ENVIRONMENT – WIDE ASSOCIATION STUDY ON CHILDHOOD OBESITY

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DISSERTATION

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By

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ABSTRACT

Background: Obesity is both a global and national public health issue with increasing prevalence over the last decades. It is associated with adverse health effects as well as social and economic costs. Both children and adults are affected; however, much more impact and prevalence are seen in children because of their growing bodies. While the etiology and prevention of childhood obesity are not fully understood, studies have linked it to lack of built environment, diet, lack of physical activities, and genetic susceptibility, with growing evidence that it could also result from other environmental factors. Studies linking it to other environmental factors are quite limited, unsystematic, incomprehensive and inconclusive. Thus, using the concept of an environment-wide association study (EWAS) and while accounting for already known risk factors (lifestyle factors) associated with childhood obesity, the aims of this dissertation were 1) to comprehensively and systematically investigate all the environmental factors available in the National Health and Nutrition Examination Survey (NHANES) to determine factors associated with childhood obesity and 2) to validate my findings from aim1 on a different cohort of children and adults to see if factors persist.

Methods: I utilized NHANES datasets 1999-2016, retrieving data files for children/adolescents (6-17yrs) and adults (>18yrs). Obesity was measured using BMI measures and waist to height ratio. A multinomial and binary logistic regression was conducted while adjusting for age, sex, race/ethnicity, creatinine, calorie intake, physical activity, screen time (TV hours & computer/video games hours), limitation to physical activities, and socioeconomic status. As in EWAS, multiple hypothesis testing was controlled, and validation analyses were done.

Results: I found that metals such as beryllium (OR: 3.305 CI: 1.460-7.479) and platinum (OR: 1.346 CI: 1.107-1.636); vitamins such as gamma- tocopherol (OR: 8.297 CI: 5.683-12.114) and delta- tocopherol (OR: 1.841 CI:1.476-2.297); heterocyclic aromatic amines such as 2-Amino-9H-pyrido (2,3-b) indole

(A-a-C) [OR: 1.323 CI: 1.083-1.617] and 2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C) [OR: 2.799 CI: 1.442-5.433]; polycyclic aromatic amines such as 9- fluorene (OR: 1.509 CI: 1.230-1.851), 4-phenanthrene (OR: 2.828 CI: 1.632-4.899) and caffeine metabolites such as 1,3,7-trimethyluric acid (OR: 1.22 CI: 1.029-1.414) and 1,3,7-trimethylxanthine(caffeine) (OR: 1.258 CI: 1.075-1.473) were positively and significantly associated with childhood obesity. More so, I found that factors such as gamma- and delta-tocopherols, as well as manganese, copper, caffeine, 2-napthol and 2-phenanthrene were associated with both childhood and adulthood obesity. Finally, I found that vitamin B6, B12 and C as well as carotenoids, enterolactone, harmane and iron are protective factors of both childhood and adulthood obesity.

Discussion: These novel findings are of public health significance since these factors are potentially modifiable risk factors of childhood obesity and they are valuable for prevention and reducing the risk of obesity among U.S. children and adolescents. Exposures to some of these factors are mainly from vehicle exhaust, tobacco combustion, tea, and contaminated air and water. They may have the capability of eliciting stress, inhibiting enzymes needed for metabolic processes or disrupting lipid homeostasis which subsequently increases the risk of obesity.

Conclusion: Despite the difficulty of ascertaining causality, this dissertation found novel pathways to the etiology of childhood obesity as well as adulthood obesity that needs further investigation.

Chapter 1

Introduction

Statement of the Problem

Obesity is a global public health issue with increasing prevalence over the last decades [1]. According to the World Health Organization (WHO), the global prevalence of obesity has tripled since 1975 [2]. Obesity increases the risks of chronic diseases such as cancer, cardiovascular diseases, nonalcoholic fatty liver disease, diabetes, and metabolic syndrome [3-5], and consequently increases the risk of death associated with these chronic diseases [6-9]. Both children and adults are affected; however, much more impact and prevalence are seen in children because of their growing bodies. Global prevalence rate of childhood obesity has significantly increased since 1980. According to a study in 2014, global prevalence of childhood obesity has increased by over 47.1% between 1980 and 2013 compared to adult prevalence rate that increased by only 27.5% during the same period [10]. This high childhood prevalence has been associated with adverse health and psychological consequences as well as social and economic costs [6, 11]. More importantly, it has been associated with reduced life expectancy when not controlled [12]. Evidence suggests an additional rise of 9% in childhood obesity by 2020 as there is a growing evidence that children/adolescents of normal weight will become either overweight or obese, and those already obese will remain obese in adulthood [13-17].

Compared to other countries, the United States (U.S.) tends to have a larger obese/overweight population, with over 17% of all U.S. children and adolescents obese according to the Centers for Disease Control and Prevention (CDC) in 2014 [18]. In 2016, a study confirmed that its prevalence has tripled since 1980. The rising prevalence of childhood obesity in the U.S. is predominantly seen among minority groups and groups of lower socioeconomic status, indicating the presence of racial and income

disparities [19, 20]. In addition, there is gender disparity, as high prevalence of obesity is seen more in girls than in boys [21-23]. With the steady rise in prevalence and health consequences associated with obesity, there is evidence of a rising U.S. health care cost. In 1998 alone, Finkelstein et al. [24] estimated that about $93 billion per year, which represents 9.1% of the total medical expenditures, were linked to treatments of conditions associated with overweight and obesity. In 2006, Trogdon et al. [25] estimated an annual medical expenditure of about $147 billion on obesity-related conditions. With these increases, Wang et al. [15] projects that the total medical expenditures associated with obesity related conditions will double every ten years to amount to a total of about $860.7- $956.9 billion by 2030, which will represent about 16 - 18% of the total U.S. medical expenditures.

Despite numerous research on childhood obesity, prevalence rates are steadily rising partly due to the fact that the etiology and prevention of childhood obesity are not fully understood [26]. Substantial evidence indicates that the etiology of childhood obesity is multifaceted and there is no single cure to the disease. Childhood obesity has been linked to diet, lack of physical activity, genetic susceptibility, and lack of built environment; however, the role of other environmental factors are yet to be fully explored [27, 28]. Studies linking it to other environmental factors such as chemicals, metals, air pollution, and so on, are quite limited and most of these studies have findings that are conflicting, making it difficult to draw conclusions. Meanwhile, there are hundreds more environmental factors having complex nature and interacting with other factors yet to be evaluated. Many of these other environmental factors are suggested to be endocrine and metabolic disrupting factors which affect adipogenesis, or induce epigenetic or molecular changes to metabolism, homeostasis or appetite; all of which increase the risk for obesity [26, 29-31].

In addition, the limited studies on the role of environmental factors on childhood obesity have not been systematic, comprehensive, and conclusive. Usually, these studies are hypothesis driven stemming from animal studies resulting in only one or two environmental factor(s) studied. However, the joint effects of environmental factors are often times neglected. More so, due to the complex nature of environmental factors, these studies use different and multiple exposure metrics which may affect study findings and make it difficult to draw consistent conclusions. For example; Scinicariello & Buser found a positive association between *urinary* PAH metabolites and childhood obesity while Choi et al. found a negative association between PAH (*assessed using an air monitor*) and childhood obesity. Drawing conclusions from these studies is quite difficult because of the different study findings.

Furthermore, most studies control for usual covariates such as gender, race, and social economic status; however, they fail to recognize that there are hundreds of other environment factors that could impact the relationship. In other words, there could be hidden relationships that may be explaining the cause; thus, the need for them to be explored. While factors such as home and built environment, diet, physical activity, and gene susceptibility have been linked to childhood obesity, there are other factors that may have been overlooked, and not controlling for these may lead to overestimation of effect, false positive findings or false negative findings. Following the unique concept of genome-wide association study, an environment-wide association study may be the solution to these weaknesses found in previous studies as it allows for the evaluation of many more environmental factors while controlling for already known factors to ascertain possible associations with childhood obesity.

Genome-wide association study, also known as GWAS is a type of study that uses high throughput genotyping technologies to test millions of genetic variants, linking these variants to health-related traits

or diseases while controlling for many covariates obtained from epidemiological data [32]. While genetic variants identified through GWAS have explained a certain portion of risk variability between individuals, a larger and significant portion of risk variability is yet to be explained. This is because environmental factors are not comprehensively considered in the study of diseases. Incorporating the unique concept of GWAS in terms of environment-wide association study (EWAS) will, therefore, allow for the analysis of multiple environmental factors while controlling for already known factors.

EWAS has been conducted on a few diseases with novel and unexpected associations found [33-35]. These associations have initiated further investigations/interventions to reduce disease burden. To date, this unique concept has not been applied to childhood obesity despite its rising prevalence and long adverse human impacts in the U.S. In this dissertation, a lot more factors than the ones previously evaluated in other published studies will be considered while evaluating their association with childhood obesity. This, moreover, will **help to explain** the increasing prevalence of childhood obesity and suggest possible strategy for reduction. Meanwhile, exposure to environmental toxins can be moderated; thus, the identification of these environmental toxins through EWAS will provide a pathway to disease prevention. This will help create better individual risk profiles which allows for better allocation of resources for disease monitoring and prevention.

Rationale

There are chemicals, pathogens, metals, air pollutants, and toxins from plants/animals which tend to persist in both indoor and outdoor environments. Indoor and outdoor environments are crucial parts of childhood development as they are places where children play, learn, and develop a relationship with the natural environment. Research has linked exposure to contaminants found in the outdoor environments to diseases such as asthma, cancers, other chronic diseases, and even obesity [36-39]. Some of these

environmental contaminants may be found in homes or other indoor environments, predisposing children to the health impacts associated with exposures [40-44]. Health impacts associated with these exposures tend to be more pronounced and devastating in children due to the fact that their bodies are still growing, and numerous organs are still developing.

While everyone is exposed to environmental toxins, children are more exposed to these toxins than adults. This is because of the increases in their physiological needs for more food, water and air per kilogram of body weight when compared to adults. Children tend to exhibit hand-to-mouth and hand-to-object-to-mouth behaviors which increase their risk of exposure to environmental toxins. This behavior is mostly seen in younger age group (between 2 to 6 years of age). For school aged children (6 to 12 years), increased risk of exposure to environmental toxins is associated with the greater amounts of time they spend outdoors, school, and after-school environments playing and/or engaging in other activities. This increases their exposure to toxins via ingestion or inhalation of these toxins. According to a study in California, 6 to 12 year old spend more time outdoors especially in the afternoon when air pollution levels peak [45] . For older children (age 12 to 17), their general curiosity about what is in their environment as well as their desire and enjoyment of freedom increase their risk of exposure to environmental toxins. More so, risky behaviors of alcohol, drug, and chemical usage increase their risk of exposures to environmental toxins. While many environmental toxins such as chemicals are regulated and their toxicity levels known, new and thousands of already existing chemicals are yet to be tested. This moreover may have an unknown level of toxicity which children and adolescents may be suffering from based on either acute or chronic exposures to these compounds [46]. Evidence shows only a small fraction (7%) of the chemicals have been evaluated for their impact on childhood development. These

unknown levels of toxicities of thousands of chemicals of which the induction of obesity may be part of require further investigation.

Meanwhile factors such as the home and built environment, diet, lack of physical activity, and gene susceptibility have been studied extensively and have provided evidence for the association with childhood obesity. However, there is growing evidence that there are additional hidden factors embedded in the above-mentioned risk factors that may as well contribute to the etiology of childhood obesity. Identifying these factors is necessary to understand their contribution and biological mechanism of action leading to childhood obesity. Among these factors are environmental toxins which children can be exposed to following their exposure to the aforementioned known risk factors associated with obesity. The following paragraphs present a brief discussion on why these aforementioned risk factors may not be sufficient in understanding the etiology of childhood obesity as well as how the hidden factors can be associated with these already known risk factors of childhood obesity.

With numerous researches focusing on the impact of home and built environment on childhood obesity, the role of other environmental factors is often overlooked. In the home environment which has many factors associated with it, numerous researchers have focused on the effect of time spent on watching television or on a computer on childhood obesity. While rise in prevalence rates of childhood obesity has been linked to screen time due to its tendency to replace physical activities and promote unhealthy snacking, research has ignored some environmental factors that could be associated with screen time. There is substantial evidence that indoor air quality of homes could be impacted due to the use of consumer products and electronics containing or emitting volatile organic compounds, bisphenol A, Phthalates, flame retardants, and particulate matter [47-52]. With most of these chemicals known to be

endocrine disrupting chemicals or acting on a different metabolic pathway, there is a possibility that increased amount of screen time will increase exposure to them. In addition to lack of physical activities and unhealthy snacking associated with screen time, childhood obesity may be subsequently induced. Thus, a comprehensive and systematic analysis of these factors in relation to childhood obesity is warranted.

The impact of dietary intake on childhood obesity has received much attention. While dietary intake has been associated with childhood obesity, recent studies indicate the need to evaluate the individual components of human diet and their role in inducing childhood obesity. Excessive consumption of dietary fats and carbohydrates have been examined; however, there are conflicting findings, which may be due to non-specificity of the type of dietary fats or the fact that other dietary components were not considered [53-56]. Thus, a comprehensive analysis of all dietary factors is warranted to ascertain the role of all macronutrients found in human diet on childhood obesity. In addition, it is very important not to ignore the fact that some environmental factors are associated with human diet. There is substantial evidence of the presence of environmental contaminants in human foods via the use of fertilizers, food packaging products, and absorption and accumulation of chemicals in animals used for milk and meat production as well as fruits and vegetables. Ingestion of these foods gives the contaminants access to disrupt normal human metabolic processes. For instance, there is evidence of psychologic, biochemical, and behavioral dysfunctions resulting from ingestions of foods contaminated with toxic metals. There is evidence of toxic metals displacing vital micronutrients and inducing oxidative stress which may in turn interfere with metabolic process involving energy production and expenditure, thus contributing to obesity [57-59]. Some chemicals are known to target and activate the nuclear hormone proliferator-activated receptor gamma, an important pathway for adipogenesis and obesity. While there is some

evidence on the underlying metabolic pathways involving the induction of obesity by some environmental toxin, much is still unknown as exposure to environmental toxins and prevalence of childhood obesity are on a steady rise even with preventive measures. In other words, there are still more environmental toxins (ingested) that may be associated with the development of childhood obesity that are yet to be known. This therefore warrants further research.

Lack of built environment comprising of walking network (sidewalks), neighborhood safety, cycling network, greater access to parks, recreational facilities and healthy foods have also been associated with increased risk of obesity due to the fact that it makes one less physically active and encourages access to unhealthy food [26, 29, 60, 61]. Due to study findings, interventions have been made and built environments are improved. However, substantial evidence shows that the built environment could increase exposure to environmental toxins (air pollutants). With increasing population and traffic congestions, children making use of walking and cycling networks could have increased exposure to air pollutants such as particulate matter, nitrogen, ozone, and other environmental chemicals from surrounding industrial activities. Exposure to these pollutants have been associated with adverse health outcomes such as respiratory, cardiovascular, immunological, hematological, reproductive/developmental, and neurological disorders [62-65]. There is also evidence that increased physical activity increases the uptake and deposition of air pollutants or environmental chemicals in the respiratory system which can then be distributed to other body systems. For instance, while exposure to particulate matter has been linked to cardiovascular morbidity and mortality by inducing pulmonary inflammatory response, myocardial infarction, release of proinflammatory cytokines which are harmful, endothelial dysfunction, and other physiological responses, there is growing evidence it could induce the inflammation of the adipose tissue, thus contributing to obesity [66, 67]. Exposure to environmental

chemicals such as dioxins could interfere with reproductive and neurological functions as well as the metabolic function of the adipose tissue, thus increasing the risk for obesity [68-76]. Thus, a natural question is how much of these air pollutants could negate the effect of physical activities on the development of childhood obesity and which environmental pollutant is doing so?

With increasing prevalence of childhood obesity, an EWAS approach will be an ideal way to identify more novel and overlooked associations of factors with childhood obesity. This will help provide adequate information on how this disease should be approached in terms of treatment or prevention to promote both individual health and population health.

Research Aims

Using the concept of an environmental wide association study (EWAS) and while accounting for already known risk factors (lifestyle factors) associated with childhood obesity, this study was guided by the following aims:

1. Aim 1: To comprehensively and systematically investigate all the environmental factors available in NHANES to determine factors associated with childhood obesity;
2. Aim 2: To determine the validity of findings from Aim 1 by
    a. Validation on a different cohort of children
3. Aim 3: To determine the robustness of findings from Aim 1 by;
    a. EWAS on adults to see if factors persist

Chapter 2

Review of Literature

This section presents an overview of obesity and a comprehensive literature review of all environmental factors. It aims at identifying gaps in the literature while justifying the need for further research. It also presents an overview of genome-wide association study, its strengths and an overview of environmental wide association study.

Obesity

Obesity is defined as the abnormal accumulation of fat in the human body which results from the imbalance between energy intake and expenditure, thus increasing the risks of chronic diseases [26, 77]. It is associated with hyperinsulinemia, lipid abnormalities, and insulin resistance [78]. It is considered a global health issue and the fifth leading risk for global deaths because of its increasing prevalence and association with increased morbidity and disability rates [1, 7, 79]. Since 1975, the prevalence rate of obesity has tripled globally with over 2 billion people including children and adults either overweight or obese in 2016 [80]. This increase has been associated with higher economic, personal and health costs as well as other adverse health consequences [3-5, 11, 81]. It has been estimated that over 2.3 million additional people will become obese or overweight in the next 50 years [82]. With the increasing prevalence, there is a much growing concern for children as childhood obesity has had a dramatic increase between 1975 and 2016 globally [10, 83]. Among countries, evidence shows a higher prevalence of childhood obesity in the Americans, followed by Europeans, and finally the indigenes of the Middle East [84]. In the U.S specifically, there has been a three-fold increase in prevalence rates of childhood obesity since 1980 according to the Centers for Disease Control and Prevention (CDC) [27, 29, 85-87].

The complexity of childhood obesity is concerning as there is no single cause or cure [77]. While childhood obesity has been linked to diet, lack of physical activities, and genetic susceptibility [27, 28], limited evidence shows that behavioral, environmental, and metabolic factors [26, 77] or complex interactions of these factors [26, 77, 88-96] may play significant roles in the understanding of the etiology of childhood obesity. Therefore, research should focus on these factors to understand their contribution to the development of childhood obesity. Currently, environmental factors which include – diet (nutrients and vitamins), drugs, chemical pollutants, metals, ecological processes, infectious agents, ultraviolet radiation, secondhand cigarette smoke, metabolites of environmental chemicals/infectious agents, air pollution, toxins from animals and plants, occupational risk factors, and climate have received little attention with regards to their relationship with childhood obesity in their entirety [89]. While a few epidemiological studies of environmental factors have been conducted, a lot of more environmental factors are yet to be evaluated. More so, the majority of the findings from these studies are inconclusive and lack the accounting of multiple comparison of factors [97-103]. Thus, a systematic and comprehensive analysis of all environmental factors needs to be conducted. This will help reveal factors contributing to the development of childhood obesity that have been overlooked. While there may be no evidence of the biological mechanism explaining the role of the factors to the etiology of childhood obesity, the statistically significant findings of these factors provide a hypothesis for further metabolic research studies.

Epidemiological studies of environmental factors

Bisphenol A, alkylphenols and phthalates

The few environmental factors that have currently been receiving attention include exposure to bisphenol A [104-110], alkylphenols [77, 111, 112], and phthalates [113-119]. These are non-persistent ubiquitous chemicals known to disrupt the endocrine system by changing the endogenous hormone

signaling and metabolism through targeting the nuclear hormone proliferator-activated receptor gamma (PPARγ), genomic estrogen receptors 1 and 2, thyroid hormone receptor, androgen receptor, and membrane-bound estrogen receptors [83, 120, 121]. These, therefore, regulate and promote the accumulation of lipids and subsequently affect adipogenesis or induce epigenetic or molecular changes to metabolism, homeostasis or appetite [26, 28, 122-127]. These chemicals have received attention due to their high production and excessive usage in many consumer products such as beverages/food, children toys, baby bottles and powder, food packaging, microwave ovenware, building materials, and production of polycarbonate plastics and epoxy resins [77, 108, 111, 113, 128, 129]. However, there is growing evidence of other endocrine disrupting chemicals such as melamine, bisphenol F& Sand so on that may affect adiposity which may subsequently lead to obesity [130-134]. More so, studies examining the association of these chemicals and childhood obesity have been inconclusive [135]. For example, a study by Harley et al. found a positive association between urinary bisphenol a (BPA) concentration and body mass index (BMI), waist circumference(WC), fat mass and overweight/obesity in children and adolescents after controlling for several confounding factors such as education, race/ethnicity, social economic status and so on [136]; while in a different cohort, Yamano et al. found no association [137]. Likewise, Trasande et al. found a positive association between low molecular weight phthalates and obesity in non-Hispanic black children [116]; while on the contrary, Hatch et al. found no association [113]. More so, Hao et al. found a positive association between 4-nonylphenol (4-NP) and induction of adipogenesis which would subsequently increase the risk of obesity [112] while on the contrary Choi et al. found no association between 4-nonylphenol and 4-tert-octylphenol (4-t-OP) and childhood obesity [77].

Metals

Exposure to metals is another environmental factor that may be associated with childhood obesity through their ability to replace essential metals and micronutrients or induce oxidative stress in a biological system [26, 57]. Studies examining this association are limited and have conflicting conclusions [57, 138-145]. For example, Padilla et al. found a positive association between barium exposure and body mass index (BMI) as well as waist circumference (WC) in children. They also found a negative association between exposures to cobalt and lead and BMI and WC in the same cohort. No association was found between other metals such as cesium, thallium, cadmium, tungsten, antimony and molybdenum and body mass index and waist circumference in the same cohort [57]. On the contrary, Huzior et al. found no association between lead and obesity in children [142]. Gender differences have been seen among these studies examining the effect of metal exposure [138, 139, 145]. There are, however, other metals such as platinum and uranium that may be associated with childhood obesity that are yet to be investigated, thus warranting further research.

Air Pollutants

Exposure to air pollutants is another environmental factor that may be associated with childhood obesity. While exposure to air pollutants has been linked to respiratory diseases, cardiovascular diseases and neurocognitive disorders [26, 146], a few of these pollutants has been explored to discover their relationship with childhood obesity. For example, exposure to secondhand tobacco smoke has been linked to the development of childhood obesity [147]. However, there are limited studies examining exposure to particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen oxides and carbon monoxides and body mass index in children. The few studies examining these pollutants have found a significant association between these pollutants and increased body mass index in children [39, 148]. These associations have been based on indirect measurements of air pollutants. Studies have used traffic density and proximity to

freeways/highways as a proxy for exposure to these air pollutants which, however, do not specify a single air pollutant, thus making it difficult to identify a specific air pollutant responsible for effect (increased body mass index). Currently, researchers are beginning to use more direct approaches such as air monitoring and biological monitoring to accurately assess exposure to specific air pollutants [149]. Using these approaches, a few studies have examined the impact of exposures to polycyclic aromatic hydrocarbons (PAH), nitrogen oxides and carbon monoxides on childhood obesity, however, study findings have been contradictory. Rundle et al. [150] found a statistically significant association between prenatal exposure to polycyclic aromatic hydrocarbons and childhood obesity while Choi et al. [151] and Perera et al [152] found negative associations between prenatal exposure to polycyclic aromatic hydrocarbons (PAH) and birth weight as well as birth size and head circumference among African Americans. A study by Scinicariello and Buser [153] found that the total urinary PAH metabolites and naphthalene metabolites were positively associated with childhood obesity, waist circumference and body mass index. Numerous other studies have found no association between these pollutants and either childhood obesity or birth weight [154-157]. Interestingly, studies examining the impact of polycyclic aromatic hydrocarbons have only evaluated some of the metabolites of naphthalene, pyrene, fluorene, and phenanthrene, ignoring other metabolites of these compounds especially that of phenanthrene and the metabolites of fluoranthene. With recent discoveries of the endocrine disrupting capabilities of phenanthrene and fluoranthene as indicated by Chang & Liao [158] and Vinggaard et al [159], further research is warranted to examine their effect on childhood obesity.

Caffeine intake

Relationship between obesity and caffeine intake is inconclusive as a few studies have shown that the intake of caffeine promotes weight management and weight loss by enhancing physical performance, lipid oxidation, and lipolytic and thermogenic activities [160-163], while some other studies have found

no association between caffeine intake and body mass index (BMI) [164, 165]. Numerous other studies have shown that caffeine intake promotes weight gain [166]. Irrespective of these study findings, caffeine intake has been assessed by gathering information about subjects' consumption of coffee or caffeinated drinks through the use of dietary intake data such as 24-h dietary recalls and food frequency questionnaires. The use of questionnaire is problematic as the actual amount of caffeine in these dietary sources may be difficult to ascertain and more so the use of questionnaire has been shown to be subject to recall bias thus leading to the under/overestimation of caffeine intake [167]. In addition, the use of the consumption of caffeine-containing foods to ascertain caffeine intake has been shown to confound any identified link to health effect. Studies have shown that components of these foods are a contributing factor to the risk of some of the identified health effects such as increased/decreased risk of either body weight or type 2 diabetes [168-170]. This, therefore, indicates the need to use biological markers such as the urinary concentration of caffeine and caffeine metabolites to accurately assess caffeine intake [171, 172]. Currently there are no studies examining the relationship between caffeine intake through the use of biological markers and obesity. The use of urinary concentrations of caffeine and caffeine metabolites has been shown to identify the differences in metabolic activity as caffeine is metabolized by the liver, thus engaging in different chemical reactions and producing metabolites [171, 173, 174]. Thus, there is need for further research using its biological markers.

Pathogens

Exposure to pathogens is another factor that may be associated with obesity. Based on study findings from animal models, several pathogens have been identified to increase the risk of obesity, however, there is limited evidence on whether these pathogens and other pathogens not yet identified in animal studies also contribute to obesity in humans [175-179]. Among pathogens identified in animal studies, avian adenovirus SMAM-1 and a human adenovirus AD-36 have received lots of attention. Some

studies have found positive association between these viruses and higher body mass index in both children and adults with distinct differences in the level of serum lipids [180-188] while others have found no association [189-191]. While numerous studies have focused on the relationship between Adenovirus type 36 (AD-36) and human obesity, there are still unclear responses to the mechanism by which AD 36 increases the risk of obesity in humans [185]; thus, further research is required. A few other pathogens have been examined to determine their relationship with the increasing prevalence of obesity in adults not children. A study by Thjodleifsson et al. [192] investigated the relationship between obesity and IgG antibodies for Helicobacter pylori, hepatitis A virus, Toxoplasma gondii, herpes simplex virus 1, chlamydia pneumoniae, Epstein-Barr virus, and cytomegalovirus. This study found a positive association between being overweight and having helicobacter pylori and chlamydia pneumoniae only. Another study by Lajunen et al. [193] also found a positive correlation between exposure to chlamydia pneumoniae and being overweight but only in women. With the above evidence, it is obvious that there are numerous pathogens infecting humans and increasing prevalence of obesity. Thus, there is a huge possibility that infection may be a contributing factor to obesity in humans, and therefore, extensive epidemiological and longitudinal studies are required to identify the role of more pathogens in increasing the risk of obesity especially in children. Established relationship between pathogens and human obesity from these studies will help in the prevention and treatment of obesity [194].

Persistent Organic Compounds

Persistent organic compounds such as flame retardants (polybrominated diphenyl ethers (PBDE), chlorinated and non-chlorinated organophosphate, and Firemaster 550(FM550)), polychlorinated biphenyls (PCB), dioxins, furans, perfluorinated compounds, and organochlorinated pesticides are

environmental factors that may be associated with obesity due to their abilities to disrupt endocrine and metabolic functions.

Flame retardant

Flame retardants are substances added to consumer products to reduce their ability to ignite and to meet federal and state fire safety regulations [26]. Commonly used flame retardants are polybrominated diphenyl ethers and these compounds are known to be ubiquitous, accumulating and persisting in the environment for a long time [195, 196]. Studies have found a significant association between exposure to PBDE and diverse adverse health outcomes including social, behavioral and learning deficits and obesity [197-199]. With substantial evidence of the adverse impact associated with PDBE, its use has been banned in various European countries and some states in the U.S, warranting the use of other chemicals as flame retardants in consumer products. Despite the ban of PBDE in products, studies still show the presence of PDBE in human serum confirming the long persistency of this chemical in the environment and the potential for increases in adverse human health outcomes [200]. Currently, other chemicals such as chlorinated and non-chlorinated organophosphates and Firemaster 550 (FM550) (which contains 2-ethylhexyl tetrabromobenzoate (TBB), bis (2-ethylhexyl) tetrabromophthalate (TBPH), triphenyl phosphate (TPP), and isopropylated triphenyl phosphate (IPTP)) are used as flame retardants, and there is growing evidence from animal and in vitro studies of their adipogenesis capabilities [201]. There are currently no human studies, thus the need for further research on these compounds and their ability to increase obesity in humans especially children.

Polychlorinated biphenyls (PCB)

Polychlorinated biphenyls (PCB), another persistent organic compound is of great concern due to its endocrine disrupting capabilities of mimicking the function of thyroid hormones and estrogens and interfering with glucose metabolism [202]. Its use started in the 1930s for industrial purposes and was

banned in the 1970s in some countries such as Europe and U.S after various evidences of bioaccumulation and adverse impacts being associated with exposure [203-207]. Despite its ban, there is substantial evidence that polychlorinated biphenyls are still in the environment as they are stable lipophilic compounds in the environment which resist any form of degradation, thus persisting for a very long time in the environment and bioaccumulating in most compartments of the ecosystem and human tissues [208-211]. Apart from their industrial sources which have been banned, they are known to be formed unintentionally as by-products from many other chemical and thermal reactions [212]. There is also substantial evidence confirming human exposure to polychlorinated biphenyls even at low concentration through the food chain [213]. Humans are mostly exposed to PCB through intake of dairy products, meat and fish [214, 215]. There have been limited studies on the relationship between exposure to polychlorinated biphenyls and childhood obesity. Study findings from the few studies have been inconsistent. Fein et al. [216] found a significant association between prenatal exposure to PCB and lower birth weight as well as smaller head circumference. In contrast, Patandin et al. [217] found no association between prenatal exposure to PCB and body weights of toddlers. While Verhulst et al. [218] found a positive association between intrauterine exposure to PCBs and DDE and body mass index among children of age 1 to 3 years old. Reasons for the inconsistencies in study findings may be unclear; however, it is evident that sample size may have affected most study findings. More so, chemical dosage may have contributed to the differences in study findings. Numerous results from animal findings have indicated a U-shape association between PCB and obesity. Arsenescu et al [219] found a positive association between low doses of PCB 77 and increased adipocyte differentiation and expression of peroxisome proliferator-activated receptor γ, thus increasing the risk of obesity. The increased adipogenesis comes as a result of the binding of these compounds to the aryl hydrocarbon receptor in adipocytes. In the same study, high doses of PCB-77 hindered adipocyte differentiation.

With adult participants, there is substantial evidence of a strong relationship between exposure to PCB and being obese even though some studies had conflicting results [220-223].

Dioxins and Dioxin-like compounds

Dioxins are halogenated hydrocarbons which persist for a long time in the environment because of their lipophilic nature and their resistance to biological and chemical degradation. They do not have natural sources but are known to be formed as by-products from pesticide production, organochlorine chemicals production and incineration processes [218]. Considerable amounts of dioxins are found in fish, meat and human breast milk; and human exposure is mainly through the food chain as found with exposures to polychlorinated biphenyls [224-226]. Evidence from animal and in vitro studies show that Dioxins interfere with adipogenesis and the metabolic function of the adipose tissue by targeting the ligand-activated nuclear receptor, aryl hydrocarbon receptor (AhR), thus increasing the risk for obesity [68-73]. More so, dioxin exposure has been linked to significant adverse effects on neurobehavioral and reproductive functions as well as dermal and immune toxicity [74-76]. These associations are suggested to be due to low doses of the dioxin chemical compound. Numerous animal studies have depicted a U-shape association between dioxin and obesity, whereby low doses of dioxin especially 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) increases the expression of the peroxisome proliferator activated receptor gamma (PPARγ). This, therefore, initiates adipocyte differentiation which increasing the chances of having a positive association with obesity primarily during childhood. Higher dose of the chemical exposure inhibits adipocyte differentiation, thus producing no association with childhood obesity [76, 227]. Human studies are sparse, a few studies have evaluated the synergistic effect of dioxins and polychlorinated biphenyls and found no association with child or adult obesity [217]. Even though dioxin and polychlorinated biphenyls tends to occur at the same time and have the same receptor target, further research on the single effect of dioxin on childhood obesity is still needed. Burns et al.

[228] found a negative association between serum levels of dioxin and growth in Russian boys aged 8 and 9 years. Further research is also required to confirm the association between dioxin exposure and childhood and adult obesity as a few studies presented conflicting results [220-223].

Pesticides

Various types of pesticides including organochlorines, pyrethroid, organophosphates, carbamates, dichlorophenols and herbicide compounds are being used at varying concentrations with the ultimate goal of altering the physiological characteristics of target organisms thus leading to their dysfunction and decreasing their impact on crops and animals. With increased use of these pesticides, both adults and children are at risk of exposure via contaminated food, soil, water, air and consumer products, with children at a greater risk of exposure due to their physiological characteristics and their general tendency to explore their environment [229]. While there are evidences of health effects associated with human exposure to pesticides [229-232], research on its relationship with obesity is limited [233].

Among the different types, organochlorine pesticides are the most researched and concerned about due to their lipophilicity and long half-lives which aid in their accumulation in the environment and long-term body burden. They tend to travel long distances in the air, soil, and surface or ground water [234]. Examples of Organochlorine pesticides include dieldrin, kepone, chlordane, methoxychlor, toxaphene, lindane, mirex, benzene hexachloride (hexachlorobenzene), and Dichlorodiphenyltrichloroethane (DDT). Most of the organochlorine pesticides are no longer in use in the U.S; however, in other countries they are. Humans are exposed mainly through inhalation or ingestion of contaminated foods. Presence of these pesticides in human biological samples indicate recent or current exposures. While there are controversial findings, some studies examining the impact of organochlorine pesticides especially DDT which metabolizes to dichlorodiphenyldichloroethylene (p,p′ -DDE) have showed

significant associations with higher body mass index in children and adults, and this evidence has been attributed to the impact of DDE on lipid metabolism [89, 218, 235]. More so, exposure to hexachlorobenzene has been associated with increased risk of overweight and obesity in children [236]. While a few of these studies found a positive association between organochlorine pesticides and childhood obesity, some found no or negative associations [237-239]. This may be attributed to small sample size and the lack of adjustment of important variables that are known to be related to childhood obesity [28]. In addition, while these few studies examined the impact of prenatal exposure to DDE and hexachlorobenzene, only one study [240] examined postnatal exposures to these pesticides and their role in childhood obesity. This study [240] moreover examined this association between adolescents age 14-15 and adults 50-65 and found a negative association between exposure to hexachlorobenzene and body mass index among the adolescents and a reverse association between BMI and hexachlorobenzene as well as DDE among adults. With only one study examining postnatal exposures together with the limitations found in other studies, further research is warranted. With the use of NHANES dataset as purported in this dissertation, the problem of sample size and adjustment of relevant confounding variables will be solved while examining if there is an association between organochlorines and childhood obesity.

With very limited studies on the relationship between chlorophenol pesticides and childhood obesity, Claudia and Wei [241] found a positive association between 2,5 dichlorophenol and childhood obesity while urinary concentration of 2,4 dichlorophenol had no significant association with childhood obesity. However, another study found both 2,5 dichlorophenol and 2,4 dichlorophenol associated with increased body weight measures (BMI z-score, Waist circumference and obesity) in children and adolescents [242]. In that study, the positive association remained only in the adolescent group after stratification by

age groups and no association was found between triclosan and body weight measures among the study group even when stratified by age. The differences in the results of these two studies may be attributed to the number of variables controlled for, of which the latter controlled for more variables that have been associated with obesity than the former. Parastar et al. [243] examined the association between childhood obesity and 2,5 dichlorophenol and 2,4 dichlorophenol as well as 2,4,5-trichlorophenol (2,4,5-TCP) and 2,4,6-trichlorophenol (2,4,6-TCP), metabolites of hexachlorobenzene (HCB) and hexachlorocyclohexane (HCHs) respectively. While this study found a positive association between 2,5 dichlorophenol and BMI z-score as well as waist circumference, no association was found between 2,4 dichlorophenols and BMI among adolescents age 6-18 as indicated in the other study conducted by Claudia and Wei. In addition, 2,4,5-TCP was associated with waist circumference and not BMI. These findings may also be a result of inadequate adjustment of confounding variables and sample size, thus demanding further research with larger sample size and adequate confounding variables to adjust for.

While the neurotoxic effects of organophosphate pesticides (including chlorpyrifos, diazinon, and malathion) have been established, there is a growing evidence of its metabolic disrupting capabilities [244]. Animal studies have showed a significant weight gain in adult rats with early life exposures to organophosphates [245, 246]. More so, there is evidence of interactions between metabolic abnormalities caused by early-life organophosphate exposure and other factors which could be relevant to the understanding of the etiology of obesity in humans. Based on a few animal studies, a larger weight gain was observed in animals who had perinatal exposures to organophosphates and who consumed high fat (saturated fats) diets [244, 247-250]. This, therefore, points to the need for further research in humans especially children identifying the role of specific diet compositions in eliminating, reducing or worsening the obesogenic effects associated with exposures to organophosphates. More so, further

research on the role of other pesticides as well as herbicides in the etiology of childhood obesity is highly needed while investigating their interaction with other risk factors.

Phytoestrogens (Plants metabolites)

Phytoestrogens are active substances found in plants such as whole grains, vegetables, legumes, fruits, and seeds. They have several classes including Isoflavones (Daidzein and Geinstein) and lignans (o-Desmethylangolensin (O-DMA), Equol, Enterodiol, Enterolactone). The chemical structures of phytoestrogens are similar to estradiol, thus having the ability to bind to estrogen receptors and cause either estrogenic or antiestrogenic effects when consumed by humans [78, 251-254]. While there are numerous evidences that phytoestrogens especially isoflavones act through endocrine receptors, there is growing evidence that they also act through other pathways including those regulated by peroxisome proliferator-activated receptor (PPAR). As earlier stated PPAR is known to regulate adipogenesis and affect lipid storage and metabolism as well as glucose and cholesterol metabolism [255, 256]. With phytoestrogens acting through the pathway regulated by PPAR, there is a tendency they may play either a positive or negative role in adipogenesis and regulation of lipid and glucose metabolism which could in turn increase or decrease the risk of obesity. Meanwhile, animal studies have shown that at low doses, geinstein, a class of phytoestrogen, increases adipose tissue fat deposition especially in males. This, therefore, increases the risk of obesity and insulin resistance. At high doses, it inhibits adipose tissue fat deposition, thus preventing the risk of obesity or helping with the treatment of obesity [257, 258]. In addition, with developmental exposure, a positive association between geinstein and weight gain have been seen [259]. Confirming these associations on humans, Xu et al. [260] on the contrast found no association between all the classes of the phytoestrogens and obesity except for enterolactone which was negatively associated with obesity in adult males. Studies by Frankenfeld et al. [261] found a negative association between a metabolite of daidzein, O-desmethylangolensin and obesity. The differences in the

results may be attributed to an inadequate accounting of variables (factors) that have been associated with obesity. Therefore, with the above identified conflicting results from the limited studies examining the effects of phytoestrogens on obesity, further research is warranted to understand the role of phytoestrogens on childhood obesity while adequately controlling for factors already confirmed to be associated with obesity especially lifestyle factors.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are organic compounds formed mostly as a result of the incomplete combustion of organic materials and are widely distributed in the universe. Exposure to PAH is mostly through ingestion and inhalation of vehicle exhaust, refined fossil fuels, cigarette smoke, contaminated water, milk and food products, grilled/charred foods, processed foods and contaminated air due to surrounding hazardous sites [262]. While exposure to polycyclic aromatic hydrocarbons are known to cause cancer, there is growing evidence that they may play a significant role in the etiology of obesity. With limited research on the effects of polycyclic aromatic hydrocarbons, evidence shows that they may have endocrine disrupting capabilities, thus affecting the development of obesity. Chemical structure of their metabolites is seen to be similar to estrogen, thus increasing their ability to bind to estrogen receptors and causing some estrogenic or antiestrogenic effects [263, 264]. Some of the PAHs such as phenanthrene and fluoranthrene have some anti-androgenic effects while metabolites of naphthalene acts as antagonists to thyroid hormone receptors [159, 265]. In the body, PAH are easily stored in the adipose tissue because of its lipophilic properties and has the tendency of accumulating when there are repeated and long-term exposures to them [153, 266]. As indicated by animal studies, accumulation of PAH disrupts adipose tissue lipolysis by activating the nuclear hormone proliferator-activated receptor gamma (PPARγ) receptor, which in turn leads to increases in weight gain and fat mass as well as changes in food intake [267]. In vitro studies, increases in the activation of PPARα and

PPARβ/δ after exposure to PAH have also been found [268]. In human studies, findings have been contradictory, making it difficult to draw conclusions on the contribution of PAH to the etiology of obesity. Choi et al. found a negative association between prenatal exposures to PAH and birth weight as well as head circumference among African Americans [151]; while, Rundle et al found a positive association between prenatal exposures to PAH and childhood obesity [150]. Studies by Scinicariello and Buser found a positive association between the molecular sum of all polycyclic aromatic hydrocarbons and obesity as well as waist circumference and BMI z-score in children and to some extent in adolescents. A few individual PAH metabolites such as 2-napthol, 1-phenanthrene and 2-phenanthre were positively associated with BMI z-score and waist circumference in both children and adolescents. 2-napthol was also positively associated with obesity in children and adolescents in that study [153]. In support, Kim et al. [269] found a positive association between PAH and childhood obesity. In addition, the authors found that in the presence of environmental tobacco smoke, exposure to PAH increased the risk of obesity 20-30 times. Conflicting results found in these studies may be attributed to the fact that some important confounding factors which have been proven to be associated with obesity were not accounted for.

Allergens

While there are numerous studies examining the role of obesity on the etiology of allergic disease [270-272], there has been very limited studies examining the role of allergic diseases or atopy on the etiology of childhood obesity. The only study so far was conducted by Silverberg [273], and he examined if asthma, hay fever and eczema increased the risk for obesity, hypertension, hyperlipidemia and diabetes. Results of the study found that childhood allergic disease increases the odds of obesity, hypertension and hyperlipidemia. However, findings from this study need to be confirmed as there were no clinical examinations and use of objective measures in assessing obesity (adiposity) and allergic diseases.

Author only made use of questionnaires to ascertain their exposure and outcome variables. The proposed use of NHANES dataset to confirm this finding is ideal as it has clinical measurements of allergy (atopy) in the form of serum total IgE levels and allergen specific IgE levels and objective measures of adiposity in the form of BMI & waist to height ratio. Studies have proven that serum total IgE levels is a good predictor of allergies in children [274].

Perchlorate, nitrates and thiocyanates

Perchlorate, nitrate and thiocyanates are chemicals known to disrupt thyroid function by acting as inhibitors to sodium-iodide symporter, thus obstructing the uptake of iodide into the thyroid gland which is essential for normal growth and development [275, 276]. These chemicals occur naturally in air, water and food and sometimes can be synthesized in the atmosphere, thus making them readily available in the environment. This increases their chances of exposure to humans and the route of exposure is mainly through ingestion of food and water [277, 278]. While there are numerous studies even though with mixed results on the roles of iodine deficiency on growth, there are very limited studies on whether perchlorate, nitrate and thiocyanates would actually impact growth negatively or positively with or without iodine adequacy. A study by Mervish et al.,[279] investigated whether perchlorate, nitrate and thiocyanates were associated with height, waist circumference and body mass index in young U.S girls with adequate iodine intake. The authors found an inverse association between these chemicals and waist circumference as well as body mass index in the study population. With adequate levels of iodine in the study population throughout the study period, the findings of the study suggest that these chemicals may have affected the growth of the study population through another mechanism other than inhibiting the uptake of iodine or depleting the amount of iodine in human body. With this in mind, further research is warranted as there are other chemicals such as bisphenol A, phthalates and polychlorinated biphenyls that have been associated with increased body mass index and waist

circumference in humans, and these associations are somewhat attributed to their interference with thyroid functions [280]. Their interference with the thyroid gland has been associated with their ability to increase the obstruction of thyroid hormone synthesis or metabolism of thyroid hormones through the activation of deiodinases [281]. In addition, their association with thyroid function may be linked to the production of leptin by adipocyte tissue or modification of human energy output [280].

Parabens

Parabens are chemicals most commonly used as antimicrobial preservatives in food, drug and cosmetics manufacturing [282] and are ubiquitous in the environment due to the fact that some of them are naturally occurring in the environment [283]. They include methyl-, ethyl-, propyl-, butyl-, benzyl- and heptyl parabens and are known to disrupt the endocrine system [284]. Human exposure is widely seen and occurs through ingestion, inhalation and dermal contact [285]. While there are very limited human studies on the role of parabens on obesity, both in vitro and in vivo studies indicate that parabens promote adipogenesis through the activation of gamma- peroxisome proliferator-activated receptor and/or glucocorticoid receptor and this increases with the length of its linear alkyl chain [286, 287], thus increasing the risk for obesity. The only human study on the role of parabens on childhood obesity found that 3, 4 dihydroxybenzoic acid (3,4 DHB), a metabolite of parabens was positively associated with childhood obesity among Indian children. No significant association was found between methyl parabens, ethyl parabens and propyl parabens and childhood obesity while controlling for limited number of confounding variables [288]. The role of other alkyl chain of parabens on childhood obesity with the study population was not investigated. Moreover, authors' findings however may be due to inadequate control of factors that are known to be associated with obesity, indicating the need for further research. More so, the role of other alkyl chain paraben on childhood obesity needs also be investigated.

Finally, the role of parabens on childhood obesity needs to be investigated among U.S children as U.S is the leading country with the highest prevalence of childhood obesity.

Acrylamide & Glycidamide

Acrylamides are chemical compounds widely used in the industries for the manufacture of papers, dyes, and plastics and for wastewater and drinking water treatments [289]. They are formed in carbohydrate rich foods when foods are cooked at high temperatures and can be found in tobacco smoke [290]. It is a probable carcinogen and human exposure is mostly via ingestion, inhalation, and dermal contact [291]. Upon exposure, some acrylamide is converted to glycidamide in the human body and both bind to hemoglobin, to form adducts [292]. While there are numerous evidences with some inconsistencies linking acrylamide exposure to cancer in the human population, little is known about its contribution to obesity [293-295]. Limited studies have associated acrylamide exposure to endocrine system disruptions and insulin resistance. This however may indicate that acrylamide may play a role in the etiology of obesity as obesity is associated with endocrine disruptions and insulin resistance. The only human study investigating the role of acrylamide on obesity found a positive association between acrylamide, as well as glycidamide and adult obesity [296]. No study has evaluated its role on childhood obesity.

Heterocyclic aromatic amines

Heterocyclic aromatic amines (HCA) are chemical compounds formed when amino acids, sugars and creatinine found in muscle meats react at high temperatures [297]. They are known to have mutagenic properties and are known to be probable carcinogens [298, 299] however their role in the induction of childhood obesity has not been explored. Heterocyclic aromatic amines are lipophilic and have the tendency of accumulating in human adipose tissue when there are repeated and long-term exposures to them [300]. In the adipose tissue, several studies have indicated the capabilities of these chemicals to induce changes in gene expression in various genes that are related to obesity, diabetes, cancers and

inflammation [301, 302]. Nothing is known if they negatively or positively impact adipogenesis. More so, some heterocyclic aromatic amines such as 2-amino-1-methyl-6-phenylimidazo(4,5-b) pyridine, the abundant lipophilic HCA in cooked meat has been found to interact with both the estrogen and androgen receptors, thus causing either estrogenic, antiestrogenic or androgenic effects [303, 304]. Further research on the role of this dietary probable carcinogen on childhood obesity is needed.

Phenols-triclosan, bisphenol f & S, triclocarban, chlorinated phenols

While substantial research has focused on the impact of bisphenol A, a type of phenol, further research on other types of phenols is needed. Other types of phenol include triclosan, bisphenol f & S, triclocarban and chlorinated phenols. Triclosan is a chemical widely used as antimicrobial agent in personal care products such as mouthwash, soaps, kitchenware, deodorants, toothpastes, toys, and medical devices [300, 305] and are suspected to either disrupt the endocrine system especially the endogenous thyroid hormones or the gut microflora both of which have been linked to increased risk of obesity [306]. While a few studies have examined the role of triclosan on obesity, results presented are still inconclusive. Study by Kalloo et al. [307] found no association between early life exposures to triclosan and childhood adiposity. On the other hand, Li et al. [308] found a negative association between urinary triclosan concentrations and BMI as well as waist circumference in both children and adults. The discrepancies in result could be attributed to sample size and inadequate adjustment of confounding variables.

Bisphenol-F (BPF) & -S (BPS) are seen and used as alternatives to Bisphenol A (BPA), a known endocrine disrupting chemical in both consumer and commercial products however the safety of these chemicals is not confirmed as there are very limited studies on their effects on physiological functions in humans and animals. Studies by Eladak et al [309] found that both BPF and BPS have antiandrogenic

effects as BPA in both humans and animals. Other studies have found both chemicals to have estrogenic and androgenic activities similar to BPA, thus supporting them to be endocrine disrupting chemicals as well [310-312]. With similar metabolism, potencies and mechanism as BPA, BPF & BPS may pose similar health effects as BPA if exposure to the chemicals are not controlled [313]. While there is a substantial evidence on the role of BPA on obesity and other health effects [105, 314]and the fact that the use of BPA on consumer and commercial products have been phased out, the role of BPS and BPF on obesity is urgently warranted as the prevalence of childhood obesity still increasing. Already, study by Del Moral et al has shown that BPS could led to obesity in mice at low dosage [315].

Chlorinated phenols are organochlorides of phenols that are used in the manufacture of pesticides and are found in industrial wastes. They are known to persist in the environment and are toxic, carcinogenic, and mutagenic to living organisms[316]. They include mono-, di-, tri-, tetra-, and penta-chlorinated phenols and have possible 19 congeners, of which 4 including 2-chlorophenol (2-CP), 2,4-dichlorophenol (2,4-DCP) , 2,4,6-trichlorophenol (2,4,6-TCP) and pentachlorophenol are among the priority pollutants monitored by U.S Environmental Protection Agency [317]. They are suspected to have endocrine disrupting abilities in both humans and animals. While a few studies have examined the role of chlorinated phenols on obesity, these studies focused on 2,5-dichlorophenol and 2,4-dichlorophenol ignoring other chlorinated phenols. Studies on 2,5-dichlorophenol and 2,4-dichlorophenol found a positive association between these chemicals and obesity both in children/adolescents and adults [233, 241, 242]. With these positive associations seen in 2,5-dichlorophenol and 2,4-dichlorophenol, there is a need to further examine the role of other chlorinated phenols on childhood obesity as these chemicals are seen to have similar chemical structure as estradiol [242].

Atrazine

Atrazine is an herbicide that has been in use since the 1960s. It persists in the environment under normal soil conditions and readily contaminate U.S drinking water. A few animal studies have linked exposure to chronic low doses of atrazine to abdominal obesity and insulin resistance [318] while others have associated atrazine exposure at high concentration to decreased or unchanged body weights in animals [319, 320]. While findings from animal studies have been inconclusive about what role atrazine plays on obesity [318-320], there are no human studies on whether exposure to atrazine contributes to obesity in humans especially children/adolescents.

Perfluoroalkyl and polyfluoroalkyl chemicals

Both perfluoroalkyl and polyfluoroalkyl chemicals (PFC) are perfluorinated chemicals that has varying length of carbon atoms with either a carboxylate or sulfonate functional group, and has been widely used in the industry since the 1940s [321]. They are added to commercial household products such as waxes, lubricants, polishes, paints, surfactants, cleaning products, paper and textile coatings and foams. They are also added to food packages [322-324]. They are found in U.S drinking water systems and at workplaces such as production facilities or industries that does chrome plating and oil recovery or produce electronics [321]. Their abundant use makes their exposure to humans and animals possible. Route of exposure is through inhalation, ingestion and sometimes dermal contacts. Evidence shows that these chemicals persist in the environment and bioaccumulate, binding to proteins in the liver and serum in human body when taken in [323, 325]. Exposure to these chemicals have been associated with different kinds of cancers and low birth weight in humans [326, 327] whereas in animals, it is known to affect the liver, kidney and has some developmental and reproductive toxicity as well as cause cancer [328-330]. Their role in the induction of obesity has received little attention even when their chemical structure is similar to fatty acids. Evidence shows that PFCs can bind to and activate peroxisome

proliferator-activated receptors and nuclear receptors, receptors known to play a significant role in adipogenesis and lipid metabolism [331, 332]. As earlier stated PPARγ is known to regulate adipogenesis and affect lipid storage and metabolism as well as glucose and cholesterol metabolism [255, 256, 333]. With PFCs acting through the pathway regulated by PPAR, there is a tendency they may play either a positive or negative role in adipogenesis and regulation of lipid and glucose metabolism which could in turn increase or decrease the risk of obesity. While studies have found both a weak and strong association between exposures to polyfluoroalkyl chemicals and body size and insulin resistance in adolescents and adults [324] [334, 335], there is a huge need for further research on the role of PFCs on obesity especially childhood obesity. Moreover, the conflicting findings found in these studies may be as a result of inadequate sample size and control of confounding factors.

Melamine and cyanuric acid

Melamine is an organic compound with about 67% of nitrogen by mass. It is used in the manufacture of plastics and household products such as utensils and accessories. It is also used to make fire retardants. While its use in human and animal food preparation is prohibited, it is still found in food packages [336]. Human exposure to melamine has been recorded especially in children and adverse health effects such as renal failure, retarded growth, kidney stone formation (urolithiasis), and even deaths have been associated with its exposure [337, 338]. When taken in, it could be metabolized to cyanuric acid by bacteria found in the gut and the presence of cyanuric acid in the body has also led to kidney malfunction. Apart from the formation of cyanuric acid in the gut, cyanuric acid is also a chemical compound used in the manufacture of herbicides, bleaches, and disinfectants and its route of exposure is through inhalation, ingestion and dermal contacts. Exposure to cyanuric acid has also been associated with lung damage and death. While it has been established that exposure to cyanuric acid and melamine could impact renal function, there is a growing evidence that these chemicals could have some endocrine

disrupting capabilities [339]. Animal studies have indicated impacts on body weights and lengths as well as reproductive and neurological functions [340-342]. Thus, human studies on the role of melamine and cyanuric acid on the endocrine system especially pathways resulting to the induction of obesity is warranted.

Genome-wide association study (GWAS) and its limitations

A genome-wide association study is a unique methodology that involves a comprehensive analysis of genetic factors to identify common genetic loci associated with a disease or a phenotype while controlling for multiple comparison of factors and many covariates obtained from epidemiological data [343]. It is agnostic and data-driven, not hypothesis driven and calls for both systematic and comprehensive associations of genetic factors and phenotype/disease within an individual study and multiple studies. This, therefore, helps with the understanding of the genetic structure of complex traits/diseases. It does not need prior evidence regarding the identity, function or location of genes before association with a disease/trait of interest can be identified. It takes advantage of the large collection of DNA samples obtained from a population whose clinical characteristics are well defined, and it uses specific and rigorous statistical methods to identify any relationship between each genetic variants and health-related traits or diseases [344].

This unique methodology reduces the risk for selection biases, family-wise error rates, and false positive reporting. This is made possible when multiple comparison of genetic factors is accounted for through the use of Bonferroni correction method and the calculation of a false discovery rate. This methodology allows all significant findings to be validated in a different independent population at the same stringent level and in the context of other common genotypes assayed [345]. Numerous studies have been conducted using this methodology, and various genes associated with a health-related trait or disease

have been found. For example, genes associated with abnormal cardiac repolarization intervals, type 1 & 2 diabetes, age-related macular degeneration, prostate cancer, inflammatory bowel disease, myocardial infarction, breast cancer, and schizophrenia have been identified [32, 346-352]. The identification of these genes has helped with the development of better strategies to detect, treat and prevent diseases in some cases. That is to say, healthcare providers are now able to provide more individualized information to patients about their risk of developing a certain disease as well as provide treatments based on an individual's genetic makeup. More so, results from these studies encourage further metabolic studies on the biological mechanisms of the identified genetic factors. In addition to finding the genetic basis and molecular mechanism of human diseases, GWAS has been beneficial to the agricultural sector as it has helped to study in different environmental conditions, numerous genetic variants found in plants and animals and linking these variants to traits of agricultural importance such as adaptation, flowering, defense, milk yield, fitness, dormancy or plant senescence [353-359].

The environment-wide association study (EWAS) framework

The overall goal of this research is to conduct an environment-wide association study on childhood obesity, a unique concept similar to GWAS. This unique methodology is a growing area of interest as it complements previous environmental studies that examine a few numbers of factors at a time while focusing on either refuting or validating a current body of knowledge. While some previous environmental studies have been successful in presenting novel findings, these studies may be affected by false positive findings due to lack of accounting for other environmental factors. In addition, these studies may be problematic when only subset of analyses that are statistically significant are reported [97-103]. As discussed by Boffetta et al. [102] and others [98-101], more comprehensive and systematic analysis of factors is needed as drawing conclusions from findings of epidemiological studies is difficult

due to problems relating to the differences in exposure metrics, lack of accounting for other factors, and baseline reference categories used in epidemiological studies.

The concept of EWAS is agnostic, systematic and comprehensive as the GWAS methodology. It evaluates the association of multiple environmental factors with a disease of interest in a high-throughput, unbiased manner, thus eliminating the risk for selective bias and false positive reporting. It calls for the calculation of false discovery rate to control for type I error resulting from multiple hypothesis testing in finding associations between factors and disease of interest. In addition, validation of significant findings in an independent cohort is required as well as the systematic and comprehensive sensitivity analysis of validated factors, much like the GWAS for genetic effects.

With a few studies exploring this approach, confirmation and refutation of some findings from epidemiological studies of environmental factors have been achieved. More importantly, unexpected associations between some human diseases and certain environmental factors with known and unknown metabolic pathways have been revealed indicating the presence of many overlooked pathways and suggesting the need for metabolic studies on such factors. This approach helps in the generation of new hypotheses regarding the relationship between environmental factors and human diseases and helps to explain the etiology of human disease of interest in context of other factors.

Among the EWAS studies published, Patel et al. [33] investigated the role of about 266 unique environmental factors on type 2 diabetes. While this study confirmed for instance, the inverse associations between isoforms of β-carotenes and type 2 diabetes as seen in epidemiological studies [360-362], it found a novel and significant association between γ-tocopherol, a form of vitamin E, and

type 2 diabetes. Already, it has been established that exposure to γ-tocopherol reduces the risk of colon cancer with substantial evidence on its biological mechanism [363]. With this novel insight from conducting an EWAS, metabolic studies on how exposure to γ-tocopherol could increase type 2 diabetes will be needed. This is further supported by the fact that γ-tocopherol, a form of vitamin E is seen abundantly in the U.S diet [364] and more than 1.4 million new cases of type 2 diabetes are diagnosed every year in the U.S. [365].

In addition, EWAS has been conducted on Hematocrit, a risk factor for cardiovascular disease [34]. From a systematic and comprehensive analysis of 74 environmental and lifestyle factors, Zhong et al [34] found novel and significant associations between hematocrit and serum calcium as well as serum magnesium and alcohol use. This study also found vitamin A and physical inactivity as major drivers of high and low hematocrit respectively as identified in other epidemiological studies [366, 367]. While the biological mechanism/metabolic pathway by which vitamin A increases hematocrit has been established, the identification of these other unexpected associations reveals the need to study more on the new factors and identify how they drive hematocrit. Thus, helping with the understanding of the etiology of cardiovascular diseases.

The concept of EWAS has been applied to other diseases such as preterm birth, blood pressure, all-cause mortality, metabolic syndrome and other conditions related to the risk of heart disease with the identification of novel pathways that warrant more investigations and provision of information about the disease etiology [33-35, 368-371]. This concept, however, has not been applied to childhood obesity despite the increasing prevalence of childhood obesity and the growing evidence of the impact of environmental factors on childhood obesity. Therefore, for this dissertation, a wide panel of

environmental factors were determined and evaluated simultaneously to ascertain their association with childhood obesity while controlling for multiple comparisons using an array of laboratory measurements from the National Health and Nutrition Examination Survey (NHANES) from years 1999-2016.

Chapter 3

Methods

Data source

The datasets used in this dissertation were obtained from the National Health and Nutrition Examination Survey (NHANES). NHANES was designed and conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) to estimate the health and nutritional status of the U.S. civilian, non-institutionalized population comprising of both adults and children to determine the risk factors associated with some major diseases and the prevalence of such diseases. This program started in the 1960s concentrating on different study aims and/or different population groups. The NHANES protocol was approved by the National Center for Health Statistics Institutional Review Board, and the consent document was approved by the CDC institutional Review Board. Written informed consent was obtained from adult participants (≥18yrs) and from parents/guardians of study participants less than 18 years of age [372].

To select a participant, NHANES uses a complex, multistage probability sampling design. This enables the selection of study participants that are representative of the U.S population. Some sub-populations (e.g., racial and ethnic minorities), however, are oversampled to ensure the reliability and precision of estimates of health status indicators because they are believed to be at a greater health risk. Some individuals such as those in the military and nursing homes, institutionalized individuals and U.S nationals living outside the country are ineligible for sampling. The NHANES sampling occurs in four stages. The first stage is the determination of the primary sampling unit (PSU) which was mostly counties. The second stage involves selection of segments within the primary sampling unit, that is blocks or clusters of households. The third stage involves the random selection of households within

each segment and finally the fourth stage involves the selection of individuals within each household to participate in the survey.

The NHANES survey comprises of a home interview and health examination involving physical examination and laboratory tests. During the home interview, data on demographics, dietary and health information are obtained from the study participants by NCHS- trained personnel. Health examinations are performed at the specially equipped mobile examination centers, and results documented are by qualified staff. NHANES data are released to the public through the CDC website. The easily accessible public data files are released in two-year cycles (i.e. NHANES 1999-2000, NHANES 2001-2002, and so on) and are grouped as demographics, dietary, examination, laboratory and health questionnaires. Weights are also supplied together with the datasets so that conclusions drawn from estimates will be representative of the U.S population.

For this dissertation, I used the NHANES dataset comprising of NHANES 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016. That is, I downloaded and merged these publicly available NHANES datasets using the NCHS recommendation [373] which involves appending each variable within a survey cycle and then merging the data files using a unique identifier for each sample person to get a combined dataset. This was necessary to obtain an adequate sample size for the proposed comprehensive statistical analysis. The first, middle and last data sets (1999/2000, 2007/2008 & 2015/2016) were excluded from the primary analysis but used for validation.

Inclusion and exclusion criteria

For Aim 1 & 2a which were to conduct an EWAS on childhood obesity and validate factors on a different cohort, children/adolescents between the age of 6 and 17 years who participated in the NHANES 1999-2016 were eligible for analysis in this dissertation. This age group was appropriate for this dissertation because from age 6, children are learning to become part of the larger world through school, activities and friends. They tend to have greater exposure to numerous environmental factors due to their high level of curiosity as well as the greater amount of time they spend playing and/or engaging in activities within both in- and outdoor environments. More so, among this age group there is evidence of increases in their physiological needs because of their growing bodies. As such, their exposure to numerous environmental factors increases with such needs. For Aim 2b which was to conduct an EWAS on adult obesity, adults age 18 and above who participated in the NHANES 1999-2016 were eligible for analysis in this dissertation.

Outcome variables

The outcome variables for this dissertation were general obesity and abdominal obesity (ascertained by waist to height ratio). Following a standard protocol, all NHANES participants had their body measurements (height, weight and waist circumference) recorded by a NCHS-trained examiner in the mobile examination center. For this dissertation, because obesity indicates excessive body fat, the body mass index (BMI) of the study participants (which is an indirect measure of body fat) was ascertained. Although there are other direct measures of body fat such as dual-energy x-ray absorptiometry (DXA), air displacement plethysmography (ADP), skin thickness measurement, densitometry, bioelectrical impedance, research has shown a significant correlation between body mass index (BMI) and the direct measures of body fat [374-376]. More so, the use of body mass index (BMI) is still recommended by the

Centers for Disease Control and Prevention and the American Academy of Pediatrics because it is a simple, inexpensive and noninvasive test unlike some of the other direct measures of body fat [377].

The body mass index was calculated as weight (mass) in kilogram divided by the square of the body height measured in meters squared. In addition, because part of the study population comprises of children and the reference made through BMI is dependent on the age and sex of a child, the BMI for age presented as percentile rankings was used. This was calculated using the Centers for Disease Control and Prevention 2000 reference standards [378]. The BMI percentiles were used to group these study participants as underweight/normal weight, overweight and obese as depicted in table 1.

Table 1: Classification of children population based on BMI percentiles

Category	BMI percentiles
Underweight/normal weight	$<85^{th}$ percentile
Overweight	$85\leq$ BMI $<95^{th}$ percentile
Obese	$\geq 95^{th}$ percentile

The above classification was based on the recommendations by the American Medical Association [379]. For the adult population, the body mass index used and grouped as underweight/normal weight, overweight, and obese as depicted in table 2.

Table 2: Classification of the adult population based on BMI.

Category	BMI
Underweight/normal weight	≤ 24.9
Overweight	25 – 29.9
Obese	$\geq$ 30

In addition to the body mass index, the waist to height (WH) ratio was calculated. This measures body fat and correlates with abdominal obesity. Abdominal obesity is considered to be a waist to height ratio greater than or equal to 0.5 [380].

Explanatory variables

Analysis of environmental factors followed standard procedures and was performed by the Division of Laboratory Sciences of the National Center for Environmental Health, CDC. All environmental factors including metals, chemical toxins, pollutants, allergens, bacterial/viral/parasitic organisms and nutrients in NHANES which were measured in either blood or urine were used in the statistical analysis. This was necessary to avoid self-report bias associated with the use of questionnaire data to determine exposure to environmental pollutants. Red blood counts, low density lipoprotein cholesterol levels, and other factors measured in a medium other than blood and urine were not considered.

More than 500 environmental factors were found in NHANES; however, not all factors were found in all cohorts: 143 factors were measured in the 1999–2000 cohort, 163 from 2001–2002, 234 from 2003–2004, 223 from 2005–2006, 159 from 2007-2008, 154 from 2009-2010, 138 from 2011-2012, 155 from 2013-2014, and 163 from 2015-2016. Two hundred and ninety-three (293) factors were measured in more than one cohort. Different environmental factors were measured in different age groups. Environmental factors with more than 90% of the observations below a detection limit threshold as indicated in the NHANES codebook were excluded. In addition, environmental factors that targeted only a specific subpopulation such as females or males were excluded (in the NHANES dataset, there are quite a few (2) of these environmental factors targeting a specific subpopulation). Details about these factors and how they were measured are shown in the appendix.

Controlling variables

For this dissertation, all analyses were adjusted for age, sex, race/ethnicity, creatinine, calorie intake, physical activity, screen time (TV hours & computer/video games hours), limitation to physical activities, and socioeconomic status. Due to the difficulty in estimating an individual's socioeconomic

status, the poverty income ratio (PIR) was used instead. The PIR was calculated by dividing the family income by a poverty threshold. The poverty threshold is adjusted for family size and updated every year to avoid inflation [381-383].

Race/ethnicity was grouped as non-Hispanic whites, non-Hispanic blacks, Mexican Americans, other Hispanics and other races. Sex was grouped as male and female. Physical activity was estimated based on "moderate recreational activity". Screen time was estimated from responses to "number of hours watch TV or videos?". Limitation to physical activities was estimated based on children's limitation to crawl, walk, run and play and this was grouped as "yes" or "no". For adults, I controlled for physical, mental and emotional limitations. I adjusted for creatinine because some environmental factors such as heavy metals sometimes target and damage the kidney, an organ responsible for the filtering of creatinine [384], thus increasing the amount of creatinine in the blood/urine. Adjusting for creatinine in this analysis was necessary to know the actual impact of environmental factors on obesity despite their effect on the kidney. The amount of creatinine in urine was measured using the Jaffé rate reaction method.

For this dissertation, the calorie intake is the total energy intake (kcal) in the dietary data of the NHANES cycle. Note: some cycles had a 24-hour dietary recall interview (NHANES 1999-2000 & NHANES 2001-2002) and others had two 24-hour dietary recall interviews (NHANES 2003-2004, NHANES 2005-2006, …, NHANES 2015-2016) to estimate the total energy intake of study participants. To ensure consistency, I adjusted for total energy intake estimates calculated for the first day.

Statistical analysis

Due to the complex survey design of NHANES and the fact that data were combined, sample weights were recalculated and used according to NHANES guidelines [385]. As in EWAS, a multinomial logistic regression was conducted to investigate the relationships between each of the environmental factors and obesity while controlling for covariates. A multinomial logistic regression was used instead of the ordinal logistic regression because the proportional odds assumption would not make sense in this case. That is to say that it cannot be assumed that the relationship between each pair of the outcome groups is the same. In addition, a multivariate logistic regression was used to investigate the relationships between each of the environmental factors and waist to height ratio while controlling for covariates. Variables depicting environmental factors were presented as either categorical or continuous variables. For analysis, the reference category for categorical variables was negative result of environmental factor (i.e. negative results of test). For continuous variables without normal distribution, a log transformation was done. In order to control for type I error due to multiple comparisons, the false discovery rate (FDR) was calculated. The FDR is the estimated proportion of errors committed by falsely rejecting the null hypothesis [386]. The calculation of FDR was done using the approach from Benjamini & Hochberg [387]. P values resulting from the analysis were used to calculate the q-values, which were compared to a given threshold 0.05. This method controls the proportion of false positives among the rejected hypotheses at a 0.05 level.

Validation analysis

Factors that were deemed significantly associated with childhood obesity beyond the region of false discovery were validated in independent cohorts of children and adults. These independent cohorts were obtained from NHANES datasets 1999/2000, 2007/2008 and 2015/2016. Statistically significant factors were considered as true discoveries. All statistical analyses were carried out using SAS version 9.4.

Chapter 4

Results

In this dissertation, a total of 50,048 children/adolescents (aged 6-17years) were eligible for analysis. The mean age of these participants was approximately 12 years and about 51% were males. A majority of the study population was non-Hispanic whites (57.81%), and families above poverty level (74.01%) as shown in table 1.

Table 1: Weighted Characteristics for children and adolescents in NHANES 2001-2013[a]

	All	**Underweight/normal**	**Overweight**	**Obese**	**Healthy waist to height ratio**	**Abdominal obesity**
All	50048	66.58(0.71)	15.37(0.42)	18.06(0.55)	69.54(0.72)	30.46(0.72)
Sex (% SE)						
Male	50.85(0.55)	33.66(0.49)	7.68(0.30)	9.52(0.37)	36.77(0.53)	14.09(0.45)
Female	49.15(0.55)	32.92(0.59)	7.69(0.26)	8.54(0.35)	32.76(0.59)	16.39(0.49)
Race (% SE)						
Mexican American	13.75(1.05)	8.01(0.65)	2.47(0.19)	3.27(0.27)	7.83(0.63)	5.93(0.45)
Other Hispanic	6.10(0.60)	3.63(0.35)	1.11(0.13)	1.36(0.18)	3.78(0.38)	2.32(0.26)
Non-Hispanic White	57.81(1.76)	40.15(1.18)	8.43(0.54)	9.24(0.62)	41.38(1.18)	16.43(0.97)
Non-Hispanic Black	14.53(0.96)	9.05(0.59)	2.31(0.17)	3.16(0.25)	10.60(0.70)	3.93(0.29)
Other race-including multi-racial	7.81(0.53)	5.73(0.43)	1.05(0.10)	1.03(0.11)	5.95(0.45)	1.86(0.15)
PIR (%SE)						

<=1 indicates at or below poverty level	25.91(1.02)	16.09(0.60)	4.16(0.23)	5.65(0.31)	16.67(0.66)	9.23(0.45)
>1 above poverty level	74.09(1.02)	50.48(1.03)	11.21(0.43)	12.40(0.48)	52.85(1.05)	21.24(0.68)
Physical limitation (%SE)						
Yes	4.34(0.21)	2.32(0.17)	0.77(0.11)	1.24(0.13)	2.39(0.18)	1.94(0.15)
No	95.66(0.21)	64.26(0.70)	14.60(0.39)	16.81(0.52)	67.15(0.72)	28.52(0.66)
Age (mean SE)	11.49(0.05)	11.42(0.06)	11.56(0.09)	11.70(0.09)	11.33(0.06)	11.89(0.07)

[a] excludes dataset from 2007/2008

Aim 1

There were 288 unique environmental factors, each evaluated for its association with general obesity and abdominal obesity. I conducted an unadjusted analysis on each environmental factor and obesity. Results showed that some factors were significantly associated with overweight, general obesity, and abdominal obesity at FDR <5% as shown in table 2, 3 and 4. (Note: tables 2, 3, & 4 are from the same multinomial logistic regression model).

Table 2: Significant factors from unadjusted analysis of factors with overweight for children/adolescents

Environmental factors	**Overweight**	
	OR (95% CI)	**Q values**
Beryllium	1.995(1.399-2.846)	0.0013
Platinum	1.236(1.092-1.399)	0.0058
Thiocyanate	1.188(1.069-1.320)	0.0094
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	0.897(0.828-0.972)	0.044
Mono-(2-ethyl-5-oxohexyl) phthalate	0.889(0.819-0.965)	0.0288
Enterolactone	0.827(0.752-0.910)	0.0013
2-napthol	1.282(1.162-1.415)	<.0001

lead	0.846(0.767-0.934)	0.0063
Vitamin B12	0.603(0.488-0.745)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)	0.824(0.718-0.946)	0.0359
4-pyridoxic acid	0.714(0.597-0.853)	0.0021
Vitamin C	0.71(0.587-0.859)	0.0035
Iron	0.658(0.539-0.803)	<.0001
manganese	1.926(1.346-2.755)	0.003
Gamma tocopherol	1.796(1.438-2.244)	<.0001
a-carotene	0.794(0.702-0.898)	0.0021
trans-b-carotene	0.534(0.460-0.619)	<.0001
total b-Carotene	0.462(0.365-0.585)	<.0001
cis-b-carotene	0.49(0.407-0.589)	<.0001
a-Cryptoxanthin	0.482(0.352-0.660)	<.0001
b-cryptoxanthin	0.708(0.624-0.803)	<.0001
Lutein	0.43(0.276-0.670)	0.0021
cis- Lutein/Zeaxanthin	0.489(0.307-0.778)	0.016
Combined Lutein/zeaxanthin	0.624(0.499-0.781)	<.0001
Zeaxanthin	0.505(0.346-0.736)	0.0035
Vitamin A	1.772(1.275-2.464)	0.0053
Vitamin D	0.582(0.449-0.755)	<.0001
25-hydroxyvitamin D3	0.51(0.404-0.645)	<.0001
epi-25-hydroxyvitamin D3	0.702(0.602-0.819)	<.0001
Phosphorus	0.37(0.186-0.738)	0.0288
PCB74	0.465(0.304-0.711)	0.0035
PCB138	0.386(0.261-0.572)	<.0001
PCB146	0.701(0.583-0.843)	0.0021
PCB153	0.345(0.235-0.507)	<.0001
PCB156	0.778(0.694-0.871)	<.0001
PCB157	0.862(0.774-0.962)	0.0426
PCB170	0.631(0.481-0.827)	0.0058
PCB172	0.834(0.732-0.951)	0.0397
PCB177	0.815(0.725-0.917)	0.0053
PCB178	0.781(0.694-0.878)	<.0001
PCB180	0.399(0.258-0.617)	<.0001
PCB183	0.756(0.650-0.879)	0.003
PCB187	0.612(0.467-0.802)	0.0035
PCB194	0.781(0.670-0.910)	0.0098
PCB196	0.771(0.659-0.902)	0.0075

PCB199	0.784(0.683-0.901)	0.0049
2,3,4,7,8 pncdf	0.149(0.064-0.346)	<.0001
1,2,3,4,7,8 hcxdf	0.276(0.108-0.704)	0.0401
1,2,3,6,7,8 hxcdf	0.269(0.127-0.572)	0.0049
3,3',4,4',5,5' hxcb	0.217(0.106-0.602)	0.0244
p,p' DDE	0.612(0.460-0.813)	0.0053
2,2',4,4',5,5'-hexabromodiphenyl ether	0.521(0.380-0.713)	<.0001

Table 3: Significant factors from unadjusted analysis of factors with obesity for children/adolescents

Environmental factors	**Obesity**	
	OR (95% CI)	**Q values**
Barium	1.129(1.029-1.238)	0.039
Thalium	1.313(1.122-1.535)	0.0034
Thiocyanate	1.381(1.264-1.510)	<.0001
Mono(carboxyoctyl) phthalate	1.171(1.048-1.308)	0.0205
Mono-ethyl phthalate	1.085(1.021-1.154)	0.033
Enterodiol	0.804(0.728-0.888)	<.0001
Enterolactone	0.781(0.720-0.848)	<.0001
2-napthol	1.532(1.393-1.684)	<.0001
2-fluorene	1.195(1.069-1.336)	0.0075
1-phenanthrene	1.242(1.106-1.396)	0.0016
2-phenanthrene	1.423(1.259-1.609)	<.0001
9-fluorene	1.35(1.177-1.548)	<.0001
4-phenanthrene	1.47(1.252-1.725)	<.0001
Malathion diacid	1.508(1.211-1.879)	0.0011
Dimethylphosphate	0.861(0.782-0.948)	0.0103
1-methyluric acid	1.244(1.043-1.483)	0.0497
7-methyluric acid	1.115(1.024-1.215)	0.0434
1,3-dimethyluric acid	1.211(1.045-1.404)	0.0395
3,7-dimethyluric acid	1.156(1.058-1.262)	0.0059
1,3,7-trimethyluric acid	1.328(1.164-1.515)	<.0001
1,3-dimethylxanthine(theophylline)	1.357(1.137-1.620)	0.0034
1,7-dimethylxanthine(paraxanthine)	1.276(1.083-1.503)	0.0146
3,7-dimethylxanthine(theobromine)	1.183(1.092-1.283)	<.0001
1,3,7-trimethylxanthine(caffeine)	1.347(1.159-1.566)	0.0006
5-acetylamino-6-amino-3-methyluracil	1.17(1.031-1.327)	0.0497

Cockroach IgE antibody	1.338(1.164-1.537)	<.0001
Shrimp IgE antibody	1.393(1.169-1.660)	0.0011
lead	0.781(0.707-0.863)	<.0001
Cadmium	0.771(0.659-0.901)	0.0051
Folate	0.565(0.455-0.703)	<.0001
5-Methyl-tetrahydrofolate	0.612(0.421-0.891)	0.0385
Vitamin B12	0.344(0.279-0.425)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)	0.762(0.664-0.875)	0.0006
4-pyridoxic acid	0.581(0.474-0.711)	<.0001
Vitamin C	0.54(0.447-0.653)	<.0001
Iron	0.435(0.372-0.509)	<.0001
manganese	2.681(1.845-3.894)	<.0001
Gamma tocopherol	5.887(4.390-7.896)	<.0001
d-Tocopherol	1.675(1.447-1.940)	<.0001
a-Tocopherol	0.481(0.275-0.844)	0.039
a-carotene	0.597(0.530-0.671)	<.0001
trans-b-carotene	0.261(0.226-0.300)	<.0001
total b-Carotene	0.228(0.171-0.305)	<.0001
cis-b-carotene	0.207(0.168-0.254)	<.0001
a-Cryptoxanthin	0.338(0.245-0.466)	<.0001
b-cryptoxanthin	0.504(0.431-0.589)	<.0001
Lutein	0.294(0.224-0.385)	<.0001
cis- Lutein/Zeaxanthin	0.39(0.304-0.500)	<.0001
Combined Lutein/zeaxanthin	0.332(0.268-0.411)	<.0001
Zeaxanthin	0.448(0.337-0.595)	<.0001
Vitamin A	3.252(2.355-4.491)	<.0001
Vitamin E	0.535(0.347-0.824)	0.018
Vitamin D	0.277(0.218-0.353)	<.0001
25-hydroxyvitamin D3	0.273(0.213-0.351)	<.0001
epi-25-hydroxyvitamin D3	0.505(0.431-0.591)	<.0001
Phosphorus	0.221(0.113-0.432)	<.0001
Chloride	1.108(1.066-1.153)	<.0001
Copper	1.018(1.012-1.025)	<.0001
Cytomegalovirus Ig M	3.54(1.729-7.248)	0.0026
PCB74	0.43(0.298-0.621)	<.0001
PCB99	0.393(0.255-0.606)	<.0001
PCB118	0.421(0.263-0.674)	0.0016
PCB138	0.284(0.158-0.511)	<.0001

PCB146	0.676(0.539-0.848)	0.0034
PCB153	0.241(0.133-0.438)	<.0001
PCB156	0.768(0.668-0.668)	0.0011
PCB170	0.635(0.478-0.844)	0.0079
PCB177	0.78(0.660-0.922)	0.0146
PCB178	0.826(0.710-0.960)	0.0434
PCB180	0.379(0.255-0.563)	<.0001
PCB183	0.776(0.656-0.918)	0.0129
PCB187	0.651(0.504-0.841)	0.0047
PCB194	0.768(0.667-0.883)	0.0011
PCB196	0.726(0.619-0.852)	<.0001
PCB199	0.746(0.626-0.890)	0.0055
1,2,3,6,7,8 hxcdd	0.361(0.184-0.708)	0.0127
2,3,4,7,8 pncdf	0.418(0.220-0.793)	0.0296
1,2,3,4,6,7,8,9 ocdf	2.206(1.210-4.021)	0.0371
3,4,4',5 tcb	0.346(0.148-0.812)	0.0492
Hexachlorobenzene	0.311(0.126-0.766)	0.0395
p,p' DDE	0.412(0.248-0.686)	0.0034
2,2',4,4',5,5'-hexabromodiphenyl ether	0.524(0.366-0.751)	0.0021
Cyanuric acid	0.455(0.313-0.661)	<.0001
Perfluorohexane sulfonic acid	0.825(0.707-0.963)	0.0492
2- (N-Methyl-perfluorooctane sulfonamido) acetic acid	0.786(0.651-0.951)	0.0446
Perfluorodecanoic acid	0.582(0.432-0.784)	0.0021

Table 4: Significant factors from unadjusted analysis of factors with abdominal obesity for children/adolescents

Environmental factors	**Abdominal Obesity**	
	OR (95% CI)	**Q values**
Beryllium	1.719(1.135-2.602)	0.0364
Thiocyanate	1.228(1.134-1.330)	<.0001
Glycidamide	1.424(1.240-1.635)	<.0001
2-Amino-6-methyldipyrido[1,2-a:3',2'-d] imidazole (Glu-P-1)	0.132(0.028-0.619)	0.0362
Mono-ethyl phthalate	1.073(1.019-1.130)	0.0277
o-Desmethylangolensin (O-DMA)	0.929(0.888-0.972)	0.0068
Enterodiol	0.849(0.774-0.932)	0.003

Enterolactone	0.776(0.719-0.836)	<.0001
2-napthol	1.408(1.299-1.526)	<.0001
2-fluorene	1.174(1.066-1.293)	0.005
1-phenanthrene	1.206(1.098-1.325)	<.0001
2-phenanthrene	1.289(1.177-1.413)	<.0001
9-fluorene	1.206(1.095-1.327)	0.0006
4-phenanthrene	1.23(1.082-1.398)	0.0071
Malathion diacid	1.277(1.059-1.540)	0.0362
Dimethylphosphate	0.875(0.819-0.935)	<.0001
Diethylphosphate	0.939(0.900-0.980)	0.0158
1,3-dimethyluric acid	1.205(1.038-1.399)	0.0497
1,3,7-trimethyluric acid	1.317(1.170-1.482)	<.0001
1,3-dimethylxanthine(theophylline)	1.309(1.119-1.532)	0.0037
1,7-dimethylxanthine(paraxanthine)	1.234(1.073-1.419)	0.0138
1,3,7-trimethylxanthine(caffeine)	1.346(1.197-1.514)	<.0001
Cockroach IgE antibody	1.165(1.046-1.297)	0.0212
Shrimp IgE antibody	1.204(1.064-1.363)	0.0138
Aspergillus IgE antibody	0.804(0.723-0.894)	<.0001
lead	0.723(0.667-0.783)	<.0001
Folate	0.594(0.500-0.707)	<.0001
5-Methyl-tetrahydrofolate	0.733(0.588-0.912)	0.0207
Folic acid (nmol/L)	0.816(0.733-0.908)	0.0011
Vitamin B12	0.392(0.316-0.487)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)	0.748(0.671-0.834)	<.0001
4-pyridoxic acid	0.623(0.532-0.729)	<.0001
Vitamin C	0.567(0.487-0.659)	<.0001
Iron	0.464(0.397-0.542)	<.0001
Selenium	5.651(2.186-14.608)	0.002
manganese	2.548(1.884-3.447)	<.0001
Gamma tocopherol	3.624(2.931-4.481)	<.0001
d-Tocopherol	1.407(1.184-1.672)	0.0006
a-carotene	0.708(0.650-0.771)	<.0001
trans-b-carotene	0.367(0.326-0.412)	<.0001
total b-Carotene	0.34(0.273-0.423)	<.0001
cis-b-carotene	0.313(0.267-0.367)	<.0001
a-Cryptoxanthin	0.388(0.310-0.486)	<.0001
b-cryptoxanthin	0.581(0.509-0.664)	<.0001
Lutein	0.322(0.248-0.419)	<.0001

cis- Lutein/Zeaxanthin	0.42(0.324-0.543)	<.0001
Combined Lutein/zeaxanthin	0.41(0.342-0.492)	<.0001
Zeaxanthin	0.497(0.390-0.632)	<.0001
Vitamin A	2.924(2.220-3.853)	<.0001
Vitamin D	0.416(0.333-0.519)	<.0001
25-hydroxyvitamin D3	0.318(0.253-0.400)	<.0001
epi-25-hydroxyvitamin D3	0.562(0.489-0.645)	<.0001
Phosphorus	0.155(0.092-0.262)	<.0001
Chloride	1.095(1.057-1.133)	<.0001
Copper	1.015(1.007-1.022)	0.0011
PCB74	0.475(0.358-0.631)	<.0001
PCB99	0.449(0.329-0.614)	<.0001
PCB118	0.487(0.309-0.769)	0.0087
PCB138	0.314(0.214-0.463)	<.0001
PCB146	0.739(0.634-0.862)	0.0006
PCB153	0.283(0.191-0.419)	<.0001
PCB156	0.822(0.739-0.915)	0.0015
PCB170	0.696(0.580-0.835)	<.0001
PCB177	0.839(0.747-0.943)	0.0138
PCB178	0.854(0.768-0.951)	0.0158
PCB180	0.436(0.327-0.581)	<.0001
PCB183	0.809(0.729-0.896)	<.0001
PCB187	0.705(0.588-0.846)	0.0011
PCB194	0.804(0.721-0.898)	0.0006
PCB196	0.784(0.692-0.888)	0.0006
PCB199	0.801(0.703-0.911)	0.0037
1,2,3,6,7,8 hxcdd	0.368(0.215-0.630)	0.0015
2,3,4,7,8 pncdf	0.246(0.124-0.488)	<.0001
1,2,3,4,7,8 hcxdf	0.377(0.189-0.753)	0.0213
1,2,3,6,7,8 hxcdf	0.282(0.116-0.684)	0.0198
Hexachlorobenzene	0.32(0.144-0.710)	0.0198
Oxychlordane	0.541(0.346-0.846)	0.0262
p,p' DDE	0.54(0.388-0.753)	0.0015
Trans-nonachlor	0.596(0.401-0.885)	0.0362
2,2',4,4',5,5'-hexabromodiphenyl ether	0.47(0.373-0.592)	<.0001
Cyanuric acid	0.485(0.293-0.800)	0.0184
Perfluorodecanoic acid	0.696(0.563-0.860)	0.0037

While the goal of this dissertation was to adjust for all covariates mentioned in the methods section when evaluating each environmental factor with general and abdominal obesity, I was unable to adjust for all covariates for some factors because either the covariate was not measured or there was not enough sample size that could allow for the adjustment of all covariates. Results from the multivariate analysis of all the factors showed that 29 factors were significantly associated with overweight, 56 with general obesity and 70 with abdominal obesity at FDR <5%. These results are presented in tables 5, 6 and 7. (Note: tables 5, 6, & 7 are from the same multinomial logistic regression model). Table 8, therefore summarizes the factors associated with overweight, obesity and abdominal obesity. As shown in table 5, factors such as 2-napthol, 1,2,3,4,6,7,8,9 Octachlorodibenzofuran (ocdf) and gamma tocopherol were positively associated with overweight while the rest were negatively associated with overweight in children/adolescents.

Table 5: Significant factors from adjusted analysis of factors with overweight for children/adolescents

Environmental factors	**Overweight**	
	OR (95% CI)	**Q values**
2-napthol	1.438(1.138-1.818)	0.0278
2,4-D	0.409(0.236-0.710)	0.0181
manganese	2.423(1.320-4.446)	0.0416
Gamma tocopherol	1.557(1.142-2.124)	0.0477
trans-b-carotene	0.508(0.409-0.631)	<.0001
total b-Carotene	0.461(0.334-0.636)	<.0001
cis-b-carotene	0.551(0.425-0.714)	<.0001
b-cryptoxanthin	0.658(0.529-0.818)	0.0041
25-hydroxyvitamin D3	0.596(0.418-0.850)	0.0416
PCB74[a]	0.246(0.104-0.581)	0.0181
PCB138[b]	0.386(0.261-0.572)	<.0001
PCB146[b]	0.701(0.583-0.843)	0.0021
PCB153[b]	0.345(0.235-0.507)	<.0001
PCB156[a]	0.616(0.532-0.713)	<.0001

PCB170[b]	0.631(0.481-0.827)	0.0058
PCB177[b]	0.815(0.725-0.917)	0.0053
PCB178[b]	0.781(0.694-0.878)	<.0001
PCB180[b]	0.399(0.258-0.617)	<.0001
PCB183[b]	0.756(0.650-0.879)	0.003
PCB187[b]	0.612(0.467-0.802)	0.0035
PCB194[b]	0.781(0.670-0.910)	0.0098
PCB196[b]	0.771(0.659-0.902)	0.0075
PCB199[b]	0.784(0.683-0.901)	0.0049
2,3,4,7,8 pncdf[a]	0.123(0.050-0.303)	<.0001
1,2,3,6,7,8 hxcdf[a]	0.885(0.817-0.959)	0.0301
1,2,3,4,6,7,8,9 ocdf[a]	2.028(1.267-3.246)	0.0344
3,3',4,4',5,5' hxcb[a]	0.217(0.077-0.611)	0.0404
p,p' DDE[b]	0.612(0.460-0.813)	0.0053
2,2',4,4',5,5'-hexabromodiphenyl [b]ether	0.521(0.380-0.713)	<.0001

[a] adjusted for all covariates except physical activity and limitation
[b] unadjusted

In table 6, beryllium, thalium, thiocyanate, 2-Amino-9H-pyrido[2,3-b]indole (A-a-C), 2-napthol, 1-phenanthrene, 9-fluorene, 4-phenanthrene, manganese, gamma tocopherol, d-Tocopherol, Vitamin A, ethyl mercury, Copper and 1,2,3,4,6,7,8,9 ocdf were all positively associated with obesity in children/adolescents while the rest were negatively associated with obesity.

Table 6: Significant factors from adjusted analysis of factors with obesity for children/adolescents

Environmental factors	**Obesity**	
	OR (95% CI)	**Q values**
Beryllium	3.305(1.460-7.479)	0.0229
Cobalt	0.649(0.499-0.844)	0.0083
Molybdenum	0.729(0.593-0.896)	0.017
Lead	0.739(0.623-0.877)	0.004
Tin	0.812(0.695-0.949)	0.0451
Thalium	1.49(1.140-1.948)	0.0207

Thiocyanate	1.641(1.382-1.949)	<.0001
2-Amino-9H-pyrido(2,3-b)indole (A-a-C)	1.323(1.083-1.617)	0.0339
2-napthol	1.71(1.454-2.011)	<.0001
1-phenanthrene	1.387(1.095-1.757)	0.0354
2-phenanthrene	2.418(1.647-3.549)	<.0001
9-fluorene	1.509(1.230-1.851)	<.0001
4-phenanthrene	2.828(1.632-4.899)	0.0017
Vitamin B12	0.203(0.124-0.333)	<.0001
4-pyridoxic acid	0.626(0.465-0.842)	0.0122
Vitamin C	0.444(0.296-0.668)	<.0001
Iron	0.409(0.232-0.718)	0.0122
manganese	3.88(2.483-6.063)	<.0001
Gamma tocopherol	8.297(5.683-12.114)	<.0001
d-Tocopherol	1.841(1.476-2.297)	<.0001
a-carotene	0.67(0.544-0.826)	0.0017
trans-b-carotene	0.259(0.185-0.363)	<.0001
total b-Carotene	0.152(0.074-0.315)	<.0001
cis-b-carotene	0.256(0.176-0.373)	<.0001
b-cryptoxanthin	0.502(0.354-0.712)	0.001
Lutein	0.183(0.088-0.384)	<.0001
cis- Lutein/Zeaxanthin	0.225(0.114-0.443)	<.0001
Combined Lutein/zeaxanthin	0.276(0.166-0.458)	<.0001
Zeaxanthin	0.238(0.159-0.357)	<.0001
Vitamin A	5.531(2.816-10.867)	<.0001
Vitamin E	0.317(0.146-0.690)	0.0216
Vitamin D	0.338(0.196-0.584)	<.0001
25-hydroxyvitamin D3	0.318(0.218-0.218)	<.0001
epi-25-hydroxyvitamin D3	0.667(0.528-0.842)	0.0052
Mercury, ethyl	2.919(1.301-6.548)	0.0478
Copper	1.024(1.014-1.035)	<.0001
PCB74[a]	0.164(0.066-0.407)	<.0001
PCB99[b]	0.393(0.255-0.606)	<.0001
PCB138[b]	0.284(0.158-0.511)	<.0001
PCB146[b]	0.676(0.539-0.848)	0.0034
PCB153[b]	0.241(0.133-0.438)	<.0001

PCB156[b]	0.502(0.366-0.688)	<.0001
PCB170[b]	0.635(0.478-0.844)	0.0079
PCB177[b]	0.78(0.660-0.922)	0.0146
PCB180[b]	0.379(0.255-0.563)	<.0001
PCB183[b]	0.776(0.656-0.918)	0.0129
PCB187[b]	0.651(0.504-0.841)	0.0047
PCB194[b]	0.768(0.667-0.883)	0.0011
PCB196[b]	0.726(0.619-0.852)	<.0001
PCB199[b]	0.746(0.626-0.890)	0.0055
1,2,3,4,6,7,8,9 ocdf[a]	2.521(1.374-4.624)	0.0173
p,p' DDE[b]	0.412(0.248-0.686)	0.0034
2,2',4,4',5,5'-hexabromodiphenyl ether[b]	0.524(0.366-0.751)	0.0021
Cyanuric acid[b]	0.455(0.313-0.661)	<.0001
Perfluorodecanoic acid	0.27(0.119-0.615)	0.0411

[a] adjusted for all covariates except physical activity and limitation
[b] unadjusted

In table 7, beryllium, Platinum, thiocyanate, 2-Amino-9H-pyrido[2,3-b]indole (A-a-C), 2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C), Mono-ethyl phthalate, 2-napthol, 1-phenanthrene, 2-phenanthrene, 9-fluorene, 4-phenanthrene, 1,3,7-trimethyluric acid, 1,3,7-trimethylxanthine(caffeine), D. Farinae IgE antibody , manganese, gamma tocopherol, Vitamin A, Copper and 1,2,3,4,6,7,8,9 ocdf were all positively associated with abdominal obesity in children/adolescents while the rest were negatively associated with abdominal obesity.

Table 7: Significant factors from adjusted analysis of factors with abdominal obesity for children/adolescents

Environmental factors	**Abdominal Obesity**	
	OR (95% CI)	**Q values**
Beryllium	4.336(1.836-10.244)	0.0058
Molybdenum	0.777(0.650-0.928)	0.0248

Lead	0.796(0.691-0.916)	0.0097
Platinum	1.346(1.107-1.636)	0.0162
Tungsten	0.794(0.687-0.918)	0.0111
Thiocyanate	1.498(1.275-1.759)	<.0001
Butyl paraben	0.865(0.786-0.952)	0.017
2-Amino-9H-pyrido[2,3-b]indole (A-a-C)	1.593(1.178-2.154)	0.0142
Harman	0.709(0.552-0.912)	0.0339
2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C)	2.799(1.442-5.433)	0.0136
Mono-ethyl phthalate	1.163(1.039-1.302)	0.038
Enterolactone	0.761(0.623-0.930)	0.0339
2-napthol	1.572(1.342-1.841)	<.0001
1-phenanthrene	1.45(1.147-1.834)	0.0115
2-phenanthrene	2.055(1.437-2.938)	<.0001
9-fluorene	1.478(1.182-1.847)	0.0048
4-phenanthrene	1.987(1.325-2.978)	0.0061
Diethylphosphate	0.833(0.726-0.955)	0.0377
1,3,7-trimethyluric acid	1.22(1.029-1.414)	0.0369
1,3,7-trimethylxanthine(caffeine)	1.258(1.075-1.473)	0.0219
D. Farinae IgE antibody	1.156(1.045-1.278)	0.0232
Vitamin B12	0.384(0.245-0.603)	<.0001
4-pyridoxic acid	0.673(0.534-0.846)	0.0053
Vitamin C	0.514(0.370-0.713)	<.0001
Iron	0.489(0.282-0.796)	0.0226
manganese	3.049(1.984-5.353)	<.0001
Gamma tocopherol	4.267(2.783-6.542)	<.0001
a-carotene	0.745(0.647-0.858)	<.0001
trans-b-carotene	0.396(0.306-0.502)	<.0001
total b-Carotene	0.282(0.179-0.446)	<.0001
cis-b-carotene	0.397(0.295-0.534)	<.0001
b-cryptoxanthin	0.648(0.504-0.833)	0.0053
Lutein	0.353(0.197-0.632)	0.0043
cis- Lutein/Zeaxanthin	0.339(0.206-0.560)	<.0001
Combined Lutein/zeaxanthin	0.466(0.305-0.712)	0.0043
Zeaxanthin	0.435(0.271-0.697)	0.0048
Vitamin A	3.373(1.729-6.578)	0.0027

Vitamin D	0.452(0.299-0.685)	<.0001
25-hydroxyvitamin D3	0.295(0.201-0.432)	<.0001
epi-25-hydroxyvitamin D3	0.624(0.501-0.777)	<.0001
Copper	1.023(1.011-1.035)	0.0019
PCB74[a]	0.186(0.107-0.325)	<.0001
PCB99[b]	0.449(0.329-0.614)	<.0001
PCB138[b]	0.314(0.214-0.463)	<.0001
PCB146[b]	0.739(0.634-0.862)	0.0006
PCB153[b]	0.283(0.191-0.419)	<.0001
PCB156[a]	0.604(0.484-0.753)	<.0001
PCB170[b]	0.696(0.580-0.835)	<.0001
PCB177[b]	0.839(0.747-0.943)	0.0138
PCB178[b]	0.854(0.768-0.951)	0.0158
PCB180[b]	0.436(0.327-0.581)	<.0001
PCB183[b]	0.809(0.729-0.896)	<.0001
PCB187[b]	0.705(0.588-0.846)	0.0011
PCB194[b]	0.804(0.721-0.898)	0.0006
PCB196[b]	0.784(0.692-0.888)	0.0006
PCB199[b]	0.801(0.703-0.911)	0.0037
1,2,3,7,8 pncdd[a]	0.391(0.209-0.734)	0.0179
1,2,3,6,7,8 hxcdd[a]	0.356(0.193-0.658)	0.0066
2,3,4,7,8 pncdf[a]	0.249(0.124-0.499)	<.0001
1,2,3,6,7,8 hxcdf[a]	0.911(0.849-0.978)	0.042
1,2,3,4,6,7,8,9 ocdf[a]	2.192(1.380-3.481)	0.0061
Hexachlorobenzene[b]	0.32(0.144-0.710)	0.0198
Oxychlordane[b]	0.541(0.346-0.846)	0.0262
p,p' DDE[b]	0.54(0.388-0.753)	0.0015
Trans-nonachlor[b]	0.596(0.401-0.885)	0.0362
2,2',4,4',5,5'-hexabromodiphenyl ether[b]	0.47(0.373-0.592)	<.0001
Cyanuric acid[b]	0.485(0.293-0.800)	0.0184

[a] adjusted for all covariates except physical activity and limitation
[b] unadjusted

From the multivariate analysis, I saw that 2-napthol, 1,2,3,4,6,7,8,9 Octachlorodibenzofuran (ocdf) and gamma tocopherol were consistently associated with overweight, obesity and abdominal obesity while beryllium, thiocyanate, 2-Amino-9H-pyrido[2,3-b]indole (A-a-C), 1-phenanthrene, 9-fluorene, 4-phenanthrene, manganese, copper, and 1,2,3,4,6,7,8,9 ocdf were consistently associated with both general and abdominal obesity.

Table 8: Factors associated with overweight, general obesity and abdominal obesity among children/adolescents after adjusting for covariates

Environmental Factors	**Obesity measures using BMI**		**Waist to height ratio**
	Overweight	Obese	Abdominal Obesity
Positive Associations			
Metals			
Manganese	+	+	+
Beryllium		+	+
Platinum			+
Copper		+	+
Mercury, ethyl		+	
Thallium		+	
Vitamins			
Gamma tocopherol	+	+	+
d-Tocopherol		+	
Heterocyclic aromatic amines			
2-Amino-9H-pyrido(2,3-b)indole (A-a-C)		+	+
2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C)			+
Polychlorinated biphenyls			
1,2,3,4,6,7,8,9 ocdf	+	+	+
Polycyclic aromatic hydrocarbons			

2-napthol	+	+	+
1-phenanthrene		+	+
2-phenanthrene		+	+
9-fluorene		+	+
4-phenanthrene		+	+
Phthalates			
Mono-ethyl phthalate			+
Caffeine metabolites			
1,3,7-trimethyluric acid			+
1,3,7-trimethylxanthine(caffeine)			+
Thiocyanates			
Thiocyanate		+	+
Allergens			
D. Farinae IgE antibody			+
Negative Associations			
Metals			
Cobalt		-	
Molybdenum		-	-
Iron		-	-
Lead		-	-
Tungsten			-
Tin		-	
Vitamins			
Vitamin B12		-	-
4-pyridoxic acid		-	-
Vitamin C		-	-
a-carotene		-	-
trans-b-carotene	-	-	-
total b-Carotene	-	-	-
cis-b-carotene	-	-	-
b-cryptoxanthin	-	-	-

Lutein		-	-
cis- Lutein/Zeaxanthin		-	-
Combined Lutein/zeaxanthin		-	-
Zeaxanthin		-	-
Vitamin E		-	
Vitamin D		-	-
epi-25-hydroxyvitamin D3		-	-
25-hydroxyvitamin D3	-	-	-
Parabens			
Butyl paraben			-
Heterocyclic aromatic amines			
Harman			-
Phytoestrogens			
Enterolactone			-
Pesticides			
Diethylphosphate			-
2,4-D	-	-	
p,p' DDE		-	-
Hexachlorobenzene			-
Oxychlordane			-
Trans-nonachlor			-
Perfluorodecanoic acid		-	
Cyanuric acid		-	-
Polychlorinated Biphenyls			
PCB74		-	-
PCB99	-	-	-
PCB138	-	-	-
PCB146	-	-	-
PCB153	-	-	-
PCB156	-	-	-
PCB170	-	-	-
PCB177	-		-
PCB178	-	-	-
PCB180	-	-	-

PCB183	-	-	-
PCB187	-	-	-
PCB194	-	-	-
PCB196	-	-	-
PCB199	-		-
2,3,4,7,8 pncdf	-		-
1,2,3,6,7,8 hxcdd			-
2,3,4,7,8 pncdf			-
1,2,3,6,7,8 hxcdf	-		-
3,3',4,4',5,5' hxcb	-	-	
2,2',4,4',5,5'-hexabromodiphenyl ether		-	-

+ positive association; - negative association

Aim 2

To check the validity of my findings, some significant factors from my multivariate analysis were re-evaluated on a different cohort of children/adolescents using merged data from NHANES 1999/2000, 2007/2008 and 2015/20016. Among the significant factors associated with overweight, none was validated. Among factors associated with obesity, 11 were validated at FDR <5% as shown in table 9.

Table 9: Validated factors associated with obesity in children/adolescents after adjusting for covariates

Environmental factors	**Obesity**	
	OR (95% CI)	**Q values**
Thiocyanate	1.491(1.264-1.759)	<.0001
2-napthol	2.933(1.693-5.084)	0.0005
1-phenanthrene	2.101(1.360-3.246)	0.0034
2-phenanthrene	2.206(1.175-4.142)	0.0427
9-fluorene	1.875(1.204-2.920)	0.0184
lead	0.481(0.363-0.637)	<.0001
Vitamin B12	0.301(0.164-0.551)	0.0005
4-pyridoxic acid	0.446(0.371-0.537)	<.0001
Vitamin A	1.074(1.045-1.103)	<.0001
Copper	1.026(1.015-1.037)	<.0001
Perfluorodecanoic acid	0.564(0.382-0.832)	0.0147

Among factors significantly associated with abdominal obesity in children/adolescents, 11 were also validated as shown in table 10.

Table 10: Validated factors associated with abdominal obesity in children/adolescents after adjusting for covariates

Environmental factors	**Abdominal Obesity**	
	OR (95% CI)	**Q values**
Tungsten	0.503(0.347-0.731)	0.0023
Thiocyanate	1.29(1.181-1.409)	<.0001
2-napthol	2.495(1.794-3.469)	<.0001
1-phenanthrene	2.269(1.559-3.303)	<.0001
2-phenanthrene	2.612(1.620-4.211)	<.0001
lead	0.626(0.475-0.826)	0.0046
4-pyridoxic acid	0.566(0.400-0.802)	0.0064
Vitamin A	1.057(1.025-1.090)	0.0026
Copper	1.022(1.014-1.030)	<.0001
Oxychlordane	0.325(0.152-0.696)	0.0159
Trans-nonachlor	0.356(0.198-0.642)	0.0035

Other significant factors such as beryllium, tin, 2-Amino-9H-pyrido[2,3-b]indole (A-a-C), harman, 2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C), 4-phenanthrene, 1,3,7-trimethyluric acid , 1,3,7-trimethylxanthine(caffeine), D. Farinae IgE antibody, vitamin C, gamma tocopherol, d-Tocopherol, a-carotene, trans-b-carotene, total b-Carotene, cis-b-carotene, b-cryptoxanthin, Lutein , cis-Lutein/Zeaxanthin, Combined Lutein/zeaxanthin, Zeaxanthin, PCB194, PCB196 , PCB199, 2,2',4,4',5,5'-hexabromodiphenyl ether, and cyanuric acid, were not re-evaluated in this cohort as they were measured in a single cycle other than the one used for validation analysis. Thus, these findings remained unvalidated.

Aim 3

To check the robustness of our findings from Aim 1, a comprehensive and systematic evaluation of the same 288 unique environment factors were done using the adult population. This was necessary to see if significant factors found in children/adolescents persist in adulthood. As seen in the multivariate analysis of factors with measures of obesity in children/adolescent population, I was unable to adjust for all covariates while evaluating some factors. Table 11 presents factors that were statistically associated with overweight at FDR <5% in the adult population.

Table 11: Significant factors from adjusted analysis of factors with overweight for adult population

Environmental factors	**Overweight**	
	OR (95% CI)	**Q values**
Tungsten	0.831(0.726-0.952)	0.046
Acrylamide	0.67(0.580-0.580)	<.0001
Ethyl paraben	0.899(0.834-0.969)	0.0381
Harman	0.688(0.582-0.814)	<.0001
Enterodiol[a]	0.907(0.845-0.974)	0.046
Bis(1,3-dichloro-2-propyl) phosphate	1.431(1.179-1.738)	0.0032
lead	0.76(0.664-0.868)	<.0001
Cadmium	0.83(0.753-0.914)	0.0024
Vitamin B12	0.788(0.690-0.901)	0.0048
Iron	0.705(0.636-0.782)	<.0001
Gamma tocopherol	1.797(1.539-2.097)	<.0001
d-Tocopherol	1.623(1.403-1.877)	<.0001
a-carotene	0.862(0.792-0.938)	0.0054
trans-b-carotene	0.744(0.684-0.810)	<.0001
total b-Carotene	0.694(0.616-0.782)	<.0001
cis-b-carotene	0.66(0.603-0.723)	<.0001
a-Cryptoxanthin	0.687(0.538-0.878)	0.0212
b-cryptoxanthin	0.76(0.671-0.860)	<.0001
cis-Lycopene	1.343(1.139-1.585)	0.0048
total Lycopene	1.411(1.221-1.631)	<.0001
Lutein	0.687(0.531-0.887)	0.0293
cis- Lutein/Zeaxanthin	0.59(0.481-0.724)	<.0001

Combined Lutein/zeaxanthin	0.743(0.610-0.906)	0.0248
trans-lycopene	1.392(1.229-1.576)	<.0001
Total (cis- and trans-) Lycopene	1.351(1.089-1.675)	0.0412
Vitamin A	1.538(1.134-2.085)	0.0381
Vitamin E	2.461(1.951-3.106)	<.0001
Vitamin D	0.639(0.522-0.781)	<.0001
25-hydroxyvitamin D3	0.66(0.537-0.810)	<.0001
Phosphorus	0.491(0.335-0.719)	0.0032
Chloride	1.063(1.038-1.088)	<.0001
Copper	1.009(1.004-1.015)	0.0118
PCB99[b]	1.342(1.134-1.589)	0.0054
PCB138[b]	1.291(1.124-1.483)	0.0032
PCB153[b]	1.216(1.063-1.392)	0.0322
PCB187[b]	1.196(1.050-1.363)	0.046
Beta-hexachlorocyclohexane[b]	1.244(1.058-1.463)	0.0495
Heptachlor Epoxide[b]	2.047(1.577-2.657)	<.0001
3,3',4,4',5,5' hxcb	0.476(0.345-0.658)	<.0001
Oxychlordane[b]	1.376(1.173-1.614)	<.0001
p,p' DDE[b]	1.224(1.082-1.385)	0.0113
Trans-nonachlor[b]	1.382(1.195-1.597)	<.0001
Dieldrin[b]	2.397(1.764-3.258)	<.0001
2,4,4'-tribromodiphenyl ether	1.314(1.133-1.523)	0.024
2,2',3,4,4',5',6-heptabromodiphenyl ethr	1.738(1.160-2.603)	0.0041
Perfluoroundecanoic acid	0.823(0.725-0.935)	0.0215

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Among factors that were statistically significant, Bis(1,3-dichloro-2-propyl) phosphate, gamma tocopherol, d-tocopherol, Lycopene, vit A & E, chloride, copper, PCB99, PCB138, PCB153, PCB187, Beta-hexachlorocyclohexane, Heptachlor Epoxide, Oxychlordane, p,p' DDE, Trans-nonachlor, Dieldrin, 2,4,4'-tribromodiphenyl ether,and 2,2',3,4,4',5',6-heptabromodiphenyl ether were positively associated with overweight among adults. As shown in table 12 & 13, many more factors were associated with general and abdominal obesity at FDR <5%.

Table 12: Factors associated with obesity at FDR <5% among adults after adjusting for covariates

Environmental factors	**Obesity**	
	OR (95% CI)	**Q values**
Cadmium	0.453(0.330-0.623)	<.0001
Lead	0.722(0.608-0.858)	0.001
Platinum	0.994(0.990-0.997)	0.0035
Acrylamide	0.58(0.500-0.673)	<.0001
Triclocarban	1.216(1.109-1.334)	<.0001
2-Hydroxy-4-metoxybenzophenone (Benzophenone-3)	0.907(0.866-0.950)	<.0001
Butyl paraben	0.871(0.808-0.939)	0.0014
Ethyl paraben	0.725(0.659-0.797)	<.0001
Methyl paraben	0.855(0.793-0.921)	<.0001
Propyl paraben	0.908(0.852-0.968)	0.0117
3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)	0.293(0.117-0.732)	0.0286
Mono(carboxynonyl) phthalate	1.183(1.063-1.063)	0.0079
Mono-benzyl phthalate	1.202(1.0671.354)	0.0093
Enterolactone[a]	0.838(0.754-0.930)	0.0039
1-napthol	0.806(0.708-0.918)	0.005
2-napthol	1.29(1.061-1.568)	0.0344
3-fluorene	0.799(0.686-0.929)	0.0134
2,4,5-trichlorophenol	0.512(0.336-0.779)	0.0073
Bis(1,3-dichloro-2-propyl) phosphate	1.818(1.436-2.301)	<.0001
Bis(2-chloroethyl) phosphate	1.263(1.071-1.490)	0.0192
1,3-dimethyluric acid[a]	1.214(1.065-1.385)	0.0134
1,7-dimethyluric acid[a]	1.226(1.091-1.378)	0.0027
1,3,7-trimethyluric acid[a]	1.283(1.153-1.427)	<.0001
1,3-dimethylxanthine(theophylline)	1.248(1.091-1.427)	0.0054
1,7-dimethylxanthine(paraxanthine)[a]	1.182(1.044-1.338)	0.0286
1,3,7-trimethylxanthine(caffeine)[a]	1.212(1.078-1.363)	0.0057
Folate	0.619(0.503-0.761)	<.0001
5-Methyl-tetrahydrofolate	0.682(0.584-0.797)	<.0001
Folic acid	0.83(0.752-0.917)	0.001
5,10-Methenyl-tetrahydrofolate	0.461(0.268-0.794)	0.0187
Vitamin B12	0.605(0.517-0.707)	<.0001

Vitamin B6(Pyridoxal 5'-phosphate)	0.744(0.694-0.797)	<.0001
4-pyridoxic acid	0.813(0.739-0.894)	<.0001
Vitamin C	0.591(0.521-0.670)	<.0001
Total mercury(organic + inorganic)	0.781(0.725-0.840)	<.0001
Iron	0.397(0.351-0.449)	<.0001
manganese	1.628(1.171-2.262)	0.0134
Gamma tocopherol	4.445(3.564-5.543)	<.0001
d-Tocopherol	2.357(1.882-2.954)	<.0001
a-carotene	0.543(0.495-0.596)	<.0001
trans-b-carotene	0.418(0.376-0.464)	<.0001
total b-Carotene	0.395(0.344-0.454)	<.0001
cis-b-carotene	0.323(0.287-0.365)	<.0001
a-Cryptoxanthin	0.309(0.230-0.417)	<.0001
b-cryptoxanthin	0.446(0.393-0.507)	<.0001
Lutein	0.316(0.215-0.467)	<.0001
cis- Lutein/Zeaxanthin	0.236(0.161-0.344)	<.0001
Combined Lutein/zeaxanthin	0.346(0.286-0.418)	<.0001
Phytofluene	0.768(0.622-0.947)	0.0421
Zeaxanthin	0.511(0.375-0.695)	<.0001
Vitamin A	0.638(0.456-0.894)	0.0296
Vitamin D	0.286(0.229-0.356)	<.0001
25-hydroxyvitamin D3	0.312(0.257-0.378)	<.0001
epi-25-hydroxyvitamin D3	0.579(0.491-0.684)	<.0001
Phosphorus	0.33(0.219-0.497)	<.0001
Sodium	0.957(0.935-0.980)	0.001
Chloride	1.101(1.072-1.131)	<.0001
Mefox oxidation product	1.363(1.216-1.527)	<.0001
Mercury, methyl	0.76(0.647-0.893)	0.0035
Copper	1.018(1.014-1.021)	<.0001
PCB66[b]	1.603(1.099-2.336)	0.0441
PCB74[b]	2.567(1.695-3.887)	<.0001
PCB99[b]	1.587(1.381-1.823)	<.0001
PCB105	1.929(1.556-2.392)	<.0001
PCB118	1.954(1.489-2.564)	<.0001
PCB138[b]	1.31(1.180-1.453)	<.0001
PCB194[b]	0.898(0.836-0.964)	0.0114

1,2,3,4,7,8 hxcdd	2.204(1.235-1.235)	0.0255
1,2,3,6,7,8 hxcdd	1.539(1.111-2.131)	0.0309
1,2,3,7,8,9 hxcdd	3.195(2.297-4.444)	<.0001
1,2,3,4,6,7,8 hpcdd	3.305(2.268-4.817)	<.0001
1,2,3,4,6,7,8,9 ocdd	2.713(1.901-3.873)	<.0001
1,2,3,4,7,8 hcxdf	1.024(1.011-1.037)	0.001
1,2,3,6,7,8 hxcdf	1.027(1.012-1.042)	0.0014
3,3',4,4',5 pncb	2.307(1.679-3.170)	<.0001
Beta-hexachlorocyclohexane[b]	1.354(1.143-1.603)	0.0018
Hexachlorobenzene[b]	1.875(1.196-2.939)	0.021
Heptachlor Epoxide[b]	2.978(2.310-3.839)	<.0001
3,3',4,4',5,5' hxcb[b]	0.551(0.364-0.833)	0.0172
Oxychlordane[b]	1.468(1.274-1.692)	<.0001
p,p' DDE[b]	1.277(1.141-1.429)	<.0001
p,p' DDT[b]	1.5(1.283-1.753)	<.0001
Trans-nonachlor[b]	1.398(1.208-1.618)	<.0001
Dieldrin[b]	3.864(2.768-5.394)	<.0001
2,4,4'-tribromodiphenyl ether	1.379(1.214-1.566)	0.0093
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid	0.825(0.735-0.926)	0.0047
Perfluorodecanoic acid	0.799(0.672-0.951)	0.0365
Perfluoroundecanoic acid	0.597(0.486-0.734)	<.0001

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Among factors that were statistically significant, triclocarban, mono(carboxynonyl) phthalate, Mono-benzyl phthalate, 2-napthol, Bis(1,3-dichloro-2-propyl) phosphate, Bis(2-chloroethyl) phosphate, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 1,3,7-trimethyluric acid, 1,3-dimethylxanthine(theophylline), 1,7-dimethylxanthine(paraxanthine), 1,3,7-trimethylxanthine(caffeine), manganese, Gamma tocopherol, d-Tocopherol, Chloride , Mefox oxidation product, Copper, PCB66, PCB74, PCB99, PCB105, PCB118, PCB138, 1,2,3,6,7,8 hxcdd, 1,2,3,7,8,9 hxcdd, 1,2,3,4,6,7,8 hpcdd, 1,2,3,4,6,7,8,9 ocdd, 1,2,3,4,7,8 hcxdf, 1,2,3,6,7,8 hxcdf, 3,3',4,4',5 pncb, Beta-hexachlorocyclohexane, Hexachlorobenzene, Heptachlor

Epoxide, Oxychlordane, p,p' DDE, p,p' DDT, Trans-nonachlor, Dieldrin and 2,4,4'-tribromodiphenyl ether were positively associated with obesity among adults.

Table 13: Factors associated with abdominal obesity among adults after adjusting for covariates

Environmental factors	**Abdominal Obesity**	
	OR (95% CI)	**Q values**
Barium	1.194(1.053-1.354)	0.0243
Cadmium	0.634(0.468-0.858)	0.0148
Acrylamide	0.773(0.670-0.891)	0.0025
Glycidamide	1.205(1.046-1.388)	0.0393
2-Hydroxy-4-metoxybenzophenone (Benzophenone-3)	0.941(0.896-0.988)	0.0496
Ethyl paraben	0.879(0.803-0.961)	0.021
Methyl paraben	0.901(0.829-0.979)	0.0497
Harman	0.731(0.579-0.922)	0.0334
Enterolactone[a]	0.822(0.729-0.927)	0.0068
2-napthol	1.246(1.048-1.481)	0.0462
2-phenanthrene	1.468(1.145-1.883)	0.0121
Bis(1,3-dichloro-2-propyl) phosphate	1.349(1.088-1.673)	0.0273
1-methyluric acid[a]	1.223(1.047-1.427)	0.0414
1,3-dimethyluric acid[a]	1.24(1.090-1.411)	0.0059
1,7-dimethyluric acid[a]	1.205(1.064-1.363)	0.015
3,7-dimethyluric acid[a]	1.146(1.036-1.267)	0.0334
1,3,7-trimethyluric acid[a]	1.306(1.148-1.485)	<.0001
1,3-dimethylxanthine(theophylline)[a]	1.279(1.091-1.499)	0.0118
1,3,7-trimethylxanthine(caffeine)[a]	1.23(1.049-1.441)	0.0408
lead	0.693(0.616-0.780)	<.0001
Folate	0.696(0.568-0.854)	0.003
5-Methyl-tetrahydrofolate	0.632(0.531-0.753)	<.0001
Folic acid	0.842(0.738-0.960)	0.0398
Vitamin B12	0.561(0.483-0.652)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)	0.803(0.721-0.895)	<.0001
Vitamin C	0.602(0.519-0.698)	<.0001
Total mercury(organic + inorganic)	0.804(0.745-0.868)	<.0001
Iron	0.58(0.513-0.656)	<.0001

Gamma tocopherol	2.89(2.522-3.312)	<.0001
d-Tocopherol	2.206(1.884-2.583)	<.0001
a-carotene	0.651(0.602-0.704)	<.0001
trans-b-carotene	0.533(0.485-0.586)	<.0001
total b-Carotene	0.499(0.418-0.595)	<.0001
cis-b-carotene	0.475(0.419-0.539)	<.0001
a-Cryptoxanthin	0.431(0.330-0.563)	<.0001
b-cryptoxanthin	0.508(0.455-0.568)	<.0001
Lutein	0.487(0.371-0.639)	<.0001
cis- Lutein/Zeaxanthin	0.39(0.309-0.491)	<.0001
Combined Lutein/zeaxanthin	0.498(0.427-0.580)	<.0001
Vitamin E	2.44(1.591-3.740)	<.0001
Vitamin D	0.346(0.275-0.435)	<.0001
25-hydroxyvitamin D3	0.368(0.305-0.445)	<.0001
epi-25-hydroxyvitamin D3	0.63(0.531-0.747)	<.0001
Phosphorus	0.332(0.227-0.485)	<.0001
Chloride	1.106(1.073-1.139)	<.0001
Mefox oxidation product	1.241(1.090-1.413)	0.0059
Mercury, methyl	0.819(0.722-0.929)	0.0095
Copper	1.015(1.011-1.020)	<.0001
PCB99[b]	1.55(1.302-1.845)	<.0001
PCB138[b]	1.431(1.253-1.635)	<.0001
PCB146[b]	1.254(1.095-1.435)	0.0057
PCB153[b]	1.295(1.146-1.464)	<.0001
PCB156	0.595(0.437-0.810)	0.0057
PCB157	0.675(0.547-0.832)	0.0013
PCB170[b]	1.226(1.091-1.378)	0.0036
PCB177[b]	1.202(1.075-1.343)	0.0064
PCB180[b]	1.171(1.052-1.304)	0.0182
PCB183[b]	1.195(1.055-1.354)	0.0229
PCB187[b]	1.283(1.145-1.437)	<.0001
PCB199[b]	1.144(1.037-1.262)	0.0311
1,2,3,7,8,9 hxcdd	2.257(1.358-1.358)	0.0087
1,2,3,4,7,8,9-hpcdf (fg/g)	2.128(1.218-3.718)	0.0332
Beta-hexachlorocyclohexane[b]	1.801(1.564-2.075)	<.0001

Hexachlorobenzene[b]	2.202(1.552-3.124)	<.0001
Heptachlor Epoxide[b]	2.665(2.072-3.428)	<.0001
3,3',4,4',5,5' hxcb	0.389(0.254-0.595)	<.0001
Oxychlordane[b]	1.758(1.569-1.971)	<.0001
p,p' DDE[b]	1.479(1.327-1.649)	<.0001
p,p' DDT[b]	1.681(1.379-2.049)	<.0001
Trans-nonachlor[b]	1.661(1.458-1.892)	<.0001
PCB209[b]	1.392(1.142-1.698)	0.0059
Dieldrin[b]	3.914(2.925-5.236)	<.0001
2,4,4'-tribromodiphenyl ether	1.372(1.197-1.574)	0.0007
Perfluorooctanoic acid	0.794(0.684-0.920)	0.0446
Perfluorodecanoic acid	0.825(0.713-0.955)	0.0396
Perfluoroundecanoic acid	0.725(0.624-0.843)	<.0001

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Among factors that were statistically significant, barium, glycidamide, 2-napthol, 2-phenanthrene, Bis(1,3-dichloro-2-propyl) phosphate, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 1,3,7-trimethyluric acid, 1,3-dimethylxanthine(theophylline), 1,7-dimethylxanthine(paraxanthine), 1,3,7-trimethylxanthine(caffeine), Gamma tocopherol, d-Tocopherol, vit E, Chloride , Mefox oxidation product, Copper, PCB99, PCB138, PCB146, PCB153, PCB170, PCB177, PCB180, PCB183, PCB187, PCB199, 1,2,3,7,8,9 hxcdd, 1,2,3,4,7,8,9-hpcdf, Beta-hexachlorocyclohexane, Hexachlorobenzene, Heptachlor Epoxide, Oxychlordane, p,p' DDE, p,p' DDT, Trans-nonachlor, Dieldrin and 2,4,4'-tribromodiphenyl ether were positively associated with obesity among adults. Table 14 summarizes the factors that were significantly associated with both general and abdominal obesity among adults.

Table 14: Factors associated with overweight, general obesity and abdominal obesity among adults after adjusting for covariates

Environmental Factors	**Obesity measures using BMI**	**Waist to height ratio**

	Overweight	Obese	Abdominal Obesity
Positive Associations			
Metals			
Manganese		+	
Copper	+	+	+
Barium			+
Vitamins			
Gamma tocopherol	+	+	+
d-Tocopherol	+	+	+
cis-Lycopene	+		
total Lycopene	+		
trans-lycopene	+		
Total (cis- and trans-) Lycopene	+		
Vitamin A	+		
Vitamin E	+		+
Glycidamides			
Glycidamide			+
Phenols			
Triclocarban		+	
Polychlorinated Biphenyls			
PCB66		+	
PCB74		+	
PCB99	+	+	+
PCB105		+	
PCB118		+	
PCB138	+	+	+
PCB146			+
PCB153	+		+
PCB170			+
PCB177			+
PCB180			+
PCB183			+

PCB187	+		+
PCB199			+
PCB209			+
1,2,3,4,7,8 hxcdd		+	
1,2,3,6,7,8 hxcdd		+	
1,2,3,7,8,9 hxcdd		+	+
1,2,3,4,7,8,9-hpcdf			+
1,2,3,4,6,7,8 hpcdd		+	
1,2,3,4,6,7,8,9 ocdd		+	
1,2,3,4,7,8 hcxdf		+	
1,2,3,6,7,8 hxcdf		+	
3,3',4,4',5 pncb		+	
Pesticides			
Bis(1,3-dichloro-2-propyl) phosphate	+	+	+
Bis(2-chloroethyl) phosphate		+	
Beta-hexachlorocyclohexane	+	+	+
Heptachlor Epoxide	+	+	+
Oxychlordane	+	+	+
p,p' DDE	+	+	+
p,p' DDT		+	+
Trans-nonachlor	+	+	+
Dieldrin	+	+	+
2,4,4'-tribromodiphenyl ether	+	+	+
2,2',3,4,4',5',6-heptabromodiphenyl ethr	+		
Hexachlorobenzene		+	+
Polycyclic aromatic hydrocarbons			
2-napthol		+	+
2-phenanthrene			+
Phthalates			
Mono(carboxynonyl) phthalate		+	
Mono-benzyl phthalate		+	
Caffeine metabolites			
1,3,7-trimethyluric acid		+	+
1,3,7-trimethylxanthine(caffeine)		+	+

1-methyluric acid			+
1,3-dimethyluric acid		+	+
1,7-dimethyluric acid		+	+
3,7-dimethyluric acid			+
1,3-dimethylxanthine(theophylline)		+	+
1,7-dimethylxanthine(paraxanthine)		+	
Negative Associations			
Metals			
Iron	-		-
Lead	-	-	-
Tungsten	-		
Cadmium	-	-	-
Platinum		-	
Polycyclic aromatic hydrocarbons			
1-napthol		-	
3-fluorene		-	
Phenols			
2,4,5-trichlorophenol		-	
Acrylamides			
Acrylamide	-	-	-
Vitamins			
Vitamin B6(Pyridoxal 5'-phosphate)		-	-
Vitamin B12	-	-	-
4-pyridoxic acid		-	
Vitamin C		-	-
a-carotene	-	-	-
trans-b-carotene	-	-	-
total b-Carotene	-	-	-
cis-b-carotene	-	-	-
a-cryptoxanthin	-	-	-
b-cryptoxanthin	-	-	-
Lutein	-	-	-

cis- Lutein/Zeaxanthin	-	-	-
Combined Lutein/zeaxanthin	-	-	-
Phytofluene		-	
Zeaxanthin		-	
Vitamin E			
Vitamin A		-	
Vitamin D	-	-	-
epi-25-hydroxyvitamin D3		-	-
25-hydroxyvitamin D3	-	-	-
Folate		-	-
5-Methyl-tetrahydrofolate		-	-
Folic acid		-	-
5,10-Methenyl-tetrahydrofolate		-	
Parabens			
Butyl paraben		-	
Ethyl paraben	-	-	-
Methyl paraben		-	-
Propyl paraben		-	
Heterocyclic aromatic amines			
Harman	-		-
3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)		-	
Phytoestrogens			
Enterolactone		-	-
Enterodiol	-		
2-Hydroxy-4-metoxybenzophenone (Benzophenone-3)		-	-
Pesticides			
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid		-	
Perfluorooctanoic acid			-
Perfluoroundecanoic acid		-	-
Perfluorodecanoic acid	-	-	-
Polychlorinated Biphenyls			
PCB156			-
PCB157			-

PCB194		-	
3,3',4,4',5,5' hxcb	-		-

+ positive association; - negative association

To check the validity and robustness of these findings among adults, some significant factors from my multivariate analysis were re-evaluated on a different cohort of adults using merged data from NHANES 1999/2000, 2007/2008 and 2015/20016. Among the significant factors associated with overweight, 7 were validated at FDR <5% as seen in table 15.

Table 15: Validated factors associated with overweight among adults after adjusting for covariates

Environmental factors	**Overweight**	
	OR (95% CI)	**Q values**
Iron	0.633(0.447-0.898)	0.0383
Gamma tocopherol	1.846(1.473-2.314)	<.0001
Vitamin D	0.576(0.411-0.807)	0.0113
25-hydroxyvitamin D3	0.636(0.468-0.864)	0.0203
Phosphorus	0.231(0.090-0.592)	0.015
Chloride	1.074(1.018-1.133)	0.0383
Perfluoroundecanoic acid	0.618(0.484-0.788)	0.0013

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Among factors associated with obesity, 34 were validated at FDR <5% as shown in table 16.

Table 16: Validated factors associated with obesity among adults after adjusting for covariates

Environmental factors	**Obesity**	
	OR (95% CI)	**Q values**
Cadmium[a]	0.511(0.284-0.919)	0.0432
Lead[a]	0.695(0.552-0.876)	0.0076
Butyl paraben[a]	0.848(0.758-0.949)	0.0118
Ethyl paraben[a]	0.848(0.758-0.949)	0.0118
Methyl paraben[a]	0.764(0.704-0.829)	<.0001

Propyl paraben[a]	0.824(0.768-0.883)	<.0001
Enterolactone[a]	0.831(0.753-0.916)	0.0009
1-napthol[a]	0.836(0.734-0.953)	0.0168
3-fluorene[a]	0.819(0.701-0.957)	0.0251
2,4,5-trichlorophenol[a]	0.564(0.391-0.814)	0.0076
Folate[a]	0.528(0.398-0.701)	<.0001
Vitamin B12[a]	0.537(0.430-0.671)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)[a]	0.564(0.482-0.661)	<.0001
4-pyridoxic acid[a]	0.735(0.614-0.880)	0.0031
Iron	0.25(0.185-0.339)	<.0001
Gamma tocopherol[a]	3.534(2.522-4.952)	<.0001
Vitamin D[a]	0.231(0.159-0.337)	<.0001
25-hydroxyvitamin D3[a]	0.303(0.210-0.437)	<.0001
epi-25-hydroxyvitamin D3[a]	0.463(0.367-0.585)	<.0001
Phosphorus	0.13(0.024-0.693)	0.0322
Copper[b]	1.01(1.003-1.018)	0.0162
PCB66[a]	4.917(1.999-12.099)	0.0021
PCB74[a]	1.627(1.108-2.388)	0.0264
PCB105[a]	2.233(1.131-4.408)	0.0382
1,2,3,4,6,7,8 hpcdd[a]	2.042(1.482-2.813)	<.0001
1,2,3,4,6,7,8,9 ocdd[a]	1.617(1.148-2.279)	0.0161
1,2,3,4,7,8 hcxdf[a]	1.551(1.155-2.083)	0.0118
3,3',4,4',5 pncb[a]	1.367(1.088-1.716)	0.0168
Beta-hexachlorocyclohexane[a]	1.869(1.349-2.591)	0.0009
Heptachlor Epoxide[a]	2.137(1.237-3.694)	0.0162
3,3',4,4',5,5' hxcb$_a$	0.482(0.293-0.793)	0.0118
Oxychlordane	1.777(1.124-2.811)	0.0273
p,p' DDT[a]	1.653(1.066-2.563)	0.0432
Perfluoroundecanoic acid[q]	0.645(0.464-0.898)	0.0203

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Among factors associated with abdominal obesity, 14 were validated at FDR <5% as shown in table 17.

Table 17: Validated factors associated with abdominal obesity among adults after adjusting for covariates

Environmental factors	**Abdominal Obesity**	
	OR (95% CI)	**Q values**
Cadmium[a]	0.468(0.285-0.768)	0.0098
Ethyl paraben[a]	0.875(0.791-0.968)	0.0316
Methyl paraben[a]	0.686(0.588-0.801)	<.0001
Enterolactone[a]	0.859(0.780-0.946)	0.0078
Folate[a]	0.746(0.589-0.945)	0.0467
Vitamin B12[a]	0.542(0.415-0.708)	<.0001
Vitamin B6(Pyridoxal 5'-phosphate)[a]	0.608(0.512-0.722)	<.0001
Iron	0.302(0.179-0.508)	<.0001
Gamma tocopherol[a]	2.709(2.164-3.390)	<.0001
Vitamin E[a]	2.145(1.649-2.792)	<.0001
Vitamin D[a]	0.324(0.226-0.463)	<.0001
25-hydroxyvitamin D3[a]	0.397(0.271-0.581)	<.0001
epi-25-hydroxyvitamin D3[a]	0.541(0.413-0.708)	<.0001
Phosphorus [a]	0.123(0.038-0.393)	0.0017

[a]adjusted for all covariates except for physical activities, limitations and screen time
[b]no adjustment of covariates

Comparing significant factors across populations (children/adolescents and adult), 5 factors were consistently associated with overweight among children and adults as shown in table 18.

Table 18: Factors associated with overweight among children and adults after adjusting for covariates

Environmental factors	**Children/adolescents**	**Adults**
	OR (95% CI)	**OR (95% CI)**
Gamma tocopherol	1.557(1.142-2.124)	1.797(1.539-2.097)
trans-b-carotene	0.508(0.409-0.631)	0.744(0.684-0.810)
total b-Carotene	0.461(0.334-0.636)	0.694(0.616-0.782)
cis-b-carotene	0.551(0.425-0.714)	0.66(0.603-0.723)

b-cryptoxanthin	0.658(0.529-0.818)	0.76(0.671-0.860)

As presented in table 16, gamma tocopherol was associated with increased odds of overweight among children and adults whereas trans-b-carotene, total b-carotene, cis-b-carotene, b-crytoxanthin and 25-hydroxyvitamin D3 served as protective factors. Other factors were associated with overweight in a different way among children/adolescents and adults. Likewise, 19 factors were associated with obesity across both populations as seen in table 19.

Table 19: Factors associated with obesity among children and adults after adjusting for covariates

Environmental factors	**Children/adolescents OR (95% CI)**	**Adults OR (95% CI)**
Lead	0.739(0.623-0.877)	0.722(0.608-0.858)
2-napthol	1.71(1.454-2.011)	1.29(1.061-1.568)
Vitamin B12	0.203(0.124-0.333)	0.605(0.517-0.707)
4-pyridoxic acid	0.626(0.465-0.842)	0.813(0.739-0.894)
Vitamin C	0.444(0.296-0.668)	0.591(0.521-0.670)
Iron	0.409(0.232-0.718)	0.397(0.351-0.449)
manganese	3.88(2.483-6.063)	1.628(1.171-2.262)
Gamma tocopherol	8.297(5.683-12.114)	4.445(3.564-5.543)
d-Tocopherol	1.841(1.476-2.297)	2.357(1.882-2.954)
a-carotene	0.67(0.544-0.826)	0.543(0.495-0.596)
trans-b-carotene	0.259(0.185-0.363)	0.418(0.376-0.464)
total b-Carotene	0.152(0.074-0.315)	0.395(0.344-0.454)
cis-b-carotene	0.256(0.176-0.373)	0.323(0.287-0.365)
b-cryptoxanthin	0.502(0.354-0.712)	0.446(0.393-0.507)
Lutein	0.183(0.088-0.384)	0.316(0.215-0.467)
cis- Lutein/Zeaxanthin	0.225(0.114-0.443)	0.236(0.161-0.344)
Combined Lutein/zeaxanthin	0.276(0.166-0.458)	0.346(0.286-0.418)
Zeaxanthin	0.238(0.159-0.357)	0.511(0.375-0.695)
Copper	1.024(1.014-1.035)	1.018(1.014-1.021)

Based on comparison, 2-napthol, manganese, gamma tocopherol, d-tocopherol and copper were positively associated with obesity across both populations while lead, vit B12, 4-pyridoxic acid, vit C,

iron, metabolites of carotene, b-cryptoxanthin, lutein, zeaxanthin, metabolites of vit D and perfluorodecanoic acid were negatively associated with obesity across populations. Across both populations, 20 factors were statistically associated with abdominal obesity as seen in Table 20.

Table 20: Factors associated with abdominal obesity among children and adults after adjusting for covariates

Environmental factors	**Children/Adolescents OR (95% CI)**	**Adults OR (95% CI)**
Harman	0.709(0.552-0.912)	0.731(0.579-0.922)
Enterolactone	0.761(0.623-0.930)	0.822(0.729-0.927)
2-napthol	1.572(1.342-1.841)	1.246(1.048-1.481)
2-phenanthrene	2.055(1.437-2.938)	1.468(1.145-1.883)
1,3,7-trimethyluric acid	1.22(1.029-1.414)	1.306(1.148-1.485)
1,3,7-trimethylxanthine(caffeine)	1.258(1.075-1.473)	1.23(1.049-1.441)
Lead	0.796(0.691-0.916)	0.693(0.616-0.780)
Vitamin B12	0.384(0.245-0.603)	0.561(0.483-0.652)
Vitamin C	0.514(0.370-0.713)	0.602(0.519-0.698)
Iron	0.489(0.282-0.796)	0.58(0.513-0.656)
Gamma tocopherol	4.267(2.783-6.542)	2.89(2.522-3.312)
a-carotene	0.745(0.647-0.858)	0.651(0.602-0.704)
trans-b-carotene	0.396(0.306-0.502)	0.533(0.485-0.586)
total b-Carotene	0.282(0.179-0.446)	0.499(0.418-0.595)
cis-b-carotene	0.397(0.295-0.534)	0.475(0.419-0.539)
b-cryptoxanthin	0.648(0.504-0.833)	0.508(0.455-0.568)
Lutein	0.353(0.197-0.632)	0.487(0.371-0.639)
cis- Lutein/Zeaxanthin	0.339(0.206-0.560)	0.39(0.309-0.491)
Combined Lutein/zeaxanthin	0.466(0.305-0.712)	0.498(0.427-0.580)
Copper	1.023(1.011-1.035)	1.015(1.011-1.020)

Among factors associated with abdominal obesity across both populations, 2-napthol, 2-phenanthrene 1,3,7-trimethyluric acid, 1,3,7-trimethylxanthine(caffeine), gamma tocopherol, and copper had positive

associations. Table 21 summarizes the factors that were significantly associated with overweight, general and abdominal obesity in both children/adolescents and adults.

Table 21: Factors associated with overweight, general obesity and abdominal obesity in both children/adolescents and adults after adjusting for covariates

Environmental Factors	**Obesity measures using BMI**		**Waist to height ratio**
	Overweight	Obese	Abdominal Obesity
Positive Associations			
Metals			
Manganese		+	
Copper		+	+
Vitamins			
Gamma tocopherol	+	+	+
d-Tocopherol		+	
Polycyclic aromatic hydrocarbons			
2-napthol		+	+
2-phenanthrene			+
Caffeine metabolites			
1,3,7-trimethyluric acid			+
1,3,7-trimethylxanthine(caffeine)			+
Negative Associations			
Metals			
Iron		-	-
Lead		-	-
Vitamins			
Vitamin B12		-	-
4-pyridoxic acid		-	

Vitamin C		-	-
a-carotene		-	-
trans-b-carotene	-	-	-
total b-Carotene	-	-	-
cis-b-carotene	-	-	-
b-cryptoxanthin	-	-	-
Lutein		-	-
cis- Lutein/Zeaxanthin		-	-
Combined Lutein/zeaxanthin		-	-
Zeaxanthin		-	
Heterocyclic aromatic amines			
Harman			-
Phytoestrogens			
Enterolactone			-

+ positive association; - negative association

Table 22 summarizes the total number of factors that were associated with childhood obesity as well as adulthood obesity. Of the 288 environmental factors evaluated, 75 factors were associated with childhood obesity while 110 factors were associated with adulthood obesity. In total, 185 factors were associated with either childhood or adulthood obesity.

Table 22: Total number of environmental factors positively and negatively associated with both childhood and adulthood obesity after adjusting for covariates

Environmental factors	Childhood Obesity	Adulthood obesity	Total
Positive	21	61	82
Negative	54	49	103
Total	75	110	185

Chapter 5

Discussion

In this dissertation, I conducted an EWAS evaluating hundreds of environmental factors to ascertain their association with childhood obesity. Childhood obesity was measured in two ways-using BMI and waist to height ratio. I found some positive and negative associations between these factors and obesity. To test the validity and robustness of my findings, I also validated some of my findings across a different cohort of children/adolescents and adults. I will focus on factors that were associated with childhood obesity and are considered novel based on a comprehensive literature review of environmental factors. Then I will extensively discuss factors that were consistently significant in both children/adolescents and adult population. This will show the consistent presence of these factors during childhood and adulthood. More so, these factors will provide a pathway to disease prevention and treatment. Meanwhile, there is sufficient evidence that childhood obesity will lead to adulthood obesity [13-17]. I will finally present the strengths and limitations of my study.

Factors associated with childhood obesity

Metals

In this study, I found that higher concentrations of beryllium (OR: 3.305 CI: 1.460-7.479) were positively associated with childhood obesity. To my knowledge, this is a novel finding as no study has evaluated this factor in relation to childhood obesity. Beryllium is a metal commonly found in petroleum, coals, volcanic dusts, and rocks. Due to its ability to increase firmness and durability of other metals, it is widely produced and used in the industries and this increases their emissions into the environment. It has been detected in the air, water, soil, foods (such as carrots and corn) and cigarette smoke [388]. Human exposure to this metal is through inhalation, ingestion and dermal contact. There is a substantial evidence linking beryllium exposure to lung diseases and different forms of cancers [389];

however, nothing is known about its relationship with obesity. One plausible mechanism for the observed relationship in this study may be linked to the fact that beryllium is a potential inhibitor of various enzymes such as adenosine triphosphate. When this happens, many metabolic processes may be disrupted [390], increasing the risk of obesity. Further investigation is needed to better understand how this metal contributes to the etiology of obesity.

More so, I found that higher concentrations of platinum (OR: 1.346 CI: 1.107-1.636) were positively associated with childhood obesity. To my knowledge, this also is a novel finding as no study has evaluated this factor in relation to childhood obesity. Platinum is a metal found naturally in the earth's crust. Due to its unique properties, platinum is used in chemical, petroleum and pharmaceutical industries which also increases their emissions into the environment and human exposure. Significant concentrations have been detected in the air as well as in the soil. Human exposure is through inhalation, dermal contact and ingestion. With substantial evidence, platinum has been associated with bronchitis, asthma, and contact dermatitis [391]. While there is no biological mechanism explaining the role of this metal in the etiology of obesity, there is a growing evidence that platinum may elicit stress and secrete proinflammatory cytokines [392] which could result to obesity. This finding needs to be further confirmed and metabolic studies conducted to better understand the impact of platinum on childhood obesity.

Vitamins

In this study, higher levels of gamma- tocopherol (OR: 8.297 CI: 5.683-12.114) and delta- tocopherol (OR: 1.841 CI:1.476-2.297) were positively associated with childhood obesity. To my knowledge, this also is a novel finding as no study has evaluated these factors in relation to childhood obesity. Gamma

and delta tocopherol are forms of vitamin E [364]. These factors are also seen in adulthood and is associated with adulthood obesity. Further explanation on plausible mechanisms by which these factors might contribute to obesity is presented in the other section.

Heterocyclic aromatic amines

In this study, I found that higher concentrations of 2-Amino-9H-pyrido (2,3-b) indole (A-a-C) [OR: 1.323 CI: 1.083-1.617] and 2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C) [OR: 2.799 CI: 1.442-5.433] were positively associated with childhood obesity. This finding is also novel as no studies have been done on these factors in relation to childhood obesity. These factors are heterocyclic aromatic amines formed during the combustion of tobacco. Due to its lipophilic nature, evidence indicates its tendency to accumulate in fat cells, however, its effect on adipogenesis is unknown. In the adipose tissue, a few studies have indicated the capabilities of these chemicals to induce changes in gene related to diabetes, cancers and inflammation [301, 302]. For example, these compounds are metabolized to form intermediates (electrophilic N-oxidized metabolites) that react with DNA to form persistent adducts, which can lead to mutations and risk of hepatocellular cancers as well as digestive tract cancers [393, 394]. While the role of these chemicals on obesity is unknown, one plausible biological mechanism for the observed association with childhood obesity could be linked to its ability to induce oxidative stress [394]. There is a growing evidence that obesity could also be as a result of oxidative stress [395, 396]. Further studies are warranted to confirm this and better understand the metabolic effects of these compounds.

Polycyclic aromatic hydrocarbons

In this study, I found that higher concentrations of the metabolite of fluorene, 9- fluorene (OR: 1.509 CI: 1.230-1.851) and the metabolite of phenanthrene, 4-phenanthrene (OR: 2.828 CI: 1.632-4.899)

were positively associated with childhood obesity. To my knowledge, this is the first study to evaluate the impact of these specific metabolites of fluorene and phenanthrene on childhood obesity. Fluorene and phenanthrene are polycyclic aromatic hydrocarbons formed by the incomplete combustion of organic materials. When formed, they persist in the environment. Human exposure is through inhalation of cigarette smoke, fossil fuels and vehicle exhaust, as well as the ingestion of grilled meats and contaminated foods such as pickled foods, bread products, and milk. As polycyclic aromatic hydrocarbons, they are known to be carcinogenic and are suspected to disrupt the endocrine system. A few studies examining the impact of the other metabolites of fluorene and phenanthrene found a positive association between 1- & 2-phenanthrene and obesity among children and adolescents [153, 269]. The biological mechanism for action is their ability to disrupt metabolism or lipid homeostasis through the activation of nuclear hormone proliferator-activated receptor gamma (PPARγ), which promotes lipid accumulation [397]. While this is the first study on these specific metabolites of fluorene and naphthalene, it is assumed that the plausible mechanism for the observed relationship in this study will be similar to the already known mechanism for the other metabolites of these compounds. Further investigation is required for these compounds to better understand their role on obesity.

Caffeine

In this study, higher levels of 1,3,7-trimethyluric acid (OR: 1.22 CI: 1.029-1.414) and 1,3,7-trimethylxanthine(caffeine) (OR: 1.258 CI: 1.075-1.473) were positively associated with childhood obesity. 1,3,7-trimethyluric acid is a metabolite of caffeine and is also known as trimethyluric acid and 8-oxy-caffeine. 1,3,7-trimethylxanthine, on the other hand, is commonly known as caffeine. Caffeine is naturally found in plants such as coffee beans, tea leaves, cocoa beans, and kola nuts [398].While the role of caffeine intake on obesity has been evaluated by previous studies, findings have been inconclusive, and this may be due to how caffeine intake was assessed. To my knowledge, this is first

study to use biomarkers to estimate caffeine intake while evaluating its role on obesity. These factors are also seen in adulthood and is associated with adulthood obesity. Further explanation on them and the plausible mechanisms by which they might contribute to obesity is presented in the other section.

In conclusion, findings of this exploratory study reveal that beryllium, platinum, gamma-tocopherol, delta-tocopherol, 2-Amino-9H-pyrido (2,3-b) indole (A-a-C), 2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C), 9-fluorene, 4-phenanthrene, 1,3,7-trimethyluric acid and 1,3,7-trimethylxanthine(caffeine) are positively associated with childhood obesity. These novel findings are of public health significance since these factors are potentially modifiable risk factors of childhood obesity and they are valuable for prevention and reducing the risk of obesity among U.S. children and adolescents. Meanwhile, there is a rising prevalence of childhood obesity among this population, hence there is a need to understand factors responsible for the etiology of childhood obesity. Exposures to some of these factors are mainly from vehicle exhaust, tobacco combustion, tea, and contaminated air and water. They may have the capability of eliciting stress, inhibiting enzymes needed for metabolic processes or disrupting lipid homeostasis which subsequently increases the risk of obesity. Further investigation is needed to confirm the associations between these factors and childhood obesity while understanding their mechanism of action.

Factors consistently associated with childhood and adulthood obesity

Factors considered protective against obesity

Vitamins

In this study, I found that higher concentrations of b-cryptoxanthin (OR: 0.502 CI:0.354-0.712), trans-beta carotenes (OR: 0.259 CI: 0.185-0.363), cis-beta carotenes (OR: 0.256 CI: 0.176-0.373), a-carotene

(OR: 0.67 CI: 0.544-0.826), lutein (OR: 0.183 CI: 0.088-0.384), and zeaxanthin (OR: 0.238 CI: 0.159-0.357) were protective against obesity. These factors are otherwise called carotenoids and are mostly found in fruits and vegetables such as mangoes, carrots, kale, yams, sweet potatoes, papaya, spinach, watermelon, tomatoes, bell peppers, and in some animal products such as eggs and salmon. Briefly, carotenoids are pigments found in the cells of plants, bacteria, and algae. They are responsible for the red, yellow, and orange colors found in most of our fruits and vegetables [399]. They are classified as carotenes (which includes β-carotene, α-carotene and β-cryptoxanthin) and xanthophylls (which includes lutein, zeaxanthin, meso-zeaxanthin, astaxanthin and canthaxanthin). They have the ability to generate vitamin A and its metabolite (retinoic acid). While my findings are consistent with evidence from both animal and human studies [400-405], a few studies indicated that serum concentrations of some of these carotenoids are relatively low in obese people compared to normal people [406, 407] and this may be due to the sequestration of some of these compounds in body fat compartments [408]. Findings from Canas et al. [409] showed that the administration of supplements rich in carotenoids increased serum levels of these carotenoids and was accompanied by reduced body mass index score and waist to height ratio. The association with BMI score and waist to height ratio remained significant even after controlling for diet and physical activity. The plausible pathway for this effect could be linked to their action in promoting fatty acid oxidation in adipocytes and other tissues as well as their involvement in adipocytes differentiation and proliferation which therefore reduces the risk of obesity [410, 411].

I also found that higher concentrations of vitamin B12 (OR: 0.203 CI: 0.124-0.333) were protective against obesity. This finding is supported by evidence from other studies [412-414]. While there have not been systematic/extensive metabolic studies on how vitamin B12 could reduce the risk of obesity, one plausible explanation for this association could be their effect on metabolism. Vitamin B12 an essential vitamin found in foods obtained from animals such as eggs, meats (chicken, beef, liver, lamb),

and dairy products [415], is seen to be an important cofactor in the pathways controlling energy production/availability and caloric use in the body. It is involved in the Krebs cycle, a series of chemical reactions that release stored energy through fats, proteins and carbohydrate metabolism [416]. It actually serves as a cofactor of methylmalonyl CoA mutase which leads to succinyl CoA, an intermediate reaction in the energy production pathway of the Krebs cycle. Vitamin B12 also contributes to the production of red blood cells which are essential for the production of energy carrier Adenosine Triphosphate (ATP). It is also involved in epigenetic modulation processes including DNA methylation, synthesis and repair [417]. The deficiency of this vitamin is known to lead to anemia which is associated with fatigue and lack of interest to exercise [418], which could subsequently lead to weight gain. Also, a study by Allin et al., [419] indicated a positive association between lower serum concentrations of this vitamin and higher body mass index (BMI). Among obese individuals, a few studies have indicated that serum concentration of vitamin B12 is generally low and this may be due to decreased dietary intake or absorption, increased catabolism, or sequestration in adipose tissue [420, 421], however with the administration of vitamin B12 supplements a significant decrease in weight gain was observed [412]. The biological mechanism involving vitamin B12 and the reduction of the body weight/ risk of obesity needs further investigation.

I also found that higher concentrations of vitamin C (OR: 0.444 CI: 0.296-0.668) were protective against obesity. This finding is supported by evidence from other studies [422-424]. Johnston et al.[423] found that plasma vitamin C was inversely associated with BMI especially among women after controlling for age, body mass and vitamin C supplement use. Likewise Canoy et al.[424] found an inverse association between plasma vitamin C and abdominal obesity ascertained by waist-hip circumference after controlling for age, supplement use, social class, BMI and smoking. Several studies found that the administration of vitamin C supplement was significantly associated with weight loss in obese children

[425] and adults [426] while Bahadoran et al. [427] showed that it prevented weight and abdominal fat gain after a 3-yr follow up in adults. Vitamin C is an essential vitamin found in our fruits and vegetables and is required for proper immune function. It is beneficial effect on the reduction/prevention of obesity can be associated with its antioxidant capabilities [428]. As obesity has been associated with oxidative stress through mitochondrial dysfunction and overproduction of reactive oxygen species (ROS), studies have indicated that vitamin C inhibits ROS overproduction as well as reduces other oxidative stress markers such as C-reactive protein plasma level, cobalt-albumin binding score and 8-iso-prostaglandin F2 α, β [429, 430]. It has also been shown to inhibit glucocorticoid release from adrenal glands which could act as a protective effect over weight gain [431]. It is also shown to inhibit the secretion of leptin and glucose metabolism, which helps to reduce oxidative stress, thus reducing the risk of obesity. Evidence also shows that it reduces the secretion/expression of inflammatory markers in the adipose tissue, which helps to prevent/reduce risk of obesity [428, 432].

I also found that higher concentrations of 4-pyridoxic acid (OR: 0.626 CI: 0.465-0.842) were protective against obesity. 4-pyridoxic acid is a major catabolic product of vitamin B6 and serves as a clinical marker to ascertain an individual's vitamin B6 status [433]. Vitamin B6 is an essential vitamin found in meats (such as turkey, pork, & beef), nuts (like pistachios), chickpeas, potatoes, dark chocolate, and fortified breakfast cereals [434]. It is important in amino acid, glucose and lipid metabolism as well as in gene expression and hemoglobin synthesis and function [434]. My study findings conflict with other studies that found a positive association between vitamin B6 and obesity [435-438], however, this may be due to how this vitamin was measured. Other studies made use of questionnaires that may not adequately reveal the actual amount of vitamin ingested. Meanwhile, there is evidence indicating that the use of questionnaires is subject to recall bias which could lead to the under/overestimation of vitamin intake [167]. When this happens, study findings may be biased. My study, on the other hand, assessed

vitamin intake through its measurement in blood. This was important to avoid the self-report bias associated with the use of questionnaire data to determine exposures. An animal study by Liu et al. [439] indicated that vitamin B6 may play a protective role in reducing obesity by preventing insulin resistance and lipid accumulation. Further investigation on the mechanism of vitamin B6 in the prevention of obesity is required.

Metals

I also found that higher concentrations of iron (OR: 0.409 CI: 0.232-0.718) were protective against obesity. This finding is consistent with findings from other studies. Tussing-Humphreys et al.,[440] found that elevated iron levels were associated with weight loss and this was due to reduced serum levels of systemic iron regulatory protein hepcidin. Komolova et al.[441] revealed that a low concentration of iron could lead to obesity and this may be through its association with sedentary behavior. It is evident that iron deficiency leads to anemia which subsequently leads to a lack of energy that encourages sedentary behaviors. While the mechanism explaining the relationship between iron and obesity remains unclear, numerous studies have predicted a lower concentration of this compound in obese population and this may be due to adipose tissue inflammation, increased levels of hepcidin from inflammation-mediated dysregulation of systemic iron metabolism or even poor iron diet [442-445]. Nevertheless, further investigation is needed to better understand the relationship between iron levels and obesity as iron is an essential element needed for enzyme activity, hemoglobin synthesis, redox reaction, cell proliferation and apoptosis in various cells as well as in maintaining other vital functions.

I also found that higher concentrations of lead (OR: 0.739 CI: 0.623-0.877) were protective against obesity. Lead is a heavy metal found in the air, soil, water and even foods such as root vegetables, and fruits (when absorbed by these plants) and has been associated with neurological disorders [446, 447].

The negative association between lead and obesity found in my study is supported by findings from other studies [57, 240, 448-450] but conflicts with others [142, 446, 451-453]. Scinicariello et al.[448] found that increased levels of lead in the blood were associated with decreased body weight in both children and adolescents as well as in adults after adjusting for age, gender, race/ethnicity, calorie intake, TV and video game use, poverty income rate, education, alcohol consumption, physical activity, and serum cotinine. Likewise, Padilla et al.[57] found a negative association between lead levels and body mass index as well as waist circumference among adults. On the contrary, Huzior-Balajewicz et al.[142] found no association between blood lead levels and obesity among children. Ronco et al.[143] also did not find any association between lead and fat mass percentage among adults. While the inconsistencies in study findings make the association between lead and obesity inconclusive, a few animal studies support an inverse relationship between lead levels and body weight. Donald et al.[454] found that lead exposure induced weight loss among mice. Likewise, Leasure et al., [145] found that higher levels of lead exposure led to a decrease in body weight among rats. The plausible mechanism by which lead could reduce the risk of obesity may be through its effect on corticosterone which disrupts the hypothalamic-pituitary-adrenal (HPA) axis [448, 455, 456]. Lead exposure decreases the basal level of corticosterone [457, 458]. Meanwhile, increased basal levels of corticosterone have been associated with the etiology of obesity. Chronically elevated stress increases glucocorticoids which in turn inhibits the normal stress-response network and recent evidence has indicated a positive association between stress and obesity [456, 459]. Another plausible mechanism could be their effect on appetite. There is evidence that lead exposure/poisoning could lead to loss of appetite which could subsequently lead to weight loss [460]. While there is evidence of the negative association between lead exposure and obesity, exposure to lead is still highly discouraged because of its adverse effects on the central and peripheral nervous system.

Heterocyclic aromatic hydrocarbon

I also found that higher concentrations of Harman (OR: 0.709 CI: 0.552-0.912) were protective against obesity. Harman is also known as harmane, and it is a heterocyclic amine defined as a chemical compound formed as a result of high temperature cooking of foods and smoking of plants. This chemical compound is found in coffee, cooked meats and fish, sauces like soy sauce, toasted bread, cigarette smoke and alcoholic beverages [461]. To my knowledge, this is the first study to examine the role of harmane on obesity. Other studies on harmane found that it is positively associated with essential tremors and Parkinson's disease [462]. It also has several effects on the central nervous system [463]. Celikyurt et al.[464] found that the administration of harmane affected learning and memory functions in rats. While there no studies examining the role of this chemical on obesity, the only plausible mechanism for this association could be from their effect on monoaminergic pathways. A few studies have indicated that harmane is a monoamine oxidase inhibitor [465, 466] which tends to reduce the risk of obesity. Meanwhile, monoamine oxidase is known to be highly expressed in adipocytes and when activated generates hydrogen peroxides that are associated with oxidative stress. It is also known to increase adipogenesis and fat deposition which increases the risk of obesity [467]. With the impact of harmane on this enzyme, further investigation is required to better understand how it reduces obesity.

Phytoestrogen

I also found that higher concentrations of enterolactone (OR: 0.761 CI: 0.623-0.930) were negatively associated with obesity. This finding is consistent with findings from other studies [260, 468-471]. Frankenfeld [468] found that higher concentrations of enterolactone were associated with a lower likelihood of being overweight and obese among children and adults after controlling for covariates. Likewise, Xu et al. [260] found an inverse relationship between enterolactone and obesity but among

adult men only [260]. Enterolactone is a phytoestrogen found in vegetables, cereals, flaxseed, sesame seeds, fruits and berries [472] and they are known to affect energy metabolism in a positive way. While the plausible mechanism through which enterolactone exert beneficial effect on obesity may be unclear, evidence shows their effects on lipid metabolism, insulin-stimulated glucose oxidation, low-density lipoproteins oxidation, and basal metabolic rate could explain their positive effect on obesity [78]. More so, findings from Prasad [473] suggest that the antioxidation capabilities of enterolactone could also play a huge part in reducing the risk of obesity. As a result of their structural similarities to endogenous estrogens, there is growing evidence that their effect on obesity may also be through both estrogen receptor- and non-estrogen receptor-mediated mechanisms [78, 474]. Further investigation is needed to better understand how this chemical compound plays a positive role in the prevention of obesity.

In conclusion, findings of this exploratory study suggest that vitamin B6, B12 and C as well as carotenoids, enterolactone, harmane and iron are protective factors of obesity that is seen both in childhood and adulthood. That is to say that continuous exposure of these factors during childhood and adulthood may reduce or even eliminate the risk of obesity as well as adverse effects associated with obesity. As previously noted, these factors act by promoting fatty acid oxidation in adipocytes, inhibiting the overproduction of ROS that have been associated with oxidative stress, reducing the secretion of leptin, other oxidative stress and inflammatory markers found in adipose tissues and preventing lipid accumulation. These findings, therefore, suggest that both prevention and treatment strategies of obesity should focus on these factors. Exposures to these factors can be from foods, however, supplements have been seen to be more effective in achieving the desired effect, in this case, reducing weight gain or the risk of obesity. Intervention should therefore be focused on them.

Significant factors considered as risk factors of obesity

Vitamins

While there are negative effects of some factors on obesity as seen above among both children/adolescents and adults, I will further discuss on factors that were positively associated with obesity among the same population in the following paragraphs. I found higher levels of gamma-tocopherol (OR: 8.297 CI: 5.683-12.114) and delta- tocopherol (OR: 1.841 CI:1.476-2.297) to be positively associated with obesity. To my knowledge, this is a novel finding as no study has evaluated these factors in relation to obesity. As previously indicated, gamma and delta tocopherol are forms of vitamin E [364]. Briefly, vitamin E occurs in 8 different forms- 4 tocopherols (alpha, beta, delta, and gamma) and 4 tocotrienols (alpha, beta, delta, and gamma) and all of which are known to be antioxidants. However, gamma- tocopherol has less antioxidation capabilities compared to the other forms of vitamin E [364]. Humans do not make their own vitamin E, rather they acquire it from plants, the only source of this vitamin. Among all the forms of vitamin E, gamma-tocopherol is more prevalent (70%) in plants and hence in products made from them, e.g. supplements and processed foods [475]. As such, gamma-tocopherol is abundant in U.S. diets. Examples of plants products rich in vitamin E include grains (e.g. corn, rice), nuts (e.g. peanuts, pecan, Brazilian, walnut), seeds (e.g. sesame), vegetables/vegetable products (e.g. peppers, edamame, peas, potatoes, lettuce, onions), seed oils (e.g. soybean, corn, cottonseed, palm, sesame), legumes (e.g. beans, lentils) and so on [476-478]. While this vitamin is naturally found in foods, higher concentrations are evident in processed foods. They serve as additives to inhibit rancidity and prolong the shelf life of processed foods [479]. Already, there is sufficient evidence linking the intake of processed foods to obesity. Processed foods may lead to 'mindless eating', disrupting the internal processes that control satiety and appetite [480, 481]. More so, with its high glycemic load, human insulin response is often increased thus promoting weight gain by

directing nutrients away from oxidation in muscle and towards storage in fat tissues [482-485]. Despite the identification of the different forms of vitamin E, gamma- and delta- tocopherols are not extensively studied to know their role in human health which could either be negative or positive. A few studies have indicated that they are well absorbed and accumulate to a significant degree in human tissues [364, 486]. Both experimental and epidemiological studies have indicated their effects in reducing the risk of cancer [487-489] and cardiovascular diseases [490, 491]. However, findings from clinical trials have been contradictory [490, 492-495]. Lonn et al.[494] found that the use of vitamin E supplementation increased the risk of heart failure and did not prevent any cancer and other major cardiovascular events among patients with vascular disease or diabetes mellitus. Likewise, Virtamo et al.[495] found that vitamin E supplementation did not have any significant effect on coronary heart disease outcomes among participants. There is growing evidence that gamma-tocopherol may be associated with type 2 diabetes [33], however, the mechanism for action is unclear. Meanwhile there is evidence from in vitro studies that vitamin E may have pro-oxidation capabilities [496-499] which may increase the risk of oxidative stress and hence obesity. Further research is needed to elucidate the role of these forms of vitamin E on obesity.

Metals

I also found that higher serum concentrations of copper (OR: 1.024 CI: 1.014-1.035) were positively associated with obesity. In spite of this finding, the literatures have generated mixed results [500-503]. In support, Fan et al. [500] found a positive association between serum copper levels and obesity among U.S. children/adolescents after controlling for age, race, PIR, screen time and calorie intake. While on the contrary, Fang et al. [503] found no association between copper and obesity among Chinese adults after controlling for smoking, alcohol, physical activity, medication use. The inconsistency in study findings may be due to small sample size and insufficient adjustment of covariates. In this dissertation, a

lot more covariates such as age, sex, race/ethnicity, creatinine, calorie intake, physical activity, screen time (TV hours & computer/video games hours), limitation to physical activities, and socioeconomic status were adjusted in my analysis. This was important to know the actual impact of copper on obesity measures. More so, there was a larger sample size due to the use of nationally representative data of the U.S. population. Copper is an essential element in the human body with antioxidation capabilities and is necessary for cellular respiration and the formation of myelin and melanin [504, 505]. It occurs naturally in the environment and spreads throughout the environment through human activities. Copper is used both in the industries and in agriculture and these increase their concentrations in air, water and soil. Due to its presence in water and soil, it is also found in proteins (such as liver, oysters, lobsters), nuts (such as almonds and cashew nuts), sesame seeds, and vegetables (such as mushrooms, Swiss chard, kale, and spinach) but in small quantity. Exposure to this compound is mainly through inhalation and ingestion. While the underlying mechanism for which copper may be contributing to obesity remains unclear, one plausible explanation for my findings could be linked to its pro-oxidation capabilities. Copper in higher concentrations is seen to be associated with oxidative stress/damage by catalyzing reactive nitrogen species (RNS) as well as highly reactive hydroxyl radical (OH−) which is a species of reactive oxygen species (ROS). This therefore contributes to obesity as evidence shows that obesity could also be as a result of oxidative stress and inflammation [395, 396]. Meanwhile, 90% of copper in the blood is in the form of ceruloplasmin (Cp) and evidence shows that elevated plasma concentration of Cp is associated with obesity due to its pro-oxidation capabilities as well [506, 507]. It increases the release of nitric oxide (NO^-) which reacts with superoxide anion (O_2^-) to generate peroxynitrite anion (ONOO−), an important RNS. When there is ROS/RNS imbalance, oxidative stress is induced which may activate transcription factors (including activator protein-1 (AP-1), hypoxia-inducible factor 1-alpha (HIF-1α), and nuclear factor kappa-B (NF-κ B)) and the signaling pathways that upregulate pro-

inflammatory cytokines and chemokines (interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor (TNF), interleukin-8 (IL-8)). When these happen, obesity-related inflammation is induced [501, 505].

I also found that higher serum concentrations of manganese (OR: 3.88 CI: 2.483-6.063) were positively associated with obesity. Looking at the research literatures, there are evidences of mixed results [500, 508-511]. Fan et al. [500] found that the highest concentrations of manganese in the blood was positively associated with obesity among U.S. children and adolescents. Zhou et al. [510] on the other hand, found an inverse association between manganese and abdominal obesity among Chinese men [510]. Choi and Kim [512] found no association between manganese and obesity among Korean men. To my knowledge, the positive association between manganese and obesity seen among U.S adults in my study is the first and only study in the U.S. Meanwhile, the discrepancies in these studies findings may be due to how manganese intake was assessed or the fact that adequate factors that may affect the association were not adjusted. In this dissertation, manganese intake was assessed through its measurement in the blood. In the other studies, questionnaires were used to ascertain manganese intake. This is problematic as evidence shows that it is prone to recall bias, leading to the under/overestimation of compound which could also bias study findings [167]. Manganese is a metal and an essential micronutrient found both in our environment (water) and foods such as grains, nuts, rice, tea, bread, leafy vegetables (spinach), beans and legumes. It is needed for protein, fat and carbohydrate metabolism as well as the regulation of other physiological processes such as immune function and skeletal development [513-515]. Its deficiency has been linked to reproductive dysfunction and other metabolic disorders [513-516]. While evidence shows that manganese has antioxidation capabilities and plays significant roles in cancer prevention, reduction of oxidative stress and inflammatory responses [515, 517], it is unclear how it may contribute to the etiology of obesity. Findings from Li & Lang [509]

indicated that excessive exposure to manganese may increase the generation of reactive oxygen species in the mitochondria which results in further oxidative stress [509]. With growing evidence suggesting that oxidative stress and the overproduction of reactive oxygen species could be associated with obesity [395, 396], further investigation is needed to explore the role of manganese in obesity.

Polycyclic aromatic amines

I also found that higher concentrations of 2-napthol (OR: 1.71 CI: 1.454-2.011) and 2-phenanthrene (OR: 2.055 CI: 1.437-2.938) were positively associated with obesity. These findings are supported by evidence from other studies [153, 269, 518]. Its association with adulthood obesity has not been explored by other studies, making my study the first to evaluate these factors on adulthood. This implies that these factors are also present in adulthood. Among childhood studies, Scinicariello & Buser [153] found that 2-napthol, total naphthalene metabolites, total polycyclic aromatic hydrocarbons (PAH) metabolites and 1- & 2- phenanthrene were positively associated with BMI z-score, waist circumference and obesity among children and adolescents after adjusting for age, race/ethnicity, sex, urinary creatinine, poverty: income ratio (PIR), cotinine, C-reactive protein (CRP), calorie intake, and television, video game, and computer use. Likewise, Kim et al.[269] found that total naphthalene metabolites (1-naphthol & 2-naphthol) and total PAH metabolites were positively associated with adiposity measures after controlling for similar covariates among children and adolescents. Polycyclic aromatic hydrocarbons are groups of chemicals formed mostly as a result of the incomplete combustion of organic materials and are ubiquitous. They are present in the air, vehicle exhaust, refined fossil fuels, cigarette smoke, contaminated water, milk and food products such as grilled/charred foods as well as processed foods. The simplest forms of PAH include naphthalene, anthracene and phenanthrene and they all have one to two metabolites when ingested or inhaled. 2-napthol and 2-phenanthrene are considered the major metabolites of naphthalene and phenanthrene. The negative impact of PAH can be

linked to its endocrine disrupting abilities. They act by increasing the expression of the nuclear hormone proliferator-activated receptor gamma (PPARγ) and by serving as thyroid hormone receptor antagonist [83, 120, 121]. This, therefore, disrupts the endogenous hormone signaling and metabolism which subsequently affects adipogenesis by promoting the accumulation of lipids in adipocytes [153]. It is seen to be associated with the development of oxidative stress [519] and inflammation [520, 521], which could subsequently lead to obesity.

Caffeine metabolites

I also found that higher concentrations of 1,3,7-trimethyluric acid (OR: 1.22 CI: 1.029-1.414) and 1,3,7-trimethylxanthine (OR: 1.258 CI: 1.075-1.473) were positively associated with obesity. 1,3,7-trimethyluric acid is a metabolite of caffeine and is also known as trimethyluric acid and 8-oxy-caffeine. 1,3,7-trimethylxanthine, on the other hand, is commonly known as caffeine. Caffeine is naturally found in plants such as coffee beans, tea leaves, cocoa beans, and kola nuts [398]. It serves both as additives in beverages and as drugs in its entirety or in conjunction with other compounds [522]. It has been associated with mental, behavioral, and developmental effects as well as cardiovascular disease and hypertension [523-526]. While there are numerous studies on its role in obesity, study findings have been inconclusive. My study findings are supported by evidence from a few studies [166, 527] while in confliction with others [160-165]. Berkey et al.[165] found no association between caffeine and weight gain while on the other hand, Lopez-Garcia found a positive association between caffeine and obesity among adults. The discrepancies in findings may be due to how caffeine intake was ascertained. The use of questionnaires by these authors to ascertain intake could bias study findings because evidence shows that the use of questionnaires is subject to recall bias thus leading to the under/overestimation of caffeine intake [167]. More so, the use of caffeine-containing foods to ascertain its intake has been shown to confound any identified link to health effect [168-170]. While the plausible mechanism by which

caffeine increases the risk of obesity is not explicit, animal studies indicate that caffeine alters both glucose and lipid metabolic pathways which subsequently may increase the risk of obesity [528, 529]. In a recent study by Calamaro et al.[530], it was found that intake of caffeinated beverages was associated with inadequate sleep. Numerous evidences have associated inadequate sleep with increased risk of obesity through its alteration of the hormonal mechanism that regulate carbohydrate metabolism and appetite. It also increases the risk of obesity by increasing the time available to eat [165, 531, 532]. Further investigation on how caffeine may increase the risk of obesity is highly needed as caffeine is widely consumed in the U.S.

In conclusion, findings of this exploratory study also suggest that factors such as the two forms of vitamin E- gamma- and delta-tocopherols, as well as manganese, copper, caffeine, 2-napthol and 2-phenanthrene are positively associated with obesity and these compounds tend to be present during childhood and adulthood. While these findings need to be further investigated and confirmed, elimination or reduction of exposures to these factors may play a huge role in reducing the risk of obesity. As previously noted, these factors have pro-oxidation capabilities and the ability to disrupt the endogenous hormone signaling and metabolism pathways which subsequently increases the risk of obesity. Exposures to some of these factors are mainly from vehicle exhaust, refined fossil fuels, cigarette smoke, and contaminated air and water, hence the reduction or elimination of these exposures is highly recommended. Consumption of foods and intake of supplements are also sources of exposure to these factors, which indicates that I cannot rule out the effect of foods in contributing to the etiology of obesity. However, the intake of supplements can be minimized. Further investigation is needed on supplements, especially vitamin E to rule out the adverse effects associated with them as well as to ensure that their benefits (if any) is worth their consumption.

Public health significance

The findings of these exploratory studies are of public health significance because the prevalence of obesity among children/adolescents and adults keeps rising. While some of the factors identified in this study are novel and need to be further confirmed, their identification alone provides preliminary evidence on how obesity should be approached in terms of treatment or prevention to promote both individual and population health. For example, this study found that some metals, heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, forms of vitamin E and caffeine intake were positively associated with obesity. This means that interventions should focus on eliminating or reducing human exposures to these factors which may help prevent or reduce the occurrence of obesity in the U.S. Interventions could be in the form of community education on the possible impacts of these factors and where they can be found, policy change that will disallow the proximity of residential areas to highways and providing caution to the intake of caffeine as well as vitamin E supplements. This study also found that certain vitamins and phytoestrogens were negatively associated with obesity, hence they serve as protective factors of obesity. This also suggests that efforts should be aimed at encouraging the U.S. population to take advantage of these factors to prevent obesity during childhood and adulthood.

This study is not without limitations. First, this is a cross-sectional study and causality cannot be inferred. Likewise, reverse causality cannot be ruled out. However, this study design served to generate numerous hypotheses that can be tested using prospective studies or clinical trials. Second, although the use of biological markers is ideal to accurately determine exposure, it does not provide any information on when the exposure occurred or the duration of exposure. However, the presence of these factors (especially the significant ones) indicate their presence in child and adulthood. More so, some of the environmental factors had a non-detect values. The absence of an environmental factor does not mean an

exposure did not occur. Each environmental factor has different half-lives and clearance rates. Thus, no or negative association could be a result of the non-detection of these factors or sampling timing. More studies are needed to confirm the role of these factors on obesity. Third, not all participants in the NHANES have available measurements on all the environmental factors evaluated. More so, with some factors present in more surveys than others; validation of some significant associations was not possible. Those findings could be considered false positive findings however, we cannot rule out their possibility of being true positives. Therefore, more studies are required to validate those findings. Fourth, I adjusted for all covariates for some of the analyses, but for others, I could not because either the covariate was not measured or there was not enough sample size that could allow for the adjustment of all covariates. More studies with larger sample size are needed to confirm these associations while adjusting for all covariates. Finally, I cannot claim that the comprehensive analysis of the environmental factors found in NHANES datasets covers all the environmental factors. Factors measured in the NHANES dataset are as a result of prevalence, feasibility of measurement, and assumed influence on population health.

Despite these limitations, my study had major strengths. First, this study has shown a comprehensive and systematic approach to identifying strong associations between environmental factors and obesity. Instead of focusing on a few environmental factors at a time, this approach allowed the evaluation of multiple environmental factors to determine their impacts on obesity while controlling for covariates. This approach has revealed novel associations that may have been overlooked, providing direction for future studies of potential risk or protective factors of obesity. That is to say that, this approach allowed the creation of robust hypotheses regarding associations of environmental factors with obesity which needs to be further elucidated in future researches. This, therefore, will shed more light on the etiology of obesity with corresponding implications for the prevention and treatment of obesity. This systematic

approach also confirmed other already known associations implied by other epidemiological studies. It is believed that when there are small changes at the individual level across the population, there will be a significant impact on population health. Second, the comprehensive and systematic use of hundreds of environmental factors together with the accounting of multiple hypotheses reduced false positive reporting and selective bias which are evidenced in other epidemiological studies of environmental factors. Finally, the findings of this study are generalizable following the use of nationally representative data of the U.S. population.

Recommendations for Future Research

Based on the findings of this study, the following recommendations for research are suggested. First, further research is required to confirm the novel positive associations seen among some metals, vitamins, heterocyclic aromatic amines, polycyclic aromatic hydrocarbons as well as caffeine metabolites and obesity. Confirmation of these positive associations with obesity is important as they will provide a clearer and in-depth understanding of the etiology of obesity. More so, it will provide a pathway for prevention as well as treatment among children and adults that could be exposed to these factors. Second, with evidences that there could be gender disparity, as high prevalence of obesity is seen more in girls than in boys [21-23], future research should examine if these factors act differently based on gender to induce obesity. There is need for metabolic studies to understand how these factors act in human body. Finally, knowing that the influence of some of these factors may differ at different ages and stages of development, future research is needed to account for these differences.

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Appendix

Environmental factors and how they were measured.

Environmental factors	where it was measured	How it was measured
Creatinine	urine	Creatinine was analyzed using a Jaffé rate reaction. Here, creatinine reacted with picrate in an alkaline solution to form a red creatinine-picrate complex. The reaction was measured with a CX3 analyzer. The rate of the color development was measured 25.6 sec after sample injection at 520 nm and at 560 nm. The rate difference between the two wavelengths is proportional to the concentration of creatinine in the reaction cup.

lead	blood	Cadmium and lead are simultaneously measured in whole blood using adaptations of the methods of Miller et al, Parsons et al, and Stoeppler et al. Cadmium and lead quantification is based on the measurement of light absorbed at 228.8 nm and 283.3 nm, respectively, by ground-state atoms of cadmium and lead from either an electrodeless discharge lamp (EDL) or hollow cathode lamp (HCL) source. Human blood (patient or study) samples, bovine blood quality control pools, and aqueous standards are diluted with a matrix modifier (nitric acid, Triton X-100, and ammonium phosphate). The cadmium and lead contents are determined on a PerkinElmer Model SIMAA 6000 simultaneous multi-element atomic absorption spectrometer with Zeeman background correction.
Cadmium		
Folate	blood	Both serum folate and vitamin B12 are measured by using the Bio-Rad Laboratories "Quantaphase II Folate/vitamin B12" radioassay kit Five folate forms, 5-methyl-tetrahydrofolate, folic
5-Methyl-tetrahydrofolate		
Folic acid		
5-Formyl-tetrahydrofolate		

Tetrahydrofolate		acid, 5-formyl-tetrahydrofolate, tetrahydrofolate, 5,10-methenyl-tetrahydrofolate, and an oxidation product of 5-methyl-tetrahydrofolate called MeFox (pyrazino-s-triazine derivative of 4-α-hydroxy-5-methyl-tetrahydrofolate) are measured by isotope-dilution high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS)
5,10-Methenyl-tetrahydrofolate		
Mefox oxidation product		
Vitamin B12		
Vitamin B6(Pyridoxal 5'-phosphate)	blood	Vitamin B6, in the form of PLP, and the metabolite 4-PA are measured by reversed-phase HPLC using fluorometric detection at 325 nm excitation and 425 nm emissions.
4-pyridoxic acid		
Vitamin C	blood	Vitamin C is measured by isocratic HPLC with electrochemical detection at 650 mV.
Total mercury (organic + inorganic)	blood	Total mercury in whole blood is measured by flow injection cold vapor atomic absorption analysis with on-line microwave digestion, based on the method by T. Guo and J. Bassner.
inorganic mercury		
Mercury, ethyl		
Mercury, methyl		

Iron	blood	Iron is measured by a modification of the automated AAII-25 colorimetric method, which is based on the procedures of Giovaniello et al. (1) and of Ramsey (2). The method has been modified further to be performed on an Alpkem Flow Solutions IV (rapid-flow analysis) system.
Selenium	blood	Selenium is measured in serum by atomic absorption spectrometry in a procedure based on the methods described by Lewis et al. (1) and by Paschal and Kimberly (2).
manganese	blood	measured using mass spectrometry after a simple dilution sample preparation step.
Copper	blood	Copper and Zinc are measured using the inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS), a multi-element analytical technique capable of trace level elemental analysis.
Zinc		
Gamma tocopherol		measured using high performance liquid chromatography with multiwavelength
d-Tocopherol		
Retinyl Palmitate		
Retinyl stearate		
a-Tocopherol		

a-carotene	blood	photodiode-array absorbance detection.
trans-b-carotene		
total b-Carotene		
cis-b-carotene		
a-Cryptoxanthin		
b-cryptoxanthin		
g-tocopherol		
cis-Lycopene		
total Lycopene		
Lutein		
cis- Lutein/Zeaxanthin		
Combined Lutein/zeaxanthin		
trans-lycopene		
Phytofluene		
Phytoene		
Zeaxanthin		
Total (cis- and trans-) Lycopene		
Vitamin A		
Vitamin E		measured using high performance liquid chromatography with photodiode array detection
Vitamin D	blood	measured using a standardized liquid chromatography-tandem mass spectrometry (LC-MS/MS) method
25-hydroxyvitamin D2		
25-hydroxyvitamin D3		
epi-25-hydroxyvitamin D3		

Calcium, total	urine	Calcium reacts with o-cresolphthalein complexone in the presence of 8-hydroxyquinoline to form a purple chromophore. The intensity of the final color reaction is proportional to the amount of calcium in the specimen.
Phosphorus	urine	Inorganic phosphorus reacts with ammonium molybdate in an acidic solution to form ammonium phosphomolybdate with a formula of (NH4) 3 [PO4 (MoO3)12]. The ammonium phosphomolybdate is quantified in the ultraviolet range (340 nm), utilizing a sample blanked endpoint method.
Sodium	urine	Sodium, Potassium, and Chloride were measured using the Ion-Selective Electrode (ISE)
Potassium		
Chloride		
Cytomegalovirus Ig G	blood	CMV specific IgG was measured with an ELISA by Quest International, Inc., Miami FL. Sera with values near the ELISA cutoff (approx. 5.2% of total) were confirmed with a second ELISA assay by bioMerieux, Inc., Durham, NC.

Cytomegalovirus Ig M	blood	Screening of specimens for CMV IgM was performed using ELISA assay by Diamedix, Miami Lakes, FL and the automated analyzer MAGO. Confirmatory testing for CMV IgM was performed on specimens within a wide range above and below the MAGO test cutoff using the VIDAS ELISA assay by bioMerieux, Inc., Durham, NC.
Dioxins, Furans and Coplanar PCB	Blood	These analytes are measured in serum by high-resolution gas chromatography/ isotope-dilution high-resolution mass spectrometry (HRGS/ID-HRMS).
Hepatitis A antibody	blood	Measured by using solid-phase competitive enzyme immunoassay (EIA) (1-3).
Hepatitis B core antibody	blood	The Ortho HBc ELISA Test System was used and is a qualitative enzyme-linked immunosorbent assay (ELISA) for the detection of total antibody to anti-HBc in human serum or plasma.
Barium	urine	Element measured in urine by inductively coupled plasma-mass spectrometry (ICP-MS) on the method by Kevin J. Mulligan et al.
Beryllium		
Cadmium		
Cobalt		
Cesium		
Molybdenum		
Manganese		

Lead		
Platinum		
Antimony		
Tin		
Strontium		
Thalium		
Tungsten		
Uranium		
Nitrate	urine	Samples were analyzed for perchlorate, thiocyanate and nitrate using ion chromatography tandem mass spectrometry
Thiocyanate		
Perchlorate		
DEET	urine	measured using two mass spectrometric methods
DEET acid		
Desethyl hydroxy DEET		
Malathion diacid		
3,5,6-trichloropyridinol		
Oxypyrimidine		
Paranitrophenol		
Dimethylphosphate	urine	Urinary organophosphate pesticides use azeotropic codistillation of urine, derivitization, gas chromatography-tandem mass spectrometric method (GC-MS/MS).
Diethylphosphate		
Dimethylthiophosphate		
Diethylthiophosphate		
Dimethyldithiophosphate		
Diethyldithiophosphate		
4-fluoro-3-phenoxybenzoic acid	urine	measured using two mass spectrometric methods
dibromovinyl-dimeth prop carboacid(ug/L) or cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid		
trans dichlorovnl-dimeth carboacid(ug/L) or trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid		
3-phenoxybenzoic acid		
2,5-dichlorophenol		

O-Phenyl phenol		
2,4-dichlorophenol		
2,4,5-trichlorophenol		
2,4,6-trichlorophenol		
Hexachlorobenzene	blood	Thirty-eight ortho-substituted polychlorinated biphenyls (PCBs), 13 persistent chlorinated pesticides, and selected pesticide metabolites are measured in serum by high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry (HRGC/ID-HRMS).
Beta-hexachlorocyclohexane		
Gamma-hexachlorocyclohexane		
p,p'-DDE		
p,p'-DDT		
o,p'-DDT		
Oxychlordane		
Trans-nonachlor		
Heptachlor Epoxide		
Mirex		
Aldrin		
Dieldrin		
Endrin		
Mono(carboxynonyl) phthalate	urine	Human urine samples were processed using enzymatic deconjugation of the glucuronides followed by solid-phase extraction.
Mono(carboxyoctyl) phthalate		
Mono-n-butyl phthalate		
Mono-cyclohexyl phthalate		
Mono-ethyl phthalate		
Mono-(2-ethyl)-hexyl phthalate		
Mono-isononyl phthalate		
Mono-n-octyl phthalate		
Mono-benzyl phthalate		
Mono-n-methyl phthalate		
Mono-(3-carboxypropyl) phthalate		
Mono-(2-ethyl-5-hydroxyhexyl) phthalate		
Mono-(2-ethyl-5-oxohexyl) phthalate		
Mono-isobutyl pthalate		
Mono-2-ethyl-5-carboxypentyl phthalate		
MHNC -monohydroxyisononyl ester		

Cyclohexane 1,2-dicarboxylic acid monohydroxy isononyl ester		
Daidzein	urine	HPLC-MS/MS method was used, and the method uses enzymatic deconjugation of the phytoestrogens followed by solid-phase extraction and reverse-phase HPLC to resolve the analytes.
o-Desmethylangolensin (O-DMA)		
Equol		
Enterodiol		
Enterolactone		
Genistein		
1-napthol	urine	The procedure involves enzymatic hydrolysis of urine (to hydrolyze PAH conjugates), solid-phase extraction, derivatization, and analysis using capillary gas chromatography combined with high-resolution mass spectrometry (GC/HRMS). This method uses isotope dilution with 13C-labeled internal standards.
2-napthol		
3-fluorene		
2-fluorene		
3-phenanthrene		
1-phenanthrene		
2-phenanthrene		
1-pyrene		
9-fluorene		
4-phenanthrene		
2 & 3-Hydroxyphenanthrene		
Acrylamide	blood	The method used to measure these compounds was based on modified Edman reaction, which uses the effect of N-alkylated amino acids being able to form Edman products in neutral or alkaline conditions without changing the pH to acidic conditions required in conventional Edman reaction procedures
Glycidamide		
2,2',4,4',5,5'-hexabromobiphenyl	blood	This is done by measuring the concentration in serum/plasma through
2,2',4-tribromodiphenyl ether		
2,4,4'-tribromodiphenyl ether		

2,2',4,4'-tetrabromodiphenyl ether		the use of solid-phase extraction (SPE) and subsequent sample clean-up
2,2',3,4,4'-pentabromodiphenyl ether		
2,2',4,4',5-pentabromodiphenyl ether		
2,2',4,4',6-pentabromodiphenyl ether		
2,2',4,4',5,5'-hexabromodiphenyl ether		
2,2',4,4',5,6'-hexabromodiphenyl ether		
2,2',3,4,4',5',6-heptabromodiphenyl ether		
2,3',4,4'-tetrabromodiphenyl ether		
Diphenyl phosphate	urine	The method uses 0.4 mL urine and is based on enzymatic hydrolysis of urinary conjugates of the target analytes, automated off-line solid phase extraction, reversed phase high-performance liquid chromatography separation, and isotope dilution-electrospray ionization tandem mass spectrometry detection
Bis(1,3-dichloro-2-propyl) phosphate		
Bis(1-chloro-2-propyl) phosphate		
Bis(2-chloroethyl) phosphate		
Dibutyl phosphate		
2,3,4,5-tetrabromobenzoic acid		
Bisphenol A	urine	Bisphenol A (BPA) and Alkylphenols (APs) have been previously measured in biological matrixes by using gas chromatography (GC) or high-performance liquid chromatography (HPLC) coupled with different detection techniques.
Bisphenol F		
Bisphenol S		
Triclocarban		
2-Hydroxy-4-metoxybenzophenone (Benzophenone-3)		
4-tert-octylphenol		
2,4,4'-Trichloro-2'-hydroxyphenyl ether (Triclosan)		
Butyl paraben		
Ethyl paraben		
Methyl paraben		
Propyl paraben		
Melamine	urine	measured using a high-performance liquid chromatography system (HPLC)
Cyanuric acid		

Perfluorooctanoic acid	blood	The test principle utilizes solid phase extraction-high performance liquid chromatography-turboionspray ionization-tandem mass spectrometry (SPE-HPLC-TCI-MS/MS) for the quantitative detection of PFCs
Perfluorooctane sulfonic acid		
Perfluorohexane sulfonic acid		
2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid		
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid		
Perfluorodecanoic acid		
Perfluorobutane sulfonic acid		
Perfluoroheptanoic acid		
Perfluorononanoic acid		
Perfluorooctane sulfonamide		
Perfluoroundecanoic acid		
Perfluorododecanoic acid		
n-perfluorooctanoic acid (n-PFOA) (ng/mL)		
Branch perfluorooctanoic acid isomers (Sb-PFOA)		
n-perfluorooctane sulfonic acid		
n-perfluorooctane sulfonic acid		
D. Farinae IgE antibody	blood	Serum samples were analyzed for total and allergen specific IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan).
D. Pteronyssinus IgE antibody		
Cat IgE antibody		
Dog IgE antibody		
Cockroach IgE antibody		
Alternaria IgE antibody		
Peanut IgE antibody		
Egg IgE antibody		
Milk IgE antibody		
Ragweed IgE antibody		
Rye grass IgE antibody		
Bermuda grass IgE antibody		
Oak IgE antibody		
Birch IgE antibody		
Shrimp IgE antibody		
Aspergillus IgE antibody		
Thistle IgE antibody		

Mouse IgE antibody		
Rat IgE antibody		
1-methyluric acid	urine	Caffeine and 14 of its metabolites are quantified in urine by use of high-performance liquid chromatography-electrospray ionization-tandem quadrupole mass spectrometry (HPLC-ESI-MS/MS) with stable isotope labeled internal standards.
3-methyluric acid		
7-methyluric acid		
1,3-dimethyluric acid		
1,7-dimethyluric acid		
3,7-dimethyluric acid		
1,3,7-trimethyluric acid		
1-methylxanthine		
3-methylxanthine		
7-methylxanthine		
1,3-dimethylxanthine(theophylline)		
1,7-dimethylxanthine(paraxanthine)		
3,7-dimethylxanthine(theobromine)		
1,3,7-trimethylxanthine(caffeine)		
5-acetylamino-6-amino-3-methyluracil		
	urine	measured by an isotope-dilution high-performance liquid chromatography/electrospray ionization tandem mass spectrometry (ID HPLC-ESI MS/MS)
2-Amino-9H-pyrido[2,3-b]indole (A-a-C)		
2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1)		
2-Aminodipyrido[1,2-a:3',2'-d] imidazole (GLU-P-2)		
Harman		
2-amino-3-methyl-3H-imidazo[4,5-f]quinolone		
2-Amino-3-methyl-9H-pyriodo[2,3-b]indole (MeA-a-C)		
Norharman		
2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)		
3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)		
1-Methyl-3-amino-5H-pyrido[4,3-b]indole (Trp-P-2)		