DISSERTATION

ASSOCIATIONS OF SELF-REPORTED AND BIOLOGICAL MARKERS OF SECONDHAND SMOKE EXPOSURE WITH METABOLIC DISORDERS IN CHILDREN AND ADULTS

Submitted by

Brianna Faye Moore

Department of Environmental and Radiological Health Sciences

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Doctoral Committee:

Advisor: Jennifer L. Peel
Co-Advisor: Maggie L. Clark

Annette Bachand
Tracy L. Nelson
Stephen J. Reynolds

ABSTRACT

ASSOCIATIONS OF SELF-REPORTED AND BIOLOGICAL MARKERS OF SECONDHAND SMOKE EXPOSURE WITH METABOLIC DISORDERS IN CHILDREN AND ADULTS

Background: Obesity and obesity-related metabolic disorders are now global crises (Stevens et al. 2012). High caloric diets and low physical activity levels are accepted as risk factors for metabolic disorders (Newbold et al. 2009; Park et al. 2003); however, the extent of the prevalence of metabolic disorders cannot be entirely explained by these risk factors (Holtcamp 2013; Thayer et al. 2012). Evidence is building that exposures to chemicals in the environment may play a role in the onset of metabolic disorders (Behl et al. 2013). Specifically, exposure to secondhand smoke is an important and common exposure that may be involved. A limited number of studies have reported a relationship between exposure to secondhand smoke (SHS) and obesity (von Kries et al. 2008), metabolic syndrome (Weitzman et al. 2005) and hyperglycemia (Clair et al. 2011). Furthermore, metabolic disorders are likely influenced by the joint effect of diet and exposure to SHS (Behl et al. 2013), yet the combined influence of these risk factors has not been investigated thoroughly.

Objectives: The overall scope of the dissertation was to evaluate the association between exposure to SHS and metabolic disorders among both children and adults. In addition to using a self-report and a reliable and established biomarker (cotinine), we evaluated exposure to SHS using NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a novel and potentially more accurate indicator of exposure than self-report or cotinine (Avila-Tang et al. 2012). The central

hypothesis was that higher exposure to SHS is associated with an increased prevalence of metabolic disorders. We also investigated the joint effects of diet and exposure to SHS on metabolic disorders. The dissertation evaluated this hypothesis among two distinct populations: 1) a sample of U.S. children, ages 6-19 years, from the 2007- 2010 National Health and Nutrition Examination Survey (NHANES), and 2) a subset of lifetime non-smokers selected from a nested case-control study of cardiovascular disease within the Singapore Chinese Health Study. Project 1 evaluated the independent effects of exposure to SHS and the joint effects of diet and exposure to SHS on obesity among U.S. children, ages 6-19 years. Project 2 evaluated the independent effects of exposure to SHS and the joint effects of diet and exposure to SHS on metabolic syndrome among U.S. children, ages 12-19 years. Project 3 evaluated the independent effects of exposure to SHS and the joint effects of diet and exposure to SHS on glycated hemoglobin (HbA1c) levels among U.S. children, ages 12-19 years. Project 4 evaluated the independent effects of exposure to SHS and the joint effects of diet and exposure to SHS on HbA1c levels among a sample of non-smoking Singaporean adults of Chinese ethnicity, aged 45–74 years at time of enrollment.

Methods: We characterized exposure to SHS using a novel biomarker (NNAL) (Projects 1, 2, & 3 only), an established biomarker (cotinine), and self-report of household smokers. Logistic regression models examined the association of exposure to SHS on the prevalence of obesity (Project 1) and metabolic syndrome (Project 2) among U.S. children. Multiplicative interaction by diet was assessed by introducing product terms of dichotomized exposure to SHS variables and dichotomized individual nutrients (dietary fiber, vitamin C, vitamin E, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], and omega-3 polyunsaturated fatty acids) into separate logistic regression models. Additive interaction was calculated within these

models by calculating the relative excess risk due to interaction (RERI). The RERI is defined as $OR_{11}–OR_{10}–OR_{01}+1$, where an RERI value of 0 suggests a perfectly additive interaction. Linear regression models examined the relationship between exposure to SHS on HbA1c levels among U.S. children (Project 3) and Singaporean adults (Project 4). Additive interaction by diet was assessed by introducing product terms of dichotomized exposure to SHS variables and dichotomized individual nutrients (dietary fiber, vitamin C, vitamin E, EPA, DHA, and omega-3 polyunsaturated fatty acids) into separate linear regression models.

Results: Despite the relatively low proportion of children reporting living with one or more household smokers, nearly half of the children had NNAL levels above the limit of detection, indicating exposure to SHS (Projects 1, 2 and 3). An overwhelming majority (92%) of the adults had cotinine levels above the limit of detection (Project 4). Exposure to SHS was independently related to obesity (Project 1) and metabolic syndrome (Project 2) among U.S. children. Interaction results suggest that the prevalence of obesity among children with both high exposure to SHS and low levels of certain nutrients (dietary fiber, DHA, or EPA) is greater than would be expected due to the effects of the individual exposures alone (Project 1). Similarly, the joint effect between high exposure to SHS and low levels of certain nutrients (vitamin E and EPA) on metabolic syndrome risk was greater than would be expected due to the effects of the individual exposures alone (Project 2). There was limited evidence that exposure to SHS was independently related to HbA1c levels among U.S. children (Project 3) or Singaporean adults of Chinese ethnicity (Project 4). Measures of additive interaction suggest that increases in the mean HbA1c among U.S. children with both high NNAL levels and low levels of certain nutrients (dietary fiber, DHA, or vitamin C) are greater than would be expected due to the effects of the individual exposures alone

(Project 3). In general, the results were similar when exposure to SHS was examined using self-report of exposure to SHS, cotinine, or NNAL.

Discussion: Results from Project 1 are consistent with a number of epidemiologic studies that demonstrate an association between exposure to SHS and obesity among children. Similarly, Project 2 adds to the limited evidence supporting a positive association between exposure to SHS and metabolic syndrome. Conversely, epidemiologic evidence investigating the potential role of exposure to SHS on hyperglycemia is mixed and results from Projects 3 and 4 do not support the hypothesis that exposures to SHS are independently associated with HbA1c levels. Interaction results from Projects 1, 2, and 3 identified several dietary factors (dietary fiber, antioxidants, and omega-3 polyunsaturated fatty acids) that may counteract the adverse metabolic effects provoked by exposure to SHS. The identification of statistical interaction supports the biological mechanisms (i.e. inflammation, oxidative stress, and endothelial dysfunction) linking SHS and metabolic disorders. In general, the results were consistent regardless of whether exposure to SHS was determined using NNAL, cotinine, or self-report of household smokers. Since self-report is easier and less expensive to measure than cotinine and NNAL (Avila-Tang et al. 2013), one could argue that the latter is not necessary for studies evaluating this particular research question, especially among children.

Conclusions: This dissertation builds on previous research evaluating the relationships between SHS exposures and precursors to type 2 diabetes and cardiovascular disease. Furthermore, the identification of statistical interactions between diet and exposure to SHS is particularly novel and clarifies the potential biological mechanisms linking SHS to metabolic disorders. In particular, our results indicate that diets high in dietary fiber, antioxidants, or

omega-3 polyunsaturated fatty acids may inhibit the adverse metabolic responses potentially triggered by higher exposure to SHS. Prevention strategies for metabolic disorders aimed at both reducing SHS exposures and improving diets may exceed the expected benefits based on targeting these risk factors separately.

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DEDICATION

This dissertation is dedicated to my husband, Matthew Moore. Thank you for being supportive of my ambitions, for the countless hours of listening to me work out my ideas, and for helping me to find the humor in everything. I wouldn't be who I am today without you.

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CHAPTER 1

OVERVIEW OF DISSERTATION

INTRODUCTION

Summary of Literature and Rationale for Study

The obesity pandemic is a phenomenon that transcends geographic, socioeconomic, and demographic factors (Stevens et al. 2012). Worldwide, the age-standardized prevalence of obesity doubled between 1980 and 2008 (Stevens et al. 2012). By these estimates, one in nine individuals (508 million) were classified as obese in 2008 (Stevens et al. 2012). The prevalence of obesity in the United States (U.S.) is higher than any other developed country; however, the epidemic has spread to other countries as a result of the increased adoption to a Western lifestyle (Hossain et al. 2007). The emergence of the obesity epidemic is especially important to the development of metabolic syndrome (Messiah et al. 2007), a cluster of conditions including abdominal fatness, hypertension, an adverse lipid profile, and hyperglycemia, which may increase the risk of multiple chronic diseases (Wilson et al. 2005). Furthermore, rapid increases in the prevalence of obesity have also lead to the increased prevalence of prediabetes (Li et al. 2009), a serious and costly disease that is an important risk factor for both type 2 diabetes and coronary heart disease (Colette and Monnier 2007).

The increase in prevalence of obesity and other metabolic disorders threaten to bankrupt the healthcare system (Haslam et al. 2006). As the prevalence of metabolic disorders has increased, health care spending has also risen dramatically. Specifically, obesity accounts for 9% of all U.S. health care spending, which amounts to nearly $150 billion U.S. dollars per year (Finkelstein et al. 2009). The financial burden from metabolic disorders is also driven by the

increased risk for type 2 diabetes and cardiovascular disease (Wang et al. 2011) and health care spending is likely to rise dramatically. Specifically, diabetes-related spending in the U.S. has been projected to triple between 2009 and 2034 (Huang et al. 2009). Metabolic disorders also have substantial health consequences (Wang et al. 2011; Zhang et al. 2010). Metabolic disorders have been shown to decrease quality-of-life, productivity and overall life expectancy (Wang et al. 2011). Moreover, obesity is poised to overtake smoking as the leading preventable cause of chronic disease and premature death in the U.S. (Mokdad et al. 2004).

As the health and financial burdens resulting from metabolic disorders continue to escalate, it is now critical to identify potential intervention strategies aimed to reduce these burdens (Swinburn et al. 2011; Withrow and Alter 2011). The traditional risk factors for metabolic disorders include modifiable lifestyle factors, such as dietary composition, physical activity levels, active smoking, and weight (Newbold et al. 2009; Park et al. 2003); however, the extent of metabolic disorders observed cannot be entirely explained by these risk factors (Newbold et al. 2009). An emerging hypothesis suggests that exposures to chemicals in the environment may be involved in the onset of metabolic disorders (Holtcamp 2013; Thayer et al. 2012); specifically, exposure to SHS may play a role. Exposure to SHS is independently associated with increased inflammatory responses, oxidative stress, and endocrine disruption, and these adverse health effects could ultimately lead to obesity, metabolic syndrome, and other metabolic disorders (Barnoya and Glantz 2005; Tziomalos and Charsoulis 2004).

Research addressing the role of exposure to SHS on metabolic disorders has expanded rapidly in the past few years (Behl et al. 2013). Most research has been dedicated to addressing the role of exposure to SHS on obesity, with both epidemiologic and toxicological studies supporting a positive association between exposure to SHS and obesity (Thayer et al. 2012).

Multiple epidemiologic studies have reported that self-reported exposure to SHS was positively associated with obesity among children, ages 1-17 years (Apfelbacher et al. 2008; Chen et al. 2012; Ittermann et al. 2013; Kwok et al. 2010; Mangrio et al. 2010; McConnell et al. 2015; Pagani et al. 2015; Raum et al. 2011; von Kries et al. 2008; Wen et al. 2013; Yang et al. 2013). Furthermore, experimental animal studies have demonstrated that exposure to cigarette smoke or nicotine has negative effects on adiposity among rats (Gao et al. 2005; Holloway et al. 2005; Somm et al. 2008). Epidemiologic studies have also reported positive associations between exposure to SHS and metabolic syndrome (Weitzman et al. 2005; Xie et al. 2010) and hyperglycemia (Houston et al. 2006; Jefferis et al. 2010; Thiering et al. 2011; White et al. 2014).

Although the epidemiologic evidence is growing, the associations observed in previous studies may be limited by the methods used to assess exposure to SHS and also by the potential for uncontrolled confounding, particularly by diet. It is also possible that the joint effect of poor diet quality and SHS exposures on metabolic disorders may be more than would be expected based on the individual effects, yet no published studies have explored the potential interactions between dietary factors and exposure to SHS on metabolic disorders (Behl et al. 2013).

Specific Aims

The overall scope of the proposed study is to evaluate the association between exposure to SHS and metabolic disorders among both children and adults. In addition to using a reliable and established biomarker (cotinine), we will also quantify exposure using NNAL, a novel and potentially more accurate indicator of secondhand smoke exposure than self-report or cotinine (Avila-Tang et al. 2012). The central hypothesis is that higher exposure to SHS is associated with an increased prevalence of metabolic disorders. The proposed study will evaluate this hypothesis among two distinct populations: 1) a sample of U.S. children, ages 6-19 years, from

the 2007-2010 NHANES; and 2) a subset of lifetime non-smokers selected from a nested case-control study of cardiovascular disease within the Singapore Chinese Health Study.

Using data from NHANES, the following aims are proposed to evaluate this hypothesis:

Aim 1a: Evaluate the association between exposure to SHS (measured by urinary NNAL, serum cotinine, and self-report of household smokers) on the prevalence of overweight and obesity (as compared to underweight/normal) among 6-19 year olds, adjusting for diet, physical activity, and other potential confounders. *Hypothesis 1: High exposure to SHS is positively associated with an increase in obesity prevalence.*

Aim 1b: Investigate the interaction between diet and exposure to SHS on the prevalence of overweight and obesity among 6-19 year olds. *Hypothesis 1b: Increases in the prevalence of obesity among children with both high exposure to SHS and low levels of certain nutrients will be greater than would be expected due to the effects of the individual exposures alone.*

Aim 2a: Evaluate the association between exposure to SHS (measured by urinary NNAL, serum cotinine, and self-report of household smokers) on the prevalence of metabolic syndrome among 12-19 year olds, adjusting for diet, physical activity, and other potential confounders. *Hypothesis 2a: High exposure to SHS is positively associated with an increase in metabolic syndrome prevalence.*

Aim 2b: Investigate the interaction between diet and exposure to SHS on the prevalence of metabolic syndrome among 12-19 year olds. *Hypothesis 2b: Increases in the prevalence of metabolic syndrome among children with both high exposure to SHS and low levels of certain nutrients will be greater than would be expected due to the effects of the individual exposures alone.*

Aim 3a: Evaluate the relationship between exposure to SHS (measured by urinary NNAL, serum cotinine, and self-report of household smokers) on HbA1c, fasting plasma

glucose, and two-hour post-challenge glucose levels among 12-19 year olds, adjusting for diet, physical activity, and other potential confounders. *Hypothesis 3a: High exposure to SHS is positively related to an increase in mean HbA1c and glucose levels.*

Aim 3b: Investigate the interaction between diet and exposure to SHS on HbA1c levels among 12-19 year olds. *Hypothesis 3b: Increases in mean HbA1c levels among children with both high exposure to SHS and low levels of certain nutrients will be greater than would be expected due to the effects of the individual exposures alone.*

Using data from the Singapore Chinese Health Study, the following aims are proposed:

Aim 4a: Evaluate the relationship between exposure to SHS (measured by urinary cotinine and by self-report) and HbA1c levels among a sample of Singaporeans of Chinese ethnicity, aged 45–74 years at time of enrollment. *Hypothesis 4a: High exposure to SHS is positively related to higher HbA1c levels.*

Aim 4b: Investigate the interaction between diet and exposure to SHS on HbA1c levels. *Hypothesis 4b: Increases in mean HbA1c levels among adults with both high exposure to SHS and low levels of certain nutrients will be greater than would be expected due to the effects of the individual exposures alone.*

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

BACKGROUND

Outcome of Interest: Metabolic Disorders

The extent of metabolic disorders observed worldwide is a serious global crisis (Withrow and Alter 2011) and warrants collaborative efforts to curtail the pandemic (Swinburn et al. 2011). Metabolic disorders are associated with lifelong effects, particularly increased morbidity and mortality due to lifestyle-related diseases such as type 2 diabetes, kidney disease, and cardiovascular disease (Flegal et al. 2010). The financial burden from metabolic disorders is largely driven by the increased risk for type 2 diabetes, cardiovascular disease, and several forms of cancer (Wang et al. 2011); these chronic diseases impose considerable medical costs due to ongoing treatment (Wang et al. 2011; Zhang et al. 2010). In the U.S., the estimated health care spending of cardiovascular disease exceeds $258 billion per year (Mensah and Brown 2007) and the estimated health care spending of diabetes exceeds $176 billion per year (American Diabetes Association 2013). The estimated global health expenditure on diabetes is estimated to be at least 12% of the total health expenditure ($376 billion U.S. dollars) (Zhang et al. 2010). Beyond the direct financial burden of obesity and obesity-related diseases, other indirect costs are also incurred, such as the lost educational opportunity, the lost economic contribution, the lost days of employment by the individual or a caregiver in the family if medical attention is needed (Lobstein et al. 2004).

To decrease the health and financial burden related to obesity, the U.S. established a Healthy People 2020 goal to reduce obesity rates among U.S. adults from 33.5% to less than

30.5% (U.S. Department of Health and Human Services 2010). A similar Healthy People 2020 goal aims to reduce obesity rates among U.S. children ages 2-19 years from 16.1% to less than 14.5% (U.S. Department of Health and Human Services 2010). Furthermore, a World Health Organization (WHO) global target for 2025 aims to ensure that there is no increase in the rate of children who are overweight or obese (WHO 2012). The proposed study is designed to identify factors that contribute to the obesity epidemic, in order to identify potential intervention strategies aimed to reduce these burdens.

Obesity

Obesity was first recognized as a medical condition in which excess body fat leads to many comorbidities and premature death in the 18th century (Haslam 2007). Many of the comorbities related to overweight and obesity are lifelong and fatal, including cardiovascular disease, type 2 diabetes, respiratory illnesses, cancer, and other abnormalities (Haslam and James 2005). Obesity at the age of 40 years has also been shown to decrease life expectancy by 7 years (Peeters et al. 2003).

Clinical Expression of Obesity

Overweight and obesity is most often described through the use of body mass index (BMI), an objective approximation designed to estimate an individual's body fatness based on height and weight (Kuczmarski et al. 2002). This measure is calculated by using the standard formula, which divides weight in kilograms by height in meters squared. For U.S. adults, the weight status categories based on BMI (kg/m^2) are "underweight" (<18.5 kg/m^2), "normal" (18.5-24.9 kg/m^2), "overweight" (25-29.9 kg/m^2), and "obese" (≥30 kg/m^2).

Challenges in Assessing Obesity

Although BMI is a useful tool for approximating an individual's body fatness, BMI cut-points for obesity can vary considerably across age groups (Wang and Beydoun 2007). Consequently, different definitions for obesity have been established for different age and racial/ethnic groups. The adult BMI cut-points for overweight and obesity fail to measure body fat changes among children. Consequently, the Center for Disease Control and Prevention (CDC) growth charts were developed to be an appropriate representation of weight status among children, ages 2-20 years (CDC 2011). Childhood overweight is defined as having a BMI above the 85th percentile and below the 95th percentile and childhood obesity is defined as having a BMI at or above the 95th percentile (CDC 2011). Although the CDC cutoffs have been shown to be a sensitive and specific indicator of excess adiposity among children (Freedman and Sherry 2009), the cutoffs are somewhat arbitrary as compared to other methods of assessing obesity among children. (Cole et al. 2000) developed an international definition of overweight and obesity among children. The International Obesity Task Force (IOTF) developed BMI cut-off values for childhood overweight and obesity based on the large data sets from six countries including Brazil, Britain, Hong Kong, the Netherlands, Singapore, and the U.S. (Cole et al. 2000). These cut-off values are linked with the adult cut-off values of 25 and 30 for overweight and obesity, respectively, by age and sex (Cole et al. 2000). Despite the slight variation in cutoffs for determining overweight and obesity, there tends to be strong agreement between the CDC and IOTF definitions in the assessment of the prevalence of overweight/obesity among children (Hajian-Tilaki and Heidari 2013).

Among adults, there are also issues related to the appropriateness of the established cutoffs for defining overweight and obesity among Asian populations. Although the U.S. cut-

points for overweight and obesity are designed to characterize an individual's potential risk for chronic disease, these cut-points are not considered appropriate for characterizing risk for chronic disease among Asian populations. Therefore, the World Health Organization (WHO) has recommended lower BMI cut-offs of 23 and 27.5 to define overweight and obese in Asian populations to correspond to risk for chronic disease among Asian populations (WHO 2004).

Prevalence of Obesity

The global obesity pandemic is now a phenomenon that transcends geographic, socioeconomic, and demographic factors (Stevens et al. 2012). Worldwide, the age-standardized prevalence of obesity doubled between 1980 and 2008 (Stevens et al. 2012). By these estimates, one in nine individuals (508 million) were classified as obese in 2008 (Stevens et al. 2012). Furthermore, an estimated 170 million children, ages 2 to 18 years, are classified as overweight or obese (Swinburn et al. 2011). Although the prevalence of obesity in the U.S. is higher than any other developed country, the epidemic has spread to other countries as a result of the increased adoption to a Western lifestyle involving decreased physical activity levels and the overconsumption of readily available, energy-dense food (Hossain et al. 2007).

Hyperglycemia

Hyperglycemia is defined as having high blood glucose, a required metabolic fuel for the brain under physiologic conditions (Jellinger 2007). Hyperglycemia is related to insulin resistance, a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption (Jellinger 2007). Insulin is a hormone produced by beta cells in the pancreas which regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose (Sonksen and Sonksen 2000).

Hyperglycemia has many adverse health effects. Glucose induces vascular inflammation, which impairs the immune status of an individual by inhibiting leukocyte function (Jellinger 2007). Additionally, hyperglycemia increases the production of oxygen-derived free radicals, which induces endothelial dysfunction (Jellinger 2007). Moreover, hyperglycemia is causally related to many chronic illnesses, including diabetes (American Diabetes Association 2010; Nathan et al. 2009), metabolic syndrome (Gallagher et al. 2011; Wilson et al. 2005), and cardiovascular disease (Duckworth 2001; Gerich 2003).

Diabetes

Type 2 diabetes, previously known as noninsulin-dependent diabetes mellitus or adult-onset diabetes, is an illness marked by chronic hyperglycemia and requiring continuous medical care with risk reduction strategies to manage glycemic control and other comorbidities (American Diabetes Association 2014). Type 2 diabetes was first recognized as a serious and fatal medical condition in 1812 (Polonsky 2012). In 1910, Edward Albert Sharpey-Schafer, MD, performed a study of the pancreas, which led to the discovery of insulin (Polonsky 2012). Insulin was first used to treat diabetes in 1922 and, after one year of clinical testing, became commercially available in 1923 (Polonsky 2012). In 1970, research established an association between obesity and type 2 diabetes (Haslam 2010). Type 2 diabetes is often observed among individuals with marked obesity associated with insulin resistance (Dabelea et al. 1999; Kahn et al. 2006). Furthermore, around 60% of type 2 diabetes cases could be prevented if individuals maintained a normal weight (Hart et al. 2007). Due the risk of progression to type 2 diabetes (Abraham and Fox 2013), there has been increasing awareness of prediabetes, an intermediate medical condition that is an important risk factor for both type 2 diabetes and coronary heart

disease (Colette and Monnier 2007). Similar to type 2 diabetes, prediabetes is often observed among overweight and obese individuals (Sinha et al. 2002; Weiss et al. 2003).

It is important to distinguish the etiology of type 2 diabetes and prediabetes with that of type 1 diabetes. Type 1 diabetes, formerly known as insulin-dependent diabetes or juvenile diabetes, is distinct from type 2 diabetes and prediabetes. Type 1 diabetes is an autoimmune disease in which pancreatic beta cells are destructed, which leads to the subsequent inefficient production of insulin and the inefficient absorption of glucose (Daneman 2006). Furthermore, type 1 diabetes is a heritable disease caused by the mutation of the human leukocyte antigen (HLA) genotype and is not influenced by weight status (Daneman 2006).

Biomarkers of Hyperglycemia

There are several biological tests that can be performed to measure glucose in the blood, including glucose tests (fasting plasma glucose and 2-hour post-challenge glucose test) and the glycated hemoglobin test (American Diabetes American Diabetes Association 2014). The American Diabetic Association currently recommends that only adults and children with substantial risk for type 2 diabetes should be screened for the disease (American Diabetes Association 2015). The risk factors which warrant screening for type 2 diabetes include overweight or obese weight status, as well as having any two of the following symptoms: having a family history of type 2 diabetes in a first- or second-degree relative; being Native American, African American, Latino, Asian American, or Pacific Islander race/ethnicity; exhibiting signs of insulin resistance or conditions associated with insulin resistance (hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight); or having a maternal history of diabetes or gestational diabetes during the child's gestation (American Diabetes Association 2015).

Fasting Plasma Glucose.

The fasting plasma glucose test is a glucose test that is used to determine the amount of glucose in the blood following a fast from food (typically for 8-12 hours) prior to the test. A fasting plasma glucose ≥100 and <126 mg/dL indicates prediabetes and a fasting plasma glucose ≥126 mg/dL indicates type 2 diabetes (American Diabetes Association 2014). In order to confirm a diagnosis of prediabetes or type 2 diabetes, a second fasting plasma glucose test is required (American Diabetes Association 2015).

Two-Hour Post-Challenge Glucose.

The oral glucose tolerance test (OGTT) is a glucose test that is used to determine the amount of glucose in the blood following a fast from food (typically for 8-12 hours), followed by the administration of the glucose challenge drink containing 75g of glucose. A 2-hour post-challenge glucose level ≥140 mg/dL and <200 mg/dL indicates prediabetes and a 2-hour post-challenge glucose level ≥200 mg/dL indicates type 2 diabetes. In order to confirm a diagnosis of prediabetes or type 2 diabetes, a second OGTT is required (American Diabetes Association 2015).

Glycated hemoglobin (HbA1c).

Glycated hemoglobin (HbA1c) is an alternative measure of hyperglycemia and is also used to diagnose diabetes. Glycation is the process of glucose forming a covalent bond with a protein or lipid molecule; HbA1c is the product of glucose forming a covalent bond with hemoglobin in the erythrocytes (Sacks 2011). Since glycation takes place throughout the life span of hemoglobin, HbA1c reflects the degree of hyperglycemia during the life span of the erythrocyte, which is ~120 days (Sacks 2011), and is believed to represent the average glucose concentration over the preceding 8–12 weeks (Nathan et al. 2008). Glucose levels within the past

30 days contribute considerably more to the final level of HbA1c than do glucose levels within the past 120 days. As a result, HbA1c is considered a weighted average of glucose levels during the preceding 120 days, with plasma glucose levels in the preceding 30 days contributing 50% to the final HbA1c level and glucose levels from 90–120 days earlier contributing less than 10% (Tahara and Shima 1995). An HbA1c level ≥6.0% and <6.5% indicates prediabetes and an HbA1c level ≥6.5% indicates type 2 diabetes.

Comparison of Biomarkers

The oral glucose tolerance test (OGTT) has for many years been considered the gold standard for the diagnosis of type 2 diabetes because the 2-hour post-challenge glucose levels are a more sensitive indicator of type 2 diabetes than fasting plasma glucose levels (Sacks 2011; The International Expert Committee 2009). However, the OGTT test is time-consuming, costly, and inconvenient to the individual (Hu et al. 2010). HbA1c is now endorsed by the American Diabetes Association as a better indicator of chronic hyperglycemia than fasting or 2-hour post-challenge glucose (American Diabetes Association 2015). Furthermore, HbA1c is likely a better indicator of type 2 diabetes than glucose measurements (Bonora and Tuomilehto 2011; Hu et al. 2010; Sacks 2011). Despite the potential advantages of HbA1c over glucose measures, there are many disadvantages of HbA1c to consider.

Advantages of HbA1c over Glucose

1) HbA1c is a more stable indicator of chronic hyperglycemia. HbA1c is highly reproducible (Dunn et al. 1979; Selvin et al. 2005b), whereas fasting and 2-hour post-challenge glucose levels vary considerably in a single person from day to day. One study that analyzed repeated measurements from 685 fasting participants without diagnosed diabetes from the NHANES 1988-1994 data revealed that only 70% of people with fasting glucose >126 mg/dL on

the first test had fasting plasma glucose >126 mg/dL when analysis was repeated ~2 weeks later (Selvin et al. 2007). Similarly, the OGTT has been shown to have poor reproducibility (Kosaka et al. 1966; Mooy et al. 1996; Olefsky and Reaven 1974), even among individuals with high HbA1c levels (Ko et al. 1998).

2) HbA1c is a better indicator of type 2 diabetes. HbA1c has a strong predictive value for prediabetes and type 2 diabetes (International Expert Committee, 2009). Kohnert et al. (2007) demonstrated that HbA1c levels were better predictors of chronic sustained hyperglycemia among individuals with type 2 diabetes than fasting plasma glucose levels.

3) HbA1c is a better indicator of cardiovascular risk. HbA1c and 2-hour post-challenge glucose are more informative indicators of cardiovascular risk as compared to fasting plasma glucose (American Diabetes Association 2015). The presence of elevated HbA1c and 2-hour post-challenge glucose levels are independent risk factors for coronary heart disease, even among individuals without type 2 diabetes (Barr et al. 2009; de Vegt et al. 1999; Ikeda et al. 2013; Khaw et al. 2001; Selvin et al. 2005a). Conversely, fasting plasma glucose have very little predictive value for identifying cardiovascular risk, particularly when other cardiovascular risk factors are taken into account (Meigs et al. 2002; Park et al. 1996; Stern et al. 2002).

4*) HbA1c is not impacted by food consumption prior to testing.* While diet is an important predictor of both glucose and HbA1c (Feskens et al. 1995; Hales and Randle 1963; Sargrad et al. 2005), the consumption of certain foods or beverages on the evening before glucose testing have been shown to impact fasting and 2-hour post-challenge glucose differently than HbA1c. In a clinical trial of 12 healthy, non-diabetic males, higher 2-hour post-challenge glucose concentrations were attained when the OGTT was preceded by the high-fat, low-carbohydrate evening meal then when preceded by the low-fat, high-carbohydrate evening meal (8.8 compared

with 7.8 mmol/L, p< 0.01) (Robertson et al. 2002). Additionally, alcohol consumption on the evening before a glucose test can substantially lower plasma and 2-hour post-challenge glucose (McMonagle and Felig 1975; Turner et al. 2001). Finally, several clinical trials have demonstrated that caffeine ingestion before glucose testing can substantially raise plasma glucose (Cheraskin et al. 1967; Graham et al. 2001; Robinson et al. 2004).

5) Glucose is impacted by acute changes in extraneous factors. Fasting and 2-hour post-challenge glucose can be dramatically impacted by extraneous factors, including acute stress, exercise, smoking, and time of day the test is performed. Acute increases in cortisol levels have been shown to decrease sensitivity to insulin and impair glucose metabolism (Agwunobi et al. 2000; Rizza et al. 1982) and individuals who are worried about glucose testing or experience a stressful situation in the hours preceding glucose testing may exhibit higher glucose levels (Bonora and Tuomilehto 2011). Exercise can temporarily lower plasma glucose and brief exercise (e.g. <15 minutes) on the evening or morning of glucose testing could result in an reading that is not representative of an individual's usual glucose levels (Adams 2013). Smoking acutely impairs glucose tolerance and sensitivity to insulin. One experimental study among 20 chronic smokers reported that the OGTT results were significantly higher when the test was performed within 30 minutes of smoking 3 cigarettes as compared to a control test (mean for smoking OGTT: 26 mmol/l, 95% CI: 23–28; mean for control OGTT: 22 mmol/l; 95% CI: 19–24; p<0.01) (Frati et al. 1996). Finally, time of day the glucose test is performed impacts the results because fasting and 2-hour post-challenge glucose levels have a diurnal variation (Monnier et al. 2003; Troisi et al. 2000).

6) The HbA1c test is quicker, easier, and more convenient. A considerable advantage of an HbA1c test is that is it quicker, easier, and more convenient for the patient than the fasting or two-hour post-challenge glucose test (Bonora and Tuomilehto 2011).

Disadvantages of HbA1c over Glucose

1) Diabetes is clinically defined by high blood glucose and not by the glycation of proteins. HbA1c measures glycation of proteins in the body, which is not equivalent to directly measuring hyperglycemia through glucose measures (Bonora and Tuomilehto 2011). High HbA1c levels are observed in response to high blood glucose levels and is considered to be an appropriate indicator of hyperglycemia (American Diabetes Association 2015).

2) Screening with HbA1c may delay diagnosis of type 2 diabetes. In general, the HbA1c criteria for type 2 diabetes diagnoses fewer adults and children with type 2 diabetes, as compared to the fasting or 2-hour post-challenge glucose criteria (Cowie et al. 2010; Nowicka et al. 2011; Picon et al. 2012). HbA1c may miss a large proportion of asymptomatic early cases of diabetes that can only be identified by the OGTT (Bonora and Tuomilehto 2011). Using data obtained from 1998-2004 NHANES, Cowie et al. (2010) reported that HbA1c detected only 30% of type 2 diabetes cases among individuals who did not have a confirmed diagnosis, whereas the fasting and 2-hour post-challenge glucose detected 50% and 90% of undiagnosed diabetes, respectively.

3) HbA1c may not be an appropriate biomarker for diagnosing type 2 diabetes among children. The usefulness of HbA1c as a diagnostic tool for type 2 diabetes among children is currently under debate. Some researchers have enthusiastically recommended the use of HbA1c to diagnose type 2 diabetes among obese children (Kapadia and Zeitler 2012; Shah et al. 2009), while others have questioned the usefulness of HbA1c among children due to low sensitivity and specificity using the cutoffs for prediabetes and type 2 diabetes established for adults by the

American Diabetes Association (Lee et al. 2011; Nowicka et al. 2011). Despite the unclear evidence, the American Diabetes Association continues to recommend the use of HbA1c among children (American Diabetes Association 2015).

3) HbA1c varies across racial/ethnic groups. Strong evidence exists for the heterogeneity of HbA1c levels across racial/ethnic groups. In a meta-analysis of 11 epidemiologic studies, Kirk et al. (2006) demonstrated that non-Hispanic blacks had HbA1c levels that were 0.65% higher than non-Hispanic whites but no difference in fasting plasma glucose levels. It is likely that the differences in HbA1c levels are a results of the biological differences in hemoglobin glycation (Cohen et al. 2010).

4) The correlations between HbA1c, fasting plasma glucose and 2-hour post-challenge glucose are weak. The relationships between glucose measurements and HbA1c are complex (Rohlfing et al. 2002). In general, HbA1c is not well-correlated with one-time measurements of fasting plasma glucose (Saudek et al. 2008). For instance, among a multiethnic cohort of 1,156 obese children and adolescents without a diagnosis of diabetes, a weak positive relationship between HbA1c and fasting glucose ($r = 0.29$; $P < 0.01$), and between HbA1c and 2-hour post-challenge glucose ($r = 0.32$; $P < 0.01$) has been observed (Nowicka et al. 2011). However, there is some evidence that HbA1c is correlated with continuous, daily measurements of glucose. In a clinical trial, Nathan et al. (2008) measured plasma glucose over the course of three months to be compared with HbA1c levels, measured at the end of the 3 month trial period among a total of 507 study subjects. Based on approximately 2,700 glucose measurements taken over three months per HbA1c measurement, there was a strong positive relationship between average glucose and HbA1c ($r=0.92$, $P < 0.01$).

6) The HbA1c assay is more expensive to analyze than the glucose assay. Fasting plasma glucose is unquestionably less expensive to measure than 2-hour post-challenge glucose and HbA1c (Bonora and Tuomilehto 2011). Furthermore, HbA1c is especially expensive in many low and middle-income country settings, which may prohibit its use in many countries worldwide (Hare et al. 2012).

Trends in HbA1c and Glucose

Over the past several decades, there has been a distributional shift in fasting plasma glucose and HbA1c. The global age-standardized mean fasting plasma glucose was 5.50 mmol/L (95% CI 5.37–5.63) for men and 5.42 mmol/L (95% CI 5.29–5.54) for women, having risen by 0.07 mmol/L and 0.09 mmol/L per decade, respectively (Danaei et al. 2011). HbA1c distributions have also shifted slightly, with mean HbA1c levels increasing from 5.2% in 1999-2000 to 5.4% in 2009-2010 among the U.S. population aged ≥12 years (Bullard et al. 2013).

Prevalence of Type 2 Diabetes

Due to the differences in quality, completeness and analysis of data, the global prevalence of type 2 diabetes is difficult to accurately determine (Danaei et al. 2011). Recent estimates of the global age-standardized prevalence for type 2 diabetes may be as low as 6.4% (Shaw et al. 2010) and as high as 9.8% (Danaei et al. 2011). In general, the prevalence of type 2 diabetes tends to be higher among men than women in most populations (Danaei et al. 2009). In China, the prevalence is 12.1% among men and 11.0% among women (Xu et al. 2013); in the U.S., the prevalence is 13.7% among men and 11.7% among women (Danaei et al. 2009). It has been estimated that the number of people with diabetes worldwide is projected to increase from 171 million in 2000 to 366 million by 2030 (Wild et al. 2004).

Given the prevalence of type 2 diabetes, there is a critical need to understand the prevalence and extent of prediabetes, the hyperglycemic state immediately preceding type 2 diabetes (Abraham and Fox 2013). The global prevalence of prediabetes has not yet been estimated; however, it is estimated that 34% of U.S. adults (Abraham and Fox 2013) and 16% of U.S. children (Li et al. 2009) have prediabetes.

Metabolic Syndrome

Metabolic syndrome is a clustering of metabolic illnesses that was first recognized by Gerald Reaven, MD, in 1988 (Haslam 2007). Obesity, dyslipidemia, hyperglycemia, and hypertension are the constellation of symptoms that make up metabolic syndrome, a medical condition that may ultimately lead to the development of coronary heart disease and type 2 diabetes (Gallagher et al. 2011; Wilson et al. 2005). The greatest benefit of diagnosing metabolic syndrome is that risk for coronary heart disease and type 2 diabetes is not limited to the exclusive presence of obesity, dyslipidemia, hyperglycemia, or hypertension, but rather the clustering of these symptoms (Reaven 2002).

Clinical Expression of Metabolic Syndrome

Abdominal Obesity

Abdominal obesity is the form of obesity that presents clinically as increased waist circumference (Grundy et al. 2005). Although similar, abdominal obesity is distinct from obesity because excess adipose tissue around the abdominal area correlates closely with other metabolic syndrome risk factors (Grundy et al. 2005). Abdominal obesity is an important constituent of metabolic syndrome; as the degree of abdominal obesity increases, the prevalence of metabolic syndrome increases (Steinberger et al. 2009). A recent study indicated that four of five children

with metabolic syndrome are overweight (Cook et al. 2003). Furthermore, a surprising number of children (20-50% of children who are obese) are also diagnosed with metabolic syndrome (Messiah et al. 2007).

Hyperglycemia

Hyperglycemia is the metabolic state of sustained excessive glycation and is present in the majority of individuals with metabolic syndrome (Grundy et al. 2005). A cut-point of <110 mg/dL for fasting plasma glucose has been established by the American Diabetes Association; individuals with levels above this cut-point are considered to have either prediabetes (also called impaired fasting glucose) or diabetes (Genuth et al. 2003).

Dyslipidemia

Low high-density lipoprotein (HDL) cholesterol (HDL cholesterol <40 mg/dL for men; <50 mg/dL for women) and high triglycerides (triglycerides >150 mg/dL) are the dyslipidemias included in the definition for metabolic syndrome (Barnoya and Glantz 2005; Goldberg et al. 2005). Low HDL is an important independent predictor for the development of cardiovascular disease (Assmann et al. 1996; Curb et al. 2004; Gordon et al. 1977; Sharrett et al. 2001) and type 2 diabetes (Abbasi et al. 2013; D'Agostino et al. 2004; Haffner et al. 1990), independent of other risk factors. High triglycerides are also considered a risk factor for cardiovascular diseases (Austin et al. 1998), particularly atherosclerosis (Miller et al. 2011). However, controlling for HDL levels and other cardiovascular risk factors has been shown to substantially attenuate the association between high triglycerides and cardiovascular diseases (Bitzur et al. 2009). Although not officially included in the definition, high low-density lipoprotein (LDL) cholesterol is often associated with metabolic syndrome (Holvoet et al. 2004) but is not considered to be an independent predictor of cardiovascular disease (Poss et al. 2011).

Hypertension

Hypertension, a condition marked by abnormally high blood pressure, is often associated with obesity and commonly occurs in hyperglycemic individuals (Grundy et al. 2005; Reaven 1997). Although traditional blood pressure cut-points for defining hypertension are greater than 140 mmHg systolic and 90 mmHg diastolic blood pressure (National Institutes of Health [NIH], 2013), high-normal blood pressure levels (130–139 mmHg systolic and/or 85–89 mmHg diastolic) are also indicative of increased risk for coronary heart disease; these lower values are used to describe metabolic syndrome (Grundy et al. 2005).

Definitions of Metabolic Syndrome

The clinical criterion for metabolic syndrome varies depending on the definition used by different health agencies. The World Health Organization defines metabolic syndrome in adults as having hyperglycemia plus two of any of the following symptoms: 1) hypertension (taking antihypertensive medication or blood pressure ≥130/85 mmHg); 2) high triglyceride levels (triglycerides >150 mg/dL); 3) low HDL cholesterol (HDL <35 mg/dL for men and <39 mg/dL for women); 4) obesity (BMI >30 kg/m^2 and/or waist-to-hip ratio >0.9 for men and >0.85 for women); or 5) having a urinary albumin excretion rate >20 ng/minute (Alberti et al. 1998). Although similar, the U.S. National Cholesterol Education Program Adult Treatment Panel III (2002) defines metabolic syndrome as having at least three of the following symptoms: 1) abdominal obesity (waist circumference ≥ 40 inches for male and ≥ 35 inches for women); 2) high triglyceride levels (triglycerides >150 mg/dL); 3) low HDL cholesterol (HDL< 40 mg/dL for men and < 50 mg/dL for women); 4) hypertension (taking antihypertensive medication or blood pressure ≥ 130/85 mmHg); or hyperglycemia (fasting plasma glucose ≥ 110 mg/dL). Among children, there is no universally accepted definition for the metabolic syndrome

(Weitzman et al. 2005). The National Cholesterol Education Program Adult Treatment Panel III (2002) defines metabolic syndrome in children as having at least three of the following symptoms: 1) abdominal obesity (waist circumference ≥ 90th percentile for age and sex); 2) high triglyceride levels (triglycerides >110 mg/dL); 3) low HDL cholesterol (HDL <40 mg/dL); 4) hypertension (taking antihypertensive medication or blood pressure ≥ 90th percentile for age and sex); or hyperglycemia (fasting plasma glucose ≥ 110 mg/dL).

Prevalence of Metabolic Syndrome

Due to the differences in the criterion for metabolic syndrome across agencies, the national or global prevalence of metabolic syndrome is difficult to determine. It has been estimated that the global prevalence of metabolic syndrome among adults is between 20-30% (Grundy 2008). In the U.S., the age-adjusted prevalence among adults is approximately 24% (Beltran-Sanchez et al. 2013; Ford et al. 2002). It is similarly difficult to determine the global or regional prevalence of the metabolic syndrome among children (Grundy 2008). A systematic review of 85 published papers estimated that between 2-10% of children worldwide has metabolic syndrome (Friend et al. 2013). The metabolic syndrome prevalence was lowest for studies of European and Asian populations and highest for Middle Eastern and North American populations (prevalence of 3.3 to 4.2% and 4.2 to 10%, respectively) (Friend et al. 2013). Approximately one million U.S. children have metabolic syndrome (Cook et al. 2003) and the U.S. prevalence of metabolic syndrome among children is higher than the median prevalence across all countries included in the systematic review (prevalence of 4% and 3.3%, respectively) (Friend et al. 2013).

Exposure of Interest: Secondhand Smoke

Secondhand smoke is a complex mixture of gases and particles that contains more than 5,000 chemicals emitted by the combustion of tobacco products exhaled by smokers. At least 69 toxic chemicals in SHS, such as arsenic and benzene, have been shown to cause cancer (NIH 2000). Worldwide, approximately 40% of children and 35% of non-smoking adults are exposed to the complex mixture of air pollutants that make up SHS (Öberg et al. 2011). In the U.S., half of children and 40% of non-smoking adults are regularly exposed to SHS (CDC 2010).

Health Effects of Secondhand Smoke

In 1964, Luther L. Terry, Surgeon General of the U.S., published the controversial report on the effects of smoking entitled *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service* (U.S. Department of Health and Human Services 2014). This early report outlined cigarette smoking as the single most important source of preventable morbidity and premature mortality and linked cigarette smoking to lung cancer and laryngeal cancer. Since the original report, 31 additional reports have been published to expand upon the health effects of smoking. The report now lists cigarette smoking as a cause of numerous cancers, including lung, breast, and prostate cancer, cardiovascular disease, autoimmune diseases, reproductive issues, diabetes, and many other adverse health effects.

In 1986, the Surgeon General's report on The Health Consequences of Involuntary Smoking was published (U.S. Department of Health and Human Services 2014). The report provided the first comprehensive review of the health effects of exposure to SHS. Furthermore, according to the 2014 Surgeon General report on tobacco smoke, secondhand smoke is recognized as a known carcinogen among nonsmokers. In particular, exposure to SHS increases non-smokers risk for lung cancer (Fontham et al. 1994; Janerich et al. 1990). Exposure to SHS is

also associated with increased risk for coronary heart disease (Barnoya and Glantz 2005), chronic obstructive pulmonary disease (Thun et al. 2013), and stroke (Thun et al. 2013) among non-smoking adults. Among children, exposure to SHS during early life has been consistently linked to sudden infant death syndrome, low birth weight, upper and lower respiratory tract infections, asthma onset, acute otitis media, and hearing loss among exposed children (Öberg et al. 2011; Zhou et al. 2014).

Recently, it has been postulated that exposure to SHS may increase the risk for metabolic disorders. Several compounds found in SHS, including nicotine and polycyclic aromatic hydrocarbons, are suspected endocrine disruptors (Tziomalos and Charsoulis 2004). Other constituents, such as cadmium, may directly alter glucose homeostasis or sensitivity to insulin in exposed animals and humans (Edwards and Prozialeck 2009; Schwartz et al. 2003).

Financial Burden of Secondhand Smoke

The economic toll of SHS exposure is substantial. Productivity losses from premature death caused by exposure to SHS is now estimated to be $6.6 billion per year, which amounts to $158,000 per premature death (Max et al. 2012). The economic burden due to exposure to SHS is higher among females as compared to males and higher among non-Hispanic blacks and Hispanics as compared to non-Hispanic whites (Max et al. 2012). Furthermore, the total indirect costs of secondhand smoke exposure are estimated to be at least $6 billion per year due to the lost wages, benefits, and household services (Behan et al. 2005).

Exposure Assessment

The assessment of exposure to SHS continues to be a methodological challenge presented in tobacco-related health research and there is currently no gold standard for the measurement of exposure to SHS (Al-Delaimy and Willett 2008). Epidemiological studies evaluating the health

effects of exposure to SHS often determine exposure through self-report and biological markers of exposure (cotinine and NNAL). It is often the goal of epidemiological research to quantify long-term exposure to SHS when examining the relationship between SHS and chronic disease.

There are advantages and disadvantages of each exposure assessment. Self-report is a subjective measure of an individual's typical (daily) exposure to SHS (Al-Delaimy and Willett 2008). Cotinine is an objective measure of an individual's short-term exposure to SHS and is most useful when taken in close temporal proximity to exposure to SHS, whereas NNAL is an objective measure of an individual's long-term exposure to SHS that is sensitive to intermittent, non-daily exposure (Goniewicz et al. 2011). Thus, for chronic disease-related epidemiological studies of intermittent non-daily exposure to SHS, NNAL may be of greater utility than cotinine (Goniewicz et al. 2011).

Self-report

Self-report is the most common method of measuring exposure to SHS because it is the most convenient to the researchers and imposes a very low burden to the research subjects (Al-Delaimy and Willett 2008). Despite these advantages, self-report of exposure to SHS may introduce measurement error and bias because subjects often fail to accurately and/or objectively report their exposure to SHS (Al-Delaimy and Willett 2008).

Due to the potential for reporting bias, self-report of exposure to SHS could potentially lead to misclassification of exposure (Lee et al. 2005). Observational studies have investigated the accuracy of self-report to determine exposure to SHS, as compared with cotinine. Among U.S. adults who have a level of cotinine above the limit of detection, more than 87% also self-reported exposure to SHS within their workplace and home (Arheart et al. 2008).

Among children, there is moderate agreement (r=0.62) between self-report of household smokers and serum cotinine levels (Wilkinson et al. 2006). Furthermore, using both child and parental self-reports of number of household smokers may result in high sensitivity (85%) and high specificity (90%) for determining exposure to SHS (Lee et al. 2005).

Cotinine

Cotinine is an objective measure of exposure to SHS and is generally preferred to subjective measures of exposure to SHS because it limits the potential for reporting bias (Al-Delaimy and Willett 2008). Cotinine is the major proximate metabolite of nicotine and is a biomarker of daily nicotine intake (Khariwala et al. 2014). Cotinine is the most widely used biomarker of secondhand smoke exposure due to its moderate specificity, relative abundance, and ease of measurement (Benowitz 1996). Cotinine accumulates in the urine, blood, saliva, hair or toenails (Avila-Tang et al. 2013; Bernert et al. 2010). Urine, blood and saliva cotinine concentrations have a half-life of approximately 16 hours and are eliminated from the body within 3-4 days. Hair and toenail cotinine, although used less frequently, have a longer half-life and take longer to be eliminated from the body; specifically, 1 millimeter of a toenail sample and 1 centimeter of hair sample provide cotinine concentrations that represent exposure to SHS over the past month (Avila-Tang et al. 2013). In general, urinary assays have higher sensitivity than serum assays and are the generally preferred method (Avila-Tang et al. 2013).

Several studies have evaluated the effectiveness of cotinine to distinguish between active smoking and exposure to SHS (Goniewicz et al. 2011). A cut-off of 50 ng/mL for urinary cotinine has been determined to distinguish active smokers from passive smokers (Avila-Tang et al. 2013; Zielinska-Danch et al. 2007). For serum cotinine, there are several cut-offs used to distinguish active smokers from passive smokers; a cut-off 3 ng/mL has been established for

determining low exposure to SHS (Avila-Tang et al. 2013) whereas a cutoff of 15 ng/mL is often used for high exposure to SHS (Weitzman et al. 2005).

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)

Tobacco-specific nitrosamines are present in substantial quantities in both unburned tobacco and tobacco smoke (Hecht 1998). NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, is a nitrosamine that is rapidly distributed to most tissues and is rapidly metabolized by the lungs and liver following exposure to tobacco smoke (Hecht 1998). NNAL is the predominant NNK metabolite with a half-life of approximately 10-16 days and takes 3-4 weeks to be eliminated from the body (Goniewicz et al. 2011; Hecht et al. 2001). Therefore, it is possible that NNAL represents the cumulative exposure to SHS over a longer period of time than cotinine (Goniewicz et al. 2011). Although NNAL may be a more specific measure of exposure to SHS, the analytic methods used to determine NNAL are more costly and more difficult to implement than the analytic methods used to determine cotinine (Avila-Tang et al. 2013).

NNAL accumulates in urine, blood, plasma, and toenails (Carmella et al. 2005; Hecht et al. 1999; Jacob et al. 2008). Urine is the major route of elimination of NNK metabolites and is the preferred assessment; several studies have reported that 90% of the dose of SHS appeared in urine within a 24-hour period (Hecht et al. 1980; Morse et al. 1990; Murphy et al. 1995).

NNAL is a more objective measure of exposure than self-report (Caraballo et al. 2004; Connor Gorber et al. 2009; Jeemon et al. 2010) and may be an improvement over cotinine because it is specific to tobacco smoke and has longer half-life (Goniewicz et al. 2011; Hecht et al. 2001; Thomas et al. 2011). Furthermore, NNAL may be a more accurate indicator of exposure for non-daily exposure to SHS (Khariwala et al. 2014). Despite these advantages, few studies have compared the usefulness of cotinine and NNAL to determine exposure to SHS. One

study compared cotinine and NNAL among a sample of non-smoking adult from NHANES 2007-2008; Bernert et al. (2010) observed a strong correlation between serum cotinine and total urinary NNAL concentrations ($r = 0.92$; $p < 0.05$).

Factors Affecting the Accuracy of Biomarkers

There are several factors to consider when assessing exposure to SHS. Specifically, biological markers of exposure to SHS may be impacted by both characteristics of the individual, such as the individual's age and/or race/ethnicity, as well as the source and type of the exposure.

Age. Cotinine and NNAL concentrations may vary by age, due to the slower nicotine clearance rates among children as compared with adults (Avila-Tang et al. 2013). Research has reported that children, ages 6-11 years, have urinary NNAL levels 2.5 times the levels in adult nonsmokers (Bernert et al. 2010), likely due to the higher dose relative to the smaller body sizes.

Race/ethnicity. Cotinine and NNAL concentrations may vary by race/ethnicity, due to differences in smoking behaviors and perhaps in cotinine metabolism (Avila-Tang et al. 2013; Benowitz et al. 2009). Specifically, at the same daily level of cigarette smoking, higher serum cotinine concentrations are observed in blacks than in whites (Caraballo et al. 1998; Wagenknecht et al. 1990) Specifically, higher cotinine concentrations among blacks compared with whites can be explained by both slower clearance of cotinine and higher intake of nicotine per cigarette in blacks (Benowitz et al. 2002; Perez-Stable et al. 1998).

Electronic cigarettes (e-cigarettes). E-cigarettes are products that deliver a nicotine-containing aerosol (commonly called vapor) to users by heating a solution typically made up of glycerol, nicotine, and flavoring agents (Grana et al. 2014). Although e-cigarettes are often promoted as a safer alternative to conventional cigarettes and as a smoking cessation aid (Yamin et al. 2010), the effectiveness of e-cigarettes as a cessation aid is not yet clear (Grana et al. 2014).

E-cigarettes do not burn or smolder and do not emit side-stream smoke in the way that conventional cigarettes do; however, nonsmokers are still exposed to aerosol exhaled by the smoker (Grana et al. 2014). Chamber studies have demonstrated that low levels of nicotine, formaldehyde, various polycyclic hydrocarbons, and many other chemicals are emitted into the air from e-cigarettes (Flouris et al. 2013; Schober et al. 2014). Furthermore, Flouris et al. (2013) observed that serum cotinine levels were similar among non-smokers sitting near cigarette smoke and e-cigarette aerosol (0.8 ng/mL for cigarette smoke and 0.5 ng/mL for e-cigarette smoke).

Menthol. Menthol cigarettes are heavily marketed to racial/ethnic minority groups and are used at higher rates among racial/ethnic minority smokers relative to non-Hispanic White smokers (Gardiner 2004). Due to its effects as a sensory stimulant, menthol could enhance tobacco's addictiveness (Eccles 1994; Henningfield et al. 2003). Menthol cigarette use may also have race-specific effects on levels of biological indicators of exposure to SHS. As compared to non-menthol cigarette use, menthol cigarette use is associated with higher cotinine levels (Clark et al. 1996; Muscat et al. 2009) and lower NNAL levels among non-Hispanic Blacks (Muscat et al. 2009); these effects are not seen among non-Hispanic Whites.

Non-tobacco sources of nicotine. Nicotine is present in small amounts in various foods and medications and it is possible that cotinine could reflect exposure to the non-tobacco sources of nicotine (Benowitz 1996; Siegmund et al. 1999). Davis et al. (1991) estimated that average daily consumption of tomatoes, potatoes, cauliflower, and black tea together could result in a daily intake of 8.8 pg nicotine, which could result in urinary cotinine levels ranging between 0.6 to 6.2 ng/ml (Davis et al. 1991). However, the levels of nicotine in foods are quite low and it has been determined that the levels of cotinine produced by even a diet high in nicotine-containing foods is lower than that seen in individuals exposed to moderate levels of SHS (Benowitz 1996).

Biological Mechanisms

Active smoking is associated with metabolic disorders. A meta-analysis of 13 prospective cohort studies representing 56,691 smoking adults (ages 19-60 years) estimated a 42% higher risk for metabolic syndrome among heavy smokers as compared to light smokers (pooled adjusted relative risk [RR] 1.42; 95% confidence interval [CI] 1.27, 1.59) (Sun et al. 2012). Similarly, a meta-analysis of 25 prospective cohort studies representing 1.2 million adults (ages 16-60 years) reported a 44% higher rate of type 2 diabetes among smoking adults than among non-smoking adults (pooled adjusted RR 1.44; 95% CI 1.31, 1.58) (Willi et al. 2007). Active smoking may increase the risk for metabolic syndrome and type 2 diabetes most likely through increased inflammation, oxidative stress, endothelial dysfunction, and endocrine disruption (Chen et al. 2008; Chiolero et al. 2008) and it is likely that biological mechanisms linking exposure to SHS and metabolic disorders involve a combination of these mechanisms.

Inflammation

Systemic inflammation, the biological response of body tissues to pathogens, pollutants, or other harmful stimuli, is a hypothesized mechanism of the association between exposure to SHS and metabolic disorders (Barnoya and Glantz 2005). Exposure to SHS triggers an immunologic response to vascular injury which is associated with increases in circulating biomarkers of inflammation, including C-reactive protein, interleukin-6 (IL-6), tumor-necrosis factor alpha (TNF-α), and fibrinogen (Chiu et al. 2011; Jefferis et al. 2010; Lee and Pratley 2005; Matsunaga et al. 2014; Panagiotakos et al. 2004; Weitzman et al. 2005; Wilkinson et al. 2007).

Inflammation and Obesity

Growing evidence suggests that obesity is a pro-inflammatory disease that activates inflammatory signaling pathways in cells (Shoelson et al. 2007). Obesity is associated with the

accumulation of lipid in the adipocytes and the expansion of the adipose tissue; as a result, the hypertrophic adipocytes secrete inflammatory cytokines, such as IL-6 and TNF-α (Shoelson et al. 2007). In adipose issue, IL-6 is thought to play a role in insulin resistance by inhibiting the binding of insulin to insulin receptors and disrupting hepatic insulin action in liver (Klover et al. 2003) whereas TNF-α exacerbates insulin resistance through its overexpression in adipose tissue (Hotamisligil et al. 1993; Hotamisligil et al. 1995).

While adipocytes are indisputably sources of inflammation in obesity, it has also been postulated that intestinal inflammation precedes the development of obesity (Ding et al. 2010; Ding and Lund 2011; Kim et al. 2008). Toxicological studies among mice have reported that changes in the gut microbiota leads to increased levels of lipopolysaccharides, endotoxins produced by Gram-negative bacteria in the gut (Cani et al. 2007; Cani et al. 2008a; Cani et al. 2008b). Metabolic endotoxemia, the state of elevated lipopolysaccharides, elicits a chronic low-grade pro-inflammatory and pro-oxidative stress status associated with obesity (Neves et al. 2013). Furthermore, Cani et al. (2007) provide evidence supporting the role of intestinal inflammation in the development of obesity among mice.

Inflammation and Hyperglycemia

Inflammation may initiate a state of insulin resistance by impairing insulin signaling. For example, inflammatory cytokines TNF-α and IL-6 may disrupt insulin signaling, which may result in insulin resistance (McArdle et al. 2013). It is also possible that obesity mediates the association between SHS-induced inflammation and hyperglycemia by secreting inflammatory cytokines. Specifically, obesity-associated inflammation within the pancreas may result in insulin resistance and pancreatic β-cell failure (Donath et al. 2009).

Inflammation and Dyslipidemia

Inflammation may lead to dyslipidemia by dramatically altering lipid metabolism (Zuliani et al. 2007) and the lipoprotein profile (Jahangiri 2010). Circulating inflammatory cytokines IL-6 and TNF-α may influence HDL levels by inhibiting the activity of the triglycerides lipases. It has reported that pro-inflammatory cytokines inhibit the activity of lipoprotein lipase (Grunfeld and Feingold 1996) and enhance the activity of endothelial lipase (Jin et al. 2003); both of these actions may lower HDL levels during inflammatory states (Zuliani et al. 2007). Furthermore, IL-6 may stimulate triglyceride secretion by inducing the hepatic acute phase proteins (Nonogaki et al. 1995).

Inflammation and Hypertension

Inflammatory mechanisms may also be important to the development of hypertension (Savoia and Schiffrin 2006). Higher levels of C-reactive protein may increase blood pressure through a variety of biological effects within endothelial cells (Schillaci and Pirro 2006). For instance, C-reactive protein may increase the number of cell adhesion molecules and endothelin-1 production, which may ultimately result in vasoconstriction (Schillaci and Pirro 2006). On the other hand, Smith et al. (2005) have hypothesized that the relationship between inflammation and hypertension reflects reverse causation whereby hypertension induces inflammation and raises circulating C-reactive protein levels.

Oxidative Stress

Cigarette smoke is an abundant source of reactive oxygen species (Church and Pryor 1985), chemically reactive molecules that are produced in cells as a result of the respiratory process that uses oxygen (Kosecik et al. 2005). Excessive accumulation of reactive oxygen species (ROS) can lead to oxidative stress, which is the body's inability to readily detoxify the

ROS or to repair the resulting damage (Kosecik et al. 2005). Both toxicological and epidemiological studies report a direct increase in oxidative stress following exposure to SHS (Csordas and Bernhard 2013; van der Vaart et al. 2004). The oxidative stress caused by exposure to SHS may influence the development of metabolic disorders by delivering free radicals to the vascular system and by depleting antioxidants that would normally be available to protect against reactive oxygen species (Barnoya and Glantz 2005).

Oxidative Stress and Obesity

At present, it is not yet clear whether inflammation precedes obesity or if oxidative stress arises in the adipose cells (Aroor and DeMarco 2014). The overproduction of ROS correlates with excess fat accumulation in both humans and mice (Evans et al. 2002; Halliwell 1995; Rösen et al. 2001). Obesity likely contributes to oxidative stress through the secretion of inflammatory cytokines, overconsumption of oxygen, and fatty acid oxidation within the adipose tissue (Fernández-Sánchez et al. 2011). Conversely, it has also been postulated that oxidative stress may play a causal role in obesity by initiating ROS overproduction (Furukawa et al. 2004). In a knockout mouse model, Youn et al. (2014) demonstrated that transgenic mice overexpressing p22phox, an important subunit of the superoxide-producing enzyme nicotinamide adenine dinucleotide phosphate (NADPH), in vascular smooth muscle exhibited a rapid induction of obesity, independent of the total number of calories consumed.

Oxidative Stress and Hyperglycemia

Oxidative stress impairs glucose uptake in adipose tissue (Maddux et al. 2001; Rudich et al. 1998) and decreases insulin secretion from pancreatic β cells (Matsuoka et al. 1997). Oxidative stress within the adipose tissue may also lead to insulin resistance. Furthermore,

oxidative stress is known to impair glucose transport within the adipose tissue (Rudich et al. 1998).

Oxidative Stress and Dyslipidemia

Dyslipidemia may induce oxidative stress in the endothelium (Matsuda and Shimomura 2013). While it is widely accepted that dyslipidemia is a precursor to oxidative stress, it is also possible that oxidative stress may contribute to dyslipidemia by increasing ROS generation and an over-expression of the NADPH oxidase (Hopps et al. 2010).

Oxidative Stress and Hypertension

It has been proposed that superoxide radicals in and around vascular endothelial cells play critical roles in the pathogenesis of hypertension (Nakazono et al. 1991). In particular, NADPH oxidase activity in vascular cells is believed to be important in the pathogenesis of hypertension (Cohen and Tong 2010). Under physiological conditions, NADPH oxidase is the primary source of ROS in the vasculature and is involved in ROS homeostasis within the vessel wall (Lee and Yang 2012). However, under pathological conditions, inflammatory cytokines IL-6 and TNF-α lead to excessive stimulation of NADPH oxidase resulting in oxidative stress (Lee and Yang 2012). This inflammatory cascade leads to a damaging effect on the vasculature (Paravicini and Touyz 2008), which can ultimately contribute to hypertension.

Endothelial Dysfunction

Endothelium is the inner lining of blood vessels and is a vital layer of the arterial wall because it maintains vessel integrity and controls vascular tone (Barnoya and Glantz 2005). Endothelial dysfunction is an imbalance between vasodilation and vasoconstriction substances produced by the endothelium (Barnoya and Glantz 2005). Exposure to SHS has been shown to

dramatically decrease endothelial function by damaging endothelial cells and interfering with the endothelium repair mechanism (Frey et al. 2012). Oxidative stress may be involved in the process by which SHS results in endothelial dysfunction; SHS increases endothelial superoxide anion (O2) production, thereby reducing bioavailability of nitric oxide (NO) and resulting in endothelial dysfunction (Jaimes et al. 2004).

Endothelial Dysfunction and Obesity

Obesity, through the secretory hormones and cytokines of adipose tissue, may influence endothelial function (Avogaro and de Kreutzenberg 2005; Mauricio et al. 2013). Obesity may lead to endothelial dysfunction through inflammatory responses and oxidation reactions (Avogaro and de Kreutzenberg 2005). Furthermore, obesity is associated with increased levels of free fatty acids, which impair endothelial function (Avogaro and de Kreutzenberg 2005).

Endothelial Dysfunction and Hyperglycemia

Hyperglycemia is the major causal factor in the development of endothelial dysfunction (Hadi and Suwaidi 2007). Hyperglycemia activates protein kinase C (PKC) (Hadi and Suwaidi 2007), which leads to overproduction of the superoxide NADPH oxidase and decreased NO generation (Ceriello 2003; Hink et al. 2003). These processes result in acute endothelial dysfunction in blood vessels that may also contribute to the development of diabetic complications (Ceriello 2003). Although hyperglycemia typically precedes endothelial dysfunction, epidemiologic research has also demonstrated that endothelial dysfunction predicts hyperglycemia, independent of other known risk factors (Meigs et al. 2004; Song et al. 2007).

Endothelial Dysfunction and Dyslipidemia

Dyslipidemia is independently associated with endothelial dysfunction (Steyers and Miller 2014). Specifically, elevated LDL and lowered HDL levels are associated with impaired endothelial function (Norata et al. 2002). Dyslipidemia may contribute to endothelial dysfunction by modulating NO and ROS production (Vladimirova-Kitova et al. 2008). Additionally, oxidized LDL can also initiate the activation of inflammatory pathways within endothelial cells leading to endothelial dysfunction (Stancu et al. 2012).

Endothelial Dysfunction and Hypertension

Although there is a well-established association between endothelial dysfunction and hypertension (Panza et al. 1990; Treasure et al. 1992; Vita et al. 1990), it remains unclear whether hypertension is a cause or a consequence of endothelial dysfunction (Dharmashankar and Widlansky 2010; Quyyumi and Patel 2010). Endothelial dysfunction plays an integral role in mediating the structural changes in the vasculature (Budhiraja et al. 2004). There are a variety of processes that link endothelial dysfunction to hypertension. In particular, endothelial dysfunction leads to decreased bioavailability of NO and impairs endothelium-dependent vasodilation (Puddu et al. 2000). Additionally, endothelial dysfunction may also contribute to hypertension by altering the production of anticoagulant factors (Budhiraja et al. 2004). On the other hand, it is also widely accepted that hypertension is a cause rather than a consequence of endothelial dysfunction (Quyyumi and Patel 2010). Hypertension may contribute to endothelial dysfunction by precipitating endothelial NO deficiency, increasing inflammatory responses, and contributing to excessive ROS production (Dharmashankar and Widlansky 2010).

Endocrine Disruption

Endocrine disruptors are chemicals that interfere with the normal function of the endocrine system by affecting the production and utilization of insulin and metabolic imbalance (Tziomalos and Charsoulis 2004). Certain compounds found in SHS, including nicotine and polycyclic aromatic hydrocarbons (PAHs), are suspected endocrine disruptors (Tziomalos and Charsoulis 2004). Over the past several years, there has been growing concern that metabolic disorders, including obesity and metabolic syndrome, may be linked with endocrine disrupting chemicals (Casals-Casas and Desvergne 2011). Important targets for endocrine-disrupting chemicals within the body are peroxisome proliferator–activated receptors (PPARs), genes that play a crucial role in metabolism (Casals-Casas et al. 2008).

Endocrine Disruption and Obesity

Endocrine-disrupting chemicals may induce obesity through the activation of PPARs (Grun and Blumberg 2006). In particular, endocrine disrupting chemicals may target the activation of PPARγ, which regulates food intake, metabolic efficiency, and energy storage (Grun and Blumberg 2006). PPARγ can be targeted by endocrine disrupting chemicals at the transcriptional level via modification of the chromatin structure (Janesick and Blumberg 2011). By modifying chromatin structure, endocrine-disrupting chemicals disrupts the ability of PPARγ to bind to its target genes (Janesick and Blumberg 2011). This can ultimately lead to adipogenesis, the process of cell differentiation by which preadipocytes become adipocytes (Janesick and Blumberg 2011).

LITERATURE REVIEW

Epidemiologic Evidence

A literature review was performed to identify epidemiological studies related to exposure to SHS and metabolic disorders (obesity, metabolic syndrome, and hyperglycemia). Nineteen studies presented original data that assessed these associations. Table 2.1 summarizes the results of the relevant studies.

Exposure to SHS and Obesity

Previous epidemiological studies have consistently reported a positive association between exposure to SHS and obesity. Eleven observational studies have examined the association between exposure to SHS and obesity among children. Parental self-report of exposure to SHS in early childhood has been shown to increase the risk for overweight and obesity among children, ages 1-17 years (Apfelbacher et al. 2008; Chen et al. 2012; Ittermann et al. 2013; Kwok et al. 2010; Mangrio et al. 2010; McConnell et al. 2015; Pagani et al. 2015; Raum et al. 2011; von Kries et al. 2008; Wen et al. 2013; Yang et al. 2013). Nine of the eleven studies report an association between exposure to SHS and childhood obesity; the adjusted odds ratios ranged from 1.30 to 2.90.

Five prospective cohort studies have reported positive associations between self-reported exposure to SHS and obesity among children, ages 6 to 10 years (Kwok et al. 2010; McConnell et al. 2015; Pagani et al. 2015; Wen et al. 2013; Yang et al. 2013). The largest prospective cohort study consisting of 21,083 mother–child pairs in the U.S. Collaborative Perinatal Project demonstrated that heavy maternal smoking (20+ cigarettes/day) was associated with obesity among children at 7 years of age compared to no maternal smoking (adjusted OR 1.49; 95% CI 1.31, 1.69) (Wen et al. 2013). McConnell et al. (2015) evaluated the association between

exposure to secondhand smoke on estimated BMI growth and attained BMI among a prospective cohort of 3,318 participants enrolled in the Southern California Children's Health Study. Results suggested that any self-report of exposure to SHS was associated with attained BMI (adjusted OR 1.23; 95% CI: 0.86, 1.61), but not estimated BMI growth (adjusted OR 0.81; 95% CI: 0.36, 1.27) over 8-year follow-up period. Furthermore, there was a relationship between the number of household smokers and growth and attained BMI. Specifically, the adjusted odds ratio for one household smoker was 0.95 (95% CI: 0.42, 1.47) and the adjusted odds ratio for two or more household smokers was 1.77 (95% CI: 1.04, 2.51). The remaining three prospective cohort studies reported similar patterns between self-reported exposure to secondhand smoke and childhood obesity; the adjusted odds ratios ranged from 1.23 to 1.40 (Kwok et al. 2010; Pagani et al. 2015; Yang et al. 2013).

Two of the five prospective cohort studies investigated the interaction between exposure to SHS and other important behavioral or environmental factors on obesity. Wen et al. (2013) evaluated effect modification of breastfeeding on the association between exposure to heavy maternal smoking and obesity by stratifying on breastfeeding status. Stratified analyses suggested that the association between exposure to heavy maternal smoking and obesity were stronger among children who were exclusively breastfed than among children who were bottle-fed (adjusted OR 2.22, 95% CI 1.53, 3.20 vs. adjusted OR 1.46, 95% CI 1.28, 1.66). Meanwhile, McConnell et al. (2015) evaluated the interaction between exposure to secondhand smoke and exposure to air pollution on estimated growth and attained BMI. Results suggested that there is an interaction between exposure to SHS and exposure to air pollution. Specifically, compared with the attained BMI among participants with both low exposure to SHS and air pollution, the

attained BMI among participants with both high exposures to SHS and air pollution was 2.15 kg/m^2 higher (95% CI: 1.52, 2.77; interaction p-value < 0.05).

Six cross-sectional studies also evaluated the association among self-reported exposure to SHS and obesity among children, ages 4 to 17 years. Chen et al. (2013) evaluated the association between exposure to SHS and obesity among Taiwanese children, ages 9-14 years. Compared to children whose parents reported no household smokers, children whose parents reported at least one household smoker had increased odds for obesity (crude OR 1.4; 95% CI 1.2, 1.5). Raum et al. (2011) investigated the association between parental self-report of exposure to SHS at various postnatal periods and obesity among children, aged 6 years, in Germany. Children whose parents reported exposure to SHS at age 1 year and at age 6 years had higher odds for obesity (OR 2.90; 95% CI 1.86–4.54) compared to children whose parents reported no exposure to SHS, after adjusting for parity, birth weight in grams, breastfeeding, watching TV, sports, visits to fast food restaurants, highest parental education, maternal BMI, and age of mother. The largest study conducted among a sample of 35,434 children ages 5-7 years, reported a positive, non-significant association between parental self-report of household smoking and childhood obesity (adjusted OR 1.13; 95% CI 0.98, 1.32), after adjusting for sex, age, nationality, study region/location, study year, education, size of residence, number of persons in residence, number of siblings, attendance at a day nursery, maternal smoking during pregnancy, breastfeeding for more than three months, preterm delivery, and birth weight (Apfelbacher et al. 2008).

Although the literature on the association between exposure to SHS and childhood obesity is fairly consistent across studies, it is possible that unmeasured lifestyle factors may have contributed to the observed associations. In particular, diet is likely an important confounder of these associations because it is strongly related to both the exposure and the

outcome (Carr et al. 2000; Ford et al. 2003; Kimokoti et al. 2010; Kranz et al. 2012; Kris-Etherton 2003; Wang et al. 2006), but was not appropriately adjusted for in the previous epidemiologic studies. Only two studies have examined the association between exposure to SHS and obesity among adults adjusting for diet; one cross-sectional study utilized serum cotinine among non-smoking adults, aged 59-80 years, in the United Kingdom (U.K.) adjusted for diet in terms of total caloric intake (Jefferis et al. 2010), and a second cross-sectional study utilized serum cotinine measurements among adults aged 18 years or older using 1988-1994 NHANES data adjusted for diet in terms of % kilocalories in fat (Steenland et al. 1998). Both studies demonstrated a statistically significant increase in BMI among adults with serum cotinine levels indicating exposure to SHS. However, the results for crude effect estimates and the adjusted effect estimates were not presented in either study; therefore, conclusions about the adequacy of controlling for diet cannot be determined. Furthermore, measuring diet in terms of total caloric intake or % kilocalories in fat may be too broad and would not capture an individual's overall diet quality. Due to the potential for confounder misclassification, it is not likely that adjusting for diet in terms of total caloric intake or % kilocalories in fat would have reduced confounding bias in these studies.

Exposure to SHS and Hyperglycemia

Six studies have evaluated the association between exposure to SHS and hyperglycemia among both children (Thiering et al. 2011; White et al. 2014) and adults (Clair et al. 2011; Houston et al. 2006; Jefferis et al. 2010; Xie et al. 2010). Only one study, conducted among adults (NHANES, 1999-2008), has incorporated HbA1c as an indicator of hyperglycemia; Clair et al. (2011) observed a relationship between higher serum cotinine levels and elevated HbA1c levels. Compared to those with serum cotinine level below 0.05 ng/mL, those with a serum

cotinine >3 ng/mL had a 0.05% increase in HbA1c levels (standard error 0.01%; p for trend<0.01), after adjusting for age, sex, education, race/ethnicity, waist circumference, alcohol consumption, and physical activity (Clair et al. 2011); results were similar when exposure to SHS was assessed using self-report of exposure to SHS.

The associations between exposure to SHS and fasting plasma glucose appear to be stronger in younger populations (ages 10-30 years) than older populations (ages 30+ years). Two studies have evaluated the relationship between exposures to SHS and elevated fasting plasma glucose among children. White et al. (2014) demonstrated that 16-19 year old children with serum cotinine levels > 0 ng/mL were associated with large increases (coefficient: 15.43, 95% CI: 6.09, 24.77, p<0.01) in fasting blood glucose. On the other hand, Thiering et al. (2011) observed that 10 year old children who self-reported five or more years of exposure to SHS in the household had significantly higher insulin but had no meaningful impact on fasting plasma glucose as compared to children who self-reported no exposure to SHS. Among adults, the association between exposure to SHS and hyperglycemia appears to be stronger among younger adults than older adults. Houston et al. (2006) reported a strong relationship between serum cotinine levels and fasting plasma glucose among 18-30 year olds, whereas Xie et al. (2010) reported no relationship between self-report of exposure to SHS and fasting plasma glucose among 30-54 year olds and Jefferis et al. (2010) reported no relationship between serum cotinine levels and fasting plasma glucose among 59-80 year olds.

Exposure to SHS and Metabolic Syndrome

Limited evidence suggests exposure to SHS is independently associated with each of the individual components of metabolic syndrome, including obesity (von Kries et al. 2008), hyperglycemia (Houston et al. 2006), hypertension (Alshaarawy et al. 2013), and dyslipidemia

(Jefferis et al. 2010). Only two published studies have examined the association between exposure to SHS and metabolic syndrome; one utilized self-reported SHS among adult non-smokers in China (Xie et al. 2010) and the second utilized cotinine measurements among children ages 12-19 years using 1988-1994 NHANES data (Weitzman et al. 2005). Xie et al. (2010) observed that adults who self-reported exposure to SHS 5–7 days per week had increased odds for metabolic syndrome (adjusted OR 2.8; 95% CI 1.2, 6.6), after adjusting for age, sex, education, income, alcohol consumption, and active smoking. Exposure to SHS was also independently associated with hypertriglyceridemia (adjusted OR 2.1; 95% CI 1.1, 3.9), abdominal obesity (adjusted OR 2.7; 95% CI 1.6, 4.5), and low HDL cholesterol (adjusted OR 1.9; 95% CI 1.1, 3.1), but not hyperglycemia (adjusted OR 1.1; 95% CI 0.6, 1.9) or hypertension (adjusted OR 1.1; 95% CI 0.6, 1.9). Weitzman et al. (2005) observed that adolescents with the highest levels of serum cotinine (1.36-15 ng/mL) had increased odds for metabolic syndrome (OR 6.7; 95% CI 1.5, 29.7), after adjusting for age, sex race/ethnicity, the poverty index ratio, geographic region, and parental history of diabetes and heart attack.

Exposure to SHS and Other Metabolic Disorders

Exposure to SHS may also be associated with other metabolic disorders, including hypertension, dyslipidemia, and type 2 diabetes (Thayer et al. 2012).

Hypertension. Eight epidemiologic studies have evaluated the relationship between exposure to SHS and hypertension (Alshaarawy et al. 2013; Huntington-Moskos et al. 2014; Makris et al. 2009; Seki et al. 2010; Simonetti et al. 2011; Steenland et al. 1998; Xie et al. 2010). Four of the eight studies reported a positive relationship between high exposures to SHS and elevated systolic blood pressure (Alshaarawy et al. 2013; Makris et al. 2009; Seki et al. 2010;

Simonetti et al. 2011), but only one study reported a positive relationship between high exposures to SHS and elevated diastolic blood pressure (Makris et al. 2009).

Conversely, experimental studies consistently report an association between acute exposure to SHS and blood pressure (Mahmud and Feely 2004; Yarlioglues et al. 2010). Mahmud and Feely (2004) observed that controlled acute exposure (less than 20 minutes) to SHS had a deleterious effect on aortic systolic blood pressure in a sample of healthy adult males, aged 20-29 years; this association was not observed among healthy adult females. Conversely, Yarlioglues et al. (2010) observed that acute exposure to SHS (less than 30 minutes) had an adverse effect on systolic and diastolic blood pressure in a sample of healthy adult females.

Dyslipidemia. Fourteen epidemiologic studies have evaluated the relationship between exposure to SHS and dyslipidemias among both children and adults (Feldman et al. 1991; Hirata et al. 2010; Iscan et al. 1996; Jefferis et al. 2010; Kallio et al. 2007; Le-Ha et al. 2013; Lu et al. 2014; Moffatt et al. 1995; Moskowitz et al. 1990; Neufeld et al. 1997; Panagiotakos et al. 2004; Steenland et al. 1998; Venn and Britton 2007; Xie et al. 2010; Zakhar et al. 2015). Ten of the fourteen studies reported lower adjusted mean HDL levels among individuals exposed to SHS than among individuals with no exposure to SHS (Feldman et al. 1991; Hirata et al. 2010; Iscan et al. 1996; Le-Ha et al. 2013; Lu et al. 2014; Moffatt et al. 1995; Moskowitz et al. 1990; Neufeld et al. 1997; Panagiotakos et al. 2004; Xie et al. 2010). On the other hand, only a few of the studies reported that individuals exposed to SHS exhibit higher adjusted mean cholesterol levels (Iscan et al. 1996; Moskowitz et al. 1990) and higher adjusted mean LDL levels (Iscan et al. 1996), as compared to individuals with no exposure to SHS. None of the ten published studies reported a relationship between exposure to SHS and triglyceride levels.

Type 2 Diabetes. A 2014 meta-analysis of 6 prospective cohort studies representing 154,406 adults (ages 18–74 years) estimated that exposure to SHS increases the risk for type 2 diabetes by 21% (pooled adjusted RR 1.21; 95% CI 1.07, 1.38) (Sun et al. 2014). Lajous et al. (2013) observed that exposure to SHS during childhood was associated with a higher rate of type 2 diabetes (age-adjusted hazard ratio 1.18, 95% CI 1.02–1.36), as well as exposure to SHS during adulthood (age-adjusted hazard ratio 1.36, 95% CI 1.05–1.77). Houston et al. (2006) found that exposure to secondhand smoke was associated with development of type 2 diabetes (adjusted relative risk: 1.40, 95% CI 0.84, 2.33). The largest study conducted among a sample of 100,526 adults ages 41-55 years, observed that there was an increased risk of diabetes among nonsmokers who were occasionally (relative risk: 1.10, 95% CI 0.94–1.23) or regularly (relative risk: 1.16, 95% CI 1.00–1.35) exposed to passive smoke, as compare to nonsmokers who were never exposed to SHS (Zhang et al. 2011).

Several studies have evaluated the potential interaction between exposure to secondhand smoke and other important behavioral or environmental factors on type 2 diabetes. Lajous et al. (2013) assessed effect modification by stratifying by BMI categories (BMI<25 and BMI>25) and running a test for heterogeneity; no statistical effect modification was observed. Eze et al. (2014) assessed the potential interaction of various factors (age, sex, BMI, hypertension, chronic obstructive pulmonary disease (COPD), educational level, vigorous physical activity, triglycerides, HDL cholesterol levels, C-reactive protein, and menopause status among women only) by adding interaction terms into the logistic regression models. There was some evidence of more than multiplicative interaction by age (50 years or older) and by COPD status. The hypothesized biological mechanisms for these interactions are not clear; however, it is possible that exposure to SHS among older individuals or individuals with COPD may worsen the SHS-

induced release of plasma fibrinogen levels (Eze et al. 2014), an important marker of type 2 diabetes (Barazzoni et al. 2000; Henkin et al. 1999).

Toxicological Evidence

Toxicological corroboration of epidemiological evidence can help to establish the biological plausibility of relationships (Adami et al. 2011), an important component of Hill's criteria for causality (Hill 1965). Animal studies have suggested that perinatal nicotine exposure has long-lasting cardio-metabolic disturbances and might be a contributing factor for the occurrence of metabolic disorders (Thayer et al. 2012).

Exposure to Nicotine and Obesity

Exposure to nicotine, the main stimulant found in tobacco smoke, may disrupt the control of fat storage and homeostasis of energy expenditure (Somm et al. 2009). Several published studies have reported an association between postnatal exposure to nicotine and increased adiposity among Wistar rat pups (Gao et al. 2005; Holloway et al. 2005; Somm et al. 2008).

Exposure to Nicotine and Hyperglycemia

Published studies have reported an association between exposure to nicotine and impaired glucose tolerance during lactation among Wistar rats (Bruin et al. 2010; Holloway et al. 2005). Similarly, the presence of cigarette smoke among Balb/c mice during mating led to impaired glucose tolerance among offspring at 20 days of age.

The joint effect of diet and exposure to SHS on adiposity in animal models is not yet clear. Chen et al. (2011) demonstrated the exposure to maternal exposure to cigarette smoke independently programmed adverse health outcomes in mice pups, regardless of whether the mother was exposed to a high-fat diet. Conversely, Somm et al. (2008) reported that the

association between prenatal exposure to nicotine and subsequent weight gain was stronger among nicotine-exposed rat pups exposed to a postnatal high-fat diet after weaning.

In utero evidence

Active Smoking during Pregnancy and Obesity in Offspring

A 2008 meta-analysis of 14 observational studies representing 84,563 children and adults (ages 3-33 years) estimated that maternal active smoking during pregnancy increases the risk for obesity among children by 50% (pooled adjusted OR 1.50, 95% CI 1.36, 1.65) (Oken et al. 2008). A 2010 meta-analysis of 16 observational studies representing 94,997 children and adults (ages 3-33 years) estimated that that maternal active smoking during pregnancy increases the risk for obesity among children by 64% (pooled adjusted OR 1.64, 95% CI 1.42, 1.90) (Ino 2010). All of the epidemiologic studies included in the meta-analyses relied upon maternal self-report of active smoking. It is possible that mothers under-reported their smoking behaviors, which could result in a bias towards the null. Additionally, Oken et al. (2008) and Ino (2010) note that publication bias likely exists, as smaller studies reported stronger effects than larger ones, and no published studies reported null or inverse associations. A more recent meta-analysis identified 42 studies that evaluated the association between maternal active smoking and childhood obesity (Behl et al. 2013). Most of the studies (34 of 42) supported a positive association between maternal active smoking during pregnancy and childhood obesity (Behl et al. 2013).

Active Smoking during Pregnancy and Metabolic Syndrome in Offspring

Only one study has evaluated the association between maternal smoking during pregnancy and metabolic syndrome in offspring. Power et al. (2010) reported an independent association between maternal smoking during pregnancy and metabolic syndrome [crude OR

1.21, 95% CI 1.05, 1.39). However, after adjustment for confounding factors such as social class, education, physical activity, smoking, dietary quality, and alcohol consumption, maternal smoking during pregnancy appeared protective (adjusted OR 0.55, 95% CI 0.47, 0.64).

Active Smoking During Pregnancy and Hyperglycemia in Offspring

Few studies have looked at associations between maternal smoking during pregnancy and hyperglycemia in offspring. One prospective cohort study of 7,518 men and women from the 1958 British birth cohort enrolled in the Perinatal Mortality Survey (PMS) evaluated the association between maternal active smoking during pregnancy and hyperglycemia in offspring; Thomas et al. (2007) reported a modest association between maternal active smoking and HbA1c $\geq$ 6% among offspring at 45 years of age (adjusted OR 1.33, 95% CI 1.04, 1.71). Montgomery and Ekbom (2002) evaluated the association between at maternal active smoking during pregnancy and hyperglycemia in offspring among the same cohort; heavy maternal active smoking during pregnancy was positively associated with type 2 diabetes among offspring at 33 years of age (adjusted OR 4.02, 95% CI 1.14, 14.14).

Maternal Exposure to SHS during Pregnancy and Obesity in Offspring

Maternal exposure to SHS may be associated with obesity in childhood. Braun et al. (2010) observed that compared to children born to women with a serum cotinine level below the limit of detection, children born to women with prenatal serum cotinine concentrations indicative of exposure of SHS had higher BMI at 2 years of age (mean difference 0.3, 95% CI 0.1, 0.7) and 3 years of age (mean difference 0.4, 95% CI 0, 0.8), after adjusting for the child's age (in years) and maternal age, education, race/ethnicity, marital status, depression at baseline home visit and breastfeeding duration.

Limitations of Previous Studies

Evidence is building that exposure to SHS is associated with obesity (von Kries et al. 2008), hyperglycemia (Clair et al. 2011), and metabolic syndrome (Weitzman et al. 2005); however, there are many limitations of the previous epidemiological studies.

Subjective Measurement of Exposure to SHS

Most previous research has relied on self-report to assess exposure to SHS. Self-report is a subjective measure of exposure to SHS that has been shown to be less reliable than the use of biomarkers, such as NNAL or cotinine (Avila-Tang et al. 2012; Caraballo et al. 2004; Connor Gorber et al. 2009; Hecht et al. 2001; Jeemon 2010).

Currently, there is no gold standard for assessing exposure to SHS (Al-Delaimy and Willett 2008). Cotinine and NNAL offer the advantage of providing an objective measure of exposure and can be used to validate self-report of exposure to SHS. The use of NNAL as a biomarker of exposure to SHS has the potential to reduce measurement error, particularly when exposure to SHS is intermittent (Goniewicz et al. 2011). Finally, few studies have compared all three measures to assess exposure to SHS and this will be the first study to evaluate multiple measures for this particular research question.

Measurement Error of Hyperglycemia

Previous literature has often relied on plasma glucose levels to determine hyperglycemia, which may be inaccurate due to day-to-day fluctuations in glucose levels (Sacks 2011). Although HbA1c is now endorsed as a better indicator of hyperglycemia than glucose (Sacks 2011), it is not often used in studies evaluating this particular research question. Only one study among adults has incorporated HbA1c as an indicator of hyperglycemia to evaluate the association between hyperglycemia and exposure to SHS (Clair et al. 2011).

Confounding

Confounding bias could limit the previous research, because very few studies have accounted for important potential confounders, particularly diet (Behl et al. 2013). Diet is strongly and consistently associated with both the exposure and the outcome (Carr et al. 2000; Ford et al. 2003; Kimokoti et al. 2010; Kranz et al. 2012; Kris-Etherton 2003; Wang et al. 2006), yet only two published studies have attempted to adjust for diet at all when evaluating this hypothesis (Houston et al. 2006; Panagiotakos et al. 2004). Although previous studies have consistently reported positive associations between SHS and obesity, it is possible that unmeasured residual confounding may have contributed to these associations (Behl et al. 2013).

Interaction by Diet and Other Factors

Metabolic disorders are likely influenced by the joint effects of behavioral and environmental factors (Behl et al. 2013), but no published studies have investigated the interaction between diet, physical activity, or socioeconomic status and exposure to SHS. In particular, high dietary fiber intakes may reduce SHS-induced inflammatory responses (Ma et al. 2008) and high intakes of antioxidant or omega-3 polyunsaturated fatty acids may reduce oxidative stress (Barnoya and Glantz 2005; Romieu et al. 2008). High physical activity levels may counteract the adverse SHS-induced metabolic responses by lowering blood pressure (Whelton et al. 2002), improving dyslipidemia (Kiens et al. 1980), and restoring the antioxidant–prooxidant balance (Elosua et al. 2003). Finally, low socioeconomic status may modify the association indirectly through other factors, such as sociocultural (perceptions, social norms, knowledge), physical factors (access to care, built environment), or environmental factors (air quality).

Diet. Dietary factors may influence susceptibility to metabolic disorders within certain sub-populations. Previous epidemiologic evidence indicates that the interaction between active

smoking and poor diet quality (a low Framingham Nutritional Risk Score) on weight gain among adults is more than additive (Kimokoti et al. 2010). An animal study also demonstrated that the association between prenatal exposure to nicotine and subsequent weight gain was stronger among rats exposed to a postnatal high-fat diet (Somm et al. 2008).

High intakes of dietary fiber may counteract the detrimental effects of exposure to SHS by inhibiting hyperglycemia (Davis et al. 2004; Walter et al. 2003), reducing inflammatory responses (Liu et al. 2002; Vork et al. 2007), and improving the antioxidant–prooxidant balance (A Larrauri et al. 1996; Eastwood 1999). Additionally, high dietary fiber consumption has the potential to inhibit the absorption of cadmium (Kim et al. 2010), an important constituent of SHS that alters glucose homeostasis among individuals exposed to SHS and could lead to obesity (Edwards and Prozialeck 2009). Dietary fiber may also protect against the adverse effects of exposure to SHS on cardiovascular disease-related mortality (Clark et al. 2013) and may also protect against adverse effects on metabolic disorders.

Antioxidants, such as vitamins C and E, may improve SHS-induced LDL cholesterol oxidation (Carr et al. 2000; Ford et al. 2003) and block the oxidative stress caused by free radical exposure from SHS, which could prevent insulin resistance (Barnoya et al. 2005). High dietary intakes of antioxidants also inhibits the N-nitroso compound formation by destroying nitrosating agents (Lampe 1999). Both animal and human studies have reported that antioxidant supplementation (with vitamin C or vitamin E) mitigates the oxidative stress response induced by exposure to SHS (Al-Malki and Moselhy 2013; Dietrich et al. 2003; Howard et al. 1998).

Omega-3 polyunsaturated fatty acids may modulate the adverse effects of environmental exposures by reducing the generation of reactive oxygen species (Romieu et al. 2008) or improving endothelial dysfunction (Goodfellow et al. 2000), both of which could improve sensitivity to insulin

(Celermajer et al. 1996). EPA, in particular, may be an important modifier of this association whereby high levels of EPA inhibit endothelial cell apoptosis caused by nicotine-derived nitrosamino ketone (NNK), the precursor to NNAL (Tithof et al. 2001). Epidemiologic evidence supports the hypothesis that omega-3 polyunsaturated fatty acids may limit the harmful effects of SHS. Two studies have observed that omega-3 polyunsaturated fatty acids found in fish modified the association between smoking and coronary heart disease incidence, one among a prospective cohort of 8,006 Japanese-American men aged 45 to 65 years who lived in Hawaii (Rodriguez et al. 1996) and one among a prospective cohort of 72,012 Japanese men and women aged 45–74 years (Eshak et al. 2014).

Physical Activity. Low physical activity levels may contribute to metabolic disorders by elevating blood pressure (Whelton et al. 2002), decreasing HDL cholesterol levels (Kiens et al. 1980), and interfering with the antioxidant–prooxidant balance (Elosua et al. 2003). Furthermore, exposure to SHS leads to mitochondrial damage and increased oxidative stress, which directly affects the body's ability to produce energy to sustain physical activity. Smoking may attenuate the beneficial effect of physical activity on the prevention of carotid atherosclerosis among young and middle-aged smokers (Katano 2011).

Socioeconomic Status. Socioeconomic status may also be an important moderator of the association between exposure to SHS and metabolic disorders. Low socioeconomic status is associated with circulating inflammatory markers (Jousilahti et al. 2003; Wamala et al. 1999), obesity (Tuan et al. 2012), and hypertension (van den Berg et al. 2013), irrespective of race/ethnicity. Wamala et al. (1999) suggested that socioeconomic status may play a role in metabolic disorders by adversely influencing endocrine responses and increasing circulating cortisol levels, which may decrease sensitivity to insulin, raise triglycerides levels, and lower

HDL levels. On the other hand, van den Berg et al. (2013) postulated that obesity is primarily responsible for the differences in hypertension by socioeconomic status. Therefore, the biological mechanisms linking exposure to SHS and low socioeconomic status to metabolic disorders likely involve endocrine disruption, increased stress responses, and increased adiposity.

Although socioeconomic status could be an important moderator of the association between exposure to SHS and metabolic disorders, it is possible that socioeconomic status may be a surrogate for other behavioral, sociocultural, physical, or environmental factors. For instance, an important factor that is closely related to socioeconomic status is race/ethnicity. Sharma et al. (2008) reported that maternal race/ethnicity modified the association between maternal smoking during pregnancy and childhood obesity. The proposed mechanisms of this interaction include genetic polymorphisms, variations in enzyme activity, differences in tobacco products used or preferences for certain types of cigarettes by race/ethnicity (Sharma et al. 2008). However, it is also possible that race/ethnicity is a substitute measure of socioeconomic status (Kaufman et al. 1997) and thus the effect modification by race/ethnicity observed by Sharma et al. (2008) could actually be effect modification by socioeconomic status. On the other hand, socioeconomic status may modify the association between exposure to SHS and metabolic disorders whereby low socioeconomic status is a surrogate for behavioral factors (poor diet quality, low physical activity), sociocultural (social norms, knowledge), physical factors (access to care, built environment), or environmental factors (air quality) (Adler et al. 1994).

Table 2.1. Summary of Epidemiological Evidence

Obesity Reference	Study description	Exposure to SHS[a]	Outcome	Adjusted ORs/β Coefficients (95% CIs)
Raum et al. 2011	Germany; Cross-sectional; 6 years (n=1,954)	Parental Self-Report	Obesity	2.90 (1.86, 4.54)
Xie et al. 2010	China; Cross-sectional; 18+ years (n=389)	Self-report	Central obesity	2.7 (1.6, 4.5)
von Kries et al. 2008	Germany; Cross-sectional; 5-9 years (n=5,889)	Parental Self-Report	Obesity	2.50 (1.70, 3.70)
Mangrio et al. 2010	Sweden; Cross-sectional; 4 years (n=9,009)	Parental Self-Report	Obesity	1.51 (1.06, 2.16)
Wen et al. 2012	U.S.; Cohort; 7 years (n=21,083)	Parental Self-Report	Obesity	1.49 (1.31, 1.69)
Pagani et al. 2015	Canada; Cohort; 10 years (n=1,323)	Parental Self-Report	Obesity	1.43 (1.12, 1.81)
Yang et al. 2013	Canada; Cohort; 6.5 years (n=13,889)	Parental Self-Report	Obesity	1.40 (1.10, 1.70)
Itterman et al. 2013	Germany; Cross-sectional; 11-17 years (n=5,918)	Self-Report	Obesity	1.33 (1.07, 1.66)
Chen et al. 2012	Taiwan; Cross-sectional; 9-14 years (n=7,930)	Parental Self-Report	Obesity	1.30 (1.20, 1.50)
McConnell et al. 2015	U.S.; Cohort; 10 years (n=3,318)	Parental Self-Report	Difference in BMI	1.23 (0.86, 1.61)
Apfelbacher et al. 2008	Germany; Cross-sectional; 5-7 years (n=35,434)	Parental Self-Report	Obesity	1.13 (0.98, 1.32)
Steenland et al. 1998	U.S.; Cross-sectional; 18+ years (n=3,338)	Serum Cotinine	BMI	0.60 (N/A) β
Kwok et al. 2010	China; Cohort; 11 years (n=7,889)	Parental Self-Report	BMI	0.16 (0.07, 0.26) β
Jefferis et al. 2010	U.K.; Cross-Sectional; 59-80 years (n=5,029)	Serum Cotinine	BMI	0.11 (0.04, 0.19) β
Low HDL Reference	Study description	Exposure to SHS	Outcome	Adjusted Means (non-exposed vs. exposed); p-values
Feldman et al. 1991	U.S.; cross-sectional; 15 years (n=444)	Serum cotinine	HDL	N/A; p<0.05
Hirata et al. 2010	Japan; cross-sectional; 11 years (n=121)	Urinary cotinine	HDL	72.2 vs. 64.4; p<0.05
Iscan et al. 1996	Turkey; cross-sectional; 4-14 years (n=194)	Parental self-report	HDL	1.24 vs. 1.21; p>0.05
Jefferis et al. 2010	U.K.; cross-sectional; 59-80 years (n=5029)	Serum cotinine	HDL	1.53 vs. 1.53; p=0.19
Kallio et al. 2007	U.S.; prospective; 8-11 years (n=402)	Serum cotinine	HDL	1.30 vs. 1.25; p=0.95
Le-Ha et al. 2013	U.S.; prospective; girls*; 17 years (n=800)	Parental self-report	HDL	1.44 vs. 1.35; N/A
Lu et al. 2014	Scotland; cross-sectional; 16+ years (n=10,001)	Salivary cotinine	HDL	1.52 vs. 1.43; N/A
Moffatt et al. 1995	U.S.; cross-sectional; 21-50 years (n=31)	Self-report	HDL	1.44 vs. 1.25; p<0.05
Moskowitz et al. 1990	U.S.; prospective; 11 years (n=216)	Parental self-report	HDL	49.1 vs. 46.0; p<0.05
Neufeld et al. 1997	U.S; cross-sectional; 2-18 years (n=161)	Parental self-report	HDL	43.6 vs. 38.7; p<0.05
Panagiotakos et al. 2004	Greece; cross-sectional; 18+ years (n=3,355)	Self-report	HDL	45 vs. 42; p<0.05
Steenland et al. 1998	U.S.; cross-sectional; 17+ years (n=3,338)	Parental self-report	HDL	56.9 vs. 56.4; p=0.60
Xie et al. 2010	China; Cross-sectional; 30-54 years (n=389)	Self-report	HDL	1.40 vs. 1.22; p=0.01
Zahkar et al. 2015	U.S.; cross-sectional; 12-19 years (n=2,008)	Serum cotinine	HDL	N/A; p=0.58
High Triglycerides Reference	Study description	Exposure to SHS	Outcome	Adjusted Means (non-exposed vs. exposed); p-values
Iscan et al. 1996	Turkey; cross-sectional; 4-14 years (n=194)	Parental self-report	Triglycerides	1.12 vs. 1.12; p>0.05
Jefferis et al. 2010	U.K.; cross-sectional; 59-80 years (n=5029)	Serum cotinine	Triglycerides	1.56 vs. 1.60; p=0.09
Kallio et al. 2007	U.S.; prospective; 8-11 years (n=402)	Serum cotinine	Triglycerides	0.77 vs. 0.80; p=0.79
Le-Ha et al. 2013	U.S.; prospective; girls*; 17 years (n=800)	Parental self-report	Triglycerides	0.89 vs. 0.93

Moffatt et al. 1995	U.S.; cross-sectional; 21-50 years (n=31)	Self-report	Triglycerides	2.17 vs. 2.06; p>0.05
Neufeld et al. 1997	U.S; cross-sectional; 2-18 years (n=161)	Parental self-report	Triglycerides	112 vs. 123; p>0.05
Steenland et al. 1998	U.S.; cross-sectional; 17+ years (n=3,338)	Self-report	Triglycerides	162.6 vs. 163.0; p=0.93
Venn et al. 2007	U.S.; cross-sectional; 19+ years (n=7,599)	Serum cotinine	Triglycerides	120.0 vs. 95
Xie et al. 2010	China; Cross-sectional; 30-54 years (n=389)	Self-report	Triglycerides	1.50 vs. 144; p=0.80
Zahkar et al. 2015	U.S.; cross-sectional; 12-19 years (n=2,008)	Serum cotinine	Triglycerides	p=0.19
Hypertension				
Reference	Study description	Exposure to SHS	Outcome	Adjusted Means (non-exposed vs. exposed); p-values
Alshaarawy et al. 2013	U.S.; cross-sectional; 18+ years (n=2,889)	Serum cotinine	Change in SBP; Change in DBP	0.39; p=0.03 0.02; p=0.89
Huntington-Moskos et al.	U.S.; cross-sectional; 15-18 years (n=148)	Salivary cotinine	SBP; DBP	117 vs. 114; p=0.50 67 vs. 65; p=0.40
Jefferis et al. 2010	U.K.; cross-sectional; 59-80 years (n=5029)	Self-report	SBP; DBP	148 vs. 150; p=0.77 82 vs. 83; p=0.31
Makris et al. 2009	Greece; cross-sectional; 30+ years (n=790)	Self-report	SBP; DBP	122 vs. 126; p<0.05 76 vs. 77; p=0.09
Seki et al. 2010	Japan; cross-sectional; 18+ years (n=579)	Self-report	SBP	113 vs. 116; p = 0.02
Simonetti et al. 2011	Germany; cross-sectional; 6 years (n=4,236)	Parental self-report	SBP; DBP	β = 0.8442; p<0.05 β = 0.1608; p=0.50
Steenland et al. 1998	U.S.; cross-sectional; 17+ years (n=3,338)	Self-report	SBP; DBP	125 vs. 126; p=0.17 78 vs. 79; p=0.11
Xie et al. 2010	China; Cross-sectional; 30-54 years (n=389)	Self-report	SBP; DBP	118 vs. 118; p=0.90 79 vs. 80; p=0.50
Hyperglycemia				
Reference	Study description	Exposure to SHS	Outcome	Adjusted ORs/β Coefficients (95% CIs)
Houston et al. 2006	U.S.; Cohort; 18-30 years (n=4,572)	Serum Cotinine	Glucose categories	1.35 (1.06, 1.71)
Clair et al. 2011	U.S.; Cross-Sectional; 18+ years (n=17,827)	Serum Cotinine	HbA1c categories	1.31 (1.09, 1.57)
Xie et al. 2010	China; Cross-sectional; 30-54 years (n=389)	Self-report	Glucose categories	1.1 (0.3, 4.1)
White et al. 2012	U.K.; Cross-section; 16-19 years (n=774)	Serum Cotinine	Glucose	15.4 (6.09, 24.8) β
Jefferis et al. 2010	U.K.; Cross-Sectional; 59-80 years (n=5.029)	Serum Cotinine	Glucose	-.002 (-.005, 0) β
Thiering et al. 2011	Germany; Cohort; 10 years (n=470)	Parental Self-Report	Glucose	0.99 [Mean Ratio]
Metabolic Syndrome				
Reference	Study description	Exposure to SHS	Outcome	Adjusted ORs (95% CIs)
Weitzman et al. 2005	U.S.; Cross-Sectional; 12-19 years (n=1,109)	Serum Cotinine	MetS	6.70 (1.50, 29.7)
Xie et al. 2010	China; Cross-sectional; 30-54 years (n=389)	Self-Report	MetS	2.80 (1.20, 6.60)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; MetS, metabolic syndrome; OR, odds ratio, SBP, systolic blood pressure.

[a]The reference category for exposure to SHS was no self-report of exposure to SHS or cotinine levels above the limit of detection.

CHAPTER 3. PROJECT 1

INTERACTIONS BETWEEN DIET AND EXPOSURE TO SECONDHAND SMOKE ON THE PREVALENCE OF CHILDHOOD OBESITY – RESULTS FROM NHANES, 2007-2010

SUMMARY

Background: Exposure to SHS may increase risk for obesity, but few studies have investigated the joint effects of exposure to SHS and diet.

Objectives: We examined the interaction of exposure to SHS and diet on the prevalence of obesity among 6-19 year olds who participated in the 2007-2010 National Health and Nutrition Examination Survey.

Methods: We characterized exposure using a novel biomarker (NNAL), an established biomarker (cotinine), and self-report. Multinomial logistic regression models examined the association of SHS exposure on the prevalence of overweight and obesity as separate outcomes (compared with normal/underweight). Interaction by diet was assessed by introducing interaction terms (with SHS) of the individual nutrients (dietary fiber, EPA, DHA, vitamin C, and vitamin E) into separate models.

Results: Approximately half of the children had NNAL and cotinine levels above the limit of detection, indicating exposure to SHS. Interaction results suggest that the prevalence of obesity among children with both high exposure to SHS and low levels of certain nutrients (dietary fiber, DHA, or EPA) is greater than would be expected due to the effects of the individual exposures alone. Little or no evidence suggesting more or less than additive or multiplicative interaction was observed for vitamin C or vitamin E.

Conclusions: Childhood obesity prevention strategies aimed at reducing SHS exposures and improving diets may exceed the expected benefits based on targeting either risk factor alone.

INTRODUCTION

Obesity and obesity-related morbidity are global crises that affect all age groups (Karnik and Kanekar 2012), especially children (Wang and Lobstein 2006). Although the prevalence of obesity may be stabilizing in recent years (Skinner and Skelton 2014), the magnitude of childhood obesity in the United States (U.S.) remains high; approximately 12.5 million (17%) children are classified as obese (Ogden et al. 2012).

High caloric diets and low physical activity levels are accepted as risk factors for obesity; however the extent of obesity prevalence cannot be entirely explained by these risk factors (Newbold et al. 2009). An emerging hypothesis suggests that environmental exposures may play a role in the onset of childhood obesity (Holtcamp 2013; Thayer et al. 2012); specifically, exposure to SHS may be involved in the onset of childhood obesity. Exposure to SHS is independently associated with increased inflammatory responses, oxidative stress, and endocrine disruption (Barnoya and Glantz 2005; Tziomalos and Charsoulis 2004), and these adverse health effects could ultimately lead to obesity (Tziomalos and Charsoulis 2004; Youn et al. 2014). Furthermore, several epidemiologic studies have reported that self-reported exposure to SHS was positively associated with obesity among children under the age of 10 years (Apfelbacher et al. 2008; Kwok et al. 2010; Mangrio et al. 2010; Raum et al. 2011; von Kries et al. 2008; Wen et al. 2013; Yang et al. 2013).

Although the epidemiologic evidence is growing, there remain important gaps in the literature evaluating the impact of exposure to SHS on childhood obesity. Specifically, previous

studies may be limited by exposure assessment because self-report of exposure to SHS may not be as accurate as biological markers of exposure (Goniewicz et al. 2011). Cotinine is a nicotine metabolite with a half-life of 16 hours and NNAL is a tobacco-specific metabolite with a half-life of 10-16 days (Hecht et al. 2001). The use of biomarkers could reduce measurement error; however, no published studies have evaluated the association between exposure to SHS and childhood obesity using cotinine or NNAL to characterize exposure to SHS.

It is also possible that the joint effect of poor diet quality and SHS exposures on childhood obesity may be more than would be expected based on the individual effects. Previous epidemiologic evidence indicates that the interaction between active smoking and poor diet quality (a low Framingham Nutritional Risk Score) on weight gain among adults is more than additive (Kimokoti et al. 2010). An animal study also demonstrated that the association between prenatal exposure to nicotine and subsequent weight gain was stronger among rats exposed to a postnatal high-fat diet (Somm et al. 2008). It is possible that high intakes of fiber, antioxidants, or omega-3 polyunsaturated fatty acids may counteract the inflammatory responses and oxidative stress induced by exposure to SHS (Barnoya and Glantz 2005; Ma et al. 2008; Romieu et al. 2008) and thus reduce the risk for adiposity (Fernandez et al. 2004); however, no published studies have explored the potential interactions between exposure to SHS and dietary factors on childhood obesity (Behl et al. 2013).

We evaluated the interaction between exposure to SHS and selected dietary nutrients on the prevalence of obesity among 6-19 year olds using data from the NHANES 2007-2010 (Centers for Disease Control and Prevention [CDC] 2015). In this analysis, we compared self-reported exposure to SHS with both an established biomarker (cotinine) and a novel biomarker (NNAL).

METHODS

Study population: NHANES is a population-based, cross-sectional survey that uses a complex, multistage approach designed to achieve a nationally representative sample of the U.S. civilian population (CDC 2015). The CDC maintains that institutional review board approval for NHANES and informed consent was obtained from all participants. The Colorado State University Institutional Review Board has designated the secondary data analysis proposed in this project as not human subjects research (see Appendix 1.0).

Trained interviewers administered surveys in participants' homes to ascertain information on demographic factors, physical activity, and diet. Children under 16 years of age answered questions with the assistance of an adult household member; children 16 years of age and older completed the survey unassisted. An exception was with the administration of the dietary recalls, for which children under age 12 years completed the dietary recalls with the assistance of an adult household member and children 12 years of age and older completed the dietary recalls without assistance. Additionally, physical exams and laboratory testing using blood and urine samples were conducted at mobile examination centers.

Urinary NNAL was first measured in NHANES during the 2007-2008 sampling cycle. Therefore, we used NHANES data obtained for 6-11 year olds and 12-19 year olds for the sampling cycles 2007-2008 (n=2,500) and 2009-2010 (n=2,596). We excluded children who were missing body mass index, laboratory measurements of serum cotinine or urinary NNAL, dietary information, or other physical activity information (n=2,249). We further excluded children with evidence of active smoking, defined as having a cotinine level >15 ng/mL and/or self-report of current active smoking (n=177, 8%) (Weitzman et al. 2005). Our final sample size was 2,670.

Overweight and obesity: Height was measured using a stadiometer with a fixed vertical backboard and an adjustable headpiece. Weight was measured in kilograms using a digital scale. Body mass index (BMI) was calculated for all children by dividing weight (kilograms) by height (meters) squared. Each child's BMI was converted to an age- and sex-specific z-score based on the CDC's BMI-for-age charts for boys and girls (Kuczmarski et al. 2002). The growth charts were then used to identify the corresponding z-scores for overweight (BMI≥85th percentile to BMI<95th percentile) and obesity (BMI≥95th percentile) (Kuczmarski et al. 2002). Underweight was defined as having a BMI less than the 5th percentile, and normal weight was defined as having a BMI greater than or equal to the 5th percentile and less than the 85th percentile, for age and sex. Due to the small proportion of underweight children in our sample (n=77; 2.8%), we combined underweight and normal into one category.

As a sensitivity analysis, we also used an international definition of overweight and obesity among children, as defined by the International Obesity Task Force (IOTF) (Cole et al. 2000). The IOTF developed BMI cut-off values for childhood overweight and obesity based on large data sets from six countries including Brazil, Britain, Hong Kong, the Netherlands, Singapore and the U.S. These cut-off values are linked with the adult cut-off values of 25 and 30 for overweight and obesity, respectively, by age and sex. In general, there is very strong agreement between the CDC and IOTF definitions in the assessment of the prevalence of overweight/obesity among children (Hajian-Tilaki and Heidari 2013).

Exposure to Secondhand Smoke: NNAL was measured in spot urine samples using liquid chromatography linked to tandem mass spectrometry (LC/MS/MS). The detection limits have changed over time in NHANES: in 2007-2008, the limit of detection was 0.001 ng/mL; in 2009-

2010, the limit of detection was 0.0006 ng/mL. For consistency, we used the higher detection limit (Clair et al. 2011). The coefficients of variation for NNAL ranged from 5.0% to 10.1% in 2007-2008; the coefficients of variation for 2009-2010 are not currently available. In order to account for urinary dilution, standardized concentrations were created by dividing NNAL by urinary creatinine (Avila-Tang et al. 2013). Although there are no established cut-off points for NNAL to classify exposure to SHS, we used methods similar to a previous study evaluating exposure to SHS among non-smoking adults (Goniewicz et al. 2011). Creatinine-adjusted NNAL was categorized as below the limit of detection (NNAL<0.001 ng/mL), low exposure (NNAL≥0.001 ng/mL and ≤0.005 ng/mL creatinine [the median value among samples above the limit of detection]), and high exposure (NNAL>0.005 ng/mL creatinine).

Serum cotinine was measured by isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS; LOD=0.015 ng/mL). The coefficients of variation for cotinine ranged from 3.6% to 7.7% among low control batches and 3.3% to 4.8% among high control batches in 2007-2008 and 4.0% to 9.0% among low controls and 3.8% to 5.0% among high controls in 2009-2010. Cotinine was categorized as no exposure using a cut-point used by previous studies evaluating a similar hypothesis (cotinine<0.05 ng/mL) (Clair et al. 2011; Weitzman et al. 2005)]), low exposure (cotinine ≥0.05 ng/mL and ≤0.268 ng/mL [the median value among samples above 0.05 ng/mL]) and high exposure (cotinine>0.268 ng/mL). Self-report of household smokers was categorized as none (no household smokers), low exposure (one household smoker), and high exposure (two or more household smokers).

Diet: NHANES measured total dietary intake by administering two consecutive 24-hour dietary recalls conducted in-person by trained interviewers. The nutrient values for the dietary recalls were based on values in the U.S. Department of Agriculture National Nutrient Database for Standard Reference (U.S. Department of Agriculture 2012). For the current study, we evaluated diet in terms of individual nutrients, including dietary fiber, omega-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]), vitamin C and vitamin E. Dietary nutrients were categorized based on the median level.

Covariates: NHANES collected detailed information about the participant's household income and family size during the household interview. A poverty index ratio was calculated by dividing family income by the poverty level, specific to family size, year of interview and state of interview. The poverty index ratio was dichotomized at 1.85, the level used to qualify for federal assistance programs, such as the Women, Infants, and Children (WIC) program (U.S. Department of Agriculture 2015). Among 6-11 year olds, children were asked how many of the past seven days he or she spent being physically active for at least 60 minutes (2007-2008) or played or exercised hard enough to sweat for at least 60 minutes (2009-2010). Among 12-19 year olds, children were asked to identify the number of minutes per day and days per week in the past week they had engaged in moderate activity or vigorous activity. These variables were dichotomized based on the recommendation for children to get at least 60 minutes of moderate-to-vigorous intensity physical activity every day (Strong et al. 2005). Report of maternal smoking during pregnancy was ascertained by asking the parent/guardian if the biological mother smoked during pregnancy.

Statistical methods: All analyses accounted for the complex survey design and NHANES probabilistic sampling weights using the svy commands in Stata version 13 (Stata-Corp LP).

Weighted multinomial logistic regression models were used to describe the interaction between exposure to SHS and dietary variables on the prevalence of overweight and obesity as separate outcomes (compared with normal/underweight). All models adjusted for sex, age, race/ethnicity, and poverty index ratio based on previous publications. The ado-command svylogitgof was used to evaluate the F-adjusted mean residual test, a test specifically developed to assess goodness-of-fit for data from a complex survey design (Archer et al. 2007), the test suggested that our final models were a good fit for the data.

We examined interaction on both the multiplicative scale and the additive scale (Knol and VanderWeele 2012). Interaction by diet was assessed by introducing product terms between dichotomous exposure to SHS (high exposure vs. other) and dichotomized diet variables in separate models. For additive interaction, we used the relative excess risk due to interaction (RERI). The RERI is defined as $OR_{11}–OR_{10}–OR_{01}+1$, where an RERI value of 0 suggests a perfectly additive interaction. We calculated 95% confidence intervals (CI) and corresponding p-values for the RERI values using the method of variance estimates recovery (MOVER) method as described by Zou (2008). For the multiplicative interaction, we calculated p-values to assess the statistical significance of the product term.

Sensitivity analyses: We conducted several sensitivity analyses. We adjusted the models for total caloric intake, physical activity levels, and maternal report of smoking during pregnancy in order to assess the impact of these potential confounders. We also performed the models using cotinine and by self-report of household smokers to describe exposure to SHS. Finally, we investigated age groups separately (ages 6–11 years and ages 12–19 years).

Finally, in our interaction models, we evaluated the diet in terms of dietary nutrients derived from a principal components analysis (PCA) as described by Kim and Mueller (1978). From our PCA, we identified four distinct nutrient patterns from the PCA, explaining 68% of the variance in dietary nutrients: 1) the fiber-fat-soluble-vitamins component; 2) the saturated-fat component; 3) the vitamin-B-complex component; and 4) the omega-3-polyunsaturated-fatty-acids component.

RESULTS

Compared to children included in our analyses (n=2,670), children who were excluded due to smoking status (n=177) were more likely to be male, to be white, to have a poverty index ratio below the poverty level, and to report one or more household smokers. Weighted proportions of weight status and exposure to SHS are shown in Table 3.1. One third of children were either overweight (15%) or obese (19%). Approximately half of the children had levels of creatinine-adjusted NNAL and cotinine below the limit of detection (53% and 57%, respectively), and a majority of children (87%) reported no smokers within the household.

Table 3.2 presents weighted proportions of exposure to SHS and covariates by weight status categories. Exposure status was slightly different across the weight status categories. The proportion of children who had high creatinine-adjusted NNAL levels was 21% among children who were classified as normal/underweight, 23% among children who were classified as overweight, and 32% among children who were classified as obese. The sample was evenly distributed between males and females and the mean age was 12 years of age across the weight status categories. Race/ethnic proportions were slightly different across the weight status categories; for instance, the proportion of non-Hispanic white children was 62% among those classified as normal/underweight, 53% among those classified as overweight, and 51% among those classified as obese. The proportion of children

who were below the poverty level was higher among children who were classified as obese than children who were classified as normal/underweight. In general, a majority of the children reported that they met the recommendations for children to get at least 60 minutes of moderate-to-vigorous intensity physical activity every day.

Exposure to Secondhand Smoke: Among those who reported no smokers in the household, 41% had a creatinine-adjusted NNAL level above the LOD and 35% had a cotinine level above the LOD (Table 3.3). Children with high levels of creatinine-adjusted NNAL were also more likely to have reported maternal smoking during pregnancy (Pearson's chi-square; $p<0.01$); results were similar when using cotinine and self-report of household smokers.

Overweight and obesity: The proportions of children who were classified as underweight/normal using the U.S. and international definitions were similar (Table 3.1). There was some variation in how the U.S. definition and the international definition classified overweight and obesity. Specifically, among children who were classified as overweight using the international definition, approximately 24% were classified as normal/underweight using the U.S. definition (Table 3.4). An overwhelming majority of the children (98%) who were classified as obese using the international definition were also classified as obese using the U.S. definition.

Diet: The correlations between dietary fiber, vitamin C, vitamin E, DHA and EPA are shown in the Table 3.5. There was a moderate correlation between DHA and EPA (Spearman's rank correlation coefficient: 0.70) and between dietary fiber and vitamin E (Spearman's rank correlation coefficient: 0.65). However, the remaining dietary nutrients were weakly correlated (Spearman's rank correlation coefficients ranging from 0.08 to 0.39).

Interaction Analysis: The additive and multiplicative interaction results suggested that increases in obesity prevalence among children with both high NNAL levels and low levels of certain nutrients (dietary fiber, DHA, or EPA) were greater than would be expected due to the effects of the individual exposures alone (Table 3.6). For example, children with high NNAL levels and low fiber intakes were more than twice as likely to be obese as compared to children with low NNAL levels and high fiber intakes (odds ratio=2.6 [95% CI: 1.6, 4.0]). The results for overweight (versus normal/underweight) did not suggest that the interaction was important. No evidence suggesting more or less than additive or multiplicative interaction was observed for vitamin C or vitamin E (Table 3.7).

Sensitivity Analyses: The association between exposure to SHS and obesity was not changed following adjustment for total caloric intake and physical activity levels; however, the association was slightly attenuated following adjustment for report of maternal smoking during pregnancy (Table 3.8). The distributions of weight status, exposure to SHS, and covariates for the separate age groups (6-11 year olds and 12-19 year olds) were similar to the findings for age groups combined (see Appendix 3.1). The main effects results were consistent among 6-11 year olds (see Appendix 3.2) and 12-19 year olds (see Appendix 3.3).

There was limited evidence suggesting more or less than additive or multiplicative interaction for the omega-2-polyunsaturated-fatty-acids components, but no evidence suggesting more or less than additive or multiplicative interaction was observed for the other components (see Appendix 3.4). The interaction results were similar among 6-11 year olds (see Appendix 3.5) and by self-report of household smokers (see Appendix 3.6). The interaction results were similar when exposure to

SHS was determined by cotinine (see Appendices 3.7, 3.8, & 3.9) and by self-report of household smokers (see Appendix 3.10, 3.11, & 3.12).

DISCUSSION

The results of this study suggest that the joint effects of high exposure to SHS and low levels of certain nutrients (dietary fiber, DHA, or EPA) on obesity were greater than would be expected due to the effects of the individual exposures alone. For example, children with high NNAL levels and low fiber intakes were more than twice as likely to be obese as compared to children with low NNAL levels and high fiber intakes. Furthermore, the associations between exposure to SHS and obesity were stronger among children with low intakes of dietary fiber, EPA, and DHA compared to children with high intakes of these nutrients. Our results are consistent with a number of previous studies evaluating the independent associations between exposure to SHS and childhood obesity and our identification of statistical interaction with various dietary factors may support the hypothesized biological mechanisms of these associations.

Many compounds found in SHS, including nicotine and polycyclic aromatic hydrocarbons, are suspected endocrine disruptors and could negatively affect the utilization of insulin and promote metabolic imbalance (Tziomalos and Charsoulis 2004). Other potential pathways linking SHS exposures to obesity have been hypothesized; exposure to SHS is independently associated with inflammation and systemic oxidative stress (Barnoya and Glantz 2005), which could play a role in the development of obesity (Youn et al. 2014).

The inflammatory responses, oxidative stress, and endocrine disruption responses due to SHS may be counteracted by high intakes of dietary fiber and omega-3 polyunsaturated fatty acids. High

dietary fiber may improve the harmful effects of SHS exposures by increasing inflammatory responses (Ma et al. 2008). Additionally, high dietary fiber consumption may also inhibit the absorption of cadmium (Kim et al. 2010), an important constituent of SHS that alters glucose homeostasis among children exposed to SHS and could lead to obesity (Edwards and Prozialeck 2009). Furthermore, previous research has indicated that high dietary fiber consumption may ameliorate the harmful effects of exposure to SHS on the risk of coronary heart disease mortality among adults (Clark et al. 2013). Omega-3 polyunsaturated fatty acids may also modulate the adverse effects of environmental exposures by reducing the generation of reactive oxygen species (Romieu et al. 2008). High intakes of EPA may also inhibit endothelial cell apoptosis caused by nicotine-derived nitrosamino ketone (NNK), the precursor to NNAL (Tithof et al. 2001). These potential mechanisms are supported by two prospective cohort studies which observed that omega-3 polyunsaturated fatty acids modified the association between smoking and coronary heart disease incidence, one among 8,006 Japanese-American men aged 45 to 65 years who lived in Hawaii (Rodriguez et al. 1996) and one among 72,012 Japanese men and women aged 45–74 years (Eshak et al. 2014).

Previous studies have consistently observed positive associations between exposure to SHS and childhood obesity. One prospective cohort study of 21,083 mother–child pairs in the U.S. Collaborative Perinatal Project evaluated the association between exposure to SHS and childhood obesity; Wen et al. (2013) observed that heavy maternal smoking (20+ cigarettes/day) was associated with obesity among children at 7 years of age compared to no maternal smoking (adjusted OR 1.49; 95% CI 1.31, 1.69). These findings are supported by most observational studies. For instance, Raum et al. (2011) observed that children whose parents reported exposure to SHS at age 1 year and at age 6 years had higher odds for obesity (adjusted OR 2.90; 95% CI 1.86–4.54) compared to children

whose parents reported no exposure to SHS. The largest study conducted among a sample of 35,434 children ages 5-7 years, observed that parental self-report of household smoking was associated with childhood obesity (adjusted OR 1.13; 95% CI 0.98, 1.32) (Apfelbacher et al. 2008).

Strong evidence already exists for the increased risk of obesity among children exposed to SHS prenatally; a recent meta-analysis estimated that maternal smoking during pregnancy increases the risk for obesity among children by 50% (Oken et al. 2008). In order to distinguish the effects of prenatal and postnatal exposure to SHS on childhood obesity (Behl et al. 2013), we adjusted for report of maternal smoking during pregnancy in sensitivity analyses. We observed a slight attenuation in the odds for obesity in the independent effects models (see Supplemental Material, Table S2). Because a large portion of children was missing information about maternal smoking during pregnancy, we also limited our analyses to those with information about maternal smoking during pregnancy (n=2,106) and observed only a slight decrease in the odds for childhood obesity (results not presented).

This study provides valuable insight about the utility of three different exposure metrics for evaluating the impact of exposure to SHS on childhood obesity. Contrary to what was expected, our results suggest that the associations were consistent regardless of whether SHS is characterized by self-report, cotinine, or NNAL. Self-report of household smokers was limited to exposures within the home and did not attempt to capture exposure in other settings (e.g. schools, workplaces for older children, other households, multiunit housing, etc.), whereas cotinine likely captures the cumulative exposure to SHS over a shorter period of time than NNAL (Avila-Tang et al. 2013). Despite the differences in exposure classification across the three exposure metrics, the associations between SHS exposures and obesity were only slightly stronger for NNAL as compared to cotinine and self-

report of household smokers. Our results suggest that self-report of household smokers or cotinine may be just as appropriate to assess exposure to SHS among children who may be more likely to be exposed while at home. Since self-report and cotinine are easier and less expensive to measure than NNAL (Avila-Tang et al. 2013), one could argue that the latter is not necessary for studies evaluating this particular research question.

Several limitations should be considered when interpreting these results. It is possible that the associations observed in this study are due to residual confounding of physical activity and diet since these covariates are difficult to accurately measure (Thompson et al. 2010). Self-reported physical activity is subject to over-reporting due to social desirability (Prince et al. 2008) and is weakly correlated ($r<0.30$) with accelerometer-based estimates of physical activity levels (Tucker et al. 2011); these considerations could explain the relatively high proportion of children who met the recommendations for physical activity. There may be some limitations in how physical activity was measured as well. On the other hand, NHANES performs two consecutive 24-hour dietary recalls to evaluate diet, which may have eliminated some of the issues of a single measurement. Our results may also be impacted by our inability to adjust for other important covariates, such as parental BMI, because these variables were not available in the NHANES dataset.

Although the temporality of the relationship between exposure to SHS and obesity cannot be established, this study is a useful first step towards evaluating these novel associations and provides evidence for future investigation in larger-scale, prospective analyses. An important strength of the preset study is the sampling methods and the complex survey design employed by NHANES, which allows for the results to be generalized to all U.S. children.

CONCLUSIONS

Low levels of dietary fiber and omega-3 polyunsaturated fatty acids may worsen the effects of exposure to SHS on childhood obesity. Childhood obesity prevention strategies aimed at both reducing exposure to SHS and improving diets may exceed the expected benefits based on targeting either risk factor alone.

Table 3.1. Weighted proportions of weight status and exposure to SHS among 6-19 year olds, 2007-2010 NHANES (n=2,670)

	Percentage	95% CI
Weight Categories		
U.S. definition[a]		
Normal/underweight	66%	64%, 68%
Overweight	15%	14%, 16%
Obese	19%	17%, 21%
International definition[b]		
Normal/underweight	65%	63%, 67%
Overweight	20%	19%, 22%
Obese	15%	13%, 16%
Exposure Assessment		
NNAL Exposure		
Below LOD (<.001 ng/mL creatinine)	53%	48%, 57%
Low (≥.001 & <.005 ng/mL creatinine)	24%	21%, 27%
High (≥.005 & ≤.082 ng/mL creatinine)	23%	18%, 25%
Cotinine Exposure		
No (<.05 ng/mL)	57%	53%, 61%
Low (≥.05 & ≤.268 ng/mL)	21%	19%, 24%
High (≥.268 & ≤14.6 ng/mL)	22%	18%, 25%
Self-report of Household Smokers		
None	86%	85%, 89%
One	8%	7%, 10%
Two or more	6%	4%, 9%

Abbreviations: CI, confidence intervals; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS, secondhand smoke

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile and obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[b]Overweight and obesity is defined as having a body mass index that corresponds to a body mass index of 25 and 30 at age 18, respectively, based on the International Obesity Task Force growth charts.

Table 3.2. Weighted proportions by weight status of U.S. children, ages 6-19 years, 2007-2010 NHANES, n=2,670

	Normal/underweight		Overweight[a]		Obese[b]	
	Percentage	**95% CI**	**Percentage**	**95% CI**	**Percentage**	**95% CI**
Exposure Assessment						
NNAL						
Below LOD (<.001 ng/mL creatinine)	57%	52%, 62%	49%	46%, 54%	39%	33%, 47%
Low (≥.001 & <.005 ng/mL creatinine)	22%	18%, 26%	28%	25%, 31%	28%	28%, 34%
High (≥.005 & ≤.082 ng/mL creatinine)	21%	18%, 25%	23%	19%, 25%	32%	26%, 40%
Cotinine						
No (<.05 ng/mL)	60%	56%, 64%	57%	53%, 61%	47%	40%, 54%
Low (≥.05 & ≤.268 ng/mL)	21%	18%, 24%	23%	20%, 25%	22%	17%, 27%
High (≥.268 & ≤14.6 ng/mL)	19%	16%, 22%	19%	15%, 23%	31%	25%, 29%
Self-report of Household Smokers						
None	88%	85%, 90%	89%	87%, 92%	78%	71%, 83%
One	6%	5%, 8%	8%	7%, 10%	12%	8%, 17%
Two or more	6%	4%, 9%	4%	3%, 8%	10%	6%, 17%
Covariates						
Age (years, mean)	12.3	12.0, 12.6	12.5	12.2, 12.8	12.4	12.0, 12.7
Sex						
Male	51%	47%, 54%	52%	50%, 54%	56%	51%, 61%
Female	49%	46, 52%	48%	46%, 51%	44%	39%, 49%
Race/Ethnicity						
Non-Hispanic White	62%	56%, 67%	53%	47%, 59%	51%	41%, 60%
Non-Hispanic Black	13%	10%, 15%	17%	11%, 25%	19%	13%, 28%
Mexican American	12%	9%, 16%	17%	11%, 19%	17%	13%, 21%
Other Hispanic	8%	5%, 10%	6%	4%, 9%	5%	4%, 6%
Other/Multiracial	6%	4%, 9%	6%	5%, 9%	5%	3%, 7%
Poverty Index Ratio[c]						
Above poverty level (≥1.85)	62%	57%, 67%	58%	54%, 65%	51%	44%, 58%
Below poverty level (<1.85)	38%	33%, 43%	42%	37%, 47%	49%	41%, 55%
Moderate-to-Vigorous Physical Activity						
Met recommendations for 60 min/day	87%	82%, 90%	84%	81%, 87%	86%	83%, 89%
Did not meet recommendations	13%	10%, 17%	16%	13%, 19%	14%	11%, 17%

Abbreviations: CI, confidence intervals; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile, based on the 2000 Centers for Disease Control and Prevention growth charts.

[b]Obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[c]The poverty index ratio was dichotomized at 1.85, the level used to qualify for federal assistance programs, such as the Women, Infants, and Children program.

Table 3.3. Comparison of exposure to SHS categories among 6-19 year olds, 2007-2010 NHANES

	NNAL Exposure			Cotinine Exposure		
	Below LOD	Low	High	No	Low	High
Cotinine						
No	78%	20%	2%	-	-	-
Low	29%	50%	21%	-	-	-
High	4%	10%	86%	-	-	-
Self-report of household smokers						
None	59%	27%	14%	65%	24%	11%
Low	6%	13%	81%	4%	16%	81%
High	2%	9%	89%	4%	7%	89%

Abbreviations: LOD, limit of detection; NHANES; National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS, secondhand smoke.

Table 3.4. Comparison of weight categories among 6-19 year olds, 2007-2010 NHANES

	U.S. Definition[a]		
	Normal/underweight	Overweight	Obese
International Definition[b]			
Normal/underweight	99%	1%	0%
Overweight	24%	68%	8%
Obese	0%	2%	98%

Abbreviations: NHANES, National Health and Nutrition Examination Survey

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile and obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[b]Overweight and obesity is defined as having a body mass index that corresponds to a body mass index of 25 and 30 at age 18, respectively, based on the International Obesity Task Force growth charts.

Table 3.5. Spearman rank correlation coefficients for dietary nutrients among 6-19 year olds, 2007-2010 NHANES

	Dietary Fiber	Vitamin C	Vitamin E	EPA	DHA
Dietary Fiber	1				
Vitamin C	0.39	1			
Vitamin E	0.65	0.36	1		
EPA	0.18	0.11	0.28	1	
DHA	0.08	0.13	0.22	0.70	1

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NHANES, National Health and Nutrition Examination Survey

Table 3.6. Adjusted ORs and 95% CIs for overweight and obesity in relation to exposure to SHS and dietary nutrients and measures of additive and multiplicative interaction among 6-19 year olds, 2007-2010 NHANES

Dietary Nutrient	NNAL Exposure	Overweight[a] vs. Normal/Underweight		Obese[b] vs. Normal/Underweight	
		Adjusted[c] ORs (95% CIs)	Stratified ORs (95% CIs)	Adjusted ORs (95% CIs)	Stratified ORs (95% CIs)
High Fiber Intake	Below LOD/Low	1[d]	1	1	1
(≥12.75 g/day)	High	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)
Low Fiber Intake	Below LOD/Low	1.1 (0.7, 1.5)	1	1.1 (0.8, 1.4)	1
(<12.75 g/day)	High	1.6 (1.0, 2.6)	1.5 (0.9, 2.3)	2.6 (1.6, 4.0)	2.4 (1.7, 3.3)
p for multiplicative interaction[e]		p=0.47		p=0.05	
RERI (95% CI); p for additive interaction[f]		0.4 (-0.2, 1.0); p=0.19		0.8 (0.1, 1.5); p=0.03	
High EPA Intake	Below LOD/Low	1	1	1	1
(≥0.007 g/day)	High	1.4 (0.9, 2.0)	1.4 (0.9, 2.0)	1.6 (1.1, 2.3)	1.6 (1.1, 2.3)
Low EPA Intake	Below LOD/Low	1.2 (0.8, 1.8)	1	1.0 (0.8, 1.3)	1
(<0.007 g/day)	High	1.4 (0.9, 2.3)	1.2 (0.7, 2.2)	2.6 (2.0, 3.5)	2.6 (1.9, 4.0)
p for multiplicative interaction		p=0.76		p=0.05	
RERI (95% CI); p for additive interaction		-0.2 (-0.9, 0.5); p=0.56		1.0 (0.3, 1.8); p=0.01	
High DHA Intake	Below LOD/Low	1	1	1	1
(≥0.018 g/day)	High	1.2 (0.8, 1.9)	1.2 (0.8, 1.9)	1.6 (1.0, 2.5)	1.6 (1.0, 2.5)
Low DHA Intake	Below LOD/Low	1.2 (0.9, 1.7)	1	1.0 (0.8, 1.4)	1
(<0.018 g/day)	High	1.7 (0.9, 2.7)	1.4 (0.8, 2.4)	2.4 (1.7, 3.4)	2.4 (1.6, 3.5)
p for multiplicative interaction		p=0.68		p=0.19	
RERI (95% CI); p for additive interaction		0.3 (-0.4, 1.0); p=0.41		0.8 (0.1, 1.6); p=0.04	

Abbreviations: CI, confidence intervals; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LOD, limit of detection; NHANES; National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; OR, odds ratio; RERI, relative excessive risk due to interaction; SHS, secondhand smoke

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile, based on the 2000 Centers for Disease Control and Prevention growth charts.

[b]Obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[c]Adjusted for sex, age, race/ethnicity, and poverty index ratio.

[d]Reference category

[e]p for multiplicative interaction generated for the product term of each dietary factor (e.g., fiber, EPA, DHA) and exposure to SHS.
[f]p for additive interaction generated for the relative excess risk due to interaction value.

Table 3.7. Adjusted ORs and 95% CIs for overweight and obesity in relation to exposure to SHS and dietary nutrients and measures of additive and multiplicative interaction among 6-19 year olds, 2007-2010 NHANES

Dietary Nutrient	NNAL Exposure	Overweight[a] vs. Normal		Obese[b] vs. Normal	
		Adjusted[c] ORs (95% CIs)	Stratified ORs (95% CIs)	Adjusted ORs (95% CIs)	Stratified ORs (95% CIs)
High Vitamin C Intake (≥68.9 g/day)	Below LOD/Low	1	1	1	1
	High	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)	1.8 (1.3, 2.6)	1.8 (1.3, 2.6)
Low Vitamin C Intake (<68.9 g/day)	Below LOD/Low	1.2 (0.8, 1.8)	1	1.1 (0.8, 1.5)	1
	High	1.7 (1.0, 2.7)	1.4 (0.7, 2.4)	2.4 (1.7, 3.4)	2.2 (1.5, 3.6)
p for multiplicative interaction[d]		p=0.78		p=0.30	
RERI (95% CI); p for additive interaction[e]		0.2 (-0.4, 0.9); p=0.56		0.5 (-0.2, 1.3); p=0.18	
High Vitamin E Intake (≥5.42 mg/day)	Below LOD/Low	1	1	1	1
	High	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)
Low Vitamin E Intake (<5.42 mg/day)	Below LOD/Low	1.5 (1.1, 2.0)	1	1.2 (0.9, 1.5)	1
	High	2.2 (1.5, 3.3)	1.5 (0.9, 2.3)	2.6 (1.8, 3.7)	2.2 (1.5, 3.2)
p for multiplicative interaction		p=0.34		p=0.56	
RERI (95% CI); p for additive interaction		0.5 (-0.2, 1.3); p=0.20		0.5 (-0.3, 1.3); p=0.22	

Abbreviations: CI, confidence intervals; LOD, limit of detection; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; OR, odds ratio; RERI, relative excessive risk due to interaction; SHS, secondhand smoke

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile, based on the 2000 Centers for Disease Control and Prevention growth charts.

[b]Obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[c]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[d]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

[e]p for additive interaction generated for the relative excess risk due to interaction (RERI) value.

Table 3.8. Crude and adjusted models for the association of exposure to SHS exposure and overweight and obesity among U.S. children, ages 6-19 years, 2007-2010 NHANES

	NNAL Exposure		Cotinine Exposure		Self-report of Household Smokers	
	Overweight[a] vs. Normal ORs (95% CIs)	**Obese[b] vs. Normal ORs (95% CIs)**	**Overweight vs. Normal ORs (95% CIs)**	**Obese vs. Normal ORs (95% CIs)**	**Overweight vs. Normal ORs (95% CIs)**	**Obese vs. Normal ORs (95% CIs)**
Crude						
Below LOD/No	1[c]	1	1	1	1	1
Low	1.2 (0.9, 1.6)	1.6 (1.2, 2.3)	1.2 (0.9, 1.6)	1.2 (1.0, 1.5)	1.2 (0.8, 1.9)	1.8 (1.3, 2.3)
High	1.2 (1.0, 1.6)	1.9 (1.4, 2.6)	1.1 (0.1, 1.4)	1.8 (1.4, 2.3)	0.8 (0.4, 1.3)	1.6 (1.0, 2.4)
p for trend	p=0.18	p<0.01	p=0.40	p<0.01	p=0.59	p<0.01
Model 1[d]						
Below LOD/No	1	1	1	1	1	1
Low	1.3 (0.9, 1.8)	1.7 (1.2, 2.5)	1.2 (0.9, 1.6)	1.3 (1.0, 1.6)	1.2 (0.7, 1.9)	1.7 (1.2, 2.4)
High	1.3 (1.0, 1.7)	2.2 (1.6, 3.1)	1.2 (0.8, 1.6)	1.9 (1.4, 2.5)	0.8 (0.5, 1.6)	1.7 (1.1, 2.8)
p for trend	p=0.08	p<0.01	p=0.29	p<0.01	p=0.84	p<0.01
Model 2[e]						
Below LOD/No	1	1	1	1	1	1
Low	1.5 (1.1, 2.1)	1.8 (1.3, 2.7)	1.3 (0.9, 1.9)	1.6 (1.1, 2.0)	1.2(0.6, 2.4)	2.0 (1.4, 3.0)
High	1.4 (0.9, 2.0)	2.5 (1.7, 3.5)	1.1 (0.8, 1.6)	2.1 (1.5, 3.0)	0.8 (0.3, 1.7)	2.1 (1.3, 3.3)
p for trend	p=0.04	p<0.05	p=0.36	p<0.05	p<0.05	p=0.74
Model 3[f]						
Below LOD/No						
Low	1.4 (0.9, 2.1)	2.1 (1.5, 3.0)	0.9 (0.6, 1.4)	1.7 (1.1, 2.5)	0.8 (0.4, 1.7)	1.0 (1.0, 1.1)
High	1.1 (0.7, 1.6)	1.8 (1.2, 2.7)	1.6 (1.1, 2.5)	1.6 (1.1, 2.5)	0.5 (0.2, 1.4)	2.0 (1.4, 2.8)
p for trend	p=0.44	p<0.01	p=0.67	p=0.01	p=0.10	p=0.27

Abbreviations: CI, confidence intervals; LOD, limit of detection; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; OR, odds ratio; SHS, secondhand smoke

[a]Overweight was defined as having a body mass index ≥85th percentile and <95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[a]Obesity was defined as having a body mass index ≥95th percentile by age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts.

[c]Reference category.

[d]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[e]Model 1 plus additional adjustment for the total caloric intake and physical activity levels.

[f]Model 2 plus for additional adjustment for report of maternal smoking during pregnancy.

CHAPTER 4. PROJECT 2

INTERACTIONS BETWEEN DIET AND EXPOSURE TO SECONDHAND SMOKE ON THE PREVALENCE OF METABOLIC SYNDROME AMONG CHILDREN – RESULTS FROM NHANES 2007-2010

SUMMARY

Context: Metabolic syndrome is likely influenced by a complex interaction between exposure to SHS and diet, but no studies have evaluated this relationship.

Objective: Metabolic syndrome is likely influenced by a complex interaction between exposure to SHS and diet, but no studies have evaluated this relationship.

Design and Participants: We used weighted logistic regression, adjusting for potential confounders, to examine interaction of these risk factors on the prevalence of metabolic syndrome among 12-19 year olds participating in NHANES (2007-2010). Interaction was assessed by introducing product terms between SHS (NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol], cotinine, and self-report) and the individual nutrients (dietary fiber, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], vitamin C, and vitamin E) and nutrient patterns in separate models; the relative excess risk due to interaction (RERI) was used to evaluate additive interaction.

Results: The joint effect between high exposure to SHS and low levels of certain nutrients (vitamin E and omega-3 polyunsaturated fatty acids) on metabolic syndrome risk was greater than would be expected due to the effects of the individual exposures alone (for example, RERI for SHS and vitamin E = 7.5; 95% confidence interval [CI]: 2.5, 17.8]).

Conclusions: Prevention strategies for metabolic syndrome aimed at both reducing exposure to SHS and improving diet quality may exceed the expected benefits based on targeting these risk factors separately.

INTRODUCTION

The epidemic of obesity in children has been well-documented (Wang and Lobstein 2006). Concordantly, but not as well-known, a surprising number of children (20-50% of children who are obese) are also diagnosed with metabolic syndrome (Messiah et al. 2007), a cluster of conditions including abdominal fatness, hypertension, an adverse lipid profile and insulin resistance, which may increase the risk of multiple chronic diseases (Wilson et al. 2005). Based on the 1988-2010 NHANES, the prevalence of metabolic syndrome among U.S. children has fluctuated between 4% and 9% (Johnson et al. 2009). Hypothesized risk factors for metabolic syndrome include modifiable lifestyle factors, such as dietary composition, physical activity levels, active smoking, and weight (Park et al. 2003). However, these factors do not entirely account for the prevalence of metabolic syndrome, and it has recently been suggested that exposure to chemicals in the environment may lead to an increase in risk for metabolic syndrome (Wang et al. 2014). SHS is a common environmental exposure among U.S. children. Despite the steady decline in smoking rates in the U.S. since 1964 (Giovino et al. 1994), nearly half of children are exposed to SHS on a regular basis (CDC 2010).

Limited evidence suggests exposure to SHS is independently associated with each of the individual components of metabolic syndrome, including obesity (von Kries et al. 2008), hyperglycemia (Houston et al. 2006), hypertension (Alshaarawy et al. 2013), and dyslipidemia (Jefferis et al. 2010). Only two published studies have examined the association between

exposure to SHS and metabolic syndrome; one utilized self-report of exposure to SHS among adult non-smokers in China (Xie et al. 2010) and the second utilized serum cotinine, the metabolite of nicotine, among adolescents (ages 12-19 years) using data obtained from 1988-1994 NHANES (Weitzman et al. 2005). Although both studies demonstrated a positive association between exposure to SHS and metabolic syndrome, the results may be limited by the methods used to assess exposure to SHS and also by the potential for uncontrolled confounding (particularly by diet). Furthermore, metabolic syndrome is likely influenced by a complex interaction between lifestyle and environmental factors (Behl et al. 2013), but no published studies have evaluated the potential interactions between exposure to SHS and dietary factors.

We examined the interaction between exposure to SHS and selected dietary factors with anti-oxidant and/or anti-inflammatory properties on the prevalence of metabolic syndrome among adolescents (ages 12-19 years) using data obtained from the 2007-2010 NHANES. We utilized two biomarkers to objectively characterize exposure to SHS, an established biomarker (serum cotinine) and a novel biomarker (urinary NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol]) (Avila-Tang et al. 2013), along with self-report of household smokers.

METHODS

Study population: NHANES is a population-based survey that uses a complex, multistage approach designed to achieve a nationally representative sample of the non-institutionalized civilian population in the U.S. The CDC maintains that institutional review board approval for NHANES and informed consent was obtained from all participants. The Colorado State University Institutional Review Board has designated the secondary data analysis proposed in this project as not human subjects research (see Appendix 1.0).

Participants were evaluated by trained staff during a home interview to determine demographic factors, dietary recalls, physical activity, and self-report of household smokers. In general, children under 16 years of age answered questions with the assistance of an adult household member; children 16 years of age and older completed the survey unassisted. For the dietary recalls, children 12 years of age and older completed the dietary recalls without assistance. Extensive physical examinations, which included blood and urine collection, were conducted at mobile examination centers.

In the 2007-2010 NHANES, data from 2,577 children (ages 12-19 years) were collected. The components of metabolic syndrome were only available for a portion of the children (n=925). Among children with components of metabolic syndrome, we further excluded children who were missing laboratory measurements of serum cotinine or urinary NNAL, dietary information, or other physical activity information (n=309). Active smokers, defined as those with cotinine levels >15 ng/mL (Weitzman et al. 2005) or those who reported current smoking, were excluded from our sample (n=57). Therefore, our final sample size was n=559.

Metabolic Syndrome: The criteria for defining metabolic syndrome among children varies (Ford and Li 2008). We used the definition as described by several published studies, including a previous study evaluating a similar hypothesis (Weitzman et al. 2005). Metabolic syndrome in children was defined as exhibiting three or more of the following clinical conditions: abdominal obesity, hyperglycemia, hypertension, high triglycerides, and low high-density lipoprotein (HDL) cholesterol (Weitzman et al. 2005).

The individual components of metabolic syndrome were defined as follows. Waist circumference measurements were made between the bottom of the ribcage and the top of the

iliac crest, with the participant at minimal respiration. Abdominal obesity was defined as having a waist circumference that was greater than the age- and sex-specific 90th percentile previously developed using a nationally representative sample of U.S. children (Fernandez et al. 2004). Blood specimens were collected following a fast for 8-12 hours. HDL cholesterol and triglycerides were measured in serum using the Roche Modular P chemistry analyzer (Roche Diagnostics, 9115 Hague Road, Indianapolis, IN 46250). Hyperglycemia was defined as having fasting glucose levels ≥100 mg/dL (American Diabetes Association 2014). High triglycerides were defined as having triglycerides ≥110 mg/dL (U.S. Department of Health and Human Services 2002) Low HDL cholesterol was defined as having HDL ≤40 mg/dL (U.S. Department of Health and Human Services 2002). Blood pressure was measured using a mercury sphygmomanometer after resting quietly in a sitting position for five minutes. Each participant provided at least three but up to four blood pressure readings; the average of these measurements was used. Hypertension was defined as having a blood pressure level that was greater than the age-, sex-, and height-specific 90th percentile based on previously defined cut-points developed using a nationally representative sample of U.S. children (National Cholesterol Education Panel 1996).

Secondhand smoke: Urinary NNAL was measured in spot urine samples using liquid chromatography linked to tandem mass spectrometry, as detailed by Xia et al. (2005). The detection limits for NNAL have changed over time in NHANES: in 2007-2008, the limit of detection (LOD) was 0.001 ng/mL; in 2009-2010, it was 0.0006 ng/mL. For consistency, we used the higher detection limit to determine exposure status. NNAL concentrations were corrected for creatinine by dividing the urinary NNAL concentrations by urinary creatinine concentrations, in order to account for variation in dilution in spot urine samples (Avila-Tang et al. 2013). Creatinine-adjusted NNAL was categorized as below the LOD (NNAL<0.001 ng/mL),

low exposure (NNAL≥0.001 ng/mL and ≤0.005 ng/mL creatinine [the median value among samples above the LOD]), and high exposure (NNAL>0.005 ng/mL creatinine).

Serum cotinine was measured by isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (LOD=0.015 ng/mL), as detailed by Jacob et al. (2008). Cotinine was categorized as no exposure (cotinine<0.05 ng/mL [a cut-point used by a previous study evaluating a similar hypothesis]) (Weitzman et al. 2005), low exposure (cotinine ≥0.05 ng/mL and ≤0.268 ng/mL [the median value among samples above the cut-point for no exposure to SHS]) and high exposure (cotinine>0.268 ng/mL). Self-report of household smokers was categorized as none (no household smokers), low exposure (one household smoker) and high exposure (two or more household smokers).

Diet: Dietary information was collected through the use of two 24-hour dietary recalls conducted in person by trained interviewers. Nutrient values for the dietary recalls were based on values in the U.S. Department of Agriculture National Nutrient Database for Standard Reference (U.S. Department of Agriculture 2012). Diet was evaluated in terms of individual nutrients that may improve the metabolic responses induced by exposure to SHS, including dietary fiber (Liu et al. 2002), antioxidants (vitamin C, vitamin E) (Barnoya and Glantz 2005), and omega-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) (Romieu et al. 2008; Tithof et al. 2001). Nutrient patterns were determined through the use of a principal component analysis (PCA) (Kim and Mueller 1978). We determined the number of meaningful components to be retained for rotation based on the eigenvalue criterion (>1.0), the scree test, the proportion of variance accounted for, and the interpretability criteria (Kim and Mueller 1978). The principal components were rotated using the varimax rotation, which maximizes the variance of the factor loadings. For each nutrient pattern, a component score was computed as a linear composite of the

nutrients with meaningful loading scores (>0.20). Dietary variables were dichotomized based on the median value.

Covariates: Information about the participant's household income was collected during the household interview and this information was used to create a ratio of family income to poverty. The poverty index ratio was dichotomized at 1.85, the level used to qualify for the Women, Infants, and Children program (Centers for Disease Control and Prevention 2015). During the household interviews, children were asked to identify the number of minutes per day and days per week in the past week they had engaged in moderate activity or vigorous activity. These variables were dichotomized based on the recommendation for children to get at least 60 minutes of moderate-to-vigorous intensity physical activity every day (Strong et al. 2005).

Statistical analysis: We used the svy commands in Stata version 13 to account for the complex survey design in our analyses (Stata-Corp LP, College Station, TX). Weighted means, standard deviations, and proportions for demographic characteristics, levels of exposure to SHS, and metabolic syndrome classification were computed. We used weighted logistic regression models to examine the association between exposure to SHS (in separate models for the three metrics) and metabolic syndrome. All multivariable models adjusted a priori for sex, age, race/ethnicity, and poverty index ratio. The addition of diet (in terms of the individual nutrients and nutrient patterns described previously), physical activity, or report of maternal smoking during pregnancy did not meaningfully change the results. The ado-command svylogitgof was used to evaluate the F-adjusted mean residual test, a test specifically developed to assess goodness-of-fit for complex survey design data (Archer et al. 2007); the test suggested that our final models were a good fit for the data.

We examined interaction on both the additive and multiplicative scales using the multivariable model described above and within the framework described by Knol and VanderWeele (2012). Interaction was assessed by introducing product terms between SHS and individual selected nutrients (dietary fiber, EPA, DHA, vitamin C, and vitamin E) and nutrient patterns in separate models. For additive interaction, the relative excess risk due to interaction (RERI) was calculated as $OR_{11}–OR_{10}–OR_{01}+1$, where an RERI value of 0 suggests perfect additivity (Knol and VanderWeele 2012). Using the method of variance estimates recovery method (Zou 2008), 95% CIs and corresponding two-sided p-values were calculated for the RERI values. For multiplicative interaction, we calculated p-values to assess the significance of each product term in the logistic regression models and compared the ORs for SHS and metabolic syndrome across strata of diet.

RESULTS

Included children (n=559) and children who were excluded due to smoking status (n=57) were similar with respect to age, sex, race/ethnicity, self-report of household smokers, and metabolic syndrome (results not presented). Children who were excluded due to smoking status (n=57) were more likely to have a poverty index ratio below the poverty level, to live with a household smoker and to be classified as having metabolic syndrome as compared to those included in our sample (n=559), respectively (results not presented). Approximately 5% of children were classified as having metabolic syndrome, with nearly 20% exhibiting abdominal obesity (16.6%), hyperglycemia (20.5%), or high triglyceride levels (17.8%) (Table 4.1).

Approximately 40% of the children had levels of creatinine-adjusted NNAL and cotinine in the low and high exposure categories as previously defined (45% and 40%, respectively), and 12% of children reported the presence of household smokers (Table 4.2). Among those who reported no

household smokers, 39% had a creatinine-adjusted NNAL level in the low or high exposure category and 32% had a cotinine level in the low or high exposure category. Children with metabolic syndrome were likely to be male, Mexican American, and below the poverty level and less likely to be non-Hispanic white than children without metabolic syndrome (Table 4.2). A high proportion of the children reported that they met the recommendations for physical activity, regardless of metabolic syndrome classification (Table 4.2).

From the PCA, we identified four distinct nutrient patterns that explained 68% of the variance in dietary nutrient intakes: 1) the fiber-fat-soluble-vitamins component; 2) the saturated-fat component; 3) the vitamin-B-complex component; and 4) the omega-3-polyunsaturated-fatty-acids component. The fiber-fat-soluble-vitamins component was characterized by fiber, beta-carotene, vitamin E, vitamin K, lutein and zeaxanthin, food folate, linoleic acid, and total polyunsaturated fat intake. The saturated-fat component was characterized by total saturated fat intake and eight individual saturated fatty acids. The vitamin-B-complex component was characterized by retinol, folate, folic acid, fortified folate, iron, and vitamins A, D, B1, B2, B6, B12, and added B12. The omega-3-polyunsaturated-fatty-acids component was characterized by four omega-3 polyunsaturated fatty acids, including eicosatetraenoic acid (20:4), EPA (20:5), docosapentaenoic acid (22:5), and DHA (22:6).

Our results suggest that higher exposure to SHS and lower consumption of certain dietary factors, including vitamin E and omega-3 polyunsaturated fatty acids, interact to increase the odds of metabolic syndrome (Table 4.3). For example, the joint effect of exposure to SHS and vitamin E intake was more than additive; the RERI for high NNAL exposure and low vitamin E intake was 7.5 (95% CI: 2.5, 17.8) (Table 4.3). Additionally, adjusted ORs for exposure to SHS across the strata of dietary intakes indicate that high NNAL exposure was associated with no increase in

metabolic syndrome among participants with high vitamin E intake (OR=1.3; 95% CI: 0.2, 7.6) and a ten-fold increase in metabolic syndrome among participants with low vitamin E intake (OR=10.8; 95% CI: 3.1, 36.4) (Table 4.3). Similar patterns of interaction and effect modification were observed for EPA and the omega-3-polyunsaturated-fatty-acids component from the PCA (Table 4.3). The results were similar when exposure to SHS was determined by cotinine (Table 4.4) and by self-report of household smokers (Table 4.5).

We observed an independent association between exposure to SHS and metabolic syndrome (see Appendices 4.1, 4.2, and 4.3). No evidence suggesting more or less than additive or multiplicative interaction was observed for fiber, DHA, vitamin C, vitamin E, the fiber-fat-soluble-vitamins component, the saturated-fat component, or the vitamin-B-complex component (see Appendix 4.4). Results were similar when exposure to SHS was determined by cotinine (see Appendix 4.5) and self-report of household smokers (see Appendix 4.6).

DISCUSSION

Approximately 5% of children in our sample were classified as having metabolic syndrome. The joint effects of high exposure to SHS and low levels of certain nutrients (vitamin E, EPA, or omega-3-polyunsaturated-fatty-acids component) on metabolic syndrome were greater than would be expected due to the effects of the individual exposures alone. Furthermore, the associations between exposure to SHS and metabolic syndrome were stronger among children with low intakes of vitamin E or omega-3 polyunsaturated fatty acids compared to children with high intakes of these nutrients. These results add to the limited epidemiologic evidence linking exposure to SHS with metabolic syndrome (Weitzman et al. 2005; Xie et al. 2010), and our identification of statistical

interaction with various dietary factors may support the hypothesized biological mechanisms of these associations (Balhara 2012).

Exposure to SHS is a source of free radicals that lead to oxidative stress and decreased antioxidant levels (Barnoya and Glantz 2005). Vitamin E is an important antioxidant. For example, one toxicological study reported that antioxidant supplementation may counteract the oxidative stress response induced by exposure to SHS among rats (Al-Malki and Moselhy 2013). Furthermore, a randomized controlled trial of 520 active smoking and non-smoking adults concluded that the protective effects of antioxidant supplementation (vitamin C or vitamin E) against oxidative stress were stronger among smokers than non-smokers (Salonen et al. 2000).

Omega-3 polyunsaturated fatty acids may similarly inhibit SHS-induced oxidative stress response (Romieu et al. 2008) or reduce endothelial cell apoptosis (Tithof et al. 2001), a marker which may predict future metabolic syndrome (Lembo et al. 2012). Epidemiologic evidence supports our results that omega-3 polyunsaturated fatty acids may attenuate the harmful effects of SHS. Specifically, two previous studies have noted effect modification of omega-3 polyunsaturated fatty acids found in fish on the association between smoking and coronary heart disease incidence, one among a prospective cohort of 8,006 Japanese-American men (ages 45-65 years) who lived in Hawaii (Rodriguez et al. 1996) and one among a prospective cohort of 72,012 Japanese men and women (ages 45–74 years) (Eshak et al. 2014).

A challenge of the present study was the limited sample size, as evidenced by the wide confidence intervals. However, the odds ratios from our study are realistic based on the results of previous studies reporting adjusted ORs ranging from 2.8 to 6.7 for the association between exposure to SHS and metabolic syndrome (Weitzman et al. 2005; Xie et al. 2010). The present

study may also be limited by its inability to establish temporality between exposure and disease due to the cross-sectional nature of NHANES, the reliance on one-time assessments of the exposure and the outcome, and the potential for residual confounding due to diet or physical activity or other unmeasured factors.

An important advantage of the present study was the ability to compare several assessments of exposure to SHS. Self-report of household smokers was limited to exposures within the home and did not attempt to capture exposure in other settings; cotinine has a half-life of 16 hours whereas NNAL has a half-life of up to 3 weeks (Avila-Tang et al. 2013). However, our results suggest that self-report of household smokers or cotinine may be just as appropriate to assess exposure to SHS as NNAL among children; it is feasible that most of a child's exposure to secondhand smoke occurs in the home and that the exposure is relatively consistent over time (i.e., the self-report of exposure and short half-life of cotinine may not necessarily be limitations for children). Since self-report and cotinine are easier and less expensive to measure than NNAL (Avila-Tang et al. 2013), these results suggest that the latter may not be not necessary for studies evaluating this research question among children. Another important strength of our study was its ability to control for potentially important covariates, especially diet. Furthermore, the sampling methods and the complex survey design employed by NHANES allows for the results to be generalized to all U.S. children.

CONCLUSIONS

These results add to the evidence linking exposure to SHS with metabolic syndrome. Furthermore, the results suggest that diets rich in antioxidants and omega-3 polyunsaturated fatty acids may counteract some of the adverse metabolic responses potentially triggered by exposure to

SHS. Prevention strategies for metabolic syndrome aimed at both reducing SHS exposures and improving diets may exceed the expected benefits based on targeting these risk factors separately.

Table 4.1. Weighted Proportions of Metabolic Syndrome and the Components of Metabolic Syndrome, 12-19 Year Olds, NHANES 2007-2010

Characteristic	Percentage	95% CI
Metabolic Syndrome (3 or more components)	5.2%	3.4, 7.9
Components of Metabolic Syndrome		
Abdominal obesity (waist ≥90th percentile for age and sex)	16.6%	12.6, 21.6
Hyperglycemia (fasting plasma glucose ≥100 mg/dL)	20.5%	16.6, 25.2
Hypertension (blood pressure ≥90th percentile for age and sex)	6.5%	4.0, 10.4
High triglyceride levels (triglycerides ≥110 mg/dL)	17.8%	13.7, 22.8
Low HDL levels (HDL ≤40 mg/dL)	6.4%	4.5, 9.0

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; NHANES, National Health and Nutrition Examination Survey.

Table 4.2. Weighted Proportions of Secondhand Smoke Categories and Potential Covariates, 12-19 Year Olds, NHANES, 2007-2010

Characteristic	No Metabolic Syndrome		Metabolic Syndrome		All Children	
	Percentage	95% CI	Percentage	95% CI	Percentage	95% CI
Secondhand Smoke						
NNAL						
Below LOD (<0.001 ng/mL creatinine)	56.2%	49.2, 63.1	36.5%	21.3, 55.0	55.3%	48.3, 62.0
Low (≥.001 & <0.005 ng/mL creatinine)	27.5%	22.1, 33.7	17.2%	7.7, 34.2	27.0%	21.8, 32.9
High (≥.005 & ≤0.082 ng/mL creatinine)	16.3%	13.7, 19.2	46.3%	28.0, 65.6	17.7%	15.0, 20.8
Cotinine						
No (<0.05 ng/mL)	61.4%	55.0, 67.7	34.4%	20.0, 52.4	60.1%	53.7, 66.2
Low (≥0.05 & ≤0.268 ng/mL)	19.6%	14.8, 25.5	21.0%	9.4, 40.5	19.7%	15.0, 25.3
High (≥0.268 & ≤14.6 ng/mL)	18.0%	15.8, 22.6	44.5%	26.4, 64.2	20.2%	16.9, 24.0
Self-report of Household Smokers						
None	89.0%	85.9, 91.4	67.4%	47.8, 82.4	87.8%	85.0, 90.2
Report of One Household Smoker	8.2%	4.6, 12.2	23.6%	11.1, 43.2	8.4%	5.4, 12.8
Report of Two or More Household Smokers	3.5%	1.6, 7.3	9.0%	2.6, 26.6	3.7%	3.7, 7.6
Potential Covariates						
Age, Mean (SD) (years)	15.0 (2.1)	14.8, 15.3	15.0 (2.1)	14.9, 15.4	15.0 (2.1)	14.8, 15.3
Sex						
Male	53.3%	48.0, 58.3	75.5%	57.2, 87.7	51.8%	46.7, 56.9
Female	46.7%	41.6, 51.9	24.5%	12.3, 42.8	48.2%	43.1, 53.3
Race/Ethnicity						
Non-Hispanic White	59.0%	50.9, 66.7	45.2%	26.7, 65.0	58.3%	50.1, 66.1
Mexican American	15.3%	11.4, 20.2	31.7%	18.7, 48.5	14.9%	11.3, 19.6
Non-Hispanic Black	11.6%	7.9, 16.8	11.6%	4.1, 28.4	12.7%	10.6, 18.0
Other/Multiracial	7.7%	5.2, 12.0	7.6%	2.6, 20.1	7.5%	5.1, 12.4
Other Hispanic	6.4%	3.4, 11.2	4.0%	0.1, 24.9	6.5%	5.0, 10.9
Poverty Index Ratio						
Above Poverty Level (≥1.85)	64.7%	57.9, 71.0	36.9%	20.0, 57.7	63.4%	56.7, 69.5
Below Poverty Level (<1.85)	35.3%	29.0, 42.1	63.1%	42.3,80.0	36.6%	30.5, 43.2

Moderate-to-Vigorous Physical Activity						
Did Not Meet Recommendations of 60 Minutes/Day	14.0%	10.3, 18.8	5.9%	0.1, 24.3	13.6%	9.9, 18.4
Met Recommendations of 60 Minutes/Day	86.0%	81.2, 89.7	94.1%	75.7, 98.8	86.4%	81.6, 90.1

Abbreviations: CI, confidence interval; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SD, standard deviation.

Table 4.3. Interaction of Diet and Creatinine-adjusted NNAL on Metabolic Syndrome, 12-19 Year Olds, NHANES, 2007-2010

	Below LOD/Low Exposure to NNAL			High Exposure to NNAL			NNAL Within Strata of Dietary Factor	
Level of Dietary Factor	**N With /Without MetS**	**AOR[a]**	**95% CI**	**N With/ Without MetS**	**AOR[a]**	**95% CI**	**AOR[a]**	**95% CI**
High Vitamin E Intake (≥5.42 mg/day)	16/218	1	Reference	3/43	1.3	0.2, 7.6	1.3	0.2, 7.6
Low Vitamin E Intake (<5.42 mg/day)	15/186	0.8	0.3, 2.0	12/52	8.6	2.5, 29.0	10.8	3.1, 36.4
				P-value for interaction term=0.04[b]				
				RERI (95% CI) = 7.5 (2.5, 17.8); *P*=0.01[c]				
High EPA Intake (≥0.007 g/day)	18/222	1	Reference	6/52	1.8	0.4, 7.7	1.8	0.4, 7.7
Low EPA Intake (≥0.007 g/day)	11/184	0.4	0.1, 1.2	11/41	7.2	1.5, 33.3	18.0	3.6, 83.3
				P-value for interaction term=0.02[b]				
				RERI (95% CI) = 6.0 (1.8, 12.7); *P*=0.02[c]				
High Omega-3 Fatty Acids Component	17/212	1	Reference	5/37	2.1	0.6, 7.8	2.1	0.6, 7.8
Low Omega-3 Fatty Acids Component	12/194	0.7	0.3, 1.8	11/57	8.1	1.8, 37.0	11.6	2.6, 53.0
				P-value for interaction term=0.10[b]				
				RERI (95% CI) =6.3 (1.3, 16.0); *P*=0.02[c]				

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EPA, eicosapentaenoic acid; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; MetS, metabolic syndrome; RERI, relative excess risk due to interaction.

[a]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] 2-sided *P* for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

[c] 2-sided *P* for additive interaction generated for the relative excess risk due to interaction value.

Table 4.4. Interaction of Diet and Cotinine on Metabolic Syndrome, 12-19 Year Olds, NHANES, 2007-2010

	Below LOD/Low Exposure to NNAL			High Exposure to NNAL			NNAL Within Strata of Dietary Factor	
Level of Dietary Factor	**N With /Without MetS**	**AOR[a]**	**95% CI**	**N With/ Without MetS**	**AOR[a]**	**95% CI**	**AOR[a]**	**95% CI**
High Vitamin E Intake (≥5.42 mg/day)	14/220	1	Reference	3/48	1.0	0.2, 5.7	1.0	0.2, 5.7
Low Vitamin E Intake (<5.42 mg/day)	16/197	0.9	0.4, 2.1	11/50	5.8	1.8, 19.3	6.4	2.0, 21.3
				P-value for interaction term=0.05[b]				
				RERI (95% CI) = 4.9 (1.3, 12.3); *P*=0.04[c]				
High EPA Intake (≥0.007 g/day)	19/229	1	Reference	5/52	1.4	0.3, 6.5	1.4	0.3, 6.5
Low EPA Intake (≥0.007 g/day)	11/188	0.5	0.2, 1.3	9/46	4.3	1.0, 18.3	8.6	2.0, 36.6
				P-value for interaction term=0.05[b]				
				RERI (95% CI) = 3.4 (0.3, 9.0); *P*=0.05[c]				
High Omega-3 Fatty Acids Component	17/212	1	Reference	5/37	1.4	0.4, 5.3	1.4	0.4, 5.3
Low Omega-3 Fatty Acids Component	12/194	0.7	0.3, 1.8	10/58	5.3	1.4, 19.5	7.6	2.1, 28.0
				P-value for interaction term=0.06[b]				
				RERI (95% CI) = 4.2 (0.8, 10.8); *P*=0.05[c]				

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EPA, eicosapentaenoic acid; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; RERI, relative excess risk due to interaction.

[a]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] 2-sided *P* for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

[c] 2-sided *P* for additive interaction generated for the relative excess risk due to interaction value.

Table 4.5. Interaction of Diet and Self-Report of Household Smokers on Metabolic Syndrome, 12-19 Year Olds, NHANES, 2007-2010

	No/One Household Smoker			Two or More Household Smokers			Self-Report Within Strata of Dietary Factor	
Level of Dietary Factor	**N With /Without MetS**	**AOR[a]**	**95% CI**	**N With/ Without MetS**	**AOR[a]**	**95% CI**	**AOR[a]**	**95% CI**
High Vitamin E Intake (≥5.42 mg/day)	14/243	1	Reference	3/25	2.4	0.5, 9.2	2.4	0.5, 9.2
Low Vitamin E Intake (<5.42 mg/day)	18/222	1.4	0.5. 3.2	9/25	8.5	3.2, 22.7	6.1	2.3, 16.3
				P-value for interaction term=0.14[b]				
				RERI (95% CI) = 5.7 (-1.7, 18.2); *P*=0.27[c]				
High EPA Intake (≥0.007 g/day)	19/257	1	Reference	5/24	2.5	0.5, 11.8	2.5	0.5, 11.8
Low EPA Intake (≥0.007 g/day)	13/208	0.7	0.2, 2.4	7/26	5.0	1.6, 15.6	7.1	2.3, 22.2
				P-value for interaction term=0.30[b]				
				RERI (95% CI) = 2.8 (-2.4, 10.5); *P*=0.40[c]				
High Omega-3 Fatty Acids Component	21/287	1	Reference	6/29	2.5	0.6, 10.5	2.5	0.6, 10.5
Low Omega-3 Fatty Acids Component	17/257	1.0	0.4, 2.8	9/32	6.6	2.0, 21.2	6.6	1.9, 17.5
				P-value for interaction term=0.33[b]				
				RERI (95% CI) = 4.1 (-1.0, 12.8); *P*=0.24[c]				

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EPA, eicosapentaenoic acid; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; RERI, relative excess risk due to interaction.

[a]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]2-sided *P* for additive interaction generated for the relative excess risk due to interaction value.

[c] 2-sided *P* for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

CHAPTER 5. PROJECT 3

INTERACTIONS BETWEEN DIET AND EXPOSURE TO SECONDHAND SMOKE ON HBA1C LEVELS AMONG CHILDREN – RESULTS FROM NHANES, 2007-2010

SUMMARY

Background: Glycemic control in children is potentially influenced by a complex interaction between exposure to secondhand smoke (SHS) and diet but the joint effect of these risk factors has not yet been investigated.

Objectives: We examined the interaction of exposure to SHS (assessed by NNAL, cotinine, and self-report) and individual nutrients (dietary fiber, EPA, DHA, vitamin C, and vitamin E) on glycated hemoglobin, fasting plasma glucose, and two-hour post-challenge glucose among 12-19 year olds who participated in the 2007-2010 National Health and Nutrition Examination Survey.

Methods: Weighted linear regression models were used to model the cross-sectional association between exposure to SHS and HbA1c and glucose levels in separate models. Additive interaction was assessed by introducing interaction terms (with SHS) of the individual nutrients.

Results: Correlations between HbA1c and glucose measurements were weak. In linear regression analyses, we observed limited evidence that exposure to SHS was independently associated with HbA1c or glucose levels. Measures of additive interaction suggested that increases in mean HbA1c among children with both high NNAL levels and low levels of dietary fiber, DHA, or vitamin C were greater than would be expected due to the effects of the individual exposures alone.

Conclusions: Diets high in dietary fiber, DHA, or vitamin C may attenuate the adverse

metabolic responses potentially triggered by exposure to SHS. Strategies for maintaining normal HbA1c and glucose levels aimed at both reducing SHS exposures and improving diets may exceed the expected benefits based on targeting these risk factors separately. Additionally, the results highlight the need for further research to investigate the differences in HbA1c, fasting plasma glucose, and two-hour post-challenge glucose among children.

INTRODUCTION

Glycated hemoglobin (HbA1c) is an independent predictor of type 2 diabetes and cardiovascular disease and is considered a more stable indicator of chronic hyperglycemia, the state of having excess blood glucose, than fasting plasma glucose and 2-hour post-challenge glucose (American Diabetes Association 2015). Type 2 diabetes, previously known as adult-onset diabetes mellitus, has become increasingly important among children in the United States (U.S.). Between 2001 to 2009, there was a 30% increase in the prevalence of type 2 diabetes among U.S. 10-19 year olds (Dabelea et al. 2014). Furthermore, data from NHANES suggest that the mean fasting plasma glucose levels have shifted from 91 mg/dL and 94 mg/dL in 1999-2000 to 97 mg/dL and 96 mg/dL in 2007-2008 among non-diabetic U.S. 12-17 year old boys and girls, respectively (Okosun et al. 2012). This upward trend is concerning because elevated glucose in childhood, even within the acceptable range, predicts type 2 diabetes in adulthood (Nguyen et al. 2010).

HbA1c and glucose are influenced by obesity, poor nutrition, and sedentary lifestyle (Alberti et al. 2007), but it is also possible that environmental exposures may impact these metabolic biomarkers (Thayer et al. 2012). Specifically, exposure to SHS may be an important contributing factor to elevated HbA1c and glucose levels (Thayer et al. 2012). Several animal

studies have reported that prenatal and neonatal exposure to nicotine or cigarette smoke is associated with hyperglycemia among rat and mice pups (Chen et al. 2011; Holloway et al. 2005; Somm et al. 2008). Epidemiologic studies have reported positive associations between high exposure to SHS (determined through cotinine or self-report) and elevated glucose among children (Thiering et al. 2011; White et al. 2014) and non-smoking adults (Houston et al. 2006; Jefferis et al. 2010).

Despite this growing body of evidence, previous studies may be limited by measurement error. The relationship between exposure to SHS and HbA1c has been evaluated in one study among adults (Clair et al. 2011), but no published studies have evaluated this relationship among children. Additionally, no published studies have evaluated these relationships using NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a novel and potentially more accurate biological marker of exposure to SHS than self-report or cotinine (Avila-Tang et al. 2013).

Furthermore, HbA1c and glucose are likely influenced by the joint effect of diet and exposure to SHS (Alberti et al. 2007; Thayer et al. 2012). In particular, high dietary fiber intakes may reduce the inflammatory responses (Ma et al. 2008) and high intakes of antioxidant or omega-3 polyunsaturated fatty acids may reduce oxidative stress (Barnoya and Glantz 2005; Romieu et al. 2008), both of which could improve sensitivity to insulin (Celermajer et al. 1996; Temelkova-Kurktschiev et al. 2002). Therefore, it is possible that high levels of these nutrients could counteract the adverse metabolic responses triggered by exposure of SHS; however, the joint effect of diet and exposure to SHS has not yet been investigated.

We used data obtained from 12-19 year olds who participated in the NHANES. We evaluated the relationship between exposure to SHS (determined by NNAL, cotinine, and self-

report) and metabolic biomarkers (HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose). Additionally, we assessed the potential interaction between diet and exposure to SHS.

METHODS

Study population: NHANES is a population-based survey that uses a complex, multistage approach designed to achieve a nationally representative sample of the U.S. civilian population. The CDC maintains that institutional review board approval for NHANES and informed consent was obtained from all participants. The Colorado State University Institutional Review Board has designated the secondary data analysis proposed in this project as not human subjects research (see Appendix 1.0). Trained interviewers administered surveys in participants' homes to ascertain information on demographic factors, physical activity, and diet. Physical exams and laboratory testing using blood and urine samples were conducted at mobile examination centers.

We used 2007-2010 NHANES data obtained for 12-19 year olds (n=2,577). All analyses were restricted to non-smoking children, defined as having a cotinine level <15 ng/mL and no self-report of current active smoking (n=332, 13%) (Weitzman et al. 2005). We further excluded children who were missing laboratory measurements of urinary NNAL, serum cotinine, or HbA1c, dietary information, or physical activity information (n=905). Therefore, our final sample size was 1,340. Fasting plasma glucose and 2-hour post-challenge glucose were only available for a subsample of these children (n=700).

HbA1c and glucose: HbA1c was measured on whole blood from all participants ≥12 years of age at the initial laboratory examination on the A1c 2.2 Plus Glycohemoglobin Analyzer using high-performance liquid chromatography. A fasting glucose blood test was performed on a subset

of participants ≥12 years of age that were examined during a second laboratory examination, which was performed in the morning following a fast from food for 8-12 hours. An oral glucose tolerance test followed; participants were asked to drink a glucose challenge drink of Trutol with approximately 75 grams of glucose and had a second venipuncture taken 2 hours after drinking the Trutol. Glucose measurements were performed on the Roche Modular P chemistry analyzer using the hexokinase assay.

Exposure to Secondhand Smoke: NNAL was measured in spot urine samples using liquid chromatography linked to tandem mass spectrometry (LC/MS/MS). The detection limits have changed over time in NHANES: in 2007-2008, the limit of detection (LOD) was 0.001 ng/mL; in 2009-2010, the LOD was 0.0006 ng/mL. For consistency, we used the higher detection limit (Clair et al. 2011). In order to account for urinary dilution, standardized concentrations were created by dividing NNAL by urinary creatinine (Avila-Tang et al. 2013). Although there are no established levels for NNAL to classify exposure to SHS, we used methods similar to a previous study evaluating exposure to SHS among non-smoking adults (Goniewicz et al. 2011). Creatinine-adjusted NNAL was categorized as below the LOD (NNAL<0.001 ng/mL), low exposure (NNAL≥0.001 ng/mL and ≤0.005 ng/mL creatinine [the median value among samples above the LOD]), and high exposure (NNAL>0.005 ng/mL creatinine).

Serum cotinine was measured by isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS; LOD=0.015 ng/mL). Cotinine was categorized as no exposure using a cut-point used by previous studies evaluating a similar hypothesis (cotinine<0.05 ng/mL) (Clair et al. 2011; Weitzman et al. 2005)]), low exposure (cotinine ≥0.05 ng/mL and ≤0.268 ng/mL [the median

value among samples above 0.05 ng/mL]) and high exposure (cotinine>0.268 ng/mL). Self-report of household smokers was categorized as none (no household smokers), low exposure (one household smoker) and high exposure (two or more household smokers).

Diet: NHANES measured total dietary intake by administering two consecutive 24-hour dietary recalls conducted in-person by trained interviewers. The nutrient values for the dietary recalls were based on values in the U.S. Department of Agriculture National Nutrient Database for Standard Reference (U.S. Department of Agriculture 2012). For the current study, we evaluated diet in terms of individual nutrients, including dietary fiber, omega-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]), vitamin C and vitamin E.

Covariates: NHANES collected detailed information about the participant's household income and family size during the household interview. A poverty index ratio was calculated by dividing family income by the poverty level, specific to family size, year of interview and state of interview (U.S. Department of Agriculture 2015). The poverty index ratio was dichotomized at 1.85, the level used to qualify for federal assistance programs (U.S. Department of Agriculture 2015). Children were asked to identify the number of minutes per day and days per week in the past week they had engaged in moderate activity or vigorous activity. These variables were dichotomized based on the recommendation for children to get at least 60 minutes of moderate-to-vigorous intensity physical activity every day (Strong et al. 2005). The parent/guardian of each child were asked to report if biological mother smoked during pregnancy.

Statistical methods: All analyses accounted for the complex survey design and NHANES probabilistic sampling weights using the *svy* commands in Stata version 13 (Stata-Corp LP, College Station, TX). The sampling weights were designed to account for the probability of being selected to

participate in the NHANES study, as well as to adjust for the probability of being selected to be in the subsample of participants who underwent the glucose testing. Weighted linear regression models were used to describe the relationship between exposure to SHS and dietary variables on HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose. Additive interaction was assessed by introducing product terms between the dichotomous exposure to SHS (high exposure vs. other) and dichotomized diet variables (using the median split) in separate linear regression models. All models were adjusted for sex, age, race/ethnicity, and the poverty index ratio. Our primary analyses evaluated these relationships using HbA1c and NNAL; secondary analyses evaluated these relationships using fasting plasma glucose and 2-hour post-challenge glucose. Crude and adjusted means and 95% CIs were presented for linear regression models. We ran regression diagnostics and examined the distribution of the residuals to verify that our data met the assumptions of ordinary least squares regression. We identified four potential outliers of HbA1c in our data; however, exclusions of the potential outliers did not have a meaningful impact on our results. Therefore, no outliers were excluded.

Sensitivity analyses: We conducted several sensitivity analyses. We performed all analyses using cotinine and self-report of household smokers to describe exposure to SHS. We additionally adjusted the models for total caloric intake, physical activity levels, body mass index, and maternal report of smoking during pregnancy in order to assess the impact of these potential confounders. Due to a large portion of children were missing fasting plasma glucose and 2-hour post-challenge glucose, we also ran our HbA1c analyses restricted to this population (n=700).

We defined children as having prediabetes using the following criteria established by the American Diabetes Association: a) fasting glucose of ≥100 and <126 mg/dL, b) a 2-hour plasma

glucose of ≥140 and <200 mg/dL after a 75-g oral glucose tolerance test, or c) HbA1c level ≥5.7 and <6.5% (American Diabetes Association 2015). We defined children as having diabetes using the following criteria: a) fasting glucose of ≥126 mg/dL, b) a 2-hour plasma glucose of ≥200 mg/dL after a 75-g oral glucose tolerance test, or c) HbA1c level ≥6.5% (American Diabetes Association 2015). Due to the small proportion of children who self-reported having diabetes (n=11), we combined children with prediabetes and diabetes into one category. Weighted logistic regression models were used to describe the interaction between exposure to SHS and dietary variables on the prevalence of prediabetes. Multiplicative interaction was assessed by adding product terms between the dichotomized exposure to SHS and diet variables into separate logistic regression models. Crude and adjusted odds ratios and 95% CIs were calculated for logistic regression models.

RESULTS

Table 5.1 presents weighted proportions and means of exposure to SHS, HbA1c, glucose, and covariates. One in five children met the fasting plasma glucose criteria for prediabetes, whereas a much smaller proportion of children met the HbA1c or 2-hour post-challenge glucose criterion for prediabetes (prevalence of 7% and 5%, respectively). More than 40% of children had NNAL or cotinine levels that indicated exposure to SHS (47% and 41%, respectively) and 13% reported living with one or more household smokers. The mean HbA1c level was 5.21% (95% confidence interval [CI]: 5.18%, 5.24%) and the mean fasting plasma glucose level was 94 mg/dL (95% CI: 93, 95). The sample was evenly distributed between males and females and the mean age was 15 years of age. Race/ethnic proportions were 59% non-Hispanic white, 15% non-Hispanic black, 14% Mexican-American, 7% other/multiracial and 6% other Hispanic. A majority of the children reported that

they met the recommendations for children to get at least 60 minutes of moderate-to-vigorous intensity physical activity every day.

HbA1c and glucose: Correlations between HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose were weak (Spearman's rank correlation coefficient: 0.16 for HbA1c and fasting plasma glucose; 0.16 for HbA1c and 2-hour post-challenge glucose; and 0.31 for fasting plasma glucose and 2-hour post-challenge glucose). The mean fasting plasma glucose was higher among children with prediabetes (HbA1c≥5.7%) as compared to children without prediabetes (101 vs. 94 mg/dL, respectively) and the mean 2-hour post-challenge glucose was higher among children with prediabetes (HbA1c≥5.7%) as compared to children without prediabetes (110 vs. 97 mg/dL, respectively).

Exposure to Secondhand Smoke: Consistencies were observed among the three markers of exposure to SHS. Among children who had creatinine-adjusted NNAL level below the LOD, 14% had a cotinine level indicating exposure to SHS. Furthermore, only 27% of children with the highest levels of creatinine-adjusted NNAL also reported living with two or more household smokers.

Main Effects Analyses: There was limited evidence that exposure to SHS was independently associated with HbA1c, fasting plasma glucose, or 2-hour post-challenge glucose levels (Table 5.2).

Interaction Analyses: Measures of additive interaction demonstrate that increases in the mean HbA1c among children with both high exposure to SHS (as determined by creatinine-adjusted urinary NNAL) and low levels of certain nutrients (dietary fiber, DHA, or vitamin C) are greater than would be expected due to the effects of the individual exposures alone (Table 5.3). For example,

although there was no difference in the mean HbA1c level among children with high fiber intakes, the mean HbA1c level was 0.15% higher for high exposure to SHS as compared to low exposure to SHS among children with low fiber intakes. No evidence suggesting more or less than additive interaction was observed for low EPA or vitamin E intakes on the association between exposure to SHS and HbA1c. The interaction results were somewhat different for the relationships between exposure to SHS and fasting plasma glucose or 2-hour post-challenge glucose levels (Table 5.3). For instance, there was evidence of more than additive interaction for EPA on the association between exposure to SHS and fasting plasma glucose but no evidence of more or less than additive interaction for fiber, DHA, vitamin C, or vitamin E. Additionally, there was evidence of more than additive interaction for fiber, EPA, vitamin C, and vitamin E on the association between exposure to SHS and 2-hour post-challenge glucose but no evidence of more or less than additive interaction for DHA.

Sensitivity analyses: The relationships between exposure to SHS and HbA1c or glucose levels were attenuated following adjustment for total caloric intake, physical activity levels, body mass index, and report of maternal smoking during pregnancy (Appendices 5.1 and 5.2). The interaction results were consistent when exposure to SHS was determined by cotinine and by self-report of household smokers (Appendices 5.3, 5.4, and 5.5). After limiting our HbA1c analyses to those with glucose measurements (n=700), the results were similar (results not presented).

Furthermore, logistic regression analyses demonstrated an independent association between exposure to SHS and prediabetes; however, the associations were slightly different depending on which criterion of prediabetes was used (Table 5.3). Specifically, the association between exposure to SHS and prediabetes was stronger when the fasting plasma glucose criterion was used as compared to the HbA1c or 2-hour post-challenge glucose criterion (Table 5.4). The logistic

regression results were consistent when exposure to SHS was determined by cotinine and by self-report of household smokers (Appendices 5.6 and 5.7). The multiplicative interaction results varied depending on which criterion was used to define prediabetes (Table 5.5). The multiplicative interaction results were consistent when exposure to SHS was determined by cotinine and by self-report of household smokers (Appendices 5.8, 5.9, and 5.10).

DISCUSSION

We observed that the joint effects of high exposure to SHS and low levels of certain nutrients (dietary fiber, DHA, or vitamin C) on HbA1c levels were greater than would be expected due to the effects of the individual exposures alone. However, we observed limited evidence that exposure to SHS is independently associated with elevated HbA1c or glucose. Our results support the hypothesized biologic pathways through which exposure to SHS could lead to elevated HbA1c or glucose. Although SHS contains many chemicals, animal studies have suggested that fetal and neonatal exposure to nicotine may adversely affect pancreatic development, decrease beta cell mass and function, and lead to a reduced sensitivity to insulin (Bruin et al. 2010). Furthermore, nicotine increases cortisol levels, inflammatory markers, and influences peptides that regulate food intake, all of which could contribute to hyperglycemia (Yoshida et al. 1989).

Children with low levels of specific dietary factors may be more susceptible to the adverse metabolic responses induced by exposure to SHS than children with high levels. Specifically, high dietary fiber may inhibit the effects of SHS exposures by decreasing inflammatory responses (Ma et al. 2008) and thereby improving sensitivity to insulin (Temelkova-Kurktschiev et al. 2002). Dietary fiber may also inhibit the absorption of cadmium, an important constituent of SHS (Kim et al. 2010), which may improve hyperglycemia among children exposed to SHS (Edwards and Prozialeck 2009).

Furthermore, previous research has indicated that high fiber consumption may ameliorate the harmful effects of exposure to SHS on the risk of coronary heart disease mortality among non-smoking adults (Clark et al. 2013). Additionally, antioxidants may block the oxidative stress caused by free radical exposure from SHS (Barnoya and Glantz 2005); both animal and human studies have reported that vitamin C or vitamin E supplementation may counteract the oxidative stress response induced by exposure to SHS (Al-Malki and Moselhy 2013; Dietrich et al. 2003). Finally, omega-3 polyunsaturated fatty acids may modulate the adverse effects of environmental exposures by reducing the generation of reactive oxygen species (Romieu et al. 2008), which may improve sensitivity to insulin (Celermajer et al. 1996). Two prospective cohort studies among adults reported that the omega-3 polyunsaturated fatty acids found in fish modified the association between smoking and coronary heart disease incidence (Eshak et al. 2014; Rodriguez et al. 1996),

One important benefit of our study is in its ability to compare HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose among children. Consistent with previous research (Nowicka et al. 2011; Saudek et al. 2008), we observed a weak correlation between HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose. Our results were different depending on which metabolic biomarker we used to examine these relationships. Our mixed results could be explained by the limitations of fasting plasma glucose and 2-hour post-challenge glucose. Specifically, the lack of repeat glucose testing on a different day is a considerable limitation of our study. Fasting plasma glucose and 2-hour post-challenge glucose are not reproducible (Selvin et al. 2007), even among individuals with high HbA1c levels (Ko et al. 1998), because glucose testing can be dramatically influenced by acute changes in behavior (Adams 2013; Frati et al. 1996; Robertson et al. 2002). Conversely, HbA1c is reproducible and is considered to be a more stable indicator of chronic hyperglycemia than fasting or 2-hour post-challenge glucose. Some

researchers have enthusiastically recommended the use of HbA1c for epidemiologic research investigating the etiology of type 2 diabetes (Selvin et al. 2005b), even among children (Kapadia and Zeitler 2012; Shah et al. 2009), while others have questioned the usefulness of HbA1c among children (Lee et al. 2011; Nowicka et al. 2011). We believe our study adds valuable insight about the impact of exposure to SHS and highlights the need for further research to investigate the differences in HbA1c, fasting plasma glucose, and 2-hour post-challenge glucose levels among children.

Another important strength of the present study is in its ability to use both an established biomarker (cotinine) and a novel biomarker (NNAL) to objectively characterize exposure to SHS. Self-report of household smokers was limited to exposures within the home and did not attempt to capture exposure in other settings; cotinine has a half-life of 16 hours whereas NNAL has a half-life of up to 3 weeks (Avila-Tang et al. 2013). However, our results indicate that self-report of household smokers or cotinine may be just as appropriate to assess exposure to SHS as NNAL among children, which is advantageous since self-report and cotinine which are less expensive and easier to measure than NNAL (Avila-Tang et al. 2013). Additionally, our study was conducted using a nationally representative sample and the results can be generalized to all U.S. children.

Our study has several limitations, which should be considered when interpreting these results. First, even though we adjusted for many potential confounders, there is still potential for residual confounding. In particular, we considered adjusting for diet in a number of ways to address this limitation. In a previous analysis, we determined nutrient patterns through the use of a principal components analysis (PCA) as described by Kim and Mueller (1978), in order to overcome statistical issues encountered when attempting to simultaneously evaluate dietary factors that are often highly

correlated (Slattery and Boucher 1998). From the PCA, we identified four distinct nutrient patterns, which explained 68% of the variance in dietary nutrients: 1) the fiber-fat-soluble-vitamins pattern, 2) the saturated-fat pattern, 3) the vitamin-B-complex pattern, and 4) the omega-3-polyunsaturated-fatty-acids pattern. Adjusting for the nutrient patterns in our statistical models did not have a meaningful impact on the results (results not presented); however, we cannot rule out the possibility for residual confounding. Our results are also limited by the inability to establish temporality between exposure and disease due to the cross-sectional nature of NHANES.

CONCLUSIONS

Diets high in dietary fiber, antioxidants, or omega-3 polyunsaturated fatty acids may inhibit the adverse metabolic responses potentially triggered by higher exposure to SHS. Prevention strategies for maintaining normal HbA1c and glucose levels aimed at both reducing SHS exposures and improving diets may exceed the expected benefits based on targeting these risk factors separately. Additionally, the results highlight the need for further research to investigate the differences in HbA1c, fasting plasma glucose, and two-hour post-challenge glucose levels among children.

Table 5.1. Weighted proportions among a representative sample of 12-19 year olds, 2007-2010 NHANES

	Final Sample Size	
	Proportion	95% CI
Secondhand Smoke		
NNAL Exposure		
Below LOD (<.001 ng/mL creatinine)	53%	47%, 58%
Low (≥.001 & <.005 ng/mL creatinine)	28%	25%, 32%
High (≥.005 & ≤.082 ng/mL creatinine)	19%	16%, 23%
Cotinine Exposure		
No (<.05 ng/mL)	59%	54%, 63%
Low (≥.05 & ≤.268 ng/mL)	21%	17%, 24%
High (≥.268 & ≤14.6 ng/mL)	21%	18%, 25%
Self-report of Household Smokers		
None	87%	84%, 89%
One	7%	6%, 9%
Two or more	6%	4%, 10%
Biometric Measures		
HbA1c (%)	5.21	5.18, 5.24
Fasting plasma glucose (mg/dL)	94	93, 95
2-hour post-challenge glucose (mg/dL)	97	95, 100
Pre-diabetes Status		
HbA1c ≥5.7% (ADA definition)	7%	6%, 8%
Fasting plasma glucose ≥100 mg/dL	20%	16%, 24%
2-hour post-challenge glucose ≥140 mg/dL	5%	3%, 8%
Covariates		
Age	15.1	14.9, 15.3
Sex		
Male	50%	46%, 54%
Female	50%	46%, 54%
Race/Ethnicity		
Mexican American	14%	10%, 18%
Other Hispanic	6%	4%, 10%
Non-Hispanic White	59%	53%, 65%
Non-Hispanic Black	15%	12%, 18%
Other/Multiracial	7%	5%, 9%

Poverty Index Ratio		
Above poverty level (≥1.85)	63%	58%, 67%
Below poverty level (<1.85)	37%	33%, 42%
Moderate-to-Vigorous Physical Activity		
Met recommendations for 60 minutes/day	10%	8%, 13%
Did not meet recommendations minutes/day	90%	88%, 92%

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey; LOD, limit of detection; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS, secondhand smoke.

Table 5.2. Crude and adjusted models for the relationship between urinary NNAL levels and HbA1c and glucose levels among U.S. children, ages 12-19 years, 2007-2010 NHANES

	HbA1c (%) Means (95% CIs)	Fasting plasma glucose (mg/dL) Means (95% CIs)	2-hour post-challenge glucose (mg/dL) Means (95% CIs)
Crude			
Below LOD/None	5.20 (5.16, 6.23)	94 (93, 95)	97 (92, 101)
Low	5.21 (5.18, 5.25)	94 (93, 95)	94 (90, 98)
High	5.25 (5.19, 5.31)	95 (94, 96)	103 (97, 111)
p for trend	p=0.15	p=0.18	p=0.23
Model 1[a]			
Below LOD/None	4.86 (4.59, 5.13)	89 (82, 95)	97 (92, 101)
Low	5.28 (5.24, 5.32)	95 (93, 96)	94 (89, 98)
High	5.33 (5.26, 5.40)	95 (94, 96)	104 (97, 110)
p for trend	p=0.41	p=0.30	p=0.18
Model 2[b]			
Below LOD/None	5.27 (5.23, 5.31)	95 (93, 96)	104 (98, 110)
Low	5.29 (5.25, 5.33)	95 (93, 96)	101 (96, 107)
High	5.36 (5.28, 5.44)	96 (95, 98)	112 (104, 121)
p for trend	p=0.32	p=0.42	p=0.23
Model 3[c]			
Below LOD/None	5.29 (5.21, 5.38)	95 (93, 97)	112 (N/A)[d]
Low	5.31 (5.25, 5.37)	94 (92, 96)	110 (N/A)
High	5.36 (5.26, 5.47)	95 (92, 98)	121 (N/A)
p for trend	p=0.71	p=0.78	N/A

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a] Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] Model 1 plus additional adjustment for total caloric intake, physical activity and body mass index.

[c] Model 2 plus additional adjustment for maternal report of smoking during pregnancy. These estimates are based on a different sample sizes. For HbA1c, n was 767; for fasting and 2-hour post-challenge glucose, n was 371.

[d] Standard errors not available due to stratum within single sampling units.

Table 5.3. Adjusted means and 95% CIs for HbA1c and glucose in relation to urinary NNAL levels and dietary nutrients and measures of additive interaction among 12-19 year olds, 2007-2010 NHANES

		Adjusted[a] Mean HbA1c (%) (95% CI)	Mean fasting plasma glucose (mg/dL) (95% CI)	Mean 2-hour post-challenge glucose (mg/dL) (95% CI)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	5.21 (5.18, 5.25)	92 (91, 94)	96 (90, 102)
(≥12.75 g/day)	High	5.20 (5.17, 5.23)	94 (93, 95)	96 (93, 99)
Low Fiber Intake	Below LOD/Low	5.11 (5.03, 5.21)	93 (90, 95)	90 (81, 98)
(<12.75 g/day)	High	5.26 (5.21, 5.31)	95 (94, 97)	102 (97, 109)
p for additive interaction[b]		p=0.01	p=0.48	p=0.02
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	5.23 (5.21, 5.25)	94 (93, 95)	97 (94, 100)
(≥0.007 g/day)	High	5.16 (5.12, 5.20)	94 (92, 95)	94 (91, 98)
Low EPA Intake	Below LOD/Low	5.23 (5.16, 5.30)	93 (92, 94)	96 (90, 102)
(<0.007 g/day)	High	5.22 (5.14, 5.29)	98 (95, 100)	107 (98, 116)
p for additive interaction		p=0.35	p<0.01	p=0.02
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	5.22 (5.18, 5.25)	93 (92, 94)	99 (93, 104)
(≥0.018 g/day)	High	5.19 (5.15, 5.23)	94 (93, 95)	95 (93, 98)
Low DHA Intake	Below LOD/Low	5.18 (5.10, 5.26)	92 (90, 94)	97 (85, 109)
(<0.018 g/day)	High	5.26 (5.20, 5.32)	96 (94, 97)	102 (97,107)
p for additive interaction		p=0.04	p=0.16	p=0.24
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	5.23 (5.20, 5.26)	93 (92, 94)	96 (92, 100)
(≥68.9 g/day)	High	5.17 (5.13, 5.21)	94 (93, 95)	96 (93, 99)
Low Vitamin C Intake	Below LOD/Low	5.19 (5.12, 5.26)	94 (92, 97)	94 (88, 100)
(<68.9 g/day)	High	5.25 (5.20, 5.32)	95 (93, 97)	104 (96, 112)
p for additive interaction		p=0.02	p=0.62	p=0.09
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake (≥5.415 mg/day)	Below LOD/Low	5.22 (5.18, 5.25)	93 (92, 94)	94 (91, 98)
	High	5.18 (5.14, 5.22)	94 (93, 95)	98 (95, 101)

Low Vitamin E Intake	Below LOD/Low	5.23 (5.16, 5.30)	93 (92, 95)	92 (86, 98)
(<5.415 mg/day)	High	5.22 (5.15, 5.27)	96 (94, 98)	107 (100, 113)
p for additive interaction		p=0.64	p=0.31	p=0.03

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Table 5.4. Crude and adjusted models for the association of exposure to SHS determined by NNAL and pre-diabetes among U.S. children, ages 12-19 years, 2007-2010 NHANES

	Pre-diabetes (HbA1c ≥5.7%) vs. Normal ORs (95% CIs)	Pre-diabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal ORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal ORs (95% CIs)
Crude			
Below LOD/None	1[a]	1	1
Low	1.4 (0.8, 2.2)	1.1 (0.8, 1.6)	0.4 (0.1, 1.1)
High	1.7 (1.0, 2.9)	1.6 (1.2, 2.0)	2.6 (0.8, 8.6)
p for trend	p=0.04	p=0.07	p=0.26
Model 1[b]			
Below LOD/None	1	1	1
Low	1.1 (0.7, 1.9)	1.1 (0.8, 1.6)	0.4 (0.1, 1.6)
High	1.4 (0.7, 3.0)	1.6 (1.1, 2.2)	4.6 (1.0, 20.9)
p for trend	p=0.36	p=0.02	p=0.12
Model 2[c]			
Below LOD/None	1	1	1
Low	1.1 (0.6, 1.8)	0.9 (0.5, 1.8)	0.7 (0.2, 2.8)
High	1.5 (0.7, 3.1)	1.6 (0.8, 2.9)	5.1 (1.2, 22.3)
p for trend	p=0.71	p=0.28	p=0.07
Model 3[d]			
Below LOD/None	1	1	1
Low	1.2 (0.5, 2.8)	0.8 (0.3, 1.9)	0.2 (0.1, 1.4)
High	1.0 (0.4, 2.3)	1.4 (0.5, 4.4)	4.1 (0.8, 21.6)
p for trend	p=0.90	p=0.64	p=0.18

Abbreviations: CI, confidence interval; LOD, limit of detection; OR, Odds Ratio; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS, secondhand smoke.

[a] Reference category

[b] Adjusted for sex, age, race/ethnicity and poverty index ratio.

[c] Model 1 plus additional adjustment for total caloric intake, physical activity, and body mass index.

[c] Model 2 plus additional adjustment for maternal report of smoking during pregnancy. Estimates for report of maternal smoking during pregnancy are based on a different sample sizes. For HbA1c, n was 767; for fasting and 2-hour post-challenge glucose, n was 371.

Table 5.5. Adjusted ORs and 95% CIs for pre-diabetes in relation to NNAL levels and dietary nutrients and measures of multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Prediabetes (HbA1c ≥5.7%) vs. Normal AORs[a] (95% CIs)	Prediabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal ORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal ORs (95% CIs)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	1[c]	1	1
(≥12.75 g/day)	High	0.9 (0.5, 1.6)	1.1 (0.8, 1.5)	0.6 (0.1, 2.7)
Low Fiber Intake	Below LOD/Low	0.3 (0.1, 0.9)	1.5 (0.7, 3.0)	0.6 (0.1, 6.9)
(<12.75 g/day)	High	1.6 (0.7, 3.8)	1.7 (1.1, 2.6)	3.2 (0.7, 15.5)
p for multiplicative interaction[b]		p=0.01	p=0.94	p=0.14
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	1	1	1
(≥0.007 g/day)	High	0.7 (0.4, 1.3)	0.8 (0.6, 1.0)	0.8 (0.3, 1.9)
Low EPA Intake	Below LOD/Low	1.5 (0.8, 3.0)	1.0 (0.8, 1.3)	2.5 (0.3, 17.9)
(<0.007 g/day)	High	0.7 (0.3, 2.1)	2.2 (1.3, 3.7)	4.4 (1.1, 18.2)
p for multiplicative interaction		p=0.46	p<0.01	p=0.41
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	1	1	1
(≥0.018 g/day)	High	0.8 (0.4, 1.3)	0.8 (0.6, 1.1)	0.3 (0.1, 0.9)
Low DHA Intake	Below LOD/Low	0.7 (0.4, 1.3)	1.1 (0.7, 1.7)	3.1 (0.3, 33.0)
(<0.018 g/day)	High	1.6 (0.7, 3.6)	1.3 (0.8, 2.1)	1.3 (0.2, 6.4)
p for multiplicative interaction		p=0.04	p=0.18	p=0.80
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	1	1	1
(≥68.9 g/day)	High	1.1 (0.6, 1.9)	1.3 (1.0, 1.8)	0.6 (0.2, 1.5)
Low Vitamin C Intake	Below LOD/Low	1.1 (0.4, 2.6)	1.8 (1.2, 2.8)	0.9 (0.1, 7.1)
(<68.9 g/day)	High	1.9 (1.0, 3.9)	1.7 (1.1, 2.5)	4.0 (0.9, 17.8)
p for multiplicative interaction		p=0.37	p=0.28	p=0.03
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake	Below LOD/Low	1	1	1

(≥5.415 mg/day)	High	0.6 (0.4, 0.8)	1.1 (0.9, 1.5)	0.6 (0.2, 1.8)
Low Vitamin E Intake	Below LOD/Low	1.0 (0.5, 2.3)	1.7 (1.1, 2.4)	0.4 (0.1, 4.0)
(<5.415 mg/day)	High	1.2 (0.5, 2.8)	1.6 (1.0, 2.5)	4.5 (1.0, 19.4)
p for multiplicative interaction		p=0.15	p=0.61	p=0.04

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; LOD, limit of detection; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; OR, Odds Ratio; SHS, secondhand smoke.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

[c] Reference

CHAPTER 6. PROJECT 4

INTERACTIONS BETWEEN DIET AND EXPOSURE TO SECONDHAND SMOKE ON HBA1C LEVELS AMONG NON-SMOKING CHINESE ADULTS IN SINGAPORE

SUMMARY

Background: Exposure to secondhand smoke (SHS) may increase glycated hemoglobin (HbA1c) levels via inflammatory responses and oxidative stress; this response may be counteracted by diets high in dietary fiber, antioxidants or omega-3 polyunsaturated fatty acids. The purpose of this study was to evaluate the joint effect of diet and exposure to SHS on HbA1c levels among adults.

Methods: Linear regression models were used to examine the association between creatinine-adjusted urinary cotinine and HbA1c levels among a sample of Singaporean adults of Chinese ethnicity, aged 45–74 years at time of enrollment. Additive interaction by dietary variables was assessed by introducing product terms of dichotomized cotinine and dichotomized diet variables (dietary fiber, vitamin C, vitamin E, omega-3 polyunsaturated fatty acids, the meat-dim sum pattern, the vegetable-fruit-soy pattern, and adherence to the Dietary Approaches to Stop Hypertension [DASH] diet)) in separate models.

Results: Approximately 92% of the non-smoking adults had levels of creatinine-adjusted urinary cotinine above the limit of detection. The results did not support the hypothesis that exposure to SHS is associated with elevated HbA1c in the entire population. Furthermore, evidence for a joint effect of diet and exposure to SHS on HbA1c levels was not observed.

Conclusions: The current results conflict with previous findings in human models demonstrating an association between cotinine and HbA1c levels among adults.

INTRODUCTION

Glycated hemoglobin (HbA1c) is an indicator of glucose regulation and has distinct advantages over fasting plasma glucose and 2-hour post-challenge glucose for diagnosing diabetes and prediabetes (American Diabetes Association 2015). Specifically, HbA1c is a stable measure of glucose exposure over several months, has low intra-individual variability, and does not require fasting, which has lead to its acceptance as a potentially better diagnostic tool for type 2 diabetes than glucose (American Diabetes Association 2015). Furthermore, increases in HbA1c levels within the normal range can identify individuals at higher risk of cardiovascular disease and mortality (Selvin et al. 2010), whereas glucose has very little predictive value for identifying cardiovascular risk, particularly when other cardiovascular risk factors are taken into account (Meigs et al. 2004).

Excess caloric consumption and a sedentary lifestyle are important contributing factors of elevated HbA1c levels (Alberti et al. 2007); however, an emerging hypothesis suggests that chemicals in the environment may play a role (Thayer et al. 2012). Specifically, exposure to SHS is an important environmental exposure experienced by non-smoking children and adults. Despite the international decline in smoking rates since 1980 (Ng et al. 2014), nearly 40% of children and 33% of non-smoking adults are regularly exposed to SHS (Öberg et al. 2011).

The relationship between exposure to SHS and glucose regulation is not clear. Several epidemiologic studies have reported that individuals exposed to SHS, using the nicotine metabolite, cotinine, to objectively quantify exposure to SHS, have higher fasting glucose levels compared to individuals not exposed to SHS (Houston et al. 2006; White et al. 2014); however, other studies report no association between exposure to SHS and fasting glucose levels (Jefferis

et al. 2010; Thiering et al. 2011; Xie et al. 2010). Only one study using data from the 1999-2008 NHANES has observed a relationship between cotinine and HbA1c, a more stable indicator of glucose regulation than fasting plasma glucose or two-hour post-challenge glucose.

HbA1c may be influenced by the joint effect of diet and exposure to SHS (Alberti et al. 2007; Thayer et al. 2012). In particular, high dietary fiber intakes may reduce inflammatory responses (Ma et al. 2008) and high intakes of antioxidant or omega-3 polyunsaturated fatty acids may reduce oxidative stress (Barnoya and Glantz 2005; Romieu et al. 2008), both of which could lower HbA1c levels. Therefore, it is possible that high levels of these nutrients could counteract the adverse metabolic responses triggered by exposure of SHS; however, the joint effect of diet and exposure to SHS on HbA1c levels has yet to be investigated.

Using data from the Singapore Chinese Health Study, we evaluated the association between cotinine and HbA1c levels among a sample of Singaporeans of Chinese ethnicity, aged 45–74 years at the time of enrollment. We also examined the potential interaction between dietary factors and exposure to SHS on HbA1c levels.

METHODS

Study population: The Singapore Chinese Health Study is a cohort consisting of 63,257 men and women recruited between April 1993 and December 1998, from permanent residents or citizens of Singapore aged 45–74 years old at the time of enrollment and who resided in government-built housing (Hankin et al. 2001; Yuan et al. 2003). Enrollment in the cohort involved the completion of a baseline in-person interview in the participants' homes. Participants were evaluated with a home interview to determine information about demographics, physical

activity levels, and diet (Yuan et al. 2003). Diet was evaluated during baseline using a 165-item food frequency questionnaire (Hankin et al. 2001). During the first follow-up interview in 1999, information about the subject's smoking status and exposure to SHS was ascertained. Between 2000 and 2005, blood samples were obtained from 32,543 subjects (representing approximately 60% of the cohort members at that time). The study protocol was reviewed and approved by the Institutional Review Boards of the National University of Singapore and the University of Pittsburgh. Written informed consent was obtained from all study subjects prior to the baseline questionnaires, follow-up questionnaires, or biospecimen collection. The Colorado State University Institutional Review Board designated the secondary data analysis conducted in this project as not human subjects research (see Appendix 2.0).

Inclusion Criteria: A subset of self-reported lifetime non-smokers selected from a previously defined nested case-control study of cardiovascular disease was used. The nested case-control study investigators selected cases with fatal coronary heart disease or non-fatal myocardial infarction identified through the Singapore Registry of Births and Deaths and the Hospital Discharge Database, respectively. For all non-fatal cases, medical records were retrieved for review by a cardiologist; only those with confirmed myocardial infarction using the criteria of the Multi-Ethnic Study of Atherosclerosis were included as cases. Cases of fatal coronary heart disease were included only if there was evidence of prior coronary heart disease based on the questionnaire data or the Hospital Discharge Database. Matched controls were selected using the risk-set sampling strategy (Naidoo et al. 2012). Controls were participants who were alive, free of coronary heart disease at the time of the diagnosis or death of the cases, and were never smokers. Controls were matched (one to two) for sex, dialect group, year of birth, year of recruitment and date of blood collection. The study design is cross-sectional in that the

blood and urine samples and follow-up questionnaires were collected at an overlapping time period.

A total of 277, matched case-control never smoker pairs were identified and matched on the full matching criteria (Tier 1; n=554). Due to the never smoker criteria, there were not enough controls available for the cases using the original control selection criteria. Therefore, 52 case-control pairs were obtained by re-selecting from the control group; these controls were matched on sex, dialect group, year of birth, year of recruitment and date of biospecimen collection but were not matched on the diagnosis date (Tier 2; n=104). Finally, an additional nine controls were matched on sex, dialect group, and year of birth but not matched on year of recruitment, date of biospecimen collection, or diagnosis date (Tier 3; n=18). This study used case-control pairs from Tier 1 and Tier 2 for primary analyses (n=658); for secondary analyses, case-control pairs from Tier 3 were included in the analyses (n=676).

We excluded adults who were missing laboratory measurements of urinary cotinine or dietary information (n=93). We further excluded adults with evidence of active smoking, defined as having a creatinine-adjusted urinary cotinine level >50 ng/mL (n=6) (Haufroid and Lison 1998; Zielinska-Danch et al. 2007). Therefore, our final sample size was 577.

Exposure Assessment: Free urinary cotinine was measured in spot urine samples using liquid chromatography linked to tandem mass spectrometry (LC/MS/MS). In order to account for variation in dilution in spot urinary samples, urinary creatinine was determined using a Jaffé rate reaction and cotinine concentrations were corrected for creatinine by dividing the concentration of cotinine by the concentration of urinary creatinine (Bernert et al. 2010). Cotinine was categorized into three exposure categories: below the LOD (cotinine ≤0.20 ng/mL creatinine),

low exposure to SHS (cotinine ≥LOD and ≤0.95 ng/mL [the median value]), and high exposure to SHS (cotinine >0.95 ng/mL and <50 ng/mL ([the cut-point for active smoking] (Haufroid and Lison 1998; Zielinska-Danch et al. 2007).

Self-reported exposure to SHS was assessed through questionnaires during the first follow-up period (beginning in 1999). One question asked subjects to identify if anyone currently living in their home smoked cigarettes on a daily basis. Self-report of household smokers was categorized as no household smokers or one or more household smokers.

HbA1c: HbA1c was measured on whole blood samples from all participants and measurements were performed on the Bio-Rad Variant II Analyzer (Hemel Hempstead, U.K.).

Diet: The Singapore Chinese Health Study conducted a 165-item modified quantitative food frequency questionnaire (FFQ) during baseline questionnaires (between April 1993 and December 1998). We evaluated diet in terms of individual nutrients, including fiber, omega-3 polyunsaturated fatty acids, vitamin C and vitamin E. These dietary nutrients factors were dichotomized as low (lowest quartile of intake) and high (the second through fourth quartiles of intake). We also evaluated diet in terms of two dietary patterns (vegetable-fruit-soy and meat-dim sum) that emerged from a previous principal components analysis (Butler et al. 2006; Butler et al. 2010). Finally, we used the FFQ information used to derive a diet quality score, based on adherence to the DASH diet (Sacks et al. 2001). A value of 0 or 1 was assigned to the presumed beneficial foods (i.e. fruits, vegetables, legumes, nuts, cereals, fish and seafood) based on whether the subject's intake level is below or above the median value for all subjects. Conversely, a value of 1 or 0 was assigned to the presumed unfavorable foods (i.e., meat, dairy products, refined carbohydrates, and alcohol) based on whether intake level was below or above

the median value, respectively. The scores across these components were totaled to form a DASH score (range: 0–80), with a high score indicating greater adherence to the recommended levels. The vegetable-fruit-soy pattern, meat-dim sum pattern, and DASH score were dichotomized based on the median values.

Covariates: Information about the participant's age, sex, dialect, and education was collected at baseline. Self-reported height and weight were collected through baseline questionnaires. Many of the participants from the original cohort study were missing information on weight (n=9,781); therefore, self-reported weights were imputed using linear regression methods described elsewhere (Koh et al. 2010). Body mass index (BMI) was calculated by dividing weight (kilograms) by height (meters) squared.

Statistical Methods: This study uses a sample from a nested case-control study with a different health endpoint (coronary heart disease) than the present study and ignoring the sampling design could lead to biased results (Richardson et al. 2007). Therefore, our analyses incorporated sampling weights designed to account for the inverse of the probability of being selected to participate in the nested case-control study. For all cases, the weight is 1 since all coronary heart disease cases were recruited into the study. For controls, the probability of being selected is calculated using a mathematical formula that reflects the incidence density sampling nature of the nested case-control study from which the sample for this study was obtained. The probability of being selected as a control was dependent on the value of matching variables of that control, the length of follow-up, and the number of cases with the same matching factors. Sampling weight formulas were calculated as described elsewhere (Salim et al. 2012). Since the controls in this study were selected through three tiers (see above) of sampling, each with

different criteria for matching, the probability of being selected as a control is calculated using a different formula depending on the sampling tier.

Weighted linear regression models were used to describe the relationship between exposure to SHS (cotinine and self-report of household smokers) and HbA1c levels. Additive interaction was assessed by introducing product terms of the dichotomized SHS and diet variables into separate linear regression models. All models adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien); these variables are used in all analyses using data from the Singapore Chinese Health Study. We also adjusted the models for level of education (no formal education, primary school, or secondary school or higher), body mass index, and diet in order to assess the impact of these potential confounders. Crude and adjusted means and 95% CIs were presented for linear regression models. All analyses were performed using Stata version 13 (Stata-Corp LP, College Station, TX).

Sensitivity analyses: We conducted several sensitivity analyses. Using the criterion established by the American Diabetes Association, pre-diabetes was defined as having an HbA1c level >5.7% and <6.5% and type 2 diabetes was defined as having an HbA1c level >6.5% (American Diabetes Association 2014). Weighted logistic regression models were used to evaluate the association between exposure to SHS and the prevalence of prediabetes. Multiplicative interaction was assessed by adding product terms between the dichotomized exposure to SHS and diet variables into separate logistic regression models. Crude and adjusted odds ratios and 95% CIs were calculated for logistic regression models.

RESULTS

Table 6.1 presents weighted proportions and means of exposure to SHS, metabolic endpoints, and covariates. Approximately 92% of the non-smoking adults had levels of cotinine above the limit of detection, indicating exposure to SHS. A majority of adults (83%) reported no smokers within the household. Over half of the adults had HbA1c levels within the prediabetic range (HbA1c>5.7%). The average age was 55 years and the sample included a greater proportion of females (61%) than males. Only 8% of the adults in our sample were classified as obese (BMI>27.5).

Exposure to Secondhand Smoke: Among adults who self-reported living with no household smokers, only 9% had a cotinine level below the limit of detection (Table 6.2). However, approximately 74% of adults who reported living with at least one household smoker also had high cotinine levels (Table 6.2).

Diet: The correlations between dietary fiber, vitamin C, vitamin E, and omega-3 polyunsaturated fatty acids are shown in the Table 6.3. There were strong correlations between dietary fiber and vitamin C (Spearman's rank correlation coefficient: 0.73), vitamin E (Spearman's rank correlation coefficient: 0.77), and omega-3 polyunsaturated fatty acids (Spearman's rank correlation coefficient: 0.66). There were also strong correlations between vitamin C and vitamin E (Spearman's rank correlation coefficient: 0.63) and between vitamin E and omega-3 polyunsaturated fatty acids (Spearman's rank correlation coefficient: 0.77). There was a moderate correlation between vitamin C and omega-3 polyunsaturated fatty acids (Spearman's rank correlation coefficient: 0.47).

Main Effects and Interaction Analyses: We observed limited evidence that cotinine or self-report of household smokers were independently related to HbA1c levels (Table 6.4). The main

effects analyses were similar following adjustment for education levels and body mass index. Measures of additive interaction provide limited evidence that the estimated joint effect of diet and exposure to SHS was more or less than the sum of the individual exposures alone (Table 6.5).

Sensitivity analyses: We observed limited evidence that cotinine or self-report of household smokers were independently associated with prediabetes prevalence (Table 6.6). Measures of multiplicative interaction provide limited evidence that the estimated joint effect of diet and exposure to SHS was more or less than the product of the individual exposures alone (Table 6.7).

DISCUSSION

Our results do not support the hypothesis that there is an association between exposure to SHS and HbA1c levels among older Singaporean adults of Chinese ethnicity. Although several epidemiologic studies have reported that individuals exposed to SHS have higher fasting plasma glucose levels among young adults, ages 18-30 years (Houston et al. 2006; White et al. 2014), whereas other studies have provided limited evidence indicating an association among older adults, ages 30-80 years (Jefferis et al. 2010; Xie et al. 2010). On the other hand, Clair et al. (2011) observed a relationship between higher serum cotinine levels and elevated HbA1c levels among U.S. adults, ages 20-80+ years. There are several factors that could explain the differences between the results presented in the Clair et al. (2011) study and the results presented in this study. First, HbA1c levels tend to rise with increasing age, particularly after 40 years of age (Pani et al. 2008). The mean age of our study sample was 55 years of age, whereas the mean age of the non-smoking sample included in the Clair et al. (2011) study ranged from 45 to 49 years of age. The association between cotinine and HbA1c observed by Clair et al. (2011) could be driven by the younger adults included in the analyses. Additionally, approximately 24% of the

sample included in the Clair et al. (2011) study reporting being former smokers whereas our sample included only never smokers. Active smoking has been shown to increase the risk for type 2 diabetes by 44% (pooled adjusted RR 1.44; 95% CI 1.13, 1.48) (Willi et al. 2007); therefore, including former smokers in the analyses may have artificially inflated the association between exposure to SHS and HbA1c levels. Obesity may be a mediator of the association between exposure to SHS and hyperglycemia (Sankhla et al. 2012) and the low prevalence of obesity within the study population could explain why we did not observe an association. Finally, an overwhelming majority (92%) of the Singaporean adults had cotinine levels above the limit of detection and it is possible that the lack of variability in exposure status could have resulted in a bias towards the null. Regardless of the reason for these differences, it still remains unclear whether exposure to SHS is related to HbA1c levels and further studies are needed to evaluate this research question.

Our study is not without its limitations. Although we considered adjusting for important confounders, our study is limited by the inaccurate or incomplete measurement of covariates, such as body mass index and physical activity, and we cannot rule out the potential for residual confounding. Additionally, our results may not be generalizable to non-Asian populations because there is some evidence that HbA1c levels may measure higher in Asian populations (Mostafa et al. 2012). Our results estimated that the mean HbA1c level among our population was 6.1%, a figure that is much higher than the mean HbA1c level of 5.4% among the U.S. population aged ≥12 years without diabetes (Bullard et al. 2013), which may impact the external validity to non-Asian populations. Because the biospecimen collection and follow-up questionnaires were collected at an overlapping time period, the data is cross-sectional and our findings are limited by the inability to establish temporality.

This project used a sample from a previously selected nested case-control study of coronary heart disease, a different but somewhat related health endpoint. This methodological challenge can be viewed as analysis of data derived from a case–control study using disproportionate stratified subsamples of the study base (Richardson et al. 2007). Ignoring the biased sampling could have resulted in biased results, since the original recruited sample identified was not fully exploited and the recruitment of participants was biased (Weinberg and Wacholder 1990). In order to address this limitation, the analyses were weighted to adjust for the unequal probability of a control being selected to participate in the original nested case-control study. An important strength of this study is the prevalence of obesity was low in our study population, which allowed for the evaluation of these associations independent of weight status.

CONCLUSIONS

The current results conflict with previous findings in human models demonstrating an independent association between cotinine and HbA1c levels among adults.

Table 6.1. Weighted proportions and means of exposures, outcomes and covariates

	Proportion/Percentage	95% CI
Secondhand Smoke		
Cotinine Exposure		
Below LOD (<0.20 ng/mL creatinine)	8%	5%, 14%
Low (≥0.20 & ≤ 0.95ng/mL creatinine)	42%	34%, 50%
High (≥0.95 & ≤50 ng/mL creatinine)	49%	42%, 57%
Self-report of Household Smokers		
No	83%	77%, 89%
One	17%	11%, 24%
Biometric Measures		
HbA1c	6.1	5.9, 6.3
Systolic Blood Pressure[a]	135	132, 138
Diastolic Blood Pressure[a]	80	78, 81
Triglycerides[a]	1.5	1.4, 1.6
HDL[a]	1.4	1.3, 1.5
Outcomes		
Pre-diabetes/Diabetes vs. Normal	54%	46%, 61%
Hypertension[a]	13%	9%, 20%
High Triglycerides[a]	36%	28%, 44%
Low HDL[a]	25%	18%, 33%
Covariates		
Age at Interview	55	54, 56
Sex		
Male	39%	32%, 47%
Female	61%	53%, 68%
Dialect		
Cantonese	51%	43%, 59%
Hokkien	49%	41%, 57%
Education		
No formal education	23%	17%, 30%
Primary education	43%	35%, 51%
Secondary education	34%	27%, 42%
Year of Interview		
1999	18%	12%, 25%
2000	35%	28%, 42%

2001	21%	15%, 28%
2002	20%	14%, 28%
2003	5%	3%, 10%
2004	0.01%	0%, 2%
Weight Status		
Normal (BMI<23)	47%	40%, 55%
Overweight (BMI>23 & <27.5)	44%	37%, 53%
Obese (BMI>27.5)	8%	5%, 14%

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LOD, limit of detection; SHS, secondhand smoke.

[a] Sample size = 475

Table 6.2. Comparison of exposure to SHS categories

	Cotinine Exposure		
	Below LOD	Low	High
Self-report of household smokers			
None	9%	51%	40%
One or More	1%	25%	74%

Abbreviations: LOD, limit of detection

Table 6.3. Spearman rank correlation coefficients for dietary nutrients

	Dietary Fiber	Vitamin C	Vitamin E	Omega 3
Dietary Fiber	1			
Vitamin C	0.73	1		
Vitamin E	0.77	0.63	1	
Omega 3	0.66	0.47	0.77	1

Table 6.4. Crude and adjusted models for the relationship between serum cotinine and mean HbA1c levels

	Creatinine-Adjusted Cotinine Means (95% CIs)	Self-Report of Household Smokers Means (95% CIs)
Crude		
Below LOD/None	6.3 (5.8, 6.8)	6.0 (5.9, 6.2)
Low	6.1 (5.9, 6.3)	--
High/One or More	6.2 (5.9, 6.4)	6.4 (5.9, 6.8)
p for trend	p=0.95	--
Model 1[a]		
Below LOD/None	5.3 (5.8, 6.8)	6.0 (5.9, 6.2)
Low	6.0 (5.8, 6.2)	--
High/One or More	6.1 (5.9, 6.4)	6.3 (5.9, 6.7)
p for trend	p=0.70	--
Model 2[b]		
Below LOD/None	6.2 (5.7, 6.7)	6.1 (5.9, 6.2)
Low	6.0 (5.8, 6.2)	--
High/One or More	6.2 (5.9, 6.4)	6.3 (5.9, 6.7)
p for trend	p=0.76	--

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD, limit of detection.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Table 6.5. Adjusted means and 95% CIs for HbA1c levels in relation to exposure to SHS and dietary nutrients and measures of additive interaction

		Creatinine-Adjusted Cotinine Adjusted[a] Means (95% CIs)	Self-Report of Household Smokers Adjusted Means (95% CIs)
Fiber Intake	Exposure to SHS		
High Fiber Intake	Below LOD/Low	6.2 (5.9, 6.4)	6.2 (5.9, 6.4)
	High	5.9 (5.5, 6.2)	5.9 (5.7, 6.2)
Low Fiber Intake	Below LOD/Low	6.2 (5.9, 6.5)	6.3 (5.8, 6.8)
	High	6.1 (5.7, 6.5)	6.1 (5.5, 6.7)
p for additive interaction[b]		p=0.41	p=0.95
Vitamin C	Exposure to SHS		
High Vitamin C Intake	Below LOD/Low	6.2 (5.9, 6.4)	6.1 (5.9, 6.3)
	High	6.0 (5.6, 6.4)	6.0 (5.7, 6.3)
Low Vitamin C Intake	Below LOD/Low	6.1 (5.9, 6.4)	6.2 (5.7, 6.6)
	High	6.3 (5.9, 6.8)	6.6 (5.8, 6.4)
p for additive interaction		p=0.28	p=0.27
Vitamin E Intake	Exposure to SHS		
High Vitamin E Intake	Below LOD/Low	6.1 (5.9, 6.3)	6.1 (5.9, 6.3)
	High	6.1 (5.8, 6.5)	6.2 (5.8, 6.5)
Low Vitamin E Intake	Below LOD/Low	6.1 (5.9, 6.4)	6.3 (5.8, 6.8)
	High	6.2 (5.7, 6.6)	6.1 (5.5, 6.7)
p for additive interaction		p=0.99	p=0.47
Omega-3 Fatty Acids Intake	Exposure to SHS		
High Intake	Below LOD/Low	6.2 (5.9, 6.4)	6.1 (5.9, 6.3)
	High	6.0 (5.8, 6.2)	6.2 (5.8, 6.6)
Low Intake	Below LOD/Low	6.0 (5.8, 6.3)	6.3 (5.8, 6.8)
	High	6.4 (5.8, 7.0)	6.1 (5.5, 6.8)
p for additive interaction		p=0.16	p=0.48
Meat Dim Sum Pattern	Exposure to SHS		
High	Below LOD/Low	6.2 (6.0, 6.5)	6.1 (5.9, 6.4)
	High	6.0 (5.7, 6.2)	6.1 (5.8, 6.3)

Low	Below LOD/Low	6.2 (5.7, 6.6)	6.5 (5.8, 7.1)
	High	6.1 (5.9, 6.4)	6.0 (5.6, 6.5)
p for additive interaction		p=0.50	p=0.44
Vegetable-Fruit-Soy Pattern	Exposure to SHS		
High	Below LOD/Low	6.1 (5.8, 6.4)	6.1 (5.8, 6.3)
	High	6.2 (5.9, 6.4)	6.1 (5.9, 6.4)
Low	Below LOD/Low	6.1 (5.7, 6.4)	6.1 (5.6, 6.7)
	High	6.2 (5.9, 6.5)	6.3 (5.8, 6.8)
p for additive interaction		p=0.98	p=0.81
DASH diet score	Exposure to SHS		
High	Below LOD/Low	6.1 (5.8, 6.3)	6.1 (5.9, 6.4)
	High	6.2 (5.9, 6.5)	6.1 (5.9, 6.3)
Low	Below LOD/Low	6.3 (5.9, 6.7)	6.4 (5.8, 7.0)
	High	6.0 (5.7, 6.2)	6.1 (5.6, 6.6)
p for additive interaction		p=0.13	p=0.68

Abbreviations CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; HbA1c, glycated hemoglobin LOD, limit of detection; SHS, secondhand smoke.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Table 6.6. Crude and adjusted ORs and 95% CIs for the association between exposure to SHS and prediabetes

	Creatinine-Adjusted Cotinine ORs (95% CIs)	Self-Report of Household Smokers ORs (95% CIs)
Crude		
Below LOD/None	1	1
Low/One	0.3 (0.1, 1.0)	--
High/Two or More	0.4 (0.1, 1.4)	1.7 (0.7, 4.1)
p for trend	p=0.58	--
Model 1[a]		
Below LOD/None	1	1
Low/One	0.3 (0.1, 1.3)	--
High/Two or More	0.4 (0.1, 1.7)	1.4 (0.6, 3.5)
p for trend	p=0.68	--
Model 2[b]		
Below LOD/None	1	1
Low/One	0.4 (0.1, 1.7)	--
High/Two or More	0.4 (0.1, 2.1)	1.1 (0.4, 2.7)
p for trend	p=0.61	--

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD, limit of detection; OR, odds ratio; SHS, secondhand smoke.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Table 6.7. Adjusted means and 95% CIs for metabolic disorders in relation to serum cotinine levels and dietary nutrients and measures of multiplicative interaction

		Creatinine-Adjusted Cotinine AORs[a] (95% CIs)	Self-Report of Household Smokers AORs (95% CIs)
Fiber Intake	Exposure to SHS		
High Fiber Intake	Below LOD/Low	1	1
	High	0.7 (0.3, 2.0)	1.3 (0.5, 3.2)
Low Fiber Intake	Below LOD/Low	0.9 (0.4, 1.8)	1.7 (0.6, 5.2)
	High	1.9 (0.4, 5.6)	1.0 (0.2, 4.6)
p for multiplicative interaction[b]		p=0.17	p=0.41
Vitamin C	Cotinine Exposure		
High Vitamin C Intake	Below LOD/Low	1	1
	High	1.5 (0.5, 4.2)	1.5 (0.6, 3.6)
Low Vitamin C Intake	Below LOD/Low	1.1 (0.5, 2.3)	1.2 (0.4, 3.3)
	High	3.3 (1.1, 10.5)	4.9 (1.0, 24.8)
p for multiplicative interaction		p=0.39	p=0.31
Vitamin E Intake	Cotinine Exposure		
High Vitamin E Intake	Below LOD/Low	1	1
	High	1.9 (0.7, 5.2)	1.3 (0.6, 3.1)
Low Vitamin E Intake	Below LOD/Low	1.4 (0.7, 2.9)	1.6 (0.5, 4.8)
	High	1.0 (0.3, 3.0)	1.2 (0.3, 5.5)
p for multiplicative interaction		p=0.21	p=0.59
Omega-3 Fatty Acids Intake	Cotinine Exposure		
High Intake	Below LOD/Low	1	1
	High	2.7 (0.8, 8.7)	2.7 (1.1, 6.3)
Low Intake	Below LOD/Low	1.1 (0.5, 2.3)	1.8 (0.6, 5.0)
	High	2.1 (0.7, 6.0)	1.7 (0.3, 9.3)
p for multiplicative interaction		p=0.68	p=0.34
Meat Dim Sum Pattern	Cotinine Exposure		
High	Below LOD/Low	1	1
	High	0.5 (0.2, 1.1)	0.8 (0.4, 1.7)

Low	Below LOD/Low	0.8 (0.3, 2.0)	2.7 (0.7, 9.9)
	High	0.8 (0.4, 1.9)	0.7 (0.2, 2.4)
p for multiplicative interaction		p=0.23	p=0.19
Vegetable-Fruit-Soy Pattern	Cotinine Exposure		
High	Below LOD/Low	1	1
	High	1.1 (0.5, 2.8)	1.0 (0.5, 2.0)
Low	Below LOD/Low	1.2 (0.5, 3.1)	1.4 (0.3, 5.9)
	High	1.2 (0.5, 2.8)	1.4 (0.4, 4.4)
p for multiplicative interaction		p=0.76	p=0.98
DASH diet score	NNAL Exposure		
High	Below LOD/Low	1	1
	High	1.0 (0.4, 2.5)	0.9 (0.4, 1.7)
Low	Below LOD/Low	1.4 (0.5, 3.3)	1.6 (0.4, 5.9)
	High	1.0 (0.4, 2.3)	1.1 (0.3, 3.7)
p for multiplicative interaction		p=0.58	p=0.77

Abbreviations AOR, adjusted odds ratio; CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; HbA1c, glycated hemoglobin; LOD, limit of detection.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

CHAPTER 7. DISSERTATION DISCUSSION AND CONCLUSIONS

DISCUSSION

Obesity and obesity-related metabolic disorders are now global crises (Stevens et al. 2012) and threaten to bankrupt the healthcare system (Haslam et al. 2006). Globally, one in nine individuals (508 million) were classified as obese in 2008 and the prevalence of obesity continues to rise at alarmingly high rates (Stevens et al. 2012). Rapid increases in the prevalence of obesity have also contribute to the increased prevalence of hyperglycemia (Li et al. 2009), a serious and costly disease that is an important risk factor for both type 2 diabetes and coronary heart disease (Colette and Monnier 2007). Furthermore, the emergence of the obesity epidemic is especially important to the development of metabolic syndrome (Messiah et al. 2007), a cluster of conditions including abdominal fatness, hypertension, an adverse lipid profile, and hyperglycemia, which may increase the risk of multiple chronic diseases (Wilson et al. 2005). As the prevalence of metabolic disorders has increased, health care spending has also risen dramatically. Specifically, obesity accounts for 9% of all U.S. health care spending, which amounts to nearly $150 billion U.S. dollars per year (Finkelstein et al. 2009).

As the health and financial burdens resulting from metabolic disorders continue to escalate, it is now critical to identify potential intervention strategies aimed to reduce these burdens (Swinburn et al. 2011; Withrow and Alter 2011). High caloric diets and low physical activity levels are accepted as risk factors for metabolic disorders (Newbold et al. 2009; Park et al. 2003); however the extent of metabolic disorders prevalence cannot be entirely explained by these risk factors (Holtcamp 2013; Thayer et al. 2012). Evidence is now building that exposures to chemicals in the environment may play a role in the onset of metabolic disorders (Behl et al.

2013). Specifically, exposure to secondhand smoke is an important and common exposure that may be involved in the onset of metabolic disorders.

Results from this dissertation build on previous studies that support the role of exposure to SHS in the development or aggravation of metabolic disorders. The results from Project 1 are consistent with a number of epidemiologic studies that demonstrate a positive association between exposure to SHS and obesity among children, ages 1-17 years (Apfelbacher et al. 2008; Chen et al. 2012; Ittermann et al. 2013; Kwok et al. 2010; Mangrio et al. 2010; McConnell et al. 2015; Pagani et al. 2015; Raum et al. 2011; von Kries et al. 2008; Wen et al. 2013; Yang et al. 2013). Similarly, Project 2 adds to the limited evidence that suggests there is a positive association between exposure to SHS and metabolic syndrome among U.S. children (Weitzman et al. 2005) and Chinese adults (Xie et al. 2010).

Conversely, the potential role of exposure to SHS on hyperglycemia is not yet clear. Although several epidemiologic studies have reported that individuals exposed to SHS have higher glucose levels among young adults, ages 18-30 years (Houston et al. 2006; White et al. 2014); other studies do not support the hypothesis that exposure to SHS is associated with elevated glucose among older adults, ages 30-80 years (Jefferis et al. 2010; Xie et al. 2010). Only one previous study has evaluated this relationship using HbA1c levels to characterize hyperglycemia; Clair et al. (2011) reported that higher serum cotinine levels were associated with elevated HbA1c levels among U.S. adults, ages 20-80+ years. Results from Project 3 and Project 4 do not support the hypothesis that exposures to SHS are independently related to HbA1c levels in either U.S. children or Singaporean non-smoking adults. There are several factors that could explain the discrepancies between the results presented in Projects 3 and 4 and the results

presented in the Clair et al. (2011) study. Due to the strong link between active smoking and type 2 diabetes (Willi et al. 2007), it is possible that including former smokers in the analyses conducted by Clair et al. (2011) may have produced a spurious relationship between exposure to SHS and HbA1c levels. Additionally, HbA1c levels may be artificially low among children (Lee et al. 2011; Nowicka et al. 2011) or artificially high among elderly adults (Pani et al. 2008), which could have impacted the ability to detect a relationship between exposure to SHS and HbA1c levels in Projects 3 and 4. Obesity may be a mediator of the association between exposure to SHS and hyperglycemia (Sankhla et al. 2012) and the low prevalence of obesity within the Project 4 study population could explain why we did not observe an association. Moreover, the identification of statistical interaction in Project 3 and Project 4 suggests that the relationship between exposure to SHS and HbA1c levels is homogenous across individuals with different diets. Clair et al. (2011) did not stratify the results by dietary intakes and it is possible that the effect estimates would have varied across different subgroups. Finally, an overwhelming majority (92%) of the Singaporean adults had cotinine levels above the limit of detection and it is possible that the lack of variability in exposure status could have resulted in a bias towards the null (Project 4). At present, it remains unclear whether exposure to SHS is independently related to HbA1c levels. Further epidemiologic studies are warranted to evaluate this research question.

The biological mechanisms linking exposure to SHS with metabolic disorders likely involve a combination of inflammatory responses, oxidative stress, endothelial dysfunction, and endocrine disruption triggered by exposure to SHS. Systemic inflammation is an important hypothesized mechanism of the association between exposure to SHS and metabolic disorders (Barnoya and Glantz 2005). Exposure to SHS triggers an immunologic response that is associated with increases in pro-inflammatory cytokines (e.g. TNF-α and IL-6) and C-reactive

protein (Jefferis et al. 2010; Panagiotakos et al. 2004). The release of TNF-α and IL-6 disrupts insulin signaling, potentially contributing to hyperglycemia (McArdle et al. 2013) and alters the activity of lipoprotein and endothelial lipases (Grunfeld and Feingold 1996), potentially resulting in dyslipidemia (Zuliani et al. 2007). Higher levels of C-reactive protein may increase the number of cell adhesion molecules and endothelin-1 production, which may ultimately result in hypertension (Schillaci and Pirro 2006). While adipocytes are indisputably sources of inflammation in obesity, it has also been proposed that intestinal inflammation precedes the development of obesity (Ding et al. 2010; Ding and Lund 2011; Kim et al. 2008).

Other biological mechanisms linking exposure to SHS with metabolic disorders have also been proposed and likely involve a combination of oxidative stress, endothelial dysfunction, and endocrine disruption. Cigarette smoke is also an abundant source of ROS (Church and Pryor 1985) and contributes to oxidative stress (Kosecik et al. 2005). Hyperglycemia may be initiated by exposure to SHS whereby oxidative stress impairs glucose uptake in adipose tissue (Maddux et al. 2001; Rudich et al. 1998) and decreases insulin secretion from pancreatic β cells (Matsuoka et al. 1997). Exposure to SHS also promotes excessive stimulation of NADPH oxidase (Lee and Yang 2012) leading to an oxidative stress response that has damaging actions of the vasculature (Paravicini and Touyz 2008). Due to its destruction of endothelial cells and interference with the endothelium repair mechanism, endothelial function is dramatically decreased following exposure to SHS (Frey et al. 2012). Endothelial dysfunction may contribute to hypertension by decreasing bioavailability of NO, impairing endothelium-dependent vasodilation and altering the production of anticoagulant factors (Budhiraja et al. 2004; Puddu et al. 2000). Although hyperglycemia typically precedes endothelial dysfunction, epidemiologic research has also demonstrated that endothelial dysfunction predicts hyperglycemia, independent of other known

risk factors (Meigs et al. 2004; Song et al. 2007). Many compounds found in SHS, including nicotine and polycyclic aromatic hydrocarbons, are suspected endocrine disruptors and could negatively affect the utilization of insulin and promote metabolic imbalance (Tziomalos and Charsoulis 2004). Specifically, endocrine-disrupting chemicals disrupt the ability of PPARγ to bind to its target genes, which may ultimately lead to obesity (Janesick and Blumberg 2011). Our identification of statistical interaction with various dietary factors may support the hypothesized biological mechanisms of these associations (Balhara 2012).

Interaction results from Projects 1 and 3 suggest that diets high in dietary fiber may counteract obesity and hyperglycemia potentially triggered by exposure to SHS. A common biological mechanism linking dietary fiber with obesity and hyperglycemia involves inflammation (Liu et al. 2002; Vork et al. 2007). Dietary fiber intake may improve gut microbiota (De Filippo et al. 2010) and inhibit intestinal inflammation provoked by exposure to SHS (Verschuere et al. 2012), thereby potentially limiting the onset or progression of obesity (Ding et al. 2010; Ding and Lund 2011; Kim et al. 2008). Additionally, increased dietary fiber consumption may inhibit the absorption of cadmium (Kim et al. 2010), an important constituent of SHS that alters glucose homeostasis among individuals exposed to SHS (Edwards and Prozialeck 2009). These hypothesized mechanisms are also supported by epidemiologic research; Clark et al. (2013) reported that high dietary fiber consumption may ameliorate the harmful effects of exposure to SHS on the risk of coronary heart disease mortality among non-smoking adults.

The interaction results from Projects 2 and 3 support the hypothesis that antioxidants may counteract SHS-induced hyperglycemia and metabolic syndrome. Oxidative stress is a potential pathway linking exposure to SHS with hyperglycemia and metabolic syndrome. Antioxidants

may block the oxidative stress caused by free radical exposure from SHS (Barnoya and Glantz 2005); both animal and human studies have reported that antioxidant supplementation (with vitamin C or vitamin E) mitigates the oxidative stress response induced by exposure to SHS (Al-Malki and Moselhy 2013; Dietrich et al. 2003; Howard et al. 1998). By inhibiting oxidative stress responses, high intakes of vitamin C or vitamin E could potentially limit hyperglycemia, hypertension, and metabolic syndrome (Barnoya et al. 2005).

As evidenced by the results from Projects 1, 2, and 3, omega-3 polyunsaturated fatty acids may be particularly important in counteracting metabolic impacts potentially triggered by exposure to SHS. Oxidative stress appears to be an important biological mechanism linking exposure to SHS with metabolic disorders. Omega-3 polyunsaturated fatty acids may modulate the adverse effects of environmental exposures by reducing ROS generation (Romieu et al. 2008). By limiting the oxidative stress response induced by exposure to SHS, omega-3 polyunsaturated fatty acids could improve sensitivity to insulin (Celermajer et al. 1996) or inhibiting the induction of obesity (Youn et al. 2014). Diets high in omega-3 polyunsaturated fatty acids may also counteract SHS-induced endothelial dysfunction (Goodfellow et al. 2000) and therefore may prevent hyperglycemia (Meigs et al. 2004; Song et al. 2007). Epidemiologic evidence supports the hypothesis that omega-3 polyunsaturated fatty acids may limit the harmful effects of SHS. Two studies have observed that omega-3 polyunsaturated fatty acids found in fish modified the association between smoking and coronary heart disease incidence, one among a prospective cohort of 8,006 Japanese-American men aged 45 to 65 years who lived in Hawaii (Rodriguez et al. 1996) and one among a prospective cohort of 72,012 Japanese men and women aged 45–74 years (Eshak et al. 2014).

The projects described in this dissertation may be limited by several challenges inherent to the study designs and sources of the data. The data used to evaluate these relationships collected information on the exposures and the outcomes within the same time period. Due to the cross-sectional nature of the data, the results are limited by the inability to establish temporality. Despite this limitation, the dissertation findings are supported by several prospective cohort studies reporting that exposure to SHS is positively associated with obesity among children (Pagani et al. 2015; Wen et al. 2013; Yang et al. 2013).

An important consideration when interpreting the results is the potential for residual confounding. In particular, diet is an important confounder that is strongly associated with both exposure to SHS (Johnson et al. 1996; Rogers and Emmett 2003) and metabolic disorders (Carr et al. 2000; Ford et al. 2003; Wang et al. 2006). Despite the strong potential for confounding due to diet, only two published studies have attempted to adjust for diet when evaluating this hypothesis (Houston et al. 2006; Panagiotakos et al. 2004). A distinct advantage of NHANES and the Singapore Chinese Health Study is the availability of well-measured dietary variables, which allowed for the evaluation of diet in a number of ways (i.e. individual nutrients and dietary patterns) in order to identify the impact of diet quality. Furthermore, a statistical approach was employed that allowed for the assessment of the impact of potential confounding due to dietary variables and other covariates. Specifically, crude and adjusted results were presented for our analyses, in which we presented results for models: 1) adjusting for the minimum set of confounders only; 2) additionally adjusting for dietary variables (in terms of individual nutrients and dietary patterns); and 3) additionally adjusting for other covariates (e.g. maternal self-report of household smokers, physical activity, body mass index). Based on the results, the associations between exposure to SHS and metabolic disorders were not changed following adjustment for dietary variables and

other potential confounders. Given that the effect estimates were expected to change following adjustment for these important confounders, it is possible that confounding due to diet, physical activity, and other important confounders was not adequately controlled for in the statistical models. Furthermore, the results are likely to be limited by the inaccurate or incomplete measurement of important covariates, such as self-report of physical activity levels, height, and weight. The misclassification of these confounders could have reduced the degree to which confounding could be controlled for and this could have biased the results in away from the null. Therefore, the possibility that residual confounding due to diet and other important than diet cannot be ruled out.

It is possible that measurement error could have affected the results of this dissertation. Compared to the biomarkers, self-report of household smokers characterized no exposure to SHS differently. Self-report of household smokers was limited to exposures within the home and did not attempt to capture exposure in other settings (e.g. schools, workplaces, other households, multiunit housing, etc.), whereas biomarker levels attempt to objectively capture any potential exposures to SHS. Due to the potential for reporting bias (Al-Delaimy and Willett 2008), self-report of exposure to SHS could have lead to exposure misclassification (Lee et al. 2005). This exposure misclassification would be non-differential with respect to metabolic disorders, which may result in a bias towards the null for the dichotomized variable. A distinct advantage of using biomarkers to quantify exposure to SHS is that they objectively measure of an individual's exposure to SHS and limit the potential for reporting bias (Al-Delaimy and Willett 2008). Furthermore, NNAL offers the benefit of a three week half-life as compared to the 16 hour half-life of cotinine (Avila-Tang et al. 2013). Therefore, it is likely that NNAL is an objective measure of an individual's long-term exposure to SHS that is sensitive to intermittent, non-daily

exposure, whereas cotinine is an objective measure of exposure to SHS and is most useful when taken in close temporal proximity to exposure to SHS (Goniewicz et al. 2011). A potential limitation of these biomarkers is that they may be impacted by characteristics of the individual, such as the individual's age and/or race/ethnicity (Avila-Tang et al. 2013), which could result in exposure misclassification. Our models adjusted for these factors; however, we acknowledge this potential source of bias.

Contrary to what was hypothesized, the associations between SHS exposures and metabolic disorders were only slightly different for the biomarkers and self-report of household smokers. In general, the effect estimates were stronger when exposure to SHS was characterized using biomarkers as compared to self-report of household smokers. However, the difference in the effect estimates across each exposure metric did not influence our interpretation. These results provide valuable insight about the usefulness of each exposure metric and suggest that all three measures may be appropriate for evaluating the impact of SHS exposure on metabolic disorders. Since self-report is easier and less expensive to measure than cotinine and NNAL (Avila-Tang et al. 2013), one could argue that biomarkers may not be necessary for exploratory studies evaluating this research question, particularly among children. Nevertheless, determining whether to use biomarkers or self-report to quantify exposure to SHS will depend on the public health question of interest, study design, population of interest, and funding (Avila-Tang et al. 2013).

Another important consideration is the violation of the rare disease assumption in Project 1. The rare disease assumption is a mathematical assumption where the odds ratio is believed to approximate the relative risk when the prevalence of the outcome is low (e.g. less than 10%) and is believed to diverge from relative risk when the prevalence of the outcome is high (Greenland and

Thomas 1982). In Project 1, the prevalence of obesity was relatively high (19%), which means that the odds ratios may have overestimated the relative risks. Therefore, it is possible that the strength of the association between exposure to SHS and obesity was exaggerated.

An important strength of Projects 1, 2, and 3 are the sampling methods and complex survey design employed by NHANES, which allows for the results to be generalizable to all U.S. children. Furthermore, the sample sizes for Projects 1, 2, and 3 was sufficiently large, as evidenced by the relatively narrow confidence intervals. Finally, due to the low prevalence of obesity within the Project 4 study population, the potential for confounding due to weight status was reduced.

FUTURE DIRECTIONS

The results from the dissertation add to the limited epidemiologic evidence evaluating the associations between exposure to SHS and metabolic disorders; however, due to the nature of the data, the temporality of these relationships could not be established. Therefore, these relationships should be evaluated through larger-scale, prospective studies.

There is strong evidence that in utero exposure to tobacco is related to metabolic disorders in offspring. Maternal active smoking during pregnancy has been shown to increase the risk for obesity among children by at least 50% (Ino 2010; Oken et al. 2008). Additionally, there is limited evidence that active smoking during pregnancy increases the risk for hyperglycemia (Montgomery and Ekbom 2002; Thomas et al. 2007) and metabolic syndrome (Power et al. 2010) among children. Furthermore, toxicological studies report an association between in utero exposure to nicotine and increased adiposity (Gao et al. 2005; Holloway et al. 2005; Somm et al.

2008) and impaired glucose tolerance (Bruin et al. 2010; Holloway et al. 2005) among exposed Wistar rat pups. Although our analyses adjusted for maternal report of smoking during pregnancy, the possibility of residual confounding cannot be ruled out. Prospective evaluation of maternal smoking behaviors during pregnancy and in early childhood should be undertaken in order to clarify the role or pre- and postnatal exposure to SHS on childhood metabolic disorders.

CONCLUSIONS

This dissertation builds on previous epidemiologic research evaluating the relationships between SHS exposures and precursors to type 2 diabetes and cardiovascular disease. Furthermore, our identification of interactions between diet and exposure to SHS is particularly novel and clarifies the potential biological mechanisms linking SHS to metabolic disorders. Finally, this dissertation provides empirical evidence that may help to inform prevention strategies for metabolic disorders; specifically, campaigns should aim to both reduce SHS exposures and improve diets in order to exceed the expected benefits based on targeting these risk factors separately.

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APPENDICES

Appendix 1.0. Human subjects research approval documentation for NHANES

Colorado State University

Research Integrity & Compliance Review Office
Office of Vice President for Research
Fort Collins, CO 80523-2011
(970) 491-1553
FAX (970) 491-2293

Date: January 16, 2013

To: Dr. Jennifer Peel, ERHS
Brianna Moore, ERHS

From: Janell Barker, IRB Coordinator

Re: Associations of Self-Reported and Biological Markers of Secondhand Smoke with Metabolic Disorders in Children

After review of information regarding the secondary data to be analyzed for the above-mentioned project, it was determined that the data did not meet the requirements of the federal definition of human subject research. "Human subject means a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information."

Living individual – Y
About Whom – Y
Intervention/Interaction – N
Identifiable Private Information – N

Thank you for submitting this information. If you have more projects that are similar, please contact us prior to submission. The IRB must determine whether a project needs to have IRB approval.

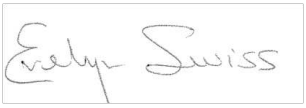
Appendix 2.0. Human subjects research approval documentation for Singapore Chinese Health Study

Colorado State University

Research Integrity & Compliance Review Office
Office of Vice President for Research
Fort Collins, CO 80523-2011
(970) 491-1553
FAX (970) 491-229

Date: June 7, 2012

To: Maggie L. Clark, Ph.D., ERHS

From: Evelyn Swiss, CIP, IRB Coordinator 

Re: Indoor Air Pollution and Indicators of Cardiovascular Health: Potential Modifying Effect of Diet in a Prospective Cohort Study (Dataset received from University of Pittsburgh)

Thank you for providing the memo from your collaborator at the University of Pittsburgh that details the firewall that will be in place so that you will never have access to any identifiers associated with the dataset that you will receive for your grant with the American Heart Association entitled: *Indoor Air Pollution and Indicators of Cardiovascular Health: Potential Modifying Effect of Diet in a Prospective Cohort Study*. After review of information regarding the secondary anonymous dataset to be analyzed here at CSU, it was determined that the data do not meet the requirements of the federal definition of human subject research. "Human subject means a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information" (45CFR46.102(f).

Living individual – Y
About Whom – Y
Intervention/Interaction – N
Identifiable Private Information – N

The OHRP Guidance on Research Involving Coded Private Information or Biological Specimens was also referenced for this determination.

Thank you for submitting this information. If you have more projects that are similar, please contact us prior to submission. The IRB must determine whether a project needs to have IRB approval.

University of Pittsburgh

University of Pittsburgh Cancer Institute

Jian-Min Yuan, MD, PhD
Associate Director for Cancer Prevention and Population Sciences
Leader of the Cancer Epidemiology, Prevention and Control Program
Professor, Department of Epidemiology, Graduate School of Public Health

UPMC Cancer Pavilion
5150 Centre Avenue, Suite 4C
Pittsburgh, PA 15232
PHONE: 412-864-7889
FAX: 412-864-7838
E-MAIL: yuanj@UPMC.edu

May 31, 2012

Maggie L. Clark, PhD.
Research Scientist/Scholar II
Department of Environmental and Radiological Health Sciences
Colorado State University
1681 Campus Delivery
Fort Collins, CO 80523-1681

RE: Data to be Provided from the Singapore Chinese Health Study

Dear Dr. Clark:

I am the Principal Investigator of the Singapore Chinese Health Study, a residential cohort of 63,257 middle-aged and older (45-74 years) Singapore Chinese men and women that was assembled between 1993 and 1998 with the primary goal to elucidate chronic disease-related mechanisms. Besides in-person interviews, more than 60% of the participants provided baseline blood and urine samples. Enclosed is a copy of our IRB certification.

I am writing in regards to your American Heart Association-funded project to measure cotinine and creatinine in urine samples in order to evaluate the relationship between secondhand smoke exposures and cardiovascular disease endpoints in the Singapore cohort. The urinary cotinine and creatinine measurements will be made by our collaborators at the University of Minnesota. These data will be compiled by the lead biostatistician, Dr. Renwei Wang (University of Pittsburgh) and sent to you with unique study subject identifiers. The dataset will not contain any personal identifying information from the study subjects. At no time will you be provided with information that can be used to link the unique study IDs with personal information.

Sincerely,

Jian-Min Yuan, MD, PhD
Professor
Associate Director, Cancer Prevention and Population Sciences

Yuan, Jian Min

From: irb@pitt.edu
Sent: Wednesday, January 04, 2012 10:16 AM
To: jiy44@pitt.edu
Subject: PI Notification: Your research study received approval under expedited review

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Dr. Jian-Min Yuan
From: Christopher Ryan PhD, Vice Chair
Date: 1/4/2012
IRB#: PRO11120129
Subject: Prospective studies of cancer etiology and prevention in Shanghai and Singapore

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110. Your research study was approved under:
45 CFR 46.110.(7)

This study is supported by the following federal grant application:
R01 CA144034 Prospective Studies of Cancer Etiology and Prevention in Shanghai and Singapore

Approval Date: 1/3/2012
Expiration Date: 1/2/2013

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

Appendix 3.1. Weighted proportions among a representative sample of 6-19 year olds, 2007-2010 NHANES, n=2,670

	Ages 6-19 years Proportion (95% CI)	**Ages 6-11** Proportion (95% CI)	**Ages 12-19 years** Proportion (95% CI)
Weight Status			
Normal/underweight	66.0% (63.8, 68.0)	66.5% (62.9, 70.0)	65.5% (13.6, 17.3)
Overweight	14.9% (13.5, 16.3)	14.3% (12.2, 16.5)	15.3% (13.6, 17.3)
Obese	19.1% (17.2, 21.3)	19.2% (16.6, 22.1)	65.6% (62.5, 68.5)
Exposure Assessment			
NNAL Exposure			
Below LOD (<.001 ng/mL creatinine)	52.6% (47.8, 57.4)	52.4% (50.3, 60.5)	52.8% (47.3, 58.2)
Low (≥.001 & <.005 ng/mL creatinine)	23.8% (20.9, 27.1)	17.5% (13.9, 21.7)	28.7% (25.4, 32.1)
High (≥.005 & ≤.082 ng/mL creatinine)	23.5% (18.3, 25.1)	30.1% (25.6, 34.9)	18.6% (15.4, 22.2)
Cotinine Exposure			
No (<.05 ng/mL)	57.3% (53.1, 61.4)	55.4% (50.3, 60.5)	58.7% (54.1, 63.2)
Low (≥.05 & ≤.268 ng/mL)	21.2% (18.5, 24.1)	22.4% (19.2, 26.0)	20.3% (17.0, 23.9)
High (≥.268 & ≤14.6 ng/mL)	21.5% (18.3, 25.1)	22.2% (18.0, 27.0)	21.0% (17.7, 24.7)
Self-report of Household Smokers			
None	86.6% (85.1, 87.8)	85.0% (80.5, 88.6)	87.0% (84.1, 89.4)
Report of one household smokers	13.6% (12.3, 14.9)	15.0% (11.4, 19.5)	13.0% (10.6, 15.9)
Report of two or more household smokers			
Covariates			
Sex			
Male	51.1% (49.2, 53.0)	52.9% (49.8, 55.9)	50.5% (46.5, 54.5)
Female	48.9% (47.0, 50.8)	47.1% (44.1, 50.2)	49.5% (45.5, 53.5)
Race/Ethnicity			
Mexican American	14.4% (10.8, 18.9)	15.4% (11.3, 20.5)	13.6% (10.1, 18.1)
Other Hispanic	6.4% (4.2, 9.4)	6.4% (4.2, 9.6)	6.3% (4.2, 9.5)
Non-Hispanic White	58.5% (52.4, 64.3)	57.9% (50.9, 64.6)	58.9% (52.8, 64.8)
Non-Hispanic Black	13.9% (11.3, 17.0)	13.2% (10.2, 17.0)	14.5% (11.8, 17.6)
Other/Multiracial	6.8% (5.1, 9.1)	7.1% (5.1, 9.8)	6.6% (4.7, 9.3)
Poverty Index Ratio			

Above poverty level (≥1.85)	59.5% (55.1, 63.7)	54.5% (49.2, 59.7)	63.2% (58.6, 67.6)
Below poverty level (<1.85)	40.5% (36.3, 44.9)	45.6% (40.3, 50.8)	36.8% (32.4, 41.4)
Moderate-to-Vigorous Physical Activity			
Met recommendations for 60 minutes/day	86.2% (83.7, 88.6)	81.2% (76.6, 85.3)	89.9% (87.5, 91.9)
Did not meet recommendations for 60	13.8% (11.4, 16.5)	18.7% (14.7, 23.4)	10.1% (8.1, 12.5)
Report of maternal smoking during			
No maternal smoking during pregnancy	86.2% (82.4, 89.4)	85.4% (81.2, 88.8)	87.3% (82.3, 91.1)
Maternal smoking during pregnancy	13.8% (10.6, 17.6)	14.6% (11.2, 18.8)	12.7% (8.9, 17.7)

Appendix 3.2. Crude and adjusted models for the association of exposure to SHS exposure and obesity among U.S. children, ages 6-11 years, 2007-2010 NHANES

	NNAL Exposure		Cotinine Exposure		Self-report of Household Smokers	
	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)
Crude						
Below LOD/None	1	1	1	1	1	1
Low	1.4 (0.9, 2.3)	1.5 (1.0, 2.3)	1.3 (0.9, 1.9)	1.1 (0.7, 1.5)	0.9 (0.5, 1.7)	1.4 (0.9, 2.2)
High	1.0 (0.6, 1.5)	1.2 (0.9, 1.7)	0.9 (0.6, 1.4)	1.3 (0.9, 1.8)	0.4 (0.2, 1.1)	1.0 (0.6, 1.8)
p for trend	p=0.94	p=0.10	p=0.89	p=0.17	p=0.10	p=0.49
Model 1[b]						
Below LOD/None	1	1	1	1	1	1
Low	1.3 (0.8, 2.1)	1.7 (1.1, 2.6)	1.4 (0.9, 2.2)	1.3 (0.8, 2.0)	1.0 (0.5, 1.8)	1.5 (0.8, 2.7)
High	1.1 (0.7, 1.8)	1.7 (1.2, 2.4)	1.0 (0.6, 1.7)	1.6 (1.0, 2.5)	0.5 (0.2, 1.3)	1.2 (0.7, 2.3)
p for trend	p=0.69	p=0.03	p=0.69	p=0.04	p=0.17	p=0.25
Model 2[c]						
Below LOD/None	1	1	1	1	1	1
Low	1.7 (1.0, 3.0)	2.1 (1.4, 3.1)	1.4 (0.8, 2.5)	1.3 (0.7, 2.5)	1.0 (0.5, 2.2)	1.7 (0.8, 3.7)
High	1.3 (0.7, 2.1)	2.0 (1.3, 3.1)	0.7 (0.3, 1.5)	0.8 (0.4, 1.1)	0.5 (0.1, 1.8)	1.5 (0.8, 2.9)
p for trend	p=0.25	p<0.01	p=0.50	p=0.53	p=0.31	p=0.07
Model 3[d]						
Below LOD/None	1	1	1	1	1	1
Low	1.6 (0.9, 2.8)	2.0 (1.3, 3.0)	1.4 (0.8, 2.3)	1.5 (0.9, 2.7)	0.8 (0.4, 1.9)	1.5 (0.7, 3.5)
High	1.1 (0.6, 2.1)	2.0 (1.3, 3.1)	1.0 (0.5, 1.8)	1.8 (1.0, 3.0)	0.4 (0.1, 1.4)	1.3 (0.6, 2.5)
p for trend	p=0.45	p<0.01	p=0.75	p=0.03	p=0.16	p=0.28

Abbreviations: SHS, secondhand smoke; OR, odds ratio; CI, confidence interval; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection

[a] Reference category

[b] Adjusted for sex, age, race/ethnicity and poverty index ratio.

[c] Model 1 plus additional adjustment for the fiber-fat-soluble-vitamins component, the saturated-fat component, the vitamin-complex component, the omega-3-fatty-acids component, and physical activity.

[d] Model 2 plus for additional adjustment for report of maternal smoking during pregnancy.

Appendix 3.3. Crude and adjusted models for the association of exposure to SHS exposure and obesity among U.S. children, ages 12-19 years, 2007-2010 NHANES

	NNAL Exposure		Cotinine Exposure		Self-report of Household Smokers	
	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)	Overweight vs. Normal ORs (95% CIs)	Obese vs. Normal ORs (95% CIs)
Crude						
Below LOD/None	1	1	1	1	1	1
Low	1.2 (0.8, 1.7)	1.8 (1.1, 2.9)	1.2 (0.8, 1.8)	1.4 (1.1, 1.8)	1.4 (0.9, 2.4)	2.2 (1.3, 3.6)
High	1.5 (0.9, 2.4)	2.9 (1.8, 5.0)	1.2 (0.8, 1.8)	2.3 (1.6, 3.5)	1.2 (0.6, 2.5)	2.3 (1.3, 4.3)
p for trend	p=0.10	p<0.01	p=0.25	p<0.01	p=0.24	p<0.01
Model 1[b]						
Below LOD/None	1	1	1	1	1	1
Low	1.4 (0.9, 2.1)	1.8 (1.1, 3.2)	1.1 (0.7, 1.7)	1.3 (1.0, 1.7)	1.3 (0.8, 2.3)	1.9 (1.1, 3.5)
High	1.6 (1.0, 2.7)	3.1 (1.8, 5.4)	1.4 (0.9, 2.1)	2.2 (1.5, 3.4)	1.4 (0.6, 3.1)	2.4 (1.3, 4.6)
p for trend	p=0.05	p<0.01	p=0.17	p<0.01	p=0.22	p<0.01
Model 2[c]						
Below LOD/None	1	1	1	1	1	1
Low	1.4 (0.9, 2.3)	1.9 (1.1, 3.5)	1.3 (0.8, 1.9)	1.4 (1.0, 2.0)	1.3 (0.7, 2.6)	2.3 (1.2, 4.1)
High	1.4 (0.8, 2.6)	3.1 (1.8, 5.5)	1.1 (07, 1.7)	2.3 (1.5, 3.5)	1.1 (0.4, 3.0)	2.7 (1.4, 5.2)
p for trend	p=0.15	p<0.01	p=0.57	p<0.01	p=0.51	p<0.01
Model 3[d]						
Below LOD/None	1	1	1	1	1	1
Low	1.2 (0.6, 2.4)	2.6 (1.3, 5.2)	2.0 (1.1, 3.7)	1.9 (1.2, 2.9)	0.8 (0.4, 1.9)	1.0 (0.5, 1.7)
High	1.0 (0.5, 2.1)	1.9 (0.8, 4.6)	0.8 (0.4, 1.5)	1.5 (0.8, 3.0)	0.8 (0.3, 2.6)	1.4 (0.5, 3.4)
p for trend	p=0.82	p=0.06	p=0.95	p=0.10	p=0.59	p=0.57

Abbreviations: SHS, secondhand smoke; OR, odds ratio; CI, confidence interval; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection

[a] Reference category

[b] Adjusted for sex, age, race/ethnicity and poverty index ratio.

[c] Model 1 plus additional adjustment for the fiber-fat-soluble-vitamins component, the saturated-fat component, the vitamin-complex component, the omega-3-fatty-acids component, and physical activity.

[d] Model 2 plus for additional adjustment for report of maternal smoking during pregnancy.

Appendix 3.4. Adjusted ORs and 95% CIs for overweight and obesity in relation to urinary NNAL levels and dietary nutrients and measures of additive and multiplicative interaction among 6-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	NNAL Exposure		
High Fiber Intake (≥12.75 g/day)	Below LOD/Low	1[d]	1
	High	1.1 (0.8, 1.6)	1.7 (1.2, 2.3)
Low Fiber Intake (<12.75 g/day)	Below LOD/Low	1.1 (0.7, 1.5)	1.1 (0.8, 1.4)
	High	1.6 (1.0, 2.6)	2.6 (1.6, 4.0)
p for multiplicative interaction[b]		p=0.47	p=0.05
RERI (95% CI); p for additive interaction[c]		0.4 (-0.2, 1.0); p=0.19	0.8 (0.1, 1.5); p=0.03
EPA Intake	NNAL Exposure		
High EPA Intake (≥0.007 g/day)	Below LOD/Low	1	1
	High	1.4 (0.9, 2.0)	1.6 (1.1, 2.3)
Low EPA Intake (<0.007 g/day)	Below LOD/Low	1.2 (0.8, 1.8)	1.0 (0.8, 1.3)
	High	1.4 (0.9, 2.3)	2.6 (2.0, 3.5)
p for multiplicative interaction		p=0.76	p=0.05
RERI (95% CI); p for additive interaction		-0.2 (-0.9, 0.5); p=0.56	1.0 (0.3, 1.8); p=0.01
DHA Intake	NNAL Exposure		
High DHA Intake (≥0.018 g/day)	Below LOD/Low	1	1
	High	1.2 (0.8, 1.9)	1.6 (1.0, 2.5)
Low DHA Intake (<0.018 g/day)	Below LOD/Low	1.2 (0.9, 1.7)	1.0 (0.8, 1.4)
	High	1.7 (0.9, 2.7)	2.4 (1.7, 3.4)
p for multiplicative interaction		p=0.68	p=0.19
RERI (95% CI); p for additive interaction		0.3 (-0.4, 1.0); p=0.41	0.8 (0.1, 1.6); p=0.04
Vitamin C Intake	NNAL Exposure		
High Vitamin C Intake (≥68.9 g/day)	Below LOD/Low	1	1
	High	1.3 (0.9, 1.9)	1.8 (1.3, 2.6)
Low Vitamin C Intake (<68.9 g/day)	Below LOD/Low	1.2 (0.8, 1.8)	1.1 (0.8, 1.5)
	High	1.7 (1.0, 2.7)	2.4 (1.7, 3.4)
p for multiplicative interaction		p=0.78	p=0.30
RERI (95% CI); p for additive interaction		0.2 (-0.4, 0.9); p=0.56	0.5 (-0.2, 1.3); p=0.18

Vitamin E Intake	NNAL Exposure		
High Vitamin E Intake	Below LOD/Low	1	1
(≥5.415 mg/day)	High	1.2 (0.9, 1.7)	1.9 (1.4, 2.6)
Low Vitamin E Intake	Below LOD/Low	1.5 (1.1, 2.0)	1.2 (0.9, 1.5)
(<5.415 mg/day)	High	2.2 (1.5, 3.3)	2.6 (1.8, 3.7)
p for multiplicative interaction		p=0.34	p=0.56
RERI (95% CI); p for additive interaction		0.5 (-0.2, 1.3); p=0.20	0.5 (-0.3, 1.3); p=0.22
Fiber-Fat-Soluble Vitamin Intake Component	NNAL Exposure		
High Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	1	1
	High	1.5 (0.9, 2.3)	2.5 (1.7, 3.6)
Low Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	1.3 (0.9, 1.9)	0.9 (0.7, 1.3)
	High	1.8 (1.1, 3.0)	2.1 (1.4, 3.1)
p for multiplicative interaction		p=0.90	p=0.65
RERI (95% CI); p for additive interaction		0 (-0.8, 0.7); p=0.99	-0.3 (-1.2, 0.5); p=0.52
Saturated-Fat-Component Intake	NNAL Exposure		
Low Saturated-Fat Component	Below LOD/Low	1	1
	High	1.4 (0.9, 2.2)	2.3 (1.5, 3.4)
High Saturated-Fat Component	Below LOD/Low	0.6 (0.4, 0.9)	0.7 (0.5, 0.9)
	High	1.0 (0.6, 1.7)	1.5 (1.0, 2.2)
p for multiplicative interaction		p=0.76	p=0.58
RERI (95% CI); p for additive interaction		0 (-0.6, 0.5); p=0.99	-0.5 (-1.3, 0.2); p=0.19
Vitamin-B-Complex Component	NNAL Exposure		
High Saturated-Fat Component	Below LOD/Low	1	1
	High	1.4 (0.9, 2.1)	2.0 (1.5, 2.9)
Low Saturated-Fat Component	Below LOD/Low	1.1 (0.8, 1.6)	1.4 (1.1, 1.7)
	High	1.7 (1.0, 2.9)	3.2 (2.1, 5.1)
p for multiplicative interaction		p=0.86	p=0.52
RERI (95% CI); p for additive interaction		0.2 (-0.6, 0.9); p=0.60	0.8 (-0.2, 1.8); p=0.11
Omega-3 Fatty Acids Component	NNAL Exposure		
High Omega-3 Fatty Acids	Below LOD/Low	1	1

Component			
	High	1.6 (0.9, 2.7)	2.0 (1.4, 2.7)
Low Omega-3 Fatty Acids Component	Below LOD/Low	1.3 (0.9, 1.8)	1.0 (0.8, 1.4)
	High	1.8 (1.2, 2.7)	2.8 (1.8, 4.3)
p for multiplicative interaction		p=0.57	p=0.18
RERI (95% CI); p for additive interaction		-0.1 (-1.0, 0.7); p=0.82	0.7 (-0.2, 1.6); p=0.12

Abbreviations: CI, confidence interval; OR, odds ratio; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

[d]Reference

Appendix 3.5. Adjusted ORs and 95% CIs for overweight and obesity in relation to urinary NNAL levels and dietary nutrients and measures of additive and multiplicative interaction among 6-11 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	NNAL Exposure		
High Fiber Intake (≥12.75 g/day)	Below LOD/Low	1	1
	High	0.9 (0.6, 1.5)	0.8 (0.5, 1.2)
Low Fiber Intake (<12.75 g/day)	Below LOD/Low	1.6 (0.8, 3.1)	1.4 (0.8, 2.6)
	High	1.2 (0.5, 2.8)	2.3 (1.4, 3.9)
p for multiplicative interaction[b]		p=0.25	p=0.03
RERI (95% CI); p for additive interaction[c]		1.4 (0.6, 3.5); p=0.43	1.3 (0.6, 1.8); p=0.51
EPA Intake	NNAL Exposure		
High EPA Intake (≥0.007 g/day)	Below LOD/Low	1	1
	High	1.0 (0.6, 1.6)	0.8 (0.6, 1.3)
Low EPA Intake (<0.007 g/day)	Below LOD/Low	1.2 (0.69, 2.1)	1.6 (0.9, 2.7)
	High	1.3 (0.8, 2.3)	1.7 (1.2, 2.6)
p for multiplicative interaction		p=0.19	p=0.83
RERI (95% CI); p for additive interaction		0.9 (0.4, 1.8); p=0.72	1.1 (0.5, 2.4); p=0.9
DHA Intake	NNAL Exposure		
High DHA Intake (≥0.018 g/day)	Below LOD/Low	1	1
	High	0.6 (0.4, 0.9)	0.7 (0.5, 1.2)
Low DHA Intake (<0.018 g/day)	Below LOD/Low	0.8 (0.3, 1.7)	1.2 (0.7, 2.4)
	High	0.9 (0.4, 2.0)	1.5 (0.8, 2.1)
p for multiplicative interaction		p=0.42	p=0.50
RERI (95% CI); p for additive interaction		1.5 (0.6, 3.6); p=0.39	1.1 (0.4, 3.4); p=0.86
Vitamin C Intake	NNAL Exposure		
High Vitamin C Intake (≥68.9 g/day)	Below LOD/Low	1	1
	High	1.0 (0.5, 1.7)	0.9 (0.6, 1.3)
Low Vitamin C Intake (<68.9 g/day)	Below LOD/Low	1.5 (0.8, 2.8)	1.9 (1.1, 3.1)
	High	1.1 (0.5, 2.1)	1.6 (1.1, 2.3)
p for multiplicative interaction		p=0.34	p=0.39
RERI (95% CI); p for additive interaction		1.5 (0.6, 4.0); p=0.37	1.5 (0.8, 2.7); p=0.22
Vitamin E Intake	NNAL Exposure		

High Vitamin E Intake (≥5.415 mg/day)	Below LOD/Low	1	1
	High	0.9 (0.6, 1.5)	0.8 (0.6, 1.2)
Low Vitamin E Intake (<5.415 mg/day)	Below LOD/Low	1.3 (0.8, 2.3)	1.5 (0.8, 3.0)
	High	1.2 (0.7, 2.1)	1.8 (1.3, 2.6)
p for multiplicative interaction		p=0.62	p=0.82
RERI (95% CI); p for additive interaction		1.3 (0.6, 2.7); p=0.53	1.0 (0.51, 1.8); p=0.90
Fiber-Fat-Soluble Vitamin Intake Component	NNAL Exposure		
High Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	1	1
	High	0.9 (0.6, 1.5)	0.8 (0.5, 1.2)
Low Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	1.6 (0.8, 2.1)	1.4 (0.8, 2.6)
	High	1.2 (0.5, 2.8)	2.3 (1.4, 2.9)
p for multiplicative interaction		p=0.67	p=0.21
RERI (95% CI); p for additive interaction		1.5 (0.4, 5.2); p=0.50	0.8 (0.4, 1.8); p=0.65
Saturated-Fat-Component Intake	NNAL Exposure		
Low Saturated-Fat Component	Below LOD/Low	1	1
	High	0.8 (0.5, 1.4)	0.9 (0.7, 1.3)
High Saturated-Fat Component	Below LOD/Low	1.2 (0.7, 2.1)	1.7 (1.0, 2.7)
	High	1.6 (0.8, 3.2)	2.4 (1.3, 4.3)
p for multiplicative interaction		p=0.70	p=0.33
RERI (95% CI); p for additive interaction		0.9 (0.3, 2.4); p=0.79	0.8 (0.4, 1.6); p=0.48
Vitamin-B-Complex Component	NNAL Exposure		
High Saturated-Fat Component	Below LOD/Low	1	1
	High	1.0 (0.7, 1.5)	0.8 (0.5, 1.2)
Low Saturated-Fat Component	Below LOD/Low	1.6 (0.8, 3.4)	2.2 (1.2, 4.0)
	High	1.4 (0.8, 2.6)	1.5 (1.0, 2.34
p for multiplicative interaction		p=0.71	p=0.08
RERI (95% CI); p for additive interaction		1.1 (0.4, 2.9); p=0.82	1.9 (1.0, 3.6); p=0.04
Omega-3 Fatty Acids Component	NNAL Exposure		
High Omega-3 Fatty Acids Component	Below LOD/Low	1	1
	High	0.8 (0.5, 1.4)	0.8 (0.5, 1.1)

Low Omega-3 Fatty Acids Component	Below LOD/Low	1.6 (0.9, 2.9)	1.7 (1.2, 3.1)
	High	1.1 (0.5, 2.2)	1.7 (1.0, 2.8)
p for multiplicative interaction		p=0.13	p=0.70
RERI (95% CI); p for additive interaction		1.7 (0.5, 5.2); p=0.35	1.5 (0.8, 2.7); p=0.18

Abbreviations: CI, confidence interval; OR, odds ratio; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.6. Adjusted ORs and 95% CIs for overweight and obesity in relation to urinary NNAL levels and dietary nutrients and measures of additive and multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	NNAL Exposure		
High Fiber Intake (≥12.75 g/day)	Below LOD/Low	1	1
	High	1.6 (1.0, 2.7)	1.6 (0.9, 2.7)
Low Fiber Intake (<12.75 g/day)	Below LOD/Low	2.5 (1.3, 4.8)	4.2 (2.2, 8.1)
	High	1.3 (0.6, 2.4)	1.7 (0.9, 3.1)
p for multiplicative interaction[b]		p=0.35	p=0.01
RERI (95% CI); p for additive interaction[c]		1.2 (0.5, 2.7); p=0.75	1.7 (0.8, 3.5); p=0.18
EPA Intake	NNAL Exposure		
High EPA Intake (≥0.007 g/day)	Below LOD/Low	1	1
	High	1.2 (0.8, 2.0)	1.1 (0.8, 1.6)
Low EPA Intake (<0.007 g/day)	Below LOD/Low	1.8 (0.9, 3.8)	4.4 (2.6, 7.4)
	High	1.4 (0.9, 2.4)	1.6 (1.0, 2.5)
p for multiplicative interaction		p=0.22	p<0.01
RERI (95% CI); p for additive interaction		1.0 (0.4, 2.6); p=0.99	2.5 (1.1, 5.7); p=0.03
DHA Intake	NNAL Exposure		
High DHA Intake (≥0.018 g/day)	Below LOD/Low	1	1
	High	1.7 (1.1, 2.8)	1.3 (0.8, 2.0)
Low DHA Intake (<0.018 g/day)	Below LOD/Low	2.8 (1.5, 5.2)	3.7 (2.3, 6.0)
	High	1.4 (0.8, 2.5)	1.5 (0.8, 2.9)
p for multiplicative interaction		p=0.31	p=0.01
RERI (95% CI); p for additive interaction		1.1 (0.5, 2.4); p=0.82	1.9 (0.9, 4.1); p=0.11
Vitamin C Intake	NNAL Exposure		
High Vitamin C Intake (≥68.9 g/day)	Below LOD/Low	1	1
	High	1.3 (0.8, 2.1)	1.2 (0.8, 1.9)
Low Vitamin C Intake (<68.9 g/day)	Below LOD/Low	1.7 (0.8, 3.6)	3.0 (1.8, 5.2)
	High	1.5 (0.9, 2.7)	2.2 (1.5, 3.5)
p for multiplicative interaction		p=0.46	p=0.66
RERI (95% CI); p for additive interaction		0.9 (0.3, 2.6); p=0.80	1.1 (0.6, 2.1); p=0.72

Vitamin E Intake	NNAL Exposure		
High Vitamin E Intake (≥5.415 mg/day)	Below LOD/Low	1	1
	High	2.0 (1.3, 3.1)	1.7 (1.2, 2.2)
Low Vitamin E Intake (<5.415 mg/day)	Below LOD/Low	3.5 (1.8, 7.1)	4.4 (2.5, 7.8)
	High	1.1 (0.7, 1.8)	2.1 (1.4, 3.1)
p for multiplicative interaction		p=0.09	p=0.08
RERI (95% CI); p for additive interaction		1.5 (0.8, 2.7); p=0.22	1.3 (0.7, 2.3); p=0.46
Fiber-Fat-Soluble Vitamin Intake Component	NNAL Exposure		
High Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	1	1
	High	1.7 (1.1, 2.7)	1.1 (0.8, 1.5)
Low Fiber-Fat-Soluble-Vitamin Component	Below LOD/Low	2.1 (1.1, 4.3)	2.8 (1.7, 4.6)
	High	1.7 (0.8, 3.6)	2.8 (1.5, 5.3)
p for multiplicative interaction		p=0.69	p=0.91
RERI (95% CI); p for additive interaction		0.7 (0.3, 1.9); p=0.49	0.9 (0.5, 1.7); p=0.77
Saturated-Fat-Component Intake	NNAL Exposure		
Low Saturated-Fat Component	Below LOD/Low	1	1
	High	0.5 (0.3, 0.7)	0.6 (0.4, 0.9)
High Saturated-Fat Component	Below LOD/Low	0.8 (0.4, 1.9)	1.5 (0.9, 2.4)
	High	1.4 (0.7, 2.6)	2.9 (1.5, 5.8)
p for multiplicative interaction		p=0.82	p=0.13
RERI (95% CI); p for additive interaction		1.3 (0.4, 3.8); p=0.68	0.9 (0.4, 1.9); p=0.75
Vitamin-B-Complex Component	NNAL Exposure		
High Saturated-Fat Component	Below LOD/Low	1	1
	High	1.3 (0.8, 2.0)	2.1 (1.5, 3.0)
Low Saturated-Fat Component	Below LOD/Low	1.9 (0.9, 3.9)	4.9 (2.7, 9.0)
	High	1.3 (0.7, 2.5)	2.8 (1.6, 5.0)
p for multiplicative interaction		p=0.62	p=0.36
RERI (95% CI); p for additive interaction		1.1 (0.4, 2.8); p=0.84	0.8 (0.3, 2.2); p=0.72
Omega-3 Fatty Acids Component	NNAL Exposure		
High Omega-3 Fatty Acids Component	Below LOD/Low	1	1
	High	1.7 (1.1, 2.6)	1.2 (0.8, 1.7)

Low Omega-3 Fatty Acids Component	Below LOD/Low	1.9 (1.0, 3.7)	3.7 (2.0, 6.9)
	High	2.0 (1.1, 3.9)	2.2 (1.5, 3.3)
p for multiplicative interaction		p=0.28	p=0.12
RERI (95% CI); p for additive interaction		0.5 (0.2, 1.3); p=0.16	1.4 (0.7, 2.7); p=0.26

Abbreviations: CI, confidence interval; OR, odds ratio; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.7. Adjusted ORs and 95% CIs for overweight and obesity in relation to serum cotinine levels and dietary nutrients and measures of additive and multiplicative interaction among 6-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Cotinine Exposure		
High Fiber Intake (≥12.75 g/day)	No/Low	1	1
	High	1.1 (0.2, 1.4)	1.1 (0.2, 1.4)
Low Fiber Intake (<12.75 g/day)	No/Low	1.1 (0.2, 1.6)	1.5 (1.0, 2.3)
	High	1.2 (0.2, 1.7)	2.1 (1.4, 3.2)
p for multiplicative interaction[b]		p=0.89	p=0.43
p for additive interaction[c]		p=0.99	p=0.11
EPA Intake	Cotinine Exposure		
High EPA Intake (≥0.007 g/day)	No/Low	1	1
	High	1.1 (0.2, 1.6)	0.9 (0.7, 1.2)
Low EPA Intake (<0.007 g/day)	No/Low	1.1 (0.2, 1.6)	1.3 (0.2, 2.0)
	High	1.1 (0.2, 1.9)	2.2 (1.7, 2.9)
p for multiplicative interaction		p=0.79	p=0.05
p for additive interaction		p=0.73	p<0.01
DHA Intake	Cotinine Exposure		
High DHA Intake (≥0.018 g/day)	No/Low	1	1
	High	1.3 (0.2, 1.7)	1.0 (0.2, 1.4)
Low DHA Intake (<0.018 g/day)	No/Low	1.3 (0.2, 2.1)	1.4 (0.2, 2.3)
	High	1.3 (0.2, 2.0)	1.8 (1.3, 2.7)
p for multiplicative interaction		p=0.52	p=0.40
p for additive interaction		p=0.40	p=0.21
Vitamin C Intake	Cotinine Exposure		
High Vitamin C Intake (≥68.9 g/day)	No/Low	1	1
	High	1.3 (0.2, 1.9)	1.2 (0.2, 1.6)
Low Vitamin C Intake (<68.9 g/day)	No/Low	1.2 (0.2, 1.7)	1.8 (1.2, 2.6)
	High	1.3 (0.2, 1.9)	2.0 (1.4, 2.7)
p for multiplicative interaction		p=0.44	p=0.71
p for additive interaction		p=0.50	p=0.99

Vitamin E Intake	Cotinine Exposure		
High Vitamin E Intake (≥5.415 mg/day)	No/Low	1	1
	High	1.6 (1.2, 2.2)	1.4 (1.1, 1.7)
Low Vitamin E Intake (<5.415 mg/day)	No/Low	1.1 (0.2, 1.5)	1.9 (1.4, 2.8)
	High	1.7 (1.1, 2.4)	2.0 (1.3, 3.1)
p for multiplicative interaction		p=0.83	p=0.23
p for additive interaction		p=0.02	p=0.41
Fiber-Fat-Soluble Vitamin Intake Component	Cotinine Exposure		
High Fiber-Fat-Soluble-Vitamin Component	No/Low	1	1
	High	1.4 (0.2, 1.9)	1.1 (0.2, 1.5)
Low Fiber-Fat-Soluble-Vitamin Component	No/Low	1.0 (0.2, 1.7)	2.3 (1.6, 3.3)
	High	1.4 (0.2, 2.1)	1.7 (1.1, 2.5)
p for multiplicative interaction		p=0.95	p=0.05
p for additive interaction		p=0.99	p=0.10
Saturated-Fat-Component Intake	Cotinine Exposure		
Low Saturated-Fat Component	No/Low	1	1
	High	0.6 (0.2, 0.8)	0.7 (0.2, 1.0)
High Saturated-Fat Component	No/Low	1.0 (0.2, 1.4)	2.0 (1.2, 3.1)
	High	0.6 (0.2, 1.3)	1.3 (0.2, 1.8)
p for multiplicative interaction		p=0.60	p=0.69
p for additive interaction		p=0.99	p=0.23
Vitamin-B-Complex Component	Cotinine Exposure		
High Saturated-Fat Component	No/Low	1	1
	High	1.3 (0.2, 1.7)	1.6 (1.3, 2.0)
Low Saturated-Fat Component	No/Low	1.2 (0.2, 1.7)	2.0 (1.5, 2.7)
	High	1.1 (0.2, 1.9)	2.5 (1.6, 4.0)
p for multiplicative interaction		p=0.20	p=0.32
p for additive interaction		p=0.20	p=0.84

Omega-3 Fatty Acids Component	Cotinine Exposure		
High Omega-3 Fatty Acids	No/Low	1	1
Component	High	1.4 (1.0, 1.8)	0.9 (0.2, 1.2)
Low Omega-3 Fatty Acids	No/Low	1.3 (0.2, 2.1)	1.4 (1.0, 2.0)
Component	High	1.1 (0.2, 1.7)	2.1 (1.3, 3.4)
p for multiplicative interaction		p=0.15	p=0.06
p for additive interaction		p=0.40	p=0.02

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.8. Adjusted ORs and 95% CIs for overweight and obesity in relation to serum cotinine levels and dietary nutrients and measures of additive and multiplicative interaction among 6-11 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Cotinine Exposure		
High Fiber Intake (≥12.75 g/day)	No/Low	1	1
	High	1.0 (0.2, 1.5)	0.9 (0.1, 1.4)
Low Fiber Intake (<12.75 g/day)	No/Low	0.8 (0.2, 2.0)	2.0 (1.2, 3.5)
	High	1.2 (0.2, 2.3)	1.1 (0.2, 1.9)
p for multiplicative interaction[b]		p=0.31	p=0.48
p for additive interaction[c]		p=0.35	p=0.01
EPA Intake	Cotinine Exposure		
High EPA Intake (≥0.007 g/day)	No/Low	1	1
	High	1.0 (0.2, 1.4)	0.9 (0.2, 1.3)
Low EPA Intake (<0.007 g/day)	No/Low	0.9 (0.2, 1.6)	1.4 (0.1, 2.3)
	High	0.8 (0.1, 1.5)	1.4 (0.2, 2.4)
p for multiplicative interaction		p=0.70	p=0.71
p for additive interaction		p=0.71	p=0.56
DHA Intake	Cotinine Exposure		
High DHA Intake (≥0.018 g/day)	No/Low	1	1
	High	0.7 (0.1, 1.0)	0.8 (0.2, 1.4)
Low DHA Intake (<0.018 g/day)	No/Low	0.8 (0.1, 1.7)	1.3 (0.2, 2.5)
	High	0.6 (0.1, 1.4)	0.8 (0.1, 1.7)
p for multiplicative interaction		p=0.82	p=0.72
p for additive interaction		p=0.74	p=0.39
Vitamin C Intake	Cotinine Exposure		
High Vitamin C Intake (≥68.9 g/day)	No/Low	1	1
	High	1.2 (0.2, 1.9)	1.1 (0.2, 1.6)
Low Vitamin C Intake (<68.9 g/day)	No/Low	1.0 (0.2, 1.6)	1.5 (0.2, 2.4)
	High	1.0 (0.2, 2.0)	1.5 (0.2, 2.5)
p for multiplicative interaction		p=0.80	p=0.92
p for additive interaction		p=0.58	p=0.82

Vitamin E Intake	Cotinine Exposure		
High Vitamin E Intake (≥5.415 mg/day)	No/Low	1	1
	High	0.9 (0.2, 1.5)	1.0 (0.2, 1.6)
Low Vitamin E Intake (<5.415 mg/day)	No/Low	0.8 (0.1, 1.3)	1.7 (1.1, 2.8)
	High	1.0 (0.2, 1.8)	1.2 (0.2, 2.2)
p for multiplicative interaction		p=0.38	p=0.18
p for additive interaction		p=0.32	p=0.19
Fiber-Fat-Soluble Vitamin Intake Component	Cotinine Exposure		
High Fiber-Fat-Soluble-Vitamin Component	No/Low	1	1
	High	1.0 (0.2, 1.5)	0.9 (0.2, 1.4)
Low Fiber-Fat-Soluble-Vitamin Component	No/Low	0.8 (0.1, 2.0)	2.0 (1.2, 3.5)
	High	1.1 (0.2, 2.3)	1.1 (0.2, 1.9)
p for multiplicative interaction		p=0.66	p=0.19
p for additive interaction		p=0.40	p=0.10
Saturated-Fat-Component Intake	Cotinine Exposure		
Low Saturated-Fat Component	No/Low	1	1
	High	0.9 (0.2, 1.3)	1.0 (0.2, 1.5)
High Saturated-Fat Component	No/Low	1.0 (0.1, 2.1)	1.7 (0.2, 3.3)
	High	0.9 (0.1, 1.9)	1.3 (0.2, 2.2)
p for multiplicative interaction		p=0.87	p=0.58
p for additive interaction		p=0.99	p=0.39
Vitamin-B-Complex Component	Cotinine Exposure		
High Saturated-Fat Component	No/Low	1	1
	High	1.1 (0.2, 1.6)	1.0 (0.2, 1.5)
Low Saturated-Fat Component	No/Low	1.2 (0.2, 2.1)	1.3 (0.2, 2.2)
	High	1.0 (0.1, 2.1)	1.8 (0.2, 3.2)
p for multiplicative interaction		p=0.49	p=0.43
p for additive interaction		p=0.49	p=0.29
Omega-3 Fatty Acids Component	Cotinine Exposure		
High Omega-3 Fatty Acids Component	No/Low	1	1
	High	1.0 (0.2, 1.6)	0.7 (0.2, 1.0)
Low Omega-3 Fatty Acids Component	No/Low	1.1 (0.2, 2.0)	1.0 (0.2, 2.0)

	High	0.9 (0.1, 1.8)	1.5 (0.2, 2.4)
p for multiplicative interaction		p=0.72	p=0.11
p for additive interaction		p=0.62	p=0.03

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.9. Adjusted ORs and 95% CIs for overweight and obesity in relation to serum cotinine levels and dietary nutrients and measures of additive and multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Cotinine Exposure		
High Fiber Intake (≥12.75 g/day)	No/Low	1	1
	High	1.1 (1.2, 3.1)	1.3 (0.8, 2.2)
Low Fiber Intake (<12.75 g/day)	No/Low	2.0 (0.9, 4.5)	1.4 (0.7, 2.8)
	High	2.2 (1.2, 4.0)	2.9 (1.5, 5.6)
p for multiplicative interaction[b]		p=0.20	p=0.20
p for additive interaction[c]		p=0.90	p=0.03
EPA Intake	Cotinine Exposure		
High EPA Intake (≥0.007 g/day)	No/Low	1	1
	High	1.2 (0.8, 1.9)	1.0 (0.7, 1.4)
Low EPA Intake (<0.007 g/day)	No/Low	1.3 (0.7, 2.3)	1.3 (0.7, 2.3)
	High	1.6 (0.7, 3.4)	3.4 (2.1, 5.4)
p for multiplicative interaction		p=0.95	p=0.02
p for additive interaction		p=0.86	p<0.01
DHA Intake	Cotinine Exposure		
High DHA Intake (≥0.018 g/day)	No/Low	1	1
	High	1.9 (1.2, 2.9)	1.2 (0.7, 1.0)
Low DHA Intake (<0.018 g/day)	No/Low	1.8 (0.8, 3.9)	1.5 (0.7, 3.2)
	High	2.3 (1.3, 4.0)	2.8 (1.7, 4.8)
p for multiplicative interaction		p=0.34	p=0.21
p for additive interaction		p=0.60	p=0.05
Vitamin C Intake	Cotinine Exposure		
High Vitamin C Intake (≥68.9 g/day)	No/Low	1	1
	High	1.4 (0.8, 2.1)	1.3 (0.8, 1.9)
Low Vitamin C Intake (<68.9 g/day)	No/Low	1.5 (0.8, 2.9)	2.2 (1.3, 3.8)
	High	1.5 (0.8, 2.6)	2.4 (1.5, 3.8)
p for multiplicative interaction		p=0.41	p=0.55
p for additive interaction		p=0.08	p=0.89

Vitamin E Intake	Cotinine Exposure		
High Vitamin E Intake (≥5.415 mg/day)	No/Low	1	1
	High	2.4 (1.6, 3.5)	1.7 (1.2, 2.4)
Low Vitamin E Intake (<5.415 mg/day)	No/Low	1.5 (0.9, 2.4)	2.2 (1.4, 3.4)
	High	2.6 (1.4, 4.8)	3.0 (1.7, 5.6)
p for multiplicative interaction		p=0.32	p=0.48
p for additive interaction		p=0.69	p=0.90
Fiber-Fat-Soluble Vitamin Intake Component	Cotinine Exposure		
High Fiber-Fat-Soluble-Vitamin Component	No/Low	1	1
	High	1.7 (1.1, 2.5)	1.3 (0.9, 1.9)
Low Fiber-Fat-Soluble-Vitamin Component	No/Low	1.1 (0.5, 2.4)	2.8 (1.7, 4.8)
	High	1.6 (0.9, 3.0)	2.3 (1.4, 3.8)
p for multiplicative interaction		p=0.79	p=0.12
p for additive interaction		p=0.72	p=0.30
Saturated-Fat-Component Intake	Cotinine Exposure		
Low Saturated-Fat Component	No/Low	1	1
	High	0.5 (0.4, 0.7)	0.6 (0.4, 0.9)
High Saturated-Fat Component	No/Low	1.0 (0.6, 1.5)	2.2 (1.1, 4.6)
	High	0.6 (0.3, 1.3)	1.3 (0.8, 2.0)
p for multiplicative interaction		p=0.59	p=0.10
p for additive interaction		p=0.75	p=0.34
Vitamin-B-Complex Component	Cotinine Exposure		
High Saturated-Fat Component	No/Low	1	1
	High	1.4 (0.9, 2.4)	2.4 (1.7, 3.3)
Low Saturated-Fat Component	No/Low	1.3 (0.7, 2.5)	3.3 (2.2, 4.9)
	High	1.3 (0.7, 2.6)	3.6 (1.8, 6.9)
p for multiplicative interaction		p=0.43	p=0.04
p for additive interaction		p=0.45	p=0.29
Omega-3 Fatty Acids Component	Cotinine Exposure		
High Omega-3 Fatty Acids Component	No/Low	1	1
	High	1.6 (1.1, 2.4)	1.1 (0.7, 1.6)

Low Omega-3 Fatty Acids Component	No/Low	1.5 (0.8, 2.7)	1.9 (1.3, 2.7)
	High	1.4 (0.8, 2.2)	2.8 (1.4, 5.5)
p for multiplicative interaction		p=0.14	p=0.44
p for additive interaction		p=0.22	p=0.23

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.10. Adjusted ORs and 95% CIs for overweight and obesity in relation to self-report of household smokers and dietary nutrients and measures of additive and multiplicative interaction among 6-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Self-report of household smokers		
High Fiber Intake (≥12.75 g/day)	None/One	1[d]	1
	Two or More	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)
Low Fiber Intake (<12.75 g/day)	None/One	0.9 (0.6, 1.4)	1.2 (0.7, 1.9)
	Two or More	1.2 (0.8, 1.8)	2.3 (1.5, 3.5)
p for multiplicative interaction[b]		p=0.56	p=0.02
p for additive interaction[c]		p=0.72	p<0.01
EPA Intake	Self-report of household smokers		
High EPA Intake (≥0.007 g/day)	None/One	1	1
	Two or More	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)
Low EPA Intake (<0.007 g/day)	None/One	1.1 (0.7, 1.7)	1.3 (0.8, 2.2)
	Two or More	1.0 (0.6, 2.0)	2.3 (1.6, 3.3)
p for multiplicative interaction		p=0.69	p=0.14
p for additive interaction		p=0.99	p<0.01
DHA Intake	Self-report of household smokers		
High DHA Intake (≥0.018 g/day)	None/One	1	1
	Two or More	1.2 (0.9, 1.6)	1.0 (0.8, 1.3)
Low DHA Intake (<0.018 g/day)	None/One	1.1 (0.6, 1.7)	1.2 (0.6, 2.2)
	Two or More	1.3 (0.8, 2.1)	2.1 (1.4, 3.1)
p for multiplicative interaction		p=0.96	p=0.08
p for additive interaction		p=0.54	p=0.30
Vitamin C Intake	Self-report of household smokers		
High Vitamin C Intake (≥68.9 g/day)	None/One	1	1
	Two or More	1.3 (0.9, 1.8)	1.1 (0.7, 1.5)

Low Vitamin C Intake (<68.9 g/day)	None/One	1.1 (0.7, 1.8)	1.6 (1.1, 2.5)
	Two or More	1.2 (0.7, 2.1)	2.1 (1.4, 3.1)
p for multiplicative interaction		p=0.80	p=0.57
p for additive interaction		p=0.47	p=0.57
Vitamin E Intake	Self-report of household smokers		
High Vitamin E Intake (≥5.415 mg/day)	None/One	1	1
	Two or More	1.6 (1.2, 2.1)	1.3 (1.2, 1.6)
Low Vitamin E Intake (<5.415 mg/day)	None/One	1.1 (0.7, 1.6)	1.9 (1.2, 2.9)
	Two or More	1.6 (1.0, 2.5)	2.0 (1.2, 3.3)
p for multiplicative interaction		p=0.82	p=0.50
p for additive interaction		p=0.77	p=0.58
Fiber-Fat-Soluble Vitamin Intake Component	Self-report of household smokers		
High Fiber-Fat-Soluble-Vitamin Component	None/One	1	1
	Two or More	1.4 (1.0, 1.8)	1.1 (0.8, 1.5)
Low Fiber-Fat-Soluble-Vitamin Component	None/One	0.9 (0.4, 2.0)	2.6 (1.7, 4.2)
	Two or More	1.4 (0.8, 2.4)	1.8 (1.1, 2.7)
p for multiplicative interaction		p=0.67	p=0.06
p for additive interaction		p=0.75	p<0.01
Saturated-Fat-Component Intake	Self-report of household smokers		
Low Saturated-Fat Component	None/One	1	1
	Two or More	0.7 (0.5, 0.9)	0.7 (0.5, 1.0)
High Saturated-Fat Component	None/One	1.1 (0.6, 1.9)	2.1 (1.2, 3.7)
	Two or More	0.7 (0.3, 1.4)	1.4 (0.8, 2.5)
p for multiplicative interaction		p=0.94	p=0.85
p for additive interaction		p=0.68	p=0.26
Vitamin-B-Complex Component	Self-report of household smokers		
High Saturated-Fat Component	None/One	1	1
	Two or More	1.2 (0.9, 1.6)	1.6 (1.2, 2.0)

Low Saturated-Fat Component	None/One	0.9 (0.4, 2.0)	2.1 (1.3, 3.5)
	Two or More	1.2 (0.7, 2.1)	2.9 (1.8, 4.5)
p for multiplicative interaction		p=0.78	p=0.69
p for additive interaction		p=0.73	p=0.69
Omega-3 Fatty Acids Component	Self-report of household smokers		
High Omega-3 Fatty Acids Component	None/One	1	1
	Two or More	1.3 (1.0, 1.7)	1.0 (0.8, 1.3)
Low Omega-3 Fatty Acids Component	None/One	1.3 (0.6, 2.7)	1.9 (1.1, 3.2)
	Two or More	1.1 (0.7, 1.9)	2.2 (1.5, 3.4)
p for multiplicative interaction		p=0.33	p=0.64
p for additive interaction		p=0.12	p=0.45

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.11. Adjusted ORs and 95% CIs for overweight and obesity in relation to self-report of household smokers and dietary nutrients and measures of additive and multiplicative interaction among 6-11 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Self-report of household smokers		
High Fiber Intake (≥12.75 g/day)	None/One	1	1
	Two or More	1.1 (0.8, 1.7)	0.9 (0.6, 1.2)
Low Fiber Intake (<12.75 g/day)	None/One	0.9 (0.3, 2.9)	2.1 (1.1, 4.0)
	Two or More	0.7 (0.4, 1.4)	1.1 (0.6, 1.9)
p for multiplicative interaction[b]		p=0.91	p=0.48
p for additive interaction[c]		p=0.99	p=0.09
EPA Intake	Self-report of household smokers		
High EPA Intake (≥0.007 g/day)	None/One	1	1
	Two or More	1.0 (0.7, 1.4)	0.9 (0.6, 1.2)
Low EPA Intake (<0.007 g/day)	None/One	0.8 (0.4, 1.6)	1.2 (0.7, 2.1)
	Two or More	0.6 (0.3, 1.5)	1.4 (0.6, 3.0)
p for multiplicative interaction		p=0.58	p=0.54
p for additive interaction		p=0.66	p=0.45
DHA Intake	Self-report of household smokers		
High DHA Intake (≥0.018 g/day)	None/One	1	1
	Two or More	0.7 (0.4, 1.0)	0.8 (0.5, 1.1)
Low DHA Intake (<0.018 g/day)	None/One	0.5 (0.2, 1.3)	1.0 (0.5, 2.3)
	Two or More	0.4 (0.2, 1.0)	1.1 (0.5, 2.4)
p for multiplicative interaction		p=0.54	p=0.41
p for additive interaction		p=0.63	p=0.14
Vitamin C Intake	Self-report of household smokers		
High Vitamin C Intake (≥68.9 g/day)	None/One	1	1
	Two or More	1.3 (0.8, 2.0)	1.1 (0.7, 1.5)

Low Vitamin C Intake (<68.9 g/day)	None/One	0.9 (0.4, 2.0)	1.3 (0.7, 2.4)
	Two or More	0.6 (0.3, 1.2)	1.55 (0.9, 2.6)
p for multiplicative interaction		p=0.27	p=0.86
p for additive interaction		p=0.42	p=0.73
Vitamin E Intake	Self-report of household smokers		
High Vitamin E Intake (≥5.415 mg/day)	None/One	1	1
	Two or More	1.0 (0.7, 1.7)	1.1 (0.7, 1.6)
Low Vitamin E Intake (<5.415 mg/day)	None/One	0.8 (0.4, 1.5)	1.7 (0.9, 3.3)
	Two or More	0.7 (0.4, 1.2)	1.0 (0.4, 2.2)
p for multiplicative interaction		p=0.71	p=0.20
p for additive interaction		p=0.63	p=0.90
Fiber-Fat-Soluble Vitamin Intake Component	Self-report of household smokers		
High Fiber-Fat-Soluble-Vitamin Component	None/One	1	1
	Two or More	1.1 (0.8, 1.7)	0.9 (0.6, 1.3)
Low Fiber-Fat-Soluble-Vitamin Component	None/One	0.9 (0.3, 2.9)	2.1 (1.1, 4.0)
	Two or More	0.7 (0.4, 1.4)	1.1 (0.6, 1.9)
p for multiplicative interaction		p=0.55	p=0.10
p for additive interaction		p=0.21	p=0.02
Saturated-Fat-Component Intake	Self-report of household smokers		
Low Saturated-Fat Component	None/One	1	1
	Two or More	0.9 (0.6, 1.4)	1.0 (0.7, 1.5)
High Saturated-Fat Component	None/One	0.9 (0.4, 1.8)	2.0 (0.9, 4.4)
	Two or More	0.6 (0.2, 2.0)	1.3 (0.6, 2.6)
p for multiplicative interaction		p=0.64	p=0.48
p for additive interaction		p=0.99	p=0.20
Vitamin-B-Complex Component	Self-report of household smokers		
High Saturated-Fat Component	None/One	1	1
	Two or More	1.1 (0.7, 1.6)	1.0 (0.7, 1.4)
Low Saturated-Fat Component	None/One	0.8 (0.2, 2.6)	1.1 (0.5, 2.2)

	Two or More	0.8 (0.4, 1.6)	2.1 (1.2, 3.7)
p for multiplicative interaction		p=0.96	p=0.10
p for additive interaction		p=0.47	p=0.10
Omega-3 Fatty Acids Component	Self-report of household smokers		
High Omega-3 Fatty Acids	None/One	1	1
Component	Two or More	1.0 (0.6, 1.6)	0.8 (0.6, 1.1)
Low Omega-3 Fatty Acids Component	None/One	0.9 (0.3, 2.8)	1.2 (0.6, 2.5)
	Two or More	0.7 (0.3, 1.5)	1.5 (0.9, 2.8)
p for multiplicative interaction		p=0.71	p=0.32
p for additive interaction		p=0.46	p<0.01

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

Appendix 3.12. Adjusted ORs and 95% CIs for overweight and obesity in relation to self-report of household smokers and dietary nutrients and measures of additive and multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Overweight vs. Normal Adjusted[a] ORs (95% CIs)	Obese vs. Normal Adjusted ORs (95% CIs)
Fiber Intake	Self-report of household smokers		
High Fiber Intake (≥12.75 g/day)	None/One	1	1
	Two or More	1.7 (1.1, 2.6)	1.3 (0.8, 2.1)
Low Fiber Intake (<12.75 g/day)	None/One	1.3 (0.5, 3.5)	1.2 (0.5, 2.7)
	Two or More	2.4 (1.4, 4.3)	3.5 (1.7, 7.1)
p for multiplicative interaction[b]		p=0.85	p=0.11
p for additive interaction[c]		p=0.52	p<0.01
EPA Intake	Self-report of household smokers		
High EPA Intake (≥0.007 g/day)	None/One	1	1
	Two or More	1.1 (0.8, 1.6)	1.2 (0.8, 1.6)
Low EPA Intake (<0.007 g/day)	None/One	1.4 (0.7, 2.8)	1.4 (0.7, 2.8)
	Two or More	3.7 (2.2, 6.3)	3.7 (2.2, 6.3)
p for multiplicative interaction		p=0.99	p=0.11
p for additive interaction		p=0.02	p<0.01
DHA Intake	Self-report of household smokers		
High DHA Intake (≥0.018 g/day)	None/One	1	1
	Two or More	1.8 (1.2, 2.7)	1.2 (0.8, 1.8)
Low DHA Intake (<0.018 g/day)	None/One	1.7 (0.8, 3.6)	1.3 (0.5, 3.0)
	Two or More	2.5 (1.4, 4.7)	3.3 (1.8, 6.1)
p for multiplicative interaction		p=0.67	p=0.09
p for additive interaction		p=0.99	p<0.01
Vitamin C Intake	Self-report of household smokers		
High Vitamin C Intake (≥68.9 g/day)	None/One	1	1
	Two or More	1.2 (0.8, 1.9)	1.2 (0.2, 1.7)
Low Vitamin C Intake (<68.9 g/day)	None/One	1.2 (0.5, 3.0)	2.0 (1.0, 3.6)

	Two or More	1.9 (1.0, 3.7)	2.8 (1.5, 5.3)
p for multiplicative interaction		p=0.72	p=0.61
p for additive interaction		p=0.34	p=0.33
Vitamin E Intake	Self-report of household smokers		
High Vitamin E Intake (≥5.415 mg/day)	None/One	1	1
	Two or More	2.2 (1.5, 3.3)	1.3 (1.2, 2.2)
Low Vitamin E Intake (<5.415 mg/day)	None/One	1.4 (0.7, 2.7)	2.0 (1.3, 3.1)
	Two or More	3.2 (1.6, 6.1)	3.8 (1.8, 8.1)
p for multiplicative interaction		p=0.91	p=0.71
p for additive interaction		p=0.46	p=0.06
Fiber-Fat-Soluble Vitamin Intake Component	Self-report of household smokers		
High Fiber-Fat-Soluble-Vitamin Component	None/One	1	1
	Two or More	1.5 (1.0, 2.8)	1.3 (1.0, 1.8)
Low Fiber-Fat-Soluble-Vitamin Component	None/One	0.8 (0.3, 2.3)	3.4 (1.6, 7.3)
	Two or More	2.2 (1.1, 4.3)	2.6 (1.5, 4.5)
p for multiplicative interaction		p=0.31	p=0.17
p for additive interaction		p=0.23	p=0.10
Saturated-Fat-Component Intake	Self-report of household smokers		
Low Saturated-Fat Component	None/One	1	1
	Two or More	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)
High Saturated-Fat Component	None/One	1.3 (0.7, 2.4)	2.4 (1.0, 5.7)
	Two or More	0.7 (0.3, 1.8)	1.6 (0.8, 2.9)
p for multiplicative interaction		p=0.89	p=0.85
p for additive interaction		p=0.80	p=0.50
Vitamin-B-Complex Component	Self-report of household smokers		
High Saturated-Fat Component	None/One	1	1
	Two or More	1.3 (0.8, 2.2)	2.3 (1.6, 3.4)
Low Saturated-Fat Component	None/One	1.1 (0.4, 3.1)	4.0 (1.8, 9.1)

	Two or More	1.7 (0.9, 3.3)	4.0 (1.9, 8.6)
p for multiplicative interaction		p=0.81	p=0.16
p for additive interaction		p=0.57	p=0.28
Omega-3 Fatty Acids Component	Self-report of household smokers		
High Omega-3 Fatty Acids	None/One	1	1
Component	Two or More	1.5 (1.2, 2.0)	1.2 (0.8, 1.8)
Low Omega-3 Fatty Acids	None/One	1.6 (0.7, 3.8)	2.6 (1.3, 5.3)
Component	Two or More	1.6 (0.8, 3.1)	3.0 (1.5, 6.0)
p for multiplicative interaction		p=0.38	p=0.90
p for additive interaction		p=0.42	p=0.81

Abbreviations: CI, confidence interval; OR, odds ratio; SHS secondhand smoke

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction generated for the relative excess risk due to interaction (RERI) value

[c]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

PROJECT 2 APPENDICES

Appendix 4.1. Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Creatinine-Adjusted NNAL levels and Metabolic Syndrome among 12-19 year olds, 2007-2010 NHANES

	Crude Model			Adjusted Model[a]		
	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend
Metabolic Syndrome	1.0 (0.4, 2.6)	3.8 (1.5, 9.6)	0.02	1.0 (0.4, 2.8)	5.4 (1.7, 16.9)	0.01
Symptoms						
Abdominal Obesity	1.7 (1.1, 2.7)	2.4 (1.6, 3.5)	<0.01	1.9 (1.1, 3.1)	2.1 (1.4, 3.3)	<0.01
Hyperglycemia	1.3 (0.7, 2.4)	1.8 (1.0, 3.1)	0.07	1.0 (0.6, 1.8)	1.6 (0.9, 3.2)	0.21
Hypertension	1.1 (0.7, 2.0)	2.1 (1.2, 4.1)	0.04	1.1 (0.6, 2.1)	2.3 (1.0, 5.4)	0.10
Low HDL levels	1.4 (0.9, 2.0)	1.9 (1.3, 2.8)	<0.01	1.3 (0.8, 2.3)	2.0 (1.2, 3.3)	0.01
High Triglycerides	0.9 (0.5, 1.9)	2.0 (1.4, 3.0)	0.01	1.0 (0.4, 2.6)	2.5 (1.4, 4.5)	0.03

Abbreviations: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection; OR, odds ratio; CI, confidence interval

[a]Adjusted for sex, age, race/ethnicity, poverty index ratio, fiber-fat-soluble-vitamins component, the saturated-fat component, the vitamin-B-complex component, and the omega-3-fatty-acids component.

Appendix 4.2. Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Serum Cotinine levels and Metabolic Syndrome among 12-19 year olds, 2007-2010 NHANES

	Crude Model			Adjusted Model[a]		
	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend
Metabolic Syndrome	1.7 (0.6, 4.6)	3.8 (1.5, 9.5)	<0.01	2.4 (0.9, 6.3)	4.7 (1.7, 13.2)	<0.01
Symptoms						
Abdominal Obesity	1.3 (0.7, 2.6)	1.5 (0.8, 3.0)	0.20	1.9 (1.0, 3.5)	1.5 (0.7, 3.4)	0.19
Hyperglycemia	1.0 (0.5, 2.2)	1.5 (0.8, 2.5)	0.26	1.0 (0.5, 2.2)	1.6 (0.9, 2.8)	0.19
Hypertension	2.1 (1.1, 3.9)	2.2 (0.9, 5.3)	0.03	1.7 (0.8, 3.8)	1.3 (0.4, 4.7)	0.49
Low HDL levels	1.0 (0.4, 2.4)	1.7 (1.0, 2.7)	0.09	1.0 (0.3, 3.2)	1.0 (0.5, 2.1)	0.97
High Triglycerides	1.0 (0.5, 1.9)	2.1 (1.4, 3.1)	<0.01	1.0 (0.5, 2.0)	2.5 (1.5, 4.3)	<0.01

Abbreviations: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection; OR, odds ratio; CI, confidence interval

[a]Adjusted for sex, age, race/ethnicity, poverty index ratio, fiber-fat-soluble-vitamins component, the saturated-fat component, the vitamin-B-complex component, and the omega-3-fatty-acids component.

Appendix 4.3. Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Self-Report of Household Smokers and Metabolic Syndrome among 12-19 year olds, 2007-2010 NHANES

	Crude Model			Adjusted Model[a]		
	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend	Low vs. Below LOD ORs (95% CIs)	High vs. Below LOD ORs (95% CIs)	*P* for trend
Metabolic Syndrome	3.9 (1.7, 8.9)	2.7 (1.3, 5.6)	<0.01	4.4 (1.6, 11.9)	5.6 (2.1, 14.5)	<0.01
Symptoms						
Abdominal Obesity	1.7 (0.8, 3.7)	2.3 (0.9, 6.0)	0.07	1.7 (0.7, 4.3)	2.5 (0.8, 8.0)	0.09
Hyperglycemia	1.7 (1.0, 3.1)	2.1 (01.2, 3.8)	0.01	1.7 (0.8, 3.5)	3.1 (1.6, 6.1)	<0.01
Hypertension	1.2 (0.4, 3.3)	1.4 (0.3, 7.3)	0.62	1.1 (0.4, 3.2)	0.4 (0.1, 3.7)	0.61
Low HDL levels	1.5 (0.7, 3.1)	2.7 (1.3, 5.6)	<0.01	1.2 (0.5, 3.1)	1.9 (0.5, 7.5)	0.35
High Triglycerides	1.7 (0.8, 3.7)	3.2 (1.9, 5.4)	<0.01	1.9 (0.7, 5.5)	4.0 (1.6, 10.0)	<0.01

Abbreviations: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection; OR, odds ratio; CI, confidence interval

[a]Adjusted for sex, age, race/ethnicity, poverty index ratio, fiber-fat-soluble-vitamins component, the saturated-fat component, the vitamin-B-complex
component, and the omega-3-fatty-acids component.

Appendix 4.4. Additive and multiplicative interaction by diet on the associations of creatinine-adjusted NNAL and metabolic syndrome among 12-19 year olds, 2007-2010 NHANES

	Below LOD/Low Exposure		High Exposure		
	N with/without metabolic syndrome	AORs[c] (95% CIs)	N with/without metabolic syndrome	AORs (95% CIs)	AORs (95% CIs) within strata of dietary factor
High Vitamin E Intake (≥5.42 mg/day)	14/220	1	3/43	2.9 (0.9, 9.5)	2.9 (0.9, 9.5)
Low Vitamin E Intake (<5.42 mg/day)	15/186	1.0 (0.4, 2.4)	12/52	8.8 (2.7, 28.3)	8.8 (3.4, 26.1)
P-value for multiplicative interaction term=0.04.[a]					
Measure of interaction on additive scale: RERI (95% CI)= 6.4 (2.0 to 15.7); P=0.07.[b]					
High EPA Intake (≥0.007 g/day)	18/222	1	6/52	2.9 (0.9, 8.9)	2.9 (0.9, 8.9)
Low EPA Intake (≥0.007 g/day)	11/184	0.6 (0.2, 1.5)	9/43	7.2 (1.8, 28.9)	12.0 (4.1, 65.0)
Measure of interaction on additive scale: RERI (95% CI)= 4.6 (0.3 to 12.9); P=0.15.					
P-value for interaction term=0.04.					
High Omega-3 Fatty Acids Component (≥median)	17/212	1	5/37	2.6 (0.8, 8.4)	2.6 (0.8, 8.4)
Low Omega-3 Fatty Acids Component (<median)	12/194	0.7 (0.3, 1.6)	10/58	7.0 (1.7, 29.5)	10.1 (2.7, 31.6)
Measure of interaction on additive scale: RERI (95% CI)= 4.7 (-0.9 to 15.1); P=0.25.					
P-value for interaction term=0.09.					
High Fiber Intake (≥12.75 g/day)	7/79	1	1/11	1.4 (0.1, 19.7)	1.4 (0.1, 19.7)
Low Fiber Intake (<12.75 g/day)	22/327	0.7 (0.2, 2.0)	14/84	4.7 (1.0, 22.6)	6.7 (2.5, 26.0)
P-value for interaction term=0.50					
Measure of interaction on additive scale: RERI (95% CI)= 3.7 (-7.2, 10.8); P=0.43					
High DHA Intake (≥0.018 g/day)	9/146	1	6/41	5.2 (1.2, 23.0)	5.2 (1.2, 23.0)

Low DHA Intake (<0.018 g/day)	20/228	0.6 (0.2, 2.0)	13/76	6.0 (1.3, 28.0)	10.0 (3.9, 60.4)
P-value for interaction term=0.48					
Measure of interaction on additive scale: RERI (95% CI)= 1.2 (-8.3, 8.7); P=0.80					
High Vitamin C Intake (≥68.9 g/day)	18/196	1	6/40	5.3 (1.4, 19.2)	5.3 (1.4, 19.2)
Low Vitamin C Intake (<68.9 g/day)	11/210	0.5 (0.2, 1.4)	9/55	3.7 (1.0, 14.3)	7.4 (3.2, 27.3)
P-value for interaction term=0.74					
Measure of interaction on additive scale: RERI (95% CI)= -1.1 (-9.7, 4.1); P=0.77					
High Fiber-Fat-Soluble-Vitamin Component	11/218	1	5/37	3.3 (0.7, 15.8)	3.3 (0.7, 15.8)
Low Fiber-Fat-Soluble-Vitamin Component	6/200	0.6 (0.2, 1.4)	10/59	5.2 (1.5, 17.6)	8.7 (4.4, 27.9)
P-value for interaction term=0.24					
Measure of interaction on additive scale: RERI (95% CI)= 2.3 (-4.2, 9.4); P=0.51					
Low Saturated-Fat Component	10/223	1	4/39	8.4 (2.6, 27.2)	8.4 (2.6, 27.2)
High Saturated-Fat Component	7/195	1.0 (0.4, 2.4)	12/56	2.7 (0.6, 11.7)	2.7 (0.4, 13.4)
P-value for interaction term=0.14					
Measure of interaction on additive scale: RERI (95% CI)= (-5.7, 25.4, 0.3); P=0.39					
High vitamin-B-complex component	8/205	1	4/37	3.5 (0.6, 20.2)	3.5 (0.6, 20.2)
Low vitamin-B-complex component	9/213	1.3 (0.5, 3.7)	10/60	8.8 (2.1, 36.4)	6.7 (2.8, 25.3)
P-value for interaction term=0.51					
RERI (95% CI)= 5.0 (-3.6, 18.3); P=0.38					

Abbreviations: AOR; adjusted odds ratio; CI, confidence interval; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; LOD, limit of detection

[a]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS

[b]p for additive interaction generated for the relative excess risk due to interaction value

[c]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

Appendix 4.5. Additive and multiplicative interaction by diet on the associations of cotinine and metabolic syndrome among 12-19 year olds, 2007-2010 NHANES

	No/Low Exposure		High Exposure		
	N with/without metabolic syndrome	AORs[c] (95% CIs)	N with/without metabolic syndrome	AORs (95% CIs)	AORs (95% CIs) within strata of dietary factor
High Vitamin E Intake (≥5.415 mg/day)	14/220	1	3/48	1.5 (0.4, 6.4)	1.5 (0.4, 6.4)
Low Vitamin E Intake (<5.415 mg/day)	16/197	1.0 (0.4, 2.4)	11/50	5.4 (1.7, 17.6)	5.4 (1.3, 16.8)
	P-value for interaction term=0.11[a] RERI (95% CI) =3.9 (-0.5, 10.7); P=0.17[b]				
High EPA Intake (≥0.007 g/day)	19/229	1	5/52	1.8 (0.5, 7.0)	1.8 (0.5, 7.0)
Low EPA Intake (≥0.007 g/day)	11/188	0.6 (0.2, 1.5)	9/46	3.7 (1.0, 14.2)	6.2 (1.4, 25.6)
	P-value for interaction term=0.13 RERI (95% CI) = 2.3 (-1.2, 7.1); *P*=0.28				
High Omega-3 Fatty Acids Component (≥median)	17/212	1	5/37	1.6 (0.5, 5.4)	1.6 (0.5, 5.4)
Low Omega-3 Fatty Acids Component (<median)	12/194	0.7 (0.3, 1.8)	10/58	4.4 (1.2, 15.9)	6.3 (1.6, 27.1)
	P-value for interaction term=0.09 RERI (95% CI) = 3.1 (-0.3, 8.5); P=0.17				
High Fiber Intake (≥12.75 g/day)	7/79	1	1/11	3.8 (0.7, 21.6)	3.8 (0.7, 21.6)
Low Fiber Intake (<12.75 g/day)	22/327	1.2 (0.4, 3.0)	14/84	4.7 (1.3, 17.1)	6.7 (3.3, 5.7)
	P-value for interaction term=0.94 RERI (95% CI)= .7 (-29.2, 7.7); P=0.95				
High DHA Intake (≥0.018 g/day)	9/146	1	6/41	3.5 (0.8, 16.6)	3.5 (0.8, 16.6)
Low DHA Intake (<0.018	20/228	0.6 (0.2, 1.8)	13/76	4.0 (0.9, 17.1)	6.7 (0.8, 16.8)

g/day)					
		P-value for interaction term=0.51 RERI (95% CI)= 0.8 (-5.7, 5.8); p=0.79			
High Vitamin C Intake (≥68.9 g/day)	18/196	1	6/40	3.4 (1.5, 8.0)	3.4 (1.5, 8.0)
Low Vitamin C Intake (<68.9 g/day)	11/210	0.6 (0.2, 1.5)	9/55	2.9 (0.7, 11.8)	4.8 (0.5, 17.8)
		P-value for interaction term=0.89 RERI (95% CI)= -0.1 (-5.8, 3.8); p=0.97			
High Fiber-Fat-Soluble-Vitamin Component	11/218	1	6/40	2.2 (0.3, 5.2)	2.2 (0.3, 5.2)
Low Fiber-Fat-Soluble-Vitamin Component	6/218	0.6 (0.2, 1.0)	9/55	3.6 (1.2, 10.8)	6.0 (0.6, 10.6)
		P-value for interaction term=0.03 RERI (95% CI)= 1.8 (-2.7, 6.6); p=0.46			
Low Saturated-Fat Component	10/223	1	4/39	4.6 (1.4, 15.3)	4.6 (1.4, 15.3)
High Saturated-Fat Component	7/195	0.9 (0.3, 2.2)	12/56	1.6 (0.4, 7.1)	1.8 (1.1, 3.3)
		P-value for interaction term=0.31 RERI (95% CI)= -2.9 (-13.9, 0.5); p=0.44			
High Vitamin-B-Complex Component	21/263	1	6/53	2.8 (0.6, 13.9)	2.8 (0.6, 13.9)
Low Vitamin-B-Complex Component	18/230	1.5 (0.5, 4.5)	9/60	5.7 (1.3, 24.6)	3.8 (2.6, 5.5)
		P-value for interaction term=0.80 RERI (95% CI)= 2.4 (-2.7, 9.4); p=0.44			

Abbreviations: AOR; adjusted odds ratio; CI, confidence interval; LOD, limit of detection
[a]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS
[b]p for additive interaction generated for the relative excess risk due to interaction value
[c]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

Appendix 4.6. Additive and multiplicative interaction by diet on the associations of self-report of household smokers and metabolic syndrome among 12-19 year olds, 2007-2010 NHANES

	No/Low Exposure		High Exposure		
	N with/without metabolic syndrome	AORs[c] (95% CIs)	N with/without metabolic syndrome	AORs (95% CIs)	AORs (95% CIs) within strata of dietary factor
High Vitamin E Intake (≥5.415 mg/day)	14/243	1	3/25	2.4 (0.5, 10.5)	2.4 (0.5, 10.5)
Low Vitamin E Intake (<5.415 mg/day)	18/222	1.3 (0.5, 3.4)	9/25	8.5 (3.1, 23.1)	6.5 (1.4, 24.3)
	P-value for interaction term=0.25[a] RERI (95% CI) = 5.8 (-1.6, 18.4); P=0.26[b]				
High EPA Intake (≥0.007 g/day)	19/257	1	5/24	3.6 (0.9, 14.6)	3.6 (0.9, 14.6)
Low EPA Intake (≥0.007 g/day)	13/208	0.8 (0.3, 2.5)	7/26	4.6 (1.5, 13.6)	5.8 (1.2, 21.0)
	P-value for interaction term=0.62 RERI (95% CI) = 1.2 (-5.9, 8.4); P=0.75				
High Omega-3 Fatty Acids Component (≥median)	21/287	1	6/29	3.1 (1.1, 8.5)	3.1 (1.1, 8.5)
Low Omega-3 Fatty Acids Component (<median)	17/257	1.0 (0.4, 2.6)	9/32	5.9 (1.8, 19.0)	5.9 (1.3, 20.1)
	P-value for interaction term=0.34 RERI (95% CI) = 2.8 (-2.9, 10.5); P=0.42				
High Fiber Intake (≥12.75 g/day)	7/79	1	1/11	2.6 (0.4, 17.2)	2.6 (0.4, 17.2)
Low Fiber Intake (<12.75 g/day)	22/327	1.1 (0.4, 3.0)	14/84	5.6 (2.1, 14.7)	5.1 (1.6, 14.9)
	P-value for interaction term=0.52 RERI (95% CI)= 2.9 (-17.4, 11.1); P=0.70				
High DHA Intake (≥0.018 g/day)	9/146	1	6/41	2.1 (0.6, 13.2)	2.1 (0.6, 13.2)
Low DHA Intake (<0.018	20/228	0.7 (0.2, 1.9)	13/76	3.7 (1.6, 12.8)	5.2 (2.1, 14.9)

g/day)					
		P-value for interaction term=0.35 RERI (95% CI)= 1.9 (-2.1, 6.6); P=0.39			
High Vitamin C Intake (≥68.9 g/day)	18/196	1	6/40	6.5 (2.8, 15.0)	6.5 (2.8, 15.0
Low Vitamin C Intake (<68.9 g/day)	11/210	0.9 (0.3, 2.4)	9/55	2.5 (0.7, 9.3)	2.7 (0.6, 13.2)
		P-value for interaction term=0.29 RERI (95% CI)=-3.9 (-14.9, 0.6); P=0.33			
High Fiber-Fat-Soluble-Vitamin Component	11/218	1	6/40	1.7 (0.3, 9.0)	1.7 (0.3, 9.0)
Low Fiber-Fat-Soluble-Vitamin Component	6/218	0.6 (0.2, 1.6)	9/55	5.2 (2.1, 12.7)	8.9 (0.9, 15.6)
		P-value for interaction term=0.10 RERI (95% CI)=3.9 (0.1, 11.1); P=0.17			
Low Saturated-Fat Component	10/223	1	4/39	6.4 (2.4, 16.6)	6.4 (2.4, 16.6)
High Saturated-Fat Component	7/195	0.7 (0.3, 1.8)	12/56	1.8 (0.4, 8.4)	2.6 (0.2, 4.7)
		P-value for interaction term=0.30 RERI (95% CI)=-4.3 (-19.4, 0.2); P=0.40			
High Vitamin-B-Complex Component	8/205	1	4.37	4.2 (0.7, 25.9)	4.2 (0.7, 25.9)
Low Vitamin-B-Complex Component	9.213	1.8 (0.6, 5.2)	10/60	8.8 (2.4, 32.6)	4.9 (3.6, 8.9)
		P-value for interaction term=0.89 RERI (95% CI)=3.8 (-6.7, 16.9); P=0.54			

Abbreviations: AOR; adjusted odds ratio; CI, confidence interval; LOD, limit of detection
[a]p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS
[b]p for additive interaction generated for the relative excess risk due to interaction value
[c]ORs adjusted for sex, age, race/ethnicity and poverty index ratio.

Appendix 5.1. Crude and adjusted models for the relationship between serum cotinine and HbA1c and glucose levels among 12-19 year olds, 2007-2010 NHANES

	HbA1c (%) Means (95% CIs)	Fasting plasma glucose (mg/dL) Means (95% CIs)	2-hour post-challenge glucose (mg/dL) Means (95% CIs)
Crude			
Below LOD/None	5.19 (5.17, 5.22)	94 (93, 95)	98 (94, 101)
Low	5.24 (5.20, 5.29)	94 (92, 95)	95 (91, 98)
High	5.23 (5.16, 5.29)	95 (94, 97)	99 (93, 105)
p for trend	p=0.14	p=0.27	p=0.94
Model 1[a]			
Below LOD/None	4.87 (4.61, 5.13)	88 (83, 93)	98 (94, 101)
Low	5.32 (5.27, 5.38)	94 (93, 96)	95 (91, 99)
High	5.30 (5.23, 5.37)	96 (94, 98)	99 (93, 105)
p for trend	p=0.26	p=0.13	p=0.78
Model 2[b]			
Below LOD/None	5.27 (5.22, 5.31)	95 (94, 97)	105 (100, 111)
Low	5.34 (5.28, 5.41)	95 (93, 97)	105 (99, 111)
High	5.33 (5.25, 5.42)	96 (94, 98)	106 (99, 114)
p for trend	p=0.22	p=0.27	p=0.92

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] Model 1 plus additional adjustment for total caloric intake, physical activity and body mass index.

Appendix 5.2. Crude and adjusted models for the relationship between self-report of household smokers and HbA1c and glucose levels among 12-19 year olds, 2007-2010 NHANES

	HbA1c (%) Means (95% CIs)	Fasting plasma glucose (mg/dL) Means (95% CIs)	2-hour post-challenge glucose (mg/dL) Means (95% CIs)
Crude			
Below LOD/None	5.20 (5.19, 5.23)	94 (93, 95)	96 (94, 99)
Low	5.24 (5.13, 5.35)	96 (94, 97)	104 (96, 111)
High	5.26 (5.18, 5.34)	96 (94, 98)	107 (92, 123)
p for trend	p=0.24	p=0.02	p=0.02
Model 1[a]			
Below LOD/None	5.01 (4.83, 5.19)	90 (86, 94)	96 (94, 98)
Low	5.01 (4.78, 5.25)	91 (86, 96)	104 (96, 112)
High	5.07 (4.90, 5.23)	93 (89, 97)	107 (91, 123)
p for trend	p=0.52	p<0.01	p=0.02
Model 2[b]			
Below LOD/None	5.28 (5.24, 5.32)	95 (94, 97)	105 (100, 109)
Low	5.38 (5.22, 5.54)	97 (95, 99)	108 (98, 119)
High	5.35 (5.26, 5.44)	98 (96, 100)	115 (101, 129)
p for trend	p=0.20	p<0.01	p=0.10

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] Model 1 plus additional adjustment for total caloric intake, physical activity and body mass index.

Appendix 5.3. Adjusted means and 95% CIs for HbA1c levels in relation to urinary NNAL levels and dietary nutrients and measures of additive interaction among 12-19 year olds, 2007-2010 NHANES

		Adjusted[a] Mean HbA1c (%) (95% CI)	Mean fasting plasma glucose levels (mg/dL) (95% CI)	Mean 2-hour post-challenge glucose (mg/dL) (95% CI)
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	5.23 (5.19, 5.27)	94 (93, 95)	94 (90, 98)
	High	5.17 (5.13, 5.21)	94 (93, 95)	96 (92, 99)
Low	Below LOD/Low	5.24 (5.15, 5.33)	95 (92, 97)	92 (87, 98)
	High	5.25 (5.19, 5.31)	96 (94, 98)	107 (99, 115)
p for additive interaction[b]		p=0.14	p=0.73	p=0.10
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	5.19 (5.14, 5.23)	94 (93, 95)	98 (94, 102)
	High	5.21 (5.18, 5.25)	94 (93, 95)	92 (89, 95)
High	Below LOD/Low	5.23 (5.16, 5.31)	96 (95, 98)	107 (100, 114)
	High	5.26 (5.17, 5.35)	95 (92, 97)	94 (86, 103)
p for additive interaction		p=0.99	p=0.35	p=0.91
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	5.22 (5.18, 5.26)	93 (92, 94)	94 (91, 98)
	High	5.18 (5.14, 5.22)	94 (93, 96)	96 (92, 99)
Low	Below LOD/Low	5.25 (5.17, 5.34)	96 (04, 98)	100 (85, 115)
	High	5.24 (5.18, 5.31)	95 (93, 97)	103 (96, 110)
p for additive interaction		p=0.53	p=0.40	p=0.29
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	5.21 (5.18, 5.24)	94 (93, 95)	95 (91, 98)
	High	5.19 (5.14, 5.23)	94 (93, 95)	95 (92, 99)
Low	Below LOD/Low	5.26 (5.18, 5.33)	94 (93, 96)	96 (91, 101)

High	5.24 (5.16, 5.31)	97 (94, 99)	107 (97, 116)
p for additive interaction	p=0.95	p=0.05	p=0.11

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 5.4. Adjusted means and 95% CIs for HbA1c levels in relation to serum cotinine levels and dietary nutrients and measures of additive interaction among 12-19 year olds, 2007-2010 NHANES

		Adjusted[a] Mean HbA1c (%) (95% CI)	Mean fasting plasma glucose levels (mg/dL) (95% CI)	Mean 2-hour post-challenge glucose (mg/dL) (95% CI)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	5.21 (5.17, 5.25)	92 (91, 94)	96 (90, 102)
(≥12.75 g/day)	High	5.20 (5.17, 5.23)	94 (93, 95)	97 (94, 99)
Low Fiber Intake	Below LOD/Low	5.14 (5.05, 5.23)	94 (92, 96)	94 (86, 101)
(<12.75 g/day)	High	5.24 (5.17, 5.31)	96 (94, 98)	102 (95, 108)
p for additive interaction[b]		p=0.05	p=0.98	p=0.25
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	5.23 (5.20, 5.25)	94 (93, 95)	98 (95, 100)
(≥0.007 g/day)	High	5.17 (5.13, 5.21)	94 (93, 95)	95 (91, 99)
Low EPA Intake	Below LOD/Low	5.22 (5.15, 5.29)	94 (92, 95)	96 (90, 103)
(<0.007 g/day)	High	5.21 (5.13, 5.29)	98 (95, 100)	104 (97, 111)
p for additive interaction		p=0.26	p=0.02	p=0.01
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	5.20 (5.17, 5.24)	93 (92, 94)	98 (93, 103)
(≥0.018 g/day)	High	5.20 (5.16, 5.23)	94 (93, 95)	96 (94, 98)
Low DHA Intake	Below LOD/Low	5.19 (5.11, 5.26)	94 (91, 96)	100 (90, 109)
(<0.018 g/day)	High	5.24 (5.17, 5.31)	96 (94, 99)	101 (96, 107)
p for additive interaction		p=0.21	p=0.30	p=0.43
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	5.23 (5.20, 5.26)	93 (92, 94)	95 (91, 99)
(≥68.9 g/day)	High	5.18 (5.14, 5.21)	94 (93, 95)	98 (95, 100)
Low Vitamin C Intake	Below LOD/Low	5.20 (5.11, 5.28)	95 (92, 98)	97 (90, 103)
(<68.9 g/day)	High	5.23 (5.16, 5.30)	96 (95, 97)	103 (94, 112)
p for additive interaction		p=0.11	p=0.84	p=0.48
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake	Below LOD/Low	5.22 (5.19, 5.25)	93 (92, 94)	95 (92, 99)

(≥5.42 g/day)	High	5.19 (5.15, 5.22)	94 (93, 95)	98 (95, 101)
Low Vitamin E Intake	Below LOD/Low	5.22 (5.15, 5.29)	94 (93, 96)	93 (87, 99)
(<5.42 g/day)	High	5.21 (5.13, 5.29)	97 (94, 99)	105 (98, 113)
p for additive interaction		p=0.71	p=0.40	p=0.02
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	5.24 (5.20, 5.27)	94 (93, 95)	95 (92, 98)
	High	5.17 (5.13, 5.22)	94 (93, 95)	97 (94, 101)
Low	Below LOD/Low	5.21 (5.12, 5.30)	94 (92, 96)	93 (85, 100)
	High	5.24 (5.16, 5.32)	97 (94, 99)	105 (96, 114)
p for additive interaction		p=0.09	p=0.12	p=0.08
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	5.19 (5.15, 5.23)	94 (93, 95)	98 (95, 102)
	High	5.22 (5.19, 5.26)	94 (93, 95)	94 (91, 97)
High	Below LOD/Low	5.22 (5.13, 5.31)	95 (92, 97)	105 (99, 112)
	High	5.24 (5.16, 5.32)	96 (93, 99)	92 (99, 112)
p for additive interaction		p=0.87	p=0.69	p=0.21
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	5.23 (5.19, 5.27)	94 (93, 95)	95 (92, 99)
	High	5.18 (5.14, 5.22)	94 (93, 95)	97 (94, 100)
Low	Below LOD/Low	5.23 (5.13, 5.34)	96 (94, 99)	101 (91, 110)
	High	5.23 (5.16, 5.30)	95 (93, 97)	100 (92, 108)
p for additive interaction		p=0.41	p=0.37	p=0.68
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	5.22 (5.198 5.24)	94 (93, 95)	96 (93, 99)
	High	5.19 (5.195 5.24)	94 (93, 94)	96 (93, 99)
Low	Below LOD/Low	5.25 (5.17, 5.33)	95 (92, 98)	94 986, 102)
	High	5.21 (5.11, 5.31)	96 (95, 98)	105 (97, 112)
p for additive interaction		p=0.78	p=0.34	p=0.04

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 5.5. Adjusted means and 95% CIs for HbA1c levels in relation to self-report of household smokers and dietary nutrients and measures of additive interaction among 12-19 year olds, 2007-2010 NHANES

		Adjusted[a] Mean HbA1c (%) (95% CI)	Mean fasting plasma glucose levels (mg/dL) (95% CI)	Mean 2-hour post-challenge glucose (mg/dL) (95% CI)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	5.19 (5.16, 5.23)	93 (91, 95)	95 (89, 101)
(≥12.75 g/day)	High	5.21 (5.18, 5.23)	94 (94, 95)	96 (94, 99)
Low Fiber Intake	Below LOD/Low	5.22 (5.03, 5.40)	94 (91, 97)	98 (92, 103)
(<12.75 g/day)	High	5.23 (5.13, 5.32)	97 (95, 98)	107 (100, 113)
p for additive interaction[b]		p=0.97	p=0.53	p=0.15
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	5.22 (5.19, 5.24)	94 (93, 95)	97 (94, 99)
(≥0.007 g/day)	High	5.19 (5.14, 5.23)	94 (93, 96)	95 (92, 99)
Low EPA Intake	Below LOD/Low	5.28 (5.17, 5.39)	94 (92, 96)	101 (92, 110)
(<0.007 g/day)	High	5.15 (5.06, 5.25)	98 (95, 100)	108 (103, 113)
p for additive interaction		p=0.20	p=0.12	p=0.12
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	5.20 (5.17, 5.24)	94 (92, 95)	97 (92, 101)
(≥0.018 g/day)	High	5.21 (5.17, 5.24)	94 (93, 95)	96 (94, 99)
Low DHA Intake	Below LOD/Low	5.16 (5.03, 5.29)	93 (91, 96)	108 (97, 118)
(<0.018 g/day)	High	5.21 (5.11, 5.31)	97 (95, 98)	104 (99, 109)
p for additive interaction		p=0.57	p=0.12	p=0.58
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	5.23 (5.20, 5.26)	94 (92, 96)	94 (90, 98)
(≥68.9 g/day)	High	5.18 (5.15, 5.22)	94 (93, 95)	98 (95, 100)
Low Vitamin C Intake	Below LOD/Low	5.21 (5.07, 5.34)	95 (93, 97)	102 (96, 108)
(<68.9 g/day)	High	5.24 (5.15, 5.33)	97 (95, 99)	107 (96, 118)
p for additive interaction		p=0.41	p=0.60	p=0.80
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake	Below LOD/Low	5.21 (5.18, 5.24)	94 (92, 95)	94 (91, 98)
(≥5.42 g/day)	High	5.20 (5.16, 5.23)	95 (94, 99)	98 (96, 101)
Low Vitamin E Intake	Below LOD/Low	5.27 (5.15, 5.39)	95 (93, 97)	98 (93, 104)

(<5.42 g/day)	High	5.17 (5.06, 5.27)	97 (95, 99)	109 (102, 117)
p for additive interaction		p=0.30	p=0.76	p=0.09
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	5.22 (5.19, 5.25)	94 (93, 95)	94 (91, 97)
	High	5.19 (5.15, 5.23)	94 (93, 95)	97 (94, 101)
Low	Below LOD/Low	5.32 (5.15, 5.50)	96 (94, 98)	97 (89, 106)
	High	5.21 (5.12, 5.31)	97 (95, 99)	109 (100, 118)
p for additive interaction		p=0.41	p=0.59	p=0.19
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	5.20 (5.16, 5.24)	94 (93, 95)	99 (95, 102)
	High	5.21 (5.17, 5.24)	94 (93, 95)	93 (90, 96)
High	Below LOD/Low	5.17 (5.07, 5.27)	96 (95, 98)	108 (100, 116)
	High	5.35 (5.22, 5.47)	98 (96, 100)	100 (92, 108)
p for additive interaction		p=0.06	p=0.50	p=0.56
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	5.22 (5.18, 5.25)	94 (93, 95)	95 (92, 98)
	High	5.19 (5.15, 5.23)	94 (93, 96)	97 (93, 100)
Low	Below LOD/Low	5.36 (5.16, 5.56)	97 (93, 101)	109 (94, 123)
	High	5.20 (5.12, 5.28)	97 (95, 99)	103 (94, 112)
p for additive interaction		p=0.22	p=0.87	p=0.41
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	5.21 (5.18, 5.24)	95 (93, 96)	95 (92, 99)
	High	5.20 (5.16, 5.25)	94 (93, 95)	96 (94, 99)
Low	Below LOD/Low	5.37 (5.24, 5.50)	97 (94, 99)	102 (95, 110)
	High	5.16 (5.05, 5.27)	97 (95, 99)	106 (98, 115)
p for additive interaction		p=0.02	p=0.58	p=0.65

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.
[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 5.6. Crude and adjusted odds ratios for the association between serum cotinine and HbA1c and glucose levels among 12-19 year olds, 2007-2010 NHANES

	Pre-diabetes (HbA1c ≥5.7%) vs. Normal ORs (95% CIs)	Pre-diabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal ORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal ORs (95% CIs)
Crude			
Below LOD/None	1	1	1
Low	1.3 (0.8, 2.0)	0.9 (0.7, 1.3)	1.3 (0.9, 1.8)
High	1.9 (1.2, 3.0)	1.4 (1.0, 1.8)	1.3 (0.9, 1.9)
p for trend	p<0.01	p=0.08	p=0.09
Model 1[a]			
Below LOD/None	1	1	1
Low	1.1 (0.7, 1.8)	1.0 (0.7, 1.4)	1.1 (0.7, 1.6)
High	1.5 (0.7, 3.0)	1.4 (1.1, 1.9)	1.1 (0.7, 1.6)
p for trend	p=0.29	p=0.05	p=0.74
Model 2[b]			
Below LOD/None	1	1	1
Low	1.2 (0.7, 2.0)	1.0 (0.7, 1.6)	1.0 (0.7, 1.6)
High	1.7 (0.8, 3.8)	1.4 (1.0, 1.9)	1.1 (0.6, 1.9)
p for trend	p=0.19	p=0.10	p=0.69

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] Model 1 plus additional adjustment for total caloric intake, physical activity and body mass index.

Appendix 5.7. Crude and adjusted odds ratios for the association between self-report of household smokers and HbA1c and glucose levels among 12-19 year olds, 2007-2010 NHANES

	Pre-diabetes (HbA1c ≥5.7%) vs. Normal ORs (95% CIs)	Pre-diabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal ORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal ORs (95% CIs)
Crude			
Below LOD/None	1	1	1
Low	1.8 (1.0, 3.4)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)
High	1.8 (0.7, 4.8)	1.4 (0.8, 2.5)	1.4 (0.8, 2.5)
p for trend	p=0.09	p=0.25	p=0.25
Model 1[a]			
Below LOD/None	1	1	1
Low	1.6 (0.7, 3.7)	0.9 (0.6, 1.6)	0.9 (0.6, 1.6)
High	1.5 (0.3, 6.8)	1.3 (0.7, 2.4)	1.3 (0.7, 2.4)
p for trend	p=0.38	p=0.63	p=0.63
Model 2[b]			
Below LOD/None	1	1	1
Low	1.8 (0.6, 5.2)	1.2 (0.6, 2.4)	1.2 (0.6, 2.4)
High	1.6 (0.4, 6.8)	1.3 (0.7, 2.6)	1.3 (0.7, 2.6)
p for trend	p=0.33	p=0.46	p=0.46

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] Model 1 plus additional adjustment for total caloric intake, physical activity and body mass index.

Appendix 5.8. Adjusted ORs and 95% CIs for pre-diabetes in relation to NNAL levels and dietary nutrients and measures of multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Prediabetes (HbA1c ≥5.7%) vs. Normal AORs[a] (95% CIs)	Prediabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal AORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal AORs (95% CIs)
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.6 (0.3, 1.1)	1.2 (0.9, 1.6)	1.9 (0.4, 9.5)
Low	Below LOD/Low	0.9 (0.5, 1.8)	1.9 (1.1, 3.2)	1
	High	1.6 (0.7, 3.4)	1.8 (1.2, 2.7)	11.6 (2.9, 46.6)
p for multiplicative interaction[b]		p=0.05	p=0.49	N/A
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	1	1	1
	High	1.9 (1.2, 3.3)	1.0 (0.7, 1.4)	0.3 (0.1, 1.6)
High	Below LOD/Low	2.1 (0.9, 4.7)	1.4 (0.9, 2.3)	5.6 (0.9, 34.9)
	High	2.7 (1.0, 7.2)	1.9 (1.1, 3.3)	1
p for multiplicative interaction		p=0.57	p=0.29	N/A
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.6 (0.3, 1.0)	1.0 (0.6, 1.5)	0.9 (0.4, 1.8)
Low	Below LOD/Low	0.9 (0.3, 2.6)	2.0 (1.1, 3.4)	4.0 (0.4, 44.7)
	High	1.5 (0.7, 2.9)	1.5 (0.9, 2.4)	6.0 (0.8, 41.9)
p for multiplicative interaction		p=0.04	p=0.55	p=0.69
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.8 (0.4, 1.4)	0.8 (0.6,1.0	0.7 (0.3, 1.5)
Low	Below LOD/Low	1.7 (0.7, 3.9)	1.4 (0.7, 2.5)	1.0 (0.1, 22.6)

High	1.2 (0.5, 2.8)	1.6 (0.9, 2.8)	7.7 (1.4, 41.7)
p for multiplicative interaction	p=0.89	p=0.36	p=0.10

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 5.9. Adjusted ORs and 95% CIs for pre-diabetes in relation to serum cotinine and dietary nutrients and measures of multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Prediabetes (HbA1c ≥5.7%) vs. Normal AORs[a] (95% CIs)	Prediabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal AORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal AORs (95% CIs)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	1	1	1
(≥12.75 g/day)	High	1.1 (0.6, 1.8)	1.3 (0.6, 2.7)	0.9 (0.2, 3.1)
Low Fiber Intake	Below LOD/Low	0.8 (0.2, 3.8)	1.1 (0.4, 2.7)	1
(<12.75 g/day)	High	1.8 (0.9, 3.6)	2.2 (0.9, 5.1)	3.9 (0.8, 18.2)
p for multiplicative interaction[b]		p=0.37	p=0.44	N/A
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	1	1	1
(≥0.007 g/day)	High	0.7 (0.4, 1.2)	1.4 (0.9, 2.2)	0.9 (0.4, 2.3)
Low EPA Intake	Below LOD/Low	1.5 (0.7, 3.4)	1.3 (0.6, 2.6)	2.6 (0.3, 19.9)
(<0.007 g/day)	High	0.8 (0.3, 2.3)	2.6 (1.3, 5.4)	3.6 (0.9, 15.6)
p for multiplicative interaction		p=0.73	p=0.34	p=0.69
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	1	1	1
(≥0.018 g/day)	High	0.9 (05, 1.5)	1.5 (0.8, 2.6)	0.4 (0.1, 1.3)
Low DHA Intake	Below LOD/Low	1.0 (0.4, 2.6)	1.5 (0.6, 3.9)	2.5 (0.3, 21.6)
(<0.018 g/day)	High	1.7 (0.7, 4.0)	2.4 (1.0, 5.8)	1.5 (0.3, 7.8)
p for multiplicative interaction		p=0.31	p=0.88	p=0.70
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	1	1	1
(≥68.9 g/day)	High	1.2 (0.7, 2.1)	1.6 (0.9, 3.0)	0.8 (0.3, 2.1)
Low Vitamin C Intake	Below LOD/Low	1.4 (0.5, 3.7)	1.8 (0.8, 4.0)	0.5 (0.1, 8.3)
(<68.9 g/day)	High	1.8 (0.9, 3.7)	2.2 (1.1, 4.2)	4.9 (1.2, 20.5)
p for multiplicative interaction		p=0.97	p=0.49	p=0.06
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake	Below LOD/Low	1	1	1

(≥5.42 g/day)	High	0.6 (0.4, 1.0)	1.3 (0.7, 2.5)	0.9 (0.3, 2.2)
Low Vitamin E Intake	Below LOD/Low	1.2 (0.5, 2.8)	1.5 (0.7, 3.0)	0.3 (0.1, 3.3)
(<5.42 g/day)	High	1.3 (0.6, 2.9)	1.9 (1.0, 3.8)	5.4 (1.2, 24.0)
p for multiplicative interaction		p=0.38	p=0.98	p=0.03
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.7 (0.4, 1.1)	1.3 (0.6, 3.0)	2.3 (0.6, 8.2)
Low	Below LOD/Low	1.1 (0.4, 2.9)	1.4 (0.5, 3.4)	0.9 (0.1, 9.5)
	High	1.5 (0.7, 3.3)	2.2 (1.1, 4.3)	10.1 (2.4, 42.1)
p for multiplicative interaction		p=0.26	p=0.77	p=0.26
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	1	1	1
	High	1.9 (1.1, 3.4)	0.8 (0.5, 1.3)	0.4 (0.1, 1.4)
High	Below LOD/Low	2.1 (1.0, 4.4)	1.3 (0.6, 2.9)	4.9 (0.9, 26.7)
	High	2.7 (0.9, 8.1)	1.6 (0.7, 3.8)	1
p for multiplicative interaction		p=0.55	p=0.47	N/A
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.6 (0.3, 1.1)	1.0 (0.5, 2.0)	1.6 (0.5, 4.8)
Low	Below LOD/Low	1.0 (0.3, 4.0)	2.3 (0.8, 7.4)	3.2 (0.3, 30.0)
	High	1.4 (0.7, 2.8)	1.2 (0.6, 2.6)	7.2 (1.1, 47.3)
p for multiplicative interaction		p=0.24	p=0.41	p=0.76
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.7 (0.4, 1.3)	1.1 (0.7, 1.7)	1.1 (0.4, 2.9)
Low	Below LOD/Low	1.7 (0.7, 4.5)	1.3 (0.5, 3.2)	0.9 (0.1, 18.3)
	High	1.1 (0.5, 2.7)	2.0 (0.9, 4.5)	6.4 (1.2, 35.3)
p for multiplicative interaction		p=0.84	p=0.59	p=0.20

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 5.10. Adjusted ORs and 95% CIs for pre-diabetes in relation to self-report of household smokers and dietary nutrients and measures of multiplicative interaction among 12-19 year olds, 2007-2010 NHANES

		Prediabetes (HbA1c ≥5.7%) vs. Normal AORs[a] (95% CIs)	Prediabetes (Fasting plasma glucose ≥100 mg/dL) vs. Normal AORs (95% CIs)	Pre-diabetes (2-hour post-challenge glucose ≥140 mg/dL) vs. Normal AORs (95% CIs)
Fiber Intake	NNAL Exposure			
High Fiber Intake	Below LOD/Low	1	1	1
(≥12.75 g/day)	High	1.4 (0.8, 2.3)	1.5 (0.7, 3.1)	1.0 (0.3, 3.3)
Low Fiber Intake	Below LOD/Low	1.9 (0.4, 8.8)	1.9 (0.7, 4.9)	1
(<12.75 g/day)	High	2.0 (0.8, 5.2)	3.3 (1.3, 8.5)	3.9 (0.8, 18.5)
p for multiplicative interaction[b]		p=0.76	p=0.80	N/A
EPA Intake	NNAL Exposure			
High EPA Intake	Below LOD/Low	1	1	1
(≥0.007 g/day)	High	0.8 (0.5, 1.5)	1.4 (0.9, 2.1)	1.2 (0.5, 3.1)
Low EPA Intake	Below LOD/Low	2.5 (0.9, 7.0)	1.4 (0.6, 3.1)	3.1 (0.4, 24.6)
(<0.007 g/day)	High	0.3 (0.1, 1.0)	4.1 (1.7, 10.0)	2.5 (0.5, 11.9)
p for multiplicative interaction		p=0.10	p=0.20	p=0.68
DHA Intake	NNAL Exposure			
High DHA Intake	Below LOD/Low	1	1	1
(≥0.018 g/day)	High	1.1 (0.6, 1.8)	1.4 (0.8, 2.6)	0.5 (0.1, 1.8)
Low DHA Intake	Below LOD/Low	1.6 (0.4, 5.8)	1.7 (0.7, 4.2)	2.2 (0.2, 22.3)
(<0.018 g/day)	High	1.6 (0.5, 5.0)	3.3 (1.3, 8.4)	1.0 (0.2, 5.5)
p for multiplicative interaction		p=0.95	p=0.58	p=0.95
Vitamin C Intake	NNAL Exposure			
High Vitamin C Intake	Below LOD/Low	1	1	1
(≥68.9 g/day)	High	1.3 (0.8, 2.1)	1.6 (0.8, 3.0)	1.0 (0.4, 2.8)
Low Vitamin C Intake	Below LOD/Low	1.7 (0.6, 5.1)	2.4 (1.1, 5.0)	0.5 (0.1, 9.4)
(<68.9 g/day)	High	1.8 (0.6, 5.7)	3.0 (1.3, 7.0)	4.9 (1.0, 23.2)
p for multiplicative interaction		p=0.75	p=0.72	p=0.12
Vitamin E Intake	NNAL Exposure			
High Vitamin E Intake	Below LOD/Low	1	1	1

(≥5.42 g/day)	High	0.8 (0.5, 1.1)	1.3 (0.7, 2.5)	1.0 (0.4, 2.6)
Low Vitamin E Intake	Below LOD/Low	1.6 (0.6, 4.3)	2.2 (1.1, 4.2)	1
(<5.42 g/day)	High	1.1 (0.3, 4.4)	2.6 (1.0, .6)	5.7 (1.2, 26.4)
p for multiplicative interaction		p=0.91	p=0.92	N/A
Fiber-Fat-Soluble-Vitamin Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.9 (0.6, 1.3)	1.3 (0.6, 2.8)	2.5 (0.8, 7.9)
Low	Below LOD/Low	1.9 (0.7, 5.4)	1.8 (0.6, 5.0)	1
	High	1.4 (0.4, 4.5)	3.0 (1.4, 6.7)	9.8 (2.4, 39.2)
p for multiplicative interaction		p=0.84	p=0.75	N/A
Saturated-Fat Component	NNAL Exposure			
Low	Below LOD/Low	1	1	1
	High	1.3 (0.8, 2.4)	0.8 (0.5, 1.2)	0.3 (0.1, 1.0)
High	Below LOD/Low	0.9 (0.4, 1.8)	1.7 (0.6, 4.7)	4.3 (0.7, 25.3)
	High	3.5 (1.1, 11.4)	2.5 (1.1, 5.9)	1
p for multiplicative interaction		p=0.08	p=0.37	N/A
Vitamin-B-Complex Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	0.8 (0.5, 1.4)	0.9 (0.5, 1.7)	1.8 (0.6, 6.1)
Low	Below LOD/Low	2.2 (0.5, 9.0)	3.0 (0.7, 12.2)	3.7 (0.3, 44.5)
	High	1.3 (0.5, 3.2)	1.8 (0.8, 3.8)	6.5 (0.8, 49.8)
p for multiplicative interaction		p=0.60	p=0.63	p=0.97
Omega-3-Fatty-Acids Component	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	1.0 (0.5, 1.8)	1.1 (0.9, 1.6)	1.5 (0.6, 4.1)
Low	Below LOD/Low	3.3 (1.1, 10.2)	1.7 (0.6, 4.8)	1.7 (0.1, 33.2)
	High	0.5 (0.2, 1.4)	2.8 (1.0, 8.0)	6.1 (0.9, 38.9)
p for multiplicative interaction		p=0.01	p=0.65	p=0.55

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LOD; limit of detection; NHANES, National Health and Nutrition Examination Survey; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

[a]Adjusted for sex, age, race/ethnicity and poverty index ratio.

[b] p for multiplicative interaction generated for the product term of each dietary factor and exposure to SHS.

Methods: In addition to HbA1c levels, we also assessed the relationship between exposure to SHS on additional metabolic endpoints, including blood pressure, triglycerides, and HDL levels. At the same time of biospecimen collection, blood pressure was measured using a mercury sphygmomanometer after resting quietly in a sitting position for five minutes. Three consecutive measures of systolic blood pressure and diastolic blood pressure were taken separated by approximately one minute, with the average of the second and third measurements to be used in data analyses. HDL cholesterol and triglycerides were directly measured in serum through enzymatic, colorimetric methods using the Siemens Advia 2400 analyzer (Siemens Healthcare, Germany). Although the methods used in the Singapore Chinese Health Study did not require participants to fast prior to the lipid panel, non-fasting lipid levels have been shown to have a similar prognostic value as that of fasting lipid levels (Doran et al. 2014). Adjusted means and 95% CIs were calculated for linear regression models.

Weighted linear regression models were used to describe the relationship between exposure to SHS and blood pressure, triglycerides, and HDL levels. Additive interaction was assessed by introducing product terms between the dichotomous exposure to SHS (high exposure vs. other) and dichotomized diet variables in separate linear regression models.

Hypertension was defined as having a systolic blood pressure level ≥ 90 mmHg and a diastolic blood pressure level ≥ 140 mmHg (National Cholesterol Education Panel 1996). High triglycerides were defined as having triglycerides ≥1.7 mmol/L (U.S. Department of Health and Human Services 2002). Low HDL cholesterol was defined as having HDL ≤1.3 mmol/L for women and ≤1 mmol/L for men (U.S. Department of Health and Human Services 2002).

Multiplicative interaction was assessed by adding product terms between the dichotomized exposure to SHS and diet variables into separate logistic regression models. Crude and adjusted odds ratios and 95% CIs were calculated for logistic regression models.

Results: We observed limited evidence that creatinine-adjusted cotinine or self-report of household smokers were independently related to systolic blood pressure, diastolic blood pressure, triglycerides, or HDL cholesterol levels (Appendices 6.1 and 6.2). Measures of additive interaction suggest that increases in the mean triglyceride levels among adults with high exposure to SHS (determined by self-report of household smokers) and low levels of certain nutrients (vitamin C or omega-3 polyunsaturated fatty acids) are greater than would be expected due to the effects of the individual exposures (Appendix 6.4). Little or no evidence suggesting more or less than additive interaction was observed for low dietary fiber, vitamin E, the meat-dim sum pattern, the vegetable-fruit-soy pattern, or the DASH diet score on the relationship between exposure to SHS and systolic blood pressure, diastolic blood pressure, triglycerides, or HDL levels (Appendices 6.3 and 6.4).

We observed limited evidence that creatinine-adjusted cotinine or self-report of household smokers were independently associated to systolic blood pressure, diastolic blood pressure, high triglycerides, or HDL cholesterol levels (Appendices 6.5 and 6.6). Interaction results indicate that the prevalence of high triglycerides among adults with both high exposure to SHS (determined by creatinine-adjusted cotinine or self-report of household smokers) and low levels of certain nutrients (fiber, vitamin C, vitamin E, or omega-3 polyunsaturated fatty acids) is greater than would be expected due to the effects of the individual exposures alone (Appendices 6.7 and 6.8). Little or no evidence suggesting more or less multiplicative interaction was observed for meat-dim sum pattern, the vegetable-fruit-soy pattern, or the DASH diet score (Appendices 6.7 and 6.8).

Appendix 6.1. Crude and adjusted models for the relationship between serum cotinine and metabolic endpoints

	SBP Means (95% CIs)	DBP Means (95% CIs)	Triglycerides Means (95% CIs)	HDL Cholesterol Means (95% CIs)
Crude				
Below LOD	137 (124, 150)	78 (73, 83)	1.4 (0.9, 1.9)	1.7 (1.5, 1.8)
Low	139 (135, 143)	80 (79, 82)	1.5 (1.4, 1.7)	1.4 (1.3, 1.5)
High	134 (130, 138)	80 (78, 82)	1.5 91.4, 1.7)	1.4 (1.3, 1.5)
p for trend	p=0.33	p=0.67	p=0.80	p=0.35
Model 1[a]				
Below LOD	139 (128, 150)	77 (72, 82)	1.4 (0.9, 1.9)	1.6 (1.5, 1.8)
Low	142 (138, 146)	80 (78, 82)	1.5 (1.4, 1.6)	1.4 (1.3, 1.5)
High	137 (133, 141)	81 (78, 82)	1.5 (1.3, 1.6)	1.4 (1.3, 1.5)
p for trend	p=0.52	p=0.61	p=0.90	p=0.32
Model 2[b]				
Below LOD	139 (128, 150)	77 (73, 82)	1.4 (0.9, 1.9)	1.6 (1.5, 1.8)
Low	142 (138, 146)	80 (79, 82)	1.5 (1.4, 1.6)	1.4 (1.3, 1.4)
High	137 (133, 141)	80 (78, 82)	1.5 (1.3, 1.6)	1.4 (1.3, 1.5)
p for trend	p=0.57	p=0.51	p=0.92	p=0.41

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; LOD, limit of detection; SBP; systolic blood pressure.
[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).
[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Appendix 6.2. Crude and adjusted models for the relationship between self-report of exposure to SHS and metabolic endpoints

	SBP Means (95% CIs)	DBP Means (95% CIs)	Triglycerides Means (95% CIs)	HDL Cholesterol Means (95% CIs)
Crude				
None	137 (134, 140)	80 (79, 82)	1.5 (1.4, 1.7)	1.4 (1.3, 1.5)
One or More	133 (128, 138)	80 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
Model 1[a]				
None	140 (137, 143)	80 (79, 81)	1.5 (1.4, 1.6)	1.4 (1.3, 1.5)
One or More	136 (130, 142)	79 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
Model 2[b]				
None	140 (137, 143)	80 (79, 81)	1.5 (1.4, 1.6)	1.4 (1.3, 1.5)
One or More	136 (130, 142)	79 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP; systolic blood pressure; SHS, secondhand smoke.
[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).
[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Appendix 6.3. Adjusted means and 95% CIs for metabolic endpoints in relation to serum cotinine levels and dietary nutrients and measures of additive interaction

		SBP Adjusted Means[a] (95% CIs)	DBP Adjusted Means (95% CIs)	Triglycerides Adjusted Means (95% CIs)	HDL Adjusted Means (95% CIs)
Fiber Intake	Cotinine Exposure				
High Fiber Intake	Below LOD/Low	138 (135, 143)	80 (78, 82)	1.6 (1.5, 1.7)	1.4 (1.3, 1.5)
	High	137 (128, 145)	79 (76, 83)	1.6 (1.4, 1.8)	1.4 (1.3, 1.6)
Low Fiber Intake	Below LOD/Low	134 (130, 138)	80 (78, 83)	1.5 (1.4, 1.6)	1.4 (1.3, 1.5)
	High	139 (131, 147)	80 (76, 85)	1.6 (1.4, 1.7)	1.3 (1.2, 1.5)
p for additive interaction[b]		p=0.31	p=0.82	p=0.60	p=0.24
Vitamin C	Cotinine Exposure				
High Vitamin C Intake	Below LOD/Low	137 (132, 141)	80 (78, 82)	1.6 (1.5, 1.7)	1.4 (1.3, 1.5)
	High	143 (136, 150)	81 (78, 84)	1.5 (1.2, 1.7)	1.4 (1.2, 1.5)
Low Vitamin C Intake	Below LOD/Low	134 (130, 138)	80 (77, 82)	1.5 (1.4, 1.7)	1.4 (1.2, 1.5)
	High	144 (136, 151)	83 (80, 86)	1.5 (1.2, 1.8)	1.5 (1.4, 1.6)
p for additive interaction		p=0.60	p=0.55	p=0.75	p=0.35
Vitamin E Intake	Cotinine Exposure				
High Vitamin E Intake	Below LOD/Low	138 (134, 142)	80 (78, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
	High	140 (132, 148)	80 (76, 84)	1.7 (1.3, 2.0)	1.4 (1.3, 1.5)
Low Vitamin E Intake	Below LOD/Low	134 (130, 138)	79 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
	High	140 (132, 148)	83 (79, 86)	1.7 (1.4, 1.9)	1.4 (1.3, 1.5)
p for additive interaction		p=0.58	p=0.29	p=0.98	p=0.52
Omega-3 Fatty Acids Intake	Cotinine Exposure				
High Intake	Below LOD/Low	138 (134, 142)	80 (78, 82)	1.6 (1.5, 1.7)	1.4 (1.3, 1.5)
	High	140 (130, 149)	79 (75, 83)	1.5 (1.3, 1.8)	1.4 (1.3, 1.6)
Low Intake	Below LOD/Low	134 (129, 138)	80 (77, 82)	1.5 (1.3, 1.7)	1.5 (1.4, 1.5)
	High	138 (131, 145)	82 (78, 86)	1.6 (1.2, 1.9)	1.3 (1.2, 1.4)
p for additive interaction		p=0.71	p=0.23	p=0.63	p=0.06
Meat Dim Sum	Cotinine Exposure				

Pattern					
High	Below LOD/Low	138 (133, 143)	79 (77, 81)	1.6 (1.4, 1.8)	1.4 (1.3, 1.5)
	High	139 (135, 143)	81 (79, 84)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
Low	Below LOD/Low	133 (128, 138)	80 (76, 82)	1.5 (1.2, 1.7)	1.4 (1.3, 1.5)
	High	137 (132, 143)	81 (79, 84)	1.6 (1.4, 1.8)	1.4 (1.3, 1.5)
p for additive interaction		p=0.47	p=0.83	p=0.54	p=0.95
Vegetable-Fruit-Soy Pattern	Cotinine Exposure				
High	Below LOD/Low	137 (132, 143)	79 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
	High	139 (134, 144)	81 (78, 83)	1.6 (1.4, 1.8)	1.4 (1.3, 1.5)
Low	Below LOD/Low	137 (132, 142)	83 (80, 85)	1.7 (1.5, 2.0)	1.4 (1.3, 1.5)
	High	133 (128, 138)	78 (75, 81)	1.3 (1.2, 1.5)	1.4 (1.3, 1.5)
p for additive interaction		p=0.25	p=0.02	p=0.01	p=0.66
DASH diet score	NNAL Exposure				
High	Below LOD/Low	136 (131, 141)	79 (77, 82)	1.6 (1.4, 1.7)	1.4 (1.3, 1.5)
	High	140 (135, 146)	81 (78, 83)	1.5 (1.3, 1.8)	1.4 (1.3, 1.5)
Low	Below LOD/Low	134 (129, 139)	79 (75, 82)	1.5 (1.2, 1.7)	1.4 (1.3, 1.5)
	High	136 (130, 141)	82 (79, 84)	1.6 (1.4, 1.8)	1.4 (1.3, 1.6)
p for additive interaction		p=0.62	p=0.51	p=0.56	p=0.46

Abbreviations CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; LOD, limit of detection; SBP, systolic blood pressure.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 6.4. Adjusted means and 95% CIs for metabolic endpoints in relation to self-report of exposure to SHS and dietary nutrients and measures of additive interaction

		SBP Adjusted Means[a] (95% CIs)	DBP Adjusted Means (95% CIs)	Triglycerides Adjusted Means (95% CIs)	HDL Adjusted Means (95% CIs)
Fiber Intake	Self-Report				
High Fiber Intake	None	136 (134, 140)	80 (79, 82)	1.5 (1.5, 1.6)	1.4 (1.3, 1.5)
	One or More	137 (130, 144)	80 (76, 83)	1.5 (1.4, 1.7)	1.4 (1.3, 1.5)
Low Fiber Intake	None	133 (126, 140)	79 (76, 82)	1.7 (1.5, 1.9)	1.5 (1.3, 1.6)
	One or More	138 (127, 149)	79 (75, 84)	1.7 (1.4, 1.9)	1.4 (1.3, 1.4)
p for additive interaction[b]		p=0.51	p=0.83	p=0.92	p=0.29
Vitamin C	Self-Report				
High Vitamin C Intake	None	136 (132, 139)	80 (78, 82)	1.6 (1.5, 1.8)	1.4 (1.3, 1.5)
	One or More	142 (136, 149)	81 (78, 84)	1.4 (1.2, 1.5)	1.5 (1.3, 1.6)
Low Vitamin C Intake	None	131 (125, 138)	79 (76, 82)	1.4 (1.2, 1.6)	1.5 (1.4, 1.6)
	One or More	146 (138, 154)	83 (79, 86)	1.8 (1.5, 2.1)	1.3 (1.2, 1.4)
p for additive interaction		p=0.29	p=0.34	p<0.01	p=0.01
Vitamin E Intake	Self-Report				
High Vitamin E Intake	None	136 (133, 139)	80 (78, 82)	1.5 (1.4, 1.6)	1.4 (1.3, 1.5)
	One or More	142 (135, 149)	82 (79, 85)	1.7 (1.4, 1.9)	1.4 (1.3, 1.5)
Low Vitamin E Intake	None	135 (127, 142)	80 (77, 83)	1.4 (1.2, 1.6)	1.5 (1.3, 1.6)
	One or More	134 (125, 144)	78 (74, 82)	1.7 (1.6, 1.9)	1.4 (1.3, 1.5)
p for additive interaction		p=0.38	p=0.26	p=0.34	p=0.30
Omega-3 Fatty Acids Intake	Self-Report				
High Intake	None	136 (133, 140)	80 (78, 82)	1.6 (1.4, 1.7)	1.4 (1.3, 1.5)
	One or More	139 (133, 146)	81 (77, 85)	1.5 (1.2, 1.7)	1.4 (1.3, 1.5)
Low Intake	None	134 (127, 141)	80 (77, 83)	1.4 (1.2, 1.6)	1.5 (1.3, 1.6)
	One or More	136 (125, 148)	78 (74, 83)	1.7 (1.6, 2.0)	1.4 (1.3, 1.5)
p for additive interaction		p=0.95	p=0.54	p=0.02	p=0.66
Meat Dim Sum Pattern	Self-Report				

Low	None	136 (132, 141)	79 (77, 81)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
	One or More	138 (134, 142)	82 (79, 84)	1.6 (1.4, 1.7)	1.4 (1.3, 1.5)
High	None	132 (124, 139)	79 (75, 82)	1.6 (1.3, 1.8)	1.5 (1.3, 1.7)
	One or More	138 (129, 145)	80 (76, 84)	1.4 (1.2, 1.7)	1.4 (1.3, 1.5)
p for additive interaction		p=0.47	p=0.80	p=0.38	p=0.62
Vegetable-Fruit-Soy Pattern	Self-Report				
High	None	139 (134, 142)	81 (79, 83)	1.6 (1.4, 1.8)	1.4 (1.3, 1.5)
	One or More	136 (132, 141)	79 (77, 82)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
Low	None	133 (123, 142)	79 (75, 83)	1.7 (1.5, 1.9)	1.4 (1.3, 1.5)
	One or More	136 (128, 143)	80 (76, 83)	1.4 (1.2, 1.6)	1.5 (1.3, 1.7)
p for additive interaction		p=0.54	p=0.37	p=0.15	p=0.08
DASH diet score	Self-Report				
High	None	136 (132, 140)	79 (77, 82)	1.5 (1.4, 1.7)	1.4 (1.3, 1.4)
	One or More	138 (133, 142)	81 (79, 83)	1.5 (1.3, 1.7)	1.4 (1.3, 1.5)
Low	None	130 (123, 137)	77 (74, 80)	1.4 (1.2, 1.6)	1.5 (1.3, 1.7)
	One or More	139 (132, 147)	82 (78, 85)	1.6 (1.4, 1.9)	1.4 (1.3, 1.5)
p for additive interaction		p=0.20	p=0.33	p=0.24	p=0.05

Abbreviations CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; SBP; systolic blood pressure; SHS, secondhand smoke.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 6.5. Crude and adjusted ORs and 95% CIs for the association between serum cotinine and metabolic disorders

	Hypertension ORs (95% CIs)	High Triglycerides ORs (95% CIs)	Low HDL ORs (95% CIs)
Crude			
Below LOD	1	1	1
Low	1.1 (0.3, 4.2)	1.4 (0.4, 4.9)	8.2 (2.3, 28.7)
High	1.3 (0.3, 5.1)	1.4 (0.4, 5.0)	4.6 (1.3, 16.9)
p for trend	p=0.61	p=0.72	p=0.98
Model 1[a]			
Below LOD	1	1	1
Low	1.4 (0.3, 6.7)	1.3 (0.3, 5.6)	7.7 (2.3, 26.4)
High	1.7 (0.4, 8.0)	1.2 (0.3, 5.3)	4.1 (1.2, 14.8)
p for trend	p=0.51	p=0.93	p=0.90
Model 2[b]			
Below LOD	1	1	1
Low	1.3 (0.3, 6.3)	1.2 (0.3, 5.1)	10.5 (2.9, 38.4)
High	1.6 (0.3, 7.8)	1.2 (0.3, 5.0)	5.1 (1.3, 19.2)
p for trend	p=0.50	p=0.89	p=0.95

Abbreviations: CI, confidence interval; LOD, limit of detection; OR, odds ratio.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Appendix 6.6. Crude and adjusted ORs and 95% CIs for the association between self-report of exposure to SHS and metabolic endpoints

	Hypertension ORs (95% CIs)	High Triglycerides ORs (95% CIs)	Low HDL ORs (95% CIs)
Crude			
None	1	1	1
Two or More	0.4 (0.1, 1.5)	1.1 (0.4, 2.8)	2.1 (0.8, 5.4)
Model 1[a]			
None	1	1	1
Two or More	0.3 (0.06, 1.1)	0.9 (0.3, 2.3)	2.3 (0.9, 6.3)
Model 2[b]			
None	1	1	1
Two or More	0.3 (0.07, 1.3)	0.8 (0.3, 2.2)	1.7 (0.6, 4.7)

Abbreviations: CI, confidence interval; OR, odds ratio; SHS, secondhand smoke.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b] Model 1 plus additional adjustment for education (no formal education, primary education, or secondary education) and body mass index.

Appendix 6.7. Adjusted means and 95% CIs for metabolic disorders in relation to serum cotinine levels and dietary nutrients and measures of multiplicative interaction

		Hypertension AORs[a] (95% CIs)	High Triglycerides AORs (95% CIs)	Low HDL AORs (95% CIs)
Fiber Intake	Cotinine Exposure			
High Fiber Intake	Below LOD/Low	1	1	1
	High	0.8 (0.2, 2.8)	0.9 (0.3, 2.9)	1.5 (0.5, 4.2)
Low Fiber Intake	Below LOD/Low	1.3 (0.5, 3.1)	0.7 (0.3, 1.7)	0.6 (0.3, 1.6)
	High	0.8 (0.3, 2.5)	2.2 (0.8, 6.4)	1.1 (0.3, 4.0)
p for multiplicative interaction[b]		p=0.75	p=0.13	p=0.82
Vitamin C	Cotinine Exposure			
High Vitamin C Intake	Below LOD/Low	1	1	1
	High	0.9 (0.3, 2.8)	0.6 (0.2, 2.2)	3.1 (1.1, 8.5)
Low Vitamin C Intake	Below LOD/Low	1.2 (0.5, 2.8)	0.8 (0.4, 1.8)	0.9 (0.4, 1.9)
	High	1.1 (0.3, 3.5)	1.2 (0.3, 4.4)	1.8 (0.5, 6.8)
p for multiplicative interaction		p=0.94	p=0.38	p=0.65
Vitamin E Intake	Cotinine Exposure			
High Vitamin E Intake	Below LOD/Low	1	1	1
	High	1.0 (0.3, 3.2)	1.8 (0.6, 5.9)	1.2 (0.4, 3.4)
Low Vitamin E Intake	Below LOD/Low	1.3 (0.6, 3.0)	0.9 (0.4, 2.1)	0.6 (0.2, 1.4)
	High	0.9 (0.3, 2.7)	2.8 (0.9, 8.1)	1.6 (0.5, 5.3)
p for multiplicative interaction		p=0.66	p=0.55	p=0.31
Omega-3 Fatty Acids Intake	Cotinine Exposure			
High Intake	Below LOD/Low	1	1	1
	High	2.6 (0.8, 8.6)	1.5 (0.5, 4.7)	1.5 (0.5, 4.6)
Low Intake	Below LOD/Low	1.2 (0.5, 3.0)	0.8 (0.4, 1.9)	0.7 (0.3, 1.7)
	High	2.1 (0.7, 7.3)	1.9 (0.7, 5.8)	0.8 (0.2, 2.8)
p for multiplicative interaction		p=0.63	p=0.58	p=0.75
Meat Dim Sum Pattern	Cotinine Exposure			
High	Below LOD/Low	1	1	1

	High	1.2 (0.4, 3.3)	0.9 (0.3, 2.6)	1.3 (0.5, 3.3)
Low	Below LOD/Low	1.0 (0.3, 3.1)	0.8 (0.3, 2.3)	0.8 (0.3, 2.4)
	High	1.6 (0.6, 4.2)	1.1 (0.4, 2.7)	0.6 (0.2, 2.0)
p for multiplicative interaction		p=0.69	p=0.65	p=0.52
Vegetable-Fruit-Soy Pattern	Cotinine Exposure			
High	Below LOD/Low	1	1	1
	High	1.3 (0.5, 3.5)	2.3 (0.8, 6.4)	1.3 (0.5, 3.1)
Low	Below LOD/Low	1.6 (0.6, 4.6)	2.8 (1.0, 7.9)	0.8 (0.3, 2.5)
	High	1.2 (0.4, 3.6)	0.8 (0.3, 2.5)	0.7 (0.2, 2.0)
p for multiplicative interaction		p=0.50	p=0.01	p=0.63
DASH diet score	NNAL Exposure			
High	Below LOD/Low	1	1	1
	High	1.5 (0.6, 3.9)	0.8 (0.3, 2.2)	0.7 (0.3, 1.8)
Low	Below LOD/Low	1.3 (0.4, 4.2)	0.8 (0.3, 2.0)	0.7 (0.3, 2.0)
	High	1.7 (0.6, 4.4)	1.0 (0.4, 2.4)	0.4 (0.1, 1.3)
p for multiplicative interaction		p=0.82	p=0.49	p=0.82

Abbreviations AOR, adjusted odds ratio; CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; LOD, limit of detection.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.

Appendix 6.8. Adjusted ORs and 95% CIs for metabolic disorders in relation to self-report of exposure to SHS and dietary nutrients and measures of multiplicative interaction

		Hypertension AORs[a] (95% CIs)	High Triglycerides AORs (95% CIs)	Low HDL AORs (95% CIs)
Fiber Intake	Self-Report			
High Fiber Intake	None	1	1	1
	One or More	0.8 (0.2, 2.0)	1.3 (0.4, 2.9)	1.7 (0.7, 4.4)
Low Fiber Intake	None	0.3 (0.07, 1.6)	0.5 (0.1, 1.8)	2.6 (0.8, 8.6)
	One or More	0.05 (0.02, 0.1)	3.2 (0.9, 11.0)	3.1 (0.8, 12.7)
p for multiplicative interaction		p=0.07	p=0.07	p=0.73
Vitamin C	Self-Report			
High Vitamin C Intake	None	1	1	1
	One or More	1.0 (0.4, 2.4)	0.4 (0.1, 1.4)	2.7 (1.0, 7.2)
Low Vitamin C Intake	None	0.3 (0.02, 1.5)	0.5 (0.1, 1.4)	2.2 (0.7, 6.9)
	One or More	0.04 (0.01, 0.2)	5.0 (1.3, 19.3)	9.0 (1.7, 46.5)
p for multiplicative interaction		p=0.06	p<0.01	p=0.71
Vitamin E Intake	Self-Report			
High Vitamin E Intake	None	1	1	1
	One or More	1.1 (0.4, 2.7)	1.5 (0.5, 4.1)	1.9 (0.7, 5.1)
Low Vitamin E Intake	None	0.4 (0.1, 1.8)	0.4 (0.1, 1.7)	2.8 (0.9, 8.9)
	One or More	0.04 (0.01, 0.1)	4.5 (1.2, 16.6)	2.7 (0.6, 11.3)
p for multiplicative interaction		p=0.02	p=0.06	p=0.49
Omega-3 Fatty Acids Intake	Self-Report			
High Intake	None	1	1	1
	One or More	2.6 (1.0, 6.9)	1.2 (0.5, 3.1)	1.4 (0.5, 3.7)
Low Intake	None	0.5 (0.1, 2.0)	0.4 (0.1, 1.6)	2.6 (0.8, 8.2)
	One or More	0.03 (0.01, 0.1)	5.3 (1.1, 25.2)	2.8 (0.6, 12.6)
p for multiplicative interaction		p=0.01	p=0.03	p=0.81
Meat Dim Sum Pattern	Self-Report			
High	None	1	1	1

	One or More	1.2 (0.6, 2.8)	1.3 (0.6, 2.8)	1.2 (0.5, 2.9)
Low	None	0.1 (0.02, 0.5)	1.4 (0.3, 5.5)	4.1 (1.0, 16.6)
	One or More	0.6 (0.1, 3.6)	0.7 (0.1, 2.8)	1.6 (0.4, 6.3)
p for multiplicative interaction		p=0.17	p=0.34	p=0.26
Vegetable-Fruit-Soy Pattern	Self-Report			
High	None	1	1	1
	One or More	1.0 (0.5, 2.1)	1.2 (0.5, 2.5)	1.0 (0.5, 2.5)
Low	None	0.05 (0.01, 0.1)	3.1 (0.8, 12.5)	4.4 (1.2, 16.9)
	One or More	0.4 (0.1, 2.0)	0.5 (0.1, 1.9)	1.9 (0.5, 6.9)
p for multiplicative interaction		p=0.04	p=0.04	p=0.31
DASH diet score	Self-Report			
High	None	1	1	1
	One or More	1.2 (0.6, 2.7)	1.0 (0.4, 2.1)	0.6 (0.2, 1.4)
Low	None	0.1 (0.02, 0.6)	0.7 (0.2, 2.9)	1.8 (0.4, 7.3)
	One or More	0.5 (0.1, 3.2)	1.0 (0.3, 3.7)	1.9 (0.5, 6.9)
p for multiplicative interaction		p=0.26	p=0.66	p=0.54

Abbreviations AOR; adjusted odds ratio; CI, confidence interval; DASH; Dietary Approaches to Stop Hypertension; SHS, secondhand smoke.

[a]Adjusted for age at follow-up interview, year of interview, and dialect group (Cantonese or Hokkien).

[b]p for additive interaction for additive interaction generated for the product term of each dietary factor and exposure to SHS.