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EXAMINING CAUSAL MECHANISMS IN THE OBESITY-ASTHMA LINK: EFFECT OF BODY MASS INDEX ON IMMUNOGLOBULIN E AND BRONCHIAL HYPERRESPONSIVENESS

By

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ABSTRACT

EXAMINING CAUSAL MECHANISMS IN THE OBESITY-ASTHMA LINK: EFFECT OF BODY MASS INDEX ON IMMUNOGLOBULIN E AND BRONCHIAL HYPERRESPONSIVENESS

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The objective of this study was to explore pathophysiologic mechanisms underlying the obesity-asthma link, specifically the effect of body mass index on atopy and bronchial hyperresponsiveness.

The analysis was based on a cohort study of 515 7-9 year old children in Hesse, Germany. Asthma was assessed based on a history of physician diagnosis, pulmonary function tests and bronchial challenge test with hypertonic saline performed at age 7-9 years. Total immunoglobulin E and esinophil count were determined and body mass index analyzed in quintiles. In multiple linear regression analysis, high body mass index obtained at four and seven years was not associated with an asthma diagnosis, bronchial hyperresponsivess or increased immunoglobulin E. However, high body mass index at age 7 was a risk factor for exercise-induced bronchospasm (p=0.05). Breastfeeding was protective for physician-diagnosed asthma (OR= 0.7 95%CI 0.5-0.9) and bronchial hyperresponsiveness (OR = 0.4, 95% CI 0.2-0.9). Body mass index was not associated with increased risk of physician diagnosed asthma or bronchial hyperresponsivesness . The positive association noted with exercise induced asthma however suggests a probable chest wall mechanism rather than an atopy mediated mechanism.

DEDICATION

I would like to dedicate this thesis to my husband, Okey. Without your constant support and loving encouragement, it would never have started or come to completion. You are indeed a very special person. To my wonderful children, Adaeze, Obiora and Emeka, you always reminded me of what was most important. I love you all.

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LIST OF ABBREVIATIONS

BMI	Body mass index
ISAAC	International study on allergy and asthma in childhood
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FEV1/FVC	Proportion of forced expiratory volume in one second to forced vital capacity
MMFR	Mid maximal expiratory flow rate
FEF50	Forced expiratory flow at 50% of the FVC maneuver
PER	Peak expiratory flow rate
TLC	Total lung capacity
BHR	Bronchial hyperresponsiveness
ATS	American Thoracic Society
CDC/NCHS	Center for Disease Control and Prevention/National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PFT	Pulmonary Function Test
BRFSS	Behavioral Risk Factor Surveillance System
WHO	World Health Organization
NHLBI	National Heart Lung and Blood Institute

CHAPTER 1

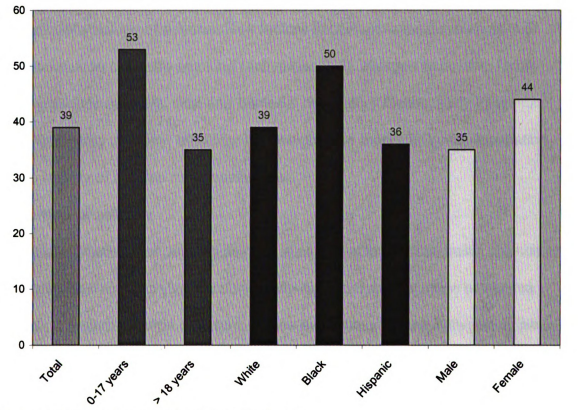
INTRODUCTION

Asthma, a serious, chronic, and potentially life-threatening disease, affects 10-13 million persons in the United States, of whom 5 million are children.[1] The prevalence of asthma has risen by 75% in the last three decades, with an especially marked increase (160%) in children aged less than five.[2] The rising prevalence transcends age, gender, ethnicity and geographic location but affects minority ethnic groups and poor inner city populations disproportionately. The reason for the increase in prevalence is unclear. Increasing environmental exposures to "synthetic" materials and indoor allergens, decreased childhood exposures to natural pattern of disease, changing meteorological patterns and decreased use of aspirin have all been suggested as possible mechanisms. A parallel increase in obesity has been seen during the same timeframe as asthma and recently obesity has been hypothesized to be a risk factor for asthma. The simultaneous rise in the frequency of these two conditions may not be coincidental.[3-23] There is evidence that obesity increases the risk of developing asthma, but our understanding of the obesity-asthma link remains speculative, as few studies have addressed plausible biological mechanisms. Chest wall mechanics may explain in part the phenomenon; however, other findings suggest that factors such as inflammatory mediators, sex hormones, leptin, genes, dietary fat and gastroesophageal reflux may all play a role.[24-30] Additionally, both disorders have been linked independently to breastfeeding, intrauterine growth, prematurity and birthweight.[31-33] It remains unclear if these early childhood

factors exert an influence as antecedent variables. Further complicating the proposed association are methodologic issues regarding the definition of asthma and obesity.

Background: Asthma, a major cause of morbidity, diagnosed in 7-15% US children during childhood, has increased dramatically within the last three decades. Collectively, people who have asthma experience well over 100 million days of restricted activity each year, and asthma is believed to be the most common reason that students miss school. [1, 34] Asthma accounts for an estimated 13 million doctor visits and 200,000 hospitalizations per year in U.S. children.[34] **Figure 1.1** shows the asthma attack prevalence per 1000 population by age, gender and ethnicity obtained from the National Health interview survey. Increased rates are shown among children, African Americans and females. In 1990, costs related to asthma were estimated to total $6.2 billion. The projected direct and indirect cost of asthma in the year 2000 was expected to double to $14.5 billion.[2]

Fig 1. Asthma attack prevalence per 1,000 population, 1998



Source: CDC/ NCHS, National Health Interview Survey

Asthma is a heterogeneous disorder marked by gene-environment interaction. The American Thoracic Society defines asthma as "a disease characterized by an increased responsiveness of the airways to various stimuli and manifested by slowing of forced expiration which changes in severity either spontaneously or as a result of therapy". In the presence of an antigen/antibody complex, mast cell degranulation releases inflammatory mediators and cytokines like histamine, tryptase, interleukin-2, interleukin-4, tumor necrosis factor and platelet activating factors. These mediators then initiate the cascade of bronchoconstriction,

hypersecretion of mucus, further infiltration of inflammatory cells such as eosinophils, basophils, neutrophils and macrophages with further cytokine release, mucosal edema and desquamation of airway epithelium characteristic of the pathophysiology of asthma. Risk factors important in the development of asthma include cigarette smoking (active/passive), allergen exposure, family history/genetic markers, viral and bacterial respiratory illness, early infant feeding, history of atopy, ethnicity, birthweight less than 2500gms, occupation, family history of asthma and possibly diet.

Definition of asthma

A validated method for defining asthma is essential for clinical, basic science or epidemiologic research, yet no universally-agreed upon definition of asthma exists. A major limitation of extant studies examining the link between asthma and obesity is the lack of a rigorous case definition for asthma, thus increasing the likelihood of misclassification bias. Clinical evaluation, questionnaire history of diagnosis, asthma symptoms, pulmonary function tests and bronchial hyperresponsiveness are methods that can distinguish between asthmatic and non-asthmatic patients. Each method is fraught with sensitivity and specificity problems, especially in children. The International Study on Allergy and Asthma in Childhood (ISAAC), a multicenter study to examine the prevalence of allergy and asthma involving 50 countries and 620,000 children, validated questions on asthma symptoms and diagnosis in 7-8 year and 13-14 year olds using surveys and video questionnaire. Most questionnaires focus on history and frequency of

wheeze within the preceeding 12 months. The history of wheeze and nocturnal cough, but particularly wheeze, correlates strongly with a diagnosis of asthma. Cough is the common primary presenting symptom of asthma but cough alone is a poor indicator for asthma because most children who cough do not have asthma. For example, over a 24-hour recording period, the mean frequency of cough among a cohort of healthy non-asthmatic 8-12 year olds was 11.3 cough episodes.[35]

Wheezing also does not provide a definite diagnosis of asthma as it can occur in smokers, bronchiolitis syndromes and chronic obstructive pulmonary disease. Clinical evaluation may miss mild cases, be contingent on the diagnostic threshold of the physician or reflect increased awareness within the population. Mackenzie et al.[36] reported over-diagnosis of asthma in children based on the symptom of cough alone, while a recent Swedish study, found the sensitivity of correctly diagnosing asthma among general physicians was only 59%.[37] Conversely, there is considerable overlap in physician diagnosis of similar lung conditions, e.g., bronchitis, thereby reducing the accuracy of diagnosing asthma. Pulmonary function measures of obstructive airway disease, e.g., Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), Forced Expiratory Volume/Forced Vital Capacity (FEV1/FVC), Mid Maximal Flow Rate (MMFR), and Forced Expiratory Flow at 50% of the FVC maneuver, provide an objective and qualitative assessment of airflow obstruction. FVC is the maximum amount of air that can be expired with rapid forceful exhalation following a maximal inspiration. FEV1 is the volume of gas expired over 1 second from the

start of an FVC maneuver, while the MMFR is the average flow in the middle 50% of an FVC maneuver.

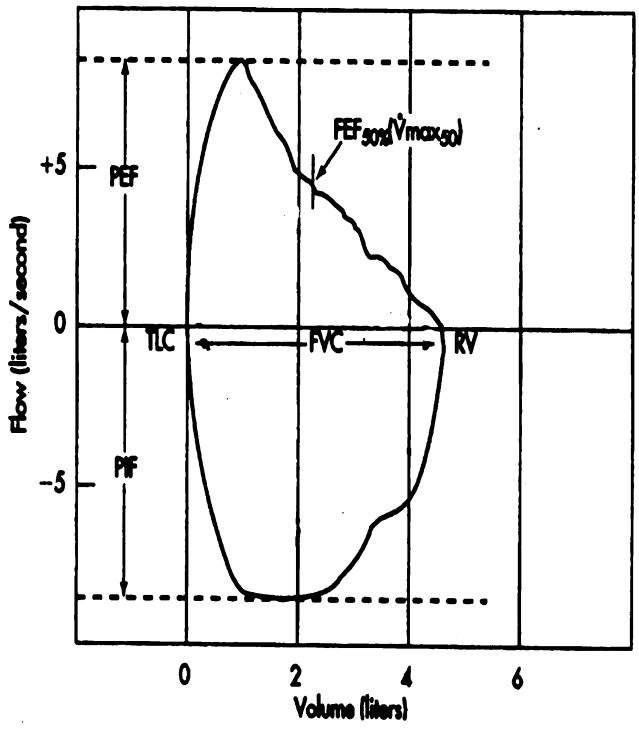


Figure 1.2 Flow-volume loop with a normal FVC maneuver
(Gregg Ruppel. Manual of Pulmonary Function Tests. 7th ed. Mosby 1998. page 41.)

The FEV1/FVC ratio is expressed as a percentage and is a strong indicator of airway obstruction. MMFR and FEF50 are more sensitive for picking up small airway disease, however these measures have a wide range of normal values. **Figure 1.2** illustrates a flow-volume loop with a FVC maneuver and different components of the flow loop.

Flow in liters/sec is plotted on the vertical axis while volume in liters is on the horizontal axis. The two largest FVC and FEV1 values within 200ml or < 5% difference is used as the reproducibility criteria. In children the 5% criterion is usually used. Serial measures of pulmonary function rather than a single

measure are more useful. Bronchial challenge testing is used to detect bronchial hyperresponsiveness and can be very useful in patients with symptoms suggestive of asthma but with normal spirometry tests. There is a consensus that the definition of asthma should focus on the presence of bronchial hyperresponsiveness (BHR) and paroxysms of airway narrowing, yet BHR is plagued by poor specificity. Increased reactivity has been reported in non-asthmatics even in the absence of respiratory symptoms. BHR is also time consuming and more invasive than other methods; thus it is impractical for most epidemiologic studies. To date, no studies have examined the obesity-asthma link using a combination of clinical, physiologic and questionnaire methods to define asthma.

Body mass index and obesity: The National Health and Nutrition Examination Survey (NHANES III 1988-1994) estimates that a quarter of children ages 6-17 years and more than 50% of adults in the United States are overweight.[38-39] The prevalence of obese children doubled between the 1970s and 1990s.[39] Obesity now accounts for about 7% of the U.S. healthcare budget, with $68 billion spent on direct medical expenses.[40] Obesity related hospitalizations for children increased between 1979-1981 to 1997-1999, with tripling of the hospital costs from $35 million to $127 million.[41] Table 1.1 provides prevalence rates for obesity from 1991-2000 from the Behavioral Risk Factor Surveliance Survey (BRFSS), a telephone survey carried out in all the states. The prevalence has risen across all categories especially African-Americans and Hispanic populations.

Table 1.1 US prevalence of adult obesity (approximately 30lbs overweight) by gender, age and ethnicity

Characteristics	Percent Obese BRFSS data by year:				
	1991	1995	1998	1999	2000
Total	12.0	15.3	17.9	18.9	19.8
Gender					
Men	11.7	15.6	17.7	19.1	20.2
Women	12.2	15.0	18.1	18.6	19.4
Age groups					
18-29	7.1	10.1	12.1	12.1	13.5
30-39	11.3	14.4	16.9	18.6	20.2
40-49	15.8	17.9	21.2	22.4	22.9
50-59	16.1	21.6	23.8	24.2	25.6
60-69	14.7	19.4	21.3	22.3	22.9
>70	11.4	12.1	14.6	16.1	15.5
Race, ethnicity					
White, non Hispanic	11.3	14.5	16.6	17.7	18.5
Black, non Hispanic	19.3	22.6	26.9	27.3	29.3
Hispanic	11.6	16.8	20.8	21.5	23.4
Other	7.3	9.6	11.9	12.4	12.0

[1]CDC/NCHS

Obesity is a complex, multifactorial disorder resulting from genetic, environmental and psychogenic factors that impact energy intake and expenditure. Complications of obesity include hyperlipidemia, type 2 diabetes, and increased incidence of cardiovascular disease, stroke, cancers and mortality. In children and adolescents, the sequelae were once felt to be predominantly psychosocial, stemming from discrimination, low self-esteem and accelerated maturation. However, with the recent rise in prevalence, medical complications previously seen only in adults, such as impaired glucose metabolism, non-insulin dependent diabetes, dyslipidemia, and hypertension, now occur in obese children and adolescents.

Body mass index (BMI), the most commonly used measure of body size, is calculated by weight (kg) divided by height^2 (m) [38]. It is practical, easy to obtain, reproducible and can be used in the clinical setting, as well as in epidemiologic studies. In adult studies, correlations between densitometry estimate of body fat composition and BMI unadjusted for age ranged from r^2= 0.67-0.85.[42] For children, the correlation is lower, ranging from 0.55-0.77. There are limitations to using BMI as a measure of body fat. It is a better indicator of heaviness because it has difficulty distinguishing between that due to fat versus muscle. In children, interpreting BMI is complicated by differing rates of growth and maturation. For this reason obesity is defined relative to a selected percentile in a reference group based on age and gender.

Childhood obesity is defined as a BMI above the 95th percentile relative to a selected age- and gender-matched reference population, while overweight is between the 85th and 95th percentile.[39] The 2000 US pediatric growth derived from data from the NHANES studies (1963-1980) is used as the reference population. A 3-4-unit change in BMI within a year is another measure of excessive weight gain.

There is a chance for differential misclassification when self-reported measures of weight and height are used to determine overweight status. This is because overweight persons are more likely to under-report their weight thus introducing differential misclassification. This effect would, however, bias the result towards the null in the relationship between asthma and obesity.

The National Heart, Lung and Blood Institute and the World Health Organization classified adult body mass index into categories (**Table 1.2**) based on deleterious effects of BMI.

Table 1.2 Classification of Obesity

Adult Categories*	BMI wt/ht^2
Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese class 1	30-34.9
Obese class 2	35-39.9
Obese class 3	>= 40.0
Children : defined relative to age and sex	
BMI >95th %tile	Obesity
BMI >85%tile-95%tile	Overweight

***(NHLBI and WHO)**

Childhood BMI between the 85th and 95th percentile increases the risk for adult obesity, while the likelihood of obesity related complications increase above the 95th percentile. A BMI >the 95th percentile in a child is analogous to an adult BMI >30.

Asthma and Obesity: Similarities exist in the epidemiology of asthma and obesity that may explain the recent interest in an association between the two conditions. Both have risen in prevalence worldwide, especially in regions where there is industrialization and urbanization. This rise has occurred during the same timeframe. For example, pediatric obesity has doubled between NHANES II (1976-80) and NHANES III (1988-94),[39] while the prevalence of asthma increased by 75%.[2] Much of the rise affects similar populations, children, minorities and low socioeconomic class.

Should a true causal association exist between asthma and obesity, the population attributable risk (PAR) would be high. For instance, if we estimate a 2-3-fold increase in risk for asthma among obese persons and the prevalence of obesity at approximately 25%, then the PAR will be 20-33 percent. The public health impact of both conditions suggests that further investigation into the relationship between asthma and obesity is warranted.

My thesis will examine the relationship between asthma and obesity. It will also explore probable pathophysiologic mechanisms underlying this association, specifically the relationship between body mass index and atopy using secondary analysis of longitudinal data.

The following goals will be addressed:

1. Determine the association between BMI and asthma.
2. Explore the role of variables such as immunoglobulin E, eosinophil count and breastfeeding.
3. Examine the effect of body mass index on FEV1, FVC, FEF50 and FEV1/FVC.
4. Examine the role of body mass index at age 4 years, on measures of atopy, pulmonary function and bronchial hyperresponsiveness ascertained at 7 years.

CHAPTER 2

LITERATURE REVIEW ON OBESITY AND ASTHMA

Over the last forty years, there have been references to a possible association between obesity and asthma.[3-23] These studies have not provided a clear understanding of the nature of the relationship. Investigators disagree on whether a causal relationship exists and have been unable to reach a consensus on which is the risk factor or the outcome. One hypothesis proposes that reduced energy expenditure in asthmatic children predisposes them to excessive weight gain. The alternate hypothesis is that obesity is the risk factor in the development of asthma. Supporting the alternate hypothesis are studies that show a greater frequency and degree of bronchospasm in the smaller airways in obese non-asthmatic children compared to their non-obese counterparts.[49-50]

The association between asthma and obesity has been examined mainly in observational studies because randomization of either disorder is neither feasible nor ethical. In contrast to experimental study design, results from observational studies are more likely to be plagued by methodologic issues of bias and confounding. An example is case ascertainment of asthma. Reported history of physician-diagnosed asthma or history of wheezing are the most commonly used methods for defining asthma in epidemiologic studies. Responses to these questions typically measure asthma prevalence and not incidence unless an inception cohort, i.e, population with no prior known history of asthma or wheezing is used. Even with inception cohort studies, where we assume we are

measuring incident cases of asthma, it is probable that some of subjects may be misclassified if they have subclinical disease. Thus, most of the published studies speak more to the association between obesity and severity of asthma rather than the development of asthma. In addition, although BMI is used widely to define obesity, its ability to accurately measure body fat versus heaviness is still being debated.

The most challenging problem facing the causal link between asthma and obesity, should one exist, is the multifactorial nature of both disorders; thus teasing apart the role of the different factors in the relationship is difficult. It is unlikely that a single identified risk factor acts independently, but rather complex interactions between chest wall mechanics, genes, proinflammatory effects of adipocytes and leptin, hormones, physical activity and diet underlie the association. In addition, as we become more aware of the independent effects of early childhood factors such as breastfeeding and birthweight on both asthma and obesity, the role of these variables needs to be considered in the causal pathway.

Tables **2.1, 2.2** and **2.3** summarize epidemiologic studies on the relationship between asthma and obesity by study design. There is a preponderance of cross sectional studies in published literature as shown in **Table 2.1**. Ten of the cross-sectional studies found a positive association, while only one reported no association. One of the earlier population based studies was carried out by Chen et al.[3] They analyzed the Canadian National Population Health Survey 1994-1995. Asthma was determined by self-report of physician-diagnosed asthma.

Sample size was 17,605 subjects older than 12 years. BMI >=28 increased prevalence of asthma in obese women but not in men. Stratifying the population into two age groups, 12-24 years and above 25 years did not alter the results. Their results suggest gender may be an effect modifier. A major concern for this study is the validity of self-reported information. However, the possibility of systematic bias introduced this way does not satisfactorily explain the observed gender differences.

Another cross-sectional that found a gender difference in the obesity-asthma link was a study of 9357 5- and 6-year old German children in two rural Bavarian areas in Germany. [10] Obesity was characterized as BMI greater than the 97th percentile. Children were defined as asthmatic if they had at least one physician diagnosis of asthma, spastic or obstructive bronchitis. The severity of asthma was assessed by number of wheezing episodes within the preceding 12 months. In a multivariate logistic regression model, obese girls had a twofold risk of having a diagnosis of asthma (OR 2.33; 95%CI 1.13-4.82). Other independent variables in the final model included birthweight <2500grams, family history of atopy, more than three febrile episodes in the first year of life and consumption of whole milk three or more times a week.

Other studies have not found gender differences. Schwartz and von Mutius, using data from National Health and Nutrition Examination Survey II (1976-1980) and III (1988-1994) respectively, reported a positive association in children regardless of gender.[5,7] Jang and Xu in adult studies report similar findings,

However, in Jang's study, carried out in a high altitude rural area in Korea, the risk of asthma was stronger in obese women compared with men.[12,13]

It is hypothesized that gender differences may be mediated by the effect of estrogen and progesterone on lung function, especially estrogen. Supporting this line of thinking is the change in gender dominance in asthma epidemiology from male to female around pubertal period. Post-menopausal women receiving hormone replacement therapy have been reported to have higher risks for incident asthma.[14] Also higher rates of skin reactivity to histamine corresponded with peak estrogen levels in women tested at different stages of the menstrual cycle.[45] These mechanisms, although biologically plausible, still remain speculative.

Castro Rodriguez et al.[8] examined the association between asthma and obesity in children aged 2 months to 12 years, using the NHANES III data. The study population included very young children, which had not been previously studied. In a multivariate model controlling for age, race, family history of asthma, and environmental and smoke exposure, obesity was associated with asthma only in African American children OR 1.64 (95% CI 1.2-2.3). Asthma was defined as a history of physician diagnosed asthma. A major problem with case ascertainment in this study is that preschool children are particularly prone to respiratory infections with accompanying wheezing. Thus, diagnosis of asthma in this age group is often difficult and imprecise.

Table 2.1: Epidemiological Studies on Causal Relationship: Cross-sectional studies

Study	Population /sample	Definition of asthma	Definition of obesity	Results
Chen[3] Canada	N= 17605 National population Health Survey	Self-report of physician diagnosis	BMI	OR 1.74-1.84 for increasing BMI but only for females
Schachter[4] Australia	17-73yrs N=1971 white 3 pooled epidemiologic studies	Self-report of wheeze or physician diagnosis. Histamine inhalation Challenge-FEV, FVC, PEF, FEF	BMI	Asthma OR 2.04 Wheeze OR 2.6 Medication use OR 2.8 FVC, FEV1 ($p<0.05$)
Schwartz[5] USA	Children 6months-11yrs 5,672 Black 18% white 82% NHANES II	Self-report of: a) physician diagnosis b) wheeze	2 SD increase in skinfold in quintiles	OR 1.6
Munoz[6] UK	14,908 4-11yrs white representative sample. Inner city	History of one asthma attack in last year or history of wheezing	BMI >90% Reference group <10% Skinfold thickness	OR 1.28 (95%CI 1.11-1.48)
von Mutius[7] USA	4-17yrs NHANES III	Physician diagnosis of asthma	BMI	OR 1.77 (95%CI 1.44-2.19)
Castro Rodriquez[8] USA	N=12,388 2 months-16yrs NHANES III	Physician diagnosis of asthma	BMI	OR 1.64 (95%CI 1.20-2.26) AA only
Celedon[9] China	N=7,109 Anhui province	Physician diagnosis of asthma Airway hyper-responsiveness Asthma attacks	BMI	BMI >30 OR 2.3 (95%CI 1.2-5.0) BMI <16 2.5 (95%CI 1.4-3.8)

Table 2.1 (cont'd.)

von Kries[10] Germany	N=9357 5-6yrs	Physician diagnosis, History of wheeze	BMI	OR for females 2.33 (95%CI 1.13-4.82) Males NS
Lusky[11] Israel	17 years N =12,000	Self-reported history of asthma or bronchitis	BMI	RR 1.8 (95%CI 1.4-2.1) for BMI <5% 1.8 (95%CI 1.4-2.1) for BMI 5-15% NS BMI >85%
Jang[12] Korea	Ages 50-93years High altitude rural area N=707	Self-reported history of wheezing	BMI	Prevalence of wheeze higher with BMI >=25 (28.6% vs. 12.6% p=0.01) OR=1.1 (95%CI 1.03-1.18)
Sin [13] USA	NHANES III (1988-1994) Ages >=17 years N=16,171	Self-reported asthma FEV1/FVC <80%	BMI (quintiles)	Asthma OR 1.50 (95%CI 1.24-1.81) Highest quintile had the lowest risk of FEV1/FVC >80% (p=0.001)

The sole dissenting cross-sectional study was conducted in Israel among 17-year-old army recruits[11]. (**Table 2.1**) Standardized questionnaires and anthropometry measurements were obtained at screening health programs in 5 induction centers. They used BMI and characterized each recruit according to his specific ethnic group distribution. Ethnicity was defined as country of origin of the paternal line. The authors found a RR of 1.8 (95%CI 1.4-2.1) for severely underweight boys (BMI <5%tile) and 1.8 (95% CI 1.4-2.1) for mild underweight (BMI 5-15%tile), but no increased risk with BMI >85%. The greatest threat to

internal validity in this study was the imprecise definition of asthma. Asthma was grouped with "chronic bronchitis" in the analysis. The study population was only males, thereby limiting generalizability of results. The findings in this study, if true, refute the hypotheses that asthma leads to sedentary behavior and then obesity.

Interestingly the study by Sin et al. using NHANES III data, found contradictory results.[13] Even though physician diagnosis of asthma was significantly associated with obesity, children in the highest quintile were least likely to have an FEV1/FVC less than 80%.

Their result suggests a separate mechanism, not mediated by decreases in end tidal volume with resultant bronchospasm. It is possible that obese children utilize more health care services, with greater opportunities to be accurately or inaccurately diagnosed as asthma. Indeed a study of clinic practices in Michigan found higher health care utilization for obese children compared with their normal weight peers. [46]

The odds ratio reported by the cross-sectional studies (**Table 2.1**) range between 1.28-2.6, reflecting a weak association between asthma and obesity. It is probably that association is stronger, but misclassification of asthma, or obesity, errors in data collection or report can bias the results. Additionally by their inherent design, these studies provide limited evidence of causation.

Table 2.2 contains cohort studies, which provide the strongest evidence to date to support the premise that obesity is a risk factor for asthma. There have been few cohort studies on the obesity-asthma link in the literature. In a prospective

cohort study of 85,911 female registered nurses, ages 24 to 44 living in one of 14 US states[14], high BMI was positively associated with the onset of physician-diagnosed asthma. The study population was part of the Nurses Health Study. Baseline information was obtained in 1989 with subsequent follow-up questionnaires in 1991, 1993, and 1995. There was greater than 90% response rate for all the surveys. Diagnosis of asthma was defined by: (1) reiterated physician-diagnosis on supplementary questionnaires and use of asthma medication since diagnosis; (2) above, plus prescribed controller medication in past year (e.g., inhaled corticosteroids); and (3) above, plus physician-diagnosis within "one month" of symptom onset. The specificity increased with later definitions. Exposure was measured using BMI and waist/hip ratio. Validation studies within the cohort on self-reported weights and diagnosis of asthma showed excellent correlation between self-report and actual measures. In a multivariate logistic regression, controlling for 9 factors: age, race, US region, smoking status, physical activity, total energy intake, hysterectomy status, birthweight, and duration of breastfeeding, the relative risk of adult onset asthma was strongly associated with an increase in BMI ($p < 0.001$) with all three case definitions. Using their strictest case definition, weight gain greater than 25kg since age 18 years, among the subgroup, had the highest risk 4.7 (95%CI 3.1-7.0) The BMI-asthma association was found in every subgroup examined, including those with a recent health screening exam, those who used nutritional supplements, nonsmokers, past smokers, and current smokers.

Table 2.2: Epidemiological Studies on Causal Relationship between Asthma and Obesity: Cohort studies

Study	Population / sample	Exposure	Outcome	Results
Camargo[14] US	Nurses health study. no. 85911 ages 24-44 inception cohort	BMI WHR wt @18yrs	Questionnaire asthma by report 3 case definitions	RR 1.1-2.7 for increasing BMI (p<.001) for trend
Shaheen[15] UK	8,960 26 years	BMI >30-obese 22.5-29.9 – overweight	Self-report of history of asthma and/or wheeze. Positive history at age 10 by maternal self-report or physical exam	1.72 (95% CI 1.29 to 2.29). Higher risk for females
Chen[16] Canada	20-64yrs 9149	BMI	Self-report of physician diagnosis of asthma	OR females 1.9 (95%CI 1.1-3.4) males OR 1.1 (95%CI 0.3-3.6)
Xu[17] Finland	Finish birth cohort 1966-1997 F/u at age 31 years N= 4719	BMI	Self-report of Physician diagnosis of asthma	BMI >=95%tile in adolescence OR 2.09 (95%CI 1.23-3.57) Young adulthood OR

The study used only incident cases, thus showing a temporal relationship between obesity and clinically apparent asthma. However, because no objective assessment of pulmonary function was done at the beginning of the cohort, it is possible that subclinical disease existed. Also the spectrum of asthma across life spans differ widely, thus it is conceivable that the women with a new diagnosis of asthma had a prior history of resolved asthma in childhood. Other limitations of the study include poor generalizability because of the make-up of the cohort and

use of self-reported measures. Although the use of a knowledgeable cohort may provide more accurate reporting of diagnosis, there is a possibility of over-reporting of illness or the cohort may be comprised of a group of individuals with healthier lifestyle behaviors than the general population. The latter occurred in this cohort. The mean weight of participants in the Nurses Health Survey was 3.3 kg less than their counterparts in the US population.

Shaheen's study, using a historical British cohort, showed a positive relation between increasing BMI and asthma when both exposure and outcome was ascertained at age 26 years.[15] The participants completed a survey at age 26 years. The prevalence of asthma rose with increasing adult BMI. After controlling for birth weight and other confounders, the odds ratio comparing highest with lowest quintile of body mass index was 1.72 (95% CI 1.29 to 2.29). However, BMI at age 10 years was unrelated to a diagnosis of asthma at the time of the survey (age 26 years), but low birthweight (<2kg) was a risk factor for asthma (OR 1.99, 95% CI 0.96 to 4.12). Although this study reported a positive association between asthma and obesity, it did not demonstrate that obesity preceded development of asthma.

Chen et al. reported a positive association between obesity and asthma, but only in females, in a population-based study.[16] They used data from the first and second cycles of the National Population Health Survey, conducted in Canada in 1994-1995 and 1996-1997, respectively. Over the two-year follow up period, 2.2% of the participants developed asthma, with twice as many women compared to men (141 vs. 68). The gender difference observed may reflect the

small number of men in the study with the outcome rather than a true underlying biological reason.

The cohort studies provide evidence of temporality, a strong criterion for causality. Three of the studies report a positive association, albeit their findings were limited to women in two of these studies. The third study found a stronger association in women compared to men. The biologic plausibility of a gender difference in an obesity-asthma link is still poorly understood. Thus, it is entirely possible that an unmeasured confounder that is strongly related to females may account for the association reported. With only four studies with differing results published to date, further studies in different populations and better ascertainment of confounders are needed to substantiate a relationship.

All the case control studies were clinic based except for the study by Belmarich et al.[22] which had patients from the emergency department as well as primary care clinics. Gennuso et al.[18] and Luder [19] examined the hypotheses in the pediatric age group, using case-control study design (**Table 2.3**). Both studies recruited patients from inner-city clinic populations and the racial make-up was predominantly Hispanic and African American. Obesity was defined as BMI >=95th percentile for age and gender and overweight above the 85th percentile and BMI <85th percentile as the referent group.

Gennuso's study found there were significantly more obese children with asthma. This finding was more marked in the group above the 95th percentile for BMI (RR 2.6

in obese children vs. 1.9 in overweight group). Asthma severity, however, was

unrelated to obesity. Luder's[19] study was conducted in New York (East Harlem and south Bronx neighborhoods). Cases were drawn from a tertiary pulmonology clinic. The controls were selected through a stratified sampling design of schools in all of New York City.

Table 2.3: Epidemiological Studies on Causal Relationship between Asthma and Obesity: Case-Control studies

Study	Population / sample	Exposure	Outcome	Results
Gennuso [18] USA	176 controls 86 asthma 4-16 yrs Medical record. review	Asthma divided by severity	BMI	RR 1.9 -2.6 No relation with severity or steroid use
Luder[19] USA	2-18 yr old black and Hispanic children. Controls 6-13 yr. old in same school district Medical record review.	Asthma classified by severity	BMI	OR 2.05-6.34 with different indicators of severity 1.3 RR (95%CI 0.99-1.52, p=. 06) BMI>=85th percentile 1.5 (95%CI 1.05-2.19, p=. 03) > 95th percentile.
Young[20] USA	17-96 yrs 386 cases 744 cases	Physician diagnosis use of bronchodi-lator	BMI 25-29.9 BMI 35-40	OR, 1.2; (95% CI, 1.1-1.4); OR, 4.8; (95% CI, 2.6-9.1)
Brenner[21] USA	265 cases 482 controls AA	Physician diagnosis	BMI	Prevalence of overweight in asthmatics (16%) non asthmatics (15%)
Belmaric h[22] USA	Children 1-4 yrs 1,528 9 month f/u AA-64% Hispanic-28%	Skin testing PEFR Steroid use ER utilization	BMI >95th Reference 5-95th%tile	Increased severity by use of steroids ER visits in obese asthmatics

Guerra[23] USA	Nested case control 102 asthmatics age >= 20 years	Physician diagnosis of incident asthma	BMI assessed before onset asthma BMI 25-27.9 BMI >= 28	OR of BMI >28 2.1 (95% CI 1.31-3.36) Association stronger for women OR 3.45 (95%CI 2.10-5.67)

This was probably done for convenience because they used the data from the New York State Department of Health. Both controls and cases had different person year experiences in relation to asthma thereby violating the study base principle. Additionally, the controls were 6-13 years old and the cases 2-18 years old. The authors acknowledged that some of their controls might have been overweight thus introducing misclassification. They found a 1.3 RR (95%CI 0.99-1.52, p=. 06) for asthma among those with BMI>=85th percentile and 1.5 (95%CI 1.05-2.19, p=. 03) for the 95th percentile. Overweight status was related to certain measures of severity, e.g., use of more than 3 asthma medications (OR 2.05 95%CI 1.02-4.13) and peak expiratory flow rate =< 60% of predicted (OR 6.34 95%CI 1.83-22.0). Both studies have limited generalizability to other populations. The only case-control study that reported a negative association between asthma and obesity was by Brenner et al.[21] in a sample of predominantly African American children. The prevalence of obesity among asthmatics and non-asthmatics was similar (16% vs. 15%).

Inherent biases in the case control study design, particularly with case ascertainment, undermine the significance of the weak positive association found in these studies. It is unlikely that further case control studies examining only the association between both disorders will be especially helpful to the current body

of literature. Studying the role of potential mediators or confounders in the obesity-asthma link using this study design may be more useful.

In **Table 2.4** are studies that examined the causal relationship from a different perspective. Their proposition is that if weight is the risk factor, then reducing or increasing the weight should affect the outcome. This approach strongly supports the causal criterion of specificity. Although these studies do not necessarily address incident asthma, they provide evidence that weight is directly related to asthma symptoms. Hence, investigating pathophysiologic mechanisms that are common to both conditions can help elucidate the causal pathway.

Chen et al.[48] in the Humboldt cohort study (1977-1983) in Canada, examined the effect of weight gain on lung function parameters. Their results showed that mean FEV1 and FVC were highest in the group that gained < 1.0kg and lowest in the group that gained >=4.0kg (p.001). Chen's study controlled for age, gender and race, and smoking status **(Table 2.4).** Interestingly when the mid maximal expiratory flow rate, which is sensitive for mild impairments in lung function was used, the result was not significant.

Stenius-Aarniala et al.[47] and Dixon et al. [51] hypothesized that decreasing body mass index should lead to improvements or resolution of asthma symptoms. Stenius-Araniala conducted a randomized controlled trial in Finland. Participants were recruited by advertisements in the newspaper. They had a history of physician-diagnosed asthma, were ages 18-60 and had a BMI of 30-42. Intervention (n=19) received weight reduction (dietary therapy for 8 weeks) and participated in a discussion group, while the controls (n=19) only took part in the

discussion group. The outcome for the study was improvement in pulmonary function tests and asthma symptoms. The weight loss was 14.5% in the intervention group and 0.3% in controls. There were statistically significant improvements in FEV1, FVC, reported shortness of breath and use of rescue medications and number of asthma exacerbation. A limitation in the study was lack of blinding to the treatment, which could introduce biases. But more importantly, the authors failed to adjust for the baseline differences in pulmonary function test (PFT) in both groups, a measure of lung function that is closely related to symptoms of asthma and medication use.

Dixon's study evaluated the prevalence of asthma in the morbidly obese and the changes in asthma after laparoscopic adjustable gastric banding (LAGB) surgery for morbid obesity.[51] This was the first study on weight loss with asthma as the primary outcome. Asthma was assessed preoperatively in all patients presenting for LAGB. 32 consecutive asthmatic patients were followed up clinically and by a standard questionnaire for at least 12 months after surgery, and any change in asthma impact determined as an asthma score was recorded. The asthma score included severity, daily impact, medications needed, hospitalization, sleep, and exercise. Neither the physician nor patient was blinded to the outcome of interest.

Table 2.4 Epidemiological Studies on Causal Relationship: Studies examining the effect of weight loss

	Study	Type	Population	Intervention / exposure	Outcome	Results
Experimental studies	Stenilus Araniala[47] Finland	RCT	19 obese and 19 controls. BMI 30-42 18-60 yrs	8 week weight reduction program.	PEFR, FVC, FEV1, quality of life. F/u @ 8 wks, 14wks & 1 yr.	Improvement in FEV1, FVC and quality of life @8wks and 1yr (p<.05)
Observational	Chen[48] Canada	Cohort study	709 adults 25-59 years 6 year F/U	Weight (kg) gain	FEV1 FVC FEV1/FVC	Mean residual FEV1 and FVC largest with >4 kg weight gain
	Gokbel[49] Turkey	Case control study	24 cases and 16 control boys. 11-15 yrs	BMI .120% of 50th %tile of norms for NHANES I	Exercise induced bronchospasm FEV1, FVC FEV1/FVC	No difference in EIB positive cases. Significant decrease in FEV1, FVC in obese boys.
	Kaplan[50] USA	Case control study	13 obese cases 14 non-obese controls 6-10 yrs	Skinfold thickness	Questionnaire FEV, PEFR, FEF	15% fall in one parameter (p<. 05) in obese nonasthmatic cases. Significant difference in EIB positive cases.

Table 2.4 (cont'd.)

	Dixon[51] Australia	Prospec-tive inter-vention study	32 morbidly obese asthmatics	Lap adjustable gastric banding surgery	Questionnaire @1yr. Asthma score reflecting severity	Significant positive reduction in asthma score (p<.0001)
	Hakala[52] Finland	Prospec-tive inter-vention study	Adults 25-62 yrs Total 14 Asthmatics Non-smokers	BMI Dietary intervention x 8 wks F/U at 8 wks	PFT measures PEF, FEV1, FVC, Histamine challenge, FEF_{25-75}	PEF, FEV(1), and FVC increased after weight loss ($p = 0.001$, $p < 0.005$, and $p < 0.05$, respectively
	Macgregor[53] USA	Prospec-tive inter-vention study	40 Adults 23-68 yrs Mean BMI 46	BMI Gastric bypass with Roux-y jejunostomy F/U 2-11 yrs. Avg. 4yrs	Asthma severity Use of medication	Decreased frequency of asthma attacks Intensity of drug therapy

Participants had a mean body weight of 125.2 kg and a BMI of 45.7 kg/m2 prior to operation, and a weight of 89.3 kg (BMI 32.9 kg/m2) at follow-up. The mean preoperative scaled asthma score was 44.5 +/- 16. There was a highly significant reduction at follow-up to a mean value of 14.3 +/- 11 (P <0.001).

In both studies, mechanisms other than direct weight loss may be responsible in the improvement noted (i.e., gastroesophageal reflux). More challenging is teasing apart less tangible factors such as the effect of improved emotional state and self-esteem on perception of symptoms. This is important because even though overall symptoms of asthma improved, use of rescue medication was unchanged in Araniala's study suggesting that airway hyperreactivity persisted.

Kaplan[49] examined the relationship between exercise-induced airway reactivity and body fat among non-asthmatic obese children using non-obese controls **(Table 2.4).** Cases and controls were recruited from a medical care center. Exclusion criteria included history of wheezing, asthma, bronchitis, bronchodilator use and cardiopulmonary disease. Body mass index and skinfold thickness was exposure of interest. Pulmonary function test with exercise challenge was done. They found obese subjects were more likely to have exercise-induced asthma versus the controls (69% vs. 42%). Also there was a significant correlation between a 15% decline in pulmonary function parameters and obesity.

Gokbel conducted a similar study with Turkish children.[50] BMI percentiles from the NHANES I study were used to define obesity. He also found significant differences between obese and non-obese subjects in FVC and PEFR, but in contrast to Kaplan's study found no difference in exercise-induced bronchospasm in both cases and controls. The average change in the parameters among the obese children at 5 and 10 minutes was 3% and 7% respectively.

Although both studies found significant differences in obstructive lung function measures between obese and non-obese children, the differences are small and will be unlikely to translate to a clinically significant asthma on an individual basis.

Summary: Most studies to date have reported a positive association between asthma and obesity. However, a causal association between asthma and obesity remains tenuous as components of Sir Bradford Hills causal criteria are lacking or have not been adequately substantiated. The strongest evidence supporting causality has been temporality provided by three cohort studies, but two were limited to women thereby hampering external generalizability. Muddling the issue of temporality is the shifting clinical spectrum of asthma over the life stages. It is yet to be teased out whether resolved asthma in childhood is a separate entity from new onset adult asthma. Strength of association ranges between risks of 1.0-2.5 in most studies. These values do not represent a convincingly strong association between both disorders. Varied definitions for obesity, particularly in adult

studies, weaken the consistency of a positive association across studies. The validity of the positive relationship is further hindered by the preponderance of observational studies, with their inherent methodologic weakness, published in its support. Because most studies used prevalent asthma as the outcome or exposure, they provide evidence that obesity is associated with asthma or increases its severity, not necessarily causality.

The multifactorial nature of both disorders and our lack of understanding of the role of third variables such as breastfeeding, genes, and hormones make unidentified confounding a real possibility. Lack of breastfeeding for instance has been independently associated with both asthma and obesity. Failure to control for this factor can lead to a spurious association.

A positive association has been reported in different populations, age groups and times supporting consistency of results. The dissenting studies are fewer and limited by case ascertainment biases. However, dose response has been inconsistent. Only five studies report increasing risk or severity of asthma with higher levels of BMI.[3,14,19,47,52] Studies that report weight gain or weight loss correlate with the risk of asthma provide evidence of specificity and suggest that indeed weight is the problem.[14, 47-53] These studies, however, do not directly provide evidence of causality in the development of asthma. Evidence supporting other causal criteria of biologic plausibility, analogy, coherence and experimentation are sparse and remain largely speculative. Finally, as with all reviews limited to published studies, publication bias poses a real

threat as studies reporting a positive association are more likely to be published.

In conclusion, the possible confounding of genetic, pathophysiologic and environmental factors is probably the most significant threat to a causal relationship between asthma and obesity. Most probably, a linear relationship between asthma and obesity does not exist. The possible confounding of genetic, pathophysiologic and environmental factors is probably the most significant threat to a causal relationship between asthma and obesity. This is further complicated by probable interactions between risk factors.

Based on existing literature, we can deduce that some relationship exists between asthma and obesity. I have thus developed 5 models that critically explore the different ways both conditions could be associated. These models are not mutually exclusive and allow us to speculate on the role of different factors drawing from collaborating evidence in the extant literature where available. Some models are better developed than others. Limiting our ability to make causal conclusions are the paucity of cohort studies or experimental studies that examined incident asthma. The key objective of developing the models is to consider all possible ramifications of an association, as there is inadequate evidence based on the existing literature to prove the models. Understanding or refuting each model requires a better understanding of the role various variables can play in the obesity-asthma link. **Table 2.5** summarizes the hypothesized role of different variables, which may be mediating, confounding or antecedent in the causal mechanism. A mediator

or intervening variable acts as a true causal pathway, while confounders tend to obscure the true relationship, thereby suggesting spurious associations. If A leads to B which in turn causes C, B is termed a mediator or intervening variable. Variations in C can be caused by B, which in turn can vary based on levels of A. For example, obesity causes gastroesophageal reflux (GERD)

Table 2.5 Proposed role of third variables in the relationship between asthma and obesity

Antecedents	Mediators or Confounders
Hormones, e.g., Hypothalamic-Pituary- Adrenal axis Underlying genetic or familial disposition B-adrenergic receptor responsiveness Level of physical activity	Hormones, e.g, Estrogen Gastroesophageal reflux Mediators, e.g., leptin, COX-2, Interleukins Atopy Diet Body fat distribution Level of physical activity

which leads to asthma. On the other hand, a confounder is a true cause of the outcome. It is associated but not caused by the exposure. Using the earlier example, GERD could be merely associated, not caused by obesity, but GERD is a risk factor for asthma. In this scenario, GERD functions as a confounder. Thus, the same variable can potentially be a confounder or a mediator of the obesity-asthma link. Mediating and confounding variables are difficult to distinguish on statistical grounds alone. Controlling for any of these variables, if they are mediators, will produce an erroneous nonsignificant relationship between asthma and obesity. On the other hand, failure to control

for them, should they be confounders, will lead to a type 1 error, leading us to assume a positive association when none exists.

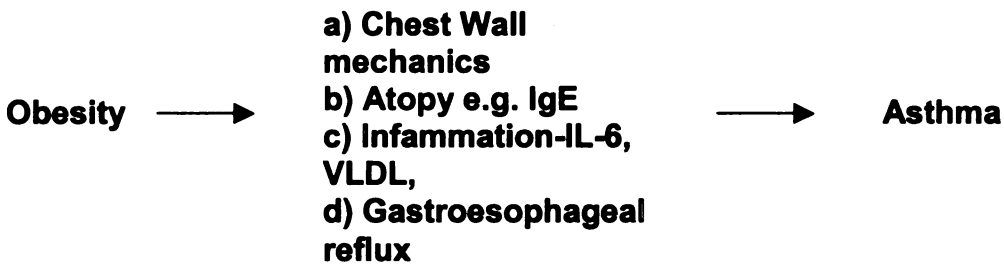
An exposure that precedes a mediator in the causal chain is an antecedent variable. Some authors refer to this as a simple antecedent. An antecedent variable (A) usually occurs early, before both variables are noted to be associated (B is associated with C). An example would be if obesity causes asthma, and obesity itself is caused by lack of breastfeeding, then the antecedent variable in this relationship is lack of breastfeeding. A simple antecedent is not a confounder, because it's associated only with the exposure. However in complex associations, an antecedent can act as a confounder. Consider the example on lack of breastfeeding described earlier. Lack of breastfeeding, which is considered the exposure, confounds the effect of obesity on asthma, if lack of breastfeeding contributes to asthma by other mechanisms (e.g., stimulates Th-2 helper cell dominance over Th1 cell type).

Finally, both extremes of BMI have been linked to asthma suggesting a probable J-shaped relationship between asthma and BMI.[4,11] A J-shaped curve has been reported for BMI and other health outcomes, such as mortality, suggesting this may represent a valid model.[43,44] In this instance, BMI acts like an effect modifier. Various levels of BMI exert different effects on the exposure. What remains unclear from the literature is the exposure BMI exerts its effect on. Decreased levels of physical activity or specific components of dietary intake common to both underweight and overweight individuals are plausible exposures. It is hoped that information gleaned from

reviewing the models will direct further studies and statistical modeling techniques that will delineate the true association between the two variables.

Conceptual models of causation: In **Model 1** obesity is a risk factor for asthma, mediated by poor chest wall mechanics or through cellular mechanisms. Alternatively, in **Model 2**, asthma may indeed be a risk factor for obesity. **Model 3** posits that the association is spurious. The association occurs as a result of a variable that is common to both disorders, e.g., low birthweight, genes. BMI is an effect modifier in **Model 4**. Different levels of BMI have varied effects on development of asthma. Finally, **Model 5**, suggests there is no relationship between asthma and obesity at an individual level, only at a group level.

Model 1: Obesity Causes Asthma



In Model 1, obesity is a risk factor for asthma. Postulated mechanisms include altered chest mechanisms, atopy, immunological pathways, hormones, gastroesophageal reflux and diet.

Pulmonary Function and Chest Wall mechanisms (a): At the physiologic level, a fall in lung capacity, with resultant small tidal volumes, leads to the development of slow cycling acting-myosin cross bridges in bronchial smooth muscle referred to as the "latch state". The latch state has been proposed as

the reason for sustained airway obstruction in hyperactive airways. Dysfunctional chest wall mechanisms due to extrinsic chest wall and intra-abdominal adipose tissue is hypothesized to prevent full downward excursion during deep inspiration with a decrease in FEV 1, FVC, total lung capacity. This in turn, can result in development of the latch phase with increased bronchial muscle tone and hyperresponsiveness.

A greater preponderance of studies report a negative correlation with FEV1, FVC, FVC/FEV1 and MMFR with different measures of obesity in children and adults.[54-57]

Collins et al.[54] in a study limited to 42 normal to mildly obese Caucasian firefighters, found upper body fat distribution was associated with modest impairments in FEV1, FVC and TLC. This study suggested that upper body fat impedes ventilatory excursions leading to impaired lung function. Major shortcomings in this study are its lack of generalizability and control for smoking, a potential confounder as well as the use of skinfold thickness, a notoriously technician-dependent measure. However, the investigators addressed this potential source of bias by using a single observer and taking the average of repeated measures.

The Normative Aging study, a longitudinal study of 2280 men 21-80 years without chronic illness, also found an inverse association between FEV, FEV/FVC ratio and increased BMI and body fat distribution but only among 50-59 year-old men ($p<0.01$).[55] The study did not control for smoking. Differential mortality rates leading to survivor bias, e.g., expected higher

mortality rates among older men and obese participants, does not adequately explain their findings as one would expect greater mortality rates among the groups older than 59 years.

The study by Ray et al.[56] did not find abnormalities in obstructive airway function. They examined pulmonary function in 43 healthy nonsmoking, obese adults (mean age 25 years) using spirometry, lung volume measurement by nitrogen washout and single breath diffusing capacity for carbon monoxide. All subjects exceeded 153% of predicted body weight. They had no control group but compared their results with standardized age predicted values. Analysis was done in groups of increasing obesity. They found measures of inspiratory capacity such as Tidal Volume, Total Lung Capacity and Vital Capacity were within normal predicted values for age and sex. The finding of normal inspiratory capacity, regardless of the severity of obesity, indicates normal lung compliance without intrinsic disease. Thus, pulmonary function abnormalities in obese subjects may be secondary to extrinsic lung disease independent of obesity.

In conclusion, it is interesting to note that despite the decrease in predicted values in these studies, most of the subjects remain within the 95% confidence intervals of the predicted population values, casting doubts that by this mechanism alone, these subjects would present with clinically apparent asthma.

Another proposed mediator in Model 1 is atopy. **(b) Atopy:** Atopy refers to allergic conditions that tend to cluster in families. The phrase atopy, which

means "strange disease", was coined as early as 1923 by Coca, who observed that in a group of people with manifestations of rhinitis or asthma, no antibody could be detected in vitro. With improvements in scientific technology, the pathophysiology of atopy involving immunoglobulin E has been better understood.

The prevalence of atopy is difficult to accurately estimate, as the definition remains controversial. Most studies use a combination of presence of symptoms and elevated IgE or skin reactivity. It is estimated 20-30% of the population are atopic; 50% of them are children.[58] There is a 2-3 fold risk of atopy in the offspring if both parents are atopic, while males are slightly more likely than females to have atopy.[58] Along with the rise in asthma, a parallel increase in the prevalence in allergy and atopy has also occurred. Urbanization, greater exposures to indoor allergens and reduction in the practice of breast feeding have been proposed to explain the rise.

Allergy sensitization in asthmatics occurs for both indoor and outdoor allergens but is more pronounced for indoor allergens. Some studies have reported odds ratios as high as 19.7 for dust mites.[59] Obese individuals are more sedentary and thus are likely to spend more time indoors thereby increasing sensitization to allergens in susceptible individuals.

There is a strong association between total and specific immunoglobulin E and asthma.[58] T cells, particularly Th2 type, primarily initiate physiologic responses in atopy. These cells stimulate inflammatory response in the presence of the offending antigen by releasing IL-4 and IL-5, which lead to

IgE production, eosinophilia and mast cell degranulation. The proinflammatory mediators of histamine, tryptase, prostaglandins, and leukotrienes result in the immediate and delayed reactions seen during an asthma attack. In addition, there is an increase in lung epithelial cell adhesion molecules for basophiles, eosinophils, lymphocytes and vascular permeability. As these cycles continue to unfold, the histopathologic signs of chronic lung inflammation take place leading to airway hyperresponsiveness. The effect of BMI on atopy has not been extensively studied.[60-61] Huang et al.[60] in Taiwan recruited 2028 eighth grade children from seven junior high schools, one in Taipei City, three in towns and three from rural areas, in a cross sectional study examining the effect of BMI on allergy. All the students in randomly sampled classes completed a questionnaire, which was modified from the ISAAC core questionnaire. To minimize misclassification bias, BMI, atopy and BHR were derived from objective measurements. Atopy was defined by a skin-prick test using six allergens. The study population was grouped into quintiles of BMI by sex. In a multivariate analysis adjusted for area of living, sibling number, parent education level and family history of asthma, using the middle three quintiles, as references, girls in the highest quintile had increased risk of atopy. (Odds ratio=1.77, 95% confidence interval=1.15-2.73).

A cross-sectional field health survey with 1129 preadolescent children in Poland concurred with Huang et al. finding a positive association between BMI and allergy.[61]

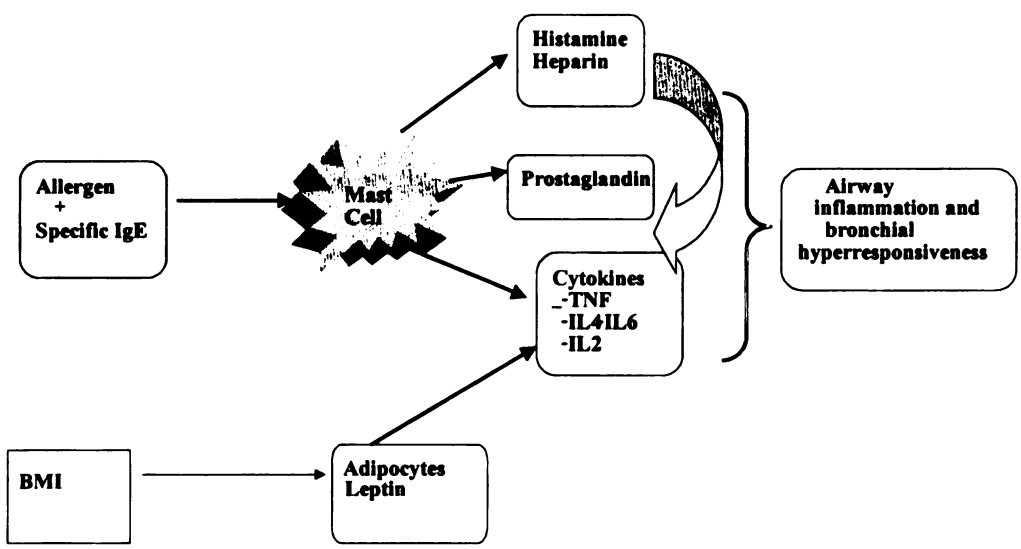
Other studies have found no effect.[7] In a recent study on 7505 children aged 4 -17 years, von Mutius et al. found a positive association between asthma and obesity but no relationship with hay fever, atopy or eosinophilia after adjusting for age, sex, ethnicity, household size, study area and passive smoke exposure.[7] Atopic sensitization was determined by skin prick tests. Across quartiles of BMI, using Z-scores, the prevalence of atopy was similar ranging for 48.6% in the 1st quartiles to 53% in the 3rd and 4th quartiles. The effect of BMI on asthma remained the same, when atopy was added to the model. Their findings suggest it is unlikely atopy is a mediator in the obesity-asthma link.

The role of atopy, if any, in the relationship between obesity and asthma remains inconclusive. The Mutius study, which found no association, was the only study to use objective assessments of atopy, thereby strengthening the credibility of its results. Further studies are needed to explore the role of atopy, especially since allergy mediated asthma is a dominant form of asthma.

Inflammatory Mediators: Inflammatory mediations and markers have been linked to obesity and asthma and may serve as mediators **(Model 1)**. Expression of interleukin-6, a proinflammatory cytokine in adipocytes, production of cyclo-oxygenase 2 (COX-2) with stimulation of prostaglandin, and beta-adrenergic receptor reactivity to these stimuli, amongst others, suggests a pathophysiologic basis that may explain the association.

Adipose tissue expresses TNF and IL-6, which are potent inflammatory mediators. IL-6 has been associated with IL-4, IL-2, and TNF stimulation and cytokines implicated in asthma. In addition, leptin, which is a protein, secreted by fat cells, has been associated with interleukins. **Figure 2.1** illustrates pathophysiology of airway inflammation and the effect of adipocytes and leptin.

Figure 2.1 Schematic diagram showing pathophysiology of airway inflammation and effect of adipocytes and leptin



A group of investigators tested the hypotheses that overweight or obesity is associated with low-grade inflammation measurable by an acute phase reactant, the C-reactive protein (CRP).[25] The study population comprised of

non-institutionalized civilians, 7938 men and 8678 women, aged 17-39 years, from the third National Health and Nutrition Examination Survey (1988-1994). Seventy-six percent were Caucasian and 34% smokers. Analysis was adjusted for potential confounders like smoking, cardiovascular disease, and inflammatory disease. They reported an OR 2.13 (95%CI1.56-2.91) for men and 6.21 (95%CI 4.94-7.81) in women for increased C-reactive protein in obese subjects. The rise in CRP was directly related with increases in BMI. Restricting the analyses to young adults aged 17-39 years did not alter the findings. A limitation in interpreting the results is the use of a single measurement of CRP. This may indicate active inflammation at a certain point in time rather than an on-going process. Although this study was carried out in the context of cardiovascular disease, the process of inflammation in atherosclerosis is analogous to that seen in asthma, so this mechanism presents a viable explanation for the obesity-asthma link.

Gonen et al.[26] investigated the release of histamine, a proinflammatory mediator, from circulating basophils. Basophils were extracted from a blood sample taken from 28 healthy volunteers and incubated with very low density lipoproteins (VLDL). Because VLDL are associated with obesity, it is conceivable that the bronchospastic and inflammatory findings in asthma may be partly mediated by this mechanism. The cells from each subject were analyzed independently. Histamine release following incubation of basophils with IgE was used as the control. VLDL showed similar kinetics in cellular response compared with IgE, a well-known immunologic factor in the

pathogenesis of asthma. Incubation of basophils with VLDL showed a dose-dependent cellular histamine release with peak histamine release occurring at about normal body temperature. Fifty percent of the maximal histamine release occurred after 5-12 minutes for both VLDL and IgE. Cyclic-AMP agonists known to inhibit IgE induced histamine release, also showed significant inhibition of VLDL-induced histamine release. There was a lack of correlation between the IgE and VLDL response among different donor basophils, suggesting different mechanisms of action.

This study, while not directly related to an asthma-obesity link, sheds some light on possible pathophysiologic mechanisms. The accuracy of invitro tests in elucidating cellular mechanism such as those used in the above study has been repeatedly demonstrated; however, in vitro tests may not accurately reflect the process in vivo.

Inflammation may represent an entirely valid mechanism, but studies linking the inflammatory process to obesity and airway hyperactivity are needed before a causal relation can be assumed.

Gastroesophageal reflux (GER): Gastroesophageal reflux has been strongly associated with asthma and obesity in multiple studies. Thus, it may explain the association between both conditions **(Model 1)**. It is still unclear whether GER is a causal agent or an exacerbating factor in asthma. The prevalence of GER in asthmatics ranges from 34-89% in studies of both adult and pediatric population[62]. Andze et al. identified severe reflux in 41% of children with asthma.[63]

Underlying pathophysiologic mechanisms include: 1) chest expansion with diaphragmatic flattening leads to air trapping and negative intrathoracic pressure. Against a positive intraabdominal pressure, the integrity of the lower sphincter becomes impaired allowing for reflux of gastric contents into the esophagus; and 2) gastric acid within the esophagus initiates a vagal response causing a bronchospastic reflex within the airways.

Reflux in the lower esophagus is also thought to potentiate other bronchospastic triggers. For instance, a provocative dose of methacholine instillation that provoked a 20% reduction in forced expiratory volume in one second was much smaller following esophageal acid exposure.[64] Other mechanisms include microaspiration of gastric contents, medication used in treating asthma such as xanthine derivatives, and systemic βeta 2 adrenergic agonists, which lower LES tone.

The association between obesity and GER is less well corroborated with scientific evidence. While some studies demonstrate an increased rate of GER with obesity, others refute this.[65-69] The strongest evidence that both are connected stems from the improvements noted in GER symptoms following weight loss.[65]

Establishing a temporal relationship between obesity and asthma is key in **Model 1**. Few studies are prospective (**Table 2.2**). Although obesity precedes asthma in these studies, we have to be cautious in the interpretation of "incident asthma", particularly in the adult population. None of the cohort studies have controlled for wheezing in childhood. Children with

transient wheezing in childhood, or children who outgrow their asthma as adolescents, can develop asthmatic symptoms later as adults.

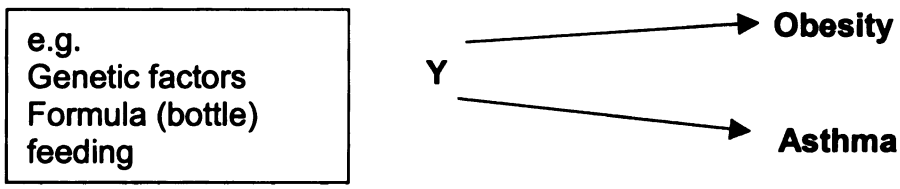
Model 2: Asthma Causes Obesity

Obesity is a consequence of asthma and may closely reflect severity of the disorder. In Model 2, asthma or airway reactivity precedes obesity. Physical activity limitation with decreased energy expenditure may tilt the sensitive metabolic balance towards energy conservation with resultant weight gain. This may be the most difficult model to refute because of the poor sensitivity of pulmonary function tests to detect very mild airway obstruction, thereby asthmatics could be classified as non-asthmatic. This error would introduce differential missclassification as mild asthmatics that could later become obese classified as non-asthmatic. Airway resistance and specific conductance measures on PFTs are particularly good at identifying airway obstruction and hyperresponsiveness.

The multiple risk factors for obesity further reduce the certainty with which asthma alone can be determined to lead to excessive weight. In addition, subnormal lung states can lead to lifestyle changes, e.g., decrease in physical activity behavior and subsequent obesity. Camargo et al.[14] posit that obesity does not occur as a result of changes in physical activity behaviors among asthmatics. In a multi-variate analysis using a variety of physical activity

measures, there was no change in the association between asthma and obesity at different levels of physical activity.

Model 3: Confounding by a variable common to both disorders



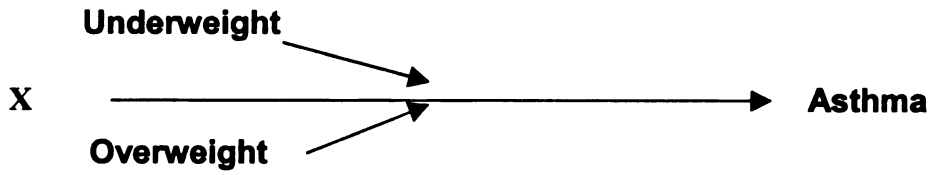
In **Model 3**, we propose there is a third variable, Y, or a constellation of variables that predispose to both asthma and obesity, e.g., gene mutation, depressed hypothalamic pituitary adrenal axis, and adrenergic receptor responsiveness. This model is largely hindered by existing biological knowledge on genetic and cellular mechanisms in the pathophysiology of obesity and asthma. Plausible evidence exists that suggest early childhood factors such as lack of breastfeeding or beta-adrenergic receptor polymorphisms may act as confounder of the obesity-asthma link. Breastfeeding has been linked to lower rates of asthma.[70] Breastfeeding, especially when exclusive, reduces exposure to external antigens during a period when the immune system is still relatively immature. Additionally, transfer of immune factors, e.g., IgA, IgG, via breast milk, may yet serve as a protective mechanism against infections, which can be stimuli for atopy. In a meta-analysis, Gdalevich et al. identified 12 articles from a MEDLINE search from 1966-1999 that examined the relationship between breastfeeding and

asthma.[70] Controlling for age, socioeconomic status, family history of atopy and parental smoking, they reported a pooled odds ratio of 0.70(0.60-0.81) between breastfeeding for at least 3 months and subsequent development of asthma. The protective effect was stronger when the analysis was restricted to children with a family history of atopy and asthma (OR 0.52).

Breastfeeding is also reported to exert a protective effect on subsequent obesity later in childhood.[72-73] Suggested biological mechanisms include nutrient composition of breast milk, suckling experience and physiologic responses to breast milk. For example, breast milk may contain growth factors that impact adipocyte proliferation. Formula-fed babies are also more prone to overfeeding, with resultant increase in size of fat cells. Additionally, breastfed infants compared with formula-fed infants have been shown to consume much less energy and protein. Von Kries (Germany)[72] and Gillman (USA)[73] reported a protective effect using retrospective data. Gillman used a nationwide cohort of 8186 girls and 7155 boys at ages 9-14 years, who were offsprings of the participants of the Nurses Health Study. After adjusting for age, sex, sexual maturity, energy intake, time spent watching television, physical activity, and socioeconomic status, infants that were mostly or exclusively breastfed for 3 months were less likely to be obese (OR 0.78; 95%CI 0.66-0.91) by early adolescence.

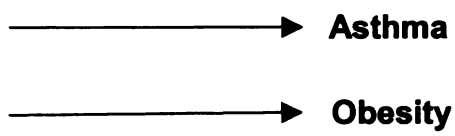
Genetic mutations common to both disorders present another important plausible mechanism that needs to be further explored. For example, beta adrenergic influence on airway reactivity and fat metabolism has been well

documented. Recently there have been studies linking polymorphisms in the B2 adrenoceptor gene with childhood obesity, asthma in women and physical activity.[74] B2 adrenoceptor Gly16 polymorphism has been associated with asthma severity while Glu 27 polymorphism has been reported more often in obese women.[74-76]



In **Model 4**, BMI is depicted as a modifier variable. The effect of Factor X on asthma is modified by BMI. Some studies have shown that underweight, characterized as BMI less than the 10%tile, is a risk factor for asthma. Schacter, in a British cohort of children, reported a two-fold increase in asthma among children below the 10%tile for age and sex.[4] (**Table 2.1**) Lusky et al. describe similar findings.[11] (**Table 2.1**) In this model, physical activity may represent factor X. Underweight and obese children have been reported to exhibit low physical activity patterns, thereby diminishing the amount of full tidal excursions.[77-78] Decreased tidal volume sets up the "latch cycle" described earlier leading to hyperactivity and bronchospasm within the bronchioles. **Model 4** remains poorly developed relative to existing literature on obesity and asthma, but is important for further study. The modifying effect of weight on different health conditions suggest that this model is entirely plausible.

Model 5: No Causal Relationship



Model 5 posits there is no relationship between asthma and obesity. The increased prevalence of asthma among the obese occurs because these are two conditions that are becoming increasingly more common. Thus, we may have ascribed to members of a group, characteristics that they do not possess as individuals. No ecological study on asthma and obesity was identified in existing literature but there may be a role for such studies. It can be useful to examine social and cultural variables underlying both disorders; for example, studing the obesity-asthma link at a period when restricted activity was standard of care for asthmatic patients. Ecological studies can also provide useful data by focusing on regions that buck the expected trend. This model has been refuted by multiple studies examining the causal relationship discussed earlier in Tables 2.1, 2.2 and 2.3.

In addition, trend analysis of BMI and asthma in 28 employment exchange areas in England and Scotland (National Study of Health and Growth) from 1972-1994 in eight and nine-year old children, obesity did not explain the rise in asthma prevalence.[79] The unadjusted odds ratio per year for trends of attacks of asthma between 1982-1994 for 9574 boys was 1.09 (95%CI 1.07-

1.11) and for 8974 girls 1.09 (95%CI 1.07-1.12). When adjusted for BMI and triceps skinfold standard deviation score, the OR remained unchanged. Although high BMI was associated with asthma, the trend in BMI did not account for the rise in asthma prevalence. This suggests that obesity may be a marker for another closely related variable that predisposes to asthma, which was unmeasured in the study. It will be useful to observe if trend analysis from different geographical regions concur with this study.

Conclusion: An overview of the conceptual models suggests that the association between asthma and obesity is complex. Discerning the nature of the relationship is compounded by methodological difficulties in case and exposure ascertainment, establishing a temporal association and objective assessment of potential confounders.

Although levels of biologic evidence provide some coherence to the likelihood of a relationship, our understanding of the causal pathway underlying the obesity-asthma link remains speculative, as few studies have addressed plausible biological mechanisms.

Examining the link between obesity and asthma does not lend itself to experimental study designs, so it is imperative we strengthen the internal validity of subsequent observational studies. The choice and framing of the study question is important, because to adequately establish time order, incident, not prevalent asthma or obesity, should be used. In addition, using a combination of clinical, physiologic and questionnaire methods to define asthma will increase specificity of diagnosis and reduce misclassification.

Finally, as many potential causal variables and interactions exist in the obesity-asthma relationship, further statistical modeling techniques need to be employed to help determine which variables are likely to be independently related to the outcome of interest.

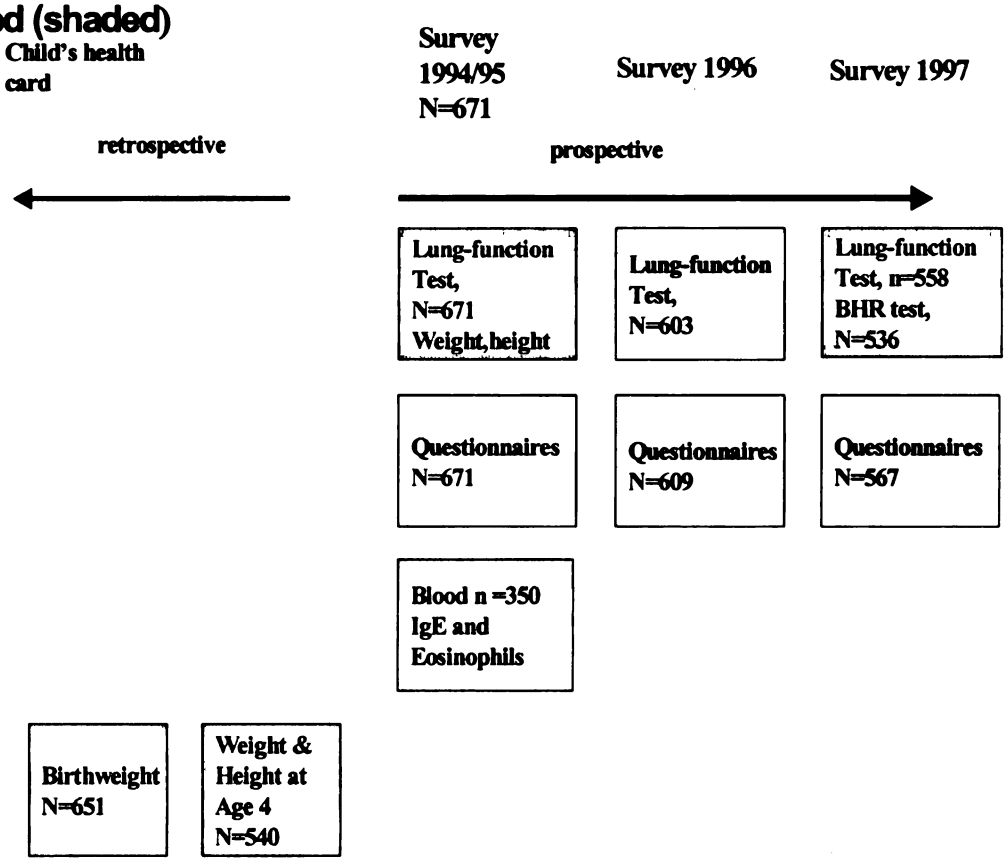
The effects of genes, hormones, prenatal and early childhood events, physical activity, gastroesophageal reflux, and diet in this association are closely interwined and present a formidible task to unravel. However, the rising prevalence and public health impact of both conditions demands further investigation into the intriguing nature of the obesity-asthma link. Using a cohort of German children, my thesis will examine the effect of body mass index on physician diagnosed asthma, bronchial hyperresponsiveness, and measures of atopy. In addition, I will explore the role of third variables such as breastfeeding and family history of atopy.

CHAPTER 3

DATA AND METHODS

Study Population: The German Child Health and Environment prospective cohort study is a longitudinal study examining environmental health risks in a region with waste incinerator and two comparative regions in Hesse, Germany. There were three consecutive surveys carried out during the winter and spring in 1994 -1995, 1996 and 1997. Figure 3.1 illustrates the data collection at each study point.

Figure 3.1: Flowchart of the various phases of the study and the data used (shaded)



In 1994, parents of second grade children in 18 townships in Hesse, Germany were invited to participate. Of the 1091 second grade school children ages 7-10 years attending the schools, 671 (61%) were enrolled in the study. To lessen selection bias, only schools with at least a 60% rate of participation were included. The Ethics Committee of General Medical Council, Hamburg, Germany authorized the study and written consent was obtained.

OUTCOME ASSESSMENT: Physician diagnosis of asthma, history of wheezing, exercise-induced bronchospasm and asthma symptoms are selected as health outcomes. Objective measures of atopy (immunoglobulin E and esinophil count), obstructive indices of pulmonary function (FEV1,

FEV1/FVC., FVC, PEF, MMEF) and bronchial hyperresponsiveness to hypertonic saline were additional outcomes assessed.

Questionnaire: A standardized self-administered questionnaire to collect data on sociodemographic factors, parental atopy, and history of respiratory symptoms was completed by the parent. The questionnaire included questions from the International Study of Asthma and Allergy in Childhood study (ISAAC). Responses to "Has your child ever had asthma?" and "Has your child ever had a doctor's diagnosis of asthma?" were used to define lifetime prevalence of asthma and physician-diagnosis of asthma respectively. Atopic eczema and hayfever were based on the question regarding physician-diagnosis of either disorders. The question related to wheeze was "Has your child had wheezing or whistling in the chest in the last 12 months?" In addition, responses to questions regarding history of nocturnal cough, coughing or wheezing with exercise, and history of physician-diagnosed wheezy bronchitis were recorded. (**Appendix A**). Responses to the questionnaire administered in the first survey 1994/95 were used in the statistical analysis.

Pulmonary Function Tests: Timing of the last asthma medication and history of recent respiratory infection was obtained at the onset of testing. All measurements were performed between 10am and 5:30pm by two technicians using a Jaeger masterscope 4.1. The instruments were calibrated daily. Each child performed two forced expiratory maneuvers according to ATS criteria. The test was considered acceptable if the difference between

FVC on both maneuvers was less than or equal to 5%. For purpose of our analysis FEV1, FEV1/FVC, FVC, PEF and MMEF measures obtained during the first survey (1994/5) were used. Asthma medications were not discontinued for the tests.

Bronchial Hyperresponsiveness (BHR) using 4.5% Hypertonic Saline: BHR was carried out during the third year of the survey in 1997. Subjects were excluded from the tests if their baseline FEV1 was < than 65% of predicted values. History of respiratory infection during the last one week was obtained. BHR was defined as a fall in FEV1 greater than 15%. The bronchial challenge test was done following standard procedures decribed by Anderson et al. [80] The 4.5% hypertonic solution was prepared by adding 45gm of dialysis grade sodium chloride to 1000ml of sterile pyrogen free water and delivered as an aerosolized solution. The mean output of the nebulizer was 2.14mL/min. During the test, the dose of hypertonic saline was increased successively by doubling the aerosol inhalation time starting with 30 seconds up to 8 minutes. One minute after each inhalation, a flow curve was recorded. The challenge test ended when FEV1 had fallen between 10 - 15%, or after a cumulative inhalation time of greater than 15.5 minutes and a cumulative dose of 23ml of hypertonic saline had been used.

Immunoglobulin E and Eosinophil count: Venous specimen was obtained from 350 (52%) of the study population during the first year of the study (1994/95). It was restricted to children whose parents smoked less than 10 cigarettes per day. A Vacutainer was used for blood sampling and about

25ml was drawn. Measurements of IgE in serum were made in the Medical, Alimentary and Veterinary Institute for Research, Middle Hesse, Division of Human Medicine, Dillenburg, Germany, using radioimmunoassay (CAP, Pharmacia, Uppsala, Sweden). The results were provided in kU/L serum.

EXPOSURE ASSESSMENT

Anthropometric Measures: We measured height (m) and weight (kg) for each child in three consecutive examinations one year apart (approximately age eight, nine and ten years) and during the lung function tests. In Germany, parents keep a record book, the Child's Health Card, that includes documentation of scheduled health check-ups from birth to school age. We asked the parents to bring their Child's Health Card to a medical examination. We recorded the child's height and respective age documented during check-ups at birth, 4-6 weeks, 3-4 months, 6-7 months, 10-12 months, 21-24 months, and 43-48 months from the child's health card. The child's age was derived from child's birth date and date when height was ascertained. Body mass index was calculated by weight(kg) divided by height(m)^2. BMI values were grouped into quintiles for statistical analysis.

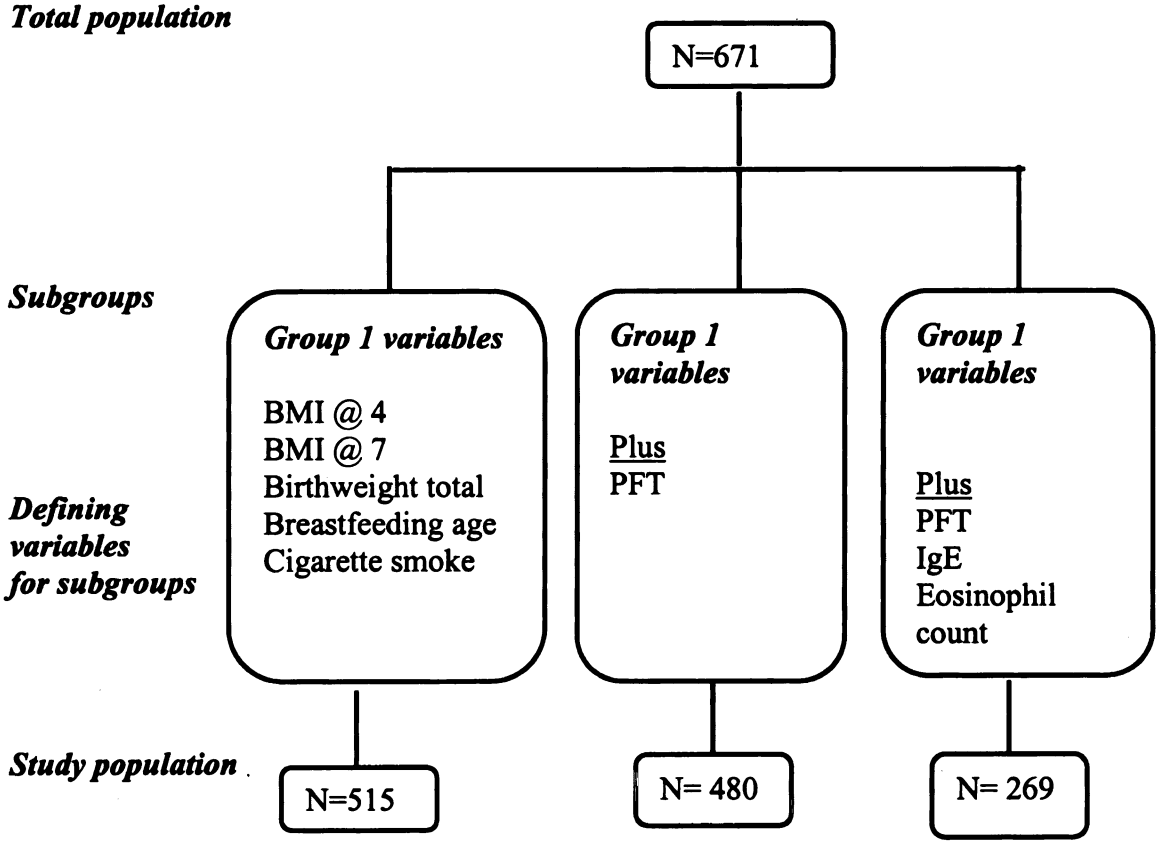
OTHER STUDY CHARACTERISTICS

Birthweight was obtained from the child's medical record. It was divided into three categories: low birthweight (<2500gms), normal birthweight (2500-<4000gms) and high birthweight (>4000gms). Duration of total and exclusive breastfeeding was grouped into 4 week intervals: none, 1-3 wks, 5-8 wks, 9-12, >12 weeks. When the patient was only breastfed, without introduction of

any other form of milk, breastfeeding was defined as exclusive. Passive smoke exposure was divided into categories based on number of cigarettes smoked in the household, with the highest category being 20 or more cigarettes per day. Paternal or maternal history of atopy was positive if either parent reported a history of atopic dermatitis or hayfever.

Statistical analysis: To address the study aims, the study population was analyzed in three subgroups based on the presence of missing data (**Figure 3.2**). Of the 671 children enrolled in the study, 515 subjects had detailed information on anthropometric measures and potential confounders. The total population used for analysis was 515, 55% of the original cohort eligible for the study. The subgroups were: 1) total population was restricted to 515 children; 2) 480 children with PFT results and bronchial hyperresponsiveness; and 3) 269 children with eosinophil counts and immunoglobulin E levels.

Figure 3.2 Defining study population and subgroups used for analyses



Indicator, or dummy, variables were created for age, sex, BMI at ages 4 and 7 years, birthweight, exposure to passive smoking and breastfeeding. Group comparisons were carried out by cross tabulations and Chi (κ^2) test of proportions. To examine predictors of asthma and bronchial hyperresponsiveness, logistic regression with BMI at age 4 and 7, sex, breastfeeding and family history of atopy in the model was carried out. To be more inclusive, children with either a wheezy bronchitis, physician-diagnosed asthma, exercise-induced bronchospasm or positive hyperresponsiveness were grouped together and logistic regression analysis also performed. Because the distributions of IgE and eosinophil count were not normal, the

geometric mean, median, and 5^{th} and 95^{th} percentiles were used. Those variables that were associated with both the outcome and exposure variables, either in our data or from other literature, were re-entered into a regression analysis along with interactions between the exposures. The variables that remained in the final model were BMI at ages 4 & 7, age, birthweight, breastfeeding, sex, height, maternal and paternal atopy, history of respiratory tract infection a week prior to PFT and passive smoke exposure. Categories of variables have been described earlier in the chapter and are presented in **Table 4.1**.These variables were also analyzed as potential indicators of eosinophil count, immunoglobulin E and pulmonary function measures in a linear regression model. All data analyses were carried out using the SAS statistical package (SAS institute, Cary, NC) version 8.

CHAPTER 4

RESULTS

Study population characteristics: The median age was 8.2 years during the first survey (1994/95) and males constituted about 55% of the population in all subgroups. In the total population, the prevalence of physician-diagnosed asthma, hayfever and atopic eczema was 5.3%, 8% and 26% respectively. Eighty-seven percent of the children were born with normal birthweight (2500-4000gm), 4.7% with low birthweight (<2500gm) and 8.7% with high birthweight(>4000gm). Thirty-six percent had been breastfed for at least 12 weeks, whereas 20.2% were not breastfed at all. About half of the children had exposure to environmental tobacco at home. One-quarter and 23% of the fathers and mothers, respectively, reported a history of atopy (**Table 4.1**).

The subgroup with data on IgE and eosinophil count differed slightly from the total population (**Table 4.1**), with a lower number of children reporting tobacco exposure (32%) and 12% with birth weights above 4000 grams versus 8.7%. Children whose families smoked >= 10 cigarettes/day had been excluded from obtaining IgE and eosinophil counts. They were also more likely to have been breastfed for longer than 12 weeks (43% vs. 36%) than the total population. However, none of the differences were statistically significant.

Relationship of BMI quintiles to US growth chart: Mean BMI at age 4 was 16.8 (range 12.6-24.2) and 16.2 (12.8-30.4) at age 7. Children with BMI greater than 95th percentile for age and sex are defined as obese. The lowest

value of BMI in the 5th quintile of BMI was comparable to the 95th percentile cut-off for BMI on the 2000 US growth chart. For age 7, the minimum value in the 5th quintile was 20.5 compared to 20.08 for boys and 20.78 for girls at the 95% in the US growth chart. Likewise, the minimum 5th quintile value at age 4 for boys and girls was similar to the US growth chart at 95th percentile (17.9 vs. 17.2) for boys and (17.9 vs. 17.4) for girls.

Table 4.1 Characteristics of study population

Characteristic	Total n=515(%)	PFT N=480(%)	IgE/Eosinophil N=259(%)
Median Age	8.2	8.2	8.2
Male sex	283 (55)	259 (54)	148 (57)
Birthweight (gms) <2500 ≥2500<4000 ≥ 4000	 24 (4.7) 446 (86.6) 45 (8.7)	 19 (4.0) 416 (86.6) 45 (9.4)	 7 (2.7) 221 (85.0) 31 (12.0)
Wheezy bronchitis Physician-Diagnosed Asthma No Physician-Diagnosed Asthma	48 (9.4) 27 (5.3) 434 (84.4)	43 (9.0) 25 (5.2) 409 (85.7)	24 (9.3) 15 (5.8) 218 (84.8)
BMI at age 4 (quintiles) <15.61 15.64-<16.44 16.44-<17.19 17.19-<17.99 ≥17.99	 102 (19.8) 104 (20.2) 96 (18.6) 107 (20.8) 106 (20.6)	 96 (20.0) 93 (19.4) 103 (21.5) 88 (18.3) 100 (20.8)	 50 (19.3) 53 (20.5) 57 (22.0) 55 (21.2) 44 (7.0)
BMI at age 7 (quintiles) >15.98 15.98-<17.05 17.05-<18.57 18.57-<20.54 ≥ 20.54	 105 (20.4) 100 (19.4) 107 (20.8) 96 (18.6) 107 (20.8)	 95 (19.8) 95 (19.8) 89 (18.5) 99 (20.6) 102 (21.2)	 58 (22.4) 44 (17.0) 47 (18.1) 54 (20.9) 56 (21.6)

Table 4.1 (cont'd.)

Total breastfeeding (wks)			
None	104 (20.2)	89 (18.5)	35 (13.5)
0 <4	98 (19.0)	93 (19.4)	41 (15.8)
≥ 4>8	68 (13.2)	66 (13.7)	36 (13.9)
≥ 8<12	58 (11.3)	57 (11.9)	35 (13.5)
≥12	187 (36.3)	175 (36.5)	112 (43.2)
Environmental smoke exposure			
Yes	282 (54.8)	260 (54.2)	86 (32.1)
No	233 (45.2)	220 (45.8)	176 (67.9)
Maternal history of atopy			
Yes	120 (23.3)	107 (22.3)	59 (22.8)
No	395 (76.7)	373 (77.7)	200 (77.2)
Paternal history of atopy			
Yes	106 (20.6)	98 (20.4)	64 (24.7)
No	409 (79.4)	382 (79.6)	195 (75.3)

Birthweight was correlated with BMI at age 4 years r^2 =0.14 (p0.0003) and BMI at age 7 years r^2 =0.18 (p< 0.0001) while body mass index at age 4 years was moderately correlated with BMI at age 7 years r^2 =0.22 (p <0.0001). Total breastfeeding was not correlated with BMI at age 4 $r^{2=}$0.005 (p=0.90) or 7 years r^2=0.005 (p=0.90), but was correlated with birthweight r^2= 0.14 (p=0.0026). (**Appendix B**).

The relationship between BMI and 1) asthma and asthma symptoms; 2) pulmonary function test; and 3) Eosinophil count, IgE and bronchial hyperresponsiveness (BHR) will now be examined.

Asthma symptoms and diagnosis: The prevalence of physician-diagnosed asthma was 5.3% and boys were more likely to be asthmatic than girls OR 3.1 (95%CI 1.2-8.2). Breastfeeding was protective for physician-diagnosed asthma (OR 0.7 95%CI 0.5-0.9) .

Children with physician-diagnosed asthma were more likely to have hayfever, 27% vs. 3.5% (p=0.0001), atopic eczema, 8.7% vs. 4% (p=0.03) and wheezing without infection, 58% vs. 3.4% (p=0.0001). Exposure to tobacco smoke at home was not a risk factor for asthma (p=0.17).

Table 4.2: Relationship of BMI, breastfeeding and family history of atopy to asthma

Variables N = 515	Physician-Diagnosed Asthma N=27		History of asthma, or exercise-induced bronchospasm, or wheezy bronchitis or BHR N=84		Any Asthma symptom N= 141	
	OR	95% CI	OR	95% CI	OR	95% CI
BMI at age 4 Ist vs 5th quintile	0.9	0.3-3.8	0.8	0.4-1.4	0.5	0.3-1.0
BMI at age7 Ist vs 5th quintile	1.7	0.4-5.9	0.7	0.4-1.4	1.8	0.9-3.5
Total breastfeeding Ist vs 5th quintile	0.3	0.1-0.8	1.5	0.8-2.7	0.7	0.4-1.8
Maternal atopy Ist vs 5th quintile	1.5	0.6-3.7	1.1	0.7-1.9	1.4	0.9-2.3
Paternal atopy Ist vs 5th quintile	2.3	1.0-5.4	0.6	0.3-0.9	1.2	0.7-1.8

The odds of physician-diagnosed asthma did not increase with BMI quintiles at age four or seven (**Table 4.2**).

Stratifying by sex, the result was unchanged. A positive effect of only female sex on the association between asthma and obesity have been reported in certain studies. However, testing for an interaction between sex and BMI on asthma in our study population, there was no significant relationship (p=0.92). Using a logistic regression model, controlling for sex, age, maternal and

paternal atopy, passive smoke exposure and breastfeeding, neither BMI at age 4 or 7 was a risk factor when asthma was redefined with the more rigorous classification described in Chapter 3.

When children with either wheezy bronchitis, physician-diagnosed asthma, exercise-induced bronchospasm or positive hyperresponsiveness were grouped together and used as the dependent variable in the regression model, there was no association with BMI at age four or seven years. (**Table 4.2**).

Reanalyzing the data at age 7 years using US growth chart BMI percentiles as a reference, the result remained unchanged (**Table 4.3**).

Table 4.3: Association between asthma and BMI using 2000 US growth charts as reference.

BMI Percentile[1]	Physician-Diagnosed Asthma OR	95% CI
Males		
≥ 95	0.7	(0.09-5.8)
≥ 85	0.56	(0.16-1.96)
≤ 10	0.7	(0.27-1.69)
≤ 5	1.5	(0.43-5.5)
Females		
≥ 95	2.7	(0.11-46.4)
≥85	1.1	(0.1-11.26)
≤10	2.9	(0.4-21.1)
≤5	1.1	(0.1-10.9)

[1]Total population >95%tile N= 49;(9.5%) >85-95%tile N= 169 (32%)

Asthma symptoms: Twenty-seven percent of the total population reported at least one asthma symptom. Of the total population of 515 children, five percent had wheezing with exercise, while three percent and 16% reported

wheezing and dry cough without upper respiratory tract infection respectively. A larger proportion of children in the 4th and 5th quintile had a diagnosis of wheezy bronchitis **(Table 4.4)**

Table 4.4: Percentages of atopic conditions and asthma symptoms within BMI quintiles for age 7 years

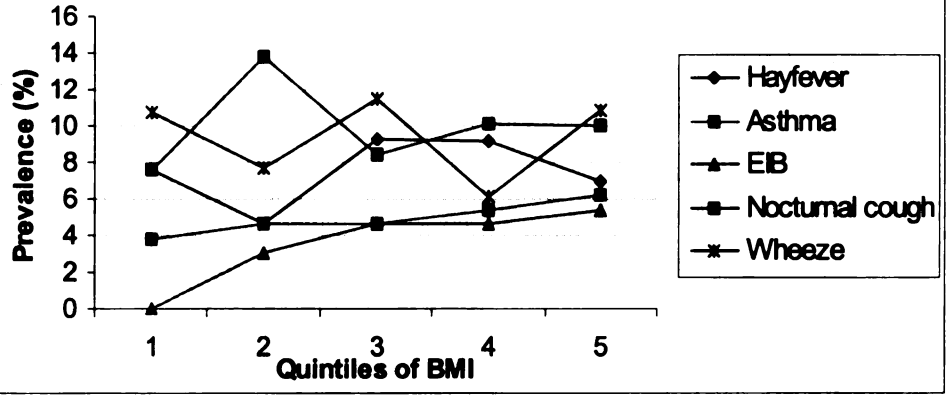
Symptoms	1st Quintile N=105	2nd Quintile N=100	3rd Quintile N=107	4th Quintile N=96	5th Quintile N=107
Age 7 years					
Asthma	4.7	6.0	3.8	5.2	6.6
Wheezy bronchitis	8.4	6.9	7.6	9.9	12.3
Hay Fever	8.5	4.0	8.4	8.3	6.5
Atopic Eczema	25.7	25.0	33.6	29.1	20.5
Dry Cough	11.4	24.0	17.7	13.5	14.9
Cough after exercise	10.4	16.1	16.8	15.7	19.8
EIB*	3.8	6.0	5.6	5.2	9.4
History of wheeze	12.3	10.0	10.3	6.2	12.2
Nocturnal cough	23.8	23.0	32.7	22.1	28.9
At least one asthma symptom	20.9	30.0	31.7	23.9	29.9
Number of asthma symptoms**					
0	79.0	70.0	68.2	76.0	70.0
1	9.5	16.0	25.2	15.6	15.8
2	6.6	6.0	3.7	4.1	7.4
3	3.8	5.0	1.8	3.1	6.5
4	0.9	3.0	0.9	1.0	0.0

* Exercise induced bronchospasm

** Number of positive responses to any of the asthma symptoms (See Appendix A)

Children with exercise-induced wheezing were more likely to be in the 5th quintile at age 7 years, 8.5% vs. 3.5% (p=0.05). However, the prevalence of hayfever, nocturnal cough and history of wheezing did not rise significantly with BMI at age 4 or 7 (**Figure 4.1**).; At age 7 years, children with EIB had more symptoms of nocturnal cough, 50% vs 3.5% (p=0.0001) and a history of hayfever, 12.5% vs 4.5(p=0.005) as illustrated in **Table 4.4**. They were also more likely to have a positive BHR 15.8% vs. 3.5% (p=0.0001).

Figure 4.1: Prevalence of Asthma, Hayfever, Exercise Induced Bronchospasm [EIB] and Asthma symptoms by Body mass Index at 7 years
*** p < 0.05**



There was no significant difference in prevalence of asthma symptoms and BMI at age 4 and 7 (**Appendix C** lists the percentages of asthma symptoms within BMI quintiles at age 4 years).

Pulmonary function tests: Spirometric tests for obstructive lung disease such as FEV1, FVC, FEV1/FVC, FEF50 and PEF were selected for analysis. Abnormalities in these measures, as discussed in Chapter 1, typically reflect airway obstruction, which is the underlying pathophysiologic process for asthma. To control for any confounding effects, multiple logistic regression analysis was used to explore the variation of pulmonary function measures by BMI, while controlling for age, sex, maternal and paternal atopy, passive smoke exposure, breastfeeding and history of recent respiratory infection **(Table 4.5).** PEF, FEV1, FVC and FEV1/FVC values were significantly higher in males than females. BMI at age 4 $\geq$ 17.9 (5^{th} quintile) was associated with a decrease in FEV1/FVC (p=0.01) and PEF (p=0.01) when compared with the group with lowest BMI. At age 7, there was an increase in FVC for BMI > 20.5, (5^{th} quintile p=0.04) but no other significant differences in FEV1, FEV1/FVC or PEF were found.

There was no consistent trend in the protective effect of breastfeeding on FEV1, FEV1/FVC, MMEF or PEF. Compared with no breastfeeding, total breastfeeding for a duration of 8 weeks was associated with a significant increase in PEF (p=0.02) and FEV1 (p=0.03), while breastfeeding for greater than 12 weeks was associated with an increase in FEF50 (p=0.02) and FEV1/FVC (p=0.0004). The results were similar when the analysis was carried out for exclusive breastfeeding.

Table 4.5. Multiple Linear Regression Results for the Effect of Breastfeeding and BMI at ages 4 and 7 years on Pulmonary Function

Variable N =480	PEF		FEF 50		FEV1		FVC		FEV1/FVC	
	Lsmean	P-value (t-test)	Lsmean	P-value (t-test)	Lsmean	P-value (t-test)	Lsmean	P-value (t-test)	Lsmean	P-value (t-test)
Sex	**(F-test**	**p=0.04)**	**(F-test**	**p=0.44)**	**(F-test**	**p=0.001)**	**(F-test**	**p=0.001)**	**(F-test**	**p=0.04)**
Male	3.53		2.19		1.76		2.04		0.87	
Female	3.36		2.15		1.64		1.86		0.88	
Breastfeeding (wks)	**(F-test**	**p=0.24)**	**(F-test**	**p=0.17)**	**(F-test**	**p=0.26)**	**(F-test**	**p=0.52)**	**(F-test**	**=0.006)**
None	3.29	----	2.02	----	1.65	----	1.93	----	0.85	----
0-<4	3.48	0.09	2.23	0.02	1.71	0.08	1.95	0.39	0.88	0.004
≥4<8	3.57	0.02	2.18	0.11	1.73	0.03	2.00	0.68	0.87	0.11
≥8-<12	3.46	0.18	2.21	0.07	1.70	0.21	1.96	0.17	0.87	0.11
≥12	3.44	0.14	2.21	0.02	1.71	0.09	1.93	0.53	0.89	0.0004
BMI at 4 (quintiles)	**(F-test**	**p=0.08)**	**(F-test**	**p=0.03)**	**(F-test**	**p=0.78)**	**(F-test**	**p=0.75)**	**(F-test**	**p=0.02)**
<15.61	3.51	----	2.25	----	1.70	-----	1.93	-----	0.88	----
15.64-<16.44	3.45	0.54	2.22	0.76	1.70	0.81	1.93	0.86	0.88	0.89
16.44-<17.19	3.55	0.77	2.21	0.66	1.71	0.88	1.95	0.70	0.88	0.81
17.19-<17.99	3.49	0.73	2.15	0.24	1.71	0.99	1.98	0.29	0.87	0.11
≥17.99	3.25	0.01	2.03	0.01	1.68	0.32		0.57	0.85	0.01
BMI at 7 (quintiles)	**(F-test**	**p=0.24)**	**(F-test**	**p=0.11)**	**(F-test**	**p=0.41)**	**(F-test**	**p=0.13)**	**(F-test**	**p=0.29)**
>15.98	3.39	----	2.21	----	1.69	----	1.93	----	0.88	----
15.98-<17.05	3.48	0.33	2.15	0.51	1.68	0.68	1.94	0.81	0.87	0.13
17.05-<18.57	3.55	0.13	2.22	0.88	1.70	0.98	1.92	0.82	0.88	0.80
18.57-<20.54	3.44	0.95	2.05	0.08	1.68	0.72	1.95	0.72	0.87	0.15
≥ 20.54	3.55	0.18	2.21	0.99	1.74	0.23	2.01	0.05	0.87	0.18

Atopy and Bronchial hyperresponsiveness: The strong association between asthma and atopy, sedentary behavior with increased exposure to indoor allergens as well as the inflammatory mechanisms of adipose tissue, suggests atopy may be a plausible biological mechanism to explain the asthma obesity link. **Table 4.6** summarizes the effect of BMI at age four years, BMI at seven years and breastfeeding on bronchial hyperresponsiveness. A total of fifteen percent of the study population tested for bronchial hyperresponsiveness using 4.5% hypertonic saline had a positive result.

Table 4.6: Effect of BMI on Bronchial Hyperresponsiveness

Variable	**Bronchial hyperresponsiveness N= 536**	
	Odds Ratio	**95%C.I**
BMI quintiles (wt/ht^2) Age 4 years		
<15.61	1.0 (ref)	
15.64-<16.44	0.9	(0.4-2.4)
16.44-<17.19	0.8	(0.3-2.2)
17.19-<17.99	1.4	(0.5-3.4)
≥17.99	1.2	(0.5-3.0)
BMI quintiles (wt/ht^2) Age 7 years		
>15.98	1.0 (ref)	
15.98-<17.05	1.2	(0.5-3.1)
17.05-<18.57	0.6	(0.2-1.4)
18.57-<20.54	0.7	(0.3-1.7)
≥ 20.54	0.8	(0.3-3.2)
Total breastfeeding (wks)		
None	1.0 (ref)	
0-<4	0.9	(0.4.-2.2)
≥4<8	0.6	(0.2-1.9)
≥8-<12	1.0	(0.4-2.6)
≥12	0.4	(0.2-0.9)

Children who had a physician-diagnosed asthma (OR = 1.2, 95%CI 1.07- 1.32), hayfever (OR = 1.3, 95%CI 1.0- 5.2), exercise-induced bronchospasm (p=0.0001) and wheezing without evidence of respiratory infection (p =0.001) but not IgE (p=0.06), were more likely to have a 15% fall in FEV1. Breastfeeding for greater than 12 weeks had a protective effect against bronchial hyperresponsiveness (OR = 0.4, 95% CI 0.2-0.9). There was no association between bronchial hyperactivity and BMI at age 4 (p=0.54) and BMI age 7 (p=0.68).

Children with asthma were more likely to have elevated IgE levels (p=0.0004).

Table 4.6 presents geometric means of eosinophil count and IgE stratified by BMI at ages 4 and 7 and breastfeeding. Log transformation of IgE and eosinophil was used for analysis. There was no significant association of BMI with serum eosinophil and IgE.

Table 4.7: Effect of BMI on Immunoglobulin E and Eosinophil Count.

Variable	IgE (KU/L) N=259		Eosinophil (absolute count/nl) N=259	
	Geometric mean	P-value (t-test)	Geometric mean	P-value (t-test)
BMI quintiles (wt/ht^2) Age 4 years	**(F-test p=0.30)**		**(F-test p=0.34)**	
<15.61	80.58	-----	251.87	-----
15.64-<16.44	80.87	0.05	225.83	0.35
16.44-<17.19	57.95	0.72	281.90	0.55
17.19-<17.99	61.10	0.85	228.86	0.94
≥17.99	49.25	0.51	258.12	0.08
BMI quintiles (wt/ht^2) Age 7 years	**(F-test p=0.92)**		**(F-test p=0.21)**	
>15.98	65.44	-----	244.67	-----
15.98-<17.05	47.84	0.53	181.98	0.79
17.05-<18.57	64.03	0.41	267.83	0.21
18.57-<20.54	83.15	0.41	286.66	0.03
≥ 20.54	68.17	0.43	277.07	0.60
Total breastfeeding (wks)	**(F-test p=0.09)**		**(F-test p=0.37)**	
None	75.37	-----	273.51	------
0-<4	35.78	0.10	205.46	0.95
≥4<8	64.26	0.01	240.53	0.05
≥8-<12	70.88	0.18	254.02	0.39
≥12	92.52	0.62	275.87	0.72

Only breastfeeding for less than 8 weeks was significantly associated with lower IgE levels (p=0.01) and eosinophil count (p=0.05).

CHAPTER 5

DISCUSSION

A high BMI was not associated with an increasing prevalence of asthma in this population of 515 German children aged 7-8 years controlling for potential confounders such as passive smoke exposure, sex, breastfeeding, birthweight, maternal and paternal atopy. There was no effect when stratifying by sex and no interaction between sex and BMI. The lack of association persisted for BMI at age 4 and subsequent history of asthma at ages 7-8 years. To be more inclusive, children who had a physician-diagnosis of asthma or exercise-induced asthma or wheezy bronchitis or any asthma symptom were grouped together. Logistic regression using this outcome measure still did not show a relationship between BMI both at ages four or seven years.

The longitudinal nature of the study design allows us to ascertain BMI at age four, prior to determination of a history asthma, bronchial hyperresponsiveness, obstructive pulmonary indices and immunoglobulin level. Regardless of whether the children were in the heaviest quintile at age 4 or 7, the results were unchanged. Thus, there was no relationship between obesity and asthma.

Our findings are in agreement with results reported by Brenner[21] and Lusky et al.[11] and others who found no association between asthma and obesity but discordant with some investigators.[3-10, 12-20,22,23] In a British study carried out between 1982-1994, Chinn et al. found that an increase in body mass index could not explain the rise in asthma.[79] The odds ratio per year for asthma across

the time period of the study remained unchanged when adjusted for BMI. Their findings suggest the obesity-asthma link may not be causal but rather reflect the effect of recent lifestyle changes. It will be important to re-examine the causal link in different populations and geographic location with varying patterns of lifestyle behaviors and physician diagnostic patterns, as most of the observational studies reporting a postive association have been carried out either in the US, UK or Canada.

Most studies that found a positive association between asthma and obesity used a history of asthma either obtained by self-report or through medical chart review and medication use to define their population. In our analysis, self-reported history of asthma symptoms, asthma diagnosis and objective measure of BHR were all used as outcome measures, thus reducing the chance of misclassification. But there was still no association found with various permutations of diagnostic definitions. It is improbable that physician diagnostic patterns may account for the lack of association found since we were unable to report a link between objective measures of airway reactivity and BMI.

An association between asthma and obesity may also have been attenuated by the high rate of breastfeeding in the sample. About 80% had been breastfed, with 36% breastfed for longer than 12 weeks. Breastfeeding has been reported to have a protective effect on both asthma and obesity. In a meta-analysis on breastfeeding and asthma by Gladevich et al. they reported a summary OR of 0.70 (95%CI 0.60-0.81).[70] Indeed, we found a protective effect of breastfeeding on physician-diagnosed asthma in our study. However, when breastfeeding was

controlled for in the model, the lack of association between asthma and BMI persisted.

In contrast, exercise-induced bronchospasm (EIB) was related to BMI at age 7 years. EIB could account for only part of the reported association between asthma and obesity. Kaplan et al. reported increased frequency and severity of EIB among 6-10 year old obese non-asthmatic children compared with their non-obese counterparts.[450] The mechanism whereby EIB occurs is thought to occur from consequences of heating and humidifying large volumes of air during exercise. It is unknown whether this process is different in overweight persons. An alternate explanation may be impaired chest wall mechanics reported in obese individuals with a resultant decrease in end tidal volume leading to slow cycling rates in the actin-myosin complex. The subsequent bronchial hyperreactivity could then be exacerbated by exercise.

A high BMI was not associated with a positive BHR test in our study population. Similar findings were reported in a study of 2,842 children aged 13-14 years who underwent exercise-challenged testing for bronchial hyperresponsiveness. The investigators found a 15% fall in FEV1 was significantly associated with lower age, female sex, high socioeconomic level and attending a private school, but not obesity.[81] There is a discrepancy between a positive effect of BMI on exercise-induced bronchospasm yet not on bronchial hyperactivity since both conditions are closely related. Failure to discontinue asthma medications prior to testing may account for this finding.

The spirometric pulmonary function measures PEF, FEF50 , FEV1, FEV1/FVC and FVC volumes were all higher in males as has been reported in the literature. High BMI measured at age four years resulted in dimunition in pulmonary function measures at age 7-9 years. At age 4, after controlling for confounders, children in the highest quintile had lower values for PEF and FEV1/FVC measured but not FEV1. FEV1/FVC and FEF50 are the most important measure in distinguishing an obstructive impairment while PEF is best used for monitoring. Because BMI at age 4 and 7 were correlated, this finding may reflect persistence of overweight in the same individuals. A 3% decline in FEV1/FVC and 0.23L reduction in FEF50 indicates obesity has some effect on airway obstruction. This effect most likely would have been more pronounced had asthma medications been discontinued for the PFTs. The increase of 0.1L in FVC among children in the 5^{th} quintile is contradictory, but this may reflect the weakness of body mass index in distinguishing between lean body mass and fat. Children who are more physically active are more muscular and have larger vital capacity.

Only pulmonary function test (PFT) results from the first survey were used in the analysis. Serial PFT measures would have been more informative. Airflow obstruction in asthma is reversible, thus a significant number of asthmatics can have normal PFT tests at a single point in time which may not truly reflect the extent of obstruction. In addition, the tests were done between 10 am-5:30 pm, a period of time during the day that airflow obstruction is likely to be at its least.

Atopy is strongly associated with asthma. About 80% of asthma in children and adults has been linked to atopic sensitization in clinical studies. It has been

hypothesized that obese subjects spend more time indoors, thus increasing their susceptibility to indoor allergens and sensitization. This hypothesis along with the strong association between asthma and atopy and inflammatory mechanisms of adipose tissue, suggest atopy may be a plausible biological mechanism to explain the asthma obesity link. However BMI was not associated with the measures of atopic sensitization, hayfever, atopic eczema, total immunoglobulin E and eosinophil count assessed in our analysis. The findings are supported by von Mutius et al.[7] that the association between BMI and asthma is not based on an atopic mechanism. Using the NHANES III data, they found BMI was not related to eosinophil count or skin prick tests to common allergens including dustmite, german cockroach, cat, grass, ragweed, Alternaria and peanuts.

The German Child Health and Environment study in Hesse, Germany contains detailed information on asthma and risk factors in a large cohort. Availability of various measures for asthma provide good data to minimize misclassification and pulmonary function tests and BHR tests were carried out according to the ATS protocol by experienced technicians.

Another strength is its longitudinal nature, which allows for assessment of causality. Shortcomings exist in this dataset and some have been mentioned earlier. Only 61% of total population eligible participated in the study because of available data and refusal to participate (total population of 515 from the 1091 eligible children). However, there were no major differences between the groups that would inherently affect the results in either direction. A major confounder like breastfeeding was obtained by self-report more than 5 years following the

event; but it is unlikely that mothers of obese children would report any differently. Finally, based on a prevalence of 5.7% of asthma in our study population of 515 children, we may not have had enough power to detect a significant association between asthma and BMI.

In conclusion, in a longitudinal study of German school children, BMI is not an independent risk factor for asthma, but is positively associated with exercise-induced bronchospasm. In addition, BMI is not related to IgE, eosinophil count or bronchial hyperresponsiveness. The decline in airway obstructive parameters at age 7 years with increasing BMI measured at four years but not at 7 years provides important information that obesity plays a role in airway hyppereactivity that may not be mediated through impaired chest wall mechanisms. Understanding the pathophysiologic mechanism underlying the effect of BMI on exercise-induced bronchospasm is important as this condition is becoming increasingly common. Further studies, with emphasis on specificity of exposure and outcome ascertainment, are needed to elucidate the relationship between asthma and obesity.

APPENDIX A

Questions on asthma and symptoms

1. Has your child ever had a doctor's diagnosis of asthma?
2. Has your child ever had a doctor's diagnosis of atopic dermatitis?
3. Has your child ever had a doctor's diagnosis of hayfever?
4. Has your child had wheezing or whistling in the chest in the last 12 months?
5. Has your child had a dry cough, apart from a cough associated with a cold or chest infection?
6. Has your child had attacks of shortness of breath or dyspnea in the last 12 months?
7. Has your child had cough or shortness of breath at night or early in the morning in the last 12 months?
8. Does your child have wheezing during or after exercise in the last 12 months?
9. Does your child have coughing during or after exercise in the last 12 months?

APPENDIX B

Spearman's correlation coefficients for selected variables.

Variable	Birthweight rank coefficient p-value	BMI@ 4 yrs. rank coefficient p-value	BMI @ 7 yrs. rank coefficient p-value	Total breastfeeding rank coefficient p-value
Birthweight	1.00	0.19 <.0001 N =554	0.14 0.0003 N =632	0.14 0.0003 N =617
BMI @ 4 yrs.		1.00	0.22 <. 0001 N=547	0.005 0.90 N=531
BMI @ 7 yrs.			1.00	0.005 <0.9002 N=619

APPENDIX C

Percentages of atopic conditions and asthma symptoms within BMI quintiles for ages 4 years

Symptoms	1st Quintile N=102	2nd Quintile N=104	3rd Quintile N=96	4th Quintile N=107	5th Quintile N=106
Age 4 years					
Asthma	4.9	5.8	6.2	4.7	4.7
Wheezy bronchitis	5.3	6.2	7.6	16.5	13.6
Hay Fever	7.8	4.8	2.0	11.3	9.4
Atopic Eczema	29.4	28.8	25.0	25.2	25.4
Dry Cough	14.7	13.4	19.7	18.6	15.0
Cough after exercise	19.6	18.6	13.6	17.7	9.4
EIB	4.9	8.6	5.2	8.4	2.8
History of wheeze	6.8	12.5	10.5	11.2	10.4
Nocturnal cough	30.3	25.0	27.3	27.1	21.7
At least one asthma symptom	33.3	26.9	25.0	28.9	22.6
# of asthma symptoms					
0	66.6	73.0	75.0	71.0	77.3
1	24.5	13.4	15.6	16.8	12.2
2	2.9	5.7	8.3	5.6	5.6
3	4.9	3.8	1.0	6.5	3.7
4	0.9	3.8	0.0	0.0	0.9

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