The Association of Overweight with Allergy and Asthma in Children: Findings from the National Health and Nutrition Examination Survey (NHANES) 1999-2006

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

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ABSTRACT

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CYNTHIA VISNESS: The Association of Overweight with Allergy and Asthma in Children: Findings from the National Health and Nutrition Examination Survey (NHANES) 1999-2006
(Under the direction of Dr. Julie L. Daniels)

Obesity and asthma prevalence have both risen among children over the last several decades, and research efforts increasingly suggest that obesity is associated with asthma. Atopy is a strong risk factor for asthma, but previous literature on the relationship between obesity and atopy has been inconsistent. In addition, some, but not all, studies have shown that the effect of obesity on asthma is stronger among non-atopic individuals than among those with atopy. Systemic inflammation may be a factor in the relationship between obesity and asthma. Breastfeeding may potentially protect against obesity, atopy, and asthma.

This dissertation used National Health and Nutrition Examination and Survey (NHANES) data from 1999-2006 to examine the relationship between obesity and asthma among U.S. children age 2-19. Data from 2005-2006, which include assays for total and allergen-specific IgE, were used to explore the relationship of obesity with IgE levels, atopy, and allergy symptoms, and also to stratify the obesity-asthma analysis by atopic status. The protective effect of breastfeeding was investigated using data for children age 1-6.

Obese children were more likely to report having current asthma than children of normal weight (OR: 1.68, 95% CI: 1.33, 2.12). The association did not differ by gender, but was stronger among non-atopic children than among children with at least 1 positive specific

IgE result (OR: 2.46, 95% CI: 1.21, 5.02 vs. OR: 1.34, 95% CI: 0.70, 2.57; interaction p-value 0.09). Total IgE levels increased with BMI in a dose response manner and the odds of having at least one positive specific IgE were elevated among obese children compared to normal weight children (OR: 1.35; 95% CI: 1.04-1.76). C-reactive protein levels were associated with both atopy and asthma, and may indicate a role for systemic inflammation for both outcomes. Breastfeeding was found to protect against obesity and asthma, but not atopy. The protective effect of breastfeeding against asthma was not modified by obesity or by atopy.

An increased risk of allergic disease and asthma may not be the most consequential health risk faced by overweight children. Nonetheless, it provides additional motivation for undertaking the difficult challenge to reduce childhood obesity.

For Katie, Sarah, and Rebecca

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BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
DXA	Dual x-ray absorbtiometry
IgE	Immunoglobulin E
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PIR	Poverty income ratio
PSU	Primary sampling unit
SES	Socio-economic status

Chapter I. Introduction and Specific Aims

The adiposity of the American population has been growing steadily. This is true both for adults and children, and it is also the case in Canada, Australia, Europe, and throughout the developed countries of the world. This increase has been most apparent since about 1980. Before that time, only about 5% of US children age 6-11 were considered overweight; by 2004 that had climbed to nearly 19%.[1]

Asthma has also been on the rise in recent decades. From 1980 to 1995, the period of steepest increase, the prevalence of asthma among children 0-17 years of age increased from 3.6% to 7.5%. In 2005, 8.9% of children were reported to have current asthma, which would total 6.5 million American children.[2] The increase in asthma has been steepest in disadvantaged populations in the United States, the same populations that have seen the steepest increases in overweight. Despite copious research, the cause or causes for the increase in asthma prevalence are unknown.

Studies over the last fifteen years have suggested that obesity is related to asthma.[3-5] At least 30 cross-sectional and 13 prospective studies have been reported between 1999 and 2006, with nearly all of them showing a positive association between obesity and asthma.[3-5] Both asthma and obesity appear to be associated with inflammation, as indicated by levels of inflammatory markers such as leptin and C-reactive protein. Thus, inflammation due to obesity may lead to airway inflammation and asthma.

Allergic disease has also been on the rise in recent decades. In the U.S. from the period 1976-1980 to 1988-1994, the prevalence of skin test reactivity to 6 common allergens increased from 22% to 42%.[6] Increases in atopy have also been observed in the

U.K. and Europe.[7-9] Asthma and allergy/atopy often go hand in hand, but it is not clear whether obesity may be related to atopy. Some researchers have also shown obesity to be related to allergy symptoms or to higher serum IgE levels (a marker for atopy),[10-12] while others have not.[13-15] While there is certainly a large allergic component to asthma, recent research estimates that only about 40% of asthma in the U.S. is attributable to atopy.[16] It is possible that obesity-related asthma and atopic asthma have different etiologies, which has implications for treatment and prevention.[17]

A new allergy module was added to the 2005-2006 National Health and Nutrition Examination Survey (NHANES). This module included survey questions about allergy symptoms, total and specific serum IgE measurements, and environmental measures of dust allergen and endotoxin. This is the largest dataset of serum IgE levels that has ever been collected, and it comes from a sample that is generalizable to the entire population of the United States. This dataset affords a new opportunity to explore the question of the relationship between obesity and allergy/atopy, and to investigate whether atopic status modifies the relationship between obesity and asthma in children.

The current research project will examine the relationship between obesity/overweight and asthma and allergy/atopy in U.S. children ages 2-19 using data from the National Health and Nutrition Examination Survey (NHANES). The specific aims of this project are:

1. To determine if there is a relationship between overweight and total and specific IgE levels and allergic symptom outcomes among U.S. children ages 2-19.
2. To examine the effect of overweight on asthma outcomes among children 2-19 in a nationally representative sample of U.S. children from 1999-2006, and to use the 2005-2006 data to examine the hypothesis that the effect of overweight on asthma is different depending on whether the child also is atopic.

3. To examine whether the relationship between overweight and asthma is modified by infant feeding method or by atopy.

Chapter II. Literature Review

A. Background and Significance of the Contemporaneous Increases in Obesity and Asthma in Children

A.1. The Growing Problem of Childhood Obesity

Obesity in children is usually defined as being above the 95th percentile in body mass index (kg/m^2) for their age. Before 1980, when these standards were developed, by definition only 5% of US children age 6-11 were considered obese; by 2004 that had climbed to nearly 19%.[1] One of the leading health indicators for the Healthy People 2010 objectives is to reduce obesity among U.S. children and adolescents aged 6-19 back down to 5%.[18]

A combination of behavioral and environmental factors is to blame for this increase in overweight. The U.S. population in general is eating more food – eating more meals away from home, eating larger portions, and consuming more sugar-sweetened drinks.[19, 20] In addition, the prevalence of snacking among U.S. children has significantly increased from 1977 to 1996, with a higher proportion of energy and a higher proportion of energy from fat coming from snacks than from regular meals.[21] At the same time, the number of children getting regular physical exercise is declining,[22, 23] and children are spending more time in sedentary activities such as television watching and using the computer.[24] The issue of childhood obesity has risen to the level of being called an "epidemic,"[25, 26] and schools and other organizations around the country are taking steps to improve the situation, such as eliminating sugary soft drinks from school vending machines in middle and high schools and mandating daily physical education or recess in elementary schools.[27]

Obesity in childhood can lead to a lifetime of health consequences. Obese children are more likely to become obese adults,[28, 29] and obesity in adults is associated with numerous health problems, such as cardiovascular disease and diabetes. And, rather than waiting until adulthood to manifest themselves, these sequelae of obesity are being seen increasingly in children. In the Bogalusa Heart Study more than half of the overweight schoolchildren had at least one cardiovascular risk factor.[30] Type II (adult onset) diabetes used to be a rare occurrence in children, but is now increasingly common,[31] and it has also been shown that childhood overweight is associated with obesity and insulin resistance in young adulthood.[32] More and more children are coming to the attention of health professionals with metabolic syndrome – a precursor to diabetes.[33, 34] The American Diabetes Association estimates that 1 in 6 overweight adolescents has pre-diabetes.[35]

In addition, a wide variety of other health conditions have been associated with childhood obesity, such as liver steatosis, cholelithiasis, menstrual abnormalities, polycystic ovary syndrome, and sleep apnea.[36] Mental health consequences for obese children should also not be trivialized.[37, 38] Another important health problem that appears to be related to obesity in children, and will be the focus of this project, is asthma.

A.2. The Growing Problem of Childhood Asthma

Asthma is the most common chronic illness in childhood and is characterized by variable airflow obstruction with airway hyper-responsiveness. Asthma is responsible for more missed school days among children than any other chronic illness.[39] According to The National Health Interview Survey, 12.1% of U.S. children have had a physician diagnosis of asthma at some time in their lives, and 5.8% have had an asthma attack in the past 12 months.[40] Asthma is a multifactorial disease that has been associated with genetic, environmental, race/ethnicity, poverty, urbanization, psychosocial, and infectious factors.[41]

Asthma symptoms are caused by inflammation of the airways, and the inflammation is chronic. It can be treated with anti-inflammatory medication such as inhaled steroids, but it never goes away. It can cause difficulty breathing, wheezing, chronic coughing, and often shortness of breath or rapid breathing; however each asthmatic individual can have a different symptomatology. This can make asthma diagnosis difficult.[42]

Asthma is especially difficult to diagnose in children. Although the inflammation is chronic, symptoms may be intermittent. Additionally, many young children develop wheezy or noisy breathing when they have a viral illness, but they do not go to develop asthma. The Tucson Children's Respiratory Study identified several different phenotypes of childhood wheezing.[43] One group, transient wheezers, appear to simply have smaller airways and low levels of lung function in early life. They may have isolated episodes of wheeze in early childhood, particularly during respiratory illnesses, but stop wheezing after age 3. As many as 80% of children who wheeze in the first year of life belong to this group.[44] Among children who continue to wheeze after age 3, about 40% are non-atopic and may have reduced lung function subsequent to lower respiratory infections, particularly with RSV.

The majority (60%) of the children that wheezed beyond age 3 were atopic.[43] Atopy is a very important risk factor for asthma in young children, and the prevalence of atopy is also increasing in the U.S. popluation.[6]

Allergic diseases and allergic asthma are caused by exaggerated Th2-biased immune responses. In the allergic response, allergens presented by antigen presenting cells activate T helper (Th) cells that lead to the production of cytokines that further regulate the production of IgE (Figure 1). This is commonly called the "allergic cascade."[45]

Figure 1. Role of T helper (Th) cells and cytokines in immune function.

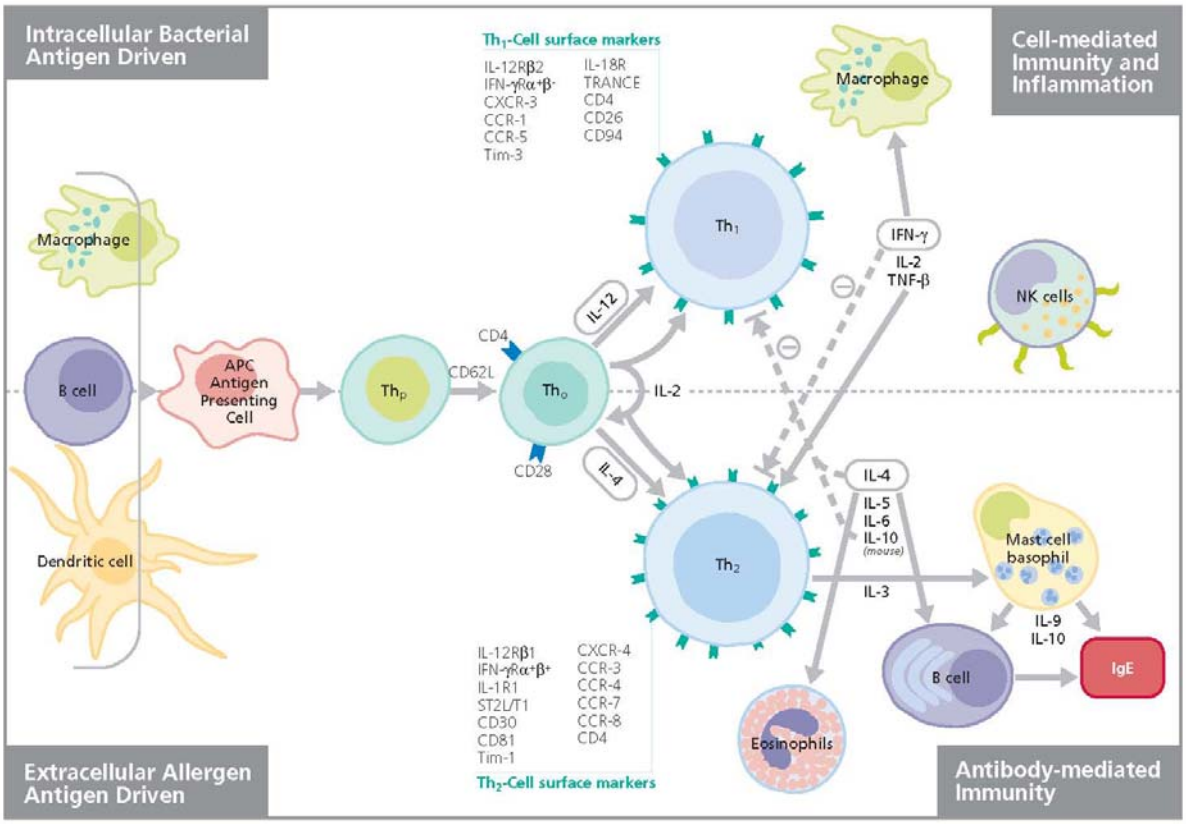


Figure reproduced from BD Biosciences. Th1 and Th2 Balance, Regulation, and Involvement in Disease. http://www.bdbiosciences.com/discovery_labware/products/display_product.php?keyID=108

Tolerance to allergens is a mechanism that normally prevents this allergic response, but in allergic individuals this tolerance is poor or non-existent for reasons that are unclear. Another subset of T-helper cells, T-regulatory cells, act to suppress (or regulate) both Th1 and Th2 cytokine production. Some have proposed that it is a defect, probably genetic, in this regulatory function that causes the Th2-skewed immune response seen in allergy.[46, 47] Still, there is continued debate over whether allergic diseases and asthma are caused by this lack of T-regulatory cell development, the loss of tolerance to environmental allergens through some as yet unknown mechanism, or the over-development of allergen-specific Th2 cells.[48]

Prescott et al. demonstrate that virtually all newborn infants display Th-2 skewed responses to common environmental allergens, in particular high levels of IL-10.[49] Most

children “outgrow” this response in the first years of life, and develop a Th1-Th2 balance. This is thought to be brought about by encountering infectious agents during early childhood and mounting the appropriate Th1 response to those infections.[49, 50] Repeated infectious encounters educate the immune system to behave appropriately. In children predisposed to allergy, however, this process is thwarted, and the child continues to mount a Th2 response to foreign bodies that the non-allergic child’s immune system simply ignores.[51] Why and how this happens in some children and not in others is not well understood at this time.

Children at genetic risk for allergic disease have been noted to have a weaker IFN-γ response.[52] Holt suggests that genetic risk for asthma is associated with a diminished capacity to produce IFN-γ, the primary Th-1 cytokine, during fetal and early postnatal life.[53, 54] Others have found that detectable cord blood IFN-γ is associated with lower risk for allergy/asthma at age 6[55] and that lower IFN-γ responses are associated with atopic disease at age 2.[56] However new research has been showing increased IFN-γ in asthmatic individuals under certain conditions.[57] These findings suggest that, even though it is a Th1 cytokine, IFN-γ may also contribute to chronic inflammation and may associated with asthma.[46]

B. The Effect of Obesity on Asthma in Children

B.1. General Evidence

Awareness in the research community regarding the concomitant increases in obesity and in asthma led to a new field of research on the relationship between the two. A number of the early studies regarding weight looked at birthweight and its effect on later asthma. One of these was reported in 1990 and examined the effect of high birthweight (≥3.8 kg) on physician-diagnosed asthma at age 6 months to 11 years. No relationship was found.[58] A series of further studies also using birthweight as a predictor of asthma also failed to find a significant effect.[59-61] Shaheen et al. reported on a British birth cohort study started

in 1970 that BMI measured at 10 years of age was not related to self-reported asthma or wheeze in adulthood.[62]

However, a 1983 population study of 72,284 adults in Italy showed an increased risk for asthma with high BMI.[63] Further large cross-sectional studies also demonstrated increased risks, though in some studies these findings were only significant in women.[62, 64] In a U.S. study among 39,637 participants of a military managed care program, a very distinct dose response was seen for higher risks of asthma with increasing BMI (BMI > 25 OR=1.2, BMI > 30 OR=1.7, BMI > 35 OR=2.3, BMI > 40 OR=2.8).[65]

Camargo, et al. analyzed prospective data from the Nurses Health Study (over 85,000 adult female subjects) using self-reported height and weight to calculate BMI and self-reported physician-diagnosed asthma after 4 years of follow-up as the outcome. A risk ratio for asthma of 1.6 was seen for women with a BMI over 25 and 2.7 for those with a BMI over 30.[66]

Since these early reports, further studies have been done, which have been extensively reviewed.[4, 5, 67] At least 30 cross-sectional and 13 prospective studies were reported between 1999 and 2006, with nearly all of them showing a positive association between obesity and asthma.[5] In a 2003 study Chen et al. found obesity (BMI ≥ 30) to be associated with diagnosed asthma among Canadian women, but not men.[68] Guerra et al. found a relationship for both men and women in the U.S.[69] In a follow-up study of NHANES I, a moderately increased risk for the development of asthma was found for adults obese at baseline.[70]

The scientific community is generally in agreement that there is a strong association between obesity and asthma in adults.[4] Prospective studies suggest that obesity precedes asthma development, providing support for the idea that obesity may be causally related to asthma.

Evidence has been more inconsistent for children, hampered in part by different age ranges being examined, differing definitions of overweight and obesity, and different morbidity endpoints being used. The differing age ranges included can affect the likelihood of a child having previously received an asthma diagnosis. Chinn and Rona found that 5-6 year-old obese children in the U.K. had an increased risk of developing asthma over 4 years of follow-up.[71] Gilliland et al. found a significant relationship between overweight and asthma among boys, but not girls,[72] while Gold et al. found a relationship only among girls.[73] Castro-Rodriguez et al. reported from the Tucson Chidren's Respiratory Study that obesity among girls at age 11 was associated with frequent wheeze at age 13.[74] No associations were seen among boys or for overweight at age 6 with later asthma. While this study has a relatively large sample size (N=448) there is a fairly low prevalence of asthma (~10%), leading to wide confidence intervals, particularly as the analyses are stratified by sex. The OR for frequent wheeze at age 13 among girls who became overweight or obese during puberty (changed categories between age 6 and 11) was 4.8 with a 95% CI of 1.2-18.8.

An interesting meta-analysis of longitudinal studies examining the effect of high weight in childhood on the subsequent development of asthma found that in early studies (published before 2000) overweight was associated with a *decreased* risk of asthma, whereas all studies published since 2001 showed a statistically significant *increased* risk of asthma among heavier children, and that the strength of the relationship appeared to increase over time. This meta-analysis concluded that high body weight in middle childhood resulted in a relative risk of 1.5 for subsequent asthma and a 6.6% population attributable risk for asthma due to overweight.[75]

B.2. Gender Differences

Many, though not all, of the studies have examined the obesity/asthma relationship separately for males and females. Most of these have found greater effects in females,

though a significant gender interaction effect did not always exist. Only 3 cross-sectional studies found greater effects in males.[70, 72, 76]

One possible reason for these differences is that the most commonly used measure of obesity or overweight, BMI, is not a direct measure of adiposity. As an index of obesity, it may perform better for one sex than for another. A male at the same BMI as a female, even at a BMI of 30 which indicates obesity, may have more muscle mass and less body fat.[5] In children, differences in the age in which peak lung growth and puberty occur (earlier for girls) may also influence these findings of gender differences.[73]

There is additionally some evidence that these gender differences could be related to female hormones. Castro-Rodriquez et al. found the strongest effects of obesity on asthma among girls that started puberty before age 11, compared to those with later pubertal development (definition of "puberty" not given by the authors),[74] and Varraso et al. found that BMI was more strongly related to asthma severity among girls with early menarche.[77] Nevertheless Chinn states in 2006 that the weight of the evidence does not support gender differences in children or adolescents.[67]

B.3. Possible Biological Mechanisms

The first studies to note a relationship between obesity and asthma were cross-sectional and thus unable to address the question of the direction of causality. It does seem plausible that asthma symptoms might lead adults and children to be less physically active, which could lead to weight gain. However, all of the 13 prospective studies were able to show that obesity preceded asthma, thus discounting this premise.[5] Mechanisms that have been proposed to explain the relationship between obesity and the development of asthma include airway inflammation, mechanical factors, decreased physical activity, and changes in diet.

B.3.1. Systemic Inflammation and Airway Inflammation

Obesity is a chronic inflammatory state characterized by increased levels of inflammatory cytokines and other markers, such as leptin and C-reactive protein.[78, 79] High leptin levels are associated with increased body fat mass.[80, 81] Leptin also stimulates the release of the pro-inflammatory cytokines IL-6 and TNF-alpha[82, 83] and also the Th1 cytokine, IFN-gamma [84]. Obesity is therefore categorized as an inflammatory state,[85] and obesity seems to be driving inflammation that is associated with other inflammatory diseases such as cardiovascular disease.[86] Because asthma is also characterized as an inflammatory disease, [87] many researchers feel that leptin may be the mediating mechanism between obesity and asthma, or may be a proximate determinant of both.[78, 88] Additionally, Matsuda et al. found an association between leptin and another appetite-modulating hormone, ghrelin, and total IgE levels, indicating a link between obesity-related inflammation and allergy.[88]

Hancox et al. found significantly reduced lung function (FEV1) to be associated with elevated C-reactive protein levels,[89] indicating systemic inflammation, and C-reactive protein has also been shown to be related to obesity in children.[90] Still in the Hancox study, the relationship between inflammation and lung function was not mediated by smoking, asthma, or obesity. Conversely, Ford et al. found that BMI significantly attenuated the odds ratio for elevated CRP in asthmatic U.S. adults.[91] Similarly, Butland et al. examined the effect of CRP levels on asthma and found that CRP was related to asthma only among non-atopics, and that the association became non-significant when controlling for BMI, suggesting that CRP may be on the causal pathway between obesity and asthma.[92]

Additionally, inflammation specific to the airway has not been demonstrated to be higher in obese individuals. Four published studies in children that examined the relationship between BMI and exhaled nitric oxide (eNO), a marker of airway inflammation, did not find an association.[93-96] Unpublished analyses in inner-city children age12-20 also did not show a

relationship between BMI and eNO (Kattan, personal communication). In a recent study of patients age 15-73, there was a negative association between BMI and eNO.[97] Using bioelectrical impedance to measure the percentage of body fat, McLachlan et al. found that while body fat was associated with asthma in women (but not men), this was not mediated by airway inflammation as indicated by eNO measurements.[98]

There was also no association seen in a recent study between BMI and airway inflammation as measured by sputum cell counts.[99] Assuming these markers are good surrogates for airway inflammation, as is claimed, there is no convincing evidence that systemic inflammation due to obesity (as measured by leptin and C-reactive protein) results in airway inflammation.

B.3.2. Mechanical Factors

A high percentage of body fat seems to be related to decreased ventilatory function.[100, 101] Shortness of breath can result from excess weight compressing the chest wall.[102] Obesity has also been shown to be related to reduced lung volumes in adults[103] and with lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in children.[100]

The tidal action of breathing is different for obese individuals, who breathe faster but with smaller tidal volumes compared to lean individuals.[104] This can result in a compromised bronchodilating mechanism and can lead to increased airway hyper-responsiveness.

Airway size has been shown to be related to asthma. Babies born prematurely have smaller airways which can result in a type of pediatric asthma that is often outgrown as the children get older. Boys, who are more likely to have asthma in childhood than girls, are also more likely to outgrow their asthma during puberty, as their airway caliber gets larger.[105]

B.3.3. Physical Activity

For those with asthma, exercise can bring on bronchospasm. Obese individuals may also become breathless during vigorous physical exertion. A low level of physical activity is

likely to be associated with weight gain or overweight, and children with asthma were found to have lower levels of physical activity, measured using an "Actiwatch".[106] Epstein et al. found that asthma and physical activity level were independently related to obesity in an analysis of NHANES III data.[107] A number of prospective studies have found that BMI was associated with an increased risk of asthma even when controlling for the level of physical activity.[66, 108, 109]

In addition, reduced physical activity, whether as a cause or effect of obesity, may result in a reduction of deep spontaneous breathing. Normal breathing forces the extension of airway smooth muscle and has a strong bronchodilatory mechanism.[110] The shallower breaths taken by obese individuals due to the mechanical factors detailed above, may hinder this process, which could lead to increased airway hyper-responsiveness.[111]

Several prospective interventions have shown improvements in lung function among asthmatic patients enrolled in exercise programs.[112-114] However, it was reported in an analysis of NHANES III survey data that time spent exercising or watching TV was not related to asthma.[115] To date, there has only been one prospective study of the effect of physical activity on the development of asthma. Rasmussen et al. showed that low physical fitness at age 9 was significantly associated with the development of asthma in adolescence.[116]

Physical activity is difficult to measure, especially in children and especially over time, which is likely why it has not been researched more fully. Lucas and Platts-Mills suggest that physical activity may emerge as a stronger determinant of asthma when better monitoring techniques are developed and used.[111]

B.3.4. Diet

Dietary studies are notoriously difficult and, while diet is clearly closely associated to weight, little research has been done on the relationship between diet and asthma. Most of this research has focused on early life intake of (or prenatal exposure to) certain nutrients

and their effect on allergic disease. For example, recent studies in two different populations, one in Boston[117] and one in Scotland[118] found that higher maternal intake of Vitamin D during pregnancy is associated with a decreased risk for wheezing illnesses in early childhood. In an interesting twist, an examination of vitamin supplementation in Swedish newborns found that infants given vitamins A and D in water-soluble form were twice as likely to develop asthma and allergies than infants given vitamins in peanut oil.[119] While it is not entirely clear whether the vitamins are responsible for the effect, or the method of delivery of the vitamins, some researchers are convinced that vitamin supplementation has the potential to significantly reduce the incidence of asthma.[120, 121]

Dietary antioxidants have also been examined for their effect on allergic disease. Seaton et al. found that low intake of vitamins E and C were both risk factors for wheezy illness in adults.[122] In young children, Martindale et al. report that maternal vitamin E intake during pregnancy was associated with less wheeze in the child's second year of life, but that vitamin C intake was associated with a higher incidence of "ever wheeze" and with eczema.[123] Litonjua et al. found higher levels of maternal intake of vitamin E and zinc during pregnancy to be associated with a lower risk for wheeze in the first 2 years.[124]

Intake of omega-3 polyunsaturated fatty acids have also been hypothesized to be related to allergic disease development in early childhood.[125] A fish oil supplementation intervention in infants showed a reduction in wheeze at age 18 months, but no difference in IgE levels.[126] Another study providing fish oil supplements to pregnant women found a significant difference in neonatal Th2 cytokine production between the intervention and control groups, including lower levels of IL-13 in cord blood. Also, infants in the supplementation group were less likely to be sensitized to egg at one year of age.[127] However, in an observational analysis of data from the Childhood Asthma Prevention Study, plasma levels of omega-3 and omega-6 fatty acids, measured at 18 months, 3 years, and 5 years, were not associated with wheeze, eczema, or atopy at 5 years of age.[128]

In addition to specific components of diet, some research has shown total energy intake to be related to asthmatic symptoms. A study of alternate day calorie restriction was successful in improving asthma symptoms and pulmonary function among 9 overweight asthma patients. Markers of oxidative stress and inflammation were also decreased.[129] The patients also lost weight. These results, and those of others who have shown improvement in asthma after bariatric surgery,[130-132] suggest that dietary interventions may have a beneficial effect on overweight individuals with asthma, but do not explain whether high-calorie diets are associated with asthma in the population in general.

Total calorie intake can be considered to be on the causal pathway to obesity. In order to confound the relationship between obesity and asthma, total calorie intake would have to have a direct effect on asthma, independent of resultant weight and obesity-induced inflammation. If a specific component of diet, such as fatty acids, anti-oxidants, or vitamins were to act as a confounder, those would need to be independently associated with obesity. Some recent studies suggest that this might be the case, at least for vitamin D. Obese individuals have been shown to have vitamin D deficiency not explained by calcium/vitamin D intake or sunlight exposure,[133] and pre-pregnancy obesity has been found to be associated with lower vitamin D levels in pregnant mothers and neonates.[134] Vitamin D levels have also been shown to be low in obese children and adolescents.[135]

B.3.5. Infant Feeding

One major exception to the paucity of research on dietary influences, is the examination the relationship of infant feeding method to both obesity and to allergic disease and asthma. Copious research has been done in both areas, especially the latter, with the general consensus being that breastfeeding is protective against both obesity and against asthma and atopy.

A large survey of more than 15,000 children in the Growing Up Today Study concluded that children who were fed exclusively or mostly breastmilk during the first 6

months of life were less likely to be overweight (≥95th percentile of BMI for age) at age 9 to 14 (OR=0.78, 95% CI: 0.66, 0.91).[136] These findings were adjusted for current energy intake, time watching television, physical activity, mother's BMI, age, sex and sexual maturity. An analysis of NHANES III data found a reduced risk of being at risk for overweight (≥85th percentile of BMI for age) at age 5 for children who were ever breastfed compared to those not breastfed (OR=0.63, 95% CI: 0.41, 0.96), but no significant risk of being overweight (≥95th percentile).[137] The authors found that the strongest predictor of a child's overweight status was the mother's weight, and suggest that current diet and lifestyles factors are more important than breastfeeding in preventing childhood overweight.

Much research has been done over the past several decades on the effect of breastfeeding on allergic diseases and asthma, and much of it has shown that breastfeeding reduces the risk of developing asthma or allergic disease.[138] However, conflicting findings have also been reported.[139, 140] The general consensus in the medical community is that breastfeeding reduces the risk of allergic disease, and some have put forth breastfeeding promotion as a method of primary prevention for asthma.[141, 142]

Findings regarding the effect of breastfeeding on allergies and asthma are sometimes different depending on the mother's asthma or allergy status. A study in Sweden found that breastfeeding (for 3-4 months or 5 or more months) was protective against asthma (at 4 years of age) among all mothers, and among those without asthma themselves, but that it was *not* protective among asthmatic mothers (OR 1.04, 95% CI: 0.35-3.09).[142] Another study from the Netherlands found that breastfeeding duration was associated with a reduced risk of recurrent wheeze independent of maternal asthma or allergy, but was associated with a lower risk of eczema during the first 2 years of life only among children whose mothers did not have allergies or asthma.[143] A recent analysis of a large birth cohort with objective outcomes for atopy and bronchial hyperresponsiveness found that breastfeeding was protective against wheeze in early childhood, but the

protective effect was not evident against atopy or asthma in older children.[144] This study also found that maternal allergy was an important confounder of the relationship between breastfeeding and atopy.

A recent review summarized literature from 1966-2001 on the effect of infant feeding on “later atopic manifestations” and concluded that the weight of the evidence suggests breastfeeding reduces the risk of atopic disease.[138] In contrast to the report above, they also reported that this association may be stronger among children with atopic heredity.

Two research studies have looked specifically at the interaction of overweight and breastfeeding to the development of asthma. In a nested case-control study, Mai et al. found an increased risk of asthma among children with a short duration of exclusive breastfeeding (< 12 weeks) who were also overweight (BMI ≥ 85th percentile for age and sex) at age 8 to 10 years. Neither of these exposures was associated with asthma in the absence of the other.[145] In this nested cast-control study, all respondents to a survey on child health who reported asthma were compared to a randomly selected group of respondents without asthma. The children were subsequently examined by a physician to confirm asthma and to measure height and weight. Breastfeeding information was collected by questionnaire. Skin prick testing for allergy was done, and a stronger effect of breastfeeding and overweight was found for atopic asthma than for non-atopic asthma. This analysis was somewhat unusual though, in that both the atopic asthmatics and non-atopic asthmatics were compared to the same reference group of non-asthmatics.[145]

In a birth cohort study, Oddy et al. determined that there was no interaction, and the duration of exclusive breastfeeding and BMI (≥85th percentile) were independent predictors of the development of asthma in 2,195 Australian children by age 6 years.[146] This analysis used a propensity score for BMI to adjust for confounding and fractional polynomials to allow curves to be fit for the separate effects of BMI and duration of breastfeeding. This

sophisticated analysis controlled each variable for the other in separate models, but the interaction effect between BMI and breastfeeding was not examined.[146]

Clearly, there are complex relationships between maternal diet during the prenatal period, breastfeeding, later diet, weight, and allergy that have an impact on the development of asthma.

B.4. Allergic vs. non-allergic asthma

It remains unclear through what sort of mechanism obesity and asthma may be related. As noted above, both asthma and obesity are associated with inflammation, as indicated by higher levels of serum leptin[78, 147] and CRP.[79, 90] Inflammation due to obesity may be a factor in the development of asthma.

The relationship between obesity and atopy has been less often examined, but a few studies have shown obesity to be related to allergy or higher IgE levels,[10-12] while others have not.[13-15] Asthma is often considered to be an allergic disease, and while there is certainly a large allergic component to asthma, recent research estimates that only about 50% of asthma in the U.S. is attributable to atopy.[16]

Two recent studies in adults have examined exactly the question of whether obesity is more strongly related to non-atopic than to atopic asthma. In an Australian study of 4,060 men and women, an increased risk for asthma was found for those with central obesity (measured by waist circumference and waist/hip ratio) who were non-atopic.[148] In a cross-sectional survey of more than 86,000 Canadian adults, BMI was associated with asthma in both allergic and non-allergic women, but the odds ratio was stronger in non-allergic women (1.85 vs. 1.21).[15] In men, the corresponding odds ratios were 1.30 and 1.18, with only the relationship in non-allergic men being significant. The authors note that women have a greater prevalence of non-allergic asthma than men (at least in this Canadian population) and that this may account for the stronger obesity-asthma relationship seen in many studies.

In a study using NHANES III data, both the prevalence of asthma and of atopy rose significantly with increasing quartiles of BMI among children age 4-17. Atopy in this study was defined as being a positive response to at least one allergen measured using skin prick testing. After adjustment for confounding, however, only the relationship with asthma remained significant. BMI was also not related to serum eosinophil counts, a marker for allergy.[115] The effects were not modified by sex or ethnic group. The authors propose that the obesity effect on asthma is mediated by mechanical properties associated with obesity or with systemic inflammation rather than by allergic inflammation.

Chapter III. Research Aims and Hypothesis

Heavier individuals seem more likely to have asthma, prospective studies suggest that overweight and obesity precede the development of asthma, gender differences have been observed for the relationship between obesity and asthma (usually, but not always, being found to be stronger for women than for men), and it is not known what sort of mechanism drives the relationship between obesity and asthma (though speculation leans toward an inflammatory mechanism rather than an allergic one).

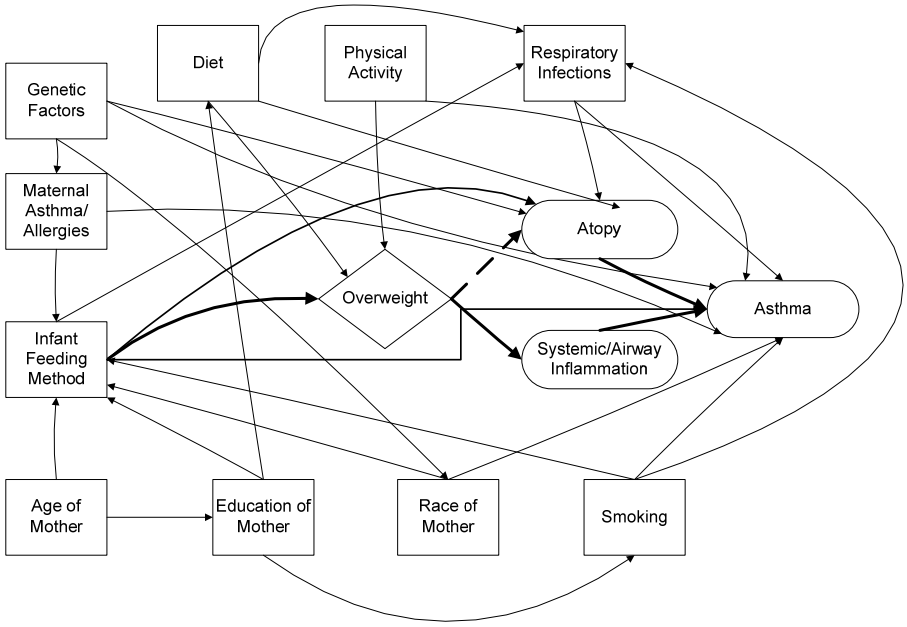
Although a lot of work has previously been done in this area, there are still some unanswered questions. Perhaps the most important is whether obesity is related to atopy/allergy or operates through an entirely different inflammatory pathway to influence the development of asthma. Because the recent allergy module of the NHANES contains a large IgE panel, including total IgE, for a large number of children it provides a new and exciting opportunity to examine exactly this question.

Many previous studies, including previous work in NHANES[6, 115] have defined atopy based on skin prick tests. This evaluation is always limited by the number of tests performed. NHANES III performed skin prick tests for 10 allergens. The allergens chosen (*Alternaria*, rye grass, ragweed, Russian thistle, white oak, cat, German cockroach, dust mites, and peanuts) reflect some of the most common allergies in the U.S., but certainly some participants could have been allergic to something that was not tested. Specific IgE levels have this same limitation, but total IgE provides a measure of the complete allergic propensity of the individual.

In addition, NHANES III only skin tested children age 6 and above, whereas NHANES 2005-2006 has IgE levels for children starting at age 1. This will allow examination of effects at younger ages, and also allow for an examination of any modification of the effect of overweight on atopy by infant feeding.

In the causal diagram in Figure 2, I suggest that overweight can operate through two different pathways in its effect on asthma -- one pathway via inflammation and the other via atopy. This arrow for atopy is drawn with a dashed line because it is unclear whether this effect exists. Infant feeding method, diet in general, and physical activity are shown to be influencing overweight status. Socio-demographic factors, such as the age, education, and race of the mother are shown to be influencing infant feeding method. The mother's asthma/allergy status is also shown to be a factor in the infant feeding decision. Smoking is shown to be related to infant feeding and to respiratory infections, and also to have a direct effect on asthma. Genetic factors influence the mother's asthma/allergy status, and are also shown to have a direct effect on asthma and atopy in the child. Diet is theorized to have a direct effect on atopy, but only through this indirect pathway on asthma; while physical activity is theorized to have an effect on asthma, but not atopy. Infant feeding is shown to have an effect on asthma through the atopic pathway, and also shown to be mediated by respiratory infections. Respiratory infections can lead to atopy by affecting immune system experience and function, and can directly cause asthma through insult to the child's developing lungs.

Figure 2. Causal Diagram: The Effect of Childhood Overweight on the Development of Atopy and Asthma



The recent allergy module of the 2005-2006 NHANES contains allergy symptom measures and IgE levels for 3,387 children and young adults age 2 to 19. This large dataset of serum allergy markers is the largest ever collected on children. These data provide an excellent opportunity to look for evidence that overweight in children is related to allergy. The present analysis examines the effect of childhood overweight on allergy and asthma using data from the United States National Health and Nutrition and Examination Survey.

This project will examine the relationship between obesity/overweight and asthma and allergy in U.S. children ages 2-19 using data from the National Health and Nutrition Examination Survey (NHANES). The specific aims are:

1. To determine if there is a relationship between overweight and total and specific IgE levels and allergic symptom outcomes among U.S. children ages 2-19.
2. To examine the effect of overweight on asthma outcomes among children 2-19 in a nationally representative sample of U.S. children from 1999-2006, and to use the 2005-2006 data to examine the hypothesis that the effect of overweight on asthma is different depending on whether the child also is atopic.

3. To examine whether the relationship between overweight and asthma is modified by infant feeding method or by atopy.
4.

Chapter IV. Methods

A. The National Health and Nutrition and Examination Survey

These questions were explored using data from the US National Health and Nutrition Examination Survey (NHANES) collected from 1999 through 2006. The NHANES is a nationally representative survey conducted periodically in the United States, and the resulting data are publicly available. The first NHANES was conducted in 1971-1975. NHANES II and NHANES III were conducted in 1976-1980 and 1988-1994, respectively, with each round becoming progressively more comprehensive. Since 1999, NHANES has taken a somewhat different approach, with smaller numbers of persons surveyed in two-year cycles, but maintaining general consistency in data collection across cycles, so that datasets can be combined to explore many questions. In these recent surveys, all data is collected directly into electronic media, decreasing the amount of time needed to release the cleaned datasets to the public. The primary objectives of NHANES are to estimate the national prevalence of certain diseases and their risk factors, and to monitor changes in these over time. There is a special emphasis on the health effects of diet and nutrition.

B. Study Population

The target population of NHANES is the civilian, non-institutionalized population of the US. Each survey round has typically oversampled persons believed to be at increased health risk – low-income persons, adolescents age 12-19, persons age 60+, African Americans and Mexican Americans. Weights are supplied with the public use dataset so that estimates can be produced that reflect the US population distribution and can be

considered to be nationally representative. Table 1 shows the population age 2-19 by age group, race/ethnicity, and survey round that completed the medical examination.

Table 1. Distribution of NHANES 1999-2006 sample of persons age 2-19 who attended the medical examination.

	Age Group				Total
1999-2000	2-5	6-10	11-14	15-19	
Mexican American	275	355	478	601	1709
Other Hispanic	45	44	48	68	205
Non-Hispanic White	206	193	230	278	907
Non-Hispanic Black	203	258	330	362	1153
Other/Multiracial	39	29	34	67	169
Total	768	879	1120	1376	4143
2001-2002					
Mexican American	254	277	338	472	1341
Other Hispanic	60	44	47	72	223
Non-Hispanic White	314	292	335	443	1384
Non-Hispanic Black	270	334	376	442	1422
Other/Multiracial	53	46	42	60	201
Total	951	993	1138	1489	4571
2003-2004					
Mexican American	242	247	312	422	1223
Other Hispanic	44	24	34	41	143
Non-Hispanic White	259	218	264	391	1132
Non-Hispanic Black	266	296	361	499	1422
Other/Multiracial	54	47	46	38	185
Total	865	832	1017	1391	4105
2005-2006					
Mexican American	356	315	328	449	1448
Other Hispanic	54	27	25	40	146
Non-Hispanic White	271	256	231	372	1130
Non-Hispanic Black	268	265	338	481	1352
Other/Multiracial	59	70	51	65	245
Total	1008	933	973	1407	4321

The NHANES uses a stratified, multi-stage probability sampling design. The stages of sampling are 1) Primary Sampling Unit (PSU) which is usually a county or block of

contiguous (low-population) counties; 2) segments within PSUs (blocks or clusters of households); 3) households within segments; 4) one or more participants within households. Eligible persons age 16 or over are interviewed directly, while interviews for those under 16 are done with a proxy. All persons who complete the household interview are invited to participate in the Medical Examination component of NHANES. Most of the health examinations are conducted in mobile examination centers – trailers outfitted with all the necessary examination equipment. Over the 4 rounds of NHANES from 1999-2006, 17,140 children and adolescents age 2-19 completed both the interview portion of the survey and the physical examination.

All of the NHANES data that is not collected at the medical examination is collected by questionnaire. For children under age 16, the questionnaire information is collected from a proxy respondent, typically a parent. The medical examination data includes anthropometric measurements, a DXA scan, and laboratory data from assays done on blood drawn at the visit. Other medical information, including medical histories and symptom information are collected during an interview.

Specific questionnaires and medical components of the NHANES vary by age and survey round. Data availability for the three main components of these analyses are listed below. Details regarding the variables used are available in Table 2.

C. Data Availability

C.1. Asthma Outcomes

All participants, one year of age or older, in all cycles, were administered the Medical Conditions questionnaire which asks if the sample person has ever been told by a health professional that they have asthma. For those with such doctor-diagnosed asthma, there is further information on age (in years) of diagnosis of asthma, current asthma, experience of

asthma attacks in the past 12 months, and emergency room visits for asthma in the past 12 months.

The Respiratory Health and Disease questionnaire collects information on all participants over age 1 on wheezing symptoms and health care and medication use for wheezing attacks. Sample persons age 6 and over are asked how much time they missed from work or school due to wheezing.

C.2. Allergy Outcomes

The questionnaire that was added to the NHANES for Allergic Diseases Module in the 2005-2006 cycle asks about previous diagnoses of hay fever, eczema, and allergies. For those reporting a diagnosis, further questions are asked regarding age at diagnosis and occurrence of symptoms over the past year. This analysis uses current symptoms – those occurring in the previous 12 months.

Participants aged 1 year and older were eligible for total and allergen-specific serum IgE testing. Blood samples were drawn and processed in the Mobile Examination Center and shipped to a laboratory where they were analyzed for total and allergen-specific IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). A detailed description of the laboratory method can be found at NHANES 2005-2006 web page (http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/al_ige_d.pdf). Total IgE is available for 3,482 (81%) of the children age 2-19. Because smaller quantities of serum were available for young children, the number and type of allergen-specific IgE tests performed varied by age. Children aged 1 to 5 years were tested for total IgE as well as specific IgE to dust mite (*D. farinae* and *D. pteronyssinus*), cat, dog, cockroach, alternaria, peanut, egg, and milk. Sample persons age 6 and above also have specific IgE measurements for ragweed, ryegrass, bermuda, white oak, birch, shellfish, aspergillus, thistle, mouse, and rat.

Atopy has been defined as the genetic propensity to develop immunoglobulin E (IgE) antibodies in response to exposure to allergen;[149] allergic hypersensitivity that affects different parts of the body that do not come in contact with allergens, substances that trigger the body's allergic reaction;[150] and a genetic predisposition toward the development of immediate hypersensitivity reactions against common environmental antigens, most commonly manifested as allergic rhinitis but also as bronchial asthma, atopic dermatitis, or food allergy.[151] The common features of these definitions are 1) production of IgE antibodies, and 2) that the IgE is produced in response to an allergen. Following these definitions, atopy has been defined in these analyses as a positive response (≥ 0.35 kU/L) to at least one of the allergens tested. In order to be included in the analyses for atopy, the individual had to have information for the full panel of allergens (9 allergens for those under age 6, and 19 for those age 6-19). Atopy information is available for 3,387 children (82%) in this age range.

C.3. Weight and Body Measurements

All participants who attended the medical examination had their weight and height measured, which is then used to calculate Body Mass Index (BMI) as weight in kilograms divided by height in meters squared.

In adults, a person with a BMI over 25 is considered overweight and a person with a BMI over 30 is considered obese. These values cannot be used to characterize overweight in children however, as normal BMI values are generally much lower and change with age. The BMI curve typically follows a J-shape, hitting a low point at around 5 or 6 years of age and then steadily increasing until children attain their adult height. This change in BMI in children is termed the “adiposity rebound.”[152] Thus, in children BMI is typically compared to normal curves (stratified by sex) and calculated as a percentile for age. Previous rounds of NHANES, combined with other datasets, have been used to create growth curves for US

children age 2-20, and the CDC recommends using the percentile of BMI for age to characterize overweight in children.[153] Children at the 85th percentile of BMI for age are considered overweight and those at or above the 95th percentile are considered obese.[154]

C.4. Infant feeding

Infant feeding information was collected in the NHANES for all children age 6 and under at the time of the survey. All of the infant feeding data is collected by self-report. The proxy respondent, typically the mother, is asked whether the child was ever breastfed or fed breastmilk, and if so, when other foods or liquids (other than water) were introduced and when breastfeeding stopped completely. Although self-report data, potentially looking back over 5 years, for breastfeeding history are not ideal, self-report has been shown to be a valid and reliable estimate for breastfeeding initiation and duration.[155] The reliability of recall regarding exclusivity of breastfeeding has been shown to be less satisfactory.[156]

C.5. Potential confounders and other variables

The potential for confounding was examined for sex, race/ethnicity, age of the child, household income and, where possible, education of the family head (this variable is only available in 2005-2006 data). In analyses using several rounds of NHANES data, survey round was also adjusted.

Birthweight was also considered as a potential modifier and as a confounder, as lower birthweight has been shown to be associated with higher percent body fat in childhood[157] and with childhood asthma.[158] As the risk of low birthweight on asthma may be due to early insults to the developing lung subsequent to prematurity, effect measure modification was examined first. No effect measure modification was observed, so low birthweight children were retained in the analyses and birthweight was considered as a confounder only.

Two other potentially important confounders for which there is data in the NHANES are diet and physical activity. Both are obviously highly associated with weight. For all children ages 2-19 (only up to age 15 in 1999-2002) there are questions regarding the number of hours spent watching TV/videos and spent on the computer. These were examined as confounders. In addition, there is a question asking how many times per week the child engages in vigorous physical activity. For children ages 12-15 there are more detailed questions about the types of physical activity they participate in, such as sports or running, bicycling, playing Frisbee, and long list of other activities. For this analysis, the number of times vigorous activities were reported were summed and recalculated as a weekly rather than a monthly total to make this information comparable to that for the younger children.

Lastly, NHANES laboratory files do not contain information about serum leptin; however, serum levels of C-reactive protein, another inflammatory marker, are available. If asthma is related to obesity through an inflammatory pathway, C-reactive protein may be on the causal pathway between obesity and asthma, or it may be a marker for systemic inflammation that is part of the causal pathway. This may be best tested in this cross-sectional data by examining whether BMI confounds the relationship of CRP to atopy and asthma.

Table 2. NHANES variables for the examination of obesity and asthma/allergy.

Variable	Source	Details	Coding	Available in Years	Available for Age
Exposure Variables					
Body Mass Index	Medical Exam – measured weight and height	Weight/Height^2	Dichotomized as <>95th percentile for age and sex; Also continuous z-score	1999-2006	Measurements for all ages 2+ months. BMI z-scores for age 2-20.
Outcome Variables					
Current asthma	Survey	Do you still have asthma? (Only asked when affirmative answer to ever having a diagnosis of asthma)	Dichotomous	1999-2006	Age 1+
Asthma attack	Survey	During the past 12 months, have you had an episode of asthma or an asthma attack?	Dichotomous	1999-2006	Age 1+
ED visit for asthma	Survey	During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?	Dichotomous	1999-2006	Age 1+
Wheeze	Survey	In the past 12 months have you had wheezing or whistling in your chest?	Dichotomous	1999-2006	Age 1+
Medical visits for wheezing	Survey	In the past 12 months how many times have you gone to the doctor's office or the hospital emergency room for one or more of these attacks of wheezing or whistling?	Dichotomized to any vs. none	1999-2006	Age 1+
Missed school or work due to wheezing	Survey	During the past 12 months, how many days of work or school did you miss due to wheezing or whistling?	Dichotomized to any vs. none	1999-2006	Age 6-69

Allergy symptoms	Survey	During the past 12 months, have you had any allergy symptoms or an allergy attack?	Dichotomous	2005-2006	Age 1+
Hay fever symptoms	Survey	During the past 12 months have you had an episode of hay fever?	Dichotomous	2005-2006	Age 1+
Eczema	Survey	During the past 12 months have you had an episode of eczema?	Dichotomous	2005-2006	Age 1+
Total IgE	Laboratory		Dichotomized <>100 kU/L	2005-2006	Age 1+
Specific IgE	Laboratory	*D. farinae* (dust mite)	Dichotomized <>0.35 kU/L for each allergen Also as yes/no vars: Pos response to any allergen Pos response to any indoor allergen Pos response to any outdoor allergen Pos response to any food allergen	2005-2006	Age 1+
		D. pteronyssinus (dust mite)			"
		Cat			"
		Dog			"
		Cockroach			"
		Alternaria (mold)			"
		Peanut			"
		Egg			"
		Milk			"
		Ragweed			Age 6+
		Ryegrass			"
		Bermuda			"
		White oak			"
		Birch			"
		Shellfish			"
		Aspergillus (mold)			"
		Thistle			"
		Mouse			"
		Rat			"
Potential Modifiers and Confounders					
Ever breastfed	Survey	Was [child] ever fed breastmilk?	Dichotomous	1999-2006	Age 0-6
Duration of	Survey	How old was [child] when	Dichotomized to <> 4	1999-2006	Age 0-6

exclusive breastfeeding		he/she was first fed something other than breastmilk or water?	months		
Duration of any breastfeeding	Survey	How old was [child] when he/she completely stopped breastfeeding or being fed breastmilk?	Dichotomized to <> 4 months	1999-2006	Age 0-6
Race/ethnicity	Survey	Recoded by NHANES: Non-hispanic white Non-hispanic black Mexican American Other Hispanic Other, including multi-racial	Categorical	1999-2006	All ages
Household income	Survey	Reported as a range value in dollars; recoded by NHANES	Categorical	1999-2006	All ages
Poverty Income Ratio	Survey	Recoded income based on household size and the corresponding poverty threshold	Continuous Range: 0-5	1999-2006	All ages
Education of household head	Survey	What is the highest grade or level of school you completed or the highest degree you have received?	Categorical: Less than HS HS, incl. GED More than HS	2005-2006	All ages
Birthweight	Survey	How much did [child] weigh at birth?	Continuous	1999-2006	Age 0-15
Low birthweight	Survey	Did [child] weigh more than 5.5 lbs or less than 5.5 lbs? (asked of those who could not provide an actual weight)	Dichotomous	1999-2006	Age 0-15
Household smoking	Survey	Does anyone who lives here smoke cigarettes, cigars, or pipes anywhere inside this home?	Dichotomous	1999-2006	All ages
ETS exposure	Laboratory	Serum cotinine	Continuous or dichotomize <> 30	1999-2006	Age 3+

Physical activity	Survey	Over the past 30 days, on average how many hours per day did you sit and watch TV or videos?	Categorical: None < 1 hour 1, 2, 3, 4, 5 hours or more	1999-2002 2003-2006	Age 2-15 Age 2+
Physical activity	Survey	Over the past 30 days, on average how many hours per day did you use a computer or play computer games?	Categorical: None < 1 hour 1, 2, 3, 4, 5 hours or more	1999-2002 2003-2006	Age 2-15 Age 2+
Physical activity	Survey	How many times per week do you play or exercise enough to make you sweat and breathe hard?	Continuous	1999-2006	Age 2+
Vitamin D	Laboratory		Continuous	2000-2002 2003-2006	Age 6+ Age 1+
Vitamin C	Laboratory		Continuous	2003-2006	Age 6+
Vitamin E	Laboratory		Continuous	1999-2002 2003-2006	Age 3+ Age 6+
Vitamin A	Laboratory		Continuous	1999-2002 2003-2006	Age 3+ Age 6+
Carotenoids	Laboratory		Continuous	1999-2002 2003-2006	Age 3+ Age 6+
C-reactive protein	Laboratory		Continuous	1999-2002 2003-2006	Age 3+ Age 1+

D. Statistical Methods and Data Analysis

D.1. Sample Size and Power

For Aim 1, which uses only the last round of the survey, there are 4,111 children age 2-19 normal weight or above with allergy symptom data. Assuming that even 1 in 6 children are overweight (remembering that national prevalence is now 19%[1]), and the baseline risk of atopy is 50%,[6] I have 99% power for overall analyses, and 96% power for analyses stratified by gender, to detect a risk ratio for overweight of 1.2. There are somewhat fewer observations for analysis of atopy (3,387), but there is still 92% power to detect a risk ratio of 1.2.

Aim 2 uses the entire database of children surveyed since 1999 (16,074 children age 2-19) to look at the effect of obesity on current asthma. Using the same assumption about obesity prevalence and assuming that the baseline risk for asthma is 8%,[159] I have 85% power to detect a risk ratio for overweight of 1.2 in overall analysis and 88% power to detect a risk ratio of 1.3 in analyses stratified by gender

The second part of Aim 2 stratifies the analysis above by atopy. Decomposing the tables in Arbes et al.[16] gives a risk for asthma of 7.5% among atopic individuals and of 2.5% among non-atopic individuals. Assuming that half of the 3,387 children are allergic and 1 in 6 are overweight, as above, I have 90% power to detect a risk ratio of 1.75 in the atopic children, but only 80% power to detect a risk ratio of 2.2 in the non-atopic children.

Aim 3 is underpowered, especially for the atopy outcome. But Aim 3 is a secondary aim, and is being examined to see if there is any signal that the effect of breastfeeding on asthma may be mediated by effects on obesity or atopy.

D.2. Overview of Analytic Approach

The analysis of the relationship between obesity and asthma has three pieces. The first piece of this analysis used only data from the recent 2005-2006 NHANES survey and examined the relationship between overweight and allergic outcomes, including total and specific IgE levels. Specific variables used for exposure and outcome are discussed below.

The second analysis began by using all four recent rounds of the NHANES survey (1999-2006) to look at the effect of overweight on report of current asthma. This analysis was then further refined to look at the effect of overweight on atopic vs. non-atopic asthma. Because this refinement required the IgE data, it again used only the 2005-2006 data.

The third analysis examined infant feeding and used a somewhat different sample – children age 1-6 – because infant feeding information is only available up to age 6. This analysis focused on the protective effects of breastfeeding against obesity, atopy, and asthma and effect measure modification of the obesity-asthma relationship by obesity and by atopy.

The NHANES sample was selected using a known sampling probability for each sample person. When the correct sample weights are applied, results can be considered to be representative of the U.S. population. In addition, the stratified, multi-stage probability sampling design requires special techniques or software to obtain correct variances and confidence intervals. All analyses were done with either SAS survey procedures or with SUDAAN, both of which can account for the survey design.

D.3. Detailed Statistical Methods

Aim 1: Overweight children age 2-19 are more likely than normal weight children to have total and specific IgE levels indicating atopy and are more likely to report allergy symptoms, hay fever and eczema.

Because underweight has been associated with increased risk for allergic disease,[160] we excluded 144 children who were less than the 5th percentile of BMI for their age and sex (3.4%). Of the 4,125 children and adolescents above this cut-off, 4,111 have data on allergy symptoms and 3,387 have data for atopy.

The effect of weight in two categories, overweight and obese, on total IgE was calculated as the ratio of the geometric means. Total IgE has a skewed distribution, so the variable was logged and the geometric means calculated. The geometric mean ratio is simply the difference on a log scale. In addition, the continuous dose response between BMI percentile-for-age and total IgE levels was examined. The effect of the weight categories on the prevalence odds of atopy was examined using logistic regression. Atopy was defined as a positive test (≥ 0.35 kU/L) to any of the allergens tested. In order to be included in the analyses for atopy, the individual had to have information for the full panel of allergens (9 allergens for those under age 6, and 19 for those age 6-19). In addition, dichotomous variables were defined for a) a positive test to any food allergen, b) a positive test to any inhalant allergen, c) a positive test to any perennial allergen, and d) a positive test to any seasonal allergen. Each allergen-specific IgE was also examined individually for its relationship to atopy.

Logistic regression was also used to look at the relationship of overweight and obese categories on allergic outcomes among the 4,111 children with symptom data. The primary outcome was the occurrence of allergy symptoms or attacks in the past year (yes/no). The occurrence of hay fever and eczema were also examined (also as yes/no variables).

<u>Aim 2; Hypothesis 1: Overweight children age 2-19 are more likely than normal weight children to have asthma.</u>

The effect of overweight and obesity on current asthma and the other outcomes, as defined above, was examined using a logistic regression model. Results are presented for 16,074 children for whom current asthma status is available in the complete 1999-2006 dataset. This analysis excluded 581 children (3.5%) that were less than the 5th percentile for their age and sex. The association of continuous BMI percentile-for-age with current asthma was also examined using logistic regression, with a 1-standard-deviation increase in the BMI z-score as the exposure. Results were plotted using a scatterplot smoothing technique.[161]

Potential modification of the effect of overweight on asthma was examined for sex and for age and race/ethnicity, separately for boys and girls. A p-value for the interaction term < 0.15 was considered evidence of interaction. No effect measure modification was observed for these factors.

Aim 2; Hypothesis 2: The effect of overweight on asthma among children age 2-19 is different depending on whether the child also is atopic.

Atopic asthma was defined as an affirmative report of current asthma in conjunction with atopy, defined as any positive allergen-specific IgE result. Non-atopic asthma was defined as an affirmative report of current asthma with no positive IgE tests. Effect modification was examined in a logistic regression model stratified by atopy for the 2005-2006 dataset (3,387 children with atopy information). A p-value < 0.15 was considered evidence of effect modification.

Aim 3. The relationship between breastfeeding and asthma is modified by overweight and/or atopy.

Breastfeeding may protect against overweight, atopy and asthma . These effects may be independent, or there may be a synergistic effect such that the effects of breastfeeding and overweight on asthma may be more than additive. This examination for

asthma was done on a subsample of the population, because breastfeeding information is only available for children up to age 6.

Because BMI percentile-for-age values begin at age 2, this analysis included examination of weight-for-length percentiles. Weight-for-length is recommended for assessing obesity in children under age 2 and in preschool children, with the 95% percentile being the criterion for obesity.[154] For 2-6 year-olds, both weight-for-length and BMI-for-age were calculated and the obesity classifications were compared for each year of age. For 2-year-olds there were more missing values for BMI-for-age than for weight-for-length, which is due to fewer 2-year-olds having their standing height measured. Thus, weight-for-length was used to determine obesity in the 1- and 2-year-olds, and BMI-for-age was used for the 3-6 year-olds.

In addition to categorizing children as having ever been breastfed (yes/no), the effects of exclusivity and duration of breastfeeding were also examined, dichotomized at 4 months in order to compare with previous NHANES work.[115]

D.4. Examination of Effect Measure Modification and Confounding

Gender differences are important in the literature on obesity and asthma. Thus, stratified models were run by sex for both the atopy and asthma outcomes. Except for total IgE, important effect modification was not seen, and therefore the stratified tables were presented in supplemental data, rather than in the main papers.

The second hypothesis of Aim 2 involved directly testing for evidence of effect measure modification. The question of interest is whether there is a true biological difference between two groups of children, e.g. atopic vs. non-atopic. Rothman suggests that such a biological effect is best tested as an additive interaction, rather than multiplicative.[162, p. 339] Although analyses for the published manuscripts included only an interaction term in the logistic model and testing for the significance of its estimate, I also performed a stratified

analysis to test the difference between effects using the interaction contrast ratio (ICR)[162, p. 339] specifically for separate and combined effects of atopy and obesity on current asthma. The ICR can be considered to be the "relative excess risk for interaction". If it is greater than 1, there is an effect on the outcome for both exposures considered simultaneously that is greater than the sum of the effect of each individual exposure.

Model covariates were selected by examining their univariate associations with the exposure and outcome variables. In addition, substantive knowledge and consideration of the conceptual diagram were used to select confounders. For models using the allergy outcomes, the selected confounders were age of the child, race/ethnicity, sex, the Poverty Income Ratio, and household smoking. The Poverty Income Ratio was chosen for use over the education of the household head because its associations were stronger, and only one SES confounder was considered necessary based on consideration of the conceptual framework. Household smoking was chosen over maternal smoking during pregnancy because information on smoking during pregnancy was only available for subjects up to age 15. Again, one smoking variable was considered sufficient. Results for simple age-adjusted and fully-adjusted models are shown.

The models using the asthma and wheeze outcomes used the same set of confounders with the addition of the level of vigorous physical activity and adjustment for survey round. The breastfeeding models were adjusted for age, sex, race/ethnicity, maternal smoking during pregnancy, low birthweight, poverty income ratio and survey round (except in models using the atopy variable).

Chapter V. Results

A. Manuscript 1: Association of Obesity with IgE and Allergy Symptoms in Children and Adolescents: Results from NHANES 2005-2006

A.1. Introduction

The adoposity of the U.S. population has been growing steadily. This is true both for adults and children, and it is also the case throughout the developed countries of the world. This increase has been most apparent since about 1980. Before that time, only about 5% of U.S. children age 6-11 were considered overweight; by 2004 that rate had climbed to nearly 19%.[1]

Allergic disease has also been on the rise in recent decades. In the U.S. from the period 1976-1980 to 1988-1994, the prevalence of skin test reactivity to 6 common allergens increased from 22% to 42%.[6] Increases in atopy have also been observed in the U.K. and Europe.[7-9]

Some researchers have shown obesity to be related to allergy symptoms or to higher serum IgE levels (a marker for atopy),[10-12] while others have not.[13-15] In an earlier study using NHANES III data, neither the prevalence of atopy (defined by skin test) nor serum eosinophil counts (another marker for allergy) were significantly related to increasing quartiles of body mass index (BMI) among children age 4-17 in adjusted models.[115] No IgE data were available in NHANES III.

Recent research suggests that systemic inflammation, as measured by C-reactive protein (CRP) levels, may be important in the relationship between obesity and asthma.[92] C-

reactive protein is a marker for systemic inflammation and is often very high in overweight individuals. Differences in CRP levels by atopic status have not been previously examined. If CRP is associated with atopy as well, that would suggest a common pathway for the effect of overweight on allergic disease and asthma.

This analysis explores the complex relationships between obesity, serum IgE, and allergy symptoms, and examines how CRP plays a role in these relationships, using data from the National Health and Nutrition Examination Survey (NHANES) 2005-2006.

A.2. Methods

A.2.1. Study Population

The NHANES is a nationally representative survey conducted periodically to assess the health and nutritional status of adults and children in the United States. The primary purpose of NHANES is to determine the prevalence of major diseases and risk factors for those diseases.[163] Details of the plan and operation of NHANES may be found online at http://www.cdc.gov/nchs/nhanes.htm. Written informed consent was obtained for all subjects.

The NHANES uses a stratified, multi-stage probability sampling design. The stages of sampling are 1) Primary Sampling Unit (PSU) which is usually a county or block of contiguous (low-population) counties; 2) segments within PSUs (blocks or clusters of households); 3) households within segments; 4) one or more participants within households. Eligible persons age 16 or older are interviewed directly, while interviews for those under age 16 are done with a proxy. All persons who complete the household interview are invited to participate in the Medical Examination component of NHANES.

The target population of NHANES is the civilian, non-institutionalized population of the U.S. The NHANES uses a stratified, multi-stage probability sampling design with oversampling of persons believed to be at increased health risk. Weights are supplied with

the public use dataset so that estimates can be produced that reflect the U.S. population distribution and can be considered to be nationally representative. In the 2005-2006 NHANES, 4,321 children age 2-19 completed both the interview and the medical examination components, and 4,269 children had their height and weight measured.

A.2.2 Allergy Outcomes

Allergy was determined in two ways: questionnaire about symptoms and serum IgE levels. The questionnaire that was added to NHANES in the 2005-2006 cycle asks individuals to report previous diagnoses of hay fever, eczema, and allergies. For those reporting a diagnosis, further questions are asked regarding age at diagnosis and occurrence of symptoms over the past year. This analysis uses current symptoms – those occurring in the previous 12 months.

Participants aged 1 year and older were tested for total and allergen-specific serum IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). A detailed description of the laboratory method can be found at NHANES 2005-2006 web page (http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/al_ige_d.pdf). Total IgE is available for 3,617 (84%) of the children age 2-19. Because smaller quantities of serum were available for young children, the number and type of allergen-specific IgE tests performed varied by age. Children age 1 to 5 were tested for total IgE and specific IgE to dust mite (*D. farinae* and *D. pteronyssinus*), cat, dog, cockroach, *Alternaria*, peanut, egg, and milk. Children and young adults age 6 and above also have specific IgE measurements for ragweed, ryegrass, bermuda, white oak, birch, shrimp, *Aspergillus*, thistle, mouse, and rat.

We definied atopy as a positive response (≥ 0.35 kU/L) to at least one of the allergens tested. Analysis of atopy included only individuals with information for the full panel of allergens (9 allergens for those under age 6, and 19 for those age 6-19). Of the

4,321 children with a physical exam, 703 (16.3%) did not have enough blood for specific IgE testing, and 100 (2.3%) did not have a full panel.

A.2.3. Weight Measurements

All participants who attended the medical examination had their weight and height measured following a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Sex-specific BMI percentile-for-age was calculated using the Centers for Disease Control and Prevention 2000 reference standards.[153] Children between the 5th and 85th percentile of BMI-for-age were considered to be normal weight, those between the 85th and 95th percentile were considered overweight, and those at or above the 95th percentile were considered obese, as recommended by the American Medical Association.[154]

A.2.4. Other Measures

The age, sex, and race/ethnicity of the child, as reported in the personal interview, were examined as potential confounders and effect modifiers. As measures of socio-economic status (SES), the highest education level obtained by the household reference person (typically the household head) and quartiles of the poverty income ratio (PIR) were also examined for their relationship to overweight and atopy. The PIR is the relationship of family income to the poverty threshold based on family size and composition.[164]

Other potential confounders considered were current household smoking (yes/no), maternal smoking during pregnancy (yes/no), birthweight (low birthweight vs. not), and several physical activity measures. All children were asked the average number of hours per day they spent either watching television or using a computer. For children age 2-11, the proxy respondent answered one question about how many times per week the child played or exercised enough to sweat or breathe hard. Children age 12-19 answered more detailed questions about the specific activities that qualified as moderate or vigorous activity and the number of times they did those activities in the past month. For this analysis, the number of

times vigorous activities were reported were summed and recalculated as a weekly rather than a monthly total to make this information comparable to that for the younger children.

A.2.5 Statistical Analyses

Because underweight has been associated with increased risk for allergic disease,[160] we excluded 144 children who were less than the 5th percentile of BMI for their age and sex (3.4%). Of the 4,125 children and adolescents above this cut-off, 4,111 have data on allergy symptoms and 3,387 have data for atopy.

The association of overweight with geometric mean total IgE was estimated using the ratio of the geometric means in a linear regression model. Logistic regression was used to determine the prevalence odds ratio for weight category in relation to atopy, a positive test to any food allergen, a positive test to any inhalant allergen (the non-food allergens), a positive test to any perennial allergen (dust mite, cockroach, mold, cat, dog, rat, mouse), a positive test to any seasonal allergen (trees and grasses), and to the allergic symptom outcomes: the occurrence of allergy symptoms or attacks in the past year (yes/no), the occurrence of hay fever symptoms in the past year (yes/no), and eczema (itchy rash coming and going for at least 6 months in the past year) (yes/no). In addition, weight was examined in relation to each allergen individually.

The association between continuous BMI percentile-for-age and total IgE was examined using linear regression. Data were plotted using a scatterplot smoothing technique.[161]

Potential modification of the effect of overweight on atopy and allergic outcomes was examined for sex, age, and race/ethnicity. A p-value for the interaction term < 0.15 was considered evidence of interaction. Stratified models were used to explore associations where evidence for interaction was found.

The potential for confounding was first examined by looking at the strength of the univariate associations between potential available confounders and the exposure and the

outcome. Age, sex, race/ethnicity, poverty income ratio, and household smoking were retained in the adjusted models based on these associations and findings from previous studies. Results for both simple age-adjusted and fully adjusted models are shown. C-reactive protein was found to be associated with both weight and atopy, but cannot be treated as a confounder in this relationship as it may be on the causal pathway. Instead, a model that assessed the relationship between CRP and atopy and potential confounding by BMI examined this possiblility.

All analyses were performed using the survey sampling weights and SAS survey sampling procedures to adjust for the NHANES complex sampling design (Version 9.1.3, Cary, NC). Figures were generated using the R system for statistical computing (version 2.7.0), which also can account for the sampling design.[161]

A.3. Results

Table 3 shows the distribution of the allergic outcomes in the NHANES 2005-2006 population age 2-19 by demographic characteristics and other potential confounding variables. Total IgE increased with age and was higher among boys. By race/ethnicity, IgE was highest in non-Hispanic blacks and lowest in non-Hispanic whites. Total IgE was higher with a lower poverty income ratio. There is also a strong relationship between CRP levels and total IgE. Total IgE was not related to smoking, birthweight, or physical activity.

The proportion classified as atopic based on at least one positive allergen-specific IgE result follows a similar pattern, with boys being more likely than girls to be atopic and non-Hispanic blacks and Mexican-Americans being more likely than non-Hispanic whites to be atopic. Children whose mothers smoked during pregnancy were less likely to be atopic than children of non-smoking mothers. Atopy was also related to the child's CRP level.

Odds of current allergy symptoms are increased at older ages, but reduced for Mexican Americans. Children whose household reference person had less than a high

school education and for those in the lowest quartile of poverty income ratio also had a reduced odds of recent allergy symptoms. Otherwise, report of recent allergy symptoms was not highly associated with any of the socio-demographic characteristics. Maternal smoking during pregnancy is related to higher odds for allergy symptoms.

The relationships of the same characteristics to obesity are shown in Table 4. Overweight was associated with older age, being non-Hispanic black or Hispanic, lower education, smoking, and lower physical activity levels, especially the number of hours of television watching. As expected, there is a strong relationship of obesity with CRP levels. The correlation between the continuous BMI z-score and the log 10 CRP level is 0.39 (95% CI: 0.37, 0.41).

Table 5 shows the age-adjusted and fully adjusted association of the overweight categories with total IgE; atopy; allergy to foods and inhalant allergens; and reported allergy symptoms, hay fever, and eczema. Both weight categories were associated with higher total IgE in both models. Being in the obese category was associated with higher odds of atopy and food allergy, and odds for children in the overweight category were also somewhat elevated. Odds for a positive test to inhalant allergens, allergy symptoms, hay fever, and itchy rash were not different by weight category in adjusted models. Results for inhalant allergens did not differ between perennial and seasonal allergens (data not shown).

With the exception of total IgE, significant gender differences were not observed; however, data are presented by sex in Table 6 in the online supplement.

Each individual allergen-specific IgE test was also examined using the same modeling process (in unadjusted models only). Because of small number of positive results for some of the allergens, a number of the estimates are imprecise, and their clinical significance is unknown. These data are available in Table 7.

Figure 3 shows the relationship between continuous BMI percentile-for-age and total IgE, stratified by sex. There is a significant linear trend (for a 1 standard deviation increase

in the BMI z-score on the log-10 value of total IgE) that is stronger for girls (slope=0.104, 95% CI: 0.064-0.143, p<0.001) than for boys (slope=0.042, 95% CI: 0.010-0.075, p=0.02) (p-value for interaction=0.04).

Race/ethnicity modified the relationship between overweight and atopy in girls (see Table 8). Figure 4 displays the percent of atopy among girls by ethnicity and weight category. The association of obesity with atopy was only significant among non-Hispanic white and non-Hispanic black girls.

To examine whether CRP (i.e. systemic inflammation) might be on the causal pathway between obesity and atopy, we examined whether CRP was related to total IgE with and without adjustment for BMI (Table 9). CRP and total IgE were correlated in age-adjusted analysis. Further adjustment for race, SES, and smoking attenuated the relationship. Adjusting for BMI in addition to socio-demographic factors decreased the model estimate by 31% (12% in boys and 70% in girls). Thus, the relationship of CRP to total IgE was confounded by BMI.

A.4. Discussion

We found a relationship between overweight and atopy in this population of American children age 2-19. This relationship has been observed before, but not consistently. Huang et al. found that Taiwanese teenage girls in the highest quintile of BMI were more likely to be atopic than girls in the middle 3 quintiles (OR 1.77, 95% CI: 1.15, 2.73).[10] Xu et al. found atopy to be associated with current BMI among Finnish adults.[12] Schachter et al. combined data from 7 epidemiological studies in Australian children and found that BMI was associated with atopic status among girls only.[11] In all of these studies, prick skin tests were used rather than allergen-specific serum IgE. In contrast, the European Community Respiratory Health Survey used allergen-specific IgE to define atopy and did not find a relationship with BMI among young adults.[13]

Previous work using NHANES III data did not find a significant relationship between overweight and atopy in children age 4-17.[115] Apart from the different age range, the major difference between the studies was that the earlier work used quartiles of BMI rather than percentiles of BMI-for-age. In order to relate the present findings more directly to this previous work, we analyzed the 2005-2006 data using quartiles of BMI. While we found a dose-response for total IgE across quartiles, we observed no relationship with atopy. While these models using quartiles of BMI were adjusted for age and sex, the method differs substantially from the recommended transformation of BMI to a percentile based on the CDC sex-specific growth curves of BMI-for-age.[153, 154] The implication is that the CDC percentiles and categories of overweight and obese for children are more informative than simple BMI for children, and that perhaps, had the NHANES III data been analyzed in this manner, the findings might have been more like those presented here.

For most of the outcomes, the associations were stronger for the obese weight category than the overweight category, providing evidence of a dose-response for weight. The analysis of continuous BMI with total IgE supports the idea that increased weight is associated with increased allergic predisposition.

Effect modification by sex was observed for total IgE but not the other allergic outcomes. Total IgE was elevated for girls (but not boys) in the overweight category, whereas it was elevated for boys (but not girls) in the obese category. In addition, the relationship of BMI examined as a continuous variable with total IgE was stronger in girls than in boys. In girls, the effect on atopy was present among non-Hispanic white and black girls, but not Mexican American girls. The mechanism for this difference among racial/ethnic groups remains enigmatic, especially given that obesity and atopy were strongly associated among Mexican-American boys.

One limitation of this analysis is that it used BMI to characterize obesity, which is not a direct measure of fatness and may misclassify some children, particularly adolescent

males, who can be heavier than average due to a larger bone structure or more muscle mass.[165] Nevertheless, BMI has been shown to correlate well with other measures of adiposity. Mei et al. compared BMI to dual x-ray absorbtiometry (DXA) in a pooled dataset of 3 studies in children and found correlations that ranged from 0.78 to 0.88, and that the area under the receiving operating characteristics curve was 0.952.[166] DXA to directly measure percent body fat was performed in the 2005-2006 NHANES, but those data are not yet publically available.

Odds ratios, as presented in this study, always overestimate the true relative risk, but are a reasonably good estimate for rare outcomes.[162] Because the prevalence of atopy is high in U.S. children (46%), the estimated odds ratio is considerably farther from the null than the relative risk. Nonetheless, reported p-values and confidence intervals remain valid. Logistic regression was used, however, because the software packages employed to handle the complex survey design do not offer a binomial regression alternative.

The relationship between CRP levels and atopy has not been previously examined. Because we found a relationship between CRP levels and atopy in this study, we therefore examined whether there was any evidence that inflammation (CRP) could be on the pathway between obesity and atopy. As it is inappropriate to control for such an intermediate variable as a confounder,[162] we tested whether the intermediate (CRP) was related to total IgE and whether that relationship was confounded by BMI. We found that CRP was positively correlated to total IgE, and that confounding of this relationship by BMI was indeed present. This suggests that there could indeed be an inflammatory component to the association between BMI and atopy.

Importantly, because these NHANES data come from a cross-sectional survey, it is not possible to assign causality to these associations. In order to understand the true causal mechanisms that underlie the relationships between adiposity and development and manifestation of atopy and allergic symptoms, it will be necessary to examine inter-

relationships among overweight, systemic inflammation, atopy, and asthma in a prospective fashion.

NHANES 2005-06 is the largest dataset of serum IgE levels that has ever been collected, and it comes from a sample that is generalizable to the population of the U.S. The NHANES employs standardized data collection methods, with strict quality control, and contains a wealth of data regarding every study subject. Our analysis, using an objective assessment of atopy, shows that overweight in children is associated with allergic predisposition. Childhood obesity may be the most important health issue facing U.S. children today. While an increase in allergy may not be the most consequential health risk faced by overweight children, it does provide additional motivation for undertaking the difficult challenge to reduce childhood obesity.

Table 3. Distribution of total serum IgE, atopy, and recent allergy symptoms by population characteristics, NHANES 2005-2006, children age 2-19.

Subject Characteristics	N	%	Geometric mean total IgE (SE)		p-value*	Percent (SE) atopic†		OR (95% CI)	Percent (SE) with allergy symptoms		OR (95% CI)
Overall	4111		50.4	(2.5)		46.4	(0.9)		18.7	(1.4)	
Age											
2-5	918	21.0	35.2	(3.9)	<0.0001	37.5	(2.1)	1.00	14.8	(2.1)	1.00
6-10	904	28.4	52.9	(3.7)		46.3	(2.5)	1.44 (1.02-2.02)	20.8	(2.3)	1.51 (1.01-2.23)
11-14	929	21.6	50.6	(4.0)		45.2	(2.1)	1.38 (1.07-1.77)	17.4	(1.9)	1.21 (0.81-1.81)
15-19	1360	29.0	59.2	(6.3)		52.1	(2.4)	1.82 (1.32-2.49)	20.6	(2.2)	1.49 (1.09-2.04)
Sex											
Male	2031	51.0	60.8	(3.7)	0.0002	49.4	(1.7)	1.29 (1.09-1.52)	19.1	(1.9)	1.05 (0.82-1.35)
Female	2080	49.0	41.4	(2.7)		43.2	(1.1)	1.00	18.4	(1.6)	1.00
Race-ethnicity											
Non-Hispanic white	1074	59.6	41.4	(3.0)	<0.0001	42.2	(1.5)	1.00	21.8	(2.4)	1.00
Non-Hispanic black	1291	14.9	83.9	(5.9)		62.2	(1.8)	2.26 (1.82-2.79)	17.5	(1.7)	0.76 (0.50-1.16)
Mexican American	1371	13.3	55.6	(3.2)		47.4	(1.7)	1.23 (1.01-1.51)	10.7	(0.9)	0.43 (0.30-0.63)
Other	375	12.2	66.6	(8.7)		47.6	(3.7)	1.24 (0.90-1.72)	14.0	(2.4)	0.58 (0.34-0.98)
Education (family referent)											
< 12th grade	1280	18.9	62.6	(4.9)	0.02	46.7	(2.2)	0.99 (0.84-1.17)	9.3	(1.4)	0.38 (0.23-0.62)
12th grade/GED	930	24.7	45.4	(4.6)		46.2	(1.6)	0.97 (0.77-1.22)	19.5	(1.8)	0.88 (0.63-1.24)
> 12th grade	1722	52.9	49.0	(3.4)		46.9	(1.7)	1.00	21.5	(2.2)	1.00
Poverty Income Ratio (quartiles)											
1st	1474	24.2	62.9	(3.1)	0.003	49.0	(1.8)	1.11 (0.88-1.39)	13.7	(1.2)	0.52 (0.39-0.69)
2nd	1064	24.2	51.3	(6.0)		44.9	(2.2)	0.94 (0.68-1.29)	19.1	(2.2)	0.77 (0.53-1.12)

Subject Characteristics	N	%	Geometric mean total IgE (SE)	p-value*	Percent (SE) atopic†	OR (95% CI)	Percent (SE) with allergy symptoms	OR (95% CI)
3rd	755	24.2	45.4 (3.2)		45.5 (2.1)	0.96 (0.78-1.19)	18.5 (2.5)	0.74 (0.52-1.07)
4th	617	24.1	43.5 (3.2)		46.5 (2.6)	1.00	23.4 (3.0)	1.00
Missing/unknown	201	3.3	54.0 (9.5)		43.2 (6.0)		19.8 (3.4)	
Any smokers in household								
Yes	667	16.3	53.5 (5.6)	0.61	44.3 (3.1)	0.90 (0.64-1.25)	20.4 (1.7)	1.13 (0.91-1.40)
No	3398	83.7	49.9 (3.0)		47.0 (1.4)	1.00	18.5 (1.5)	1.00
Mother smoked during pregnancy‡								
Yes	436	18.0	50.1 (2.6)	0.74	39.2 (2.7)	0.75 (0.59-0.96)	21.1 (1.9)	1.27 (1.00-1.62)
No	2555	82.0	47.9 (2.6)		46.1 (1.1)	1.00	17.3 (1.6)	1.00
Birthweight‡								
<2500 g	278	8.0	49.0 (6.3)	0.87	41.4 (3.9)	0.86 (0.60-1.24)	12.9 (2.6)	0.65 (0.37-1.13)
≥2500 g	2692	92.0	48.0 (2.5)		45.2 (1.2)	1.00	18.6 (1.7)	1.00
Physical Activity								
0-3 times/wk	1454	32.9	48.2 (4.4)	0.33	45.9 (1.7)	0.85 (0.65-1.10)	19.5 (1.7)	1.08 (0.83-1.40)
4-6 times/wk	730	19.0	49.8 (5.1)		48.2 (2.4)	0.93 (0.71-1.21)	19.7 (2.0)	1.09 (0.89-1.34)
7 times/wk	1100	17.9	49.7 (4.9)		43.6 (2.1)	0.77 (0.61-0.97)	17.9 (2.4)	0.98 (0.66-1.43)
8+ times/wk	752	18.3	57.1 (5.8)		50.1 (2.4)	1.00	18.3 (2.1)	1.00
Average hours of TV/videos								
0 hours/day	531	15.5	49.6 (5.1)	0.29	49.9 (2.5)	1.00	19.0 (2.5)	1.00
1-2 hours/day	2002	54.9	47.0 (2.7)		45.2 (1.4)	0.83 (0.66-1.04)	18.4 (2.1)	0.96 (0.66-1.40)
3+ hours/day	1508	29.7	58.2 (5.2)		46.9 (2.5)	0.89 (0.67-1.16)	19.8 (1.8)	1.05 (0.80-1.39)

Subject Characteristics	N	%	Geometric mean total IgE (SE)		p-value*	Percent (SE) atopic†		OR (95% CI)	Percent (SE) with allergy symptoms		OR (95% CI)
Average hours of computer use											
0 hours/day	1300	36.6	50.1	(2.8)	0.89	46.0	(1.8)	1.00	20.0	(2.0)	1.00
1-2 hours/day	1155	29.9	52.2	(4.0)		46.8	(1.7)	1.03 (0.82-1.29)	20.2	(2.3)	1.01 (0.72-1.42)
3+ hours/day	1581	33.5	49.6	(3.9)		46.6	(1.5)	1.02 (0.90-1.17)	16.4	(2.0)	0.78 (0.53-1.16)
C-reactive protein§											
Not detectable	860	23.9	42.2	(2.6)	0.0008	42.8	(1.9)	1.00	17.1	(2.3)	1.00
0.02 – 0.04 g/dL	834	20.8	49.2	(4.7)		42.5	(2.7)	0.99 (0.79-1.24)	18.1	(2.9)	1.07 (0.67-1.69)
0.04 – 0.14 mg/dL	804	18.7	55.0	(3.2)		51.7	(2.6)	1.43 (1.07-1.92)	18.5	(2.1)	1.10 (0.73-1.65)
>0.14 mg/dL	888	19.1	62.5	(5.9)		50.8	(2.4)	1.38 (1.11-1.72)	20.7	(2.3)	1.26 (0.93-1.72)
Missing/unknown	725	17.6	30.6	(8.0)	--	35.6	(6.0)	--	19.8	(2.1)	--

* Test for linear trend.
† Atopy defined as at least one positive allergen-specific IgE result.
‡ Only available for subjects up to age 15.
§ Values represent tertiles above detection.

Table 4. Distribution of overweight by population characteristics, NHANES 2005-2006, children and young adults age 2-19.

Subject Characteristics	N	Percent (SE) overweight	OR (95% CI)	Percent (SE) obese	OR (95% CI)
Overall	4111	14.2 (0.9)		16.6 (1.3)	
Age					
2-5	918	10.7 (1.7)	1.00	11.0 (1.5)	1.00
6-10	904	12.9 (2.1)	1.32 (0.79-2.21)	15.7 (2.1)	1.56 (0.96-2.55)
11-14	929	16.0 (2.2)	1.86 (1.24-2.78)	21.3 (3.4)	2.40 (1.51-3.83)
15-19	1360	16.6 (1.4)	1.85 (1.32-2.59)	18.0 (2.0)	1.95 (1.30-2.92)
Sex					
Male	2031	14.2 (1.2)	1.02 (0.87-1.21)	17.2 (1.4)	1.10 (0.94-1.30)
Female	2080	14.1 (0.9)	1.00	15.9 (1.4)	1.00
Race-ethnicity					
Non-Hispanic white	1074	14.3 (1.3)	1.00	14.1 (1.7)	1.00
Non-Hispanic black	1291	14.2 (1.1)	1.12 (0.85-1.48)	21.9 (1.6)	1.74 (1.24-2.46)
Mexican American	1371	16.1 (0.8)	1.34 (1.06-1.70)	23.7 (1.8)	2.00 (1.48-2.72)
Other	375	11.4 (1.9)	0.78 (0.52-1.16)	14.4 (2.3)	0.99 (0.62-1.58)
Education (family referent)					
< 12^{th} grade	1280	15.3 (1.9)	1.28 (0.94-1.76)	19.5 (1.4)	1.50 (1.22-1.85)
12^{th} grade/GED	930	14.9 (1.7)	1.24 (0.86-1.79)	19.2 (1.9)	1.46 (1.15-1.86)
> 12^{th} grade	1722	13.2 (1.1)	1.00	14.4 (1.5)	1.00
Poverty Index (quartiles)					
1st	1474	15.0 (1.6)	1.30 (0.87-1.95)	20.4 (1.8)	1.80 (1.31-2.47)
2nd	1064	13.5 (1.2)	1.11 (0.85-1.46)	18.3 (1.5)	1.53 (0.94-2.50)
3rd	755	14.9 (2.5)	1.18 (0.75-1.86)	14.2 (2.5)	1.15 (0.69-1.90)
4th	617	13.1 (1.3)	1.00	13.0 (2.2)	1.00
Missing/unknown	201	16.0 (2.4)		20.0 (4.2)	
Any smokers in household					
Yes	667	15.2 (2.2)	1.17 (0.88-1.56)	20.0 (2.4)	1.36 (0.97-1.89)

Subject Characteristics	N	Percent (SE) overweight	OR (95% CI)	Percent (SE) obese	OR (95% CI)
No	3398	14.0 (0.9)	1.00	15.9 (1.4)	1.00
Mother smoked during					
Yes	436	13.3 (1.2)	1.04 (0.78-1.39)	19.6 (2.4)	1.39 (1.00-1.92)
No	2555	13.6 (1.1)	1.00	15.0 (1.5)	1.00
Birthweight					
<2500 g	278	12.0 (3.8)	0.82 (0.43-1.56)	13.0 (3.3)	0.75 (0.45-1.24)
≥2500 g	2692	13.6 (0.8)	1.00	16.1 (1.4)	1.00
Physical Activity					
0-3 times/wk	1454	13.7 (1.3)	0.81 (0.62-1.04)	21.3 (1.6)	1.57 (1.12-2.20)
4-6 times/wk	730	14.3 (1.4)	0.78 (0.50-1.21)	15.0 (2.2)	1.02 (0.75-1.38)
7 times/wk	1100	12.3 (2.1)	0.64 (0.37-1.11)	14.1 (1.4)	0.92 (0.56-1.51)
8+ times/wk	752	17.8 (2.4)	1.00	14.2 (2.7)	1.00
Average hours of TV/videos					
0 hours/day	531	12.4 (2.5)	1.00	8.6 (1.4)	1.00
1-2 hours/day	2002	14.2 (1.1)	1.28 (0.79-2.09)	15.6 (1.4)	2.03 (1.37-3.02)
3+ hours/day	1508	14.9 (1.2)	1.52 (0.94-2.45)	22.8 (2.5)	3.35 (2.09-5.37)
Average hours of computer					
0 hours/day	1300	13.3 (1.4)	1.00	16.1 (1.8)	1.00
1-2 hours/day	1155	16.3 (1.7)	1.32 (0.92-1.90)	18.1 (1.9)	1.21 (0.90-1.62)
3+ hours/day	1581	13.1 (1.4)	0.98 (0.70-1.35)	15.8 (1.3)	0.98 (0.78-1.26)
C-reactive protein*					
Not detectable	860	7.9 (0.9)	1.00	1.8 (0.5)	1.00
0.02 – 0.04 g/dL	834	14.2 (1.3)	2.19 (1.60-3.00)	11.9 (1.9)	8.14 (5.36-12.4)
0.04 – 0.14 mg/dL	804	19.3 (1.7)	3.82 (2.94-4.97)	23.1 (2.1)	20.2 (10.8-37.9)
>0.14 mg/dL	888	18.4 (2.6)	4.66 (3.23-6.73)	36.5 (3.4)	40.9 (26.4-63.3)
Missing/unknown	725	12.5 (1.7)		13.8 (2.2)	

* Values represent tertiles above detection.

Table 5. Allergic outcomes by weight category (BMI percentile for age), NHANES 2005-2006, children and young adults age 2-19.

Allergy Outcome	Measure (SE)	Ratio* (95% CI) Unadjusted Model†	Ratio* (95% CI) Adjusted Model‡
Total IgE (geometric mean kU/L)			
Normal weight	45.7 (2.6)	1.00	1.00
Overweight	57.8 (5.1)	1.22 (0.99-1.51)	1.25 (1.02-1.54)
Obese	66.6 (5.8)	1.40 (1.19-1.66)	1.31 (1.10-1.57)
Any positive specific IgE result (%)			
Normal weight	44.5 (1.3)	1.00	1.00
Overweight	48.9 (2.6)	1.14 (0.91-1.44)	1.16 (0.93-1.45)
Obese	51.8 (2.1)	1.28 (1.05-1.58)	1.26 (1.03-1.55)
Any positive food IgE result (%)			
Normal weight	21.1 (0.9)	1.00	1.00
Overweight	24.4 (2.0)	1.26 (0.99-1.60)	1.27 (0.98-1.65)
Obese	29.2 (2.2)	1.61 (1.30-1.98)	1.59 (1.28-1.98)
Any positive inhalant IgE result (%)			
Normal weight	39.2 (1.4)	1.00	1.00
Overweight	42.7 (3.2)	1.05 (0.80-1.37)	1.08 (0.83-1.42)
Obese	45.6 (2.7)	1.18 (0.95-1.48)	1.17 (0.91-1.50)
Allergy symptoms in previous year (%)			
Normal weight	19.3 (1.5)	1.00	1.00
Overweight	18.1 (2.0)	0.90 (0.73-1.10)	0.96 (0.77-1.20)
Obese	17.0 (1.7)	0.83 (0.68-1.02)	0.90 (0.74-1.10)
Hay fever in previous year (%)			
Normal weight	2.9 (0.7)	1.00	1.00
Overweight	2.0 (0.9)	0.66 (0.24-1.81)	0.68 (0.23-1.99)
Obese	3.5 (0.8)	1.19 (0.61-2.32)	1.37 (0.71-2.62)
Itchy rash in previous year (%)			
Normal weight	6.0 (0.7)	1.00	1.00
Overweight	8.3 (1.7)	1.50 (0.79-2.85)	1.58 (0.82-3.05)
Obese	7.9 (1.7)	1.43 (0.96-2.13)	1.50 (0.96-2.32)

* The effect measure for total IgE is the geometric mean ratio. The effect measure for all percents is an odds ratio.

† Model adjusted for age only.

‡ Model adjusted for age, race, sex, poverty income ratio, and household smoking.

Table 6. Allergic outcomes by weight category (BMI percentile for age) and gender, NHANES 2005-2006, children and young adults age 2-19.

	Boys (N=2,031)				Girls (N=2,080)				
Allergy Outcome	Measure (SE)		Ratio* (95% CI) Unadjusted Model[†]	Ratio* (95% CI) Adjusted Model[‡]	Measure (SE)		Ratio* (95% CI) Unadjusted Model[†]	Ratio* (95% CI) Adjusted Model[‡]	Inter-action p-value
Total IgE (geometric mean kU/L)									
Normal weight	56.4	(4.2)	1.00	1.00	36.6	(2.3)	1.00	1.00	0.02
Overweight	57.7	(4.6)	1.02 (0.80-1.29)	1.02 (0.78-1.34)	58.0	(7.8)	1.45 (1.12-1.87)	1.47 (1.16-1.86)	
Obese	84.3	(10.9)	1.47 (1.16-1.86)	1.42 (1.12-1.80)	50.8	(6.9)	1.30 (1.00-1.70)	1.19 (0.89-1.57)	
Any positive specific IgE result (%)									
Normal weight	48.3	(2.2)	1.00	1.00	40.5	(1.2)	1.00	1.00	0.54
Overweight	50.8	(3.5)	1.08 (0.78-1.48)	1.10 (0.80-1.52)	47.0	(3.5)	1.25 (0.90-1.72)	1.21 (0.86-1.71)	
Obese	52.5	(4.1)	1.12 (0.78-1.61)	1.20 (0.89-1.63)	50.9	(2.3)	1.48 (1.22-1.79)	1.32 (1.06-1.64)	
Any positive food IgE result (%)									
Normal weight	24.3	(1.8)	1.00	1.00	17.8	(0.8)	1.00	1.00	0.62
Overweight	26.1	(3.4)	1.12 (0.79-1.60)	1.13 (0.80-1.62)	22.7	(2.8)	1.45 (1.01-2.08)	1.44 (0.97-2.12)	
Obese	31.7	(3.6)	1.50 (1.12-2.03)	1.60 (1.16-2.23)	26.2	(2.2)	1.73 (1.38-2.16)	1.56 (1.20-2.03)	
Any positive inhalant IgE result (%)									
Normal weight	43.0	(2.5)	1.00	1.00	35.1	(1.3)	1.00	1.00	0.45
Overweight	44.3	(4.8)	1.00 (0.64-1.56)	1.01 (0.65-1.57)	41.1	(3.3)	1.14 (0.85-1.51)	1.14 (0.83-1.56)	
Obese	45.5	(4.6)	0.99 (0.67-1.48)	1.04 (0.72-1.52)	45.7	(2.5)	1.43 (1.18-1.74)	1.29 (1.01-1.63)	
Allergy symptoms in previous year (%)									
Normal weight	20.0	(2.1)	1.00	1.00	18.6	(1.6)	1.00	1.00	0.71
Overweight	17.1	(2.5)	0.83 (0.58-1.18)	0.85 (0.58-1.23)	19.2	(3.2)	0.94 (0.63-1.41)	1.05 (0.66-1.68)	
Obese	17.4	(2.7)	0.85 (0.60-1.20)	0.90 (0.65-1.25)	16.7	(3.0)	0.82 (0.54-1.25)	0.90 (0.57-1.43)	

Allergy Outcome	Boys (N=2,031) Measure (SE)	Ratio* (95% CI) Unadjusted Model†	Ratio* (95% CI) Adjusted Model‡	Girls (N=2,080) Measure (SE)	Ratio* (95% CI) Unadjusted Model†	Ratio* (95% CI) Adjusted Model‡	Inter-action p-value
Hay fever in previous year (%)							
Normal weight	2.5 (0.7)	1.00	1.00	3.4 (1.4)	1.00	1.00	0.73
Overweight	1.3 (1.2)	0.52 (0.05-4.99)	0.53 (0.05-5.40)	2.7 (1.3)	0.78 (0.21-2.84)	0.82 (0.20-3.41)	
Obese	2.3 (0.5)	0.92 (0.42-2.01)	0.95 (0.41-2.20)	4.8 (1.5)	1.43 (0.54-3.79)	1.74 (0.67-4.49)	
Itchy rash in previous year (%)							
Normal weight	6.0 (1.0)	1.00	1.00	5.9 (0.8)	1.00	1.00	0.02
Overweight	4.4 (1.8)	0.77 (0.27-2.20)	0.82 (0.28-2.36)	12.3 (2.1)	2.28 (1.29-4.03)	2.35 (1.30-4.25)	
Obese	8.4 (2.5)	1.60 (0.93-2.75)	1.88 (1.02-3.45)	7.4 (1.7)	1.28 (0.70-2.34)	1.18 (0.62-2.27)	

* The effect measure for total IgE is the geometric mean ratio. The effect measure for all percents is an odds ratio.
† Model adjusted for age only.
‡ Model adjusted for age, race, sex, poverty income ratio, and household smoking.

Table 7. Positive specific IgE tests by weight category, NHANES 2005-2006, children and young adults age 2-19, overall and by gender.

Specific IgE Results	Normal weight (reference)		Overweight		OR (95% CI)	Obese		OR (95% CI)
Overall								
Percent positive: *D. Farinae*	17.5	(1.0)	19.6	(2.3)	1.15 (0.86-1.55)	22.3	(2.6)	1.36 (1.04-1.77)
Percent positive: *D. Pteronyssinus*	17.4	(0.9)	20.3	(1.9)	1.21 (0.96-1.53)	22.7	(2.3)	1.40 (1.09-1.90)
Percent positive: Cat	12.1	(1.3)	12.5	(1.8)	1.03 (0.74-1.44)	13.4	(2.1)	1.12 (0.79-1.60)
Percent positive: Dog	13.9	(0.9)	14.0	(2.1)	1.00 (0.72-1.39)	15.8	(2.6)	1.16 (0.84-1.60)
Percent positive: Cockroach	8.5	(0.8)	7.2	(1.5)	0.83 (0.53-1.31)	16.2	(1.7)	2.08 (1.56-2.77)
Percent positive: Alternaria	11.6	(1.4)	10.4	(1.7)	0.88 (0.61-1.27)	10.9	(1.7)	0.93 (0.70-1.24)
Percent positive: Peanut	9.6	(1.1)	8.4	(1.5)	0.86 (0.55-1.35)	11.8	(1.7)	1.25 (0.83-1.89)
Percent positive: Egg	5.2	(0.6)	8.7	(1.5)	1.73 (1.13-2.63)	4.7	(1.1)	0.90 (0.54-1.47)
Percent positive: Milk	10.0	(0.9)	12.3	(2.0)	1.27 (0.98-1.65)	12.0	(1.4)	1.24 (0.95-1.61)
Percent positive: Ragweed	15.6	(1.8)	15.2	(2.0)	0.97 (0.67-1.40)	22.1	(2.6)	1.54 (1.13-2.08)
Percent positive: Rye grass	21.6	(1.7)	19.2	(1.6)	0.86 (0.64-1.16)	25.1	(2.1)	1.22 (0.96-1.55)
Percent positive: Bermuda grass	17.1	(1.9)	17.5	(2.6)	1.02 (0.68-1.55)	20.5	(1.9)	1.25 (0.93-1.68)
Percent positive: Oak	14.8	(1.5)	12.2	(1.9)	0.80 (0.52-1.22)	17.6	(1.9)	1.23 (0.92-1.64)
Percent positive: Birch	12.9	(1.0)	10.2	(1.5)	0.77 (0.50-1.18)	14.9	(2.3)	1.18 (0.83-1.68)
Percent positive: Shellfish	5.1	(0.5)	5.2	(1.7)	1.02 (0.55-1.88)	10.6	(1.3)	2.18 (1.76-2.70)
Percent positive: Aspergillus	9.6	(1.4)	6.9	(1.6)	0.70 (0.49-1.01)	8.4	(1.2)	0.87 (0.53-1.43)
Percent positive: Thistle	13.3	(1.6)	10.0	(1.6)	0.72 (0.51-1.04)	14.8	(1.8)	1.13 (0.75-1.72)

Specific IgE Results	Normal weight (reference)		Overweight		OR (95% CI)	Obese		OR (95% CI)
Percent positive: Mouse	1.1	(0.2)	1.9	(0.7)	1.69 (0.67-4.29)	2.6	(0.7)	2.36 (1.11-5.01)
Percent positive: Rat	1.0	(0.3)	0.8	(0.4)	0.77 (0.23-2.59)	2.1	(0.6)	2.14 (0.94-4.86)
Boys								
Percent positive: *D. Farinae*	19.4	(1.6)	21.1	(3.2)	1.11 (0.75-1.64)	24.8	(3.9)	1.37 (0.88-2.13)
Percent positive: *D. Pteronyssinus*	18.2	(1.6)	22.2	(2.6)	1.28 (0.88-1.87)	25.0	(3.4)	1.50 (0.99-2.27)
Percent positive: Cat	14.8	(2.0)	16.2	(3.3)	1.11 (0.67-1.85)	16.9	(3.1)	1.17 (0.70-1.95)
Percent positive: Dog	18.4	(1.9)	18.3	(3.6)	0.99 (0.58-1.70)	17.3	(2.6)	0.93 (0.56-1.52)
Percent positive: Cockroach	11.2	(1.2)	7.9	(2.0)	0.68 (0.40-1.16)	17.7	(2.8)	1.70 (1.09-2.66)
Percent positive: Alternaria	14.6	(2.3)	7.1	(1.8)	0.45 (0.25-0.80)	12.2	(2.6)	0.81 (0.53-1.23)
Percent positive: Peanut	12.7	(1.9)	9.7	(2.9)	0.74 (0.37-1.48)	13.6	(2.4)	1.09 (0.65-1.82)
Percent positive: Egg	5.4	(1.0)	10.5	(2.7)	2.04 (1.00-4.20)	6.1	(1.5)	1.12 (0.70-1.80)
Percent positive: Milk	11.5	(1.1)	12.9	(3.4)	1.14 (0.68-1.92)	13.6	(2.6)	1.21 (0.79-1.86)
Percent positive: Ragweed	19.2	(2.4)	15.1	(3.4)	0.75 (0.41-1.38)	26.0	(5.3)	1.48 (0.97-2.26)
Percent positive: Rye grass	27.2	(2.5)	20.5	(4.1)	0.69 (0.40-1.18)	26.8	(3.3)	0.98 (0.65-1.46)
Percent positive: Bermuda grass	21.2	(2.9)	18.2	(4.6)	0.83 (0.42-1.62)	22.8	(3.2)	1.10 (0.70-1.72)
Percent positive: Oak	18.6	(2.4)	15.7	(3.6)	0.81 (0.43-1.54)	19.2	(3.7)	1.04 (0.70-1.54)
Percent positive: Birch	16.6	(1.8)	13.4	(3.1)	0.78 (0.40-1.52)	17.0	(4.4)	1.03 (0.61-1.75)
Percent positive: Shellfish	5.7	(0.9)	4.3	(1.8)	0.74 (0.31-1.79)	10.9	(2.0)	2.02 (1.32-3.07)
Percent positive: Aspergillus	12.7	(2.3)	5.7	(1.6)	0.41 (0.22-0.79)	9.9	(2.4)	0.75 (0.37-1.52)
Percent positive: Thistle	17.0	(2.0)	9.5	(1.9)	0.51 (0.29-0.91)	15.9	(2.9)	0.93 (0.56-1.54)

Specific IgE Results	Normal weight (reference)	Overweight	OR (95% CI)	Obese	OR (95% CI)
Percent positive: Mouse	1.1 (0.3)	1.9 (1.0)	1.77 (0.46-6.72)	2.6 (1.0)	2.44 (0.87-6.83)
Percent positive: Rat	1.2 (0.3)	1.4 (0.8)	1.21 (0.28-5.31)	2.3 (0.9)	2.03 (0.65-6.34)
Girls					
Percent positive: *D. Farinae*	15.4 (1.2)	18.2 (2.3)	1.22 (0.86-1.74)	19.5 (1.9)	1.33 (1.10-1.61)
Percent positive: *D. Pteronyssinus*	16.5 (0.9)	18.4 (2.5)	1.14 (0.81-1.61)	20.1 (2.1)	1.28 (1.02-1.60)
Percent positive: Cat	9.4 (0.9)	8.9 (1.4)	0.95 (0.63-1.42)	9.5 (2.2)	1.02 (0.66-1.56)
Percent positive: Dog	9.3 (1.2)	9.7 (1.9)	1.05 (0.67-1.66)	14.2 (2.1)	1.61 (1.20-2.16)
Percent positive: Cockroach	5.7 (0.9)	6.5 (1.5)	1.14 (0.67-1.95)	14.6 (1.3)	2.81 (1.98-4.00)
Percent positive: Alternaria	8.4 (1.0)	13.5 (2.4)	1.71 (1.11-2.63)	9.3 (1.6)	1.13 (0.72-1.77)
Percent positive: Peanut	6.5 (0.6)	7.2 (1.6)	1.12 (0.68-1.82)	9.7 (1.9)	1.55 (0.93-2.58)
Percent positive: Egg	5.0 (0.6)	6.8 (2.1)	1.40 (0.75-2.64)	3.1 (1.4)	0.61 (0.23-1.64)
Percent positive: Milk	8.4 (1.0)	11.8 (2.3)	1.47 (0.91-2.36)	10.3 (1.6)	1.25 (0.81-1.92)
Percent positive: Ragweed	11.9 (1.7)	15.2 (2.8)	1.34 (0.89-2.01)	17.7 (2.9)	1.60 (1.10-2.32)
Percent positive: Rye grass	15.7 (1.9)	18.0 (2.1)	1.18 (0.91-1.53)	23.1 (3.0)	1.62 (1.22-2.13)
Percent positive: Bermuda grass	12.9 (1.6)	16.8 (2.9)	1.36 (0.92-2.03)	17.9 (2.4)	1.48 (1.10-1.98)
Percent positive: Oak	10.8 (0.8)	8.9 (1.6)	0.81 (0.55-1.19)	15.7 (2.8)	1.54 (0.95-2.50)
Percent positive: Birch	9.0 (1.1)	7.3 (1.7)	0.80 (0.50-1.27)	12.4 (2.8)	1.43 (0.85-2.41)
Percent positive: Shellfish	4.5 (0.7)	6.1 (2.1)	1.36 (0.66-2.81)	10.2 (1.9)	2.39 (1.60-3.56)

Specific IgE Results	Normal weight (reference)	Overweight	OR (95% CI)	Obese	OR (95% CI)
Percent positive: Aspergillus	6.3 (1.0)	8.0 (2.4)	1.30 (0.76-2.22)	6.7 (1.4)	1.08 (0.62-1.88)
Percent positive: Thistle	9.4 (1.5)	10.4 (3.0)	1.12 (0.67-1.86)	13.5 (2.7)	1.50 (0.90-2.50)
Percent positive: Mouse	1.2 (0.4)	1.9 (1.1)	1.62 (0.40-6.62)	2.6 (0.9)	2.28 (0.94-5.48)
Percent positive: Rat	0.8 (0.4)	0.2 (0.2)	0.23 (0.02-2.03)	1.8 (0.9)	2.26 (1.16-4.42)

Table 8. Odds ratios by age group and ethnicity for the association between BMI and atopy, overall and stratified by sex.

Stratum	Overall	P-value†	Males	P-value†	Females	P-value†
Atopy (≥ 1 positive specific IgE)						
All subjects		--				
Overweight	1.23 (0.98 - 1.54)		1.16 (0.86 - 1.57)		1.31 (0.96 - 1.79)	0.55
Obese	1.35 (1.09 - 1.65)		1.18 (0.81 - 1.74)		1.54 (1.27 - 1.86)	0.27
Age						
Overweight vs. normal		0.87		0.90		0.91
2-5	1.53 (0.75 - 3.12)		1.27 (0.57 - 2.84)		1.96 (0.63 - 6.17)	
6-10	1.17 (0.59 - 2.31)		1.26 (0.60 - 2.64)		1.08 (0.37 - 3.17)	
11-14	1.00 (0.56 - 1.77)		0.90 (0.51 - 1.59)		1.13 (0.52 - 2.44)	
15-19	1.21 (0.82 – 1.78)		1.18 (0.49 - 2.85)		1.34 (0.79 - 2.25)	
Obese vs. normal		0.13		0.08		0.67
2-5	2.58 (1.45 - 4.60)		4.74 (1.46 - 15.4)		1.39 (0.55 - 3.53)	
6-10	1.03 (0.63 - 1.69)		0.82 (0.39 - 1.70)		1.35 (0.67 - 2.73)	
11-14	1.20 (0.82 - 1.77)		1.12 (0.49 - 2.54)		1.35 (0.96 - 1.88)	
15-19	1.28 (0.88 – 1.88)		0.88 (0.45 - 1.72)		1.94 (1.23 - 3.07)	
Race Ethnicity						
Overweight vs. normal		0.75		0.28		0.82
Non-Hispanic White	1.29 (0.97 - 1.72)		1.24 (0.86 - 1.80)		1.39 (0.82 - 2.37)	
Non-Hispanic Black	0.98 (0.68 - 1.43)		0.77 (0.59 - 1.02)		1.23 (0.63 - 2.40)	
Mexican American	1.09 (0.70 - 1.70)		1.06 (0.58 - 1.96)		1.11 (0.71 - 1.74)	
Other	1.36 (0.45 - 4.11)		1.43 (0.26 - 7.81)		1.23 (0.36 - 4.16)	
Obese vs. normal		0.76		0.16		0.0004
Non-Hispanic White	1.28 (0.94 - 1.74)		0.98 (0.56 - 1.73)		1.73 (1.22 - 2.46)	
Non-Hispanic Black	1.41 (1.06 - 1.87)		1.01 (0.64 - 1.58)		1.85 (1.37 - 2.50)	
Mexican American	1.38 (1.07 - 1.78)		1.64 (1.12 - 2.41)		1.09 (0.81 - 1.47)	
Other	1.00 (0.50 - 2.00)		1.73 (1.00 - 2.97)		0.41 (0.16 - 1.04)	

† P-value testing that the association between weight category and outcome (atopy or allergy symptoms) differs across categories

Table 9. Increase in log 10 total IgE for a log 10 increase in C-reactive protein, unadjusted and adjusted models, NHANES 2005-2006, children age 2-19.

	Model 1*		Model 2†		Model 3‡		Percent
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Change§
Overall	0.087	0.036-0.137	0.084	0.032-0.136	0.058	-0.009-0.124	31%
Boys	0.090	0.007-0.172	0.095	0.007-0.183	0.084	-0.010-0.177	12%
Girls	0.091	0.032-0.149	0.066	-0.001-0.133	0.020	-0.070-0.110	70%

*Model adjusting for age only.
†Model adjusting for survey round, age, race, poverty income ratio, and household smoking.
‡Model adjusting for survey round, age, race, poverty income ratio, household smoking, and BMI z-score.
§Percent change in model coefficient between Model 2 and Model 3.

Figure 3. Association between BMI percentile-for-age and total IgE by sex, NHANES 2005-2006, children age 2-19. The shaded region represents the 95% confidence limits of the data. The black lines represent observations and show where the data lie on the BMI distribution. The x axis is plotted as the z-score for BMI-for-age and labeled with the transformation of z-scores to percentiles.

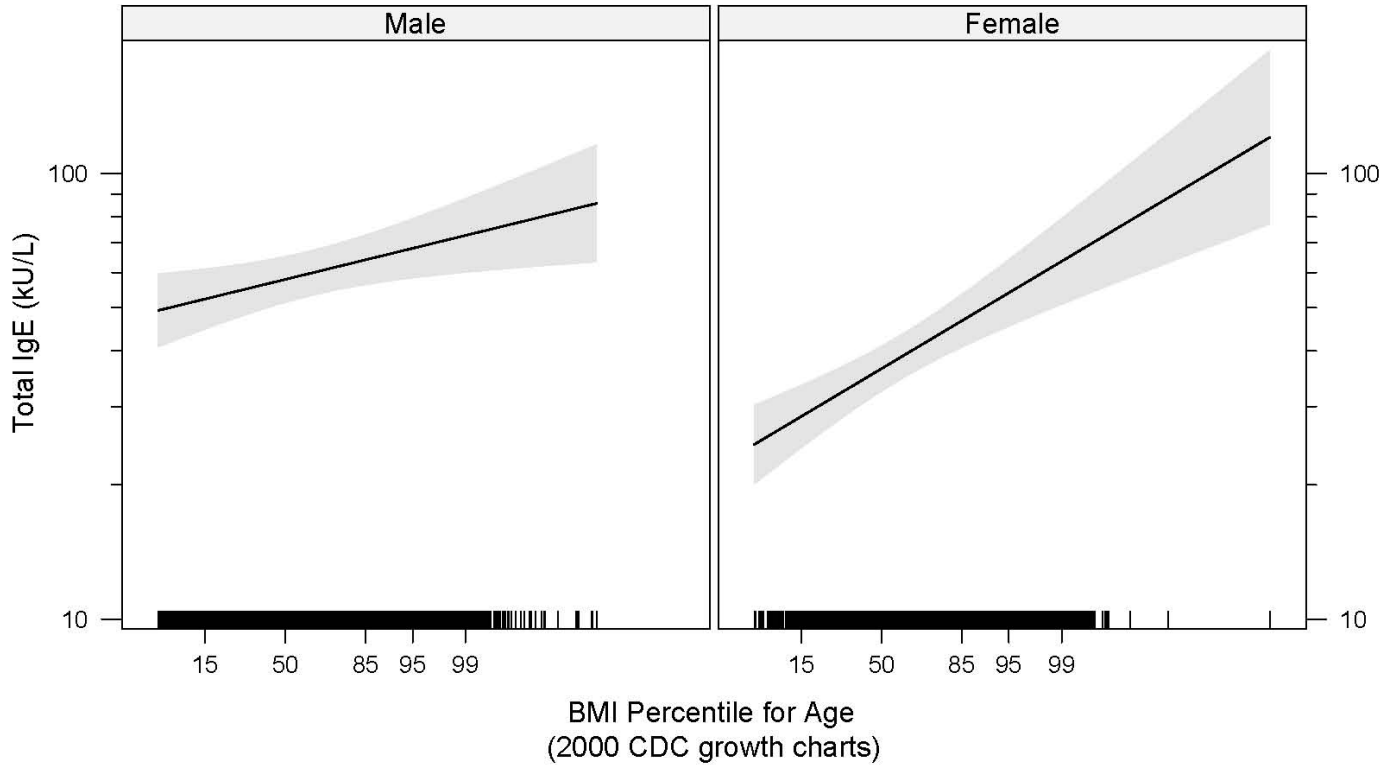
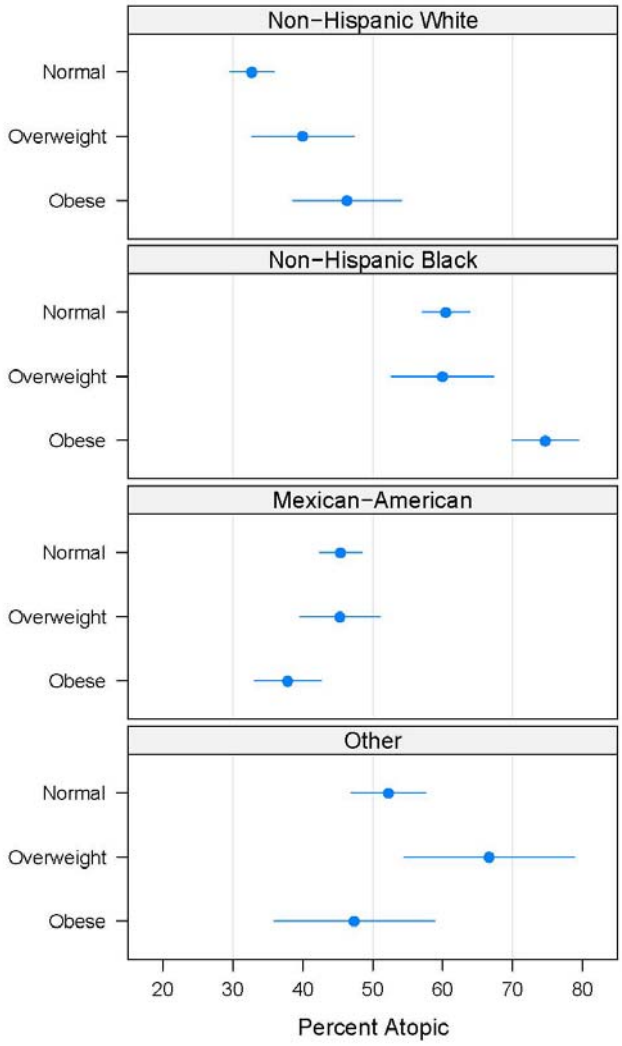


Figure 4. Prevalence of atopy by race and weight status among girls NHANES 2005-2006, children age 2-19. The dots reflect the mean prevalence of atopy and the bars represent the 95% confidence interval.



B. Manuscript 2: The Association of Obesity with Atopic and Non-Atopic Asthma in Children and Adolescents: Results from NHANES 1999-2006

B.1. Introduction

Obesity and asthma prevalence have increased over the last several decades,[1, 159] and studies over the last fifteen years have suggested that obesity is related to asthma.[3-5] At least 30 cross-sectional and 13 prospective studies have been published between 1999 and 2006, with nearly all of them showing a positive association between obesity and asthma.[5] A few of these included children, but the majority were conducted in adults.

Evidence for an obesity effect in children has been less consistent than that in adults, hampered in part by different age ranges examined, different definitions of overweight and obesity, and different morbidity endpoints.[167] A recent meta-analysis found that the strength of the relationship between obesity and asthma in children appeared to be increasing over time.[75] The authors determined the overall effect of high body weight in childhood was associated with a relative risk of 1.5 for subsequent asthma and reported a 6.6% population attributable risk for asthma due to being overweight [75]

Several studies have found that obesity was more strongly related to non-atopic than to atopic asthma in adults.[15, 148] In the National Health and Nutrition Examination Survey (NHANES) III dataset, obesity was related to childhood asthma, but only weakly and non-significantly related to atopy as assessed by skin prick tests.[115] No difference was observed in the relationship between obesity and asthma by atopic status. This study analyzed BMI by quartiles, rather than using the currently-recommended percentiles of BMI-for-age as calculated by the Centers for Disease Control.[153, 154]The authors proposed that the obesity effect on asthma was mediated by mechanical properties associated with obesity or with systemic inflammation rather than by allergic inflammation but did not examine markers of systemic inflammation.

C-reactive protein (CRP) is a marker for systemic inflammation and is often very high in overweight individuals. Butland et al. found that CRP was related to asthma only among non-atopics, and that the association became non-significant when controlling for BMI, suggesting that CRP may be on the causal pathway between obesity and asthma.[92]

While atopy is a very strong risk factor for asthma, recent research estimates that only about 40% of asthma in the U.S. is attributable to atopy.[16] It is possible that obesity-related asthma and atopic asthma have different etiologies, which has implications for treatment and prevention of allergic diseases and asthma in children.[17]

We examined the association between obesity and asthma in a representative sample of U.S. children and young adults. We used allergen-specific serum IgE results to distinguish atopic and non-atopic children. We investigated the possibility of an inflammatory pathway for the obesity-asthma relationship by examining confounding of the CRP-asthma relationship by BMI, following previous work in adults.[92]

B.2. Methods

B.2.1 Study Population

The NHANES is a nationally representative survey conducted periodically to assess the health and nutritional status of adults and children in the U.S. The primary purpose of NHANES is to determine the prevalence of major diseases and risk factors for those diseases.[163] Details of the plan and operation of NHANES may be found online at http://www.cdc.gov/nchs/nhanes.htm.

The NHANES used a stratified, multi-stage probability sampling design. The stages of sampling are 1) Primary Sampling Unit (PSU) which is usually a county or block of contiguous (low-population) counties; 2) segments within PSUs (blocks or clusters of households); 3) households within segments; 4) one or more participants within households. Eligible persons age 16 or older were interviewed directly, while interviews for those under

age 16 were done with a proxy. All persons who completed the household interview were invited to participate in the Medical Examination component of NHANES. The study protocols were IRB-approved and all participants (or their parent/guardian) gave written informed consent.

The target population of NHANES is the civilian, non-institutionalized population of the U.S. Each survey round oversampled persons believed to be at increased health risk – low-income persons, adolescents age 12-19, persons age 60+, African Americans and Mexican Americans. Weights are supplied with the public use dataset so that estimates can be produced that reflect the U.S. population distribution and can be considered to be nationally representative. In the combined 1999-2006 NHANES, 17,140 children age 2-19 completed both the interview portion of the survey and the medical examination, and 16,717 children had their height and weight measured.

B.2.2. Asthma Outcomes

All participants age 1 year and older were asked (by proxy if under age 16) whether a doctor or other health professional had ever said they had asthma. Those who answered 'yes' were asked a series of additional questions, including whether they still had asthma, whether they had experienced an asthma attack in the past year, and whether they had been to the emergency department for asthma in the past year. For the purposes of these analyses, all those who reported never having asthma were coded as giving 'no' responses to the subsequent questions. The primary outcome for these analyses is a report of current asthma (those with an asthma diagnosis who report still having asthma).

A separate set of questions were asked about wheezing. Wheeze outcomes used in these analyses include a report of wheeze in the past year (yes/no), medical visit for wheeze in the past year (yes/no) and missing school or work due to wheeze in the past year (yes/no). Again, those who reported no wheezing in the past year were coded as having 'no' responses to the remaining wheeze questions.

B.2.3. Atopy

Participants of the 2005-2006 survey age 1 year and older were tested for total and allergen-specific serum IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). A detailed description of the laboratory method can be found at NHANES 2005-2006 web page (http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/al_ige_d.pdf). Because smaller quantities of serum were available for young children, the number and type of allergen-specific IgE tests performed varied by age. Children age 1 to 5 years were tested for total IgE as well as specific IgE to dust mite (*D. farinae* and *D. pteronyssinus*), cat, dog, cockroach, *Alternaria*, peanut, egg, and milk. Children and young adults age 6 and above also have specific IgE measurements for ragweed, ryegrass, bermuda, white oak, birch, shrimp, *Aspergillus*, thistle, mouse, and rat.

Atopy was defined in these analyses as a positive specific IgE response (≥ 0.35 kU/L) to at least one of the allergens tested. In order to be included in the analyses that stratify by atopic status, the individual had to have information for the full panel of allergens (9 allergens for those under age 6, and 19 for those age 6-19).[168]

B.2.4. Weight Measurements

All participants who attended the medical examination had their weight and height measured following a standard protocol. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Sex-specific BMI percentile-for-age was calculated using the Centers for Disease Control and Prevention 2000 reference standards.[153] Children between the 5th and 85th percentile of BMI-for-age are considered to be normal weight, those between the 85th and 95th percentile are considered overweight, and those at or above the 95th percentile are considered obese, as recommended by the American Medical Association.[154]

B.2.5. Other Measures

The age, sex, and race/ethnicity of the child were examined as potential confounders and effect modifiers. As a measure of SES, quartiles of the poverty income ratio (PIR) were also examined for their relationship to overweight and asthma. The PIR is the relationship of family income to the family's appropriate poverty threshold based on family size and composition.[164] Ratios below 1 are below the poverty threshold.

Other potential confounders considered were current household smoking (yes/no), maternal smoking during pregnancy (yes/no), birthweight (low birthweight vs. not), and several physical activity measures. All children were asked the average number of hours per day they spent either watching television or using a computer. For children age 2-11, the proxy respondent answered one question about how many times per week the child played or exercised enough to sweat or breathe hard. Children age 12-19 answered more detailed questions about the specific activities they did that qualified as moderate or vigorous activity and the number of times they did those activities in the past month. For this analysis, the number of times vigorous activities were reported were summed and recalculated as a weekly rather than a monthly total to make this information comparable to that for the younger children.

B.2.6. Statistical Analyses

Because underweight has been associated with increased risk for asthma,[160, 169] this analysis excluded 581 children (3.5%) that were less than the 5th percentile for their age and sex. The effect of overweight and obesity on current asthma and the other outcomes, as defined above, was examined using a logistic regression model. Results are presented for 16,074 children for whom current asthma status is available in the complete 1999-2006 dataset, and stratified by atopy for the 2005-2006 dataset (3,387 children with atopy information).

The association of continuous BMI percentile-for-age with current asthma was also examined using logistic regression, with a 1-standard-deviation increase in the BMI z-score as the exposure. Results were plotted using a scatterplot smoothing technique.[161]

Potential modification of the effect of overweight on asthma was examined for sex and for age and race/ethnicity, separately for boys and girls. A p-value for the interaction term < 0.15 was considered evidence of interaction. No effect measure modification was observed for these factors (Table 10).

The potential for confounding was first examined by looking at the magnitude of the univariate associations between potential available confounders and the exposure and the outcome. Survey year, age, race/ethnicity, poverty income ratio, household smoking, and level of physical activity were related to both the exposure and the outcome and were retained in the adjusted models. Results for both simple age-adjusted and fully adjusted models are shown.

All analyses were performed using the survey sampling weights and SAS survey sampling procedures to adjust for the NHANES complex sampling design (Version 9.1.3, Cary, NC). Figures were generated using the R system for statistical computing (version 2.7.0), which also can account for the sampling design.[161]

B.3. Results

Table 11 shows the prevalence of current asthma and of medical visits for wheezing among the population of children and young adults age 2-19 in the four rounds of NHANES from 1999-2006. Nearly 10% of the subjects reported current asthma. Seven percent reported a medical visit for wheeze in the past year. Current asthma was somewhat more prevalent in 2005-2006, though the difference is not large. Medical visits for wheeze were more common in the 2003-06 period than in the preceding 4 years. Age did not appear to be strongly related to asthma, but medical visits for wheeze were more common in the 2-5 year

old children. More boys than girls reported current asthma. Compared to non-Hispanic whites, non-Hispanic blacks reported more asthma and visits for wheezing, whereas Mexican Americans reported less asthma and fewer visits for wheezing. In-utero exposure to tobacco smoke was associated with wheezing requiring a medical visit, and low birthweight and elevated CRP were associated with a higher prevalence of asthma. Neither asthma nor medical visits for wheeze were strongly associated with the physical activity variables.

The relationships of the same characteristics to overweight were also examined (Table 12). Fifteen percent of the population met the criteria for overweight, and 16.2% were obese. Overweight and obesity were somewhat less common in 2005-2006 than in 2003-2004 (percent obese 16.5% vs. 17.4%). Higher weight was associated with being male, being non-Hispanic black or Mexican American, lower PIR (less income), smoking, low birthweight, and decreased physical activity levels, especially with the number of hours of television watching. There was a strong relationship between obesity and CRP levels. The correlation between the continuous BMI z-score and the log 10 CRP level was 0.41 (95% CI: 0.39-0.44).

Table 13 shows the age-adjusted and fully adjusted association of the overweight categories with current asthma, and several other asthma-related outcomes occurring in the past year (asthma attack, emergency department visit for asthma, wheeze, medical visits for wheeze, and missed school or work due to wheezing). Obese children had 1.68 higher odds of having current asthma (95% CI: 1.33, 2.12) and 1.97 higher odds of having experienced an asthma attack in the previous year (95% CI: 1.66, 2.34) than normal weight children. Odds for all of the asthma-related outcomes are elevated for both categories of overweight, although the confidence intervals are wider for the emergency department visit outcome. Stronger estimates were observed for obese than for overweight categories for

every outcome, providing evidence of a dose-response effect for BMI. In general, adjustment for confounding did not have a large effect on the odds ratios.

Effect modification by sex was not observed for these outcomes, but data stratified by sex are provided in Table 14.

Table 15 shows the same set of asthma outcomes as predicted by weight category, but stratified by atopic status for the 2005-2006 survey years when specific IgE data were available. The prevalence of all of the asthma-related outcomes was higher for the atopic children. However, the obesity association was stronger among the non-atopic children, with important interaction effects ($p < 0.15$) seen for all outcomes except asthma attack and medical visits for wheeze. Very few emergency department visits were reported in this smaller population, so the data are not shown. Among non-atopic subjects, those in the obese category were more than twice as likely to have current asthma (OR 2.46, 95% CI: 1.21, 5.02), an asthma attack (OR 2.45, 95% CI: 1.31, 4.58), or wheezing (OR 2.20, 95% CI: 1.15, 4.22) in the previous year than those of normal weight youth. In contrast, there was no appreciable association between overweight or obesity and asthma among atopic subjects.

Figure 5 shows the relationship between continuous BMI percentile-for-age and the probability of current asthma, stratified by atopic status. The relationship between continuous BMI and asthma was stronger among the non-atopic subjects. For each 1-standard deviation increase in the BMI z-score the odds for asthma were increased 1.52 times (95% CI: 1.14, 2.04) among the non-atopic youth , but only 1.13 times among atopic youth (95% CI: 0.91, 1.41)(interaction p-value=0.04).

In a logistic regression model examining the association between CRP and current asthma, separately for atopic and non-atopic children, increased CRP (a 1-log increase) was associated with an increased odds of having asthma among non-atopic children (OR 1.47; 95% CI: 1.17, 1.84), but not among atopic children (OR 0.97; 95% CI: 0.65, 1.44). Among the non-atopic children, adjustment for age, race, sex, household smoking, PIR, and

physical activity did not affect the odds ratio; whereas further adjustment for BMI attenuated the OR to 1.17 (95% CI: 0.80, 1.72). This demonstrates that the relationship of CRP to current asthma among these non-atopic children is confounded by BMI.

B.4. Discussion

This analysis from a representative survey of U.S. children shows that being overweight or obese is associated with an increased likelihood of reporting current asthma. The association with BMI was uniformly stronger for the obese category than for the overweight category. We also demonstrated that the continuous BMI z-score was associated in a dose-response fashion with the odds of reporting asthma. In addition we were able to objectively classify subjects in NHANES 2005-2006 as atopic or non-atopic based on allergen-specific IgE tests. This analysis revealed that the association of overweight and obesity with asthma was stronger among the non-atopic children.

These findings differ from those using NHANES III data, which did not find a difference between atopic and non-atopic children.[115] The studies differ in their definition of obesity (quartiles vs. the AMA-recommended ranges) and in the manner of assessing atopy (skin prick tests vs. specific IgE tests). The earlier study did find a strong relationship between obesity and asthma, especially for highest quartile of obesity, but reported that there was no effect modification by atopic status. Stratified data were not presented, however, and lack of effect modification was not defined.

However, our findings are similar to studies in adults that found obesity to be more strongly related to non-atopic than to atopic asthma. In an Australian study of 4,060 men and women, an increased risk for asthma was found for those with central obesity (measured by waist circumference and waist/hip ratio) who were non-atopic.[148] In a cross-sectional survey of more than 86,000 Canadian adults, overweight was associated with

asthma in both allergic and non-allergic women, but the odds ratio was stronger in non-allergic women, whereas in men only the relationship in non-allergic men was significant.[15]

Several previous studies have found the effect of obesity on asthma to differ by gender in children. Gilliland et al. found a significant relationship between overweight and asthma among boys, but not girls,[72] while Gold et al. found a relationship only among girls.[73] Castro-Rodriguez et al. reported from the Tucson Chidren's Respiratory Study that obesity among girls at age 11 was associated with frequent wheeze at age 13.[74] The authors suggest that these gender differences may be due to female hormones. Indeed, the strongest effects of obesity on asthma were among girls that started puberty before age 11, compared to those with later pubertal development.[74] Varraso et al. also found that BMI was more strongly related to asthma severity among girls with early menarche.[77] The present analyses, with a large and representative sample of children and adolescents, did not find evidence of effect measure modification by gender.

Previous studies suggest that systemic inflammation is a potential mechanism behind the observed relationship between obesity and asthma.[79, 90] This analysis demonstrated a relationship between CRP levels and asthma, and we therefore examined whether CRP could be on the pathway between obesity and asthma. It is inappropriate to control for such an intermediate variable as a confounder,[162] and mediation models and other models that attempt to partition effects into direct and indirect effects rely on assumptions that are unlikely to hold in our data (e.g. no unmeasured common causes of CRP levels and asthma).[170, 171] The relationship of CRP to asthma in non-atopic children, and the confounding of this relationship by BMI, suggests that overweight may indeed lead to systemic inflammation that in turn leads to an increased risk of asthma in non-atopic individuals. There was no evidence of a relationship with systemic inflammation among atopic youths.

One potential limitation of these findings is that the measure of obesity used, BMI, is not a direct measure of adiposity and cannot differentiate between lean and fat mass. As an index of obesity, it may perform better for one sex than for another. A male at the same BMI as a female, even at a BMI of 30 which indicates obesity, may have more muscle mass and less body fat.[5] Nevertheless the AMA recommends the use of the CDC 2000 BMI-for-age percentiles as used in these analyses, considering them to have good sensitivity and specificity for identifying the children at greatest health risk.[154]

The asthma and wheeze outcome measures come from self-report rather than an objective medical diagnosis. However, previous studies have found strong correlations with more objective measures of asthma status. Senthilselvan et al. found self-report of asthma to be significantly related to concurrently measured pulmonary function tests.[172] Tisnado et al. found self-reported history of asthma to be in 91% agreement with medical record data.[173]

Another limitation is that the IgE data were only available for subjects surveyed in NHANES2005-2006. Thus the effect estimates for the analysis stratified by atopy are less precise than for the unstratified analysis. Some of the outcomes, such as emergency department visit for asthma, were so uncommon that reliable estimates could not be obtained.

It has been suggested that lack of physical activity may be the underlying cause of both obesity and asthma.[111] This analysis, however, did not show physical activity to be related to asthma. Physical activity is difficult to measure, especially in children, and the survey measures available in NHANES are not ideal. Better measurement of physical activity might result in different findings.

Because these NHANES data come from a cross-sectional survey it is not possible to assign causality to these associations. Confounding of the CRP-asthma relationship by BMI could represent systemic inflammation on the causal pathway to asthma, or could

indicate that obesity is a proximate cause of both inflammation and asthma. In order to understand the true causal pathways that may underlie the relationships between adiposity and the development and manifestation of atopy and asthma, it will be necessary to look at these relationships prospectively.

The NHANES is a large national dataset that uses standardized data collection procedures, contains an abundance of information regarding every study subject, and is generalizable to the U.S. population. Using an objective measure of atopy, we found that excess weight in children appears to be associated with higher rates of asthma in children, especially asthma that is not accompanied by allergic disease . Current efforts to decrease overweight and obesity among U.S. children could potentially have the added benefit of decreasing asthma as well.

Table 10. Odds ratios by age group, ethnicity, sex and atopic status for the association between BMI and asthma, overall and stratified by sex. NHANES 1999-2006, children and young adults age 2-19.

Stratum	Overall	P-value*	Males	P-value*	Females	P-value*
All subjects		--		--		--
Overweight	1.37 (1.13-1.65)		1.34 (1.08-1.67)		1.40 (1.03-1.89)	
Obese	1.66 (1.33-2.06)		1.60 (1.18-2.17)		1.72 (1.28-2.30)	
Age						
Overweight vs. normal		0.44		0.22		1.00
2-5	1.89 (1.19-3.01)		2.32 (1.43-3.75)		1.41 (0.64-3.15)	
6-10	1.25 (0.84-1.85)		1.15 (0.70-1.91)		1.44 (0.70-2.96)	
11-14	1.36 (0.99-1.86)		1.42 (0.93-2.18)		1.30 (0.81-2.06)	
15-19	1.22 (0.89-1.67)		1.03 (0.58-1.85)		1.37 (0.86-2.18)	
Obese vs. normal		0.97		0.65		0.57
2-5	1.78 (1.19-2.65)		2.02 (1.20-3.40)		1.45 (0.73-2.90)	
6-10	1.65 (1.01-2.68)		1.32 (0.67-2.59)		2.24 (1.32-3.80)	
11-14	1.63 (1.14-2.33)		1.58 (0.99-2.50)		1.69 (0.95-3.00)	
15-19	1.57 (1.13-2.18)		1.85 (1.16-2.96)		1.37 (0.86-2.19)	
Race Ethnicity						
Overweight vs. normal		0.45		0.26		0.97
Non-Hispanic White	1.45 (1.09-1.92)		1.44 (1.03-2.01)		1.46 (0.93-2.27)	
Non-Hispanic Black	1.35 (1.12-1.62)		1.39 (1.05-1.82)		1.36 (1.04-1.76)	
Mexican American	1.65 (1.25-2.18)		1.88 (1.32-2.67)		1.42 (0.87-2.33)	
Other	0.94 (0.48-1.86)		0.74 (0.28-1.93)		1.17 (0.53-2.60)	
Obese vs. normal		0.51		0.26		0.28
Non-Hispanic White	1.75 (1.18-2.59)		1.69 (1.01-2.83)		1.80 (1.10-2.93)	
Non-Hispanic Black	1.42 (1.17-1.72)		1.50 (1.14-1.98)		1.41 (1.06-1.89)	
Mexican American	1.76 (1.32-2.35)		2.25 (1.56-3.23)		1.14 (0.79-1.65)	
Other	1.65 (0.99-2.76)		1.25 (0.62-2.52)		2.22 (1.01-4.87)	
Atopic Status						
Overweight vs. normal		0.25		0.72		0.26

Stratum	Overall	P-value*	Males	P-value*	Females	P-value*
Non-Atopic	1.54 (0.80-2.99)		0.80 (0.21-3.03)		2.29 (1.03-5.09)	
Atopic	1.03 (0.71-1.50)		0.97 (0.50-1.88)		1.14 (0.39-3.37)	
Obese vs. normal		0.05		0.03		0.50
Non-Atopic	2.21 (1.12-4.35)		2.22 (1.21-4.07)		2.19 (0.76-6.28)	
Atopic	1.22 (0.67-2.22)		0.96 (0.49-1.89)		0.66 (0.76-3.61)	
Sex						
Overweight vs. normal		0.82				
Males	1.34 (1.08-1.67)					
Females	1.40 (1.03-1.89)					
Obese vs. normal		0.74				
Males	1.60 (1.18-2.17)					
Females	1.72 (1.28-2.31)					

* P-value testing that the association between weight category and outcome (atopy or allergy symptoms) differs across categories

Table 11. Current asthma and medical visits for wheezing by population characteristics, NHANES 1999-2006, children and young adults age 2-19.

Subject Characteristics	N	%	Current asthma (%, SE)		OR (95% CI)	Any medical visits for wheezing (%, SE)		OR (95% CI)
Overall	16074		9.6	(0.4)		7.0	(0.3)	
Survey Round								
1999-2000	3924	22.4	9.6	(1.1)	1.00	5.9	(0.6)	1.00
2001-2002	4124	26.3	9.1	(0.6)	0.94 (0.71-1.25)	6.3	(0.4)	1.07 (0.82-1.40)
2003-2004	3884	25.4	9.0	(0.7)	0.94 (0.70-1.26)	7.6	(0.4)	1.31 (1.01-1.69)
2005-2006	4112	25.5	10.7	(0.5)	1.13 (0.86-1.47)	7.8	(0.7)	1.34 (1.00-1.81)
Age								
2-5	3166	20.5	8.9	(0.7)	0.92 (0.74-1.15)	11.3	(0.8)	1.67 (1.26-2.21)
6-10	3467	28.6	9.6	(0.8)	1.00	7.1	(0.7)	1.00
11-14	4064	22.9	10.6	(0.6)	1.12 (0.88-1.43)	5.7	(0.5)	0.80 (0.60-1.07)
15-19	5377	28.0	9.3	(0.5)	0.92 (0.74-1.15)	4.7	(0.5)	0.65 (0.47-0.90)
Sex								
Male	7978	50.6	10.3	(0.6)	1.18 (1.02-1.38)	7.5	(0.4)	1.20 (1.02-1.42)
Female	8096	49.4	8.8	(0.4)	1.00	6.4	(0.4)	1.00
Race-ethnicity								
Non-Hispanic white	4244	59.9	9.3	(0.5)	1.00	7.3	(0.4)	1.00
Non-Hispanic black	5032	14.7	13.5	(0.7)	1.52 (1.28-1.80)	8.0	(0.5)	1.11 (0.93-1.31)
Mexican American	5396	12.5	6.4	(0.4)	0.67 (0.56-0.80)	4.3	(0.3)	0.57 (0.46-0.70)
Other	1402	12.9	9.5	(1.0)	1.03 (0.78-1.34)	6.6	(1.0)	0.89 (0.64-1.25)
Poverty Index (quartiles)								
1st	5332	23.6	9.7	(0.7)	0.98 (0.80-1.21)	7.2	(0.5)	1.07 (0.83-1.37)
2nd	4098	23.4	10.9	(0.9)	1.13 (0.94-1.36)	7.6	(0.7)	1.14 (0.86-1.51)
3rd	3007	23.7	8.3	(0.8)	0.83 (0.64-1.08)	6.7	(0.7)	0.99 (0.73-1.35)

Subject Characteristics	N	%	Current asthma (%, SE)		OR (95% CI)	Any medical visits for wheezing (%, SE)		OR (95% CI)
4th	2443	23.6	9.8	(0.7)	1.00	6.7	(0.6)	1.00
Missing/unknown	1194	5.7	8.0	(1.0)		5.3	(0.9)	
Any smokers in household								
Yes	3273	21.9	8.8	(0.6)	0.88 (0.75-1.03)	7.6	(0.7)	1.13 (0.90-1.40)
No	12609	78.1	9.9	(0.4)	1.00	6.8	(0.3)	1.00
Mother smoked during pregnancy*								
Yes	1721	18.9	10.0	(0.9)	1.07 (0.86-1.32)	9.9	(0.7)	1.43 (1.16-1.78)
No	9887	81.1	9.5	(0.5)	1.00	7.1	(0.4)	1.00
Birthweight*								
<2500 g	1004	7.4	12.5	(1.3)	1.38 (1.08-1.75)	9.1	(1.4)	1.24 (0.87-1.75)
≥2500 g	10410	92.6	9.4	(0.4)	1.00	7.5	(0.4)	1.00
Physical Activity								
0-3 times/wk	6109	34.4	9.1	(0.5)	0.83 (0.68-1.02)	5.4	(0.4)	0.74 (0.58-0.94)
4-6 times/wk	2768	18.1	9.7	(0.6)	0.89 (0.72-1.11)	7.5	(0.6)	1.05 (0.76-1.45)
7 times/wk	4043	29.2	9.3	(0.7)	0.85 (0.68-1.06)	8.6	(0.5)	1.22 (0.93-1.60)
8+ times/wk	2865	18.3	10.7	(0.9)	1.00	7.1	(0.8)	1.00
Average hours of TV/videos†								
0 hours/day	1696	14.1	9.3	(1.0)	1.00	7.3	(0.7)	1.00
1-2 hours/day	6364	50.1	9.4	(0.5)	1.01 (0.80-1.28)	6.6	(0.5)	1.10 (0.86-1.41)
3+ hours/day	5583	35.8	10.1	(0.7)	1.10 (0.87-1.40)	5.9	(0.6)	0.89 (0.68-1.17)
Average hours of computer†								
0 hours/day	4370	35.8	9.0	(0.5)	1.00	7.8	(0.6)	1.00
1-2 hours/day	3859	28.9	10.8	(0.7)	1.22 (1.04-1.45)	6.4	(0.5)	0.81 (0.66-1.00)
3+ hours/day	5409	35.3	9.4	(0.7)	1.06 (0.86-1.30)	7.6	(0.5)	0.97 (0.77-1.21)
C-reactive protein‡								
Not detectable	3472	24.3	8.7	(0.7)	1.00	5.9	(0.4)	1.00
0.02 – 0.04 mg/dL	3294	20.1	9.9	(0.7)	1.17 (0.91-1.50)	6.4	(0.6)	1.08 (0.83-1.41)

Subject Characteristics	N	%	Current asthma (%, SE)	OR (95% CI)	Any medical visits for wheezing (%, SE)	OR (95% CI)
0.04 – 0.14 mg/dL	3213	18.7	9.7 (0.8)	1.13 (0.88-1.46)	6.9 (0.7)	1.18 (0.89-1.57)
>0.14 mg/dL	3466	18.7	11.1 (0.6)	1.32 (1.09-1.58)	7.3 (0.7)	1.25 (0.97-1.60)
Missing/unknown	2629	9.6	8.8 (0.9)		8.7 (0.9)	

* Only available for subjects up to age 15.
† Only available for subjects up to age 15 in years 1999-2002.
‡ Values represent tertiles above detection.

Table 12. Distribution of overweight by population characteristics, NHANES 1999-2006, children and young adults age 2-19.

Subject Characteristics	N	Percent (SE) overweight	OR (95% CI)	Percent (SE) obese	OR (95% CI)
Overall	16074	15.0 (0.4)		16.2 (0.6)	
Survey Round					
1999-2000	3924	14.2 (0.7)	1.00	15.2 (0.9)	1.00
2001-2002	4124	14.7 (0.5)	1.05 (0.89-1.23)	15.7 (1.0)	1.04 (0.84-1.30)
2003-2004	3884	17.0 (0.7)	1.29 (1.07-1.56)	17.4 (1.3)	1.23 (0.96-1.57)
2005-2006	4112	14.2 (1.0)	1.02 (0.83-1.26)	16.5 (1.3)	1.11 (0.86-1.42)
Age					
2-5	3166	10.6 (0.7)	0.56 (0.46-0.70)	10.6 (0.8)	0.54 (0.44-0.67)
6-10	3467	16.0 (1.0)	1.00	16.8 (0.9)	1.00
11-14	4064	16.8 (0.7)	1.10 (0.86-1.40)	18.9 (1.2)	1.18 (1.01-1.38)
15-18	5377	15.9 (0.8)	1.01 (0.84-1.21)	17.6 (0.8)	1.06 (0.90-1.25)
Sex					
Male	7978	14.9 (0.5)	1.00 (0.90-1.12)	17.1 (0.7)	1.13 (1.02-1.26)
Female	8096	15.2 (0.5)	1.00	15.4 (0.7)	1.00
Race-ethnicity					
Non-Hispanic white	4244	14.7 (0.6)	1.00	14.3 (0.8)	1.00
Non-Hispanic black	5032	15.1 (0.5)	1.12 (0.97-1.30)	20.3 (0.6)	1.55 (1.32-1.83)
Mexican American	5396	17.2 (0.5)	1.34 (1.17-1.54)	21.0 (0.8)	1.68 (1.43-1.98)
Other	1402	14.3 (1.1)	0.99 (0.79-1.24)	16.0 (1.3)	1.14 (0.90-1.43)
Poverty Index (quartiles)					
1st	5332	15.5 (0.7)	1.29 (1.08-1.53)	18.4 (0.9)	1.60 (1.34-1.90)
2nd	4098	15.4 (1.0)	1.25 (1.02-1.54)	17.6 (0.9)	1.51 (1.21-1.89)
3rd	3007	15.5 (1.0)	1.24 (1.02-1.51)	16.1 (1.0)	1.35 (1.09-1.67)
4th	2443	13.5 (0.7)	1.00	12.8 (1.0)	1.00
Missing/unknown	1194	15.9 (1.8)		17.0 (1.8)	
Any smokers in household					

Subject Characteristics	N	Percent (SE) overweight	OR (95% CI)	Percent (SE) obese	OR (95% CI)
Yes	3273	15.6 (1.0)	1.12 (0.95-1.32)	19.4 (1.1)	1.35 (1.17-1.57)
No	12609	15.0 (0.4)	1.00	15.3 (0.6)	1.00
Mother smoked during pregnancy*					
Yes	1721	17.2 (1.2)	1.33 (1.09-1.62)	18.5 (1.3)	1.34 (1.13-1.59)
No	9887	14.3 (0.5)	1.00	15.1 (0.6)	1.00
Birthweight*					
<2500 g	1004	12.6 (1.6)	0.77 (0.58-1.01)	13.0 (1.5)	0.74 (0.57-0.97)
≥2500 g	10410	15.1 (0.4)	1.00	16.1 (0.7)	1.00
Physical Activity					
0-3 times/wk	6109	14.9 (0.7)	0.95 (0.80-1.12)	19.2 (0.8)	1.50 (1.22-1.86)
4-6 times/wk	2768	15.3 (0.9)	0.93 (0.74-1.16)	15.3 (1.1)	1.14 (0.95-1.38)
7 times/wk	4043	13.9 (0.9)	0.82 (0.65-1.03)	15.0 (0.8)	1.09 (0.86-1.38)
8+ times/wk	2865	16.7 (1.1)	1.00	13.5 (1.2)	1.00
Average hours of TV/videos†					
0 hours/day	1696	13.8 (1.2)	1.00	9.6 (1.0)	1.00
1-2 hours/day	6364	14.7 (0.6)	1.15 (0.92-1.45)	15.1 (0.8)	1.71 (1.34-2.19)
3+ hours/day	5583	15.8 (0.6)	1.36 (1.08-1.72)	20.1 (1.0)	2.50 (1.91-3.25)
Average hours of computer†					
0 hours/day	4370	14.8 (0.7)	1.00	15.4 (0.9)	1.00
1-2 hours/day	3859	16.0 (0.8)	1.12 (0.94-1.34)	16.7 (0.9)	1.12 (0.94-1.34)
3+ hours/day	5409	14.2 (0.6)	0.97 (0.83-1.13)	16.5 (0.7)	1.08 (0.94-1.23)
C-reactive protein‡					
Not detectable	3472	8.0 (0.7)	1.00	2.3 (0.3)	1.00
0.02 – 0.04 mg/dL	3294	15.7 (0.7)	2.37 (1.88-2.99)	9.8 (0.8)	5.10 (3.90-6.68)
0.04 – 0.13 mg/dL	3213	22.3 (1.0)	4.53 (3.63-5.66)	22.1 (1.0)	15.4 (11.8-20.0)
>0.13 mg/dL	3466	19.0 (1.1)	5.07 (3.93-6.54)	38.7 (1.6)	35.4 (26.6-47.1)
Missing/unknown	2629	12.1 (0.9)		12.8 (1.0)	

* Only available for subjects up to age 15.
† Only available for subjects up to age 15 in years 1999-2002.
‡ Values represent tertiles above detection.

Table 13. Asthma and wheeze outcomes by weight category (BMI percentile for age), NHANES 1999-2006, children and young adults age 2-19, N=16,074.

Allergy Outcome	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†
Current asthma				
Normal weight	922/10,529	8.4 (0.4)	1.00	1.00
Overweight	293/2,520	11.1 (1.0)	1.36 (1.13-1.65)	1.32 (1.08-1.60)
Obese	381/3,025	13.2 (1.1)	1.65 (1.33-2.05)	1.68 (1.33-2.12)
Asthma attack in past year				
Normal weight	515/10,529	5.0 (0.3)	1.00	1.00
Overweight	168/2,519	6.8 (0.8)	1.44 (1.15-1.80)	1.41 (1.11-1.78)
Obese	225/3,025	8.7 (0.7)	1.87 (1.57-2.22)	1.97 (1.66-2.34)
ED visit for asthma in past year				
Normal weight	203/10,529	1.5 (0.2)	1.00	1.00
Overweight	57/2,519	2.0 (0.3)	1.38 (0.84-2.27)	1.38 (0.94-2.04)
Obese	72/3,025	2.4 (0.4)	1.46 (0.93-2.29)	1.68 (1.17-2.40)
Wheeze in past year				
Normal weight	1,174/10,516	11.7 (0.5)	1.00	1.00
Overweight	321/2,518	14.2 (1.0)	1.25 (1.05-1.49)	1.25 (1.05-1.50)
Obese	451/3,022	17.4 (1.4)	1.60 (1.32-1.94)	1.63 (1.33-2.00)
Medical visit for wheeze in past year				
Normal weight	610/10,369	6.1 (0.3)	1.00	1.00
Overweight	171/2,483	8.0 (0.7)	1.43 (1.15-1.78)	1.40 (1.11-1.75)
Obese	226/2,962	8.9 (0.8)	1.64 (1.29-2.07)	1.64 (1.28-2.09)
Miss school/work due to wheezing				
Normal weight	289/10,048	3.0 (0.2)	1.00	1.00
Overweight	100/2,420	4.9 (0.7)	1.65 (1.18-2.31)	1.56 (1.10-2.22)

Allergy Outcome	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†
Obese	151/2,903	6.1 (0.7)	2.10 (1.53-2.88)	2.10 (1.50-2.96)

* Model adjusted for age only.

† Model adjusted for age, survey round, race/ethnicity, sex, poverty income ratio, household smoking, and level of physical activity.

Table 14. Asthma and wheeze outcomes by weight category (BMI percentile for age) and gender, NHANES 1999-2006, children and young adults age 2-19.

	Boys (N=7,978)			Girls (N=8,096)			
Allergy Outcome	Percent (SE)	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Percent (SE)	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Interaction p-value
Current asthma							
Normal weight	9.1 (0.6)	1.00	1.00	7.7 (0.4)	1.00	1.00	0.93
Overweight	11.8 (1.2)	1.38 (1.10-1.73)	1.39 (1.08-1.78)	10.4 (1.4)	1.35 (1.00-1.83)	1.25 (0.92-1.69)	
Obese	13.8 (1.7)	1.65 (1.21-2.26)	1.72 (1.24-2.40)	12.5 (1.3)	1.65 (1.22-2.22)	1.68 (1.23-2.29)	
Asthma attack in past year							
Normal weight	5.3 (0.4)	1.00	1.00	4.6 (0.4)	1.00	1.00	0.26
Overweight	8.1 (1.1)	1.66 (1.28-2.15)	1.64 (1.24-2.16)	5.6 (1.0)	1.21 (0.83-1.76)	1.16 (0.78-1.74)	
Obese	8.5 (1.0)	1.77 (1.36-2.31)	1.88 (1.44-2.45)	8.9 (1.0)	1.99 (1.45-2.72)	2.16 (1.59-2.93)	
ED visit for asthma in past year							
Normal weight	2.0 (0.3)	1.00	1.00	1.0 (0.1)	1.00	1.00	0.38
Overweight	2.5 (0.5)	1.38 (0.84-2.27)	1.38 (0.82-2.30)	1.4 (0.4)	1.47 (0.81-2.67)	1.38 (0.71-2.69)	
Obese	2.6 (0.5)	1.46 (0.93-2.29)	1.43 (0.89-2.29)	2.2 (0.5)	2.32 (1.30-4.13)	2.21 (1.20-4.05)	
Wheeze in past year							
Normal weight	12.1 (0.6)	1.00	1.00	11.3 (0.6)	1.00	1.00	0.67
Overweight	15.5 (1.3)	1.37 (1.10-1.72)	1.41 (1.11-1.79)	12.8 (1.5)	1.13 (0.86-1.49)	1.10 (0.83-1.46)	
Obese	18.6 (2.2)	1.72 (1.26-2.33)	1.77 (1.29-2.42)	16.0 (1.3)	1.47 (1.16-1.86)	1.52 (1.20-1.92)	
Medical visit for wheeze in past year							
Normal weight	6.8 (0.5)	1.00	1.00	5.4 (0.4)	1.00	1.00	0.04
Overweight	9.1 (1.2)	1.52 (1.09-2.12)	1.46 (1.03-2.08)	6.9 (0.9)	1.35 (0.97-1.86)	1.31 (0.93-1.83)	
Obese	8.0 (1.1)	1.33 (0.94-1.90)	1.34 (0.94-1.92)	10.0 (1.0)	2.04 (1.53-2.72)	2.05 (1.51-2.78)	

	Boys (N=7,978)			Girls (N=8,096)			
Allergy Outcome	Percent (SE)	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Percent (SE)	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Interaction p-value
Miss school/work due to wheezing							
Normal weight	3.4 (0.4)	1.00	1.00	2.5 (0.3)	1.00	1.00	0.74
Overweight	5.5 (0.9)	1.66 (1.14-2.42)	1.55 (1.04-2.32)	4.3 (0.8)	1.64 (1.05-2.58)	1.60 (0.99-2.59)	
Obese	6.4 (1.1)	1.95 (1.30-2.92)	1.91 (1.24-2.94)	5.9 (0.9)	2.29 (1.51-3.47)	2.45 (1.60-3.74)	

* Model adjusted for age only.

† Model adjusted for age, survey round, race/ethnicity, sex, poverty income ratio, household smoking, and level of physical activity.

Table 15. Asthma and wheeze outcomes by weight category (BMI percentile for age) and atopic status, NHANES 2005-06, children and young adults age 2-19, N=3,387.

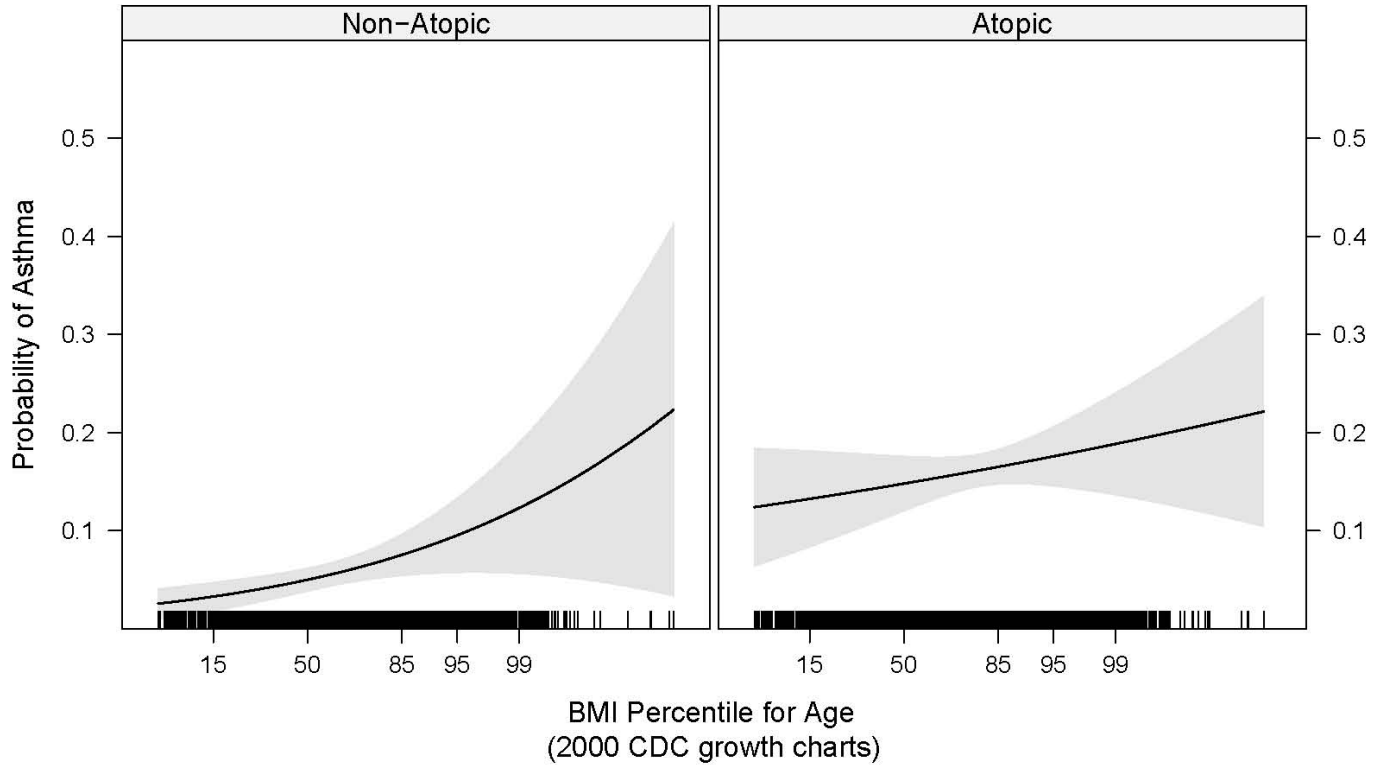
	Non-Atopic (N=1,640)				Atopic (N=1,737)				
Asthma Outcome	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Inter-action p-value
Current asthma									
Normal weight	61/1,092	5.3 (0.6)	1.00	1.00	148/1,063	15.3 (1.5)	1.00	1.00	0.09
Overweight	19/247	7.9 (2.1)	1.51 (0.78-2.89)	1.29 (0.65-2.53)	39/276	15.6 (2.1)	1.03 (0.71-1.51)	1.05 (0.76-1.45)	
Obese	23/301	10.9 (3.6)	2.16 (1.10-4.22)	2.46 (1.21-5.02)	59/398	18.0 (3.5)	1.23 (0.68-2.22)	1.34 (0.70-2.57)	
Asthma attack in past year									
Normal weight	29/1,063	3.3 (0.7)	1.00	1.00	79/1,063	9.0 (1.3)	1.00	1.00	0.42
Overweight	11/236	5.4 (2.1)	1.68 (0.70-4.03)	1.35 (0.53-3.42)	30/276	13.0 (2.5)	1.57 (0.98-2.52)	1.64 (1.10-2.43)	
Obese	13/301	6.6 (1.9)	2.07 (1.24-3.44)	2.45 (1.31-4.58)	29/398	11.0 (2.5)	1.29 (0.68-2.44)	1.47 (0.74-2.92)	
Wheeze in past year									
Normal weight	80/1,094	7.3 (1.0)	1.00	1.00	165/1,065	18.2 (2.0)	1.00	1.00	0.07
Overweight	16/247	10.3 (2.4)	1.50 (0.80-2.81)	1.52 (0.77-2.98)	45/277	18.1 (2.0)	0.98 (0.68-1.43)	0.97 (0.69-1.38)	
Obese	31/301	14.2 (3.6)	2.16 (1.10-4.23)	2.20 (1.15-4.22)	61/401	16.6 (2.3)	0.88 (0.57-1.37)	0.85 (0.54-1.36)	
Medical visit for wheeze in past year									
Normal weight	48/1,094	4.0 (0.8)	1.00	1.00	90/1,065	10.3 (1.4)	1.00	1.00	0.40
Overweight	10/247	5.3 (1.5)	1.53 (0.74-3.16)	1.68 (0.86-3.27)	22/277	8.5 (2.3)	0.86 (0.49-1.50)	0.85 (0.49-1.48)	
Obese	16/301	6.9 (2.5)	2.04 (1.02-4.10)	2.14 (0.95-4.78)	28/401	10.2 (2.4)	1.04 (0.60-1.81)	1.10 (0.60-2.00)	

	Non-Atopic (N=1,640)				Atopic (N=1,737)				
Asthma Outcome	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Number with outcome/ Total in weight category	Percent (SE) with Outcome	Odds Ratio (95% CI) Unadjusted Model*	Odds Ratio (95% CI) Adjusted Model†	Inter-action p-value
Miss school/work due to wheezing									
Normal weight	22/1,065	2.4 (0.6)	1.00	1.00	50/1,036	5.6 (1.2)	1.00	1.00	0.04
Overweight	6/245	3.4 (1.7)	1.46 (0.47-4.50)	1.54 (0.57-4.18)	15/269	7.5 (2.5)	1.36 (0.56-3.31)	1.41 (0.56-3.55)	
Obese	11/299	4.8 (1.8)	2.09 (0.86-5.08)	2.17 (1.00-4.71)	18/392	4.3 (1.3)	0.76 (0.36-1.61)	0.77 (0.35-1.69)	

* Model adjusted for age only.

† Model adjusted for age, survey round, race/ethnicity, sex, poverty income ratio, household smoking, and level of physical activity.

Figure 5. Probability of current asthma by BMI percentile-for-age and atopy, NHANES 2005-2006, children and young adults age 2-19. The shaded region represents the 95% confidence limits of the data. The black lines represent observations and show where the data lie on the on the BMI distribution. The x axis is plotted as the z-score for BMI-for-age and labeled with the transformation of z-scores to percentiles.



C. Manuscript 3: Does Obesity or Atopy Modify the Effect of Breastfeeding on Asthma?

C.1. Introduction

Both obesity and asthma have been increasing over the last several decades,[1, 159] and studies over the last fifteen years have suggested that obesity is related to asthma.[3-5] Atopy is a strong risk factor for asthma. A factor that may protect against obesity, atopy, and asthma is breastfeeding. Breastfeeding could exert its protective effect against asthma by reducing obesity or by preventing atopy.

Much research has been done over the past several decades on the effect of breastfeeding on allergic diseases and asthma, and it has largely shown that breastfeeding reduces the risk of developing these diseases.[138] However, conflicting findings have also been reported.[139, 140] The general consensus in the medical community is that breastfeeding reduces the risk of allergic disease, and some have put forth breastfeeding promotion as a method of primary asthma prevention.[141, 142]

Previous research on National Health and Nutrition Examination Survey (NHANES) III data showed a protective effect of breastfeeding on asthma and recurrent wheeze that disappeared after adjustment for confounding for sex, age, race/ethnicity, birth weight, parental education, daycare attendance, parental asthma or hay fever, household smoke exposure, and whether the mother smoked during pregnancy.[174] Another analysis of NHANES III data found a reduced risk of being overweight (≥ 85th percentile of BMI for age) at age 5 for children who were ever breastfed compared to those not breastfed (OR=0.63, 95% CI: 0.41, 0.96), but no significant protection against obesity ≥ 95th percentile of BMI for age).[137]

In two research studies that specifically examined the interaction of overweight and breastfeeding on the development of asthma, one found an interaction,[145] but the other did not.[146]

This analysis uses NHANES data from 1999-2006 to examine the associations between breastfeeding, obesity, atopy, and asthma, to investigate the possibility of a pathway to asthma from breastfeeding through atopy and through obesity, and to explore modification of the effect of breastfeeding on asthma by weight status and by atopy.

C.2. Methods

C.2.1. Study Population

The NHANES is a nationally representative survey conducted periodically to assess the health and nutritional status of adults and children in the United States.[163] Details about the NHANES may be found online at http://www.cdc.gov/nchs/nhanes.htm.

The target population of NHANES is the civilian, non-institutionalized population of the U.S. The NHANES uses a stratified, multi-stage probability sampling design with oversampling of persons believed to be at increased health risk. Weights are supplied with the public use dataset so that estimates can be produced that reflect the US population distribution and can be considered to be nationally representative. Of the 5,576 children age 1-6 in the combined 1999-2006 NHANES, 5,245 (94%) had complete information on height, weight, asthma status and breastfeeding.

C.2.2 Breastfeeding Measures

A proxy interviewee for all participants aged 0-6 years responded to questions regarding infant feeding. Information is available for whether the child had ever been breastfed (yes/no), the duration of total breastfeeding, and the duration of exclusive breastfeeding (anything to eat or drink other than breastmilk or water). For this analysis, these duration variables were categorized into two groups: < 4 months and ≥ 4 months, with

no breastfeeding serving as the reference group. Four months was chosen to allow comparison with previous work.[174]

C.2.3. Asthma Outcome

All caregivers of children age 1 and above were asked whether a doctor or other health professional had ever said their child had asthma. The primary outcome for these analyses was a report of ever having an asthma diagnosis (yes/no).

C.2.4. Atopy

Children aged 1 to 5 years were tested for allergen-specific IgE to dust mite (*D. farinae* and *D. pteronyssinus*), cat, dog, cockroach, alternaria, peanut, egg, and milk. A detailed description of the laboratory method can be found at NHANES 2005-2006 web page (http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/al_ige_d.pdf). Atopy has been defined in these analyses as a positive IgE response (≥ 0.35 kU/L) to at least one of the allergens tested. In order to be included in the atopy analyses, the child had to have information for the full panel of 9 allergens. Six-year old children were tested for a larger panel of allergens, but atopy was defined for this analysis based on the smaller panel for 1-5 year olds. Atopy information was available for 982 children in the 2005-2006 survey age 1-6 who also had information on breastfeeding, obesity, and asthma.

C.2.5. Weight Measurements

Weight and height measurements taken during the medical examination were used to calculate weight-for-length or body mass index (BMI; weight in kilograms divided by height in meters squared). Percentiles for both weight-for-length and percentile-for-age were calculated separately for boys and girls, using the Centers for Disease Control and Prevention 2000 reference standards.[153] Weight-for-length percentiles were used for children ages 1-2, and BMI percentile-for-age was used for children ages 3-6 to define obesity. Children at or above the 95th percentile were considered obese.[154]

C.2.6. Other Measures

Covariates included in modeling to adjust for factors suspected *a priori* to confound the measured associations were the age, sex, and race/ethnicity of the child, maternal smoking during pregnancy (yes/no), birthweight (low birthweight vs. not), the poverty income ratio (the relationship of family income to the family's appropriate poverty threshold based on family size and composition),[164] and survey year (except in models for atopy).

C.2.7. Statistical Analyses

The effects of breastfeeding on obesity, asthma and atopy were examined in unadjusted and adjusted models using logistic regression.

In order to examine whether there is any evidence that breastfeeding might operate through obesity or through atopy to affect asthma development, models were constructed to assess the effect on asthma of the hypothesized intermediate variables – obesity and atopy – while adjusting for each of the breastfeeding variables separately (any breastfeeding, duration of breastfeeding, and duration of exclusive breastfeeding) in addition to the other covariates. If, for example, breastfeeding were a primary determinant of obesity, and obesity were a primary determinant of asthma, without many other factors influencing these relationships, we would expect to see the obesity-asthma relationship significantly attenuated when adjusting for breastfeeding.

In addition, potential modification of the effect of breastfeeding on asthma was examined for both obesity and atopy in adjusted models. A p-value for the interaction term < 0.15 was considered evidence of interaction.

All analyses were performed using the survey sampling weights and SAS survey sampling procedures to adjust for the NHANES complex sampling design (Version 9.1.3, Cary, NC).

C.3. Results

Table 16 shows the prevalence of breastfeeding, obesity, asthma, and atopy by the model covariates. Overall, 65.2% of children had ever been breastfed, 10.5% were classified as obese at the time of the survey, 11.7% had received a diagnosis of asthma at some time in their lives, and 37.8% had at least one positive allergen-specific IgE test.

Table 17 shows that breastfeeding protected against asthma in this population of children, and that the protection did not differ for a longer duration of any breastfeeding or exclusive breastfeeding. Breastfeeding also protected against obesity, and in this case, the effect was seen most strongly among those exclusively breastfed at least 4 months. There was some evidence for a protective effect against atopy for those exclusively breastfed for 4 months or longer. Because the sample for the atopy analysis was smaller, the estimates were less precise.

Children who were obese at the time of the survey were more likely to report a diagnosis of asthma (OR 1.61, 95% CI: 1.13-2.30; Table 18). This effect estimate did not change when the model was adjusted for ever being breastfed, the duration of breastfeeding, or the duration of exclusive breastfeeding.

Atopy was shown to be a very strong risk factor for asthma (OR 3.08, 95% CI: 1.97-4.80; Table 18). This effect estimate was also unchanged when adjusting for the breastfeeding variables.

In models stratified by obesity (Table 19), breastfeeding was shown to be protective against asthma among those not obese at the time of the survey (OR 0.65, 95% CI: 0.51-0.84), but not among obese children (OR 1.04, 95% CI: 0.54-1.99). The p-value for this interaction effect was 0.19, which did not quite meet the pre-specified criterion for important effect modification. When stratified by atopic status, the relationship between breastfeeding

and asthma was similar for atopic (OR 0.54, 95% CI: 0.22-1.31) and non-atopic (OR 0.47, 95% CI: 0.17-1.27) children.

C.4. Discussion

This analysis reports findings from a representative survey of U.S. children and shows that breastfeeding is protective against both childhood obesity and asthma. These findings differ from those using NHANES III data, where an effect for breastfeeding on asthma was not observed after adjustment for confounders.[174] Longer duration of breastfeeding and longer duration of exclusive breastfeeding appear to offer somewhat greater benefit against obesity, but not asthma. Evidence for an effect of breastfeeding on atopy was less strong and imprecise, which was likely because of the smaller sample size for this analysis. Still, among children exclusively breastfed for at least 4 months, the OR for atopy was 0.75, which is in the expected direction, given the weight of evidence in the literature on breastfeeding and allergic disease.

If breastfeeding were a common determinant of obesity, atopy, and asthma, or protected against asthma by protecting against obesity and/or atopy, we would expect breastfeeding to act as a confounder in models of the effect of obesity on asthma and of atopy on asthma. This was found not to be the case in these data, suggesting that breastfeeding, obesity, and atopy have largely independent effects on the development of asthma in children.

In stratified models, we found the inverse association between breastfeeding and asthma to be present among non-obese children, but absent or masked among obese children. Similar models showed that breastfeeding did not differentially affect the risk of asthma among atopic and non-atopic children. However, the power to assess this effect modification was limited by sample size, since only the 2005-2006 survey assayed IgE levels.

These NHANES data come from a cross-sectional survey making it impossible to assign causality to these associations. There are undoubtedly many influences on the development of obesity, atopy, and asthma in children. While breastfeeding may make an important contribution early in life, it is possible that those effects can be countered or overridden by later exposures and/or genetic influences which were not measured here. A recent analysis of a large birth cohort with objective outcomes for atopy and bronchial hyperresponsiveness found that breastfeeding was protective against wheeze in early childhood, but the protective effect was not evident against atopy or asthma in older children.[144] This study also found that maternal allergy was an important confounder of the relationship between breastfeeding and atopy. Unfortunately, data on maternal allergy or asthma history are not available in the public use NHANES data since 1999.

This analysis does not provide evidence to support hypotheses that breastfeeding influences the risk of asthma by preventing obesity or atopy in children. However, breastfeeding was shown to protect against both obesity and asthma, and the association between breastfeeding and asthma was only remarkable among non-obese children. Pediatricians should continue to encourage breastfeeding according to the recommendations of the American Academy of Pediatrics.[175]

Table 16. Distribution of breastfeeding, obesity, asthma, and atopy by population characteristics, NHANES 1999-2006, children age 1-6.

Subject Characteristics	N	%	Ever BF (%)	OR (95% CI)	Obese (%)	OR (95% CI)	Ever asthma (%)	OR (95% CI)	N*	Atopy† (%)	OR (95% CI)
Overall	5258		65.2		10.5		11.7		982	37.8	
Survey round											
1999-2000	1149	23.4	62.0	1.00	9.7	1.00	13.9	1.00			
2001-2002	1264	23.7	63.9	1.08 (0.70-1.66)	9.6	0.99 (0.68-1.45)	10.6	0.74 (0.48-1.13)			
2003-2004	1330	26.2	63.6	1.07 (0.70-1.64)	11.9	1.26 (0.88-1.82)	10.1	0.69 (0.48-1.00)			
2005-2006	1515	26.7	70.8	1.49 (1.02-2.17)	10.5	1.09 (0.75-1.59)	12.1	0.85 (0.54-1.35)	982	37.8	
Age											
1-3	3017	49.0	65.5	1.02 (0.90-1.16)	7.4	0.51 (0.41-0.63)	9.3	0.63 (0.51-0.78)	531	33.6	0.72 (0.50-1.02)
4-6	2241	51.0	65.0	1.00	13.5	1.00	13.9	1.00	451	41.5	1.00
Sex											
Male	2648	50.6	65.3	1.00 (0.90-1.12)	11.2	1.16 (0.92-1.46)	14.4	1.73 (1.43-2.10)	483	38.7	1.09 (0.76-1.56)
Female	2610	49.4	65.2	1.00	9.8	1.00	8.9	1.00	499	36.7	1.00
Race-ethnicity											
Non-Hispanic white	1535	58.8	67.4	1.00	9.5	1.00	10.5	1.00	280	31.7	1.00
Non-Hispanic black	1472	13.9	43.2	0.37 (0.28-0.48)	11.0	1.19 (0.92-1.54)	18.2	1.88 (1.43-2.47)	233	50.7	2.21 (1.62-3.03)
Mexican American	1697	14.5	73.0	1.31 (0.97-1.77)	14.0	1.56 (1.19-2.04)	8.0	0.74 (0.53-1.02)	359	42.7	1.60 (1.20-2.14)
Other	554	12.8	70.5	1.16 (0.88-1.52)	10.4	1.12 (0.74-1.68)	13.9	1.37 (0.97-1.95)	110	46.4	1.87 (1.18-2.96)
Poverty Income Ratio (quartiles)											
1st	1766	23.4	52.8	0.28 (0.21-0.36)	11.1	1.25 (0.90-1.74)	12.9	1.18 (0.84-1.65)	297	40.7	1.15 (0.81-1.63)
2nd	1379	23.8	59.4	0.36 (0.27-0.48)	11.4	1.28 (0.86-1.92)	13.1	1.20 (0.88-1.63)	289	36.0	0.94 (0.62-1.41)
3rd	968	23.6	70.3	0.58 (0.42-0.80)	10.0	1.11 (0.73-1.70)	9.7	0.85 (0.54-1.33)	202	35.4	0.92 (0.68-1.24)
4th	786	23.6	80.3	1.00	9.1	1.00	11.2	1.00	148	37.4	1.00
Missing/unknown	359	5.6	57.2	--	11.2	--	10.7	--	46	54.0	--

Subject Characteristics	N	%	Ever BF (%)	OR (95% CI)	Obese (%)	OR (95% CI)	Ever asthma (%)	OR (95% CI)	N*	Atopy† (%)	OR (95% CI)
Mother smoked during pregnancy											
Yes	748	17.6	45.0	0.35 (0.29-0.43)	13.3	1.41 (1.06-1.86)	13.0	1.17 (0.90-1.53)	136	31.6	0.72 (0.51-1.01)
No	4492	82.4	69.9	1.00	9.8	1.00	11.4	1.00	844	39.1	1.00
Birthweight											
<2500 g	491	8.5	51.7	0.54 (0.38-0.76)	8.4	0.76 (0.49-1.19)	20.5	2.11 (1.53-2.92)	88	30.8	0.72 (0.41-1.26)
≥2500 g	4672	91.5	66.6	1.00	10.7	1.00	10.9	1.00	878	38.2	1.00

* Atopy information only available in the 2005-2006 survey.

† Atopy defined as at least one positive allergen-specific IgE result to egg, milk, peanut, dust mite (*D. farinae* and *D. pteronyssinus*), cat, dog, cockroach, or alternaria.

Table 17. Asthma, obesity, and atopy by breastfeeding status, NHANES 1999-2006, children age 1-6.

Outcome	n/N	Percent (SE)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)
Ever had asthma				
Breastfed	333/3245	10.0 (0.8)	0.64 (0.53-0.78)	0.74 (0.58-0.95)
Not breastfed	314/2013	14.8 (1.1)	1.00	1.00
Ever had asthma				
Breastfed ≥ 4 months	202/2038	10.0 (1.0)	0.64 (0.51-0.80)	0.71 (0.52-0.96)
Breastfed < 4 months	136/1188	10.1 (1.2)	0.65 (0.48-0.87)	0.77 (0.57-1.04)
Not breastfed	314/2013	14.8 (1.1)	1.00	1.00
Ever had asthma				
Exclusively breastfed ≥ 4	134/1417	9.7 (1.1)	0.62 (0.49-0.78)	0.72 (0.54-0.96)
Exclusively breastfed < 4	204/1816	10.3 (1.1)	0.66 (0.52-0.85)	0.76 (0.57-1.02)
Not breastfed	314/2013	14.8 (1.1)	1.00	1.00
Obese (≥ 95th percentile)				
Breastfed	347/3245	9.7 (0.7)	0.80 (0.63-1.01)	0.84 (0.62-1.15)
Not breastfed	244/2013	11.9 (1.1)	1.00	1.00
Obese (≥ 95th percentile)				
Breastfed ≥ 4 months	199/2038	8.6 (0.8)	0.70 (0.54-0.92)	0.73 (0.52-1.03)
Breastfed < 4 months	146/1188	11.7 (1.2)	0.98 (0.72-1.33)	1.03 (0.73-1.44)
Not breastfed	244/2013	11.9 (1.1)	1.00	1.00
Obese (≥ 95th percentile)				
Exclusively breastfed ≥ 4	124/1417	7.8 (0.8)	0.63 (0.47-0.83)	0.63 (0.45-0.90)
Exclusively breastfed < 4	220/1816	11.2 (0.9)	0.94 (0.71-1.23)	1.01 (0.73-1.39)
Not breastfed	244/2013	11.9 (1.1)	1.00	1.00
Atopy (at least 1 positive skin test)				
Breastfed	269/675	37.6 (2.3)	0.98 (0.75-1.29)	0.90 (0.67-1.22)
Not breastfed	132/307	38.0 (2.4)	1.00	1.00
Atopy (at least 1 positive skin test)				
Breastfed ≥ 4 months	176/442	37.2 (3.1)	0.96 (0.68-1.36)	0.89 (0.61-1.29)
Breastfed < 4 months	92/228	39.1 (4.3)	1.05 (0.72-1.52)	0.98 (0.68-1.41)
Not breastfed	132/307	38.0 (2.4)	1.00	1.00
Atopy (at least 1 positive skin test)				
Exclusively breastfed ≥ 4	117/312	33.9 (3.4)	0.84 (0.60-1.16)	0.75 (0.51-1.09)
Exclusively breastfed < 4	151/361	41.2 (3.1)	1.14 (0.81-1.59)	1.08 (0.76-1.52)
Not breastfed	132/307	38.0 (2.4)	1.00	1.00

*Adjusted for age, race/ethnicity, birthweight, sex, poverty income ratio, smoking during pregnancy, and survey round (except in atopy models).
†Atopy available in 2005-06 data only.

Table 18. Association of obesity and of atopy with asthma, adjusted for breastfeeding, NHANES 1999-2006, children age 1-6.

Outcome	Odds Ratio* (95% CI)	Odds Ratio Adjusted for Any Breastfeeding (95% CI)	Odds Ratio Adjusted for Breastfeeding Duration (95% CI)	Odds Ratio Adjusted for Exclusive Breastfeeding Duration (95% CI)
Ever had asthma				
Obese	1.61 (1.13-2.30)	1.60 (1.11-2.30)	1.61 (1.11-2.33)	1.61 (1.11-2.32)
Not obese	1.00	1.00	1.00	1.00
Ever had asthma				
Atopic	3.08 (1.97-4.80)	3.06 (1.98-4.74)	3.03 (1.95-4.69)	3.04 (1.99-4.64)
Not atopic	1.00	1.00	1.00	1.00

*All odds ratios are adjusted for age, race/ethnicity, birthweight, sex, poverty income ratio, and smoking during pregnancy. The obesity models are further adjusted for survey year.

Table 19. Association of breastfeeding wtih asthma, stratified by obesity and by atopy, NHANES 1999-2006, children age 1-6.

Outcome	Odds Ratio for Any Breastfeeding (95% CI)	Interaction p-value	Odds Ratio for Breastfeeding Duration (95% CI)	Interaction p-value	Odds Ratio for Exclusive Breastfeeding Duration (95% CI)	Interaction p-value
Obese		0.19		0.06		0.22
Breastfed ≥ 4 months/Any breastfeeding	1.04 (0.54-1.99)		1.38 (0.69-2.76)		0.78 (0.33-1.86)	
Breastfed < 4 months			0.67 (0.29-1.56)		1.22 (0.62-2.40)	
Not breastfed	1.00		1.00		1.00	
Not Obese						
Breastfed ≥ 4 months/Any breastfeeding	0.65 (0.51-0.84)		0.66 (0.48-0.89)		0.66 (0.49-0.90)	
Breastfed < 4 months			0.66 (0.48-0.89)		0.65 (0.47-0.89)	
Not breastfed	1.00		1.00		1.00	
Atopic		0.99		0.38		0.80
Breastfed ≥ 4 months/Any breastfeeding	0.54 (0.22-1.31)		0.63 (0.27-1.47)		0.59 (0.23-1.52)	
Breastfed < 4 months			0.39 (0.11-1.41)		0.50 (0.18-1.44)	
Not breastfed	1.00		1.00		1.00	
Not Atopic						
Breastfed ≥ 4 months/Any breastfeeding	0.47 (0.17-1.27)		0.36 (0.12-1.11)		0.36 (0.11-1.18)	
Breastfed < 4 months			0.73 (0.26-2.02)		0.61 (0.23-1.65)	
Not breastfed	1.00		1.00		1.00	

CHAPTER VI: DISCUSSION

A. Findings and Strengths

These studies used cross-sectional survey data from a large representative survey of the U.S. population to examine the relationships among obesity, infant feeding, allergic disease, and asthma. The large size and representativeness of the NHANES sample provide a wonderful opportunity to examine these relationships in U.S. children in the 21st century. This dataset is the largest dataset of serum IgE levels ever collected, providing an objective assessment of allergic disease in the U.S. population.

In the first analysis, it was shown that overweight and obesity were related to total IgE levels and to atopy, defined as at least one positive allergen-specific IgE result, but not to allergy symptoms and hay fever. The relationship between weight and atopy has not been examined often in children, and never, to my knowledge, using total and allergen-specific IgE tests.

Previous work using the NHANES III dataset[115] did not find a significant relationship between overweight and atopy in children age 4-17. Apart from the different age range, the major difference between the studies was that the earlier work used quartiles of BMI rather than percentiles of BMI-for-age. In order to relate the present findings more directly to this previous work and to examine why the findings were different, a separate analysis was run using quartiles of BMI in the 2005-2006 data. A dose-response effect for total IgE was still found across these quartiles (see Table A1 in the Appendix), lending credence to the finding of a continuous relationship as pictured in Figure 3. No relationship was found with atopy in this analysis, however. These analyses used quartiles of “raw” BMI, and while the models

were adjusted for age and sex, the method differs substantially from the recommended transformation of BMI to a percentile based on the CDC sex-specific growth curves of BMI-for-age. The implication is that the CDC percentiles and categories of overweight and obese for children are more informative than simple BMI for children, and that perhaps, had the NHANES III data been analyzed in this manner, the findings might have been more like those presented in Chapter IV.

The relationship between obesity and atopy did not differ by gender, although the correlation between BMI and total IgE was stronger for girls than it was for boys. These analyses using the IgE data were surprisingly consistent across weight categories and between males and females. The finding that BMI was associated in a continuous fashion with total IgE has never been shown before and demonstrates that overweight may increase allergic predisposition. There were some interesting findings regarding race and gender, particularly that there was no relationship in Mexican-American girls, but at this level of stratification the estimates become somewhat imprecise, and it is probably prudent not to make too much of this finding.

In the second analysis, overweight and obesity were found to be related to asthma. This finding is not new; however, there have been inconsistencies in the literature about this relationship in children. Because the main analysis of the obesity/asthma relationship was done on such a large dataset (more than 16,000 U.S. children and young adults) and the findings were so consistent across categories of weight and various asthma and wheeze outcomes, we can feel confident that this relationship is real. It is also interesting, perhaps even reassuring, that the findings were consistent for males and females. A number of previous studies have found gender differences, but Chinn noted in a recent review that evidence was very weak for gender differences in children or adolescents.[67] This is an important contribution to the literature, if not a definitive statement about the relationship between obesity and asthma in U.S. children.

In both studies a dose response effect was seen for the weight categories on atopy and on asthma, in that the effect was typically stronger for the obese category than the overweight category. In addition, BMI as a continuous variable was found to be related to total IgE and to the probability of current asthma in a linear fashion. This suggests that there is nothing magic about the clinical cut-offs for overweight and obesity in children, but that increasing weight at any level is associated with increasing risk for allergic disease and asthma.

Other previous work in this area has found that the effect of weight on asthma is stronger or only exists among persons without atopy or allergic disease. This study found essentially the same thing. The odds ratio for non-atopic children was 2.46 (95% CI: 1.21, 5.02), while that for atopic children was 1.34 (95% CI: 0.70, 2.57). These confidence intervals don't quite exclude the estimates for the other group, but the p-value for the interaction test is 0.09, so it seems reasonable to claim that there is effect modification here by atopic status.

Given the weak or non-existent relationship between BMI and atopic asthma, researchers have focused on systemic inflammation as a mechanism whereby overweight could lead to an increased of asthma. CRP is a marker for such inflammation and is strongly related to weight. Although it cannot be proved in this cross-sectional data, it is generally accepted in the medical community that this inflammation is caused by the excess weight. Certain hormones with inflammatory properties, such as leptin, are produced by adipose tissue. In these studies, CRP was also shown to be related to total IgE/atopy and to asthma. The relationship was stronger for asthma than for atopy.

The idea most commonly expressed in the literature is that obesity leads to systemic inflammation and that this generalized inflammatory state causes deficits in lung function (asthma symptoms being a result of inflammatory processes in the lung). Because of the cross-sectional nature of the NHANES dataset, this sequence of events could not be tested

directly. I was able to examine the association between CRP levels and atopy/asthma and to test whether BMI operated as a confounder in those models. If it did, that could be taken as a piece of evidence that some of the effect of obesity on atopy/asthma might operate through the effect of excess weight on CRP/inflammation.

In both analyses, the effect of CRP on atopy/asthma was shown to be confounded by obesity. Although not strictly causal evidence, this does suggest that some of the effect of CRP/inflammation could be caused by increasing weight being responsible for that inflammation. The effect on inflammation on atopy was especially interesting in this regard. A number of researchers have suggested that, since obesity seems to result in more asthma mainly among non-atopic children, obesity might operate through an inflammatory mechanism separate from the atopic mechanism. My findings show that an inflammatory mechanism might be associated with an increased risk for atopy as well. To my knowledge, this has not been examined before among children.

The findings of the first two papers seem contradictory, in that obesity was found to be associated with atopy, but not with atopic asthma. However, there was at least some evidence of an elevation of risk associated with obesity in the atopic children (OR=1.34). This may mean that obesity is indeed a risk factor for atopy, but once a child has become atopic, the atopy overshadows the effect of weight. Again, because these data come from a cross-sectional survey, it is not possible to test this possible time sequence in this dataset.

Finally, it was shown in the third analysis that infant feeding was related to the development of obesity and asthma, but not atopy. The protective effect of breastfeeding against obesity and asthma has been shown previously in other work, and this analysis confirms those findings in a rather large sample of U.S. children. The atopy model was underpowered, unfortunately, and while there was no association observed, the observed effect was protective (OR=0.75), and it is possible that an effect could have been detected in a larger dataset.

I wanted to examine the question of whether breastfeeding might result in less asthma *because* it led to less obesity and/or less atopy. In models examining the effects of the intermediates – obesity and atopy – on the development of asthma, breastfeeding did not act as a confounder. This would suggest that any correlation between breastfeeding and obesity (my analyses did not show a correlation between breastfeeding and atopy) is not the driving force behind asthma being less common in breastfed children. The effect of breastfeeding on asthma was stronger among children not obese at the time of the survey than among obese children, but evidence for this being a true case of effect modification was modest. Thus, I was not able to demonstrate that breastfeeding protected against asthma because it protected against obesity or against atopy. There are certainly other ways that breastfeeding could operate to protect against asthma. Probably the most important would be through reduction of respiratory infections in early childhood.

B. Limitations

The time sequence of events cannot be determined in cross-sectional data, which limits one's ability to draw conclusions regarding causality. It is plausible, for example, that asthma could lead to obesity if asthmatic children were more sedentary than non-asthmatic children. Other researchers, however, have investigated this possibility in longitudinal datasets and concluded that obesity typically precedes the development of asthma rather than the other way around. The NHANES datasets may not be entirely appropriate for a study on the causal mechanisms of obesity and inflammation on development of atopy and asthma, but because they come from such a large sample and are generalizable to the U.S. population, it is well worth examining the associations that exist as springboards for further exploration in mechanistic research studies.

Another potential limitation of these analyses was the use of BMI as the measure of adiposity. The obvious advantage of using BMI in obesity research is that height and weight

measurements are easy to obtain and are available in most datasets pertaining to children's health. It is not a direct measure of fatness, however, and may misclassify some children. Children grow at different rates, will have growth spurts at different ages, and reach sexual maturity at different times. Thus, an individual child whose growth or sexual maturity level is in the vanguard or lagging behind others of the same age may fall into the outer reaches of the percentile scale, but still be a reasonable weight for their height and own growth trajectory. BMI has also been shown to misclassify individuals, particularly adolescent males, who are heavier than average due to a larger bone structure or more muscle mass.[165]

Nevertheless, BMI has been shown to correlate quite well with other measures of adiposity. Mei et al. compared BMI to DXA in a pooled dataset of 3 studies in children and found correlations that ranged from 0.78 to 0.88, and that the area under the receiving operating characteristics curve was 0.952.[166] In other research examining obesity and asthma symptoms among inner-city children (Kattan, personal communication), DXA measures were found not to add to the ability to predict asthma morbidity once BMI had been accounted for.

Although the NHANES datasets are large (more than 16,000 children age 2-19 across the 1999-2006 rounds of the survey), in certain subsets of my analyses sample size was an issue. This was particularly important for analyses that included the IgE/allergy symptom variables, since these were only available for the most recent 2005-2006 round of data collection (N=3,387 children 2-19 at normal weight and above). I looked at effect modification by sex, age, and ethnicity, and by age group and ethnicity separately for boys and girls. At this level of stratification, imprecision started to become a problem. While I did show the varying rates for atopy among girls of different ethnicities in the first paper, I felt it was better not to make too much of this finding. Because of the sample weighting, when cell sizes become small, a single observation can sometimes have undue influence. This is also

why analysis of individual allergen-specific IgE tests was relegated to the online supplement. For a number of the allergens, there were only a few positive tests, and it is difficult to draw conclusions from those findings. Other researchers in our working group are looking into interrelationships among these allergen-specific IgE results, a task well beyond the scope of the present work.

A set of these analyses used serum IgE levels, an objective measure of atopy; however, other outcomes included asthma and allergy symptom outcome data that were collected by self-report, rather than via an objective medical diagnosis. With respect to self-report of asthma, previous studies have found strong correlations with more objective measures of asthma status. Senthilselvan et al. found self-report of asthma to be significantly related to concurrently measured pulmonary function tests.[172] Tisnado et al. found self-reported history of asthma to be in 91% agreement with medical record data.[173] On the other hand, it is interesting that with respect to allergy/atopy, obesity was related to the objective measures of allergic tendency, but not to self-report of symptoms. Other efforts in the NHANES working group (Hoppin, personal communication) have shown that the questions asked regarding allergic symptoms do not predict atopy as measured by total or specific IgE with any degree of confidence.

C. Changes from Originally Proposed Analyses

One of the pieces of my original proposal was to compare my findings using BMI to findings using percent body fat from DXA. DXA was developed to measure bone density for clinical assessment of osteoporosis, but recent software and hardware developments allow the direct measurement of body composition in terms of bone mass, lean mass, and body fat. The DXA machine scans the body with a very weak, but focused, x-ray that can differentiate between these different types of tissue.[152] Each compartment is measured in grams, and the entire body mass can be decomposed into percents by dividing the mass of

each compartment by the body weight. Because DXA is a direct measure of fat mass, it has become the standard for body fat measurement in recent decades.

There were a number of challenges to the use of DXA in this analysis, and it was determined that it was not really central or necessary, and might be too large a distraction. The DXA datasets for 1999-2004 did become available early in 2008. It should be noted that the available DXA data do not at this time overlap with the 2005-2006 IgE/allergy data. In addition, DXA is only available for participants age 8 and above. More significantly perhaps, there are no agreed-upon clinical cut-offs for what percent body fat indicates overweight and obesity in children, making a comparable analysis to that for BMI less than straightfoward.[154] There are a number of interesting research questions that could be answered using the NHANES DXA data and comparing them to BMI, but these were considered to be beyond the scope of the present work.

Another analysis I had proposed was to examine confounding by a number of dietary components, notably anti-oxidants and specific vitamins (A, C, D, E, and carotenoids) that are available in laboratory files from NHANES. Again, these variables were not available for the 2005-2006 data (except Vitamin D which recently became available), and complications surrounding only being able to look at this confounding for certain subsets of the population dissuaded me from including these variables in my primary analyses. I have, however, included in Table A2 of the Appendix an analysis of differences in these serum markers of diet by weight status, current asthma, and atopy. A number of these dietary components are related to weight status, but none were related to asthma. The only one showing any relationship to atopy was Vitamin D. Since Vitamin D is a suspected risk factor for allergic disease, I ran a set of adjusted models including this variable, but found it did not act as a confounder in the obesity-atopy relationship. Questions regarding specific effects of Vitamin D may be addressed by other researchers in our working group, so I did not attempt to examine effect modification or do further analyses with this variable.

Both obesity and atopy are risk factors for asthma. Thus, additivity of the effects is may demonstrate a biological interaction.[162] A test for additive interaction revealed an interaction contrast ratio of 0.89 (95% CI: 0.31, 2.54). This implies that there is no actual biological synergy between atopy and obesity in the development of asthma. Indeed, effect modification was shown to exist by atopic status for the association between obesity and asthma, with a p-value for the interaction test of 0.09. Obesity was found to be associated with asthma in non-atopic children, but not in atopic children, rather than there being a synergistic effect.

D. Clinical and Public Health Significance

While obesity and asthma have been shown to be related in a number of studies, it is still not understood why this is the case. Although both obesity and asthma are medical conditions characterized by inflammation, a direct link to airway inflammation in obese individuals has not been established. The recent NHANES datasets provide valuable information regarding relationships between C-reactive protein (a marker of systemic inflammation) and obesity, atopy, and asthma. The new allergy module of the 2005-2006 survey also contains total and allergen-specific IgE levels for examination of whether an allergic mechanism may be involved in the association between obesity and asthma.

Asthma is large and growing problem in the U.S. and around the world. A number of exposures have been shown to be related to asthma development in children, but none have been shown to entirely explain the increases over the past several decades. The cause of asthma appears to be multi-factorial, and indeed, there are those that suggest that asthma may be more than a single disease. Understanding some of the relationships between exposures and mechanisms of disease development could lead to strategies to prevent and treat allergic diseases and asthma among certain at-risk children. Reducing overweight in children may be one such strategy.

Childhood obesity may be the most important health issue facing U.S. children today. Recent reports discuss children as young as 2 having significant obesity, setting them up for a lifetime of medical problems.[176] The public health community has begun to address the problem of childhood obesity, and numerous efforts are underway. Messages about healthy nutrition and physical activity are being increasingly incorporated into regular health education.[177] Various school-based programs have been successful in increasing physical activity among children, improving diet, and reducing overweight, using approaches such as interactive computer media,[178] hands-on educational activities,[179] or simply providing game equipment to increase physical activity at recess.[180]

An increased risk of allergic disease and asthma may not be the most consequential health risk faced by overweight children. Nonetheless, it provides additional motivation for undertaking the difficult challenge to reduce childhood obesity.

APPENDIX

Table A1. Comparison of NHANES 2005-2006 with NHANES III published data using quartiles of BMI, children age 4-17.

Allergy Outcome	NHANES 2005-2006[†] (N=2610)	NHANES III[‡] (N=7505)
Atopy		
1st quartile	1.00	1.00
2nd quartile	1.11 (0.86-1.44)	1.07 (0.91-1.27)
3rd quartile	1.05 (0.80-1.38)	1.20 (1.01-1.43)
4th quartile	0.82 (0.62-1.07)	1.14 (0.96-1.35)
Total IgE (geometric mean kU/L)		
1st quartile	1.00	
2nd quartile	1.17 (0.91-1.52)	
3rd quartile	1.30 (1.05-1.62)	
4th quartile	1.49 (1.18-1.89)	
	NHANES 2005-2006	NHANES III
Atopy (using same quartile definitions)		
1st quartile	1.00	1.00
2nd quartile	0.98 (0.66-1.46)	1.07 (0.91-1.27)
3rd quartile	1.14 (0.83-1.55)	1.20 (1.01-1.43)
4th quartile	0.97 (0.66-1.42)	1.14 (0.96-1.35)

* Models in current paper for ages 2-19 adjusted for race, age, sex, poverty income ratio, and household smoking.

[†]Model using NHANES 2005-2006 data ages 4-17 adjusted for race, age, sex, household size, and household smoking. Quartiles: First 11.7-16.5; Second 16.6-19.4; Third 19.5-23.5; Fourth 23.6-62.1.

[‡]Model from von Mutius paper ages 4-17 adjusted for race, age, sex, household size, study area and passive smoke exposure. Quartiles: First 7.3-15.4; Second 15.5-17.1; Third 17.2-20.4; Fourth 20.5-37.2.

Table A2. Distribution of dietary micronutrients by weight category, current asthma, and atopy, NHANES 1999-2006, children age 2-19.

Subject Characteristics	N	%	Geometric mean total IgE (SE)		p-value* test for trend
Vitamin A					
Weight category	9378				
Normal	5988	66.7	41.9	(0.3)	<0.0001
Overweight	1567	16.2	43.7	(0.5)	
Obese	1823	17.1	44.7	(0.4)	
Current Asthma	9340				
No	5467	90.6	42.7	(0.3)	0.72
Yes	496	9.4	42.4	(0.6)	
Atopy	0				
No	0				
Yes	0				
Vitamin C					
Weight category	2736				
Normal	1677	62.4	1.2	(0.03)	<0.0001
Overweight	501	18.5	1.1	(0.03)	
Obese	558	19.0	1.0	(0.04)	
Current Asthma	2724				
No	2436	90.9	1.1	(0.02)	0.57
Yes	288	9.1	1.1	(0.06)	
Atopy	0				
No	0				
Yes	0				
Vitamin D					
Weight category	9889				
Normal	6337	66.6	26.2	(0.4)	<0.0001
Overweight	1617	16.0	24.7	(0.5)	
Obese	1935	17.4	22.3	(0.4)	

Subject Characteristics	N	%	Geometric mean total IgE (SE)	p-value* test for trend
Current Asthma	9848			
No	8840	90.1	25.3 (0.4)	0.58
Yes	1008	9.9	24.6 (0.5)	
Atopy	3375			
No	1636	53.6	24.4 (0.5)	0.06
Yes	1739	46.4	23.0 (0.6)	
<u>Vitamin E</u>				
Weight category	6652			
Normal	4306	68.4	801.7 (6.3)	0.50
Overweight	1066	15.2	788.2 (11.5)	
Obese	1280	16.5	795.5 (11.2)	
Current Asthma	6627			
No	3938	90.5	800.3 (6.8)	0.28
Yes	352	9.5	784.3 (13.1)	
Atopy	3375			
No	0			
Yes	0			
<u>Total b-carotene</u>				
Weight category	2712			
Normal	1671	62.8	11.7 (0.3)	<0.0001
Overweight	499	18.6	9.1 (0.3)	
Obese	542	18.6	7.4 (0.3)	
Current Asthma	2699			
No	2413	90.9	10.3 (0.3)	0.47
Yes	286	9.1	10.4 (0.5)	
Atopy	0			
No	0			
Yes	0			

*Test for asthma and atopy among normal weight only.

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