driver behind any apparent associations between phthalates and leptin. Second, by relaxing the assumption of linearity, we discovered that the association between some phthalate metabolites and leptin may be non-linear. Third, by using BKMR, we were able to obtain the joint association between phthalate metabolite mixture and leptin, which is of great public health interest because people are exposed to mixtures of phthalates in real life. Together with Lee et al. 2019, our study does not support strong associations between phthalates and leptin independent of BMI in women. Whether this is also true in men requires further studies, which will benefit from carefully considering the role of BMI and potential non-linear dose-response relationships in study design and analysis.

Our findings for HMW adiponectin are also consistent with previous studies. In Lee et al. 2019, MnBP, MBzP, and the sum of DEHP metabolites were significantly associated with higher serum adiponectin levels (26). Similarly, among people with impaired glucose tolerance and diabetes, Duan et al. found that almost all phthalate metabolites, including MEHP, were significantly associated with higher serum adiponectin levels independent of BMI (27). In this study, we identified a strong, positive association between MEHP and HMW adiponectin. This

association contributed to a statistically significant, positive association between phthalate metabolite mixture and HMW adiponectin. It is unclear why the other metabolites in our study were not significantly associated with higher HMW adiponectin. However, if the non-linear association between MEHP and HMW adiponectin detected by BKMR were true, one potential explanation is that for some metabolites, their associations with HMW adiponectin were truly null at their respective levels of exposure. This could be a reasonable explanation because the concentrations of many metabolites in this study were higher than those in previous studies, as well as higher than MEHP in this study. Overall, our findings suggest that unlike in rodents, phthalates do not seem to reduce adiponectin in women at typical levels of exposure.

Our findings that phthalate exposure was not associated with an adverse adipokine profile as characterized by higher levels of leptin and lower levels of HMW adiponectin independent of BMI is somewhat unexpected based on existing epidemiological and animal data. Phthalate exposure has been associated with faster gains or slower declines in body weight and body fat in women, including women in this study (35, 48–52). The amount of body fat is one of the most important determinants of leptin and adiponectin. Increases in body fat generally lead to higher leptin and lower adiponectin (53,54). This is indeed the case in experimental studies with rodents, in which DEHP-exposed animals showed increases in circulating leptin and decreases in adiponectin along with body fat gain (22,23,25). The fact that significant increases in leptin with DEHP were found in animals but not in the fully-adjusted models in this study suggest that body fat increases may be an important mechanism through which phthalates affect leptin levels. Inconsistency in findings for adiponectin between this study and animal studies may be due to dose differences. The average daily intake of DEHP for a reproductive-aged woman consuming a typical diet in the early- to mid-2000s in the US was estimated to be 5.7 μg/kg body weight/day

(42). This number is 10 times lower than the lowest dose of DEHP in the animal studies (0.05 mg/kg or 50 μg/kg body weight/day) (25). Given the potentially non-linear relationship between MEHP and HMW adiponectin, it is possible that at lower exposure levels, MEHP enhances adiponectin secretion, while at higher exposure levels, it suppresses adiponectin secretion. A recent study exposing cultured murine adipocytes to physiologically relevant doses of MEHP supports this view. In this study, exposed cells synthesized more, not less, adiponectin compared to controls (55). The study also showed that the increased synthesis was likely due to the activation of proliferator-activated receptor gamma (PPAR-γ) by MEHP.

Many phthalate metabolites can activate PPAR-γ in addition to MEHP (56–58). In adipose tissues, the activation of PPAR-γ leads to adipogenesis, lipid uptake into adipocytes, and the upregulation of adiponectin (59). These mechanisms are thought to underlie both the therapeutic and side effects of thiazolidinediones, a class of anti-diabetic medications that through activating PPAR-γ, increases adiponectin production and insulin sensitivity at the expense of body weight gain (59). That phthalates have been associated with body weight gain but increased adiponectin suggests that phthalates are behaving like PPAR-γ agonists. These data are inconsistent with the associations between phthalate exposure and insulin resistance and diabetes (10). If phthalate exposure truly causes insulin resistance and diabetes, some other mechanisms must be involved to cancel the insulin-sensitizing effects typical of PPAR-γ activation.

Overall, the apparently paradoxical findings concerning phthalates, adipokines, obesity, and metabolic diseases across the molecular, animal, and epidemiologic evidence streams underscore the complexity of phthalates' toxicological effects. These chemicals likely act upon many physiological pathways, exerting multifaceted, potentially dose-dependent effects. It is also possible that the effects of phthalates may vary across species. These complexities highlight the

need to examine subclinical endpoints to uncover potential mechanisms of metabolic disturbances in epidemiologic studies of phthalates. Doing so will help us develop a more nuanced understanding of these chemicals, potentially make better predictions of their effects, and thus develop better strategies to manage their risks. To this end, we hope this study on phthalates and leptin and HMW adiponectin serves as a starting point, from which a better understanding of phthalates' impact on adipocyte biology and its metabolic consequences may be developed.

This study has several limitations. First, it is a cross-sectional study, making it difficult to draw causal conclusions. In particular, it is difficult to discern the role of BMI in the relationship between phthalates and adipokines. Whether BMI is a mediator or a confounder, we would expect the same changes in beta estimates comparing models with and without BMI adjustment. Longitudinal studies with repeated measures of adipokines and BMI are needed to clarify the interrelationships between phthalates, body fat, and adipokines. Second, phthalate metabolites were measured once in spot urine samples. Phthalate metabolites have short half-lives in the body (60), and exposure to many phthalates is episodic in nature. Phthalate metabolites in one spot urine sample are therefore imperfect measures of habitual phthalate exposure. Using metabolites in spot urine samples as phthalate exposure markers could have led to random exposure measurement error and thus attenuated associations with outcomes. Third, the set of adipokines we examined was limited. Adipose tissues secrete a plethora of hormones and cytokines. Leptin and HMW adiponectin are but two members of a complex adipokine milieu. Further studies considering other adipokines will help generate a more complete understanding of phthalates' impact on adipose tissue's endocrine function. Fourth, as an observational study, residual confounding is possible, including confounding by other environmental chemicals, although it is reassuring that our results

remained similar upon adjustment for methyl paraben. Lastly, statistical significance should be interpreted cautiously as we did not adjust for multiple comparisons.

This study also has several strengths. The study population was large and diverse, which facilitates the generalization of our findings to other populations. Further, we employed a state-of-the-art statistical approach, BKMR, to estimate the joint associations between phthalate metabolites and adipokines, identify key metabolites, and obtain mutually adjusted dose-response curves for each metabolite. This analytic approach provides insights into the associations between phthalates and adipokines that are absent in single-pollutant analyses. For example, several phthalate metabolites were found to be non-linearly associated with leptin in fully-adjusted single pollutant models. BKMR identified a non-linear association for MCPP only, suggesting that results for other phthalate metabolites in single-pollutant analyses might be confounded by MCPP. With BKMR, we were also able to estimate the potential effects of phthalate mixtures on adipokines, which previous studies did not accomplish.

3.6 Conclusions

In conclusion, in a diverse cohort of midlife women in the US, we found that exposure to most phthalate metabolites except MEHP was associated with higher levels of leptin, but the associations were attenuated upon adjustment for BMI. We also found that regardless of BMI adjustment, MEHP was positively associated with HMW adiponectin, while most other phthalate metabolites were not associated with HMW adiponectin. Consistent with these findings, phthalate metabolites were not associated with a higher leptin:HMW adiponectin ratio independent of BMI, except for MEHP, which was inversely associated with the leptin:HMW adiponectin ratio regardless of BMI adjustment. Taken together, phthalates were not associated with an adverse

adipokine profile independent of body size. Some phthalate metabolites, such as MEHP, may even be associated with increases in HMW adiponectin, an anti-inflammatory adipokine associated with better metabolic outcomes. The apparent contradictions between these findings and phthalates' associations with obesity, insulin resistance, and diabetes underscore the complexity of phthalates' toxicological effects. As we seek to understand the role of phthalates and other synthetic chemicals in the ongoing obesity epidemic and its metabolic complications, we must pay attention to these complexities and investigate not only clinical outcomes but also the underlying physiological perturbations associated with chemical exposure in humans. Doing so will increase our understanding of the mechanisms through which these chemicals may cause metabolic diseases, which will inform risk predictions and risk management.

3.7 References

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Table 3.1 Participant characteristics in 2002/2003

	Median (Q1, Q3)[1]
Age (years)	52.4 (50.4, 54.5)
BMI (kg/m^2)	26.2 (22.6, 31.6)
Leptin (ng/mL)	19.30 (10.51, 34.32)
HMW adiponectin (μg/mL)	5.88 (3.26, 9.73)
Leptin:HMW adiponectin ratio (ng/μg)	3.43 (1.28, 8.81)
	N (%)
Site	
Detroit, MI	200 (16.0%)
Boston, MA	210 (16.8%)
Oakland, CA	276 (22.1%)
Los Angeles, CA	353 (28.2%)
Pittsburgh, PA	211 (16.9%)
Race/ethnicity	
White	655 (52.4%)
Black	243 (19.4%)
Chinese	154 (12.3%)
Japanese	198 (15.8%)
Education	
High school or less	212 (17.0%)
Some college	398 (31.8%)
College degree	320 (25.6%)
Postgraduate	320 (25.6%)
Smoking	
Never	781 (62.5%)
Past	350 (28.0%)
Current	119 (9.5%)
Menopausal status	
Pre- or peri- menopausal	520 (41.6%)
Natural/surgical menopause	591 (47.3%)
Unknown due to hormone therapy	139 (11.1%)
Currently on hormone therapy	
No	908 (72.6%)
Yes	342 (27.4%)
Obesity status[2]	
Normal/underweight	460 (36.8%)
Overweight	360 (28.8%)
Obese	430 (34.4%)

[1] "Q1" stands for 1st quartile and "Q3" stands for 3rd quartile.

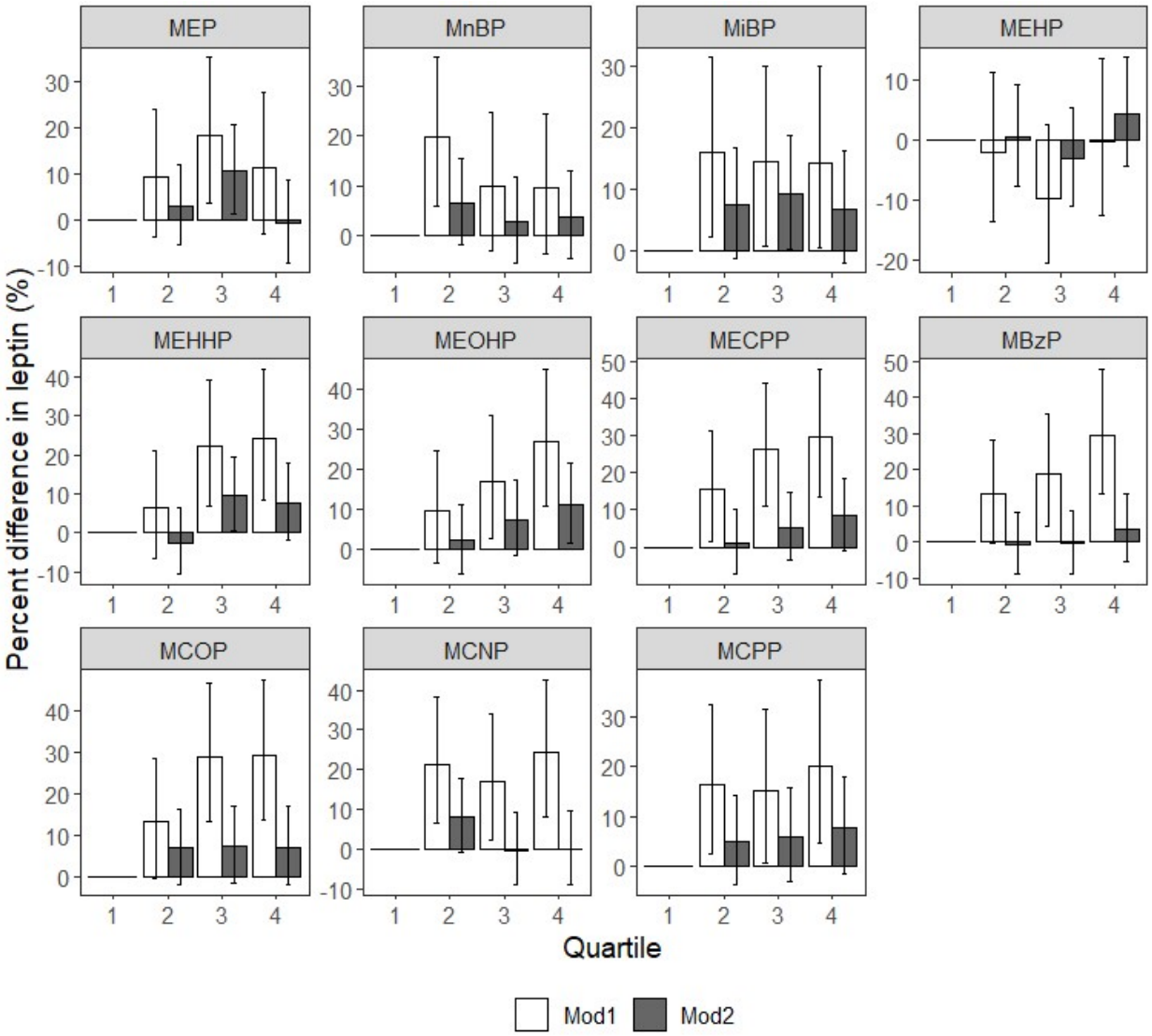
[2] Obesity was defined with body mass index (BMI) using race-specific cut-points. For Black and White, Normal/underweight: BMI < 25 kg/m^2; Overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2; Obese: BMI ≥ 30 kg/m^2. For Chinese and Japanese, Normal/underweight: BMI < 23 kg/m^2; Overweight: 23 kg/m^2 ≤ BMI < 27 kg/m^2; Obese: BMI ≥ 27 kg/m^2.

Table 3.2 Phthalate metabolite concentrations in 2002/2003

Parent phthalate	Phthalate metabolite[1]	N (%) detected	Median (Q1, Q3) (ng/mL)
Di-ethyl phthalate (DEP)	MEP	1248 (99.8%)	56.73 (24.49, 149.95)
Di-n-butyl phthalate (DnBP), Butylbenzyl phthalate (BBzP)	MnBP	1248 (99.8%)	16.98 (10.60, 30.58)
Di-isobutyl phthalate (DiBP)	MiBP	1248 (99.8%)	3.13 (1.90, 5.14)
Di(2-ethylhexyl) phthalate (DEHP)	MEHP	1028 (82.2%)	2.66 (1.46, 5.61)
	MEHHP	1250 (100%)	21.17 (10.98, 41.80)
	MEOHP	1250 (100%)	10.34 (5.45, 20.32)
	MECPP	1250 (100%)	23.60 (12.36, 42.52)
Butylbenzyl phthalate (BBzP)	MBzP	1245 (99.6%)	7.26 (3.92, 12.43)
Di-isononyl phthalate (DiNP)	MCOP	1240 (99.2%)	3.04 (1.82, 5.35)
Di-isodecyl phthalate (DiDP)	MCNP	1237 (99.0%)	1.93 (1.08, 3.46)
DnBP, Di-n-octyl phthalate (DnOP) and other high-molecular-weight phthalates	MCPP	1219 (97.5%)	1.54 (0.99, 2.32)

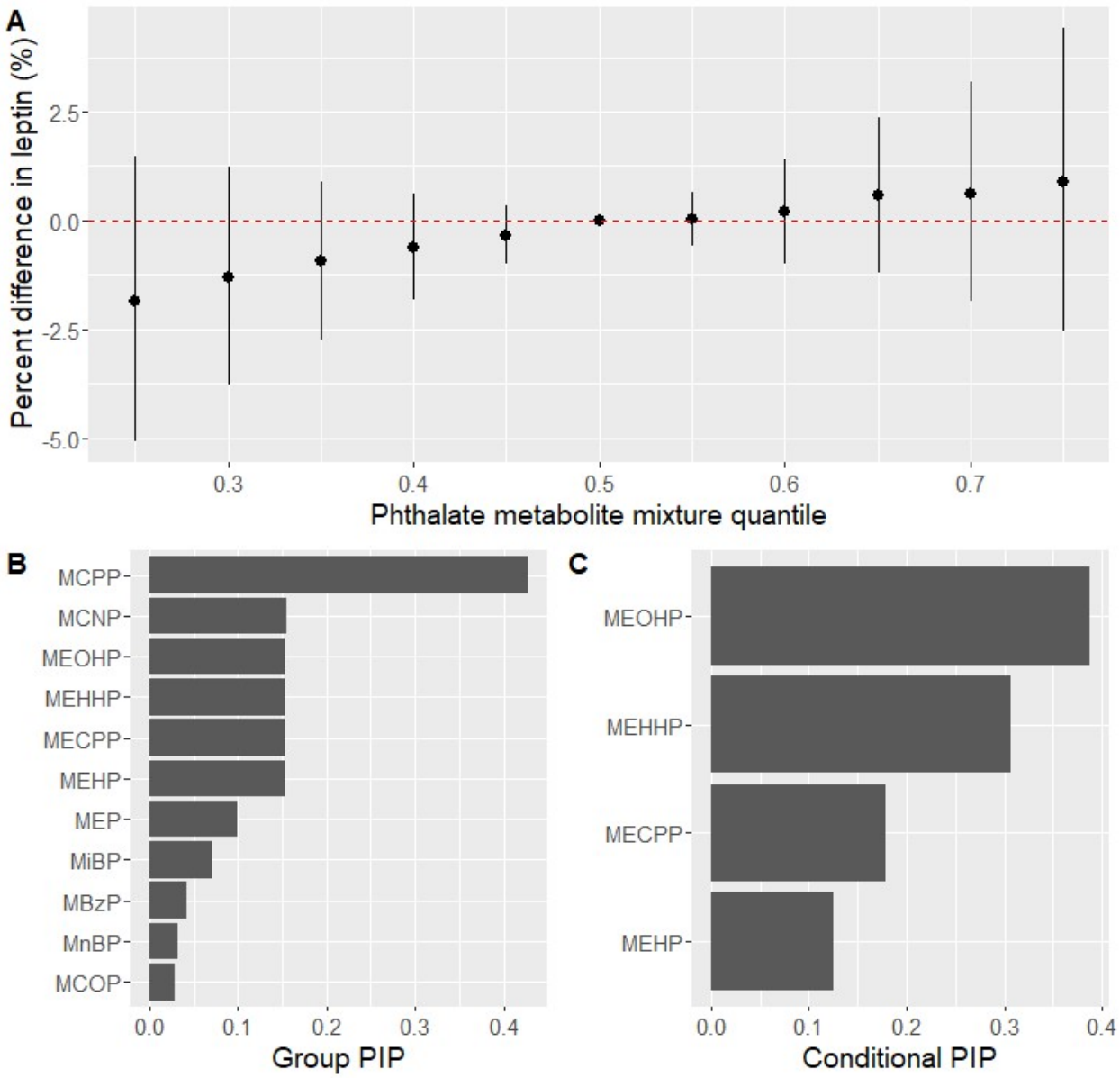
[1] All phthalate metabolites were adjusted for hydration using the "covariate-adjusted creatinine standardization" method. Median and the 1st ("Q1") and 3rd ("Q3") quartiles are reported.

Figure 3.1 Percent differences in leptin associated with phthalate metabolite concentration quartiles



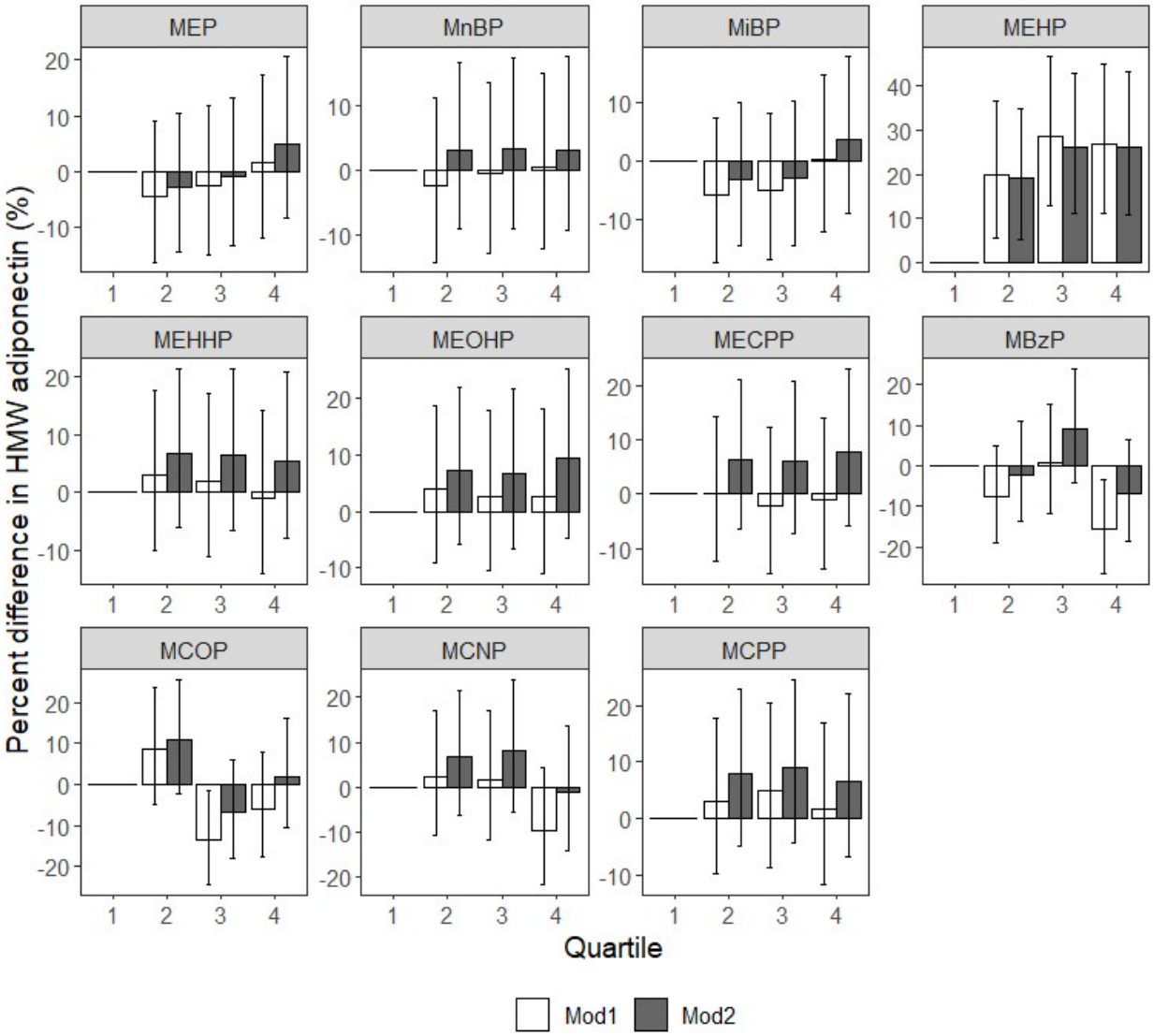
Model 1 (Mod1): Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2 (Mod2): Mod1 + BMI (natural spline with knots at the 25th and 75th percentiles).

Figure 3.2 The joint association between phthalate metabolites and leptin



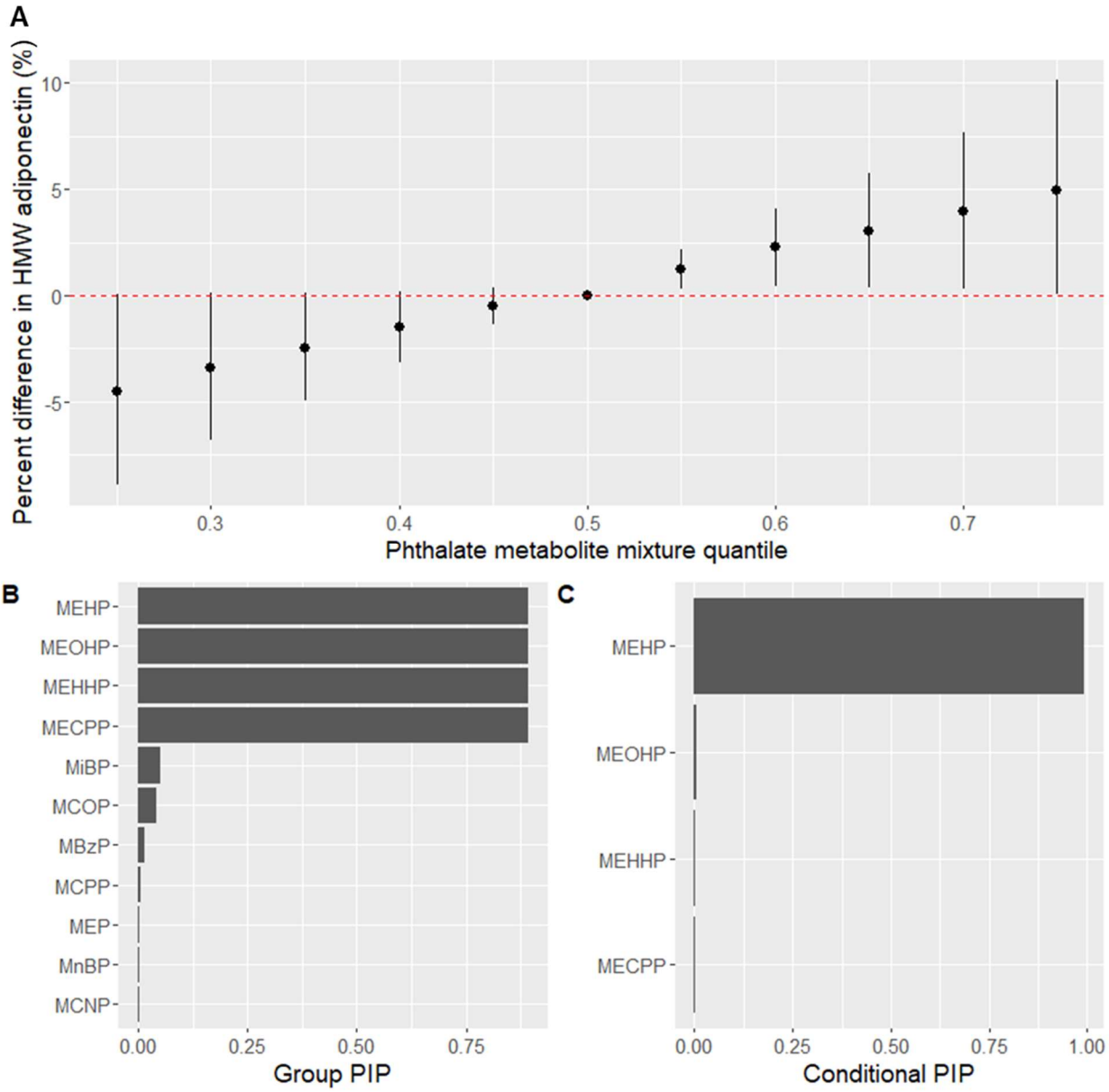
The joint association between phthalate metabolites and leptin as estimated by BKMR. (A) Percent difference in leptin comparing the metabolite mixture at various quantiles to when the mixture was at the 50th percentile. (B) Group posterior inclusion probabilities (PIP). The four DEHP metabolites, MEOHP, MEHHP, MECPP, and MEHP, had the same group PIP because they belonged to the same group. (C) Conditional PIPs for the four DEHP metabolites. The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Figure 3.3 Percent differences in HMW adiponectin associated with phthalate metabolite concentration quartiles



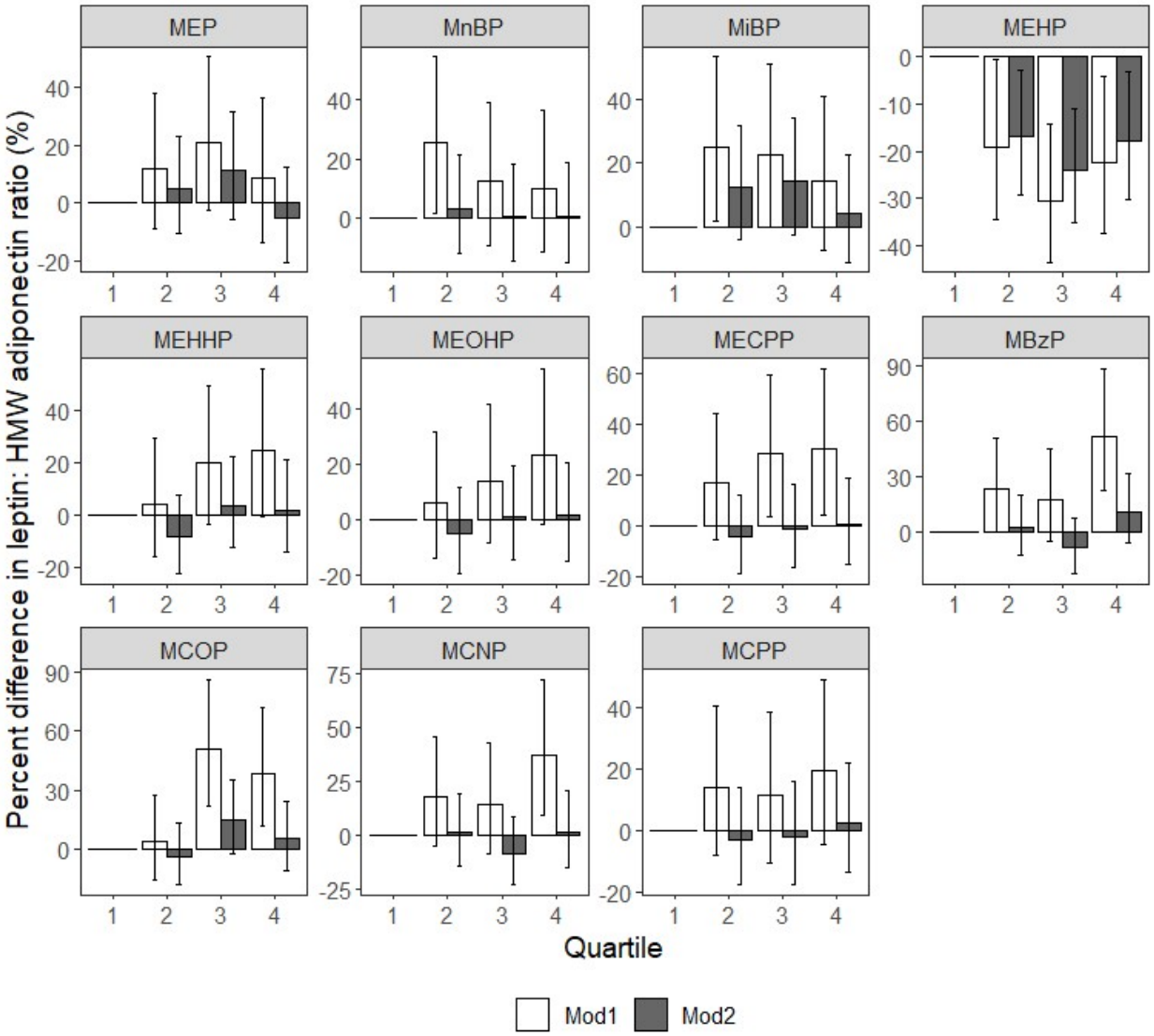
Model 1 (Mod1): Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2 (Mod2): Mod1 + BMI (natural spline with knots at the 25th and 75th percentiles).

Figure 3.4 The joint association between phthalate metabolites and HMW adiponectin



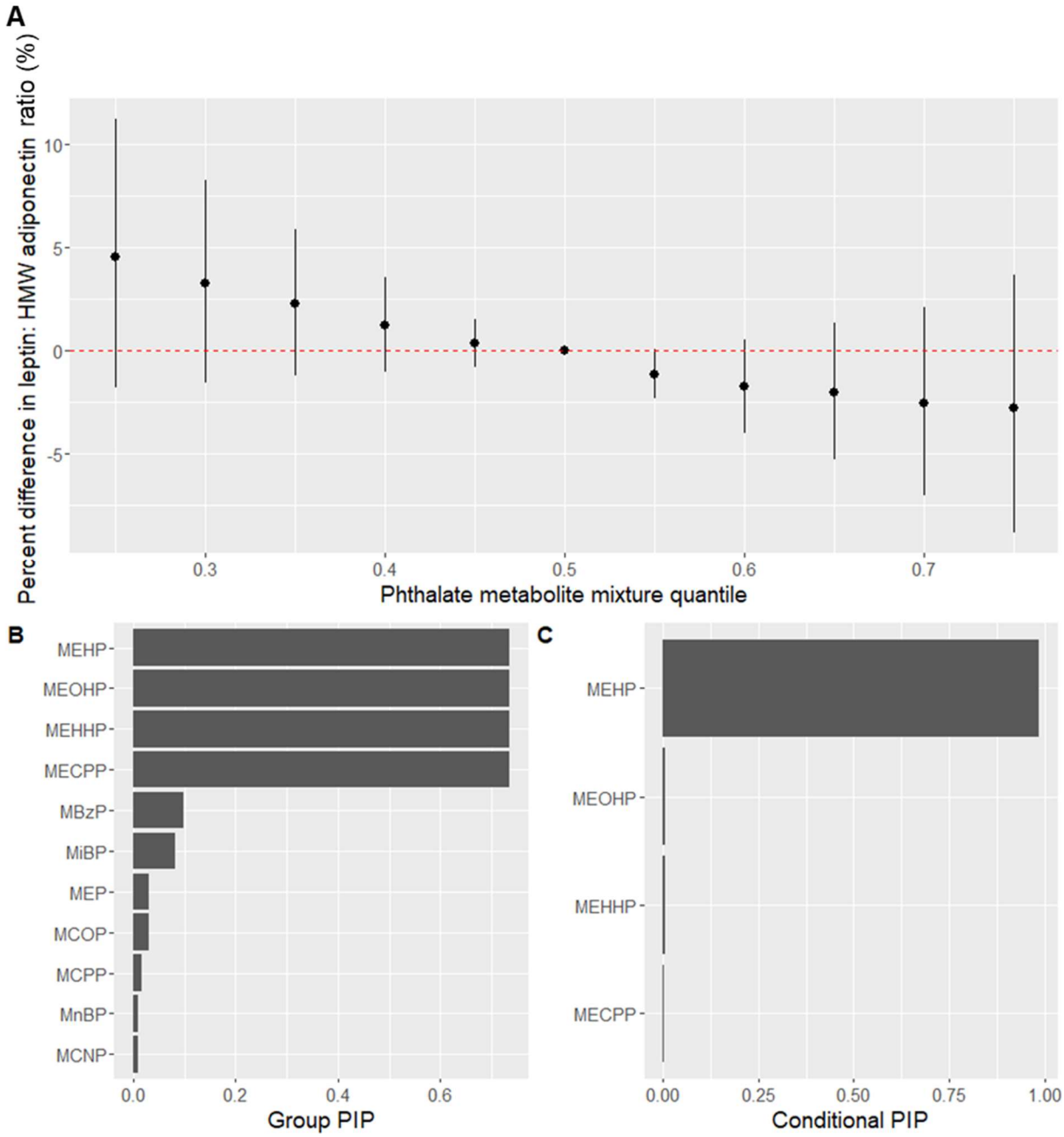
The joint association between phthalate metabolites and HMW adiponectin as estimated by BKMR. (A) Percent difference in HMW adiponectin comparing the metabolite mixture at various quantiles to when the mixture was at the 50th percentile. (B) Group posterior inclusion probabilities (PIP). The four DEHP metabolites, MEOHP, MEHHP, MECPP, and MEHP, had the same group PIP because they belonged to the same group. (C) Conditional PIPs for the four DEHP metabolites. The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Figure 3.5 Percent differences in the leptin:HMW adiponectin ratio associated with phthalate metabolite concentration quartiles



Model 1 (Mod1): Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2 (Mod2): Mod1 + BMI (natural spline with knots at the 25th and 75th percentiles).

Figure 3.6 The joint association between phthalate metabolites and the leptin:HMW adiponectin ratio



The joint association between phthalate metabolites and leptin:HMW adiponectin ratio as estimated by BKMR. (A) Percent difference in leptin:HMW adiponectin ratio comparing the metabolite mixture at various quantiles to when the mixture was at the 50th percentile. (B) Group posterior inclusion probabilities (PIP). The four DEHP metabolites, MEOHP, MEHHP, MECPP, and MEHP, had the same group PIP because they belonged to the same group. (C) Conditional PIPs for the four DEHP metabolites. The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Supplementary Table 3.1 Adipokine concentrations by covariates

	N	Leptin	HMW adiponectin	Leptin: HMW adiponectin ratio
		Median (Q1, Q3)[1] ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL
Age				
≤ 52	555	19.50 (10.53, 34.35)	5.97 (3.42, 9.60)	3.19 (1.26, 8.42)
> 52	695	19.05 (10.51, 33.74)	5.81 (3.00, 9.96)	3.56 (1.31, 9.00)
p-value[2]		0.78	0.44	0.49
Site				
Detroit, MI	200	35.50 (19.04, 47.61)	3.65 (2.16, 6.14)	9.13 (3.85, 17.87)
Boston, MA	210	24.19 (14.27, 40.09)	5.08 (2.93, 8.76)	5.10 (1.98, 12.23)
Oakland, CA	276	13.19 (7.77, 26.54)	6.62 (3.30, 10.72)	2.45 (0.79, 5.80)
Los Angeles, CA	353	13.73 (7.76, 22.29)	6.54 (3.62, 10.05)	2.01 (0.90, 5.50)
Pittsburgh, PA	211	25.01 (16.19, 38.47)	7.86 (4.76, 11.87)	2.99 (1.46, 7.28)
p-value		<0.0001	<0.0001	<0.0001
Race/ethnicity				
White	655	21.78 (11.64, 35.86)	7.52 (4.48, 11.21)	2.80 (1.18, 7.01)
Black	243	32.54 (20.52, 48.60)	3.41 (2.02, 5.43)	9.95 (4.53, 22.25)
Chinese	154	11.69 (7.49, 18.69)	5.26 (2.89, 9.70)	2.18 (0.80, 5.90)
Japanese	198	11.75 (7.13, 18.41)	5.01 (2.87, 8.93)	2.10 (0.86, 5.98)
p-value		<0.0001	<0.0001	<0.0001
Education				
High school or less	212	19.99 (11.65, 34.82)	5.43 (2.79, 9.20)	3.77 (1.63, 9.95)
Some college	398	21.53 (12.10, 36.12)	5.23 (3.01, 9.67)	3.80 (1.45, 10.26)
College degree	320	18.07 (8.99, 31.61)	6.11 (3.38, 9.83)	2.97 (1.03, 8.18)
Postgraduate	320	17.99 (9.98, 32.23)	6.73 (3.76, 10.16)	2.89 (1.05, 7.10)
p-value		0.01	0.03	0.005
Smoking				
Never	781	18.71 (10.32, 32.84)	5.73 (3.27, 9.37)	3.43 (1.31, 8.17)
Past	350	20.51 (10.90, 35.16)	7.01 (3.46, 10.89)	3.08 (1.19, 8.89)
Current	119	21.57 (11.84, 37.30)	4.62 (2.46, 7.61)	4.70 (1.87, 14.30)
p-value		0.15	0.0005	0.01
Daily calorie intake				
1st quartile: < 1280 kcal/day	313	18.51 (10.02, 34.67)	6.05 (3.35, 10.23)	3.31 (1.11, 8.34)
2nd quartile: 1280 – 1620 kcal/day	312	19.04 (11.54, 32.08)	6.14 (3.52, 10.16)	3.07 (1.34, 7.37)

	N	Leptin	HMW adiponectin	Leptin: HMW adiponectin ratio
		Median (Q1, Q3)[1] ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL
3rd quartile: 1620 – 2080 kcal/day	312	19.29 (9.86, 34.73)	6.55 (3.48, 9.92)	3.41 (1.24, 8.03)
4th quartile: > 2080 kcal/day	313	19.91 (10.18, 36.47)	4.95 (2.69, 8.71)	4.00 (1.33, 11.42)
p-value		0.80	0.01	0.10
Physical activity				
1st quartile: < 6.4	322	27.65 (13.74, 43.85)	4.91 (2.65, 8.24)	5.55 (2.09, 15.81)
2nd quartile: 6.4 – 7.6	326	19.15 (11.47, 34.71)	5.56 (2.97, 9.20)	3.67 (1.45, 8.27)
3rd quartile: 7.6 – 8.9	299	19.33 (10.73, 31.91)	6.07 (3.37, 10.52)	3.48 (1.25, 7.43)
4th quartile: > 8.9	303	13.90 (7.90, 24.02)	7.43 (3.99, 11.12)	1.98 (0.78, 4.87)
p-value		<0.0001	<0.0001	<0.0001
Menopausal status				
Pre- or peri-menopausal	520	19.46 (10.01, 35.54)	5.34 (3.27, 9.13)	3.62 (1.29, 9.33)
Natural/surgical menopause	591	19.15 (10.51, 32.68)	6.36 (3.29, 10.35)	3.22 (1.28, 7.98)
Unknown due to hormone therapy	139	19.08 (11.42, 33.69)	6.01 (3.09, 9.67)	3.22 (1.30, 8.48)
p-value		0.97	0.11	0.68
Currently on hormone therapy				
No	908	19.30 (10.50, 34.82)	5.71 (3.27, 9.58)	3.47 (1.31, 9.26)
Yes	342	19.31 (10.71, 32.37)	6.50 (3.14, 10.22)	3.35 (1.23, 7.86)
p-value		0.77	0.11	0.27
Obesity status				
Normal/underweight	460	10.02 (6.33, 15.58)	8.24 (4.88, 11.79)	1.32 (0.59, 2.79)
Overweight	360	19.67 (13.17, 27.92)	5.42 (3.32, 9.12)	3.58 (1.83, 6.46)
Obese	430	39.64 (27.75, 53.25)	3.99 (2.12, 6.77)	10.00 (4.91, 20.45)
p-value		<0.0001	<0.0001	<0.0001

[1] "Q1" means "1st quartile" and "Q3" means "3rd quartile".

[2] p-values were obtained from Kruskal-Wallis tests.

Supplementary Table 3.2 Concentrations of MEP, MnBP, and MiBP by covariates

	N	MEP[1] Median (Q1, Q3)[2] ng/mL	MnBP Median (Q1, Q3) ng/mL	MiBP Median (Q1, Q3) ng/mL
Age				
≤ 52	555	59.85 (26.70, 150.39)	18.05 (11.17, 31.54)	3.35 (2.01, 5.32)
> 52	695	53.79 (23.26, 149.68)	15.59 (10.16, 28.66)	2.94 (1.85, 4.75)
p-value[3]		0.22	0.01	0.01
Site				
Detroit, MI	200	84.73 (41.58, 218.19)	20.57 (12.52, 38.71)	3.68 (2.22, 5.70)
Boston, MA	210	76.38 (35.66, 228.44)	18.37 (10.24, 30.68)	3.17 (1.81, 5.36)
Oakland, CA	276	33.19 (17.11, 85.63)	13.53 (8.90, 22.13)	2.73 (1.70, 4.77)
Los Angeles, CA	353	42.78 (20.13, 100.55)	14.54 (10.15, 25.43)	2.71 (1.64, 4.10)
Pittsburgh, PA	211	80.29 (32.24, 195.57)	23.60 (14.31, 42.19)	3.79 (2.71, 6.24)
p-value		<0.0001	<0.0001	<0.0001
Race/ethnicity				
White	655	56.93 (27.36, 126.56)	16.62 (10.38, 29.35)	2.94 (1.80, 4.61)
Black	243	150.46 (72.51, 385.93)	26.21 (16.13, 44.87)	4.32 (2.93, 7.06)
Chinese	154	25.12 (14.20, 52.43)	13.41 (9.10, 21.48)	3.02 (1.86, 5.01)
Japanese	198	25.40 (13.98, 63.58)	13.56 (9.88, 20.94)	2.66 (1.54, 4.23)
p-value		<0.0001	<0.0001	<0.0001
Education				
High school or less	212	55.95 (21.20, 162.79)	18.02 (11.75, 31.00)	3.35 (2.21, 5.44)
Some college	398	68.83 (27.26, 178.43)	19.29 (11.50, 32.86)	3.30 (1.90, 5.27)
College degree	320	46.97 (20.73, 116.67)	16.09 (9.81, 27.43)	3.00 (1.87, 4.86)
Postgraduate	320	51.96 (25.72, 136.93)	14.73 (9.70, 28.48)	3.00 (1.80, 4.88)
p-value		0.01	0.0004	0.29
Smoking				
Never	781	46.13 (21.32, 120.79)	15.41 (9.86, 27.84)	3.03 (1.84, 4.96)
Past	350	62.56 (28.13, 177.76)	19.10 (11.14, 31.63)	3.18 (1.92, 5.24)
Current	119	101.12 (54.27, 271.32)	23.32 (14.62, 39.88)	3.67 (2.29, 5.56)
p-value		<0.0001	<0.0001	0.02
Daily calorie intake				
1st quartile: < 1280 kcal/day	313	63.05 (24.48, 150.23)	18.00 (10.62, 31.45)	3.32 (1.84, 5.38)
2nd quartile: 1280 – 1620 kcal/day	312	52.42 (27.22, 133.88)	16.92 (10.75, 30.31)	2.96 (1.94, 5.07)

	N	MEP[1] Median (Q1, Q3)[2] ng/mL	MnBP Median (Q1, Q3) ng/mL	MiBP Median (Q1, Q3) ng/mL
3rd quartile: 1620 – 2080 kcal/day	312	56.84 (23.40, 140.02)	15.39 (9.75, 29.30)	2.90 (1.78, 4.67)
4th quartile: > 2080 kcal/day	313	57.96 (23.63, 166.46)	17.35 (11.28, 30.13)	3.28 (2.10, 5.34)
p-value		0.95	0.40	0.10
Physical activity				
1st quartile: < 6.4	322	64.86 (24.36, 183.37)	18.82 (11.58, 31.65)	3.15 (1.86, 5.32)
2nd quartile: 6.4 – 7.6	326	48.33 (21.19, 107.89)	17.19 (10.78, 30.25)	3.19 (2.04, 5.37)
3rd quartile: 7.6 – 8.9	299	58.70 (25.44, 149.79)	15.17 (9.60, 27.96)	3.36 (1.90, 4.77)
4th quartile: > 8.9	303	52.68 (25.87, 157.14)	16.22 (10.09, 29.83)	2.88 (1.86, 4.83)
p-value		0.06	0.07	0.56
Menopausal status				
Pre- or peri- menopausal	520	60.27 (25.66, 161.89)	17.32 (11.20, 32.68)	3.19 (1.94, 5.28)
Natural/surgical menopause	591	55.18 (24.22, 131.86)	16.55 (10.37, 28.87)	3.06 (1.90, 5.07)
Unknown due to hormone therapy	139	51.72 (24.31, 156.36)	15.77 (9.54, 27.94)	3.13 (1.86, 4.71)
p-value		0.39	0.07	0.45
Currently on hormone therapy				
No	908	57.04 (24.25, 148.77)	16.96 (10.72, 30.60)	3.17 (1.94, 5.10)
Yes	342	54.00 (24.94, 154.45)	17.07 (10.15, 30.41)	3.06 (1.80, 5.23)
p-value		0.59	0.76	0.22
Obesity status				
Normal/underweight	460	44.16 (18.43, 103.03)	15.27 (9.48, 29.21)	2.94 (1.76, 4.74)
Overweight	360	59.24 (24.76, 145.91)	15.69 (10.56, 28.65)	2.98 (1.90, 4.60)
Obese	430	71.40 (29.50, 177.55)	19.55 (12.01, 32.71)	3.54 (2.09, 5.94)
p-value		<0.0001	<0.0001	0.0001

[1] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

Supplementary Table 3.3 Concentrations of MEHP, MEHHP, MEOHP, and MECPP by covariates

	N	MEHP[1] Median (Q1, Q3)[2] ng/mL	MEHHP Median (Q1, Q3) ng/mL	MEOHP Median (Q1, Q3) ng/mL	MECPP Median (Q1, Q3) ng/mL
Age					
≤ 52	555	3.18 (1.76, 6.25)	23.21 (12.14, 45.45)	11.20 (5.99, 23.10)	25.65 (14.38, 45.94)
> 52	695	2.39 (1.25, 5.08)	19.45 (10.24, 37.78)	8.96 (5.00, 18.50)	20.71 (11.56, 39.63)
p-value[3]		<0.0001	0.0015	0.0005	0.001
Site					
Detroit, MI	200	3.70 (1.47, 7.70)	30.47 (16.65, 70.44)	14.50 (7.42, 33.57)	29.36 (16.20, 64.65)
Boston, MA	210	3.41 (1.72, 6.91)	27.14 (14.92, 55.58)	12.66 (7.18, 26.86)	29.83 (17.63, 57.64)
Oakland, CA	276	1.93 (1.07, 3.84)	11.89 (7.43, 23.81)	5.85 (3.80, 11.44)	15.02 (9.36, 27.46)
Los Angeles, CA	353	2.41 (1.46, 4.42)	16.27 (9.12, 28.44)	7.96 (4.57, 14.55)	17.24 (10.50, 32.41)
Pittsburgh, PA	211	3.56 (1.80, 9.10)	32.42 (18.37, 62.74)	16.01 (8.76, 32.27)	34.36 (20.37, 63.78)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity					
White	655	2.68 (1.54, 5.29)	23.33 (12.78, 45.45)	11.36 (6.36, 22.84)	25.76 (14.66, 47.52)
Black	243	4.91 (2.09, 9.21)	33.24 (19.48, 70.25)	16.29 (8.74, 34.17)	35.12 (19.50, 64.05)
Chinese	154	1.94 (1.10, 3.57)	10.76 (7.06, 20.92)	4.99 (3.50, 9.63)	12.65 (8.45, 23.58)
Japanese	198	2.09 (1.28, 3.86)	11.64 (7.71, 22.92)	5.74 (3.75, 11.48)	13.86 (8.93, 27.14)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Education					
High school or less	212	2.44 (1.39, 5.30)	20.13 (11.44, 41.15)	10.18 (5.59, 18.59)	24.73 (13.06, 42.74)
Some college	398	3.02 (1.61, 6.59)	22.57 (11.27, 52.50)	11.03 (5.61, 24.43)	24.91 (12.62, 50.35)
College degree	320	2.56 (1.43, 4.85)	19.18 (9.81, 36.90)	9.19 (4.95, 16.69)	21.08 (11.36, 38.76)
Postgraduate	320	2.54 (1.38, 5.33)	21.20 (11.60, 42.47)	10.53 (5.56, 19.97)	22.90 (12.84, 41.04)
p-value		0.08	0.03	0.02	0.16
Smoking					
Never	781	2.61 (1.46, 5.17)	19.62 (10.42, 40.13)	9.69 (5.15, 18.55)	21.49 (12.00, 40.15)
Past	350	2.69 (1.40, 6.41)	23.83 (11.69, 47.00)	11.41 (5.79, 23.48)	25.61 (13.35, 50.29)
Current	119	3.29 (1.60, 6.42)	24.17 (13.15, 46.85)	11.34 (5.84, 23.52)	28.50 (13.21, 42.50)
p-value		0.30	0.01	0.02	0.03
Daily calorie intake					
1st quartile: < 1280 kcal/day	313	2.72 (1.52, 5.45)	19.62 (11.27, 41.78)	9.62 (5.50, 19.38)	22.16 (12.39, 46.89)

	N	MEHP[1] Median (Q1, Q3)[2] ng/mL	MEHHP Median (Q1, Q3) ng/mL	MEOHP Median (Q1, Q3) ng/mL	MECPP Median (Q1, Q3) ng/mL
2nd quartile: 1280 – 1620 kcal/day	312	2.61 (1.30, 6.09)	23.35 (10.96, 43.87)	11.01 (5.50, 21.12)	24.40 (12.99, 43.85)
3rd quartile: 1620 – 2080 kcal/day	312	2.76 (1.58, 5.16)	20.81 (11.00, 39.78)	10.44 (5.28, 19.33)	22.83 (12.41, 40.16)
4th quartile: > 2080 kcal/day	313	2.55 (1.44, 5.70)	21.17 (10.79, 43.19)	10.26 (5.49, 21.57)	23.57 (11.97, 43.18)
p-value		0.95	0.79	0.77	0.83
Physical activity					
1st quartile: < 6.4	322	2.51 (1.35, 4.90)	20.24 (11.27, 43.16)	9.60 (5.32, 20.87)	22.82 (11.32, 43.31)
2nd quartile: 6.4 – 7.6	326	2.49 (1.40, 5.32)	21.64 (10.71, 43.93)	10.74 (5.21, 21.42)	24.96 (12.45, 43.26)
3rd quartile: 7.6 – 8.9	299	2.70 (1.55, 6.20)	21.96 (11.23, 38.17)	10.41 (5.65, 18.73)	23.62 (12.90, 42.94)
4th quartile: > 8.9	303	3.13 (1.62, 5.93)	21.55 (10.86, 41.31)	10.49 (5.56, 20.10)	22.43 (12.74, 41.11)
p-value		0.12	1.00	0.92	0.83
Menopausal status					
Pre- or peri-menopausal	520	2.84 (1.59, 6.06)	21.47 (11.40, 41.20)	10.46 (5.66, 19.43)	22.83 (13.04, 41.27)
Natural/surgical menopause	591	2.57 (1.36, 5.46)	20.78 (10.99, 42.87)	10.21 (5.29, 20.95)	23.89 (11.94, 44.24)
Unknown due to hormone therapy	139	2.56 (1.47, 4.55)	20.10 (9.97, 39.96)	9.96 (4.53, 22.95)	20.64 (10.94, 41.87)
p-value		0.16	0.59	0.69	0.68
Currently on hormone therapy					
No	908	2.66 (1.45, 5.46)	20.73 (11.19, 41.28)	10.23 (5.50, 19.58)	22.75 (12.43, 42.56)
Yes	342	2.68 (1.48, 5.92)	22.10 (10.79, 43.86)	10.95 (5.15, 22.35)	25.09 (11.83, 42.41)
p-value		0.58	0.60	0.50	0.82
Obesity status					
Normal/underweight	460	2.56 (1.48, 4.77)	16.73 (9.12, 33.53)	8.53 (4.77, 15.87)	18.21 (10.72, 34.86)
Overweight	360	2.75 (1.40, 5.38)	20.13 (10.83, 39.74)	9.88 (5.18, 19.03)	21.33 (12.39, 39.55)
Obese	430	2.74 (1.45, 6.48)	27.07 (14.12, 56.20)	12.88 (6.55, 26.61)	28.66 (16.66, 56.92)
p-value		0.32	<0.0001	<0.0001	<0.0001

[1] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

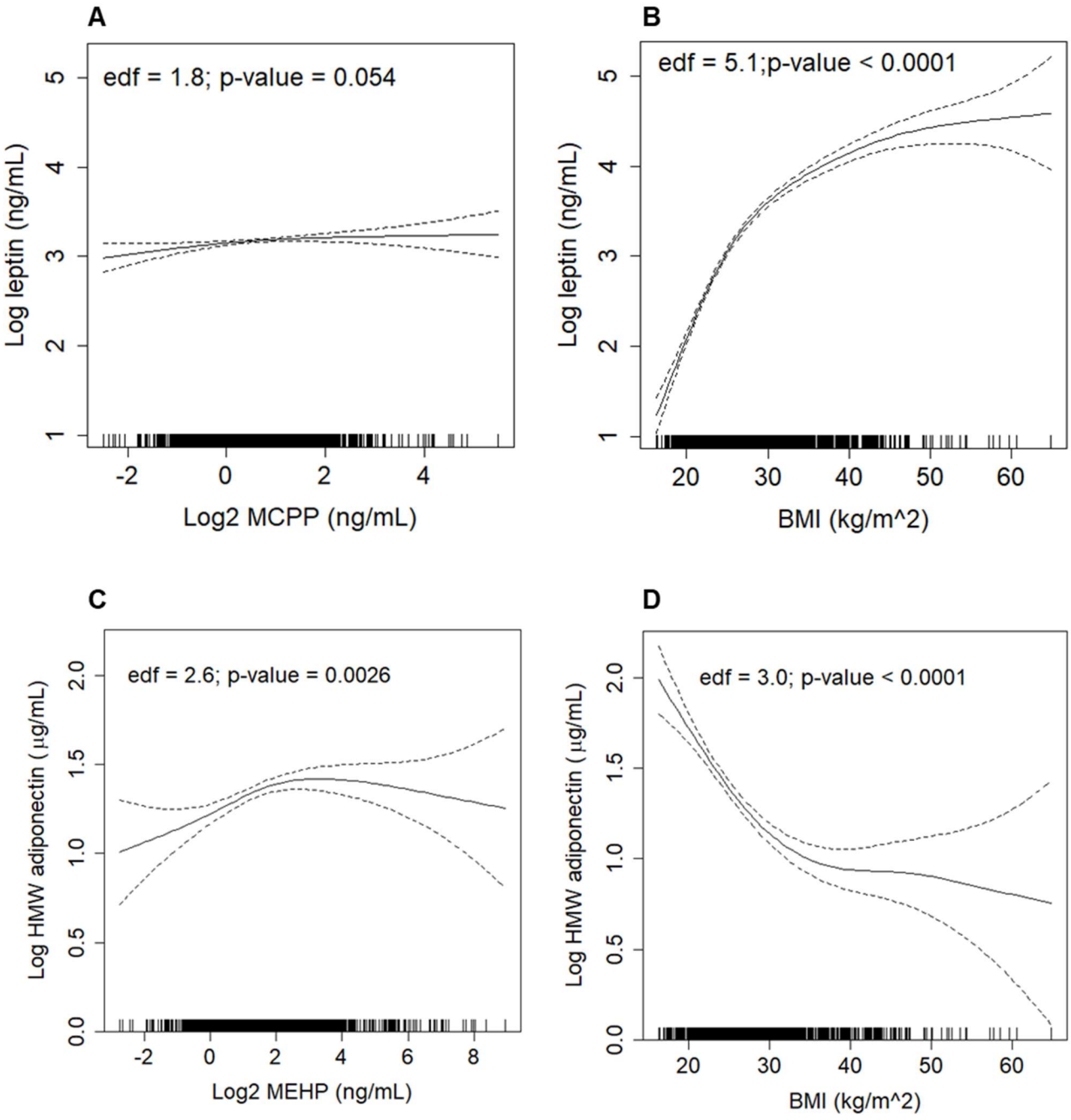
Supplementary Table 3.4 Concentrations of MBzP, MCOP, MCNP, and MCPP by covariates

	N	**MBzP**[1] Median (Q1, Q3)[2] ng/mL	**MCOP** Median (Q1, Q3) ng/mL	**MCNP** Median (Q1, Q3) ng/mL	**MCPP** Median (Q1, Q3) ng/mL
Age					
≤ 52	555	7.89 (4.36, 14.24)	3.29 (2.00, 5.57)	2.10 (1.23, 3.87)	1.58 (1.08, 2.49)
> 52	695	6.88 (3.61, 11.14)	2.74 (1.68, 5.16)	1.81 (0.99, 3.30)	1.48 (0.93, 2.17)
p-value[3]		0.0003	0.01	0.002	0.01
Site					
Detroit, MI	200	10.44 (6.12, 17.35)	3.30 (2.06, 6.00)	2.55 (1.52, 4.42)	1.80 (1.31, 2.65)
Boston, MA	210	7.65 (4.58, 12.34)	3.84 (2.40, 6.56)	2.28 (1.40, 3.73)	1.49 (1.09, 2.38)
Oakland, CA	276	4.74 (2.64, 8.82)	2.41 (1.50, 3.76)	1.42 (0.87, 2.51)	1.26 (0.75, 2.00)
Los Angeles, CA	353	5.64 (3.37, 9.82)	2.59 (1.49, 4.62)	1.47 (0.82, 2.59)	1.26 (0.86, 1.97)
Pittsburgh, PA	211	9.72 (6.08, 14.76)	4.32 (2.56, 7.00)	2.72 (1.86, 4.43)	2.07 (1.47, 3.21)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity					
White	655	7.75 (4.32, 12.99)	3.37 (2.12, 5.54)	2.30 (1.47, 3.91)	1.73 (1.23, 2.68)
Black	243	10.49 (6.43, 17.35)	4.20 (2.36, 6.77)	2.52 (1.45, 4.12)	1.73 (1.24, 2.56)
Chinese	154	3.86 (2.22, 6.69)	2.09 (1.25, 3.30)	1.04 (0.65, 1.80)	1.02 (0.63, 1.54)
Japanese	198	4.89 (3.03, 8.70)	2.09 (1.29, 3.81)	0.93 (0.59, 1.70)	0.98 (0.74, 1.59)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Education					
High school or less	212	7.36 (4.03, 13.89)	2.93 (1.78, 5.47)	1.63 (0.96, 2.64)	1.46 (0.94, 2.34)
Some college	398	8.26 (4.33, 14.20)	3.02 (1.82, 5.09)	1.84 (1.01, 3.35)	1.57 (0.99, 2.23)
College degree	320	6.55 (3.48, 11.15)	2.86 (1.62, 5.17)	1.88 (1.05, 3.71)	1.48 (0.95, 2.17)
Postgraduate	320	7.08 (3.71, 11.08)	3.32 (2.10, 5.72)	2.23 (1.36, 4.04)	1.67 (1.13, 2.63)
p-value		0.02	0.19	<0.0001	0.03
Smoking					
Never	781	6.55 (3.52, 11.01)	2.93 (1.73, 5.27)	1.80 (1.00, 3.48)	1.48 (0.94, 2.34)
Past	350	8.36 (4.33, 13.92)	3.33 (2.07, 5.43)	2.12 (1.29, 3.60)	1.63 (1.14, 2.34)
Current	119	9.46 (5.41, 17.71)	2.85 (1.76, 5.34)	1.96 (1.19, 3.05)	1.58 (1.13, 2.24)
p-value		<0.0001	0.05	0.02	0.10
Daily calorie intake					
1st quartile: < 1280 kcal/day	313	6.95 (3.61, 12.18)	3.21 (1.74, 5.44)	1.73 (0.98, 3.25)	1.45 (0.95, 2.17)
2nd quartile: 1280 – 1620 kcal/day	312	6.92 (3.83, 11.44)	3.04 (1.88, 5.27)	1.87 (1.06, 3.41)	1.61 (1.08, 2.40)

	N	MBzP[1] Median (Q1, Q3)[2] ng/mL	MCOP Median (Q1, Q3) ng/mL	MCNP Median (Q1, Q3) ng/mL	MCPP Median (Q1, Q3) ng/mL
3rd quartile: 1620 – 2080 kcal/day	312	7.16 (3.95, 10.93)	2.94 (1.70, 5.17)	1.98 (1.08, 3.61)	1.55 (0.93, 2.46)
4th quartile: > 2080 kcal/day	313	8.76 (4.36, 14.92)	3.08 (1.89, 5.40)	2.08 (1.25, 3.48)	1.57 (1.01, 2.27)
p-value		0.01	0.75	0.16	0.33
Physical activity					
1st quartile: < 6.4	322	7.63 (4.35, 13.50)	3.01 (1.70, 5.33)	1.79 (1.03, 3.24)	1.46 (0.94, 2.28)
2nd quartile: 6.4 – 7.6	326	7.22 (3.97, 11.44)	3.15 (1.82, 5.39)	1.83 (1.03, 3.60)	1.47 (0.92, 2.14)
3rd quartile: 7.6 – 8.9	299	6.74 (3.53, 11.39)	2.76 (1.81, 5.30)	1.90 (1.04, 3.45)	1.57 (1.01, 2.32)
4th quartile: > 8.9	303	7.60 (3.85, 12.42)	3.22 (1.93, 5.48)	2.18 (1.29, 3.70)	1.68 (1.18, 2.53)
p-value		0.10	0.73	0.06	0.01
Menopausal status					
Pre- or peri-menopausal	520	7.63 (4.33, 12.47)	3.03 (1.76, 5.38)	1.90 (1.10, 3.35)	1.55 (0.97, 2.33)
Natural/surgical menopause	591	7.18 (3.92, 12.74)	3.08 (1.89, 5.29)	1.88 (1.04, 3.45)	1.52 (1.02, 2.31)
Unknown due to hormone therapy	139	6.89 (3.40, 10.91)	3.00 (1.82, 5.37)	2.14 (1.20, 3.81)	1.46 (0.88, 2.29)
p-value		0.19	0.83	0.68	0.58
Currently on hormone therapy					
No	908	7.24 (3.96, 12.41)	2.99 (1.82, 5.36)	1.84 (1.05, 3.33)	1.54 (0.99, 2.33)
Yes	342	7.27 (3.70, 12.43)	3.19 (1.83, 5.33)	2.17 (1.16, 3.97)	1.55 (0.99, 2.31)
p-value		0.92	0.74	0.03	0.89
Obesity status					
Normal/underweight	460	5.62 (3.24, 10.16)	2.57 (1.54, 4.62)	1.56 (0.91, 2.92)	1.40 (0.89, 2.16)
Overweight	360	6.98 (3.58, 11.36)	2.87 (1.89, 5.00)	1.86 (1.04, 3.35)	1.45 (0.95, 2.16)
Obese	430	8.86 (5.48, 15.61)	3.93 (2.26, 6.14)	2.31 (1.40, 3.94)	1.71 (1.22, 2.60)
p-value		<0.0001	<0.0001	<0.0001	<0.0001

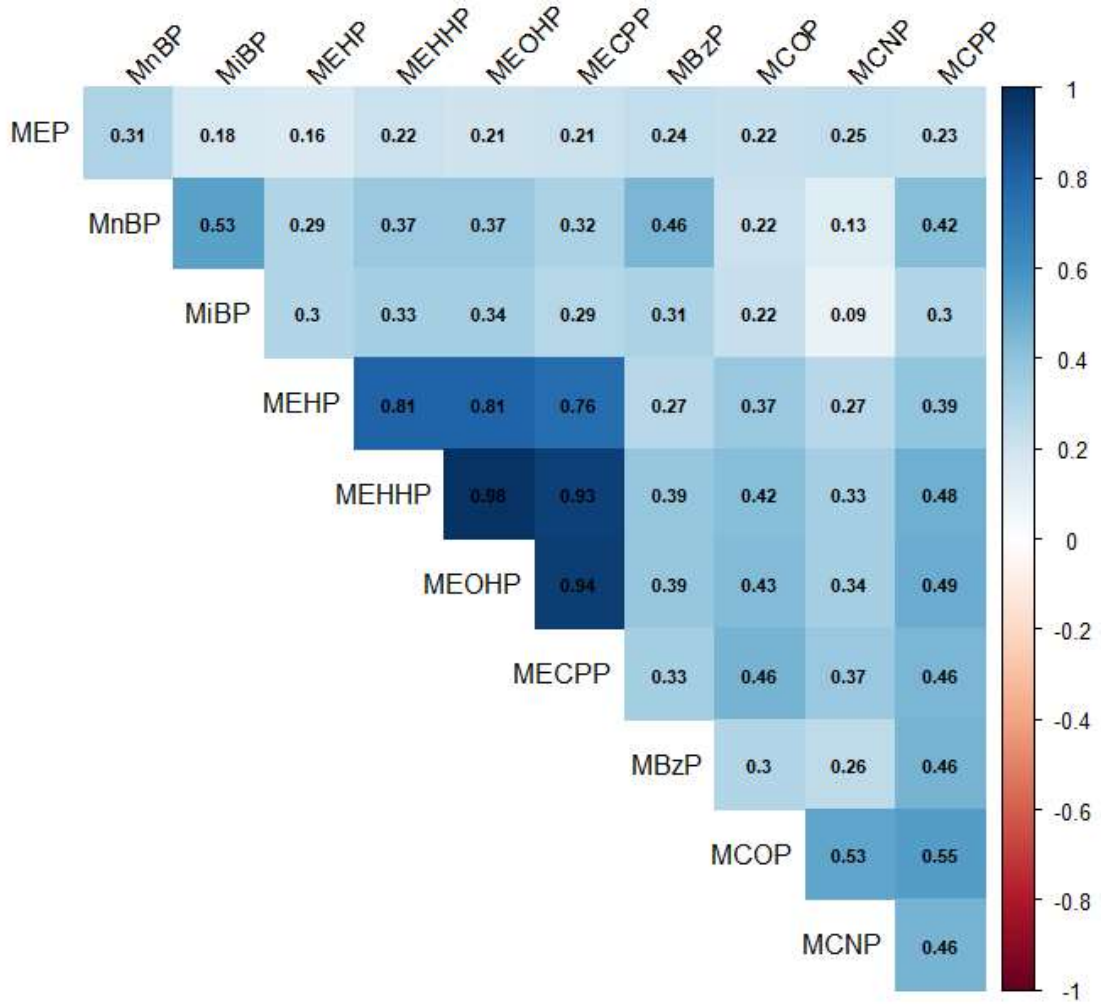
[1] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method.
[2] "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[3] p-values were obtained from Kruskal-Wallis tests.

Supplementary Figure 3.1 Select smoothing curves from generalized additive models



Smoothing curves of MCPP, MEHP, and BMI. Panels A and B came from a model with log leptin as the outcome. Panels C and D came from a model with log HMW adiponectin as the outcome. All models were fully adjusted. Edf = estimated degree of freedom of the smooth term. A value greater than 1 indicates non-linear association. P-value indicates the statistical significance of the smooth term.

Supplementary Figure 3.2 Spearman correlation coefficients between phthalate metabolites



Metabolite concentrations were adjusted for hydration using covariate-adjusted creatinine standardization.

Supplementary Table 3.5 Percent differences in leptin associated with phthalate metabolite concentration quartiles

			Percent difference in leptin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEP	1	2.36 - 24.49	ref	ref
	2	24.49 - 56.71	9.2 (-3.8, 24.0)	2.9 (-5.5, 11.9)
	3	56.74 - 149.12	**18.4 (3.7, 35.1)**	**10.5 (1.3, 20.7)**
	4	150.23 - 7862.84	11.2 (-3.1, 27.5)	-0.8 (-9.4, 8.7)
	p-trend		0.54	0.27
MnBP	1	1.45 - 10.59	ref	ref
	2	10.62 - 16.98	**19.9 (5.8, 35.9)**	6.4 (-2.1, 15.6)
	3	16.99 - 30.54	9.9 (-3.2, 24.9)	2.7 (-5.7, 11.8)
	4	30.59 - 335.21	9.5 (-3.9, 24.7)	3.7 (-4.9, 13.0)
	p-trend		0.72	0.74
MiBP	1	0.13 - 1.90	ref	ref
	2	1.90 - 3.13	**15.9 (2.3, 31.3)**	7.4 (-1.1, 16.7)
	3	3.13 - 5.14	**14.5 (0.8, 30.0)**	**9.2 (0.4, 18.7)**
	4	5.14 - 84.82	**14.3 (0.5, 29.8)**	6.8 (-1.9, 16.3)
	p-trend		0.15	0.28
MEHP	1	0.15 - 1.46	ref	ref
	2	1.46 - 2.66	-2.0 (-13.7, 11.2)	0.3 (-7.7, 9.1)
	3	2.66 - 5.59	-9.7 (-20.5, 2.5)	-3.3 (-11.1, 5.2)
	4	5.61 - 491.18	-0.3 (-12.5, 13.6)	4.3 (-4.4, 13.7)
	p-trend		0.76	0.23
MEHHP	1	1.12 - 10.98	ref	ref
	2	10.99 - 21.17	6.3 (-6.6, 21.0)	-2.4 (-10.5, 6.3)
	3	21.17 - 41.78	**22.1 (7.0, 39.2)**	**9.6 (0.4, 19.6)**

			Percent difference in leptin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEOHP	4	41.81 - 2286.01	**24.1 (8.3, 42.2)**	7.6 (-1.8, 17.7)
	p-trend		**0.0052**	0.073
	1	0.61 - 5.44	ref	ref
	2	5.46 - 10.34	9.5 (-3.7, 24.6)	2.1 (-6.3, 11.2)
	3	10.34 - 20.26	**17.0 (2.6, 33.5)**	7.4 (-1.6, 17.2)
	4	20.34 - 1006.33	**26.9 (10.7, 45.4)**	**10.9 (1.3, 21.5)**
	p-trend		**0.0019**	**0.025**
MECPP	1	2.25 - 12.35	ref	ref
	2	12.38 - 23.57	**15.4 (1.5, 31.1)**	1.2 (-7.1, 10.2)
	3	23.62 - 42.46	**26.4 (11.0, 44.0)**	5.2 (-3.6, 14.8)
	4	42.54 - 2160.10	**29.5 (13.3, 47.9)**	8.5 (-0.8, 18.6)
	p-trend		**0.0031**	0.062
MBzP	1	0.15 - 3.92	ref	ref
	2	3.93 - 7.26	13.1 (-0.2, 28.3)	-0.6 (-8.6, 8.1)
	3	7.26 - 12.40	**18.8 (4.4, 35.2)**	-0.4 (-8.7, 8.6)
	4	12.44 - 317.65	**29.5 (13.4, 47.9)**	3.5 (-5.3, 13.2)
	p-trend		**0.00045**	0.34
MCOP	1	0.24 - 1.82	ref	ref
	2	1.82 - 3.03	13.2 (-0.3, 28.4)	6.9 (-1.7, 16.3)
	3	3.04 - 5.35	**29.0 (13.4, 46.7)**	7.3 (-1.6, 17.0)
	4	5.36 - 222.53	**29.4 (13.5, 47.4)**	7.1 (-1.9, 16.9)
	p-trend		**0.00063**	0.32
MCNP	1	0.12 - 1.08	ref	ref
	2	1.08 - 1.93	**21.5 (6.6, 38.4)**	8.1 (-0.9, 17.9)
	3	1.93 - 3.46	**17.1 (2.2, 34.2)**	-0.3 (-8.9, 9.2)

			Percent difference in leptin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MCPP	4	3.46 - 321.75	**24.3 (8.3, 42.6)**	-0.02 (-8.8, 9.6)
	p-trend		**0.031**	0.42
	1	0.18 - 0.99	ref	ref
	2	0.99 - 1.54	**16.5 (2.4, 32.5)**	5.0 (-3.6, 14.3)
	3	1.54 - 2.32	**15.1 (0.8, 31.5)**	5.8 (-3.1, 15.6)
	4	2.33 - 45.44	**20.0 (4.8, 37.3)**	7.7 (-1.6, 17.8)
	p-trend		**0.039**	0.16

Model 1: Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2: Model 1 + BMI (natural spline with knots at the 25th and 75th percentiles)

Supplementary Table 3.6 Percent differences in HMW adiponectin associated with phthalate metabolite concentration quartiles

			Percent difference in HMW adiponectin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEP	1	2.36 - 24.49	ref	ref
	2	24.49 - 56.71	-4.4 (-16.3, 9.1)	-2.8 (-14.4, 10.4)
	3	56.74 - 149.12	-2.6 (-15.1, 11.8)	-0.9 (-13.2, 13.1)
	4	150.23 - 7862.84	1.6 (-11.9, 17.2)	5.0 (-8.5, 20.5)
	p-trend		0.49	0.26
MnBP	1	1.45 - 10.59	ref	ref
	2	10.62 - 16.98	-2.4 (-14.3, 11.2)	3.0 (-9.1, 16.7)
	3	16.99 - 30.54	-0.6 (-12.9, 13.5)	3.3 (-9.1, 17.3)
	4	30.59 - 335.21	0.5 (-12.3, 15.0)	3.2 (-9.4, 17.5)
	p-trend		0.82	0.74
MiBP	1	0.13 - 1.90	ref	ref
	2	1.90 - 3.13	-5.8 (-17.3, 7.2)	-3.1 (-14.5, 9.8)
	3	3.13 - 5.14	-5.1 (-16.7, 8.2)	-3.0 (-14.4, 10.0)
	4	5.14 - 84.82	0.3 (-12.2, 14.5)	3.5 (-8.9, 17.6)
	p-trend		0.69	0.43
MEHP	1	0.15 - 1.46	ref	ref
	2	1.46 - 2.66	**20.0 (5.3, 36.6)**	**19.2 (5.3, 35.1)**
	3	2.66 - 5.59	**28.6 (12.9, 46.7)**	**26.1 (11.2, 43.0)**
	4	5.61 - 491.18	**26.9 (11.0, 45.1)**	**26.0 (10.8, 43.3)**
	p-trend		**0.015**	**0.013**
MEHHP	1	1.12 - 10.98	ref	ref
	2	10.99 - 21.17	3.0 (-9.9, 17.8)	6.8 (-6.1, 21.5)
	3	21.17 - 41.78	2.0 (-11.0, 17.0)	6.5 (-6.6, 21.5)

			Percent difference in HMW adiponectin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEOHP	4	41.81 - 2286.01	-0.9 (-14.0, 14.1)	5.5 (-8.0, 20.8)
	p-trend		0.66	0.79
	1	0.61 - 5.44	ref	ref
	2	5.46 - 10.34	3.9 (-9.1, 18.7)	7.2 (-5.7, 21.9)
	3	10.34 - 20.26	2.7 (-10.4, 17.9)	6.7 (-6.5, 21.7)
	4	20.34 - 1006.33	2.6 (-10.9, 18.2)	9.3 (-4.6, 25.3)
	p-trend		0.93	0.38
MECPP	1	2.25 - 12.35	ref	ref
	2	12.38 - 23.57	0.1 (-12.4, 14.3)	6.4 (-6.4, 20.9)
	3	23.62 - 42.46	-2.1 (-14.5, 12.2)	5.9 (-7.1, 20.8)
	4	42.54 - 2160.10	-0.9 (-13.7, 13.9)	7.6 (-5.9, 23.1)
	p-trend		0.92	0.48
MBzP	1	0.15 - 3.92	ref	ref
	2	3.93 - 7.26	-7.8 (-19.1, 5.0)	-2.3 (-13.8, 10.8)
	3	7.26 - 12.40	0.7 (-11.9, 15.1)	9.0 (-4.2, 24.1)
	4	12.44 - 317.65	**-15.8 (-26.6, -3.3)**	-7.0 (-18.7, 6.3)
	p-trend		**0.018**	0.23
MCOP	1	0.24 - 1.82	ref	ref
	2	1.82 - 3.03	8.6 (-4.7, 23.8)	10.7 (-2.4, 25.6)
	3	3.04 - 5.35	**-13.6 (-24.4, -1.3)**	-6.8 (-18.1, 6.1)
	4	5.36 - 222.53	-5.9 (-17.8, 7.8)	2.0 (-10.5, 16.3)
	p-trend		0.16	0.84
MCNP	1	0.12 - 1.08	ref	ref
	2	1.08 - 1.93	2.3 (-10.7, 17.1)	6.7 (-6.4, 21.5)
	3	1.93 - 3.46	1.6 (-11.8, 17.1)	8.2 (-5.6, 23.9)

			Percent difference in HMW adiponectin (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MCPP	4	3.46 - 321.75	-9.6 (-21.7, 4.3)	-1.2 (-14.0, 13.4)
	p-trend		0.057	0.41
	1	0.18 - 0.99	ref	ref
	2	0.99 - 1.54	3.1 (-9.8, 17.8)	8.1 (-4.9, 22.8)
	3	1.54 - 2.32	4.9 (-8.7, 20.4)	9.1 (-4.4, 24.6)
	4	2.33 - 45.44	1.6 (-11.6, 16.9)	6.7 (-6.8, 22.1)
	p-trend		0.96	0.57

Model 1: Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2: Model 1 + BMI (natural spline with knots at the 25th and 75th percentiles)

Supplementary Table 3.7 Percent differences in the leptin: HMW adiponectin ratio associated with phthalate metabolite concentration quartiles

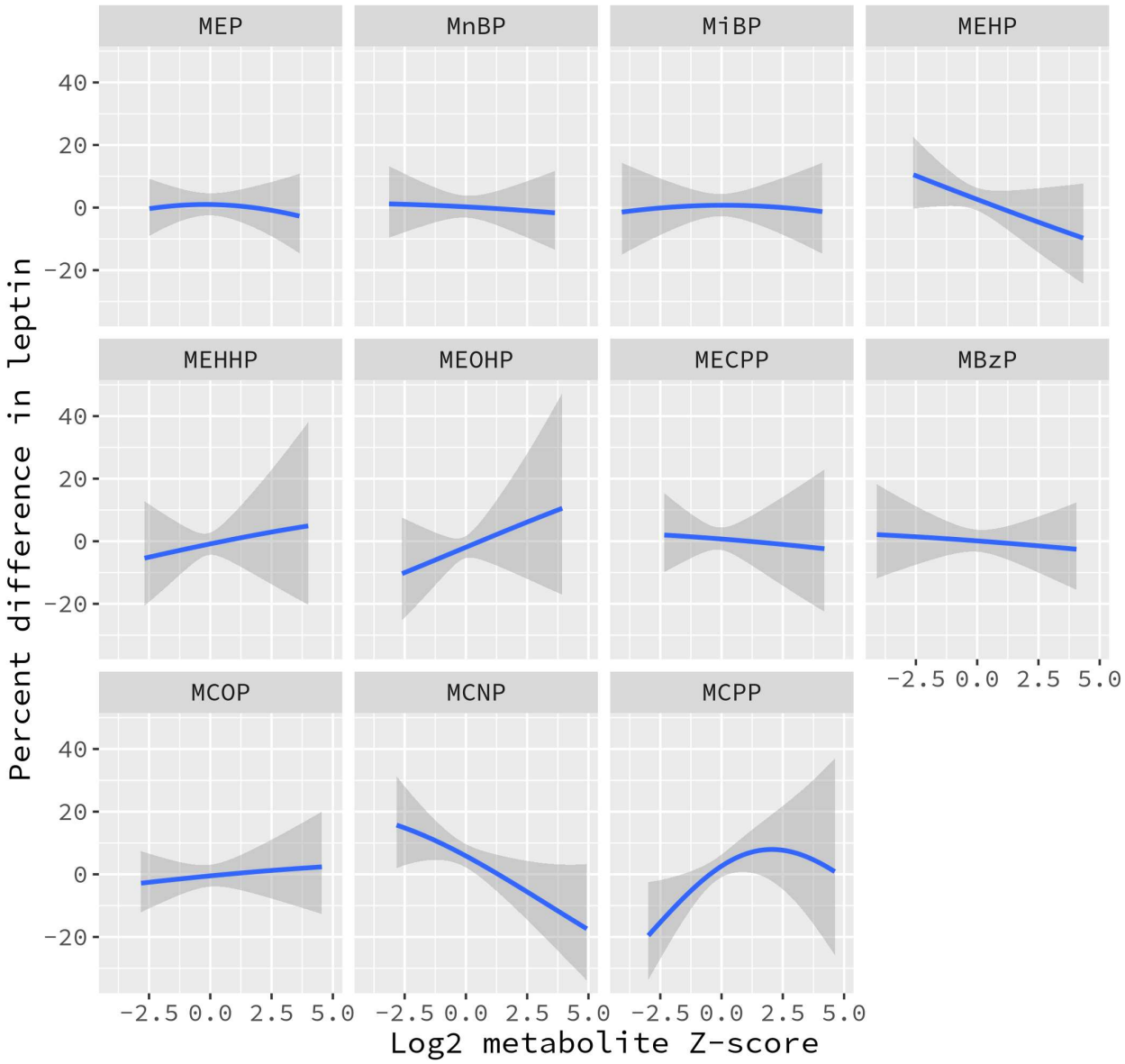
			Percent difference in the leptin: HMW adiponectin ratio (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEP	1	2.36 - 24.49	ref	ref
	2	24.49 - 56.71	12.1 (-9.1, 38.3)	5.0 (-10.6, 23.3)
	3	56.74 - 149.12	21.0 (-2.7, 50.6)	11.2 (-5.9, 31.5)
	4	150.23 - 7862.84	8.6 (-13.4, 36.2)	-5.3 (-20.4, 12.7)
	p-trend		0.96	0.17
MnBP	1	1.45 - 10.59	ref	ref
	2	10.62 - 16.98	**25.4 (2.0, 54.1)**	3.4 (-11.8, 21.2)
	3	16.99 - 30.54	12.5 (-8.8, 38.8)	0.6 (-14.4, 18.2)
	4	30.59 - 335.21	10.0 (-11.2, 36.3)	0.7 (-14.6, 18.7)
	p-trend		0.94	0.94
MiBP	1	0.13 - 1.90	ref	ref
	2	1.90 - 3.13	**24.7 (1.5, 53.2)**	12.3 (-4.1, 31.5)
	3	3.13 - 5.14	22.6 (-0.4, 51.0)	14.4 (-2.4, 34.2)
	4	5.14 - 84.82	14.3 (-7.3, 41.1)	4.4 (-11.2, 22.6)
	p-trend		0.54	0.96
MEHP	1	0.15 - 1.46	ref	ref
	2	1.46 - 2.66	**-19.2 (-34.4, -0.6)**	**-16.9 (-29.1, -2.6)**
	3	2.66 - 5.59	**-30.5 (-43.6, -14.3)**	**-24.0 (-35.2, -10.8)**
	4	5.61 - 491.18	**-22.4 (-37.4, -4.0)**	**-17.7 (-30.2, -3.1)**
	p-trend		0.16	0.19
MEHHP	1	1.12 - 10.98	ref	ref
	2	10.99 - 21.17	4.2 (-15.8, 29.0)	-8.5 (-22.3, 7.8)
	3	21.17 - 41.78	20.0 (-3.4, 49.1)	3.4 (-12.5, 22.2)

			Percent difference in the leptin: HMW adiponectin ratio (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MEOHP	4	41.81 - 2286.01	24.5 (-0.5, 55.9)	1.9 (-14.3, 21.1)
	p-trend		0.062	0.48
	1	0.61 - 5.44	ref	ref
	2	5.46 - 10.34	6.1 (-14.2, 31.3)	-5.2 (-19.4, 11.6)
	3	10.34 - 20.26	13.6 (-8.6, 41.3)	0.9 (-14.7, 19.2)
	4	20.34 - 1006.33	23.4 (-1.5, 54.5)	1.3 (-14.8, 20.5)
	p-trend		0.075	0.63
MECPP	1	2.25 - 12.35	ref	ref
	2	12.38 - 23.57	16.8 (-5.4, 44.3)	-4.5 (-18.8, 12.3)
	3	23.62 - 42.46	**28.7 (3.8, 59.6)**	-1.4 (-16.5, 16.4)
	4	42.54 - 2160.10	**30.2 (4.4, 62.2)**	0.4 (-15.3, 19.0)
	p-trend		0.077	0.72
MBzP	1	0.15 - 3.92	ref	ref
	2	3.93 - 7.26	22.8 (-0.1, 50.9)	2.2 (-12.9, 19.8)
	3	7.26 - 12.40	17.3 (-5.2, 45.0)	-9.0 (-22.8, 7.2)
	4	12.44 - 317.65	**51.5 (21.8, 88.4)**	10.8 (-6.5, 31.2)
	p-trend		**0.00053**	0.18
MCOP	1	0.24 - 1.82	ref	ref
	2	1.82 - 3.03	3.9 (-15.6, 27.8)	-3.3 (-17.6, 13.6)
	3	3.04 - 5.35	**50.7 (22.0, 86.1)**	15.2 (-2.2, 35.7)
	4	5.36 - 222.53	**38.7 (11.9, 71.9)**	5.5 (-10.7, 24.7)
	p-trend		**0.0022**	0.45
MCNP	1	0.12 - 1.08	ref	ref
	2	1.08 - 1.93	17.5 (-5.2, 45.8)	1.1 (-14.3, 19.3)
	3	1.93 - 3.46	14.0 (-8.8, 42.6)	-8.5 (-23.0, 8.7)

			Percent difference in the leptin: HMW adiponectin ratio (%) (95% CI)	
	Quartile	Metabolite range (ng/mL)	Model 1	Model 2
MCPP	4	3.46 - 321.75	**37.3 (9.4, 72.2)**	1.4 (-14.9, 20.8)
	p-trend		**0.011**	0.78
	1	0.18 - 0.99	ref	ref
	2	0.99 - 1.54	13.7 (-8.0, 40.5)	-3.1 (-17.6, 14.0)
	3	1.54 - 2.32	11.2 (-10.7, 38.5)	-2.2 (-17.3, 15.7)
	4	2.33 - 45.44	19.1 (-4.7, 48.9)	2.5 (-13.6, 21.7)
	p-trend		0.20	0.61

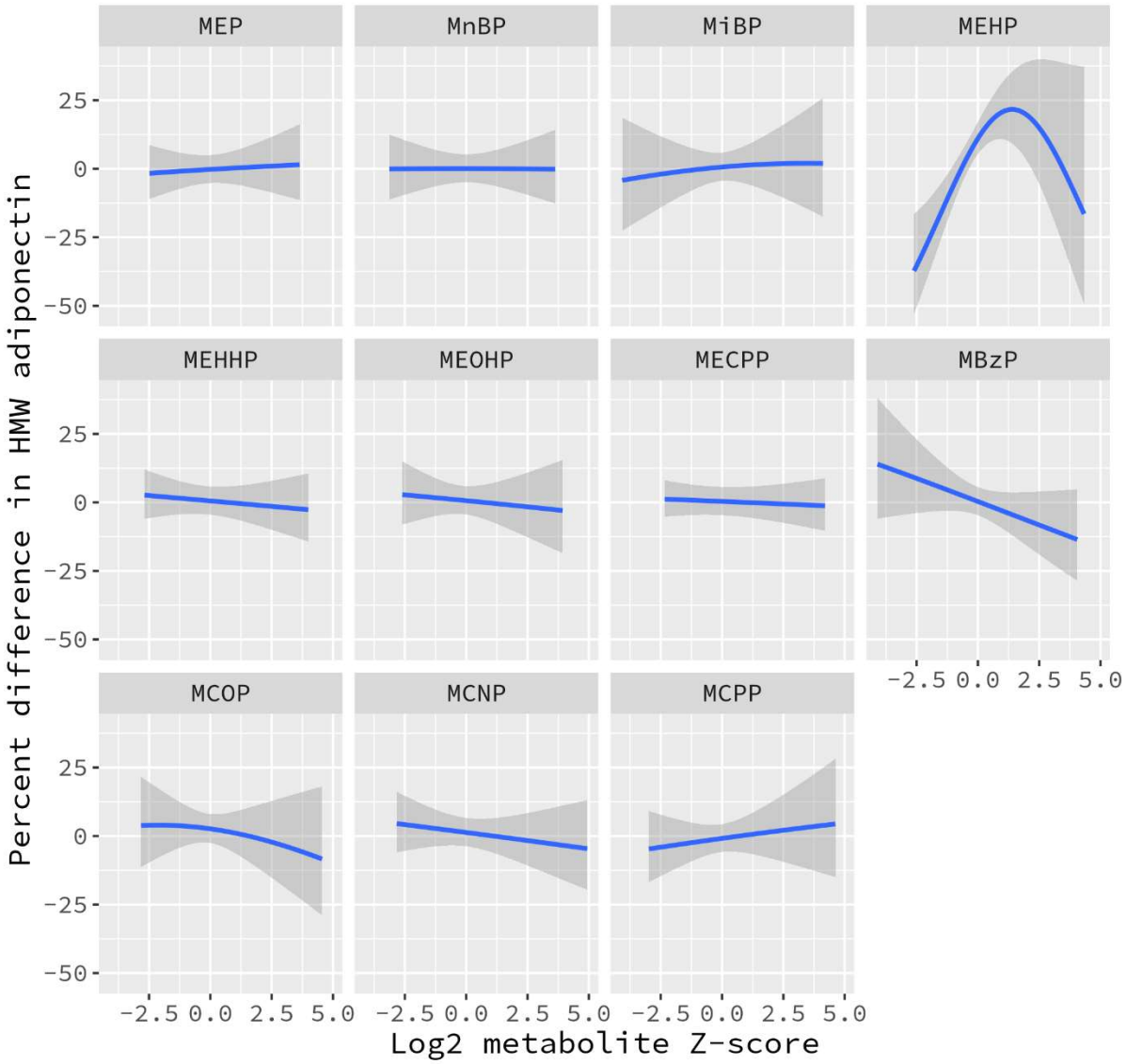
Model 1: Adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, and dietary energy intake.
Model 2: Model 1 + BMI (natural spline with knots at the 25th and 75th percentiles)

Supplementary Figure 3.3 Dose-response curves between each phthalate metabolite and leptin as estimated by BKMR



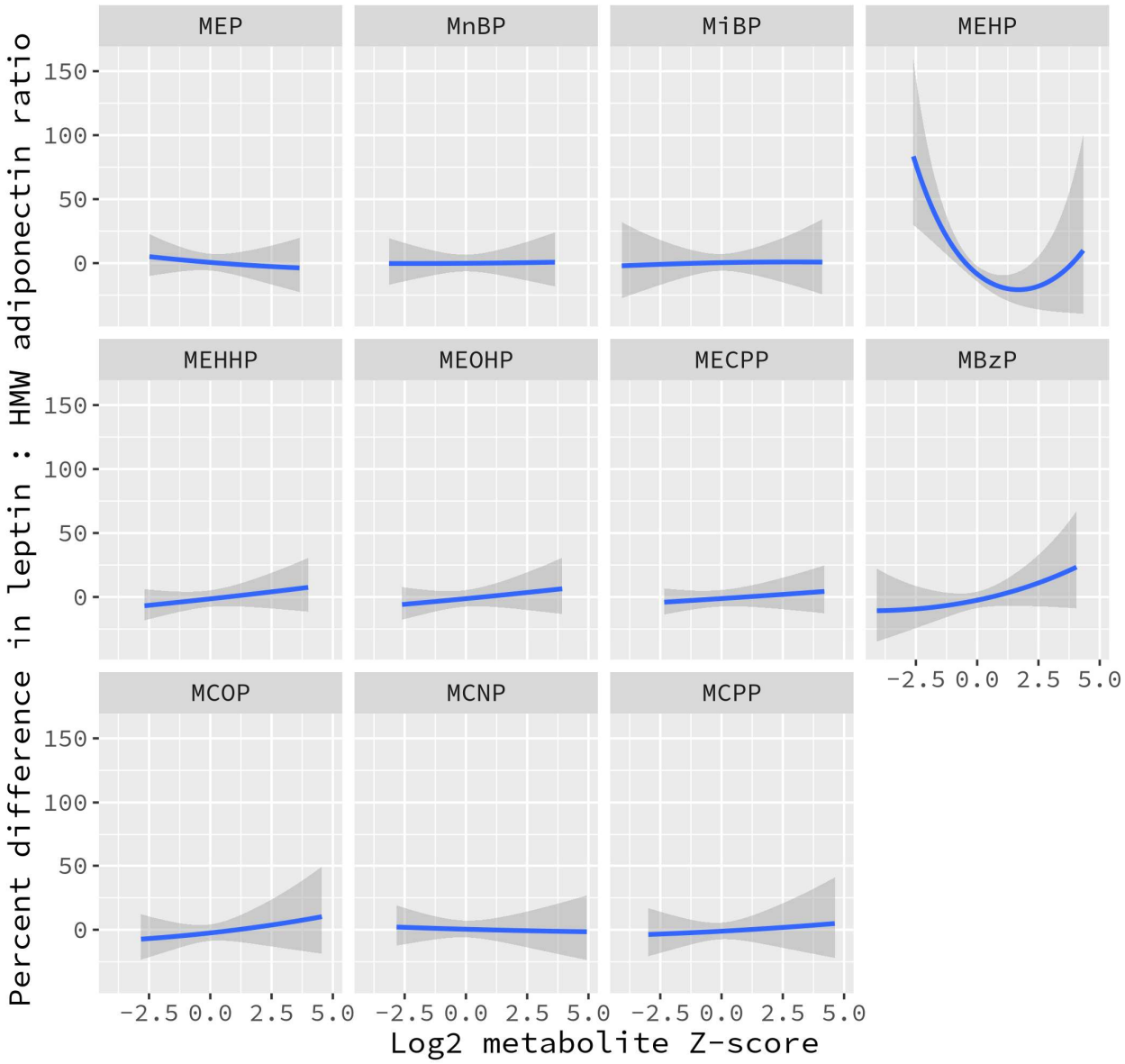
The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Supplementary Figure 3.4 Dose-response curves between each phthalate metabolite and HMW adiponectin as estimated by BKMR



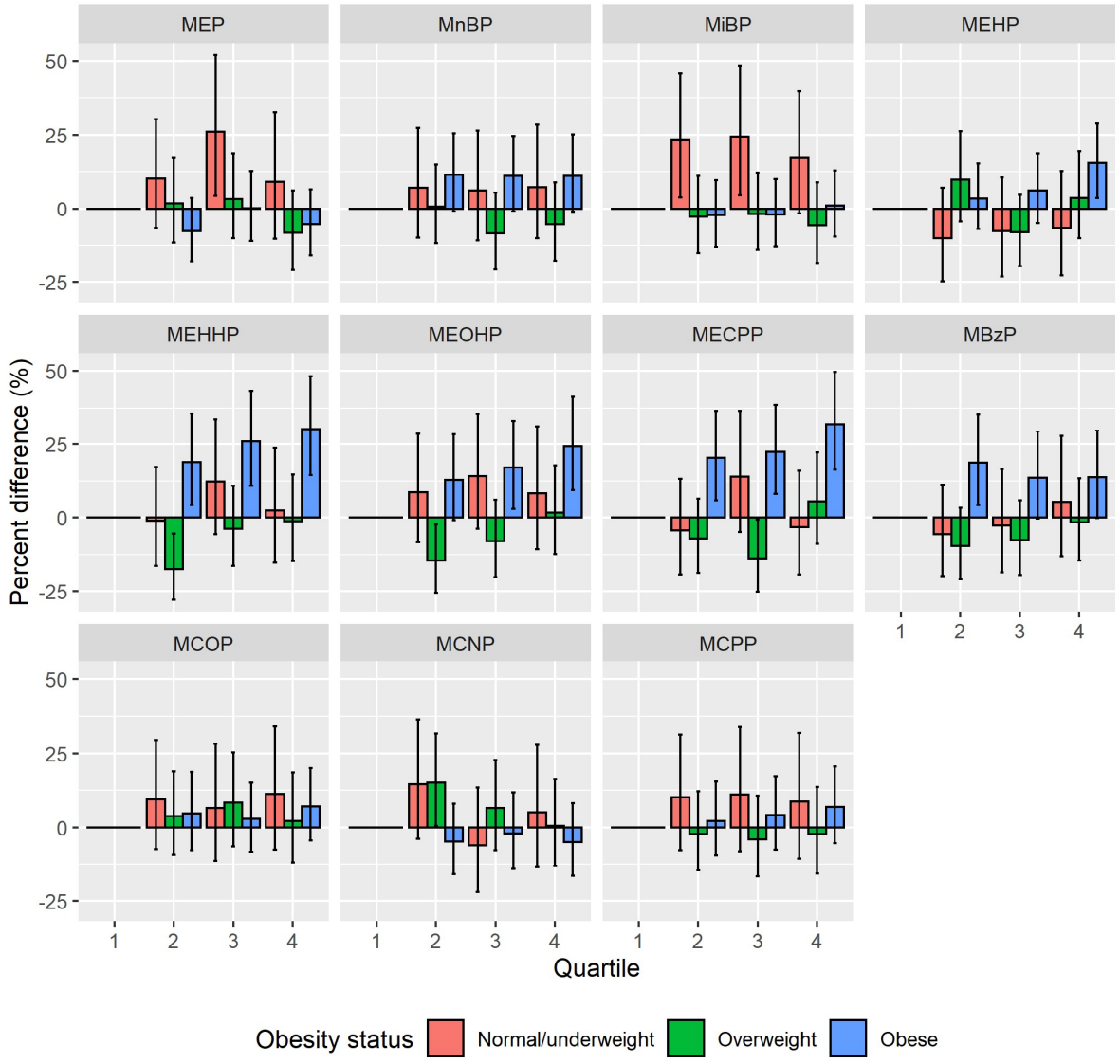
The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Supplementary Figure 3.5 Dose-response curves between each phthalate metabolite and the leptin:HMW adiponectin ratio as estimated by BKMR



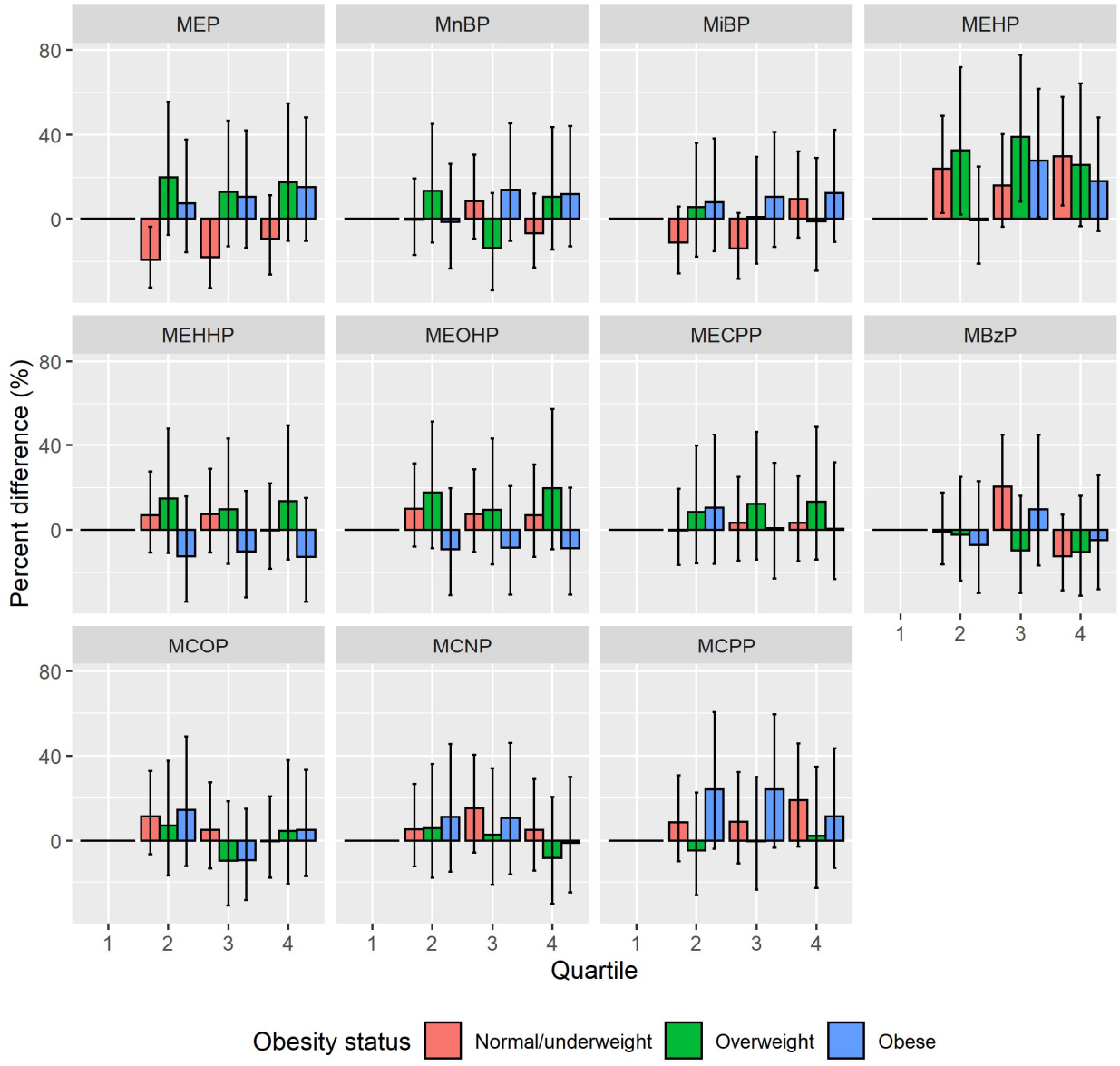
The BKMR model was adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI (natural spline with knots at the 25th and 75th percentiles).

Supplementary Figure 3.6 Percent differences in leptin associated with phthalate metabolite concentration quartiles, stratified by obesity status



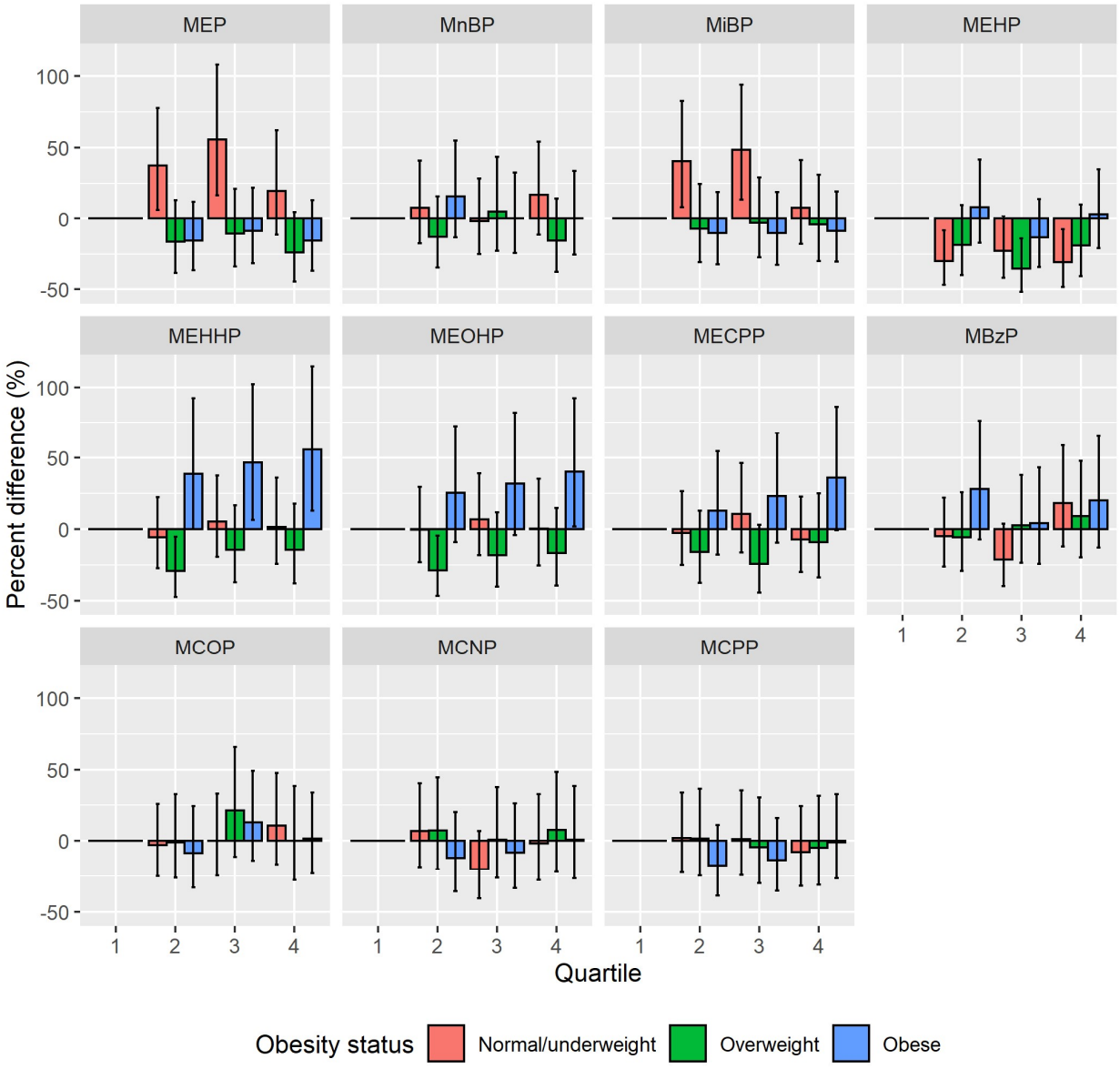
Percent differences were adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI.

Supplementary Figure 3.7 Percent differences in HMW adiponectin associated with phthalate metabolite concentration quartiles, stratified by obesity status



Percent differences were adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI.

Supplementary Figure 3.8 Percent differences in the leptin: HMW adiponectin ratio associated with phthalate metabolite concentration quartiles, stratified by obesity status



Percent differences were adjusted for age, race/ethnicity, site, education, menopausal status, hormone therapy use, physical activity, smoking status, dietary energy intake, and BMI.

Chapter 4 Phthalates and Incident Diabetes in Midlife Women: The Study of Women's Health Across the Nation (SWAN)

4.1 Abstract

Background

Phthalates are hypothesized to contribute to diabetes, but longitudinal evidence in humans is limited. We examined whether phthalate exposure was associated with a higher incidence of diabetes in a racially/ethnically diverse cohort of midlife women.

Methods

In the Study of Women's Health Across the Nation-Multipollutant Study, we followed 1308 women without diabetes in 1999/2000 for six years. Eleven phthalate metabolites were measured in spot urine samples in 1999/2000 and 2002/2003. Incident diabetes was ascertained between 1999/2000 and 2005/2006. Cox proportional hazards models with time-varying exposure were used to estimate the hazard ratio (HR) of diabetes associated with each phthalate metabolite, adjusting for demographic, lifestyle, and health-related factors. Effect modification by race/ethnicity was examined with interaction terms.

Results

Sixty-one women developed diabetes over six years (cumulative incidence = 4.7%). Among all women, several high-molecular-weight phthalate metabolites were associated with a

higher incidence of diabetes, but none were statistically significant. There was effect modification by race/ethnicity. Among White women, each doubling of the concentrations of mono-isobutyl phthalate (MiBP), monobenzyl phthalate, mono-carboxyoctyl phthalate, mono-carboxyisononyl phthalate (MCNP), and mono(3-carboxypropyl) phthalate was associated with 30-63% higher incidence of diabetes (HR = 1.30, 95% confidence interval (CI): 1.03, 1.65 for MCNP; HR = 1.63, 95% CI: 1.18, 2.25 for MiBP). In contrast, phthalate metabolites were not associated with diabetes incidence in Black or Asian women. Post-hoc analyses showed positive associations between phthalates and insulin resistance in non-White women, suggesting that non-White women were not immune to phthalates.

Conclusions

Some phthalate metabolites were associated with a higher incidence of diabetes over six years of follow-up, but the associations were inconsistent across racial/ethnic groups. Whether phthalates cause diabetes requires further investigation.

4.2 Introduction

Diabetes is one of the leading causes of death and disability. In 2017-2020, 14.7% of adults in the United States had diabetes (1). Individuals with diabetes are at increased risk of many serious chronic conditions. The disease was estimated to cost the US healthcare system $327 billion in 2017 (2), consuming a significant portion of healthcare expenditures. These enormous costs to individuals and societies have spurred ongoing interest to understand the causes of diabetes to facilitate better prevention and treatment.

The current extraordinary burden of diabetes is the culmination of six decades of continuous increases in its prevalence (3). Because this period of increasing diabetes prevalence coincided with the increasing use of synthetic chemicals in industry and commerce, exposure to metabolism-disrupting chemicals has been hypothesized to contribute to diabetes (4,5). Phthalates, di-esters of 1, 2-benzenedicarboxylic acid, are one of these chemicals. Low-molecular-weight (LMW) phthalates are frequently added to personal care products as solvents, while high-molecular-weight (HMW) phthalates are frequently added to polyvinyl chloride (PVC) plastic products as plasticizers (6). LMW phthalates are commonly found in fragrance and nail polish (7). HMW phthalates are commonly found in plastic food packaging, clothing, vinyl flooring, and other PVC applications (6). Exposure to phthalates is widespread through ingesting food contaminated during processing, packaging, and storage (8–10). Dermal contact is an additional route of exposure particularly relevant for LMW phthalates in personal care products (11).

Because of such widespread exposure, understanding phthalates' potential diabetogenic effects is important for both risk management and diabetes prevention. In animals, a growing number of studies suggest that exposure to some phthalates adversely affects glucose homeostasis, leading to elevated fasting glucose or worse glucose tolerance (12–14). In humans, epidemiologic

studies support an association between phthalate exposure and insulin resistance (15). The association between phthalates and diabetes is less certain. Most studies have been cross-sectional (15). Because diabetes is a chronic disease with a long duration, exposure to phthalates is highly dynamic, and phthalates do not accumulate in the body (11,16), cross-sectional studies are particularly problematic for causal inference. Phthalate exposure when diabetes is well-established may not represent phthalate exposure before disease onset. Only one study has examined phthalates and incident diabetes (17). That study found positive associations between some phthalate metabolites and diabetes in a group of predominantly White nurses in the US, but it is unclear if the findings are generalizable to other populations. Further, that study measured phthalate metabolites at only one time point and examined their associations with incident diabetes in the next ten years. Because phthalate metabolites in spot urine samples may not accurately reflect habitual exposure (18), the reported associations may be biased towards the null due to substantial exposure measurement error. To address these limitations, we conducted a cohort study on repeatedly-measured phthalates and incident diabetes among a diverse group of midlife women in the US.

4.3 Methods

4.3.1 Study population

Participants were drawn from the Study of Women's Health Across the Nation (SWAN). SWAN is an ongoing longitudinal study of women's health in midlife with nearly annual follow-up visits. In 1996/1997, women aged 42-52 years were recruited from seven study sites: Oakland, CA, Los Angeles, CA, Chicago, IL, Detroit-area, MI, Pittsburgh, PA, Boston, MA and Newark,

NJ. Besides the age eligibility criterion, additional eligibility criteria for SWAN include 1) self-identifying as White, Black, Chinese, Japanese, or Hispanic, 2) having an intact uterus, at least one ovary, and at least one menstrual period in the past 3 months, and 3) not having used any exogeneous reproductive hormones in the past 3 months. A total of 3302 women met these criteria and participated in SWAN.

The SWAN Multi-pollutant Study (SWAN-MPS) is an ancillary study that selected SWAN participants for environmental chemical exposure assessments using banked biospecimens from the 1999/2000 and 2002/2003 study visits. Of the 2694 women still active in SWAN in 1999/2000, SWAN-MPS excluded all 646 women from Chicago and Newark because neither site collected urine samples necessary for environmental chemical exposure assessments. An additional 648 women from the other sites were excluded because they lacked sufficient blood or urine samples for environmental chemical exposure assessments. In total, SWAN-MPS included 1400 women, most of whom (N = 1387) had phthalates data at both time points in 1999/2000 and 2002/2003.

This study aimed to examine the association between time-varying phthalate exposure and incident diabetes between 1999/2000 and 2005/2006. We chose to limit the follow-up time to six years because exposure to phthalates is episodic in nature and phthalates have short half-lives in the body (11,18). In addition, one study in rodents showed that phthalates' effects on glucose homeostasis may not be permanent (19). To be eligible for this study, women must be free of diabetes in 1999/2000 and have at least one visit with complete data for phthalate metabolites and covariates (urinary creatinine, age in 1999/2000, site, race/ethnicity, education, dietary energy intake, smoking status, physical activity, menopausal status, and body mass index (BMI)) before diabetes onset, loss to follow-up, or end of observation in 2005/2006. Based on these criteria, we excluded 80 women with prevalent diabetes in 1999/2000. We further excluded 12 women with

missing covariate data. The analytic sample thus included 1308 women. Of these, 1293 women entered the risk set in 1999/2000 and 15 entered in 2002/2003. The 15 women entered the risk set late because of incomplete covariate data in 1999/2000. The median follow-up time of the entire sample was 6 years.

All SWAN and SWAN-MPS study protocols have been approved by institutional review boards. SWAN participants provided written informed consent to participate in the study.

4.3.2 Phthalate metabolites

Women provided spot urine samples in polyethylene tubes at in-person visits in 1999/2000 and 2002/2003. The samples were transferred to -80 °C freezers for storage. In 2017/2018, these samples were thawed, and 12 phthalate metabolites were measured using on-line solid phase extraction (SPE) coupled to high-performance liquid chromatography-isotope dilution tandem mass spectroscopy (HPLC-MS). These 12 phthalate metabolites included three metabolites of LMW phthalates: mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), and mono-isobutyl phthalate (MiBP); four metabolites of di(2-ethylhexyl) phthalate (DEHP), a HMW phthalate of particular public health interest: 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); and five metabolites of other HMW phthalates: monobenzyl phthalate (MBzP), mono-isononyl phthalate (MiNP), mono-carboxyoctyl phthalate (MCOP), mono-carboxy-isononyl phthalate (MCNP), and mono(3-carboxypropyl) phthalate (MCPP). We measured these phthalate metabolites because their parents have been widely used in industry and commerce, and exposure to these phthalates is a national biomonitoring priority (20). The coefficient of variation (CV, in %) of the HPLC-MS assay ranged from an average of 4% for MEHP to 19% for MCOP. We excluded MiNP from all analyses

because it was detected in less than 1% of urine samples. For analyses, the concentrations of all other phthalate metabolites, including those below the limits of detection, were used as output by the assay, except for the few negative or zero values. To facilitate $\log_2$-transformation, we replaced 7 negative values of MiBP, 5 negative values of MEHP, 1 zero value of MCOP, and 5 negative values of MCPP with each metabolite's median below its limit of detection.

4.3.3 Diabetes

Women's diabetes status was determined longitudinally based on all data from SWAN baseline in 1996/1997 to the most recent follow-up visit in 2016/2017. At SWAN baseline and each follow-up visit, women self-reported doctor's diagnosis of diabetes. In all but three visits, women self-reported the use of any anti-diabetic medications. In all but six visits, women also provided fasting blood samples for the measurement of glucose with a hexokinase assay (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). A woman was classified as ever having diabetes if 1) she reported using anti-diabetic medications at any visit, 2) had fasting glucose $\geq$ 126 mg/dL for two consecutive visits, or 3) self-reported doctor's diagnosis of diabetes at two visits and had fasting glucose $\geq$ 126 mg/dL at one visit. For women who were classified as having diabetes based on medications, the visit of diabetes onset was defined as the first visit with fasting glucose $\geq$ 126 mg/dL before the first use of medications; otherwise, the first visit with self-reported diabetes before the first use of medications; otherwise, the first visit at which anti-diabetic medication use was reported. For women classified as having diabetes based on the other two criteria, the visit of diabetes onset was defined as the first visit with fasting glucose $\geq$ 126 mg/dL.

In our analysis, we treated Follow-up Visit 3 in 1999/2000 as the time origin and calculated time to diabetes onset as the time elapsed (in years) between 1999/2000 and the visit of diabetes

onset. For women who remained free of diabetes before loss to follow-up or the end of observation at Follow-up Visit 9 in 2005/2006, their time to diabetes onset was right-censored and calculated as the time elapsed (in years) between 1999/2000 and the date of their last follow-up visit.

4.3.4 Covariates

Creatinine was measured in urine in 1999/2000 and 2002/2003 with a Cobas Mira analyzer (Horiba ABX, Montpellier, France). Time-fixed confounders included age in 1999/2000, site, race/ethnicity, and education. Time-varying confounders included dietary energy intake, smoking status, physical activity, menopausal status, and BMI.

Age was calculated from visit date in 1999/2000 and date of birth. Site, race/ethnicity, and education were collected in questionnaires at the SWAN study baseline in 1996/1997. Dietary energy intake (kcal/day) was estimated from a modified Block Food Frequency Questionnaire (Block-FFQ) (21). This FFQ was administered in 1996/1997 and 2001/2002 only. We used diet data from 1996/1997 and 2001/2002 to approximate diet in 1999/2000 and 2002/2003, respectively. Smoking status (never, past, current), current hormone therapy use (HT) (yes, no), self-reported menstrual bleeding frequency, history of gynecologic surgeries, and the frequency of various physical activities were collected via questionnaires in 1999/2000 and 2002/2003. We determined women's menopausal status (pre- or peri-menopausal, natural or surgical menopause, and unknown due to HT use) based on menstrual bleeding frequency, history of gynecologic surgeries, and use of exogeneous hormones. We measured women's physical activity with an index that summarized the frequency and intensity of leisure time physical activity, housework, and active transport (22). BMI was calculated as body weight (kg)/height^2 (m^2). Previous studies showed that the association between phthalates and BMI may be bidirectional. On the one hand, a higher BMI is a marker of lower socioeconomic status and unhealthy behaviors, which are

associated with increased phthalate exposure (23). On the other hand, phthalate exposure may lead to more rapid body fat gain (24,25). Given this potential bidirectionality, we used BMI collected one year before phthalate exposure assessment as confounders to strengthen temporality. Obesity status was defined based on BMI using race/ethnicity-specific cut-points (26): For White and Black women, normal/underweight was defined as BMI < 25 kg/m^2, overweight as 25 kg/m^2 ≤ BMI < 30 kg/m^2, and obese as BMI ≥ 30 kg/m^2. For Chinese and Japanese women, normal/underweight was defined as BMI < 23 kg/m^2, overweight as 23 kg/m^2 ≤ BMI < 27 kg/m^2, and obese as BMI ≥ 27 kg/m^2.

4.3.5 Statistical methods

Phthalate metabolite concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method (27). Briefly, each metabolite concentration was divided by the ratio of observed to predicted urinary creatinine. Predictors of creatinine included age, race/ethnicity, BMI, and height (28). The prediction model was developed with data in 1999/2000. We calculated the molar sums of LMW phthalate metabolites ("∑LMW phthalates"), DEHP metabolites ("∑DEHP"), and other HMW phthalate metabolites ("∑HMW phthalates") to assess the impact of aggregate exposure to each group of phthalates.

We obtained descriptive statistics (median (1st and 3rd quartiles) for continuous variables; count (%) for categorical variables) of the analytic sample in 1999/2000. To examine the associations between potential confounders and phthalate metabolites in 1999/2000, we obtained the median (1st and 3rd quartiles) concentration of each phthalate metabolite by levels of confounders. Differences in median phthalate concentrations across confounder levels were compared with Kruskal-Wallis tests. To examine the associations between incident diabetes status and phthalate metabolites and potential confounders in 1999/2000, we obtained descriptive

statistics (median (1^{st} and 3^{rd} quartiles) for continuous variables; count (%) for categorical variables) by incident diabetes. Differences in the distribution of phthalate metabolites and confounders by incident diabetes status were compared with Wilcoxon rank-sum tests (continuous variables) and Chi-squared tests (categorical variables).

To examine the association between phthalate exposure and diabetes incidence, for each phthalate metabolite, we fit a series of Cox proportional hazards models with time-varying phthalate metabolites and covariates. Model 1 included the time-varying $\log_2$-transformed phthalate metabolite only. Model 2 additionally adjusted for age in 1999/2000, race/ethnicity, site, education, and time-varying physical activity, smoking status, dietary energy intake, and menopausal status. Model 3 additionally adjusted for time-varying BMI. We fit this series of models to examine the impact of confounders on the association between each phthalate metabolite and diabetes incidence. The difference between Models 2 and 3 was of particular interest because BMI was potentially both a confounder and a mediator of the association between phthalates and diabetes. Adjusting for BMI may underestimate the associations between phthalate metabolites and diabetes. From each model, we calculated the hazard ratio (HR) and 95% confidence interval (CI) for diabetes per doubling of concentrations for each phthalate metabolite.

We conducted a series of sensitivity analyses to assess the robustness of our findings. First, we fit each phthalate metabolite as tertiles in Cox models to examine potential violation of the linearity assumption. Second, we additionally adjusted for intake frequency of food items associated with phthalate exposure in Cox models to examine potential confounding by these food items. These food items included red meat, poultry, liver, processed meat, dairy, margarine, refined grains, salty snacks, desserts, meat substitutes, pizza, salad dressing, and salsa (9,10,28–32). Third, we re-analyzed our data using marginal structural models (MSM) with inverse-probability-of-

treatment weights (IPTW) (33). Details about these weights and the MSMs are available in the appendix. The IPTW-weighted MSMs allowed us to control for confounding by BMI without adjusting for this variable. Thus, they overcame potential bias induced by BMI adjustment in conventional Cox models. Results from the IPTW-weighted MSMs allowed us to further understand the impact of BMI adjustment on the association between phthalates and diabetes in the main analyses. Fourth, this analysis was based upon women who were selected into SWAN-MPS. If selection was related to determinants of phthalate exposure and incident diabetes, HR estimates from our main analyses might be biased. Although we conditioned on many of these determinants in our main analyses (age, race/ethnicity, site, education, smoking status), which should have eliminated bias due to selective participation, we applied inverse-probability-of-selection weights (IPSW) to Cox regression models in sensitivity analyses to further correct for selection bias. Details about these weights are available in the appendix. Lastly, because a major difference between this study and the other study on phthalates and incident diabetes was the racial/ethnic composition of the analytic sample, we included race/ethnicity by phthalate metabolite interaction terms in Cox regression models to investigate potential effect modification by race/ethnicity. In these models, we combined Japanese and Chinese women into one group labeled as "Asian" because of the small number of incident diabetes cases among Chinese and Japanese women (4 cases in Chinese; 5 cases in Japanese).

As post-hoc analyses, we examined the associations between phthalate metabolites and biomarkers of glucose homeostasis, including fasting glucose and homeostatic model assessment of insulin resistance (HOMA-IR), to see if racial/ethnic differences in the associations between phthalates and diabetes can potentially be explained by racial/ethnic differences in the associations between phthalates and glucose metabolism. We used repeatedly measured fasting glucose and

HOMA-IR between 1999/2000 and 2005/2006 as outcomes for these analyses. HOMA-IR was calculated as (fasting insulin (μU/mL) × fasting glucose (mmol/L))/22.5 (34). Fasting insulin was measured in serum using a solid phase radioimmunoassay (Coat-A-Count, Diagnostics Product Corp., Los Angeles, CA) (35). Observations obtained while participants were taking anti-diabetic medications were excluded. For each phthalate metabolite, percent differences in fasting glucose and HOMA-IR were estimated via mixed effects models. The models included $\log_2$-transformed phthalate metabolite, race/ethnicity (White, Black, Asian), their interaction, as well as age, site, education, lagged BMI in 1999/2000, and time-varying smoking status, physical activity, menopausal status, and dietary energy intake as predictors. Random intercepts were included to account for within-woman correlations.

Statistical analyses were conducted in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using packages "survival" (version 3.2-13) (36) and "ipw" (version 1.0-11) (37). A two-sided p-value < 0.05 was considered statistically significant.

4.4 Results

Women had a median age of 49.4 (1^{st} quartile, 3^{rd} quartile: 47.4, 51.5) in 1999/2000 (**Table 4.1**). Approximately half of the participants were White, 20.3% Black, 13% Chinese, and 15.2% Japanese. Approximately half of the participants had a college degree or higher. Most women were never smokers. Most were pre- or peri-menopausal. Approximately 29% of the participants were obese.

In 1999/2000, the detection frequency of phthalate metabolites ranged from 84.8% for MEHP to 100% for MnBP and MECPP (**Table 4.2**). Women who were younger, Black, current

smokers, or obese generally had higher concentrations of phthalate metabolites (**Supplementary Tables 4.1-4.3**). Over six years, 61 women developed diabetes (incidence rate= 8.1 per 1000 person-years). Compared to those who did not develop diabetes, women with incident diabetes had significantly higher concentrations of all phthalate metabolites except those of DEHP (**Table 4.2**).

In crude Cox regression models, all phthalate metabolites except MEP and DEHP metabolites were significantly associated with higher incidence of diabetes (**Figure 4.1**, Panel A; **Supplementary Table 4.5**). Adjustment for demographic factors, lifestyle factors, and menopausal status attenuated these associations, so that few associations remained statistically significant (**Figure 4.1**, Panel B; **Supplementary Table 4.5**). Further adjustment for BMI led to more attenuations, albeit to a smaller extent (**Figure 4.1**, Panel C; **Supplementary Table 4.5**). In fully-adjusted Cox regression models, MEP and DEHP metabolites were not associated with the incidence of diabetes (hazard ratios (HR) = 1). For the other metabolites, each doubling of concentrations was associated with 8% - 19% higher rate of diabetes, but none of the associations were statistically significant.

Cox models with phthalate metabolites fitted as tertiles did not reveal notable non-linear associations (**Supplementary Figure 4.1**). In fact, a statistically significant linear trend was detected for MiBP (p-trend = 0.01). Results did not change with additional adjustment for food items. Results from IPTW-weighted MSMs were nearly identical to those from the fully-adjusted Cox models in our main analyses (**Supplementary Figure 4.2**). Applying IPSWs did not change our results (**Supplementary Figure 4.3**). Cox models with race/ethnicity by phthalate metabolite interaction terms revealed major differences in the associations between phthalates and diabetes incidence by race/ethnicity. Among White women, MiBP, MBzP, MCOP, MCNP, MCPP, and

∑HMW phthalate metabolites were significantly associated with higher diabetes incidence. Per doubling of concentrations, the hazard ratio for diabetes ranged from 1.30 (95% confidence interval (CI): 1.03, 1.65) for MCNP to 1.77 (95% CI: 1.27, 2.46) for ∑HMW phthalate metabolites (**Figure 4.2**, Panel A; **Supplementary Table 4.6**). In contrast, among Black and Asian women, none of the phthalate metabolites were associated with increased diabetes incidence (**Figure 4.2**, Panels B and C; **Supplementary Table 4.6**). These racial/ethnic differences were inconsistent with the racial/ethnic differences in the associations between phthalate metabolites and glucose homeostasis biomarkers. While the associations between DEHP metabolites and fasting glucose were stronger in White than Black women, the associations between the other phthalate metabolites and fasting glucose did not differ by race/ethnicity or were stronger in Black women (**Supplementary Figure 4.4**). Similarly, the associations between most phthalate metabolites and HOMA-IR did not differ by race/ethnicity or were stronger in Black than White women (**Supplementary Figure 4.5**).

4.5 Discussion

In a diverse cohort of midlife women, we found that some phthalate metabolites were associated with a higher incidence of diabetes over six years, but these positive associations were apparently limited to White women only. These findings suggest that phthalates may increase the risk of diabetes. However, given inconsistent associations across racial/ethnic groups and phthalate metabolites, a causal relationship between phthalates and diabetes remains uncertain. Additional studies are needed to investigate if phthalate exposure contributes to diabetes.

Phthalates have been shown to disrupt glucose homeostasis in rodents (12–14) and are associated with insulin resistance in diabetes-free adults (15). Whether phthalates increase the risk of diabetes is unclear because few epidemiologic studies have examined the associations between phthalates and incident diabetes. In the only other study on this topic, Sun et al. conducted a case-control study on 1941 middle-aged or older women from the predominantly-White Nurses' Health Study and Nurses' Health Study II cohorts. Over approximately 10 years, women at the top quartile of exposure to some phthalates had up to three times higher odds of incident diabetes than those at the first quartile (17). Although the strengths of the associations differed by phthalate metabolites and the cohort origin of the participants, findings by Sun et al. generally support positive associations between MnBP, MiBP, and DEHP metabolites and incident diabetes in White women. Our study confirmed the positive association for MiBP. Additionally, we identified four more HMW phthalate metabolites associated with significantly increased diabetes risks in White women. The consistency between our findings and Sun et al.'s suggests a diabetogenic role of phthalates, although the apparent racial/ethnic differences in the associations between phthalates and diabetes require further investigations.

To understand if the racial/ethnic differences were potentially explained by racial/ethnic differences in phthalates' effects on glucose metabolism, we examined the racial/ethnic-specific associations between phthalate metabolites and fasting glucose and HOMA-IR. We found that unlike diabetes, the associations between phthalate metabolites and these glucose homeostasis markers were not consistently stronger in White women. Further, MnBP and MBzP were positively associated with HOMA-IR in Black and Asian women, and MiBP, MEHHP, MEOHP, MECPP, and MCPP were positively associated with HOMA-IR in Black women. These results suggest that non-White women were not immune to phthalates' potential effects on insulin

resistance, a key mechanism through which phthalates may increase the risk of diabetes (38,39). Since non-White women were not immune to phthalates' toxic effects, some other mechanisms must have contributed to the observed racial/ethnic differences in the associations between phthalates and diabetes. We speculate that the racial/ethnic differences may be due to one or more of the following factors. First, our analytic sample included only women who were free of diabetes in 1999/2000. Assuming that phthalate exposure increased the risk of diabetes, women who developed diabetes before 1999/2000 due to high levels of past phthalate exposure were excluded from the analytic sample. This process removed highly-exposed cases from analysis, creating selection bias and leading to attenuations of the associations between phthalates and incident diabetes. Because Black women are generally exposed to higher levels of phthalates (40) and develop diabetes at a younger age than White women (41), this selection bias may have affected Black women to a greater extent, resulting in greater attenuations in the hazard ratios for incident diabetes. In SWAN-MPS, the prevalence of diabetes in 1999/2000 among Black women (11.4%) was nearly three times that among White women (4.2%). Such a stark difference in diabetes prevalence seems to support selection bias as a potential explanation for the racial/ethnic differences in the associations between phthalates and incident diabetes. Second, elevated fasting glucose may be a less sensitive criterion to identify incident diabetes among Black and Asian women than White women. Studies have shown that at the same level of whole-body insulin resistance, Black women have lower rates of gluconeogenesis than White women, leading to less frequent fasting hyperglycemia (42). Similarly, the prevalence of impaired fasting glucose is lower in Asian populations than White populations, despite a higher prevalence of impaired glucose tolerance in Asian (43). Using a less sensitive marker of glucose dysregulation in Black and Asian women may have led to greater non-differential outcome misclassification, which attenuated

phthalates' associations with diabetes in these populations. Third, chance may also explain the racial/ethnic differences. This is particularly relevant for Asian women because the number of cases among them was small. Unfortunately, without additional data, we are not able to determine which factors may have caused the racial/ethnic differences. Our data do indicate that non-White women are not immune to the glucose metabolism-disrupting effects of phthalates, so better-designed studies in non-White women are needed to quantify the diabetes risks associated with phthalate exposure in these women.

A critical methodological consideration in studies on phthalates and diabetes is the potentially bidirectional relationship between phthalate exposure and adiposity. This bidirectionality means that adjusting for adiposity in conventional regression models to account for confounding may underestimate the associations between phthalates and diabetes. We addressed this concern by re-analyzing our data with IPTW-weighted MSMs, which produced results nearly identical to those from conventional models. The IPTW-weighted MSMs confirmed the validity of BMI adjustment in conventional Cox regression models. In addition, they suggest that in this study, BMI was likely not a major mediator for phthalates and diabetes. Previously, we found that in SWAN-MPS, phthalate metabolites were associated with more rapid body fat gain primarily in women who were normal/underweight in 1999/2000. In this study, a vast majority (89.9%) of women who developed diabetes over six years were overweight or obese in 1999/2000. The weaker associations between phthalates and body fat gain in overweight/obese women may explain why BMI was not a major mediator. Had we had longer follow-up or observed women earlier in the life course before they became overweight/obese, we might have found a stronger mediating effect of adiposity and hence greater differences between conventional models and IPTW-weighted MSMs.

Besides increasing body fat, phthalates are thought to cause diabetes by disrupting glycolysis and gluconeogenesis in liver (44). They may also hinder insulin signaling in liver cells (38,39), fat cells (38), and skeletal muscle cells (45) through oxidative stress and epigenetic mechanisms, leading to impaired glucose uptake and whole-body insulin resistance. Further, phthalates may increase insulin resistance indirectly by disrupting the synthesis, transportation, or metabolism of hormones important for regulating insulin sensitivity, such as thyroid hormones (46) and sex steroid hormones (47). There is also some evidence that MnBP, MiBP, and MEHP may adversely affect pancreatic β-cell viability and glucose-stimulated insulin secretion (48,49), but the data all came from *in vitro* studies and were sometimes conflicting. Intriguingly, many phthalate metabolites activate peroxisome proliferator-activated receptor gamma (PPAR-γ) (50–52). A class of PPAR-γ agonists known as thiazolidinediones (TZDs) is used to treat diabetes because it improves insulin sensitivity through PPAR-γ activation (53). It is unclear if environmental exposure to phthalates at typical levels improves insulin sensitivity similar to TZDs. If it does, other diabetogenic mechanisms, potentially independent of PPAR-γ, must be present to counter the insulin-sensitizing effects of PPAR-γ activation.

Overall, our study has added some evidence to support the potential diabetogenic effects of phthalates, but it also highlights that much is still unknown about the metabolic effects of these chemicals. Future studies should prioritize examining the associations between phthalates and diabetes in non-White populations, with the awareness that alternative diagnostic criteria may be more appropriate in some racial/ethnic groups and that the etiologically-relevant windows may differ by race/ethnicity. Recruiting younger participants and observing them for a longer period of time will also help us understand the effects of phthalates on different stages of the diabetogenic process, including whether body fat gain is an important mediator. Because phthalate exposure is

widespread and is especially high in some racial/ethnic minority groups (54), continued investments in the epidemiology and toxicology research of phthalates are warranted to inform equitable public health policies aimed to manage the risks of these chemicals and reduce the burden of chronic diseases.

This study has several limitations. First, phthalate metabolites were measured in spot urine samples. Because phthalates have short half-lives in the body and exposure to phthalates is intermittent, phthalate metabolite concentrations in spot urine samples may not accurately reflect habitual exposure. This type of exposure measurement error generally leads to attenuations of the associations between phthalates and diabetes. Second, we relied on fasting glucose to identify the time of diabetes onset. Diabetes is diagnosed by elevated fasting glucose, impaired glucose tolerance, or elevated hemoglobin A1C (HbA1c), each of which reflects different underlying pathologies and may not identify the same set of patients (55). Using fasting glucose solely to identify time of diabetes onset may have resulted in non-differential outcome misclassification. Third, we were not able to examine the effects of phthalate metabolite mixtures using state-of-the-art methods such as Bayesian kernel machine regression (56) or quantile-based g-computation (57) because these methods currently do not accommodate the analysis of time-to-event data with time-varying exposures. Fourth, our follow-up time was relatively short, and the number of cases was relatively small, which may have limited the study's power. Fifth, due to the small number of incident diabetes cases, we combined Chinese and Japanese women in our analysis of effect modification by race/ethnicity. Chinese and Japanese women may be exposed to phthalates through different sources and at different levels, and they may not have the same metabolic risks (58). The associations between phthalates and diabetes may not be homogeneous among Chinese and Japanese women, but we were not able to examine differences between these two ethnic

groups. Sixth, as with all observational studies, residual confounding was possible, including confounding by other environmental chemicals (59,60), although additionally adjusting for methyl paraben, a preservative added to personal care products, did not change our results (data not shown). Lastly, statistical significance should be interpreted cautiously as we did not account for multiple comparisons.

This study also has several strengths. Our cohort design allowed us to ensure temporality between phthalate exposure and diabetes, providing stronger evidence for causal inference. With a diverse population, we also provided the only data on phthalates and incident diabetes in non-White women. The IPTW-weighted marginal structural models we used in our sensitivity analyses is a novel application of inverse-probability-weighting in the research on phthalates and diabetes, which not only confirmed the validity of BMI adjustment in our main analyses, but also illustrates the utility of inverse-probability-weighting in the analysis of a time-varying environmental exposure and time-to-event outcome.

4.6 Conclusions

In a diverse population of midlife women, exposure to some phthalates was associated with increased incidence of diabetes, although the associations were inconsistent across racial/ethnic groups. These findings suggest that phthalate exposure may potentially contribute to diabetes, but more research, especially those in non-White populations, is needed to confirm causality. Given widespread exposure to phthalates and the enormous costs of diabetes to individuals and societies, ongoing investments in the research on phthalates' metabolic effects are warranted.

4.7 Appendix: Inverse-probability-of-treatment and inverse-probability-of-selection weights

4.7.1 Inverse-probability-of-treatment weights

For each phthalate metabolite, we weighted each observation by the following inverse-probability-of-treatment weights (IPTW):

$$\text{IPTW}_{\text{ij}} = \prod_{k=1}^{j} \frac{f(log_2\, phtha \quad\quad metabolite_{ik}\,|Z_i)}{f\,(log_2\, phthalat \quad metabolite_{ik}|\; L_{ik}, Z_i)},$$

where *i* indicates an individual, and *k* indicates a time point. *k* takes the value of 1 or 2, with $k = 1$ corresponding to Visit 3 in 1999/2000, and $k = 2$ corresponding to Visit 6 in 2002/2003. Z_i is a vector of time-constant covariates measured in 1999/2000, which included age in 1999/2000, site and race/ethnicity, and education. L_{ik} is vector of time-varying confounders for individual *i* at time point *k*, which included dietary energy intake, smoking status, physical activity, and menopausal status in IPTW-weighted marginal structural model (MSM) 1 and additionally included (lagged) BMI in IPTW-weighted MSM 2. We constructed two IPTWs to evaluate the impact of BMI on the association between phthalates and incident diabetes. Unlike our main analyses, site and race/ethnicity was combined into a 10-level variable in the construction of IPTWs. These ten levels corresponded to all observed race/ethnicity and site combinations in SWAN-MPS. We used the 10-level variable because by design, each study site recruited White women and women of one other race/ethnicity. In other words, not all possible race/ethnicity and site combinations were represented in SWAN-MPS. Using race/ethnicity and site as separate predictors of phthalate metabolites in the construction of IPTWs would have violated the positivity assumption of the inverse probability weighting method (33).

The denominator of the IPTW was the conditional probability of having a phthalate metabolite concentration infinitely close to the observed phthalate metabolite concentration for woman i at time point k, given L_{ik} and Z_i. This likelihood was evaluated at the observed value of the phthalate metabolite based on a normal density function. The mean and standard deviation of this normal density function was obtained via a generalized estimating equation (GEE). The GEE had $\log_2$ (phthalate metabolite) as the outcome, L_{ik} and Z_i as predictors, and an exchangeable correlation matrix. The numerator of the IPTW was obtained in a similar manner, except that the GEE model used to predict $\log_2$ (phthalate metabolite) included only the time-constant covariates, Z_i, as predictors. After constructing the IPTWs, for each phthalate metabolite, we fit the following IPTW-weighted marginal structural Cox proportional hazards model with a robust variance estimator:

$$\lambda(t) = \lambda_0(t) \exp\left(\beta_1 \log_2(\text{phthalate metabolite}) + \beta_z Z_i\right)$$

Weighting each observation by the IPTW created a pseudo-population in which phthalate metabolite concentrations were not associated with time-varying confounders included in L_{ik}. Thus, the MSMs allowed us to eliminate confounding by BMI and other time-varying confounders without having to adjust for them in Cox models. Note that because the numerator of the IPTW depended on Z_i, phthalate metabolite concentrations in the weighted sample were still associated with Z_i. Therefore, Z_i was adjusted in the IPTW-weighted marginal structural models to eliminate confounding by time-constant covariates (31). We created the IPTWs with the R package "ipw" (version 1.0-11). Details about this package are available in Wal and Geskus 2011 (37).

4.7.2 Inverse-probability-of-selection weights

We weighted each observation by the following inverse-probability-of-selection weights (IPSW):

$$\text{IPSW}_i = \text{IPSW}_{1i} \times \text{IPSW}_{2i},$$

where i indicates an individual, and IPSW_{1i} and IPSW_{2i} each represents the two selection processes into SWAN-MPS: 1) continuing in the SWAN Study through Visit 3 and 2) being selected into SWAN-MPS, given being active in SWAN at Visit 3 in 1999/2000.

Construction of IPSW_1

IPSW_1 was calculated as follows:

$$\text{IPSW}_{1i} = \prod_{k=1}^{3} \frac{P(C_{ik} = 0 \mid C_{i(k-1)} = 0, Z_i)}{P(C_{ik} = 0 \mid C_{i(k-1)} = 0, L_{i(k-1)}, Z_i)},$$

where *i* indicates an individual, and *k* indicates a visit. *k* takes the values of 1, 2, 3 and represents SWAN Visits 1 through 3. C_{ik} is a binary variable: $C_{ik} = 1$ represents dropping out of the SWAN Study by Visit *k*, and $C_{ik} = 0$ represents otherwise. Z_i is a vector of time-constant predictors of drop-out measured in 1996/1997, which included age in 1996/1997, race/ethnicity and site, and education. L_{ik} is vector of time-varying predictors of drop-out measured at every visit, which included marital status (single, married, separated/widowed/divorced), spouse/partner's employment change (spouse/partner lost a job vs. not), smoking status, menopausal status, self-rated health (excellent/very good, good, fair/poor), and self-reported doctor's diagnosis of having heart attack or angina (yes/no). These time-constant and time-varying predictors were previously identified as important determinants of loss to follow-up by 1999/2000 in SWAN (61).

The denominator of $IPSW_1$ was the conditional probability of continuing in SWAN by Visit *k*, given not leaving the study by the prior visit, time-constant predictors, and time-varying predictors measured at the prior visit. To estimate this probability, we fit a discrete-time survival model with pooled logistic regression using data from all SWAN participants except those from Chicago and Newark, NJ from Visit 0 through Visit 3. Participants from Chicago, IL and Newark, NJ were excluded because by design, they were not eligible for SWAN-MPS. Including them in the construction of inverse-probability-of-selection weights would have violated the positivity assumption. The pooled logistic model predicted drop-out by Visit *k* with visit *k-1* (a three-level variable: Visit 0 (reference), Visit 1, and Visit 2), Z_i, and $L_{i(k-1)}$. Subtracting model-predicted probabilities from 1 gave the conditional probabilities of continuing in SWAN through Visit *k*. For each individual, multiplying these conditional probabilities over Visits 1 through 3 gave the individual's probability of continuing in SWAN through Visit 3, given the time-constant and time-varying predictors. The numerator of $IPSW_1$ was similarly estimated, except that the pooled logistic regression model included only visit and Z_i as predictors. Adjustment for selection bias was achieved through the denominator. The numerator served to stabilize the $IPSW_1$s (62).

Construction of $IPSW_2$

$IPSW_2$ was calculated as follows:

$$\mathrm{IPSW}_{2\mathrm{i}} = \frac{P(S_i=1)}{P(S_i=1 \mid V_i)},$$

where *i* indicates an individual, S_i is a binary indicator for being selected into SWAN-MPS (S_i=1) versus not (S_i=0), given being active in SWAN at Visit 3 in 1999/2000. V_i is a vector of predictors for being selected into SWAN-MPS and includes age in 1999/2000, race/ethnicity and site, education, smoking status, menopausal status, and hypertension status (yes/no). Hypertension was

defined as self-reported doctor's diagnosis of having hypertension, self-reported use of antihypertensive medications, having a systolic blood pressure ≥ 120 mmHg, or having a diastolic blood pressure ≥ 80 mmHg based on the average of three readings. Race/ethnicity, site, and education was self-reported at SWAN baseline in 1996/1997. The other predictors were collected at SWAN Visit 3 in 1999/2000. All predictors were previously identified as important determinants of being selected into SWAN-MPS among participants of SWAN Visit 3 (61).

The denominator of $IPSW_2$ was the probability of being selected for SWAN-MPS, given V_i. To estimate this probability, we fit a logistic regression model predicting selection status, S_i, with V_i among all women who participated in SWAN Visit 3, except those from Chicago, IL and Newark, NJ. The numerator of $IPSW_2$ was the marginal probability of being selected into SWAN-MPS, given participation in SWAN Visit 3. The numerator served to stabilize the $IPSW_2$s.

Construction and application of the final IPSW

Multiplying $IPSW_1$ and $IPSW_2$ gave the final inverse-probability-of-selection weights (IPSW), which we used to weight the observations of each woman in conventional Cox regression models. The IPSWs can potentially correct for selection bias due to differential participation in SWAN-MPS because women with a low probability of being selected were up-weighted and vice versa. For completeness, we also ran MSMs weighted by the product of IPTW and IPSW to generate hazard ratios unbiased by measured confounding and differential selection into SWAN-MPS.

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Table 4.1 Participant characteristics in 1999/2000

	Median (Q1, Q3)[1]
Age (years)	49.4 (47.4, 51.5)
BMI (kg/m^2)[2]	25.5 (22.3, 30.5)
	N (%)
Site	
Detroit area, MI	225 (17.4%)
Boston, MA	211 (16.3%)
Oakland, CA	293 (22.7%)
Los Angeles, CA	346 (26.8%)
Pittsburgh, PA	218 (16.9%)
Race/ethnicity	
White	667 (51.6%)
Black	262 (20.3%)
Chinese	168 (13.0%)
Japanese	196 (15.2%)
Education	
High school or less	222 (17.2%)
Some college	409 (31.6%)
College degree	328 (25.4%)
Postgraduate	334 (25.8%)
Smoking	
Never	817 (63.2%)
Past	345 (26.7%)
Current	131 (10.1%)
Menopausal status	
Pre- or peri- menopausal	913 (70.6%)
Natural/surgical menopause	186 (14.4%)
Unknown due to hormone therapy	194 (15.0%)
Obesity status[2]	
Normal/underweight	520 (40.2%)
Overweight	395 (30.5%)
Obese	378 (29.2%)

[1] Descriptive data were based on the 1293 women who had complete data in 1999/2000. "Q1" stands for 1st quartile and "Q3" stands for 3rd quartile.

[2] BMI data came from the 1998/1999 follow-up visit for 1248 women, the 1997/1998 visit for 36 women, and the 1996/1997 visit for 9 women.

[3] Obesity was defined with BMI using race-specific cut-points. For Black and White, Normal/underweight: BMI < 25 kg/m^2; Overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2; Obese: BMI ≥ 30 kg/m^2. For Chinese and Japanese, Normal/underweight: BMI < 23 kg/m^2; Overweight: 23 kg/m^2 ≤ BMI < 27 kg/m^2; Obese: BMI ≥ 27 kg/m^2.

Table 4.2 Phthalate metabolite concentrations in 1999/2000, overall and by incident diabetes status

Group	Phthalate metabolite[1]	N (%) detected[2]	All (N = 1293) Median (Q1, Q3)	No diabetes (N = 1232) Median (Q1, Q3)	Incident diabetes (N = 61) Median (Q1, Q3)	p-value[3]
Low-molecular-weight (LMW) phthalate metabolites	MEP (ng/mL)	1292 (99.9%)	81.54 (36.64, 212.07)	80.74 (36.16, 206.44)	112.82 (47.46, 375.43)	0.03
	MnBP (ng/mL)	1293 (100.0%)	18.50 (11.63, 33.22)	18.37 (11.53, 32.01)	26.21 (14.28, 42.80)	0.005
	MiBP (ng/mL)	1266 (97.9%)	2.62 (1.55, 4.51)	2.60 (1.54, 4.42)	3.84 (2.04, 5.64)	0.03
	∑ LMW phthalate metabolites (nmol/mL)		0.57 (0.28, 1.31)	0.56 (0.28, 1.30)	0.70 (0.38, 2.19)	0.01
DEHP metabolites	MEHP (ng/mL)	1096 (84.8%)	3.06 (1.57, 5.98)	3.10 (1.59, 6.10)	2.24 (1.32, 4.95)	0.11
	MEHHP (ng/mL)	1292 (99.9%)	15.89 (8.24, 30.33)	15.89 (8.22, 30.19)	15.78 (9.37, 35.01)	0.71
	MEOHP (ng/mL)	1291 (99.8%)	9.54 (5.08, 18.60)	9.55 (4.99, 18.58)	9.42 (6.62, 19.10)	0.64
	MECPP (ng/mL)	1293 (100.0%)	16.70 (9.74, 31.28)	16.51 (9.72, 31.32)	19.00 (11.16, 30.85)	0.41
	∑ DEHP metabolites (nmol/mL)		0.15 (0.09, 0.29)	0.15 (0.09, 0.29)	0.17 (0.10, 0.28)	0.64
Other high-molecular-weight (HMW) phthalate metabolites	MBzP (ng/mL)	1290 (99.8%)	10.41 (5.81, 18.31)	10.28 (5.66, 17.94)	14.14 (7.96, 21.93)	0.01
	MCOP (ng/mL)	1289 (99.7%)	4.47 (2.63, 7.86)	4.34 (2.59, 7.65)	6.72 (3.71, 12.43)	0.002
	MCNP (ng/mL)	1289 (99.7%)	2.67 (1.51, 4.94)	2.63 (1.49, 4.86)	4.05 (1.77, 5.98)	0.02
	MCPP (ng/mL)	1275 (98.6%)	2.69 (1.70, 4.28)	2.67 (1.69, 4.26)	3.24 (2.01, 5.03)	0.09
	∑ HMW phthalate metabolites (nmol/mL)		0.08 (0.05, 0.14)	0.08 (0.05, 0.13)	0.11 (0.08, 0.16)	0.004

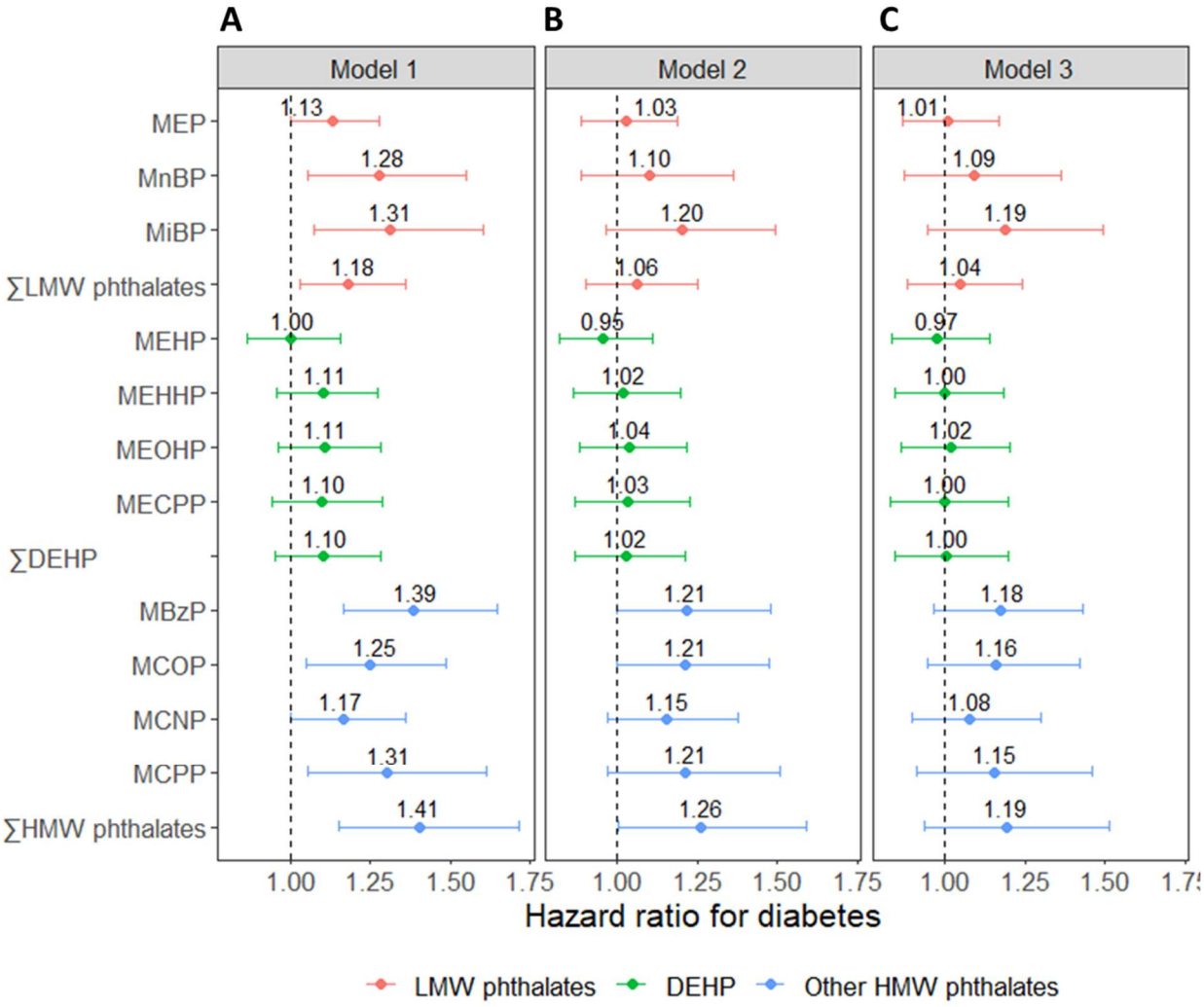
[1] All phthalate metabolite concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method. Medians and the 1st ("Q1") and 3rd ("Q3") quartiles are reported.

[2] Descriptive data were based on the 1293 women who had complete data in 1999/2000.

[3] P-values were obtained from Wilcoxon rank-sum tests comparing those who developed diabetes versus those who did not.

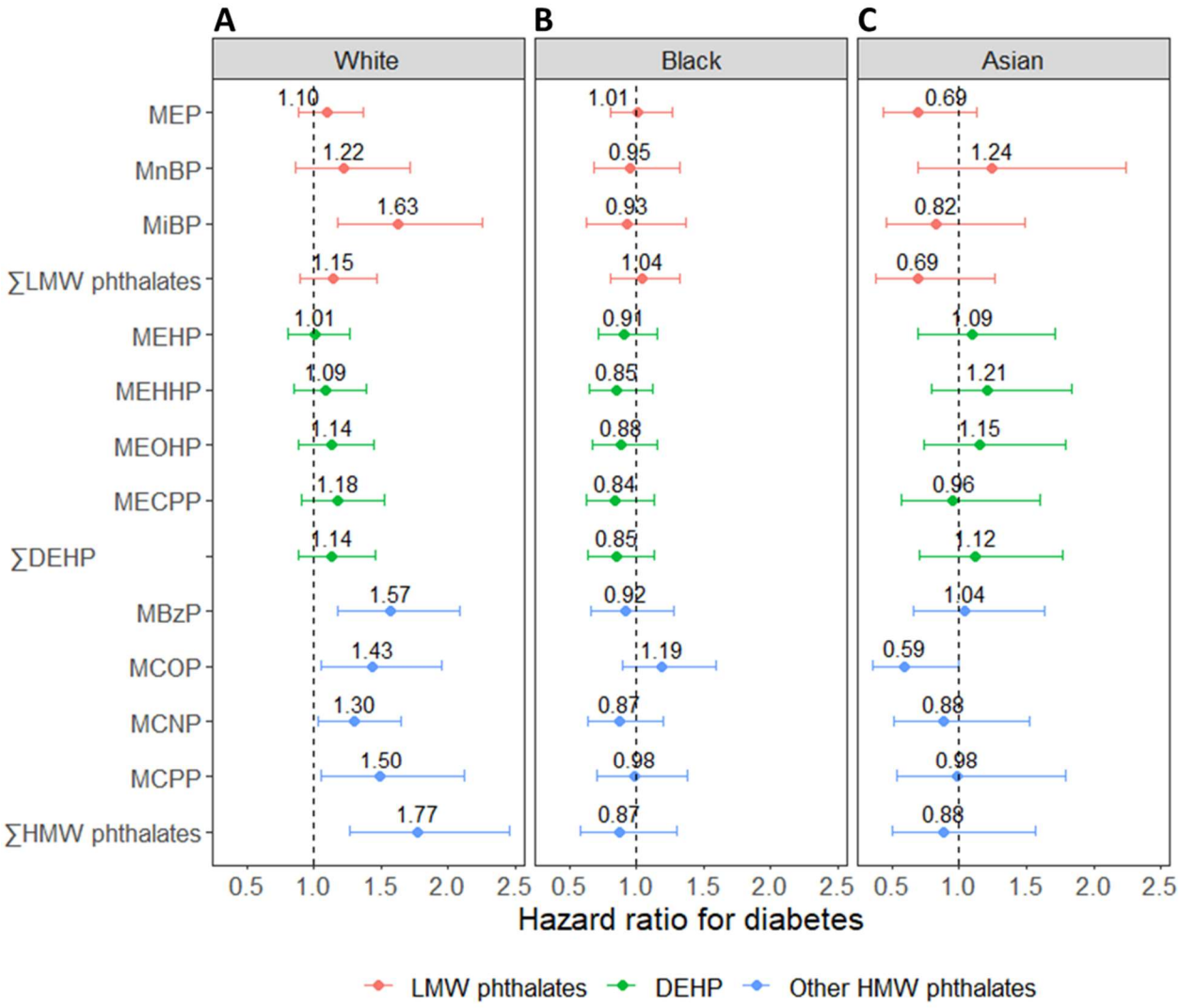
[4] ∑LMW phthalate metabolites = molar sum of MEP, MnBP, and MiBP; ∑DEHP metabolites = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalate metabolites = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 4.1 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations



Model 1: Crude model
Model 2: Adjusted for age in 1999/2000, race/ethnicity, site, education, and time-varying menopausal status, physical activity, smoking status, and dietary energy intake.
Model 3: Model 2 + time-varying BMI
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Figure 4.2 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations, by race/ethnicity



The hazard ratios were adjusted for age in 1999/2000, site, education, and time-varying menopausal status, physical activity, smoking status, dietary energy intake, and BMI. ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 4.1 Concentrations of low-molecular-weight phthalate metabolites in 1999/2000 by covariates

	N[1]	MEP[2]	MnBP	MiBP	∑ LMW phthalate metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
Age					
≤ 49	580	89.34 (36.99, 234.73)	19.78 (12.54, 35.42)	2.82 (1.63, 4.85)	0.59 (0.30, 1.44)
> 49	713	73.99 (36.16, 189.56)	17.68 (10.96, 29.71)	2.46 (1.47, 4.20)	0.54 (0.27, 1.22)
p-value[3]		0.02	0.005	0.003	0.02
Site					
Detroit area, MI	225	114.19 (61.00, 364.96)	24.35 (15.09, 50.44)	3.32 (1.84, 5.52)	0.87 (0.42, 2.19)
Boston, MA	211	133.36 (47.27, 329.50)	17.49 (11.92, 31.46)	2.76 (1.74, 4.61)	0.83 (0.36, 1.83)
Oakland, CA	293	43.46 (24.94, 112.25)	14.77 (9.39, 23.38)	2.17 (1.38, 4.28)	0.32 (0.20, 0.70)
Los Angeles, CA	346	65.86 (30.47, 142.98)	17.30 (10.82, 29.01)	2.19 (1.28, 3.72)	0.49 (0.26, 0.87)
Pittsburgh, PA	218	107.00 (47.44, 233.36)	23.30 (14.01, 42.76)	2.98 (1.84, 4.82)	0.72 (0.37, 1.38)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity					
White	667	82.83 (39.50, 181.91)	18.60 (11.66, 30.68)	2.33 (1.46, 4.01)	0.58 (0.31, 1.12)
Black	262	226.52 (100.58, 500.91)	28.29 (16.26, 53.32)	4.06 (2.58, 6.41)	1.45 (0.72, 2.89)
Chinese	168	35.92 (20.51, 70.25)	13.84 (8.06, 21.36)	2.19 (1.39, 4.31)	0.27 (0.18, 0.50)
Japanese	196	49.10 (25.02, 101.14)	14.98 (10.43, 24.89)	2.56 (1.34, 3.75)	0.40 (0.21, 0.71)
p-value		<0.0001	<0.0001	<0.0001	<0.0001
Education					
High school or less	222	89.06 (37.06, 263.43)	19.25 (11.99, 37.32)	3.03 (1.77, 5.33)	0.61 (0.30, 1.64)
Some college	409	85.44 (40.22, 230.38)	21.30 (13.18, 37.25)	2.66 (1.50, 4.76)	0.62 (0.34, 1.38)
College degree	328	72.60 (32.88, 187.04)	16.58 (10.91, 30.12)	2.47 (1.57, 4.19)	0.53 (0.26, 1.21)
Postgraduate	334	79.72 (34.59, 166.86)	16.55 (10.44, 26.81)	2.50 (1.48, 4.19)	0.52 (0.26, 1.01)
p-value		0.08	<0.0001	0.03	0.01
Smoking					
Never	817	70.25 (33.72, 184.51)	17.76 (11.20, 29.09)	2.49 (1.50, 4.35)	0.51 (0.26, 1.13)
Past	345	98.03 (44.00, 245.65)	19.16 (11.85, 32.62)	2.65 (1.55, 4.40)	0.64 (0.34, 1.45)
Current	131	132.68 (58.20, 285.92)	28.11 (13.96, 48.58)	3.15 (1.80, 5.72)	0.84 (0.44, 1.86)
p-value		<0.0001	<0.0001	0.002	<0.0001
Daily calorie intake					

	N[1]	MEP[2]	MnBP	MiBP	∑ LMW phthalate metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
1st quartile: < 1330 kcal/day	324	81.88 (37.61, 227.80)	19.41 (11.95, 35.60)	2.67 (1.55, 4.62)	0.57 (0.32, 1.33)
2nd quartile: 1330 – 1680 kcal/day	323	87.01 (36.23, 186.14)	18.00 (11.02, 28.69)	2.48 (1.49, 4.19)	0.58 (0.27, 1.23)
3rd quartile: 1680 – 2160 kcal/day	323	76.51 (37.59, 183.62)	17.49 (10.66, 32.44)	2.65 (1.51, 4.64)	0.53 (0.28, 1.12)
4th quartile: > 2160 kcal/day	323	86.88 (35.59, 234.35)	19.16 (12.46, 35.01)	2.80 (1.61, 4.65)	0.59 (0.29, 1.42)
p-value		0.93	0.09	0.27	0.76
Physical activity					
1st quartile: < 6.7	324	80.75 (36.44, 231.89)	19.08 (12.84, 31.75)	2.65 (1.53, 4.35)	0.56 (0.29, 1.45)
2nd quartile: 6.7 – 7.9	324	85.40 (38.77, 185.52)	18.40 (11.85, 33.31)	2.59 (1.55, 4.67)	0.59 (0.30, 1.16)
3rd quartile: 7.9 – 9.0	327	70.97 (34.41, 214.13)	20.25 (11.96, 36.35)	2.71 (1.60, 4.68)	0.52 (0.28, 1.33)
4th quartile: > 9.0	318	98.12 (37.21, 222.85)	15.91 (10.26, 29.58)	2.48 (1.53, 4.14)	0.62 (0.27, 1.32)
p-value		0.51	0.01	0.60	0.84
Menopausal status					
Pre- or peri- menopausal	913	82.22 (36.79, 206.92)	18.46 (11.78, 32.70)	2.67 (1.59, 4.52)	0.58 (0.29, 1.31)
Natural/surgical menopause	186	69.47 (36.89, 211.22)	15.33 (10.85, 28.97)	2.65 (1.46, 4.92)	0.51 (0.27, 1.25)
Unknown due to hormone therapy	194	85.18 (35.39, 216.44)	20.40 (11.53, 37.62)	2.37 (1.44, 3.90)	0.60 (0.28, 1.33)
p-value		0.69	0.09	0.31	0.57
Obesity status[4]					
Normal/underweight	520	68.37 (31.45, 147.37)	17.73 (10.79, 28.34)	2.48 (1.49, 4.21)	0.49 (0.26, 0.94)
Overweight	395	73.88 (35.31, 197.09)	17.86 (11.26, 31.83)	2.68 (1.48, 4.47)	0.52 (0.27, 1.32)
Obese	378	114.89 (49.51, 312.25)	20.54 (13.51, 41.34)	2.76 (1.69, 4.84)	0.78 (0.39, 1.82)
p-value		<0.0001	<0.0001	0.12	<0.0001

[1] Data in this table were based on the 1293 women who had complete data in 1999/2000.
[2] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method. "Q1" means "1st quartile" and "Q3" means "3rd quartile". ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP.
[3] P-values were obtained from Kruskal-Wallis tests.
[4] Obesity status was defined based on BMI from 1998/1999 for 1248 women, 1997/1998 for 36 women, and 1996/1997 for 9 women using race/ethnicity-specific cut points

Supplementary Table 4.2 Concentrations of DEHP metabolites in 1999/2000 by covariates

	N[1]	MEHP[2]	MEHHP	MEOHP	MECPP	∑ DEHP metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
Age						
≤ 49	580	3.65 (1.80, 7.10)	17.92 (9.20, 34.33)	10.80 (5.43, 20.87)	19.13 (10.78, 35.35)	0.18 (0.10, 0.33)
> 49	713	2.80 (1.41, 5.34)	14.27 (7.54, 26.74)	8.33 (4.67, 15.70)	15.39 (9.28, 27.42)	0.14 (0.08, 0.26)
p-value[3]		<0.0001	0.0003	<0.0001	<0.0001	<0.0001
Site						
Detroit area, MI	225	3.53 (1.98, 6.92)	21.23 (11.06, 36.69)	12.48 (6.62, 22.54)	19.61 (12.20, 36.15)	0.19 (0.11, 0.35)
Boston, MA	211	3.97 (1.89, 7.72)	20.70 (10.87, 38.75)	11.59 (6.29, 20.70)	21.08 (12.16, 42.42)	0.19 (0.11, 0.38)
Oakland, CA	293	2.28 (1.37, 4.08)	10.05 (5.74, 18.66)	5.94 (3.39, 11.46)	11.93 (7.35, 21.55)	0.10 (0.06, 0.18)
Los Angeles, CA	346	2.58 (1.35, 5.25)	12.51 (6.54, 21.90)	7.46 (3.85, 13.97)	14.39 (8.31, 25.61)	0.13 (0.07, 0.23)
Pittsburgh, PA	218	4.36 (2.27, 9.20)	23.64 (12.77, 49.71)	14.17 (7.15, 27.51)	24.91 (13.30, 46.19)	0.23 (0.13, 0.45)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity						
White	667	3.03 (1.58, 5.78)	17.38 (9.36, 30.88)	10.43 (5.62, 19.02)	18.51 (10.63, 33.60)	0.17 (0.10, 0.30)
Black	262	4.41 (2.70, 9.81)	23.64 (13.72, 48.77)	13.09 (7.79, 27.22)	21.54 (13.76, 44.68)	0.21 (0.13, 0.43)
Chinese	168	2.16 (1.34, 4.06)	7.34 (4.66, 14.90)	4.91 (2.63, 8.49)	9.96 (6.22, 17.60)	0.08 (0.05, 0.15)
Japanese	196	2.45 (1.28, 5.23)	11.21 (5.71, 20.61)	6.74 (3.54, 11.98)	12.77 (8.11, 23.56)	0.11 (0.06, 0.21)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Education						
High school or less	222	3.06 (1.35, 5.66)	13.71 (7.03, 30.16)	8.46 (4.28, 16.35)	15.48 (9.25, 29.64)	0.14 (0.08, 0.27)
Some college	409	3.36 (1.68, 6.90)	17.60 (9.05, 32.18)	10.70 (5.62, 19.61)	18.29 (10.49, 32.40)	0.17 (0.09, 0.30)
College degree	328	3.23 (1.55, 5.94)	14.63 (7.68, 29.36)	8.73 (4.73, 18.47)	15.40 (9.10, 30.03)	0.15 (0.08, 0.28)
Postgraduate	334	2.82 (1.54, 5.52)	15.94 (8.81, 30.30)	9.41 (5.34, 18.10)	17.82 (10.18, 32.11)	0.15 (0.09, 0.29)
p-value		0.10	0.10	0.07	0.19	0.10
Smoking						
Never	817	2.98 (1.53, 6.18)	15.34 (7.32, 30.84)	9.19 (4.58, 19.05)	16.70 (9.39, 32.05)	0.15 (0.08, 0.30)
Past	345	3.04 (1.64, 5.47)	17.29 (9.70, 27.00)	9.94 (5.73, 16.44)	16.64 (10.79, 29.01)	0.16 (0.10, 0.26)
Current	131	3.65 (1.51, 7.43)	17.89 (9.02, 36.42)	9.78 (5.52, 21.17)	17.08 (10.70, 35.84)	0.16 (0.09, 0.35)
p-value		0.38	0.11	0.33	0.69	0.29
Daily calorie intake						
1st quartile: < 1330 kcal/day	324	3.04 (1.52, 6.09)	16.54 (8.34, 31.71)	9.86 (5.19, 18.54)	16.64 (9.98, 32.45)	0.15 (0.09, 0.30)

	N[1]	MEHP[2]	MEHHP	MEOHP	MECPP	∑ DEHP metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
2nd quartile: 1330 – 1680 kcal/day	323	2.92 (1.47, 5.64)	14.60 (7.29, 29.10)	8.59 (4.57, 18.14)	15.67 (8.82, 29.47)	0.15 (0.08, 0.28)
3rd quartile: 1680 – 2160 kcal/day	323	3.06 (1.60, 5.75)	15.31 (8.47, 29.87)	9.16 (4.97, 17.67)	16.50 (9.89, 31.14)	0.15 (0.09, 0.28)
4th quartile: > 2160 kcal/day	323	3.37 (1.80, 6.56)	17.23 (8.89, 32.64)	10.20 (5.21, 19.14)	18.20 (10.47, 33.06)	0.17 (0.09, 0.31)
p-value		0.42	0.26	0.44	0.29	0.27
Physical activity						
1st quartile: < 6.7	324	2.81 (1.39, 5.54)	14.56 (7.31, 30.19)	8.59 (4.49, 18.98)	15.23 (9.10, 30.58)	0.15 (0.08, 0.28)
2nd quartile: 6.7 – 7.9	324	2.82 (1.48, 5.30)	15.81 (8.08, 29.51)	8.84 (5.06, 17.69)	16.66 (9.60, 30.40)	0.15 (0.08, 0.28)
3rd quartile: 7.9 – 9.0	327	3.40 (1.83, 6.45)	16.63 (8.57, 29.92)	10.10 (5.14, 17.54)	16.73 (9.77, 31.22)	0.17 (0.09, 0.28)
4th quartile: > 9.0	318	3.40 (1.68, 7.07)	16.92 (9.55, 33.97)	9.88 (5.52, 19.44)	18.24 (11.22, 33.50)	0.16 (0.10, 0.33)
p-value		0.03	0.27	0.27	0.10	0.13
Menopausal status						
Pre- or peri-menopausal	913	3.06 (1.63, 5.92)	15.89 (8.10, 30.18)	9.54 (5.04, 18.64)	16.70 (9.89, 31.30)	0.16 (0.09, 0.29)
Natural/surgical menopause	186	2.76 (1.26, 5.75)	15.32 (7.24, 32.57)	8.81 (4.25, 18.73)	15.76 (8.58, 31.47)	0.15 (0.07, 0.30)
Unknown due to hormone therapy	194	3.40 (1.61, 6.83)	17.11 (9.38, 29.21)	11.10 (5.77, 17.77)	18.34 (10.14, 29.76)	0.17 (0.10, 0.29)
p-value		0.15	0.49	0.24	0.50	0.36
Obesity status[4]						
Normal/underweight	520	2.95 (1.51, 5.94)	12.88 (6.94, 27.04)	7.75 (4.24, 15.90)	13.88 (8.39, 26.92)	0.13 (0.07, 0.26)
Overweight	395	3.04 (1.53, 5.74)	15.58 (7.97, 28.50)	9.41 (4.76, 17.27)	16.13 (9.76, 28.95)	0.15 (0.08, 0.28)
Obese	378	3.35 (1.75, 6.89)	19.87 (11.12, 40.32)	11.61 (6.73, 23.34)	21.06 (13.01, 43.20)	0.19 (0.12, 0.41)
p-value		0.24	<0.0001	<0.0001	<0.0001	<0.0001

[1] Data in this table were based on the 1293 women who had complete data in 1999/2000.

[2] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method. "Q1" means "1st quartile" and "Q3" means "3rd quartile". ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP.

[3] P-values were obtained from Kruskal-Wallis tests.

[4] Obesity status was defined based on BMI from 1998/1999 for 1248 women, 1997/1998 for 36 women, and 1996/1997 for 9 women using race/ethnicity-specific cut points.

Supplementary Table 4.3 Concentrations of other high-molecular-weight phthalate metabolites in 1999/2000 by covariates

	N[1]	MBzP[2]	MCOP	MCNP	MCPP	∑ HMW phthalate metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
Age						
≤ 49	580	11.53 (7.01, 20.53)	5.08 (3.06, 8.87)	2.99 (1.74, 5.82)	3.02 (1.97, 4.70)	0.09 (0.06, 0.15)
> 49	713	9.30 (5.09, 16.71)	3.94 (2.35, 6.72)	2.30 (1.39, 4.27)	2.44 (1.57, 3.85)	0.08 (0.05, 0.12)
p-value[3]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Site						
Detroit area, MI	225	14.40 (9.05, 23.75)	5.90 (3.80, 10.72)	3.71 (2.14, 6.55)	3.27 (2.49, 4.92)	0.11 (0.08, 0.18)
Boston, MA	211	10.54 (5.86, 18.15)	4.55 (2.86, 8.29)	3.40 (2.03, 6.73)	2.69 (1.82, 4.08)	0.09 (0.06, 0.13)
Oakland, CA	293	7.12 (4.02, 13.74)	2.99 (1.85, 5.07)	1.75 (1.06, 2.99)	2.12 (1.34, 3.33)	0.06 (0.04, 0.10)
Los Angeles, CA	346	8.83 (5.20, 14.87)	3.73 (2.35, 6.41)	1.98 (1.25, 3.62)	2.26 (1.46, 3.56)	0.07 (0.05, 0.11)
Pittsburgh, PA	218	13.43 (8.47, 23.17)	6.31 (3.86, 9.80)	3.58 (2.27, 5.70)	3.87 (2.50, 5.54)	0.12 (0.08, 0.17)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Race/ethnicity						
White	667	11.18 (6.45, 19.34)	4.81 (3.00, 7.91)	2.99 (1.98, 5.28)	3.19 (2.11, 4.88)	0.09 (0.06, 0.14)
Black	262	13.88 (8.63, 22.74)	5.86 (3.59, 11.01)	3.92 (2.12, 6.79)	3.11 (1.97, 4.72)	0.11 (0.07, 0.17)
Chinese	168	5.90 (3.17, 10.34)	2.32 (1.50, 4.29)	1.24 (0.80, 1.92)	1.64 (0.94, 2.41)	0.04 (0.03, 0.07)
Japanese	196	8.09 (4.75, 14.00)	3.49 (2.14, 6.01)	1.51 (0.99, 2.89)	1.94 (1.25, 2.58)	0.06 (0.04, 0.09)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Education						
High school or less	222	9.96 (4.96, 17.01)	4.01 (2.38, 7.04)	2.14 (1.31, 4.48)	2.69 (1.55, 4.00)	0.08 (0.05, 0.13)
Some college	409	11.84 (6.46, 21.28)	4.51 (2.85, 7.63)	2.82 (1.50, 4.97)	2.59 (1.69, 4.31)	0.08 (0.06, 0.15)
College degree	328	10.28 (5.78, 17.68)	4.52 (2.55, 8.09)	2.51 (1.51, 4.74)	2.54 (1.62, 3.91)	0.08 (0.05, 0.13)
Postgraduate	334	9.67 (5.15, 17.79)	4.58 (2.74, 7.95)	2.83 (1.72, 5.32)	2.97 (1.92, 4.64)	0.09 (0.05, 0.13)
p-value		0.01	0.36	0.02	0.01	0.23
Smoking						
Never	817	9.62 (5.36, 17.75)	4.29 (2.51, 7.44)	2.47 (1.38, 4.77)	2.56 (1.59, 4.28)	0.08 (0.05, 0.13)
Past	345	11.54 (6.01, 19.42)	4.78 (2.84, 8.46)	2.97 (1.70, 5.14)	2.86 (2.00, 4.26)	0.09 (0.06, 0.14)
Current	131	11.88 (7.77, 19.88)	4.52 (2.80, 7.14)	2.63 (1.66, 4.95)	2.82 (1.65, 4.44)	0.09 (0.06, 0.15)
p-value		0.002	0.11	0.01	0.03	0.003
Daily calorie intake						

	N[1]	MBzP[2]	MCOP	MCNP	MCPP	∑ HMW phthalate metabolites
		Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) ng/mL	Median (Q1, Q3) nmol/mL
1st quartile: < 1330 kcal/day	324	10.60 (5.87, 18.25)	4.54 (2.75, 7.38)	2.57 (1.53, 4.80)	2.66 (1.73, 4.29)	0.09 (0.05, 0.14)
2nd quartile: 1330 – 1680 kcal/day	323	10.12 (5.39, 16.68)	4.33 (2.43, 7.50)	2.42 (1.41, 4.49)	2.49 (1.60, 3.76)	0.08 (0.05, 0.13)
3rd quartile: 1680 – 2160 kcal/day	323	10.15 (5.76, 17.67)	4.41 (2.56, 7.85)	2.79 (1.41, 5.00)	2.87 (1.73, 4.34)	0.08 (0.05, 0.13)
4th quartile: > 2160 kcal/day	323	11.18 (6.22, 19.78)	4.56 (2.85, 8.13)	2.93 (1.62, 5.62)	2.80 (1.77, 4.63)	0.09 (0.05, 0.14)
p-value		0.30	0.39	0.21	0.30	0.18
Physical activity						
1st quartile: < 6.7	324	11.08 (5.89, 18.86)	4.54 (2.69, 8.09)	2.42 (1.41, 4.73)	2.57 (1.56, 3.92)	0.09 (0.05, 0.15)
2nd quartile: 6.7 – 7.9	324	10.81 (6.26, 18.54)	4.31 (2.37, 7.09)	2.29 (1.40, 4.31)	2.73 (1.58, 4.30)	0.08 (0.05, 0.13)
3rd quartile: 7.9 – 9.0	327	10.58 (6.23, 18.24)	4.33 (2.57, 7.65)	2.80 (1.46, 5.03)	2.84 (1.91, 4.37)	0.09 (0.06, 0.13)
4th quartile: > 9.0	318	9.31 (4.78, 16.65)	4.54 (2.85, 7.90)	3.04 (1.73, 5.46)	2.70 (1.76, 4.49)	0.08 (0.05, 0.13)
p-value		0.17	0.36	0.001	0.08	0.68
Menopausal status						
Pre- or peri-menopausal	913	10.31 (5.96, 18.31)	4.54 (2.75, 7.90)	2.73 (1.54, 4.91)	2.69 (1.73, 4.26)	0.09 (0.05, 0.14)
Natural/surgical menopause	186	9.53 (4.57, 18.12)	4.13 (2.33, 6.74)	2.36 (1.31, 5.00)	2.11 (1.49, 4.04)	0.08 (0.04, 0.13)
Unknown due to hormone therapy	194	11.28 (6.66, 18.32)	4.32 (2.49, 8.05)	2.69 (1.47, 5.18)	3.00 (1.96, 4.52)	0.09 (0.06, 0.13)
p-value		0.16	0.19	0.43	0.01	0.19
Obesity status[4]						
Normal/underweight	520	8.96 (4.66, 15.65)	3.72 (2.32, 6.39)	2.17 (1.32, 4.12)	2.42 (1.54, 3.93)	0.07 (0.04, 0.12)
Overweight	395	10.24 (5.78, 17.52)	4.51 (2.68, 7.30)	2.50 (1.41, 4.49)	2.75 (1.69, 4.09)	0.09 (0.05, 0.13)
Obese	378	13.28 (7.77, 22.04)	5.55 (3.50, 9.82)	3.70 (2.02, 6.07)	3.06 (2.02, 4.94)	0.11 (0.07, 0.16)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] Data in this table were based on the 1293 women who had complete data in 1999/2000.

[2] All concentrations were adjusted for hydration using the covariate-adjusted creatinine standardization method. "Q1" means "1st quartile" and "Q3" means "3rd quartile". ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

[3] P-values were obtained from Kruskal-Wallis tests.

[4] Obesity status was defined based on BMI from 1998/1999 for 1248 women, 1997/1998 for 36 women, and 1996/1997 for 9 women using race/ethnicity-specific cut points.

Supplementary Table 4.4 Distributions of covariates in 1999/2000 by incident diabetes status

	No diabetes (N = 1232)	Incident diabetes (N = 61)	
	Median (Q1, Q3)[1]	**Median (Q1, Q3)**	**p-value**[2]
Age (years)	49.4 (47.4, 51.5)	49.0 (47.2, 52.8)	0.45
BMI (kg/m^2)	25.3 (22.2, 30.0)	33.1 (29.2, 39.5)	<0.0001
Daily calorie intake (kcal/day)	1667.4 (1326.3,	2210.0 (1688.2,	<0.0001
Physical activity index	7.9 (6.7, 9.1)	7.1 (6.1, 7.9)	0.0003
	N (%)	**N (%)**	
Site			
Detroit area, MI	203 (16.5%)	22 (36.1%)	<0.0001
Boston, MA	205 (16.6%)	6 (9.8%)	<0.0001
Oakland, CA	284 (23.1%)	9 (14.8%)	<0.0001
Los Angeles, CA	338 (27.4%)	8 (13.1%)	<0.0001
Pittsburgh, PA	202 (16.4%)	16 (26.2%)	<0.0001
Race/ethnicity			
White	642 (52.1%)	25 (41.0%)	<0.0001
Black	235 (19.1%)	27 (44.3%)	<0.0001
Chinese	164 (13.3%)	4 (6.6%)	<0.0001
Japanese	191 (15.5%)	5 (8.2%)	<0.0001
Education			
High school or less	205 (16.6%)	17 (27.9%)	0.07
Some college	388 (31.5%)	21 (34.4%)	0.07
College degree	315 (25.6%)	13 (21.3%)	0.07
Postgraduate	324 (26.3%)	10 (16.4%)	0.07
Smoking			
Never	782 (63.5%)	35 (57.4%)	0.24
Past	329 (26.7%)	16 (26.2%)	0.24
Current	121 (9.8%)	10 (16.4%)	0.24
Menopausal status			
Pre- or peri- menopausal	876 (71.1%)	37 (60.7%)	0.12
Natural/surgical menopause	172 (14.0%)	14 (23.0%)	0.12
Unknown due to hormone therapy	184 (14.9%)	10 (16.4%)	0.12
Obesity status[3]			
Normal/underweight	514 (41.7%)	6 (9.8%)	<0.0001
Overweight	382 (31.0%)	13 (21.3%)	<0.0001
Obese	336 (27.3%)	42 (68.9%)	<0.0001

[1] Data in this table were based on the 1293 women who had complete data in 1999/2000. "Q1" means "1st quartile" and "Q3" means "3rd quartile".

[2] P-values were obtained from Wilcoxon rank-sum tests for continuous covariates and Chi-squared tests for categorical covariates.

[3] Obesity status was defined based on BMI from 1998/1999 for 1248 women, 1997/1998 for 36 women, and 1996/1997 for 9 women using race/ethnicity-specific cut points.

Supplementary Table 4.5 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations

	Hazard ratio (95% CI)		
	Model 1	Model 2	Model 3
MEP	**1.13 (1.00, 1.28)**	1.03 (0.89, 1.19)	1.01 (0.87, 1.17)
MnBP	**1.28 (1.05, 1.55)**	1.10 (0.89, 1.36)	1.09 (0.87, 1.36)
MiBP	**1.31 (1.07, 1.60)**	1.20 (0.97, 1.49)	1.19 (0.94, 1.49)
∑LMW phthalate metabolites	**1.18 (1.03, 1.36)**	1.06 (0.90, 1.25)	1.04 (0.88, 1.24)
MEHP	1.00 (0.87, 1.16)	0.95 (0.82, 1.11)	0.97 (0.83, 1.14)
MEHHP	1.11 (0.96, 1.27)	1.02 (0.86, 1.20)	1.00 (0.84, 1.18)
MEOHP	1.11 (0.96, 1.28)	1.04 (0.88, 1.22)	1.02 (0.86, 1.20)
MECPP	1.10 (0.94, 1.29)	1.03 (0.87, 1.23)	1.00 (0.83, 1.20)
∑DEHP metabolites	1.10 (0.95, 1.28)	1.02 (0.87, 1.21)	1.00 (0.84, 1.20)
MBzP	**1.39 (1.17, 1.65)**	1.21 (1.00, 1.48)	1.18 (0.97, 1.43)
MCOP	**1.25 (1.05, 1.49)**	1.21 (1.00, 1.47)	1.16 (0.94, 1.42)
MCNP	**1.17 (1.00, 1.36)**	1.15 (0.97, 1.37)	1.08 (0.89, 1.30)
MCPP	**1.31 (1.06, 1.61)**	1.21 (0.97, 1.51)	1.15 (0.91, 1.46)
∑HMW phthalate metabolites	**1.41 (1.15, 1.72)**	**1.26 (1.00, 1.59)**	1.19 (0.94, 1.51)

Model 1: Crude model

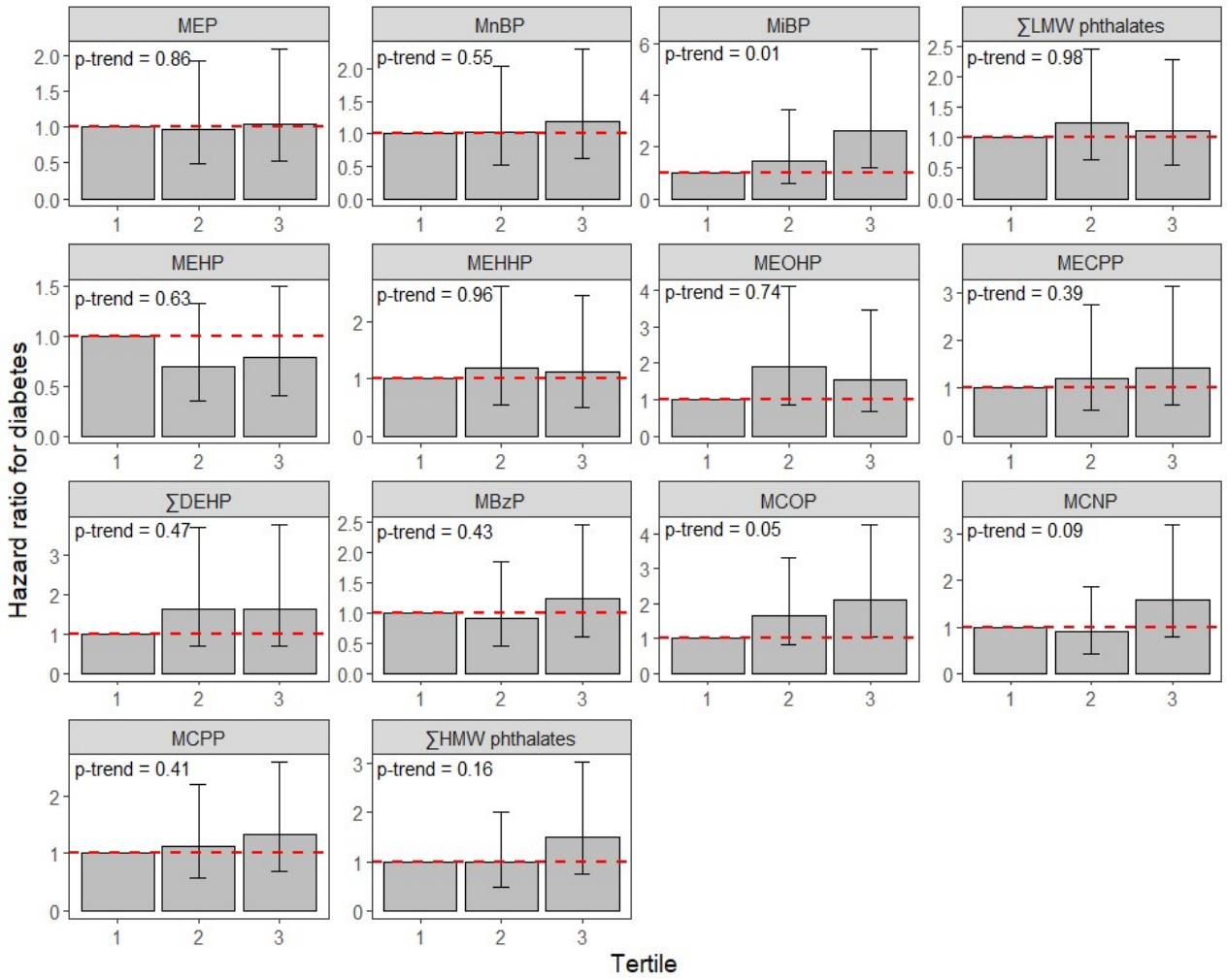
Model 2: Adjusted for age in 1999/2000, race/ethnicity, site, education, and time-varying menopausal status, physical activity, smoking status, and dietary energy intake

Model 3: Model 2 + time-varying BMI

Bold: p-value < 0.05.

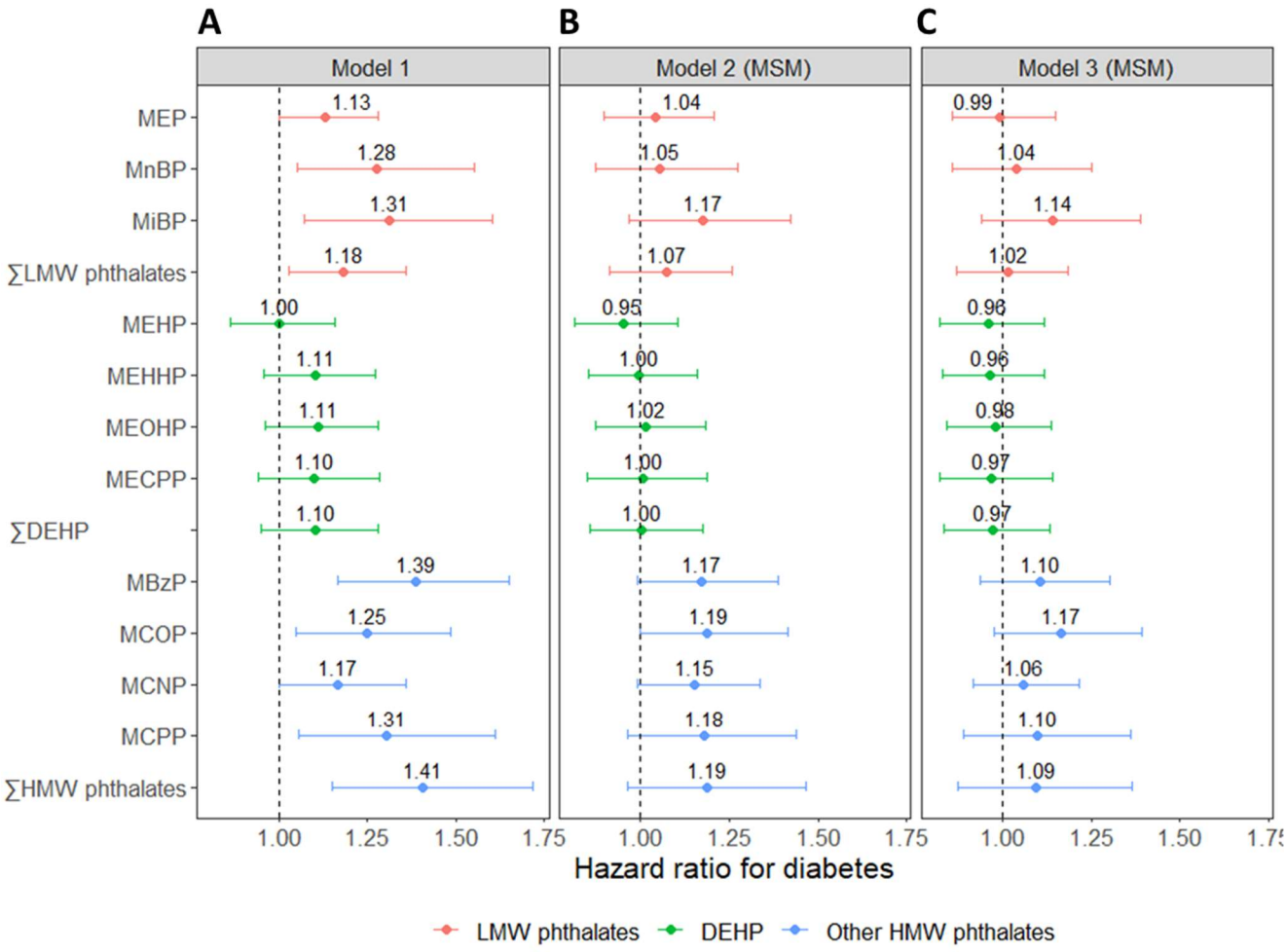
∑LMW phthalate metabolites = molar sum of MEP, MnBP, and MiBP; ∑DEHP metabolites = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalate metabolites = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Figure 4.1 Hazard ratios for diabetes associated with phthalate metabolite concentration tertiles



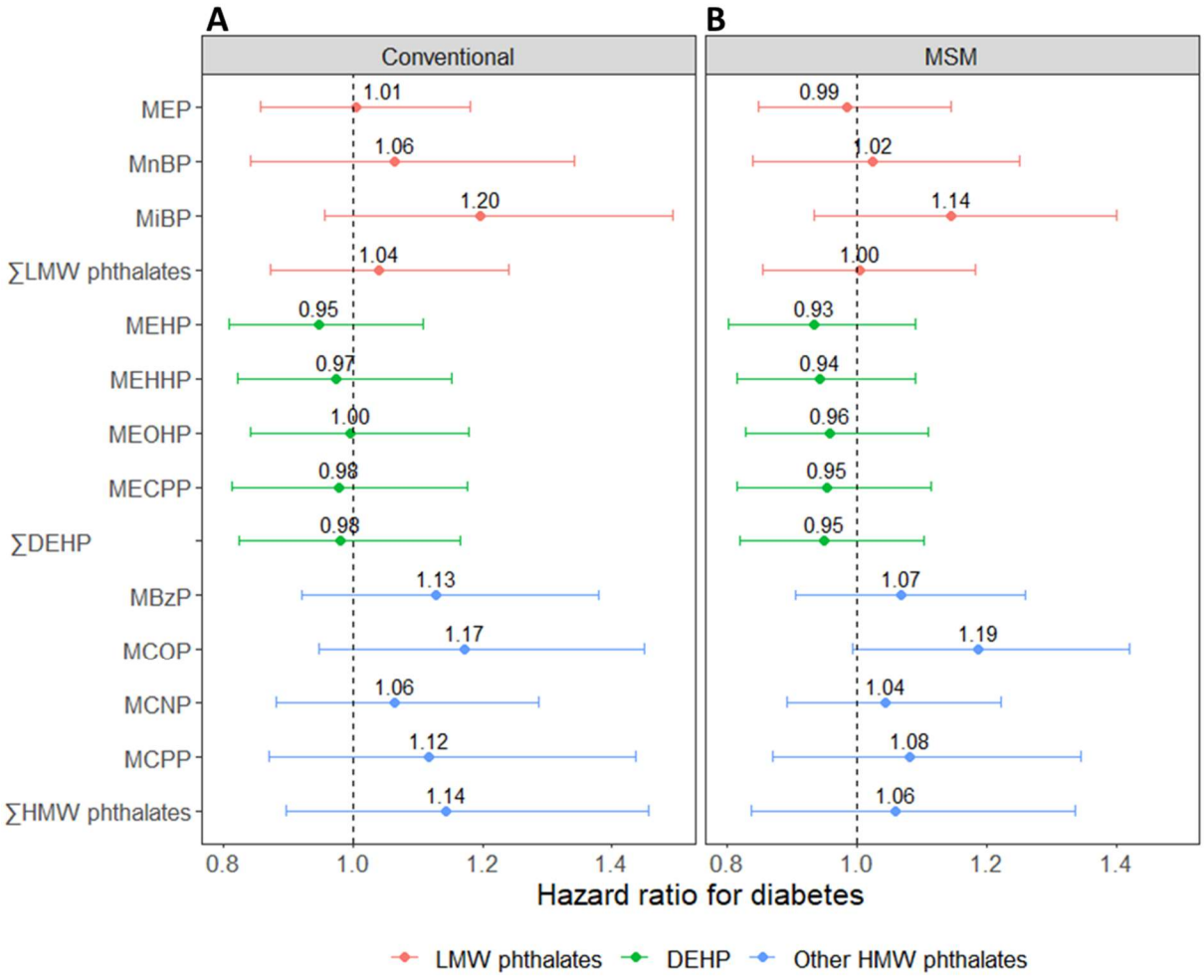
The hazard ratios were adjusted for age in 1999/2000, site, education, and time-varying menopausal status, physical activity, smoking status, dietary energy intake, and BMI. ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Figure 4.2 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations from marginal structural models with inverse-probability-of-treatment weights



Model 1: Crude model
Model 2 (MSM): Inverse-probability-of-treatment weights accounted for time-varying confounding by menopausal status, physical activity, smoking status, and dietary energy intake. In addition to weighting, the models were adjusted for age in 1999/2000, site and race/ethnicity, and education.
Model 3 (MSM): Inverse-probability-of-treatment weights accounted for time-varying confounding by menopausal status, physical activity, smoking status, dietary energy intake, and BMI. In addition to weighting, the models were adjusted for age in 1999/2000, site and race/ethnicity, and education.
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Figure 4.3 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations after incorporating inverse-probability-of-selection weights



Conventional model: Adjusted for age in 1999/2000, site and race/ethnicity, education, and time-varying menopausal status, physical activity, smoking status, dietary energy intake, and BMI, in addition to weighting for differential selection into SWAN-MPS.
Marginal structural model (MSM): Inverse-probability-of-treatment weights accounted for time-varying confounding by menopausal status, physical activity, smoking status, dietary energy intake, and BMI. Inverse-probability-of-selection weights accounted for differential selection into SWAN-MPS. In addition, the models were adjusted for age in 1999/2000, site and race/ethnicity, and education.
∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 4.6 Hazard ratios for diabetes per doubling of phthalate metabolite concentrations within each racial/ethnic group

	Hazard ratio (95% CI)		
	White	Black	Asian
N cases/ N at risk	25/674	27/265	9/369
MEP	1.10 (0.89, 1.37)	1.01 (0.81, 1.26)	0.69 (0.43, 1.13)
MnBP	1.22 (0.87, 1.72)	0.95 (0.68, 1.32)	1.24 (0.69, 2.24)
MiBP	**1.63 (1.18, 2.25)**	0.93 (0.63, 1.37)	0.82 (0.46, 1.49)
∑LMW phthalate metabolites	1.15 (0.89, 1.47)	1.04 (0.81, 1.33)	0.69 (0.38, 1.26)
MEHP	1.01 (0.80, 1.27)	0.91 (0.72, 1.15)	1.09 (0.70, 1.71)
MEHHP	1.09 (0.86, 1.39)	0.85 (0.64, 1.12)	1.21 (0.80, 1.83)
MEOHP	1.14 (0.89, 1.45)	0.88 (0.67, 1.15)	1.15 (0.74, 1.79)
MECPP	1.18 (0.91, 1.52)	0.84 (0.62, 1.13)	0.96 (0.57, 1.60)
∑DEHP metabolites	1.14 (0.88, 1.46)	0.85 (0.64, 1.13)	1.12 (0.70, 1.77)
MBzP	**1.57 (1.18, 2.09)**	0.92 (0.66, 1.28)	1.04 (0.65, 1.64)
MCOP	**1.43 (1.05, 1.95)**	1.19 (0.89, 1.59)	0.59 (0.35, 1.00)
MCNP	**1.30 (1.03, 1.65)**	0.87 (0.64, 1.20)	0.88 (0.51, 1.53)
MCPP	**1.50 (1.06, 2.12)**	0.98 (0.70, 1.38)	0.98 (0.53, 1.79)
∑HMW phthalate metabolites	**1.77 (1.27, 2.46)**	0.87 (0.58, 1.30)	0.88 (0.50, 1.56)

The hazard ratios were adjusted for age in 1999/2000, site, education, and time-varying menopausal status, physical activity, smoking status, dietary energy intake, and BMI. Racial/ethnic-specific hazard ratios were estimated from Cox proportional hazards models with race/ethnicity by phthalate metabolite interaction terms.

Between Black and White women, the interaction term was statistically significant for MiBP, MBzP, and ∑HMW phthalates, and borderline significant ($0.05 <$ p-value for multiplicative interaction < 0.10) for MECPP, MCNP, and MCPP.

Between Asian and White women, the interaction term was statistically significant for MCOP and ∑HMW phthalates, and borderline significant for MEP and MiBP.

Bold: p-value < 0.05.

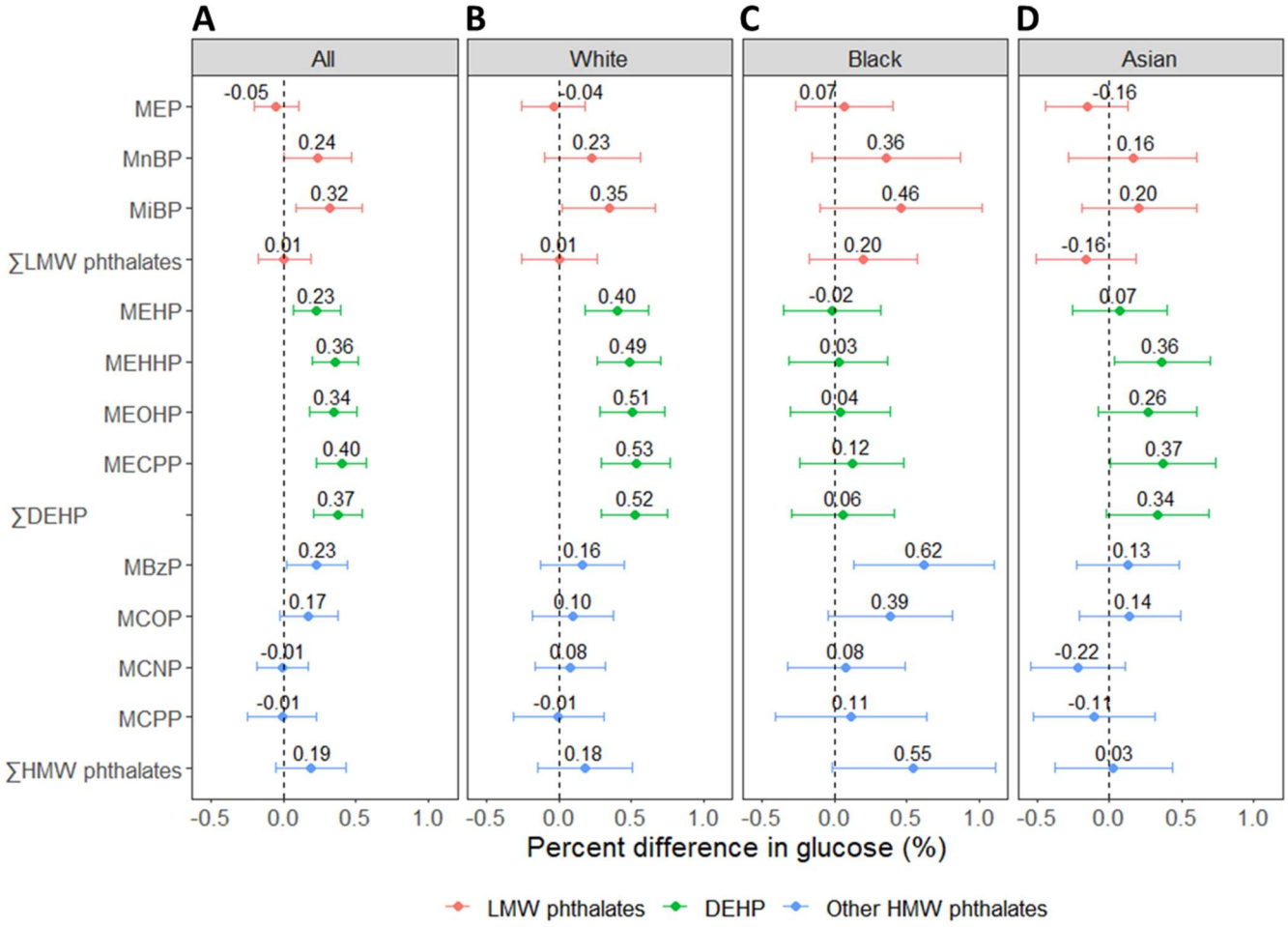
∑LMW phthalate metabolites = molar sum of MEP, MnBP, and MiBP; ∑DEHP metabolites = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalate metabolites = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Table 4.7 Distributions of covariates, glucose, and insulin in 1999/2000 by race/ethnicity

	White (N = 667)	Black (N = 262)	Asian (N = 364)	
	Median (Q1, Q3)[1]	**Median (Q1, Q3)**	**Median (Q1, Q3)**	**p-value**[2]
Age (years)	49.2 (47.3, 51.5)	49.2 (47.2, 51.4)	49.9 (47.8, 51.6)	0.03
BMI (kg/m^2)	26.0 (22.7, 31.1)	30.1 (25.8, 35.8)	22.8 (20.8, 25.3)	<0.0001
Daily calorie intake ((kcal/day)	1653.0 (1326.8, 2071.5)	1758.4 (1345.8, 2411.2)	1716.5 (1341.8, 2174.1)	0.06
Physical activity index	8.1 (7.0, 9.3)	7.3 (6.3, 8.6)	7.5 (6.4, 8.8)	<0.0001
Fasting glucose (mg/dL)	87.0 (82.0, 93.0)	89.0 (84.0, 95.0)	91.0 (85.0, 97.0)	<0.0001
Fasting insulin (μIU/ml)	8.6 (6.8, 11.6)	10.7 (7.8, 16.1)	7.9 (6.6, 10.5)	<0.0001
HOMA-IR	1.8 (1.4, 2.6)	2.4 (1.7, 3.7)	1.8 (1.4, 2.5)	<0.0001
	N (%)	**N (%)**	**N (%)**	
Site				
Detroit area, MI	98 (14.7%)	127 (48.5%)	0 (0.0%)	<0.0001
Boston, MA	141 (21.1%)	70 (26.7%)	0 (0.0%)	<0.0001
Oakland, CA	125 (18.7%)	0 (0.0%)	168 (46.2%)	<0.0001
Los Angeles, CA	150 (22.5%)	0 (0.0%)	196 (53.8%)	<0.0001
Pittsburgh, PA	153 (22.9%)	65 (24.8%)	0 (0.0%)	<0.0001
Education				
High school or less	75 (11.2%)	75 (28.6%)	72 (19.8%)	<0.0001
Some college	197 (29.5%)	103 (39.3%)	109 (29.9%)	<0.0001
College degree	167 (25.0%)	47 (17.9%)	114 (31.3%)	<0.0001
Postgraduate	228 (34.2%)	37 (14.1%)	69 (19.0%)	<0.0001
Smoking				
Never	390 (58.5%)	143 (54.6%)	284 (78.0%)	<0.0001
Past	221 (33.1%)	64 (24.4%)	60 (16.5%)	<0.0001
Current	56 (8.4%)	55 (21.0%)	20 (5.5%)	<0.0001
Menopausal status				
Pre- or peri- menopausal	448 (67.2%)	180 (68.7%)	285 (78.3%)	0.0001
Natural/surgical menopause	94 (14.1%)	42 (16.0%)	50 (13.7%)	0.0001
Unknown due to hormone therapy	125 (18.7%)	40 (15.3%)	29 (8.0%)	0.0001
Obesity status[3]				
Normal/underweight	281 (42.1%)	50 (19.1%)	189 (51.9%)	<0.0001
Overweight	193 (28.9%)	78 (29.8%)	124 (34.1%)	<0.0001
Obese	193 (28.9%)	134 (51.1%)	51 (14.0%)	<0.0001
Incident diabetes				
No	642 (96.3%)	235 (89.7%)	355 (97.5%)	<0.0001
Yes	25 (3.7%)	27 (10.3%)	9 (2.5%)	<0.0001

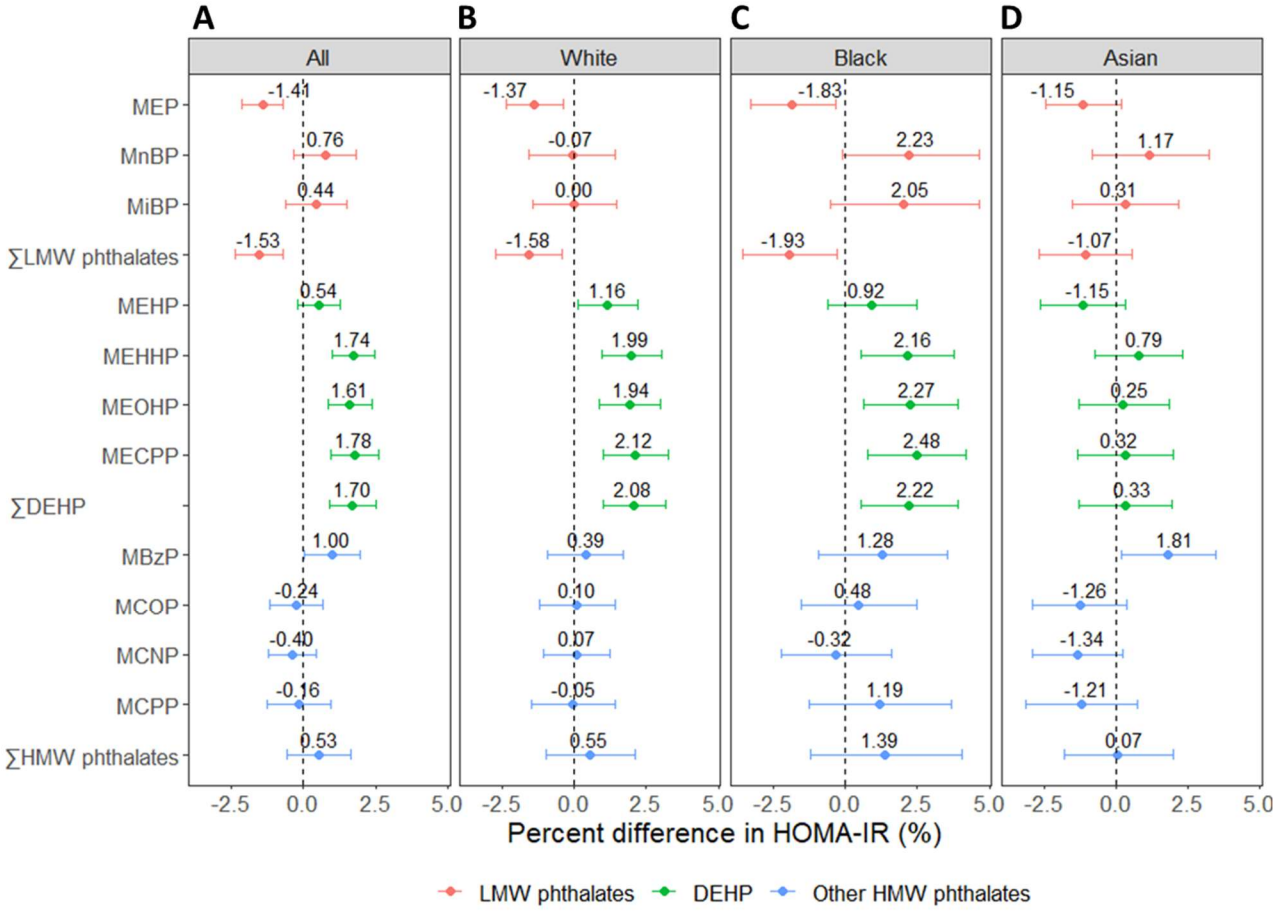
[1] Data in this table were based on the 1293 women who had complete data in 1999/2000. "Q1" means "1st quartile" and "Q3" means "3rd quartile".
[2] P-values were obtained from Kruskal-Wallis tests for continuous variables and Chi-squared tests for categorical variables.
[3] Obesity status was defined based on BMI from 1998/1999 for 1248 women, 1997/1998 for 36 women, and 1996/1997 for 9 women using race/ethnicity-specific cut points.

Supplementary Figure 4.4 Percent differences in fasting glucose per doubling of phthalate metabolite concentrations



Percent differences were adjusted for age, site, race/ethnicity, education, dietary energy intake, smoking status, physical activity, menopausal status, and BMI in 1999/2000. Between Black and White women, the interaction term was statistically significant for MEHP, MEHHP, MEOHP, and ∑DEHP (p-for-interaction ranged from 0.03 to 0.04) and borderline significant for MECPP and MBzP (p-for-interaction = 0.06 and 0.11, respectively). Between Asian and White women, the interaction term for MEHP was borderline significant (p-for-interaction = 0.10). ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Supplementary Figure 4.5 Percent differences in HOMA-IR per doubling of phthalate metabolite concentrations



Percent differences were adjusted for age, site, race/ethnicity, education, dietary energy intake, smoking status, physical activity, menopausal status, and BMI in 1999/2000. Between Black and White women, the interaction term was borderline significant for MnBP (p-for-interaction = 0.11). Between Asian and White women, the interaction term was statistically significant for MEHP (p-for-interaction = 0.01) and borderline significant for MEOHP, MECPP, and ∑DEHP (p-for-interaction all equaled 0.08). ∑LMW phthalates = molar sum of MEP, MnBP, and MiBP; ∑DEHP = molar sum of MEHP, MEHHP, MEOHP, and MECPP; ∑HMW phthalates = molar sum of MBzP, MCOP, MCNP, and MCPP.

Chapter 5 Discussion

Obesity is a major public health challenge in contemporary societies because it is highly prevalent and is associated with increased risks of numerous chronic diseases (1). Preventing obesity is important for achieving the public health goals of preventing diseases, promoting health, and prolonging life (2), and effective prevention depends on a thorough understanding of obesity's etiology. In the past decades, research in multiple disciplines has identified major risk factors of overweight and obesity (3), uncovered key physiological pathways of energy homeostasis and adipogenesis (4), and discovered molecular mechanisms linking excess body fat to metabolic diseases such as diabetes (5,6). However, the etiology of obesity, as well as its metabolic comorbidities, has remained incompletely understood (4).

The metabolism-disrupting chemical (MDC) hypothesis posits environmental chemicals as potential contributors to obesity and related metabolic disorders (7). This hypothesis was inspired by the concurrent increases in the prevalence of obesity and diabetes and the production volume of synthetic chemicals throughout the 20th century (8,9). Though the hypothesis' biological plausibility is supported by toxicological studies (10,11), the obesogenic and diabetogenic potentials of many synthetic chemicals have infrequently been examined with longitudinal data in adult human populations. Thus, whether synthetic chemicals were a source of the recent obesity-diabetes twin epidemic is uncertain.

This dissertation aimed to interrogate the MDC hypothesis with respect to phthalates, a class of synthetic chemicals often found in personal care products and polyvinyl chloride (PVC)

plastic applications such as food packaging, food processing equipment and supplies, building materials, wires, cables, plastic toys, and some medical devices (12). We conducted three studies in a well-characterized, diverse population of midlife women with longitudinal metabolic outcomes, thereby providing enhanced evidence not only for the evaluation of the MDC hypothesis, but also the risk assessments of phthalates.

5.1 Summary of Findings

In Aim 1, we examined the associations between eleven phthalate metabolites and longitudinal changes in body weight (BW), fat mass (FM), and body fat percentage (BF%) in 1369 women. We found that over 18 years, except for mono-carboxy-isononyl phthalate, higher urinary concentrations of all phthalate metabolites in 1999/2000 were associated with more rapid increases in FM and BF%. Furthermore, the associations were strongest among women who were normal/underweight at baseline, potentially because overweight/obese women had reached or were close to reaching their biological capacity for body fat. These findings provide the first piece of evidence directly linking phthalate exposure to more rapid increases in FM and BF% in a general adult population, lending support to the obesogenic potential of phthalates. It is intriguing that the associations between phthalates and BW changes were weaker and less consistent across phthalate metabolites compared to the other two adiposity measures. This may reflect the fact that body weight is not an accurate measure of body fat in an aging cohort, as increases in body fat mass are masked by the simultaneous loss of skeletal muscle mass (13). Our study thus demonstrates the value of using accurate measures of body fat in studies on phthalates and obesity, which future studies examining the MDC hypothesis may consider.

In addition to an energy reserve, adipose tissue is also an endocrine organ regulating whole-body energy and nutrient metabolism through the secretion of adipokines (5). In obesity, not only does the size of adipose tissue increase, the adipokine profiles are also altered to promote inflammation and insulin resistance, which may be the potential mechanisms linking obesity to metabolic diseases (14). In Aim 2, we examined this endocrine aspect of obesity by investigating the cross-sectional associations between eleven phthalate metabolites and leptin, high-molecular-weight (HMW) adiponectin, and their ratio in 1250 women. Consistent with previous studies (15,16), we found that phthalate metabolites were positively associated with leptin, but the associations were largely not independent of body mass index (BMI). Further, we found that none of the phthalate metabolites were inversely associated with HMW adiponectin regardless of adjustment for BMI. In fact, a strong, positive association was found between mono(2-ethylhexyl) phthalate (MEHP), the primary metabolite of di(2-ethylhexyl) phthalate (DEHP), and HMW adiponectin. Similarly, we found that phthalate exposure was not associated with a greater leptin:HMW adiponectin ratio independent of BMI, and that MEHP was inversely associated with the leptin:HMW adiponectin ratio. Overall, findings from Aim 2 does not support an adverse impact of phthalate exposure on leptin and adiponectin independent of phthalates' potential obesogenic effects. Altering the levels of these two adipokines was unlikely a mechanism through which phthalates increase the risk of obesity-related metabolic diseases.

The findings from Aims 1 and 2 suggest phthalates may increase the risk of obesity but not necessarily adversely impact adipose tissue's endocrine function. The implication of these findings for phthalates' associations with impaired metabolic health was the topic of Aim 3, where we examined the associations between eleven time-varying phthalate metabolites and the incidence of diabetes over six years in 1308 women. We found that among all women, several high-

molecular-weight (HMW) phthalate metabolites were associated with a higher incidence of diabetes, but none of the associations were statistically significant. However, the associations between phthalates and incident diabetes differed significantly by race/ethnicity. In White women, each doubling of the concentrations of mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-carboxyoctyl phthalate (MCOP), mono-carboxy-isononyl phthalate (MCNP), mono(3-carboxypropyl) phthalate (MCPP), and the sum of non-DEHP HMW phthalate metabolites were associated with 30-77% higher incidence of diabetes. In contrast, none of the phthalate metabolites were associated with diabetes incidence in Black or Asian women. Our analyses suggest that the relatively small and statistically non-significant associations between phthalates and diabetes among all women were not due to over-adjusting for BMI. Further, several phthalate metabolites were positively associated with insulin resistance in non-White women, suggesting that non-White women were not immune to phthalates' potential toxic effects on glucose metabolism. Other mechanisms, such as different degrees of left truncation in different racial/ethnic groups, may have contributed to the racial/ethnic differences in the associations between phthalates and incident diabetes. Overall, given that mono-n-butyl phthalate (MnBP), MiBP, and DEHP metabolites were positively associated with diabetes incidence in White women in a prior study (17), results from Aim 3 support a positive association between phthalate exposure and incident diabetes. However, whether this association is causal remains uncertain because the associations between phthalates and diabetes were inconsistent across racial/ethnic groups and phthalate metabolite species.

Altogether, this dissertation provides relatively clear evidence supporting a positive association between phthalates and more rapid increases in body fat, suggesting a potential role of phthalates in the development of obesity. However, this dissertation is equivocal in terms of the

associations between phthalates and the metabolic complications of obesity. There was little evidence that phthalate exposure adversely altered levels of leptin and HMW adiponectin independent of its potential obesogenic effects. There was some evidence that phthalates may increase the risk of diabetes, but the perplexing racial/ethnic differences rendered a causal association between phthalates and diabetes less convincing.

5.2 Public Health Implications

5.2.1 Research

Findings from this dissertation partially support the MDC hypothesis. Since its inception two decades ago, a growing body of epidemiologic literature has sought to examine the role of environmental chemicals, including phthalates, in the development of obesity, diabetes, and other metabolic disorders. Although substantial progress in our understanding on this important topic has been made since Baillie-Hamilton's ecological analysis in 2002 (7,8), the epidemiologic data examining the MDC hypothesis are still limited for most chemicals. Relatively few studies employed a longitudinal design, and when it was used, the study was often conducted in a birth or pregnancy cohort to examine the associations between prenatal exposures and developmental, peri-partum, or post-partum outcomes (7). For example, most of the studies on phthalates and adiposity were cross-sectional (18). Of the seven longitudinal studies in adults (19–25), three were concerned with exposures during pregnancy and post-partum weight gain (23–25). Such limited data have made it difficult to determine the metabolic impact of phthalates, which impedes the development of environmental public health measures that may contribute to the prevention of metabolic diseases. The positive associations between phthalates and longitudinal changes in

adiposity discovered in this dissertation add to the credibility of the MDC hypothesis and show that the metabolic impact of phthalates is not limited to children or pregnant women. These findings will hopefully motivate additional research on phthalates and metabolic health throughout the life-course in men and women, so that high-quality scientific information is available to help determine the risks of phthalates and the appropriate responses to those risks. To this end, increased funding on research into the metabolic effects of phthalates and other chemicals suspected to disrupt metabolism is warranted. The SWAN Multi-pollutant Study, which provided the data for this dissertation, offers an excellent, cost-effective model of integrating environmental chemical exposure assessments into existing cohort studies to accelerate MDC research.

5.2.2 Practice

Although this dissertation did not provide a definitive answer to phthalates' metabolic effects, its findings do have immediate impact on public health practice. Four phthalates, including di-n-butyl phthalate (DnBP), di-isobutyl phthalate (DiBP), DEHP, and butylbenzyl phthalate (BBzP), are recently designated as high-priority chemical substances for risk evaluations by the United States Environmental Protection Agency under the Toxic Substances Control Act (26). These risk evaluations typically require a comprehensive systematic review of epidemiologic studies concerning the human health effects of a chemical (27). The findings from Aims 1 and 3 of this dissertation will inform the systematic reviews and risk evaluations of the four phthalates. Another implication is the need to increase awareness about the health risks of phthalates among medical students and medical practitioners. Individuals typically trust one-on-one advice from healthcare providers. Further, the American Medical Association has one of the highest lobbying budgets among professional organizations in the US (28). Integrating findings from this dissertation and other research on phthalates into medical education will help raise the profile of

environmental health issues related to phthalates. Additionally, changing individual behaviors is an important target of public health practice. Findings from this dissertation suggest that avoiding products contaminated with phthalates may help reduce the risks of obesity and diabetes.

5.2.3 Policy

Without structural changes, however, it is ultimately difficult for individuals to avoid phthalate exposure because these chemicals are added to a wide range of industrial and consumer products. Motivated by concerns about phthalates' developmental and reproductive toxicity, a series of legislation since 2008 has led to the prohibition of DnBP, DiBP, DEHP, di-isodecyl phthalate (DiDP) and other HMW phthalates in children's toys and childcare articles (29). However, as recent as 2021, prohibited phthalates and unregulated analogs were still found in toys and other products marketed to children in certain discount retailers ("dollar stores") in seven US states (30). The use of phthalates in other consumer products, such as food packaging, vinyl gloves for food handling, and vinyl flooring, has never been prohibited in the US. The result is ongoing, widespread exposure to phthalates, with the extent of exposure and health risks often unbeknownst to consumers. Given the potential metabolic health risks of phthalates, one policy to address these risks is to require mandatory disclosure about phthalates in consumer products, so that individuals may make informed decisions about their purchase. It may be prudent to regulate phthalates as a group and restrict their use in consumer products beyond toys and childcare articles. A bill to ban the use of phthalates in food contact materials was introduced to the US Senate in 2021 (31). Findings from this dissertation may inform the deliberation of this piece of legislation.

5.3 Strengths and Limitations

This dissertation has several notable strengths and limitations. A key strength is the study sample's racial/ethnic diversity. Few existing studies on phthalates' metabolic impact included a significant proportion of Black women, and even fewer included Chinese and Japanese women. The racial/ethnic diversity of SWAN-MPS allowed us to produce data with greater generalizability to non-White women. Another strength is the longitudinal design employed in Aims 1 and 3, which provided stronger evidence for causal inference. Our examination of adipokines as outcomes in Aim 2 was also a novel contribution to the nascent research on phthalates' impact on adipocyte biology. Notable limitations include the lack of accurate dietary data taken at the time of exposure assessment, which may have resulted in some residual confounding. However, residual confounding by diet was unlikely to completely explain our results, as exposure to mono-ethyl phthalate (MEP), the metabolite of a phthalate not typically added to food, was associated with more rapid body fat increases. We were not able to examine body fat distribution as an outcome, which is an independent risk factor for poor metabolic health apart from the total amount of body fat (32). Further, spot urine samples were used to assess phthalate exposure. This may have resulted in higher exposure measurement error because urinary phthalate metabolites in spot urine samples reflect recent exposures, which may differ from habitual exposure (33). Finally, our analytic sample did not include men or persons with Hispanic ethnicity, so our findings' generalizability to these populations is unknown.

5.4 Future Directions

Future studies should examine phthalates and metabolic outcomes in men, where data are currently lacking. To reduce the potential impact of exposure measurement error, future studies may consider measuring phthalate metabolites more frequently within a defined period of interest and use techniques such as within-subject pooling or regression calibration to reduce or correct for measurement error (34). Additional outcomes, such as body fat distribution, sex steroid hormones, thyroid hormones, and additional adipokines, will be worth examining to further our understanding on phthalates' metabolic impact and potential metabolism-disrupting mechanisms. To understand the potential impact of phthalates at different ages and different stages of the diabetogenic process, future studies will benefit from recruiting younger participants. Doing so will also help us better understand the reasons behind the effect modifications by obesity status and race/ethnicity observed in this dissertation, because selection bias from the attrition of susceptible and highly-exposed individuals is less of a concern in a younger cohort. Incorporating detailed information on social determinants of health into future studies will help us identify social groups or social conditions with increased susceptibility to phthalates to prioritize interventions. The role of phthalate exposure as a potential mediator of health disparities by social groups should also be examined, as limiting phthalate exposure may help promote environmental justice.

5.5 Conclusions

Over the past century, obesity and its metabolic complications have become major public health problems. The MDC hypothesis suggests that environmental chemicals may play a role in this epidemic, but epidemiologic evidence is needed to test this hypothesis and inform public

health actions. This dissertation provided the evidence for phthalates, a chemical to which human exposure is essentially ubiquitous. We found that phthalate exposure was associated with more rapid increases in body fat but not an adverse adipokine profile independent of body size as measured by BMI. We also found that phthalate exposure was associated with a higher incidence of diabetes in some women. Thus, our findings partially support the MDC hypothesis. If the metabolic impact of phthalates is confirmed in future studies, limiting phthalate exposure will be an important avenue to prevent obesity and related metabolic disorders.

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