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UNIVERSITY OF CALIFORNIA,
IRVINE

Relationships between Asthma, Obesity and Fitness in Adolescent Boys and Girls

THESIS

Submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Kim Dao Lu

Thesis Committee:
Professor Hoda Anton-Culver, Chair
Professor Dan M. Cooper
Assistant Professor Shlomit Radom-Aizik
Assistant Professor John Billimek

2015

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DEDICATION

To

my husband, Tom

for his unwavering support and love

To

Ryan and Lila

I love you forever

I'll like for you always

As long as I'm living

my babies you'll be.

-Robert Munsch

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ABSTRACT OF THE THESIS

Relationships between Asthma, Obesity and Fitness in Adolescent Boys and Girls

By

Kim D. Lu

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2015

Professor Hoda Anton-Culver, Chair

Background: Obesity is associated with increased asthma risk in children. However this relationship is inconsistent between genders. While both obesity and asthma are associated with decreased fitness, it is unclear whether fitness plays a role in the relationship between obesity and asthma.

Overall objective: The objective of this study was to evaluate cardiorespiratory fitness on the relationship between obesity and asthma prevalence and morbidity in adolescents.

Methods: This is a cross-sectional analysis of participants aged 12-19 years of age in the National Health and Nutrition Examination Survey (NHANES) from 1999-2006 that completed cardiorespiratory fitness testing, body composition measurements and respiratory questionnaires.

Results: A total of 4963 participants were included. Overweight/obese females had a significant increased odds of asthma diagnoses, with OR of 1.60 (95% CI 1.14, 2.23) compared to normal weight females. Overweight/obese females had an increased odds of asthma-related ED visits, with adjusted odds ratio of 2.97 (95% CI 1.72, 5.15) compared to normal weight females. Among males, those in the highest fitness tertile had a decreased odds of wheezing visits (OR 0.36, 95% CI 0.14, 0.97) and wheezing-related missed days (OR 0.36, 95% CI 0.14, 0.97) compared to those in the lowest fitness tertile.

Conclusion: The relationship between obesity and asthma diagnoses and morbidity differs by gender. Fitness may play a role in the relationship between obesity and asthma in males but not in females. Gender and fitness should be considered when examining the association between obesity and asthma in adolescents.

Chapter 1.

INTRODUCTION

Asthma is one of the most common chronic illnesses of childhood. According to the National Health Interview Survey, 2013, more than 10 million or 14% of children and adolescents have ever been diagnosed with asthma and currently 6.1 million or 8.3% children and adolescents still have asthma. Asthma disproportionately affects minority populations particularly non-Hispanic blacks with 16% affected with current asthma compared to 9% of Hispanic and 8% of non-Hispanic whites.(1) Additionally, those living below the poverty level are more likely to have diagnosed with asthma compared to those above the poverty level.(1) Asthma is associated with significant morbidity and healthcare utilization in children; 1 in 5 children with asthma went to the Emergency department for their asthma. Asthma has significant impacts on families causing 10.5 million missed school days in 2008. Asthma also has a tremendous financial burden costing the United States $56 billion each year. Overall, asthma places tremendous health, social and economic on children and their families.

Another significant chronic illness in children that has seen significant increases over the past several decades is obesity. According to the Centers for Disease Control, over 12 million or 17% of children ages 2-19 are obese with higher prevalence among Black and Hispanic populations. The short and long term impacts of childhood obesity are significant with effects of multiple organ systems including cardiovascular, respiratory, musculoskeletal, gastrointestinal and behavioral/psychosocial. Children who are obese are more likely to become obese adults, who are at high risk for developing heart disease, diabetes, cancer and other chronic illnesses.

The prevalence of asthma and obesity, the two common chronic illnesses in children, has increased dramatically over the past few decades in a parallel manner.(1;2) A growing body of literature suggests that there is an association between these two disorders with obesity influencing asthma health. However, the mechanism(s) are unknown, hindering our ability to treat these patients.(3) Several hypotheses have been proposed to explain the obesity asthma link including: environmental factors such as sedentary lifestyle, nutritional status, direct mechanical effect(s); and systemic inflammation influenced by hormonal, immunologic and genetic factors.(4) Underlying chronic inflammation plays a key role in both asthma and obesity, potentially modulating the immune system.(5)

The Obese Asthma Phenotype in Children. Obese asthmatics have poorer asthma control resulting in increased symptoms, increased utilization of emergency departments, and increased risk of asthma related hospitalizations.(6-8) In addition, obese asthmatic children hospitalized with status asthmaticus had longer stays in the intensive care units compared to non-obese asthmatics.(9) Additionally, children of low socioeconomic status (SES) and minority populations are disproportionately affected by asthma and obesity rates and morbidity, with up to 50% of asthmatics being overweight or obese.(10;11) Thus, mounting evidence suggests that obese asthmatics are different and, in fact, have more severe disease compared to non-obese asthmatics.

Intriguingly, significant reductions in physical activity leading to decreased fitness have occurred during the same period that rates of obesity and asthma have dramatically increased.(12) Decreased physical fitness is known to be associated with obesity and asthma separately.(12) While some have postulated that fitness may play a role in the link between obesity and asthma, few studies have tried to address this question.(13) One possible mechanistic link could be related to the overall stress response in obesity and asthma since both conditions are associated with abnormal stress/inflammatory response profile.

Obesity is associated with a sedentary lifestyle and reduced participation in physical activity, leading to decreased fitness. Asthmatics have lower aerobic fitness than their non-asthmatic peers, related to decreased levels of physical activity.(12) The combination of obesity and reduced physical activity, each of which can stimulate inflammation, can lead to a vicious cycle in the obese asthmatic child. However few studies have tried to adequately evaluate how fitness influences the relationship between obesity and asthma risk and morbidity.

Rationale

While both obesity and asthma have been associated with decreased fitness, there remains a significant gap in our knowledge of how fitness impacts the relationship between obesity and asthma. Specifically, it is unknown whether obesity and fitness are each independently associated with asthma prevalence and morbidity (see Figure 1.1), whether the strength of association between obesity and asthma is a function of one's fitness level (Figure 1.2), and whether the association between obesity and asthma can be explained, in part, by the decrease in fitness that accompanies obesity (Figure 1.3). Furthermore, there are known gender differences in obesity, fitness and asthma, separately. It is unknown whether the relationships between obesity and fitness on asthma prevalence and morbidity differ by gender. Understanding the role of fitness on the link between obesity and asthma prevalence and morbidity particularly in pediatric populations provides valuable knowledge that could translate into specific interventions.

Overall objective: My broad research goals are to characterize the interaction of cardiorespiratory fitness and obesity and its effects on asthma prevalence and morbidity in children.

Specific Aim 1. To examine the degree to which obesity and fitness are each associated with asthma prevalence and asthma morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationships between obesity or fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the relationships between obesity or fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

Hypothesis: Obesity and low fitness are each associated with greater susceptibility to the development of asthma or increased asthma morbidity.

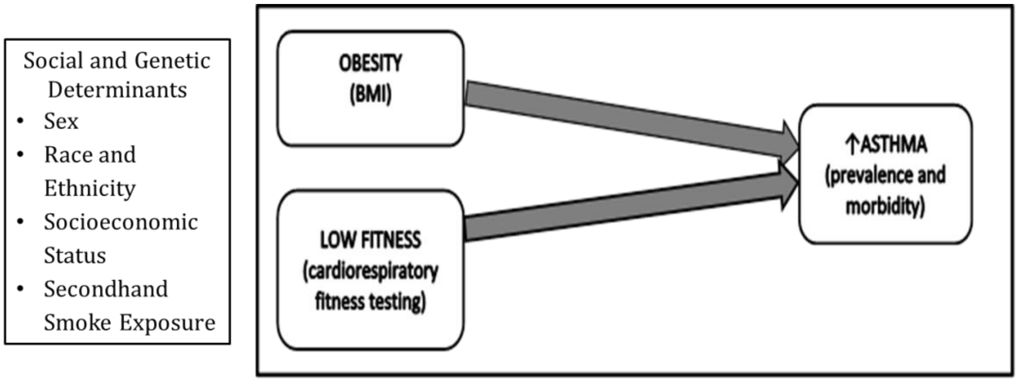

Figure 1.1 Concept Model 1

Specific Aim 2. To examine whether low fitness moderates the relationship between obesity and asthma prevalence and asthma morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

Hypothesis: Low fitness moderates the relationship between obesity and increased asthma prevalence or morbidity.

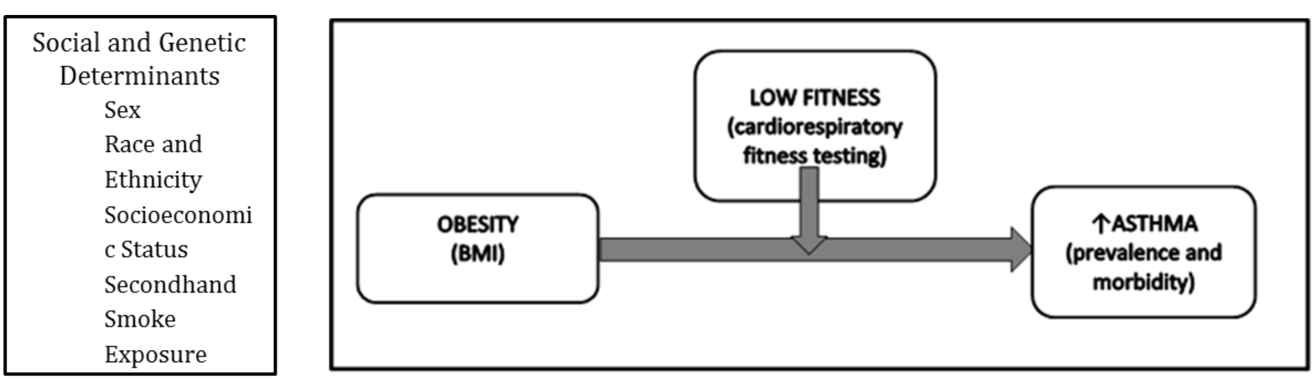

Figure 1.2 Concept Model 2.

Specific Aim 3. To examine whether low fitness mediates the relationship between obesity and asthma prevalence and asthma morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

Hypothesis: Low fitness mediates the relationship between obesity and increased asthma prevalence or morbidity.

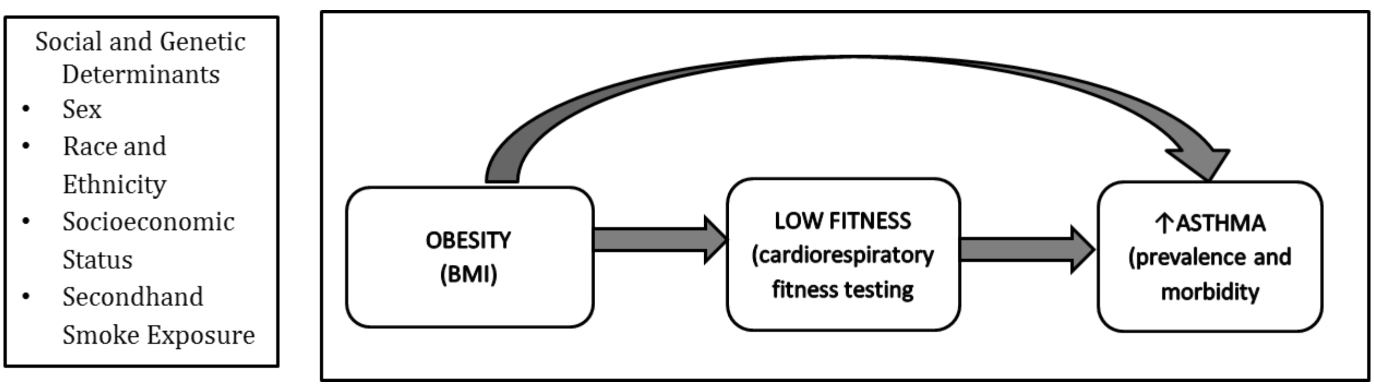

Figure 1.3. Concept Model 3.

Chapter 2.

BACKGROUND

Asthma and obesity epidemiology

Asthma is one of the most common chronic illnesses of childhood and prevalence rates continue to increase in the United States over the past few decades despite advances in management, therapies and knowledge.(1) Although asthma prevalence rates and morbidity have increased across all strata of the United States population from 1980-2009 minority populations continue to be affected to a greater extent.(1) During this same time period, the prevalence of obesity and overweight has almost tripled, with an estimated 17% of children affected.(2) Furthermore, poor, minority populations are more likely to be overweight/obese, suggesting that overweight/obesity might play a role in the perpetuating the race/ethnic disparities in asthma morbidity.(1-3) Obesity is now considered to be a risk factor for the development of asthma.(4) Recent literature suggests that obesity-related asthma may represent a distinct phenotype and is becoming a major public health issue in the United States particularly in poor minority populations.

Numerous epidemiological studies have investigated the relationship between asthma and obesity. The preponderance of studies indicates that obesity is a risk factor for the development of asthma throughout the lifespan.(14-16) Additionally, prenatal factors such as maternal weight/weight gain and birth weight may influence the risk of asthma.(17;18) We have summarized the results of systematic reviews evaluating the relationship between body mass index (BMI=weight/(height^2)) and asthma among children in Table 1. (19-23) Overall, there is a positive association between BMI and asthma or asthma-like symptoms in children, with the relative risk ranging from 1.19 to 1.35 in overweight and from 1.5 to 2.02 in obese children.

Table 2.1 Systematic Reviews: obesity and risk of developing asthma in children				
Authors	# and type of studies, time period	Outcome	Summary of Findings	Gender Differences
Egan et al (19)	6 prospective cohort studies 2001-2012	BMI and physician diagnosed incident asthma	Overweight RR 1.35 (95% CI 1.15,1.58) Obesity RR 1.50 (95% CI 1.22,1.83)	Obese boys RR 1.40 (95% CI 1.01, 1.93); Obese girls RR 1.53 (95% CI 1.09, 2.14)
Chen et al (20)	6 prospective cohort studies 2001-2012	BMI and incident asthma, gender differences	Overweight RR* 1.19 (95% CI 1.03,1.37) Obesity RR 2.02 (95% CI 1.16,3.50)	Obese boys RR 2.47 (95% CI 1.57, 3.87) Obese girls RR 1.25 (95% CI 0.51, 3.03)
Liu et al (21)	35 studies; 4 longitudinal 2001-2006	BMI and asthma	27/35 with positive association between overweight/obesity and asthmatic symptoms 3/4 longitudinal studies-higher BMI predicted future new asthma or asthma-like symptoms	Authors conclude that link between obesity and asthma is more prominent in girls.
Noal et al (22)	10 longitudinal studies 2001-2007	Nutritional status and incidence or persistence of asthma	8/10 had positive associations between overweight/obesity and asthma	3/10 studies with positive associations only in boys, 3/10 studies with positive associations only in girls
Flaherman et al (23)	4 longitudinal cohort	Body weight at birth or during	Childhood: pooled RR 1.5 (95% CI 1.2, 1.8)	Insufficient power to subset analysis

	studies (childhood) 9 longitudinal cohort studies (birth weight) 1997-2004	childhood and future asthma	Birth weight: pooled RR 1.2 (95% CI 1.1, 1.3)	by gender.
RR: Relative Risk CI: Confidence Interval From submitted manuscript " Obesity, Asthma and Fitness Review" Lu et al.				

Obesity, asthma risk and gender

A few investigators have examined whether the asthma-obesity connection differs by gender; however, the results have been mixed.(15;20;24) One systematic review and meta-analysis by Chen et al evaluated the gender difference on the relationship between obesity and asthma risk and found that obese boys had a significantly increased risk of asthma (RR 2.47; 95% CI 1.57, 3.87) compared to obese females (RR 1.25; 95% CI 0.51, 3.03). However, other studies have shown the obesity-asthma link to be stronger in girls.(24-26) These inconsistencies may be partly explained by age and/or pubertal status. Only one study has included pubertal status and they found that increased risk of asthma related to obesity was only significant in girls (24). In adults, the relationship between obesity and asthma risk is more consistent in females.(27) Furthermore, cluster analyses of asthmatics have identified a cluster of participants that are obese and female.(28;29) While the data are inconclusive about the relationship between obesity and asthma risk in males versus females, they highlight the need to stratify analyses by gender

Asthma obese phenotype

Increasing evidence suggests that obesity is associated with more severe asthma. Obese asthmatics have poorer control resulting in increased symptoms, increased utilization of emergency departments and increased risk of asthma related hospitalizations.(5, 6, 8) Obese asthmatic children hospitalized with status asthmaticus had longer hospitals stays compared to non-obese asthmatics. (7) Obesity also has substantial adverse effects on quality of life.(6) This evidence suggests that obese asthmatics are different and, in fact, have more severe disease compared to non-obese asthmatics. The mechanism(s) by which obesity may cause more severe disease are unclear.

Obese asthmatics present a unique therapeutic challenge. There is increasing evidence that obese asthmatics have altered responses to controller medications. Studies in both adults and children suggest that obese asthmatics do not achieve adequate control of their asthma when treated with inhaled corticosteroids when compared to non-obese asthmatics (10,11). Sutherland et al reported that obese patients show a decreased *in vitro* response to glucocorticoids both in blood mononuclear cells and in bronchoalveolar lavage cells.(12) This decreased response involved a blunted inhibition of mitogen-activated protein kinase phosphatase 1, a signaling molecule involved in steroid responses.(12) This evidence suggests that obesity in asthmatics causes impaired biologic response to glucocorticoids, the mainstay of asthma therapy. Lifestyles changes aimed at addressing obesity, such as weight loss through diet and exercise, specifically in the obese asthmatics have been limited (13) however the data suggest these interventions may be helpful for asthma outcomes.

The mechanism(s) linking obesity and asthma are unclear.

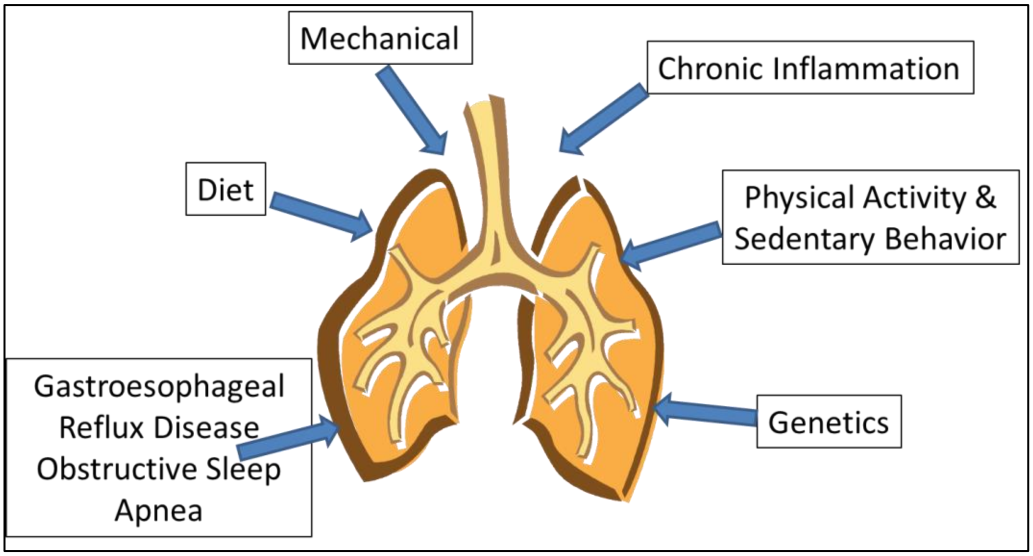

Figure 2.1. Possible mechanism(s) linking asthma and obesity.

Several hypotheses have been proposed to explain the obese asthma link including: environmental factors such as sedentary lifestyle, nutritional status, direct mechanical effect(s); and systemic inflammation influenced by hormonal, immunologic and genetic factors.(4) Adipose cells produce a variety of metabolically active cytokines and chemokines, such as IL-6, IL-1β and TNFα, as well as adipokines, including leptin and adiponectin, many of which are pro-inflammatory. The low-grade inflammatory state associated with obesity has been postulated to be the link between obesity and chronic diseases, including asthma. However, most studies have failed to show an association between obesity and increased airway inflammation via conventional biomarkers, suggesting that there may be alternate pathways.(30-32) Clearly, much work is needed to understand the mechanism(s) which link obesity and asthma.

Physical Activity and Fitness

In 2008, the Department of Health and Human Services issued the first ever Physical Activity Guidelines for Americans. These guidelines recommend that children ages 6-17 get 60mins of moderate to vigorous aerobic activity daily. In 2014, the U.S. National Report Card for physical activity for children and youth was released revealing a grade of D- indicating that the majority of children are not meeting the 2008 guidelines for daily physical activity. Additionally, the report looked at sedentary behavior and found that about half of all children engage in 2 or more hours of screen time daily, exceeding the limits the American Academy of Pediatrics recommends. The report also highlighted gender differences in physical activity with significantly decreased physical activity in females in contrast to males.(33)

Pratt et al using data from the Youth Risk Behavior Survey for high school students, found that overall 63.8% of high school students participate in vigorous activity for at least 20mins on 3 or more days per week.(34) There was differences in gender with 72.3% of boys participating in vigorous activity compared to 53.5% of girls as well as racial/ethnic differences with white reporting the highest amount of vigorous activity, 66.8% compared to 60.4% of Hispanics and 53.9% of Blacks. Physical activity levels were also seen to decrease with increasing age.

Not surprisingly, decreased levels of physical activity and increased levels of sedentary behavior have contributed to increasing rates of obesity in children and adults.(35) Obese children are less fit compared to their normal weight peers.(36)

Asthma, physical activity and fitness

Children and adolescents with asthma are less active than their healthy peers. Several studies have shown decreased levels of physical activity among children with asthma compared to non-asthmatics with asthma being the strongest predictor of reduced activity.(37;38) Both parents and children with asthma report that activities are reduced secondary to their asthma.(39;40)

There is also evidence that physical activity is protective against the development of asthma.(41;42) A systematic review and meta-analysis showed that subjects with higher physical activity levels had a lower incidence of asthma with a pooled odds ratio of 0.87 (95% CI 0.77-0.99).(42)

Several factors influencing participation in physical activity in children with asthma include beliefs by both children and families that asthma limits their activities, knowledge and attitudes of teachers and schools , and symptom perception and interpretation.(43)

Asthma, obesity and fitness

Since both asthma and obesity are independently associated with decreased levels of fitness, it is reasonable to assume that fitness may play a role in the obesity asthma link.

In adults, prospective studies exploring the relationship between obesity, physical activity and asthma have had mixed results with some studies showing that weight status was associated with increased risk of asthma, even after controlling for physical activity, while other studies showing a protective effect of asthma risk with physical activity.(44-47) In children, only a handful of prospective studies examining weight status and the risk of asthma have accounted for physical activity levels, however physical activity was measured subjectively by questionnaires and none objectively measured physical activity or fitness levels.(14;25;48-50)

Two studies examining the relationship between vigorous physical activity, television watching and risk of asthma paradoxically found that both television watching greater than 3 hours as well as vigorous physical activity increased the risk of current wheeze or asthma symptoms in children 13-14 years of age.(51;52) However, Vlaski et al found that the association between infrequent physical activity and asthma symptoms was stronger, than the association between frequent physical activity and asthma symptoms. The authors concluded that asthma symptoms related to physical activity was secondary to a sedentary lifestyle and poor fitness.(51)

A 10 year prospective study found that physical fitness was associated with a reduced risk for development of asthma.(41) Visness et al examined the association of obesity with atopic and non-atopic asthma among U.S children using data from NHANES from 1999-2006 and found that obesity was significantly related to current asthma among children and adolescents with odds ratio of 1.68 (95% CI 1.33, 2.12).(50) They did not find that asthma or wheezing were strongly associated with physical activity variables, specifically amount of physical activity per week, reported by questionnaire, or average hours of screen time. Most recently, Chen et al found that central obesity most accurately predicts asthma.(13) Furthermore, low fitness and high screen times increased the risk of central obesity but did not appear to be a link in the relationship between obesity and asthma. However, fitness was assessed using an 800 m sprint, a field test that relies on technique and motivation and therefore the results may not accurately reflect cardiorespiratory fitness.

Chapter 3.

METHODS

Study Design

This is a cross-sectional analysis of data from National Health and Nutrition Examination Survey (NHANES) from 1999-2006.

Data Source

NHANES is a survey of the civilian, non-institutionalized population in the U.S. NHANES uses a stratified, multi-stage probability sampling design. Between 1999-2006, they over sampled persons 60 and older, African-Americans, Mexican-Americans, white and others at or below 130% of federal poverty level, and adolescents 12-19 years of age. Eligible persons age 16 or older were interviewed directly, while interviews for those under age 16 were done with a proxy.

Study Sample

We studied adolescents 12-19 years of age. Cardiorespiratory fitness testing was completed in participants 12 to 49 years of age in NHANES from 1999-2006 (n=4997). We included participants that had complete data on asthma diagnosis, body composition and cardiorespiratory fitness testing (n=4963).

Those who did not complete cardiorespiratory fitness testing were excluded (n=1198). Participants with certain medical conditions were excluded from fitness testing, including participants with asthma with 12+ wheezing episodes per year or any wheezing episodes associated with speech limitations were excluded from cardiorespiratory fitness testing (n=154). We also excluded participants who completed fitness testing but did not have an estimated VO_2 max (n=743). Participants missing complete body composition data were excluded (n=34).

Power: Visness et al evaluated obesity and asthma in children among NHANES 1999-2006 and found the asthma prevalence by BMI categories was 8.4% for normal weight, 11.1% for overweight and 13.2% for obese.(50)

Currently, n=4963 for participants with both estimated fitness per cardiorespiratory fitness testing and asthma diagnosis questionnaire completed.

Sample Size	Effect Size					
4963	0.05	0.07	0.08	0.085	0.09	0.11
	Power					
	36	63	76	81	85	96

Study Measures

<u>Asthma prevalence</u> was defined as the following: asthma, ever; asthma, current; chronic cough; wheezing/whistling, current.

<u>Asthma morbidity</u> was defined as the following: asthma attacks in the past 12 months; asthma ED/urgent care visits in the past 12 months; wheezing attacks, wheezing visits, wheezing with exercise, wheezing-related missed days.

Body Composition: Body mass index (BMI) was calculated using standing height and weight (BMI=weight/height^2). BMI percentiles were calculated based on Centers for Disease Control BMI calculator.(http://nccd.cdc.gov/dnpabmi/Calculator.aspx) Underweight was defined as BMI <5%ile, healthy weight was defined as 5**th** to <85%ile, overweight was defined as BMI 85th to <95th percentile and obesity was defined as BMI ≥95th percentile.

Cardiorespiratory fitness: A submaximal exercise test was performed on a treadmill, consisting of a 2 minute warm up, two 3 minute exercise periods and a 3 minute recovery. Exercise heart rate and treadmill settings were used to calculate estimated VO_2 max. Fitness levels were split into fitness tertiles that were gender-specific. Tertile 1 was the lowest fitness tertile. Tertile 3 was the highest fitness tertile.

Covariates

Age: age in years collected from demographics.

Race and ethnicity: variable from demographic questions on race and Hispanic origin. Participants were groups into the following four groups: non-Hispanic white, non-Hispanic black, Hispanic, and other.

Poverty index ratio: index for ratio of family income to poverty. The Department of Health and Human Services poverty guidelines were used as the poverty measure to calculate this index.

Second hand smoke exposure: the variable was created if respondents answered Yes to question "does anyone smoke in the house?".

Survey year: Survey years 1999-2000, 2001-2002, and 2003-2004 were included in the study.

Statistical Analyses

Specific Aim 1. To examine the relationship between obesity or fitness on asthma prevalence/morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationships between obesity and fitness, considered separately, and asthma prevalence.
b. Characterizing the relationships between obesity and fitness, considered separately, and asthma morbidity.

Relationships between BMI categories and fitness tertiles on asthma prevalence/morbidity were first examined in bivariate analyses. Underweight participants were excluded from analyses involving models as there were too few a number (n=135). Additionally, underweight asthmatics are thought to have poor asthma control, worse lung function and asthma-related outcomes compared to normal weight asthmatics.(53;54) Overweight and obese were combined in final models. Logistic regression models were used as asthma outcomes were dichotomous. Analyses were stratified by gender. Analyses were adjusted for age, survey year, poverty index ratio, second hand smoke exposure and race/ethnicity. We also examined relationships between fitness, physical activity and obesity, which are presented in Appendix A. All analyses accounted for weighted data design of NHANES, and were performed with SAS (version 9.4). A p value < 0.05 was considered statistically significant for main effects.

Specific Aim 2: To examine whether low fitness moderates the relationship between obesity and asthma prevalence/morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

Relationships BMI categories and fitness tertiles on asthma prevalence/morbidity were first examined in bivariate analyses. Underweight participants were excluded from analyses involving models as there were too few a number (n=135). Additionally, underweight asthmatics are thought to have poor asthma control, worse lung function and asthma-related outcomes compared to normal weight asthmatics.(53;54) Overweight and obese were combined in final models. Logistic regression models were used as asthma diagnosis outcomes were dichotomous. To examine relationships obesity and fitness on asthma prevalence/morbidity, we created fit/fat groups similar to Kwon et al(55). The fit/fat groups were defined using fitness tertiles and BMI category. Tertile 1 was labeled as "unfit" and tertile 2 and 3 were combined to create "fit" group. Normal weight was labeled as "not-fat" and overweight/obese were grouped together as "fat". We examined the odds of overweight/obesity on asthma prevalence/morbidity compared to normal weight participants in fit and unfit groups. We then examined whether fitness was moderator in the relationship between obesity and asthma morbidity by creating an interaction term between obesity and fitness. If the interaction term had a statistically significant p value, then fitness was considered a moderator. Analyses were stratified by gender. Analyses were adjusted for age, survey year, poverty index ratio, second hand smoke exposure and race/ethnicity. Analyses also accounted for weighted data design of NHANES. Analyses were performed with SAS (version 9.4). A p value < 0.05 was considered statistically significant for main effects and interactions.

Specific Aim 3. To examine whether low fitness mediates the relationship between obesity and asthma prevalence/morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

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Analyses were stratified by gender. Analyses were adjusted for age, survey year, poverty index ratio, second hand smoke exposure and race/ethnicity. Analyses also accounted for weighted data design of NHANES. Analyses were performed with SAS (version 9.4). A p value < 0.05 was considered statistically significant for main effects.

Chapter 4.

DESCRIPTIVE STATISTICS

Included study sample characteristics

Participants who were included in the sample population had a mean age of 15.4 years (range of 12-19 years). 52.5% of the participants were male. In terms of race/ethnicity, the sample population was 60.4% white, 14.3% black, 18.4% Hispanic and 6.9% other. 21.6% of participants were exposed to second hand smoke. 25.1% of the study population had a family income of <$20000 (Table 2).

In terms of adiposity, 30.7% of participants were overweight or obese based on BMI percentiles. The mean estimated VO_2 max of all participants was 42.5ml/kg/min. 14.9% of participants had an asthma diagnosis, ever and 7.4% of participants had a current diagnosis of asthma. Wheezing or whistling in the chest over the past year was present in 10.0% of participants. In terms of asthma-related morbidity, 3.5% of participants had an asthma attack in the past 12 months, and 0.9% of participants needed to go the emergency department for their asthma in the past 12 months.

Included and excluded study sample characteristics

Sociodemographic as well as clinical characteristics of excluded sample population were examined and compared to included sample population (Table 4.1). The excluded sample had a mean age of 15.5 years, which was not significantly different from the included sample. 47.8% were male which was decreased in comparison to included sample (p=0.08). Poverty index threshold ratio was lower in the excluded sample with a mean ratio 2.23 (0.08), indicating lower SES compared to the included sample which had a mean ratio of 2.56 (0.06) ($p<0.001$).

In terms of adiposity, the excluded sample included 36.8% of participants who were overweight or obese, which was significantly increased compared to the included sample (p=0.003). In terms of both asthma prevalence and morbidity, the excluded sample population had significantly higher rates compared to included sample. 23.0% of excluded participants had diagnosis of asthma, ever and 15.9% had diagnosis of current asthma compared to 14.8% and 7.4%, respectively, in included sample ($p<0.001$). 22.0% of participants reported wheezing or whistling in their chest. In terms of asthma morbidity, 10.9% of participants had an asthma attack in the past 12 months and 3.5% had an asthma-related ED visit.

Fitness levels by estimated VO_2 max was similar in both groups. Excluded sample had a lower % of participants who reported participating in any moderate or vigorous activity, 63.4% and 73.9%, respectively, compared to included sample with 67.4% and 73.9%, respectively ($p<0.001$).

Table 4.1 Sociodemographic and clinical characteristics of included and excluded sample of children ages 12-19 years of age.

	Included n=4963	Excluded n=2200	P value
Age, mean (SE)	15.4 (0.06)	15.5 (0.10)	0.53
Gender			0.08
Male, %	52.5	47.8	
Race and Ethnicity, %			0.43
White	60.4	62.0	
Black	14.3	14.9	
Hispanic	18.4	16.6	
Other	6.9	6.5	
Family income, n (%)			<0.001
<20000	25.1 (22.0, 28.1)	32.8 (28.6, 37.0)	

>20000 Refused/don't know	71.4 (68.2, 74.6) 3.6 (2.7, 4.4)	64.1 (60.0, 68.3) 3.0 (2.1, 4.0)	
Family income to poverty threshold Ratio	2.56 (0.06)	2.23 (0.08)	<0.001
Second hand smoke exposure	23.4 (20.8, 26.)	28.5 (24.4, 32.7)	0.005
Asthma, ever % yes	14.9 (13.6, 16.1)	23.0 (19.8, 26.1)	<0.001
Asthma, current % yes	7.4 (6.5, 8.4)	15.9 (13.4, 18.4)	<0.001
Wheezing/whistling, n (%) yes	10.0 (8.7, 11.2)	22.0 (19.2, 24.9)	<0.001
Chronic cough, % yes (95% CI)	3.3 (2.8, 3.9)	4.8 (2.9, 6.7)	0.09
Asthma attack, n (%) yes	3.5 (2.8, 4.2)	10.9 (8.6, 13.3)	<0.001
Asthma-related ED visit, % yes (95% CI)	0.7 (0.4, 1.0)	3.5 (2.3, 4.7)	<0.001
Wheezing attack, % yes (95% CI)	9.9 (8.6, 11.1)	21.7 (18.9, 24.6)	<0.001
Wheezing visit, % yes (95% CI)	3.5 (2.7, 4.4)	9.3 (7.3, 11.3)	<0.001
Wheezing-related missed days, % yes (95% CI)	2.5 (1.7, 3.3)	8.2 (6.7, 9.6)	<0.001
Wheezing related to exercise, % yes (95% CI)	4.7 (3.7, 5.7)	14.5 (12.2, 16.8)	<0.001
BMI percentile, mean (95% CI)	62.0 (60.3, 63.6)	64.8 (62.3, 67.4)	0.05
BMI category Underweight Normal weight Overweight Obese	 3.2 66.1 15.3 15.4	 4.6 58.6 16.9 19.9	0.003
Estimated VO_2 max, mean (95% CI)	42.5 (41.9, 43.1)	41.8 (38.8, 44.9)	0.70
Any vigorous activity/30 days, % yes (95% CI)	73.9 (72.1, 75.8)	63.4 (59.1, 67.8)	<0.001
Any moderate activity/30 days, % yes (95% CI)	67.4 (65.2, 69.5)	60.6 (57.7, 63.5)	<0.001
Screen time, %>2hr (95% CI)	63.9 (61.0, 65.9)	66.2 (62.3, 70.2)	0.29
Physical activity readiness score, % Little/none activity Occasional walks/exercise Regular mod 10-60mins/week Regular mod>60mins/week Regular heavy<30mins/week Regular heavy 30-60mins/week Regular heavy 1-3hrs/week Regular heavy >3hrs/week	 5.5 12.1 19.3 33.3 0.9 3.0 7.1 18.9	 12.9 33.5 14.5 16.0 0 0 13.4 9.6	0.11
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes. P value generated from t test between means for continuous outcomes.			

Study participant selection

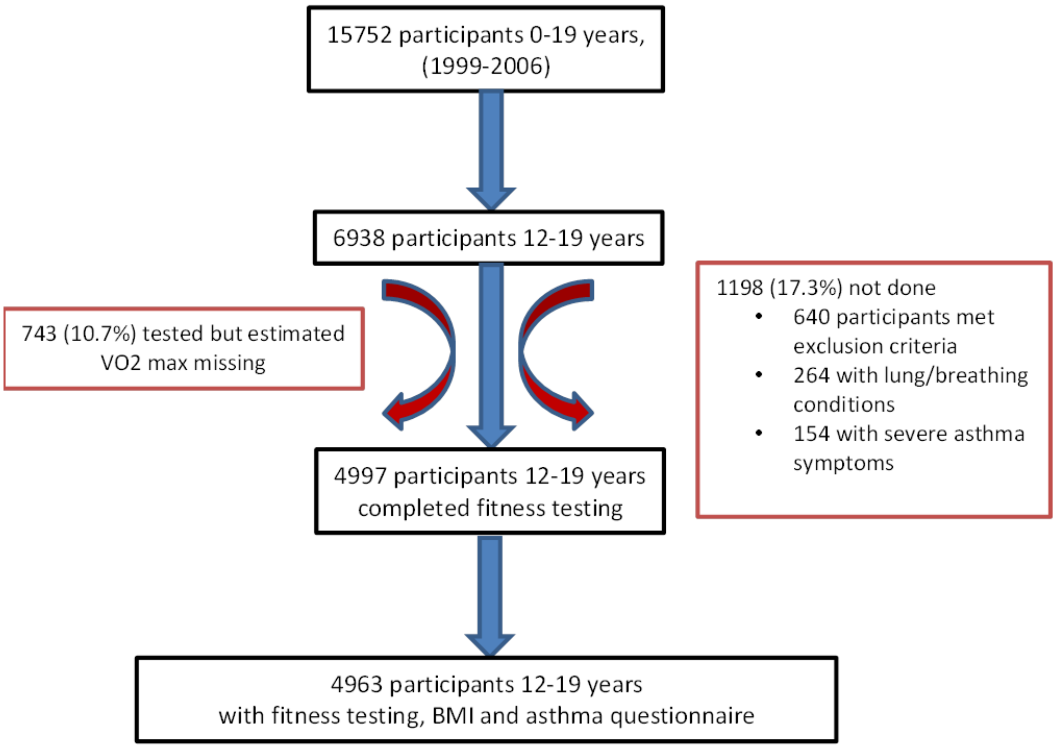

Figure 4.1 Flow diagram of participant selection.

Figure 4.1 illustrates participant selection for study sample. Of the eligible 6938 participants aged 12-19 years, 1198 (17.3%) participants did not have cardiorespiratory fitness testing done due to various exclusion criteria and 743 (10.7%) participants were tested but estimated VO_2 max was missing. Of the participants who were excluded, they included 264 participants with lung/breathing conditions and 154 participants with severe asthma.

Study sample characteristics by gender

Sociodemographic and clinical characteristics between gender of the study population was examined (Table 4.2). There was no difference between mean age or race/ethnicity between male and female participants. Female participants were more likely to have a current diagnosis of asthma, 8.5% compared to 6.4% of males ($p=0.02$) but no difference was seen in ever diagnosis of asthma ($p=0.29$) (Figure 4.2). There was no difference in asthma related morbidity between genders except for wheezing related to exercise though there was a trend of increased rates of morbidity in females compared to males (Figure 4.3). 5.8% of females reported wheezing related to exercise compared to 3.8% of males ($p=0.05$). There was no difference between BMI groups by gender. Females had a significantly lower fitness level with a mean estimated VO_2 max of 38.4ml/kg/min compared to 46.2ml/kg/min in males ($p<0.001$).

Table 4.2 Sociodemographic and clinical characteristics between male and female participants.

	Males	females	P value
Age, mean (SE)	15.5 (0.07)	15.3 (0.08)	0.68
Race and Ethnicity, %			0.34
White	61.9	58.8	
Black	13.7	14.8	
Hispanic	17.9	18.9	
Other	6.4	7.4	
Family income to poverty threshold Ratio, mean (SE)	2.6 (0.07)	2.5 (0.07)	0.05
Asthma Prevalence and Morbidity			
Asthma, ever % yes (95% CI)	14.2 (12.2, 16.2)	15.6 (14.0, 17.2)	0.29
Asthma, current % yes (95% CI)	6.4 (5.1, 7.8)	8.5 (7.4, 9.7)	0.02
Wheezing/whistling, % yes (95% CI)	9.4 (7.8, 10.9)	10.7 (8.7, 12.6)	0.29
Chronic cough, % yes (95% CI)	3.5 (2.6, 4.4)	3.2 (2.4, 4.0)	0.61
Asthma, attack % yes (95% CI)	2.8 (1.9, 3.8)	4.3 (3.1, 5.5)	0.08
Asthma, ED visit % yes (95% CI)	0.8 (0.3, 1.2)	0.7 (0.2, 1.1)	0.80
Wheezing attack, % yes (95% CI)	9.3 (7.7, 10.9)	10.5 (8.5, 12.5)	0.32
Wheezing visit, % yes	3.0 (1.9, 4.1)	4.1 (2.9, 5.2)	0.17

(95% CI)			
Wheezing-related missed days, % yes (95% CI)	2.2 (1.3, 3.1)	2.8 (1.7, 4.0)	0.21
Wheezing related to exercise, % yes (95% CI)	3.8 (2.6, 5.0)	5.8 (4.1, 7.4)	0.05
BMI and Fitness			
BMI category, % Underweight Normal weight Overweight Obese	 3.7 65.3 15.4 15.5	 2.5 67.2 15.1 15.2	0.33
Estimated VO_2 max, mean (SE)	46.2 (0.36)	38.4 (0.26)	<0.001
Fitness tertiles, mean estimated VO_2 max (range) Tertile 1 Tertile 2 Tertile 3	 37.0 (24.2, 41.7) 45.1 (41.7, 48.9) 56.6 (48.9, 76)	 30.9 (20.1, 34.6) 37.5 (34.6, 40.5) 48.1 (40.5, 76)	0.09
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes			

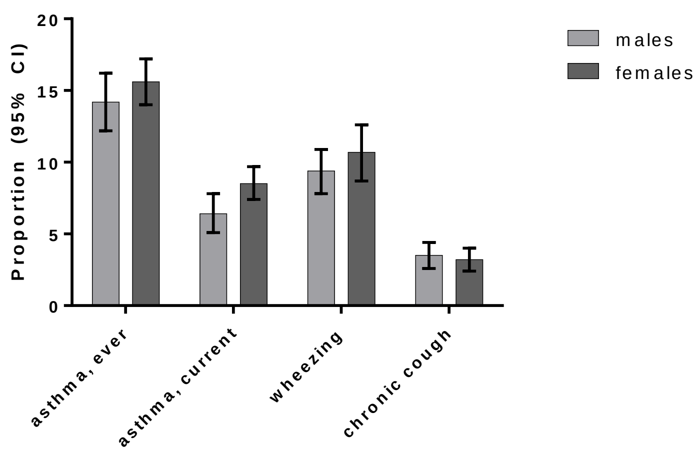

Figure 4.2 Asthma diagnoses in males and females. Significant difference seen between gender for asthma, current (p=0.02)

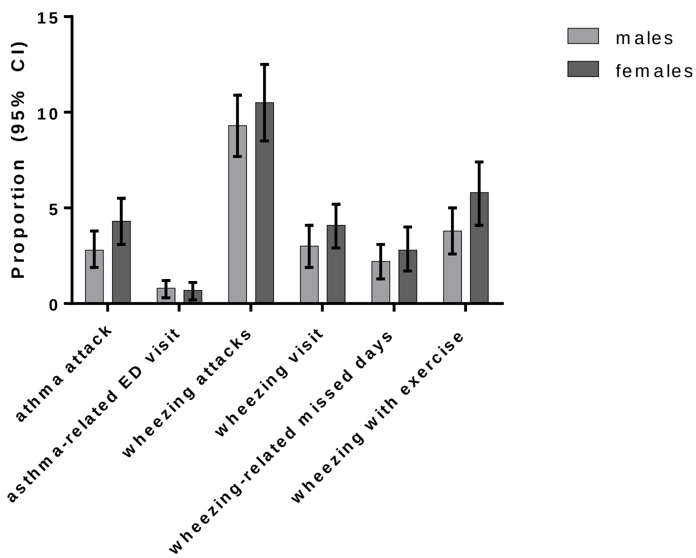

Figure 4.3 Asthma morbidity in males and females. There was a statistically significant difference by gender for wheezing with exercise (p=0.05)

Fitness

NHANES using criteria used in the FITNESSGRAM program to create 3 levels of fitness: lower, moderate and high fitness levels. The ranges for the fitness groups varied by gender and age differently. For females, ranges for the fitness groups varied depending on age (12, 13, 14, 15-19years), while ranges for the fitness groups in males did not differ by age.

We subsequently created fitness tertiles for analyses. Because fitness levels differed by gender, we created fitness tertiles that were gender-specific. Figure 3.4 and 3.5 show fitness using estimated VO_2 max levels by age, in males and females. Males had significantly higher levels of estimated VO_2 max compared to female. Fitness levels increased with age in males, however fitness levels decrease with age in females, for example, in tertile 1, lowest fitness group, males had a mean estimated VO_2 max of 37.0 ml/kg/min compared to 30.9 ml/kg/min in females.

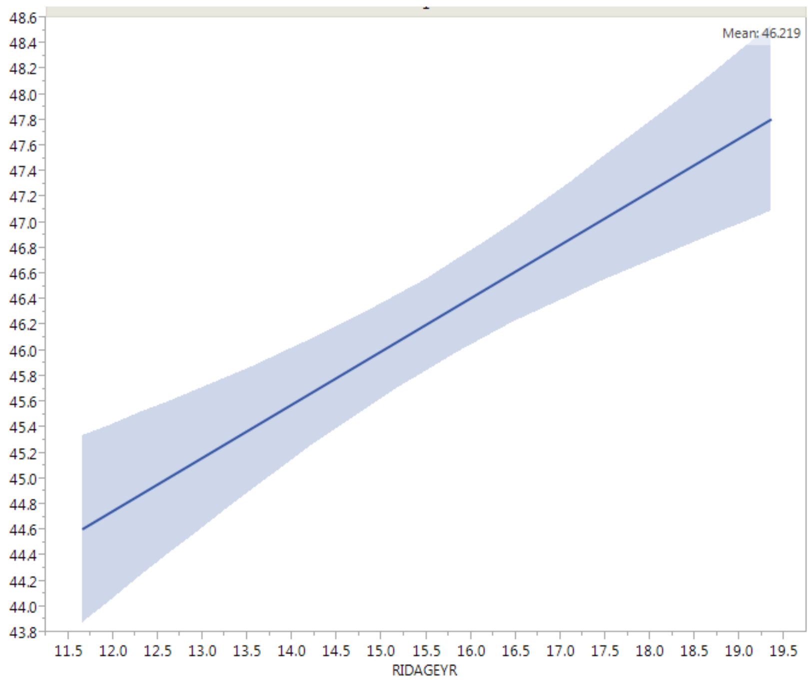

Figure 4.4 Estimated VO_2 max for males.

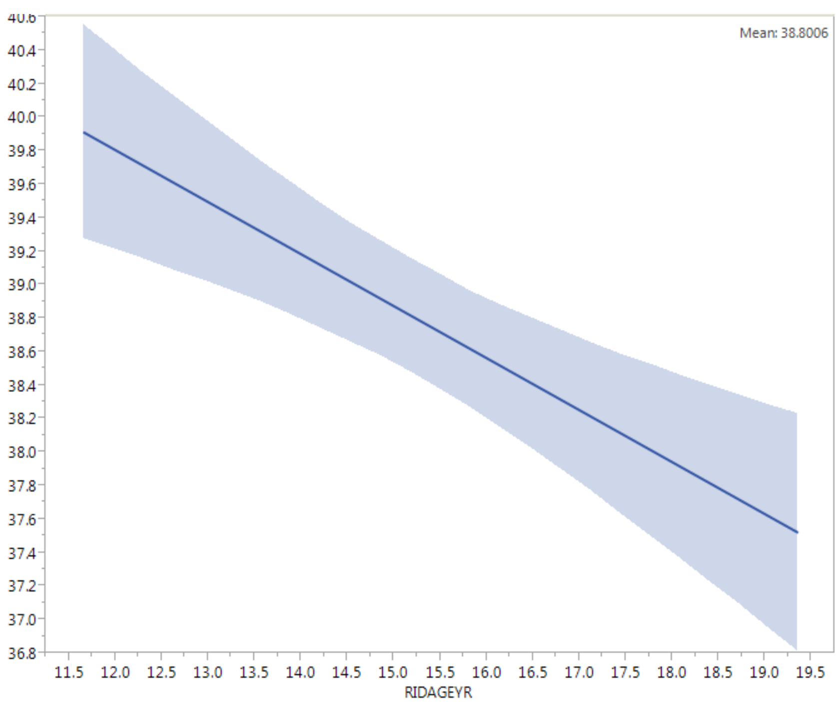

Figure 4.5 Estimated VO_2 max for females.

Chapter 5

Results: relationships between obesity and fitness on asthma prevalence and morbidity

Specific Aim 1. To examine the degree to which obesity and fitness are each associated with asthma prevalence and asthma morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationships between obesity or fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the relationships between obesity or fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

5.A.1 Relationships between obesity and asthma prevalence.

Analyses of asthma outcomes by BMI groups were performed in males and females, separately (Table 5.1 and 5.2). Among males, there were no significant differences by BMI group for asthma prevalence except for chronic cough though there was a trend of increased rates in overweight/obese compared to normal weight participants. For those males who reported chronic cough, 2.8% were normal weight, 5.8% were overweight and 3.9% were obese (p=0.04) (Figure 5.1).

Among females, overall, there were no significant differences by BMI group for asthma prevalence except for asthma, ever though there was a trend of increased rates in overweight/obese compared to normal weight participants. 15% of overweight and 15.3% of obese female participants reported asthma diagnosis, ever compared to 14.1% of normal weight (p=0.05) (Figure 5.2).

Table 5.1 Analyses of asthma diagnoses by BMI groups in males.					
	Underweight % (95% CI)	Normal weight % (95% CI)	Overweight % (95% CI)	Obese % (95% CI)	P value
Asthma, ever	8.0 (2.9, 13.1)	14.1 (11.8, 16.4)	15.0 (10.0, 19.9)	15.3 (10.5, 20.1)	0.45
Asthma, current	3.5 (0.5, 6.5)	6.4 (4.8, 8.0)	7.0 (3.7, 10.4)	6.7 (3.5, 9.8)	0.71
Chronic cough	5.2 (3.0, 7.3)	2.8 (1.9, 3.6)	5.8 (2.5, 9.1)	3.9 (1.7, 6.0)	0.04
Wheezing/whistling	10.5 (-0.4, 21.4)	8.4 (6.8, 10.1)	10.1 (6.4, 13.8)	12.3 (7.7, 16.9)	0.37
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 5.2 Analyses of asthma diagnoses by BMI groups in females.					
	Underweight % (95% CI)	Normal weight % (95% CI)	Overweight % (95% CI)	Obese % (95% CI)	P value
Asthma, ever	13.6 (6.8, 26.5)	14.0 (12.0, 16.1)	19.0 (14.3, 23.8)	19.5 (13.7, 25.2)	0.13
Asthma, current	8.0 (-0.7, 16.8)	7.5 (6.0, 9.0)	10.7 (7.2, 14.2)	11.1 (6.4, 15.7)	0.22
Chronic cough	13.3 (-1.2, 27.8)	2.6 (1.5, 3.7)	5.3 (2.0, 8.6)	2.1 (0.2, 3.9)	0.009
Wheezing/whistling	9.3 (-1.8, 20.4)	10.0 (7.8, 12.3)	9.8 (6.4, 13.2)	14.6 (10.1, 19.2)	0.21
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

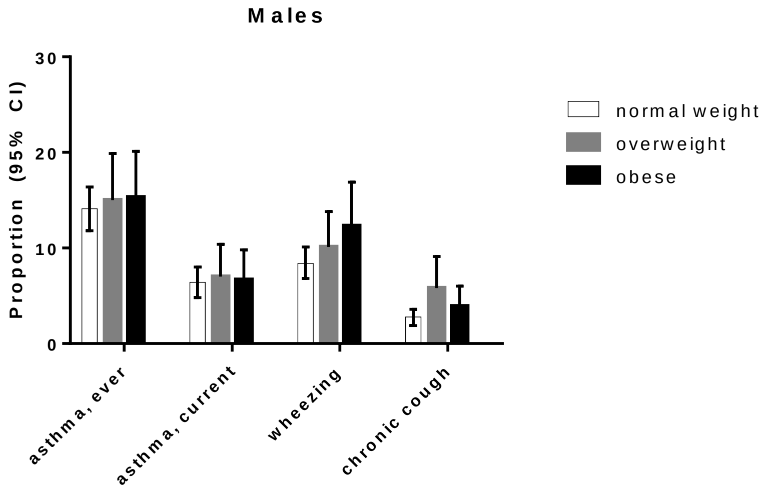

Figure 5.1. Asthma prevalence by BMI groups in males. Significant differences seen for chronic cough among males (p=0.04)

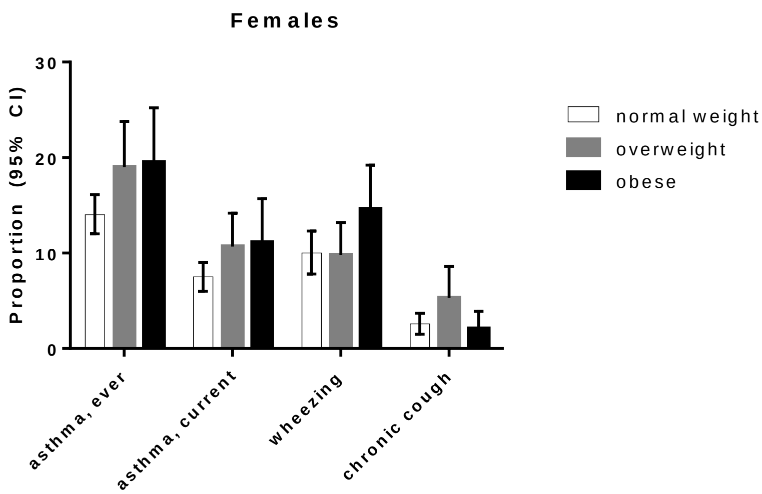

Figure 5.2 Asthma prevalence by BMI groups in females. Significant differences seen for asthma ever among females (p=0.05).

We created models looking at the effect of obesity on asthma prevalence (Table 5.3). Overall, overweight and obese participants have higher odds of asthma prevalence compared to normal weight participants. This relationship of overweight/obesity on increased asthma prevalence was significant in females for asthma, ever, asthma, current and wheezing, in multivariate models. For example, the OR for asthma, ever in females was 1.60 (95% CI 1.14, 2.23) in overweight/obese females compared to normal weight females, after adjusting for covariates. The relationship between overweight/obesity on increased asthma prevalence in males is significant for wheezing and chronic cough in simple models but not significant after controlling for covariates. For example, OR for wheezing was 1.37 (95% CI 1.00, 1.89) in overweight/obese males compared to normal weight males but became non-significant for adjusting for covariates (OR 1.40, 95% CI 0.97, 2.02).

Table 5.3 Odds of asthma diagnoses in overweight/obese compared to normal weight participants.

Outcome	OR of over/obese to normal weight (95% CI)	OR of over/obese to normal weight (95% CI) multivariate
Asthma, ever		
All	**1.26 (1.03, 1.54)**	**1.25 (1.01, 1.55)**
Males	1.09 (0.82, 1.45)	1.01 (0.73, 1.40)
Females	**1.46 (1.08, 1.99)**	**1.60 (1.14, 2.23)**
Asthma, current		
All	1.29 (0.96, 1.73)	1.30 (0.97, 1.75)
Males	1.08 (0.70, 1.67)	0.99 (0.65, 1.53)
Females	1.51 (0.99, 2.29)	**1.68 (1.09, 2.59)**
Wheezing		
All	**1.31 (1.05, 1.64)**	**1.38 (1.06, 1.79)**
Males	**1.37 (1.00, 1.89)**	1.40 (0.97, 2.02)
Females	1.25 (0.90, 1.75)	**1.44 (1.01, 2.04)**
Chronic Cough		
All	**1.64 (1.11, 2.40)**	**1.75 (1.17, 2.64)**
Males	**1.78 (1.10, 2.88)**	1.77 (0.99, 3.16)
Females	1.46 (0.67, 3.17)	1.95 (0.82, 4.66)
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio, +/- gender.		

5.A.2 Relationships between fitness tertiles and asthma prevalence.

Relationships between fitness tertiles and asthma prevalence were examined in males and females (Figure 5.3 and 5.4). Overall, there was no significant different between fitness tertiles and asthma prevalence outcomes for either males or females. However, there was a trend of decreased rates of asthma prevalence in the highest fit tertile compared to the lowest fit tertile in males. This pattern was not seen among females.

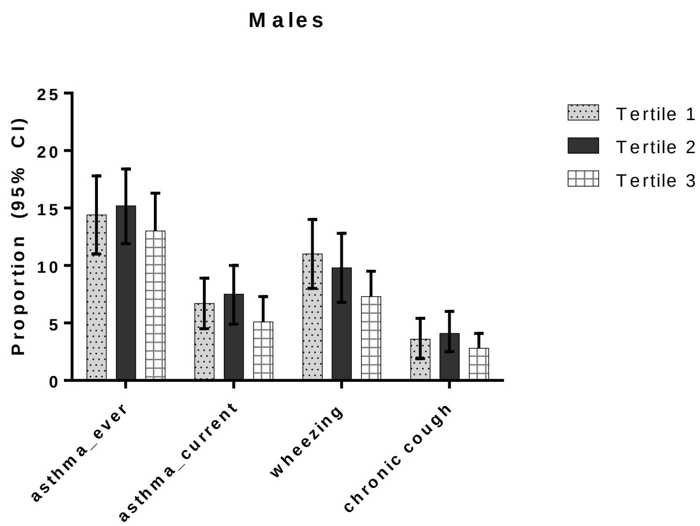

Figure 5.3 Asthma prevalence by fitness tertiles in males.

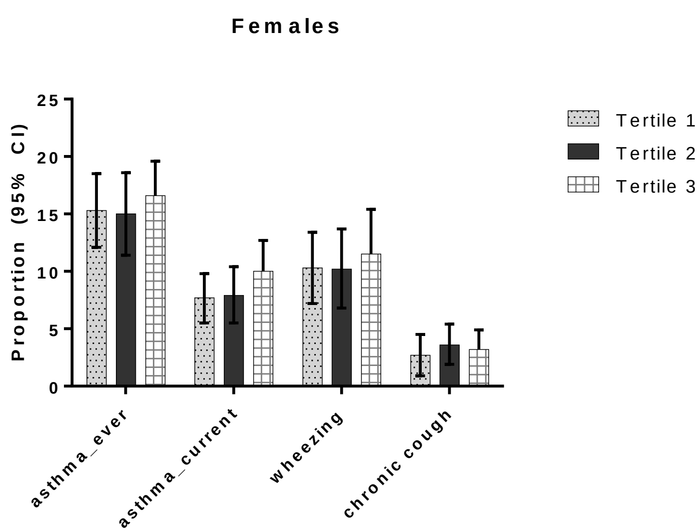

Figure 5.4 Asthma prevalence by fitness tertiles in females.

Relationships between fitness, physical activity and obesity are presented in Appendix A.

5.B.1 Relationships between obesity and asthma morbidity.

Analyses of asthma morbidity by BMI groups were performed in males and females (Table 5.4, 5.5 and Figure 5.5, 5.6). Among males, there was no statistically significant difference by BMI groups for the various asthma morbidity outcomes. However, there did appear to be a trend of increased rates of wheezing attacks and wheezing with exercise in obese males compared to normal weight males.

Among females, there was a pattern of increased rates of asthma morbidity in overweight and obese participants compared to normal weight participants. Among obese females, 8.1% had asthma attacks compared to 3.1% of normal weight participants ($p<0.01$). Obese females also had higher rates of asthma–related ED visits, 2.3% compared to 0.4% of normal weight participants ($p<0.01$). Obese females also had higher rates of wheezing visits with 8.4% compared to 3.4% of normal weight participants ($p=0.01$)

We created models looking at the effect of obesity on asthma morbidity (Table 5.6). Overall, overweight and obese participants have higher odds of asthma morbidity compared to normal weight participants in both males and females. This relationship of overweight/obesity on increased asthma morbidity was significant in females for asthma attacks and wheezing with exercise, after controlling for covariates. For example, overweight/obese females had an OR of 2.58 (95% CI 1.47, 4.54) for asthma attacks compared to normal weight females. Overweight/obese females also had an increased odds of wheezing with exercise with OR of 1.59 (95% CI 1.07, 2.36) compared to normal weight females.

Table 5.4 Analyses of asthma morbidity by BMI groups in males.					
	Underweight OR (95% CI)	Normal weight OR (95% CI)	Overweight OR (95% CI)	Obese OR (95% CI)	P value
Asthma attacks	1.7 (-0.8, 4.1)	2.4 (1.5, 3.2)	3.9 (1.2, 6.6)	3.9 (1.1, 6.8)	0.28
Asthma ED	1.0 (-1.0, 2.9)	0.5 (0.1, 1.0)	1.4 (-0.2, 3.0)	1.0 (-0.7, 2.7)	0.56
Wheezing attacks	10.5 (-0.5, 21.4)	8.3 (6.7, 10.0)	10.0 (6.2, 13.7)	12.2 (7.5, 16.9)	0.39
Wheezing visit	6.6 (-3.6, 16.7)	2.4 (1.2, 3.5)	4.6 (1.6, 7.5)	3.5 (0.9, 6.1)	0.27
Wheezing missed days	0.9 (-0.5, 2.4)	1.9 (1.0, 2.7)	3.2 (0.9, 5.4)	2.9 (0.1, 5.7)	0.37
Wheezing with exercise	3.3 (-1.2, 7.7)	3.5 (2.4, 4.6)	3.6 (1.1, 6.0)	5.3 (2.4, 8.1)	0.53
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 5.5 Analyses of asthma morbidity by BMI groups in females.					
	Underweight OR (95% CI)	Normal weight OR (95% CI)	Overweight OR (95% CI)	Obese OR (95% CI)	P value
Asthma attacks	4.8 (-2.3, 11.9)	3.1 (2.0, 4.2)	5.6 (2.4, 8.9)	8.1 (3.3, 13.0)	0.02
Asthma ED	0	0.4 (-0.01, 0.8)	0.5 (-0.1, 1.0)	2.3 (-0.05, 4.6)	0.02
Wheezing attacks	9.9 (7.4, 12.4)	9.6 (5.4, 13.9)	13.2 (8.6, 17.7)	11.2 (6.5, 15.9)	0.18
Wheezing visit	0	3.4 (2.1, 4.8)	3.3 (0.5, 6.2)	8.4 (5.0, 11.0)	0.03
Wheezing missed days	0	2.5 (1.1, 3.8)	2.8 (0.2, 5.5)	4.8 (1.7, 7.9)	0.37
Wheezing with exercise	1.4 (-1.3, 4.0)	5.3 (3.5, 7.2)	6.2 (3.4, 9.0)	8.0 (4.8, 11.2)	0.11
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

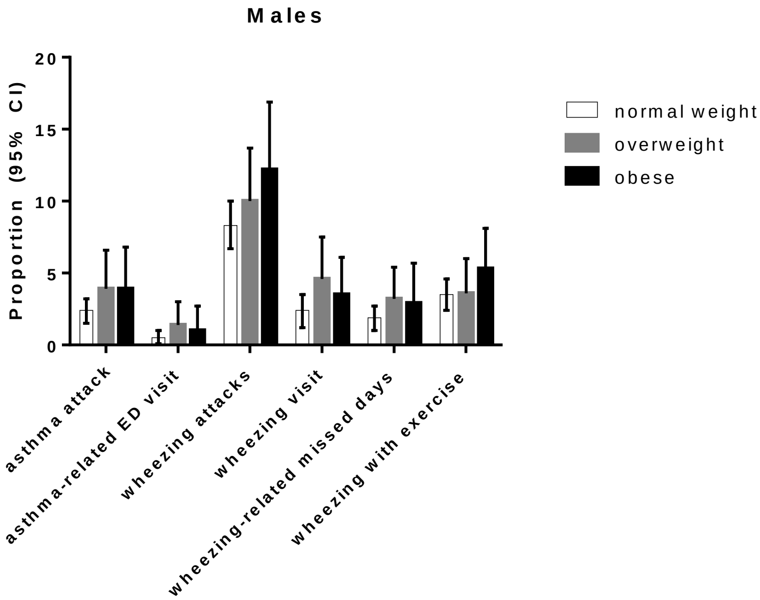

Figure 5.5 Asthma morbidity by BMI category in males. There was a trend of increased rates of asthma morbidity with overweight/obese males compared to normal weight males.

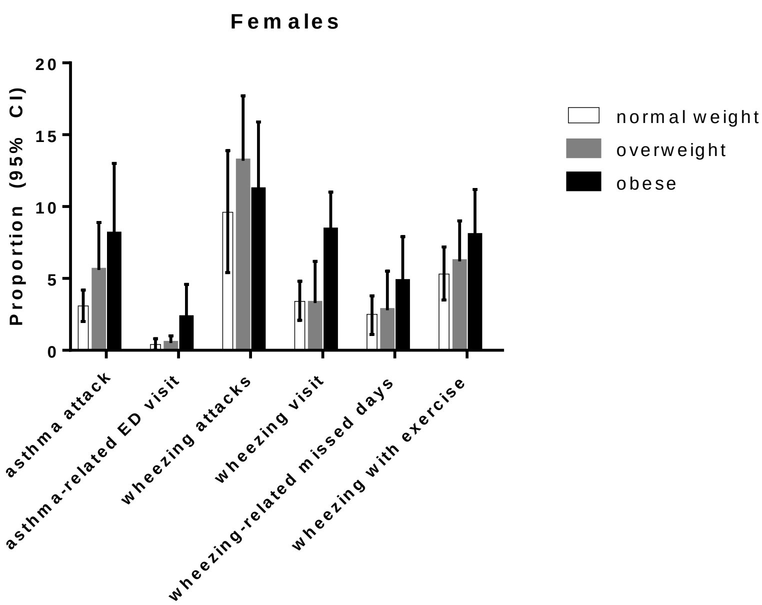

Figure 5.6 Asthma morbidity by BMI category in females. There were statistically significant differences by BMI category for asthma attacks, asthma-related ED visits, wheezing visits for females.

Table 5.6 Odds of asthma morbidity in overweight/obese compared to normal weight participants.		
Outcome	OR of over/obese to normal weight (95% CI)	OR of over/obese to normal weight (95% CI) multivariate
Asthma, attacks		
All	**2.01 (1.29, 3.13)**	**1.99 (1.26, 3.12)**
Males	1.69 (0.92, 3.08)	1.39 (0.78, 2.49)
Females	**2.31 (1.32, 4.07)**	**2.58 (1.47, 4.54)**
Asthma-related ED visits		
All	**2.75 (1.11, 6.82)**	**1.99 (1.26, 3.12)**
Males	2.21 (0.61, 8.01)	1.39 (0.78, 2.49)
Females	3.56 (0.89, 14.16)	3.22 (0.57, 18.05)
Wheezing attacks		
All	**1.32 (1.06, 1.65)**	**1.40 (1.08, 1.81)**
Males	1.37 (0.99, 1.90)	1.40 (0.96, 2.03)
Females	1.28 (0.92, 1.78)	1.60 (0.95, 2.67)
Wheezing visits		
All	**1.74 (1.12, 2.69)**	1.54 (0.95, 2.50)
Males	1.75 (0.84, 3.64)	1.48 (0.69, 3.16)
Females	1.74 (0.97, 3.13)	1.67 (0.89, 3.15)
Wheezing-related missed days		
All	1.61 (0.98, 2.64)	1.64 (0.89, 3.01)
Males	1.65 (0.86, 3.16)	1.34 (0.63, 2.85)
Females	1.58 (0.74, 3.35)	2.05 (0.87, 4.83)
Wheezing with exercise		
All	**1.31 (1.00, 1.71)**	**1.39 (1.06, 1.84)**
Males	1.26 (0.77, 2.07)	1.25 (0.74, 2.11)
Females	1.36 (0.95, 1.95)	**1.59 (1.07, 2.36)**
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio, +/- gender.		

5.B.2 Relationship between fitness and asthma morbidity.

Analyses of asthma morbidity by fitness tertile groups were performed (Table 5.6, 5.7). Overall, there were no significant differences in asthma morbidity by fitness tertiles among males and females except for wheezing-related missed days in males. Among males, 0.6% (95%CI 0, 1.2) participants in the highest fitness tertile had wheezing-related to missed days compared to 3.2% (95% CI 1.3, 5.2) in the lowest fitness tertile (p=0.02).

Table 5.7 Analyses of asthma by fitness tertiles in males.				
	Tertile1 OR (95% CI)	Tertile2 OR (95% CI)	Tertile3 OR (95% CI)	P value
Asthma, attack	3.8 (2.1, 5.4)	2.3 (1.2, 3.4)	2.4 (6.8, 4.1)	0.27
Asthma, ED	1.2 (0.1, 2.3)	0.9 (0.2, 1.6)	0.2 (0, 0.4)	0.06
Wheezing attacks	11.0 (8.0, 14.0)	9.6 (6.7, 12.6)	7.2 (5.0, 9.3)	0.13
Wheezing visits	3.7 (2.0, 5.5)	3.5 (1.7, 5.4)	1.8 (0.3, 3.3)	0.21
Wheezing, missed days	3.2 (1.3, 5.2)	2.7 (1.2, 4.1)	0.6 (0, 1.2)	0.02
Wheezing with exercise	3.8 (2.0, 5.6)	5.0 (2.9, 7.2)	2.5 (1.3, 3.8)	0.09
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes				

Table 5.8 Analyses of asthma by fitness tertiles in females.				
	Tertile1 OR (95% CI)	Tertile2 OR (95% CI)	Tertile3 OR (95% CI)	P value
Asthma, attack	3.7 (1.6, 5.7)	3.9 (1.6, 6.1)	5.4 (3.8, 7.0)	0.44
Asthma, ED	0.9 (0, 1.9)	0.7 (0, 1.6)	0.3 (0, 0.7)	0.48
Wheezing attacks	10.3 (7.2, 13.4)	9.8 (6.3, 13.3)	11.5 (7.7, 15.4)	0.77
Wheezing visits	4.5 (2.6, 6.5)	3.8 (2.0, 5.5)	3.9 (1.7, 6.1)	0.83
Wheezing, missed days	3.6 (2.0, 5.2)	2.8 (0.6, 5.0)	2.0 (0.4, 3.6)	0.46
Wheezing with exercise	4.5 (2.6, 6.4)	6.5 (3.6, 9.3)	6.4 (4.2, 8.6)	0.28
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes				

Chapter 6

Results: Examining the effect of fitness as a moderator in the relationship between obesity and asthma prevalence/morbidity.

Specific Aim 2: To examine whether low fitness moderates the relationship between obesity and asthma prevalence / morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the interaction between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

6.A.1 Relationships between obesity, fitness and asthma prevalence.

To examine relationships between asthma prevalence, obesity and fitness, we created fit/fat groups. The fit/fat groups were defined using fitness tertiles and BMI categories. Tertile 1 was labeled as “unfit” and tertile 2 and 3 were combined to create “fit” group. Normal weight was labeled as “not-fat” and overweight/obese were grouped together as “fat”. Overall, there were no significant differences among the four fit/fat groups when examining asthma prevalence as a whole and when stratified by gender (Table 6.1-6.3 and Figure 6.1, 6.2). In females, there was a pattern of increased rates of asthma diagnoses in both fat groups compared to non-fat (Figure 6.2).

Table 6.1 Asthma prevalence by fit/fat groups.

	Not fat and fit N=2358	Not fat and Not-fit	Fat and fit N=866	Fat and Not-fit	P value

	% (95% CI)	N=722 % (95% CI)	% (95% CI)	N=832 % (95% CI)	
Asthma diagnosis, ever	14.7 (12.0, 17.4)	12.2 (7.2, 17.3)	19.2 (13.8, 24.6)	19.3 (14.6, 24.0)	0.27
Asthma, current	7.2 (6.1, 8.2)	6.2 (3.6, 8.8)	9.2 (6.1, 12.2)	8.4 (6.0, 10.7)	0.32
Wheezing	8.8 (7.2, 10.4)	10.4 (7.7, 13.2)	11.9 (8.3, 15.5)	11.5 (8.7, 14.3)	0.18
Chronic cough	2.4 (1.7, 3.2)	2.7 (2.1, 3.4)	2.5 (9.1, 4.1)	4.2 (2.2, 6.2)	0.20
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 6.2 Asthma prevalence by fit/fat groups in males.

MALES	Not fat and fit N=1269 % (95% CI)	Not fat and Not-fit N=360 % (95% CI)	Fat and fit n=383 % (95% CI)	Fat and Not-fit N=453 % (95% CI)	P value
Asthma diagnosis, ever	13.5 (11.0, 16.0)	16.2 (10.7, 21.6)	16.5 (10.4, 22.6)	14.0 (9.2, 18.8)	0.65
Asthma, current	6.3 (4.7, 7.8)	6.8 (3.2, 10.4)	6.8 (3.1, 10.6)	8.9 (3.6, 10.2)	0.98
Wheezing	7.6 (5.9, 9.3)	11.3 (6.7, 15.9)	10.7 (6.2, 15.2)	11.7 (7.3, 16.0)	0.16
Chronic cough	2.8 (2.0, 3.6)	2.8 (0.5, 5.1)	5.0 (1.9, 8.0)	4.7 (2.2, 7.3)	0.18
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 6.3 Asthma prevalence by fit/fat groups in females.

FEMALES	Not fat and fit N=1089 % (95% CI)	Not fat and Not-fit N=412 % (95% CI)	Fat and fit N=483 % (95% CI)	Fat and Not-fit N=379 % (95% CI)	p value
Asthma diagnosis, ever	14.7 (12.0, 17.4)	12.2 (7.2, 17.3)	19.2 (13.8, 24.6)	19.3 (14.6, 24.0)	0.12
Asthma,	8.2 (6.3, 10.1)	5.7 (2.5, 8.9)	11.6 (7.5,	10.2 (5.6,	0.14

current			15.6)	14.5)	
Wheezing	10.1 (7.7, 12.6)	9.6 (5.4, 13.9)	13.2 (8.6, 17.8)	11.2 (6.5, 15.9)	0.59
Chronic cough	2.7 (1.4, 4.0)	2.2 (1.5, 4.2)	3.9 (0.9, 6.9)	3.4 (2.5, 6.6)	0.77
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

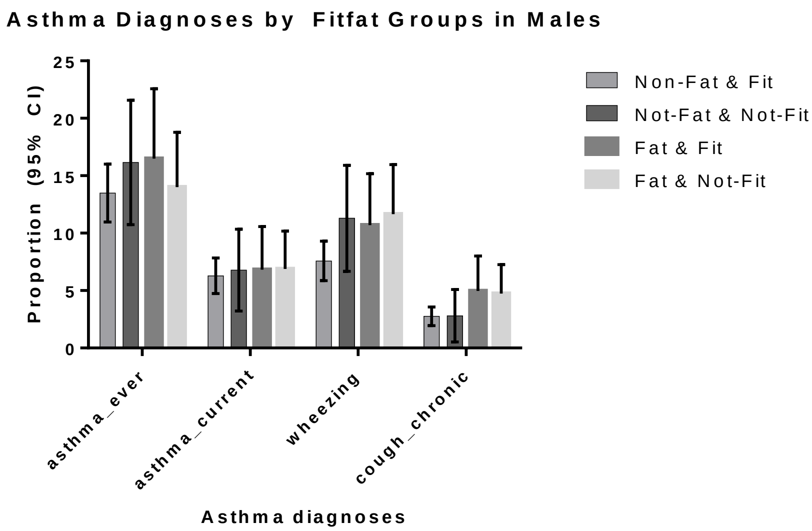

Figure 6.1 Asthma prevalence by fit/fat groups in males. Overall no significant differences were seen by fit/fat group for males.

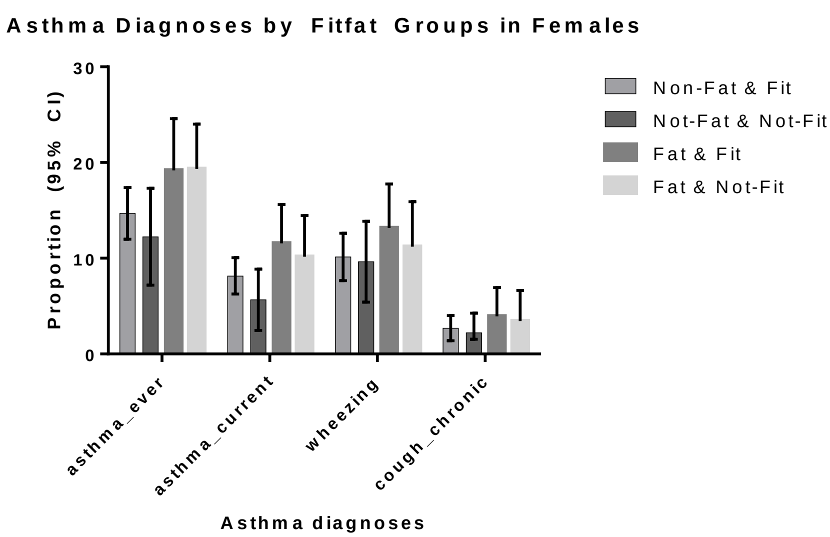

Figure 6.2 Asthma prevalence by fit/fat groups in females. Overall no significant differences were seen by fit/fat group for females.

We examined the odds of overweight/obesity on asthma prevalence among fit and unfit participants in males and females. Overall, there was no significant difference in odds of overweight/obesity on asthma prevalence between fit and unfit participants. We then tested the effect of fitness as a moderator in the relationship between overweight/obesity and asthma prevalence in models. There was a significant odds of asthma, ever and asthma, current in overweight females compared to normal weight females, after adjusting for covariates including fitness and a fitness/obesity interaction. We did not find any significant interactions between fitness and overweight/obese related to asthma prevalence in both males and females (Table 6.4, 6.5).

Table 6.4 Odds of asthma diagnoses in overweight/obese compared to normal weight, testing the effect of fitness as a moderator in males.

	OR (95% CI) in unfit	OR (95% CI) in fit	OR 95% CI, multivariate	interaction p value
Asthma ever	0.85 (0.48, 1.50)	1.27 (0.83, 1.93)	0.83 (0.48, 1.41)	0.40
Asthma current	1.02 (0.46, 2.25)	1.09 (0.61, 1.97)	0.88 (0.44, 1.77)	0.84
Wheezing	1.04 (0.56, 1.91)	1.46 (0.85, 2.24)	0.96 (0.52, 1.76)	0.25
Chronic cough	1.72 (0.68, 4.37)	1.84 (0.90, 3.73)	1.37 (0.54, 3.47)	0.64
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio				

Table 6.5 Odds of asthma diagnoses overweight/obese compared to normal weight testing the effect of fitness as a moderator in females.

	OR (95% CI) in unfit	OR (95% CI) in fit	OR 95% CI, multivariate	interaction p value
Asthma ever	1.71 (0.97, 3.06)	1.38 (0.91, 2.10)	**2.05 (1.19, 3.51)**	0.26
Asthma current	1.89 (0.79, 4.49)	1.47 (0.90, 2.42)	**2.20 (1.09, 4.43)**	0.40
Wheezing	1.19 (0.61, 2.32)	1.34 (0.92, 1.97)	1.62 (0.90, 2.90)	0.72
Chronic cough	1.58 (0.41, 6.12)	1.48 (0.56, 3.91)	2.47 (0.78, 7.87)	0.50

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio

6.B.1 Relationship between obesity, fitness and asthma morbidity.

To examine relationships between obesity, fitness, and asthma morbidity, we created fit/fat groups. The fit/fat groups were defined using fitness tertiles and BMI categories. Tertile 1 was labeled as “unfit” and tertile 2 and 3 were combined to create “fit” group. Normal weight was labeled as “not-fat” and overweight/obese were grouped together as “fat”.

Overall, there were a few statistically significant differences among the four fit/fat groups when examining asthma morbidity as a whole and when stratified by gender (Table 6.6-6.8 and Figure 6.3, 6.4). For example, among female participants, there was a statistically significant differences by fit/fat groups for rates of asthma attacks (p=0.01). Among the normal weight females, 3.7% of fit females reported an asthma attack compared to 1.5% of the not-fit females. Among the overweight/obese females, 7.5% of fit females reported an asthma attack compared to 6.2% in the not-fit females. There were no significant differences of asthma morbidity by fit/fat groups among males. However, there is a trend towards increased rates of asthma morbidity in the fat and unfit group among males compared to the other groups, for example, 3.8% of the fat/unfit males had wheezing-related missed days compared to 1.6% of the not fat/fit males.

Table 6.6 Asthma morbidity by Fit and Fat Groups.

	Not fat and fit N=2358 % (95% CI)	Not fat and Not-fit N=722 % (95% CI)	Fat and fit N=866 % (95% CI)	Fat and Not-fit N=832 % (95% CI)	P value
Asthma attack	2.9 (2.1, 3.6)	2.3 (1.0, 3.5)	5.4 (2.9, 7.9)	5.2 (3.0, 7.5)	**0.01**

Asthma, ED	0.3 (0.06, 0.6)	0.9 (0.03, 1.8)	1.3 (0.2, 2.4)	1.3 (0.2, 2.4)	0.07
Wheezing attack	8.6 (7.1, 10.2)	10.4 (7.7, 13.2)	11.8 (8.2, 15.4)	11.5 (8.7, 14.3)	0.15
Wheezing visit	2.6 (1.7, 3.6)	3.6 (2.6, 7.3)	4.9 (2.5, 7.3)	4.9 (3.0, 6.7)	**0.04**
Wheezing, missed days	1.9 (0.9, 2.9)	2.9 (1.5, 4.4)	2.7 (0.9, 4.4)	4.1 (2.0, 6.2)	0.10
Wheezing with exercise	4.5 (3.5, 5.8)	3.6 (2.0, 5.3)	6.7 (4.2, 9.2)	4.7 (3.1, 6.4)	0.10
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 6.7. Asthma morbidity by Fit and Fat Groups among males.					
	Not fat and fit N=1269 % (95% CI)	Not fat and Not-fit N=360 % (95% CI)	Fat and fit n=383 % (95% CI)	Fat and Not-fit N=453 % (95% CI)	P value
Asthma attack	2.1 (1.2, 3.0)	3.1 (0.9, 5.3)	3.2 (0.6, 5.9)	4.5 (1.6, 7.30)	0.24
Asthma, ED	0.3 (0.08, 0.5)	1.4 (-0.2, 3.1)	1.4 (-0.4, 3.2)	1.0 (-0.5, 2.5)	0.17
Wheezing attack	7.5 (5.8, 9.2)	11.3 (6.7, 15.9)	10.4 (6.0, 14.8)	11.7 (7.3, 16.0)	0.15
Wheezing visit	2.1 (0.9, 3.2)	3.4 (0.8, 6.0)	3.7 (0.8, 6.7)	4.3 (1.6, 7.1)	0.28
Wheezing, missed days	1.6 (0.7, 2.5)	2.8 (0.6, 5.1)	2.1 (0.03, 4.1)	3.8 (1.0, 6.7)	0.20
Wheezing with exercise	3.5 (2.3, 4.7)	3.8 (1.1, 6.4)	4.8 (1.7, 7.9)	4.1 (1.7, 6.5)	0.79
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes					

Table 6.8 Asthma morbidity by Fit and Fat Groups among females.					
	Not fat and fit N=1089 % (95% CI)	Not fat and Not-fit N=412 % (95% CI)	Fat and fit N=483 % (95% CI)	Fat and Not-fit N=379 % (95% CI)	P value
Asthma attack	3.7 (2.4, 5.0)	1.5 (0.3, 2.7)	7.5 (3.7, 11.4)	6.2 (1.9, 10.6)	**0.01**
Asthma, ED	0.4 (-0.2, 0.9)	0.4 (-0.03, 0.9)	1.2 (-0.1, 2.5)	1.6 (-0.4, 3.6)	0.17
Wheezing attack	9.9 (7.4, 12.4)	9.6 (5.4, 13.9)	13.2 (8.6, 17.8)	11.2 (6.5, 15.9)	0.54

Wheezing visit	3.3 (1.7, 4.9)	3.8 (1.3, 6.4)	6.1 (2.8, 9.4)	5.6 (2.5, 8.6)	0.24
Wheezing, missed days	2.3 (0.6, 4.0)	3.0 (0.7, 5.3)	3.2 (0.7, 5.8)	4.5 (1.6, 7.3)	0.52
Wheezing with exercise	6.0 (4.0, 8.1)	3.5 (1.1, 5.9)	8.6 (5.1, 12.2)	5.5 (2.6, 8.5)	0.07
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcome					

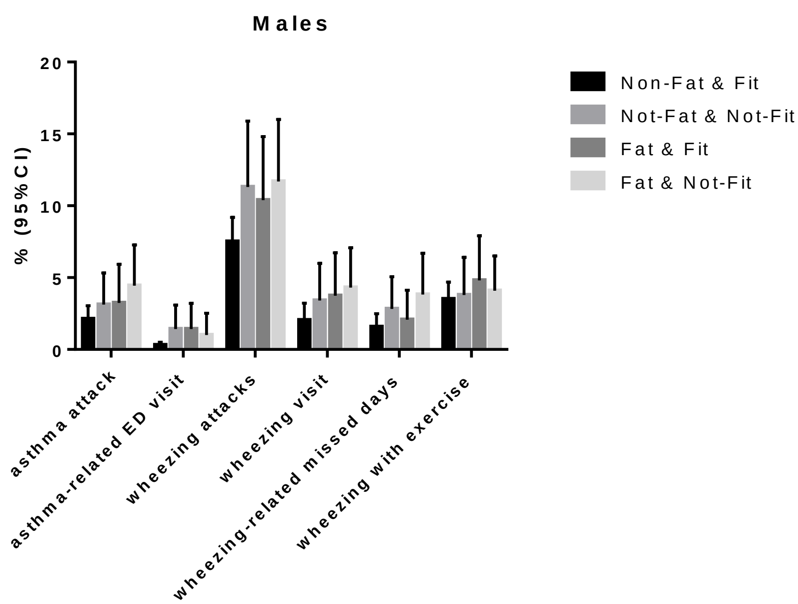

Figure 6.3. Asthma morbidity by fit/fat groups in males.

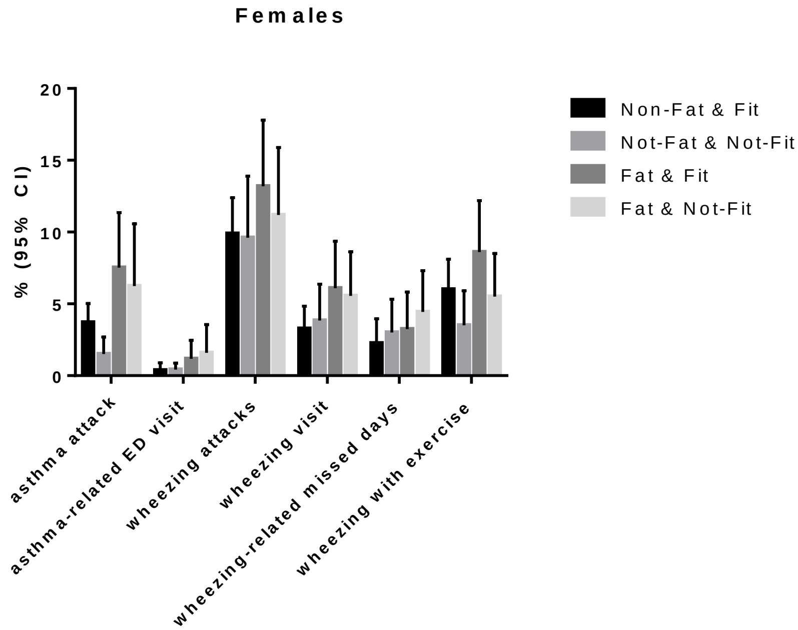

Figure 6.4 Asthma morbidity by fit/fat groups in females.

We examined the odds of overweight/obesity on asthma morbidity among fit and unfit participants in males and females (Tables 6.9, 6.10). We observed some differences in the relationship between overweight/obesity and asthma morbidity between fit and unfit participants. For example, the OR of asthma-related ED visit among unfit males was 0.69 (95%CI 0.10, 4.78) compared to fit males with an OR of 5.02 (95% CI 1.03, 24.53). Among unfit females, the OR of asthma attacks was 4.36 (95% CI 1.48, 12.79) compared to an OR of 2.11 (95% CI 1.14, 3.94) in fit females. We then created models to test the effect of fitness as a moderator (Tables 5.9, 5.10) in the relationship between overweight/obesity and asthma morbidity by creating an overweight/obesity x fitness interaction term. Overall, fitness did not appear to significantly moderate the relationship between overweight/obesity and asthma morbidity in males or females except for asthma-related

ED visits among males. Among males, the OR of asthma-related ED visits in unfit overweight/obese compared to unfit normal weight was 0.69 (0.10, 4.78) while in contrast, there was an OR of 5.02 (1.03, 24.53) of fit overweight/obese compared to fit normal weight males (interaction p value of 0.01).

Table 6.9 Odds of asthma morbidity in overweight/obese compared to normal weight stratified by fitness in Males

	OR (95% CI) in unfit	OR (95% CI) in fit	OR 95% CI, multivariate	interaction p value
Asthma attack	1.44 (0.51, 4.08)	1.54 (0.60, 3.97)	1.19 (0.43, 3.26)	0.92
Asthma related ED visit	0.69 (0.10, 4.78)	**5.02 (1.03, 24.53)**	0.64 (0.14, 2.72)	**0.01**
Wheezing attack	1.04 (0.56, 1.91)	1.44 (0.93, 2.22)	0.95 (0.51, 1.76)	0.24
Wheezing visit	1.28 (0.44, 3.73)	1.86 (0.71, 4.85)	1.07 (0.41, 2.83)	0.69
Wheezing, missed days	1.37 (0.55, 3.40)	1.33 (0.42, 4.19)	0.86 (0.36, 2.04)	0.80
Wheezing with exercise	1.10 (0.45, 2.66)	1.40 (0.72, 2.72)	1.08 (0.43, 2.70)	0.78
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio				

Table 6.10 Odds of asthma morbidity in overweight/obese compared to normal weight stratified by fitness in females

	OR (95% CI) in unfit	OR (95% CI) in fit	OR 95% CI, multivariate	interaction p value
Asthma attack	**4.36 (1.48, 12.79)**	**2.11 (1.14, 3.94)**	**4.61 (1.91, 11.13)**	0.30
Asthma related ED visit	3.77 (0.77, 18.48)	3.14 (0.49, 20.01)	2.48 (0.35, 17.71)	0.71
Wheezing attack	1.19 (0.61, 2.32)	1.38 (0.95, 2.01)	1.66 (0.92, 3.00)	0.71
Wheezing visit	1.48 (0.62, 3.54)	1.91 (0.89, 4.10)	1.74 (0.73, 4.17)	0.83
Wheezing, missed days	1.50 (0.49, 4.62)	1.45 (0.46, 4.61)	2.06 (0.65, 6.56)	0.74

Wheezing with exercise	1.59 (0.69, 3.68)	1.48 (0.89, 2.46)	1.66 (0.71, 3.88)	0.86
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio				

Chapter 7

Results: Examining the effect of fitness as a mediator in the relationship between obesity and asthma prevalence/morbidity.

Specific Aim 3. To examine whether low fitness mediates the relationship between obesity and asthma prevalence / morbidity among youth ages 12-19 years of age in males and females by:

a. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma prevalence.
b. Characterizing the relationship between obesity and fitness measured by submaximal cardiorespiratory fitness testing on asthma morbidity.

7.A.1. Examining fitness as a mediator in the relationship between obesity and asthma prevalence.

We tested fitness as a mediator in the relationship between overweight/obesity and asthma prevalence. Overall, there was no effect of fitness as a mediator in the relationship between asthma prevalence and overweight/obese participants in both males and females (Table 7.1-7.4). For example, among females, the OR of asthma, ever in overweight/obese participants compared to normal weight participants was 1.60 (95% CI 1.14, 2.23) in multivariate models not including fitness. When fitness was added to the models, the relationship between overweight/obesity and asthma, ever in females remained relatively unchanged, with an OR 1.67 (95% CI 1.16, 2.40). No significant differences were observed when comparing the higher fitness tertiles (Tertile 2 and 3) to the lowest fitness tertile.

Table 7.1 Testing fitness as a mediator between overweight/obesity and asthma, ever			
	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.09 (0.82, 1.45)	1.01 (0.73, 1.40)	0.98 (0.68, 1.40)
Fitness tertile 2 to 1			1.04 (0.67, 1.60)
Fitness tertile 3 to 1			0.86 (0.55, 1.36)
FEMALES			
Overall Model	**1.46 (1.08, 1.99)**	**1.60 (1.14, 2.23)**	**1.67 (1.16, 2.40)**
Fitness tertile 2 to 1			1.07 (0.73, 1.57)
Fitness tertile 3 to 1			1.18 (0.77, 1.82)
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio Model 1: simple model comparing odds of asthma prevalence in overweight/obese to normal weight participants. Model 2: multivariate model odds of asthma prevalence in overweight/obese to normal weight participants. Model 3: multivariate model of odds of asthma prevalence in overweight/obese to normal weight participants including fitness.			

Table 7.2 Testing fitness as a mediator between overweight/obesity and asthma, current			
	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.08 (0.70, 1.67)	0.99 (0.65, 1.53)	0.92 (0.58, 1.46)
Fitness tertile 2 to 1			1.13 (0.66, 1.92)
Fitness tertile 3 to 1			0.76 (0.42, 1.37)
FEMALES			
Overall Model	1.51 (0.99, 2.29)	**1.68 (1.09, 2.59)**	**1.78 (1.14, 2.78)**
Fitness tertile 2 to 1			1.15 (0.74, 1.77)
Fitness tertile 3 to 1			1.51 (0.93, 2.45)
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio Model 1: simple model comparing odds of asthma prevalence in overweight/obese to normal weight participants. Model 2: multivariate model odds of asthma prevalence in overweight/obese to normal weight participants. Model 3: multivariate model of odds of asthma prevalence in overweight/obese to normal weight participants including fitness.			

Table 7.3 Testing fitness as a mediator between overweight/obesity and wheezing.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	**1.37 (1.00, 1.89)**	1.40 (0.97, 2.02)	1.21 (0.80, 1.83)
Fitness tertile 2 to 1			0.90 (0.53, 1.53)
Fitness tertile 3 to 1			0.58 (0.33, 1.03
FEMALES			
Overall Model	1.25 (0.90, 1.75)	**1.44 (1.01, 2.04)**	**1.49 (1.09, 2.03)**
Fitness tertile 2 to 1			1.08 (0.68, 1.70)
Fitness tertile 3 to 1			1.16 (0.63, 2.12)
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio Model 1: simple model comparing odds of asthma prevalence in overweight/obese to normal weight participants. Model 2: multivariate model odds of asthma prevalence in overweight/obese to normal weight participants. Model 3: multivariate model of odds of asthma prevalence in overweight/obese to normal weight participants including fitness.			

Table 7.4 Testing fitness as a mediator between overweight/obesity and chronic cough.			
	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	**1.78 (1.10, 2.88)**	1.77 (0.99, 3.16)	1.59 (0.82, 3.08)
Fitness tertile 2 to 1			1.19 (0.61, 2.31)
Fitness tertile 3 to 1			0.81 (0.40, 1.66)
FEMALES			
Overall Model	**1.78 (1.10, 2.88)**	1.77 (0.99, 3.16)	1.99 (0.82, 4.84)
Fitness tertile 2 to 1			1.49 (0.59, 3.76)
Fitness tertile 3 to 1			0.85 (0.28, 2.60)
Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio Model 1: simple model comparing odds of asthma prevalence in overweight/obese to normal weight participants. Model 2: multivariate model odds of asthma prevalence in overweight/obese to normal weight participants. Model 3: multivariate model of odds of asthma prevalence in overweight/obese to normal weight participants including fitness.			

7.B.1 Examining fitness as a mediator in the relationship between obesity and asthma morbidity.

We created models to test the effect of fitness as a mediator (Tables 7.5-7.10) in the relationship between overweight/obesity and asthma morbidity. Among females, overweight/obesity was associated with increased asthma morbidity. For example, when evaluating rates of asthma attacks in females, there was an adjusted odds ratio of 2.97 (95% CI 1.72, 5.15) in overweight/obese females compared to normal weight females (Table 7.5). When we included fitness in the multivariate models, fitness did not appear to mediate the relationship between overweight/obesity and asthma morbidity in females. Among males, we did not see any significant associations between overweight/obesity and asthma morbidity. However, we did see the effect of fitness mediating the relationship between overweight/obesity and some of the asthma morbidity outcomes. For example, with wheezing visits, the most fit males had a lower odds of wheezing visits compared to the lowest fit males, with an odds ratio of 0.36 (95% CI 0.14, 0.97). We also saw a similar relationship for wheezing-related missed days in males. The most fit males had a significantly lower odds of wheezing-related missed days compared to the lowest fit males, with an odds ratio 0.21 (95% CI 0.07, 0.57).

Table 7.5 Testing fitness as a mediator between overweight/obesity and asthma attacks.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.69 (0.92, 3.08)	1.39 (0.78, 2.49)	1.23 (0.63, 2.40)
Fitness tertile 2 to 1			0.66 (0.34, 1.31)
Fitness tertile 3 to 1			0.73 (0.30, 1.81)
FEMALES			
Overall Model	**2.31 (1.32, 4.07)**	**2.58 (1.47, 4.54)**	**2.97 (1.72, 5.15)**

Fitness tertile 2 to 1			1.37 (0.68, 2.73)
Fitness tertile 3 to 1			1.87 (0.94, 3.72)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Table 7.6 Testing fitness as a mediator between overweight/obesity and asthma-related ED visits.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	2.21 (0.61, 8.01)	1.39 (0.78, 2.49)	1.48 (0.35, 6.29)
Fitness tertile 2 to 1			0.86 (0.19, 3.81)
Fitness tertile 3 to 1			0.19 (0.04, 1.01)
FEMALES			
Overall Model	3.56 (0.89, 14.16)	3.22 (0.57, 18.05)	2.94 (0.56, 15.43)
Fitness tertile 2 to 1			1.06 (0.25, 4.56)
Fitness tertile 3 to 1			0.48 (0.12, 1.92)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Table 7.7 Testing fitness as a mediator between overweight/obesity and wheezing attacks.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.37 (0.99, 1.90)	1.40 (0.96, 2.03)	1.20 (0.79, 1.83)
Fitness tertile 2 to 1			0.88 (0.52, 1.50)
Fitness tertile 3 to 1			0.57 (0.32, 1.01)
FEMALES			
Overall Model	1.28 (0.92, 1.78)	1.60 (0.95, 2.67)	0.74 (0.54, 1.02)

Fitness tertile 2 to 1			1.04 (0.65, 1.68)
Fitness tertile 3 to 1			1.16 (0.64, 2.13)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Table 7.8 Testing fitness as a mediator between overweight/obesity and wheezing visits.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.75 (0.84, 3.64)	1.48 (0.69, 3.16)	1.18 (0.52, 2.67)
Fitness tertile 2 to 1			1.01 (0.46, 2.22)
Fitness tertile 3 to 1			**0.36 (0.14, 0.97)**
FEMALES			
Overall Model	1.74 (0.97, 3.13)	1.67 (0.89, 3.15)	1.63 (0.88, 3.03)
Fitness tertile 2 to 1			0.94 (0.46, 1.93)
Fitness tertile 3 to 1			0.98 (0.50, 1.94)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Table 7.9 Testing fitness as a mediator between overweight/obesity and wheezing related missed days.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.65 (0.86, 3.16)	1.34 (0.63, 2.85)	0.90 (0.43, 1.90)
Fitness tertile 2 to 1			0.85 (0.36, 1.99)
Fitness tertile 3 to 1			**0.21 (0.07, 0.57)**
FEMALES			
Overall Model	1.58 (0.74, 3.35)	2.05 (0.87, 4.83)	1.83 (0.79, 4.28)

Fitness tertile 2 to 1			0.85 (0.37, 1.97)
Fitness tertile 3 to 1			0.60 (0.22, 1.63)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Table 7.10. Testing fitness as a mediator between overweight/obesity and wheezing with exercise.

	Model 1 OR (95% CI)	Model 2, covariates OR (95% CI)	Model 3, multivariate including fitness OR (95% CI)
MALES			
Overall Model	1.26 (0.77, 2.07)	1.25 (0.74, 2.11)	1.12 (0.63, 1.99)
Fitness tertile 2 to 1			1.39 (0.72, 2.70)
Fitness tertile 3 to 1			0.63 (0.33, 1.22)
FEMALES			
Overall Model	1.36 (0.95, 1.95)	**1.59 (1.07, 2.36)**	**1.80 (1.20, 2.69)**
Fitness tertile 2 to 1			1.69 (0.99, 2.88)
Fitness tertile 3 to 1			1.68 (1.00, 2.82)

Covariates: survey year, race/ethnicity, household smoke, age, poverty index ratio
Model 1: simple model comparing odds of asthma morbidity in overweight/obese to normal weight participants.
Model 2: multivariate model odds of asthma morbidity in overweight/obese to normal weight participants.
Model 3: multivariate model of odds of asthma morbidity in overweight/obese to normal weight participants including fitness.

Chapter 8

DISCUSSION

In this cross-sectional analysis of adolescents from NHANES, we found that the association between overweight/obesity and increased asthma prevalence was present in males and females but strongest in females. We also found an association between overweight/obesity and increased asthma morbidity in females but not males. There were significant differences in estimated fitness levels by gender with girls having significantly lower levels of fitness that declined with age in contrast to males whose fitness level increased with age. We also found that fitness does not appear to mediate or moderate the relationship between overweight/obesity and asthma prevalence. However, we did find that fitness may mediate or moderate the relationship between overweight/obesity and asthma morbidity in males but not among females.

In Chapter 5 (specific aim 1), we explored relationships between obesity or fitness on asthma prevalence/morbidity. We found that obesity is associated with increased asthma prevalence in females. The relationship between obesity and increased asthma prevalence was present but not significant in males. We also found that obesity is associated with significant increased asthma morbidity in females but not in males.

We did not find any significant relationships between fitness and asthma prevalence or morbidity in either males or females.

In Chapter 6 (specific aim 2), we explored relationships between, obesity and asthma prevalence/morbidity with fitness as a moderator. Overall, fitness did not appear to moderate the relationship between overweight/obesity and asthma prevalence in males or females. We also examined fitness as a moderator in the relationship between obesity and asthma morbidity. In males, fitness may play a role in the relationship between obesity and asthma. We found a significant interaction between obesity and fitness when examining asthma-related ED visits among males.

In Chapter 7 (specific aim 3) we examined relationship between obesity and asthma prevalence/morbidity with fitness as a mediator. Fitness does not appear to mediate the relationship between obesity and asthma prevalence. In males, fitness may mediate the relationship between overweight/obesity and some of the asthma morbidity outcomes, specifically those in the highest fitness tertile had decreased wheezing visits and wheezing-related missed days compared to those in the lowest fitness tertile.

Obesity and asthma

Though the findings are mixed, the majority of studies in children support a more consistent relationship between obesity and asthma development in females (Table 1) consistent with our findings. In the Tucson Children's Respiratory Study, a longitudinal birth cohort followed for several decades, girls who became overweight or obese between 6 and 11 years of age (OR 6.8 95% CI 2.4, 19.4 and OR 5.5 95% CI 1.3, 23.3) were more likely to develop wheezing compared to those who were normal weight (24). This relationship was not seen in males. Only a handful of studies have specifically examined the relationship between obesity and asthma risk in adolescents. Ho et al evaluated over 4000 participants between 13-15 years of age and found that girls who were overweight had an increased odds of physician diagnosed asthma (OR 1.75 95% CI 1.18-2.61) compared to those who were normal weight. No significant relationship seen in overweight/obese males

(56). Tollefsen et al examined over 2300 adolescents in Norway and found increased odds (OR 2.4 95% CI 1.3, 4.6) of stable current wheeze overweight compared to normal weight females only (25).

In contrast to our findings, a systematic review and meta-analysis examining gender differences of childhood overweight/obesity in predicting risk of incident asthma found that obese boys had a significantly larger effect on asthma risk (RR 2.47 95% CI 1.57, 3.87) compared to obese girls (RR 1.25 95% CI 0.51, 3.03)(20). However they included pediatric studies with age ranges from 5 to 18 years of age. Lee et al examined over 3500 adolescents in Taiwan and found that overweight males had RR 1.74 (95% CI 1.35, 2.26) compared to normal weight males and no relationship was seen in females(57).

Obesity, asthma and fitness

Few studies have examined fitness in the relationship between obesity and asthma and most of these studies have used subjective measures of physical activity.

Consistent with our findings, Kilpelainen et al examined BMI, physical activity in relationship to asthma in young adults and found that increased moderate physical activity was associated with a lower risk of asthma in men but not among females.(58)

Tollefsen examined several lifestyle factors including physical activity and overweight and asthma or wheeze risk in adolescents. Low physical activity was not seen to be associated with an increased risk of wheezing in males or females(25). Visness et al examined levels of subjective measures of physical activity and screen-time on asthma risk using NHANES and found no significant differences on current asthma or medical visits for wheezing related to physical activity or sedentary time (50). There was an association between overweight/obesity and asthma outcomes after adjusting for levels of physical activity.

In a study of urban, low-income adolescents by Groth et al, adolescents with asthma participated in less physical activity compared to their non-asthmatic counterparts ($p<0.01$) after controlling for BMI and age(59). They also found that girls participated in less physical activity than males regardless of asthma status ($p<0.01$). BMI did not differ between adolescents with and without asthma overall. However when gender was considered separately, girls with asthma had a higher mean BMI compared to those without asthma ($p=0.027$). Jones et al examined relationships between asthma, overweight and physical activity among high school students in the U.S. and found that significantly more students with asthma were overweight compared to those without asthma (OR 1.4 95% CI 1.1, 1.6) in both males and females. Asthmatics were also more likely to use their computers for non-school work for three or more hours daily compared to non-asthmatics (OR 1.3 95% CI 1.1, 1.5). No relationships between vigorous or moderate physical activity and asthma status were seen. All of these studies used subjective measures of physical activity or sedentary behavior which is known to correlate poorly with objective measures.

Only one study has used objective measures of fitness to examine the interrelations between central obesity, physical fitness level, sedentary time and asthma(13). In a group of over 2700 schoolchildren from Taiwan, Chen et al found that central obesity most accurately predicts asthma. Furthermore, low fitness and high screen times increased the risk of central obesity but did not appear to be a link in the relationship between obesity and asthma. However, fitness was assessed using an 800 m sprint, a field test that relies on technique and motivation and therefore the results may not accurately reflect cardiorespiratory fitness. While they adjusted for gender in their models, the authors did not examine the outcomes separately by gender. This may mask any effect of fitness or sedentary behavior in the relationship between obesity and asthma as we saw a possible effect of fitness in males only.

Limitations.

NHANES is a series of cross-sectional studies and thus we are unable to establish temporal relationships between observed variables or determine the directionality of the relationships between obesity, fitness and asthma outcomes.

During the NHANES survey years of our sample population, data re: asthma diagnoses or morbidity was subjectively based on questionnaires and unfortunately no objective measures of asthma were captured including pulmonary function testing, broncho-provocation testing. Additionally, asthma is a common condition in children, but overall rates particularly of asthma morbidity were low.

Another limitation of our study was that fitness testing was only done in children ages 12 and older and thus we are unable to evaluate the relationship between fitness, asthma and obesity among younger children, who have a higher prevalence of asthma and tend to have increased morbidity related to asthma.

There were several limitations related to the fitness testing performed. Fitness testing excluded those with specified medical conditions including those with more severe asthma or respiratory conditions. We did find statistically significant increased rates of asthma diagnoses and morbidity in the excluded sample compared to our included sample potentially introducing selection bias. Additionally, there were more overweight and obese participants in the excluded sample population.

Predicted maximal work capacity (VO_2 max) used as a measure of fitness was calculated from the submaximal treadmill test performed. Ability to perform the tests particularly in pediatric populations is highly dependent on the willingness of each child to continue exercising at relatively high work rates. Also, predicted VO_2 max levels were scaled to body weight in this study which may not accurately reflect metabolically active muscle mass. These limitations highlight the difficulty in quantifying cardiorespiratory fitness in children.

Lastly, while our analyses were stratified by gender, we did not have sufficient power to test for gender interactions, and limiting our ability to formally compare associations between males and females.

Conclusion

In our study of adolescents aged 12-19 years of age in the United States, we found that obesity is associated with increased rates of asthma diagnoses as well as increased rates of asthma morbidity among females but not males. Estimated fitness levels differ significantly by gender with girls having significantly lower levels compared to males. Higher fitness may play a role in the relationship between overweight/obesity and asthma morbidity, specifically in decreased rates of wheezing visits and missed days compared to those who are less fit in males.

Our study emphasizes the importance of examining females and males separately when evaluating the relationship between obesity and asthma and highlighting the importance of precision medicine. Future prospective studies need to elucidate the role of fitness in the relationship between obesity and asthma outcomes in a pediatric asthmatic population.

Finally, public health policies need to address these overwhelming rates of obesity, poor fitness in children with early prevention measures and advocate for effective physical education classes in all schools to mitigate the increasing rates of obesity and asthma in our children and adolescents.

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APPENDIX A

Physical activity and fitness between normal weight and overweight/obese participants.			
	Normal weight	Overweight/obese	p value
Vigorous activity/30 days, % (95% CI)	75.8 (73.3, 78.3)	71.3 (68.5, 74.0)	0.02
Moderate activity/30 days, % (95% CI)	69.1 (66.9, 71.3)	64.7 (61.1, 68.4)	0.02
Screen time >2hrs, % (95% CI)	61.3 (59.2, 63.5)	70.3 (67.2, 73.5)	<0.01
Physical activity readiness score, %			<0.01
Little/none activity	5.1	6.4	
Occasional walks/exercise	10.3	14.9	
Regular moderate 10-60mins/week	17.4	22.4	
Regular moderate >60mins/week	33.2	33.8	
Regular heavy<30mins/week	9.4	7.9	
Regular heavy 30-60mins/week	3.6	1.9	
Regular heavy 1-3hrs/week	7.9	5.4	
Regular heavy >3hrs/week	21.5	14.4	
VO_2 max, mean (SE)	43.9 (0.3)	39.4 (0.5)	<0.01
Fitness tertiles, %			<0.01
Tertile 1	24.8	51.6	
Tertile 2	37.2	27.9	
Tertile 3	38	20.4	
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes. P value generated from linear regression model for continuous outcomes.			

Analyses of physical activity by fitness tertiles.				
	Tertile1 % (95% CI)	Tertile2 % (95% CI)	Tertile3 % (95% CI)	P value
Vigorous activity/30 days	68.6 (65.7, 71.4)	75.9 (73.0, 78.8)	77.2 (74.0, 80.6)	<0.01
Moderate activity/30 days	65.9 (61.8, 70.0)	69.0 (65.5, 72.4)	67.1 (64.7, 70.6)	0.49
Screen time, yes% >2hr (95% CI)	68.6 (64.6, 72.7)	64.3 (61.0, 67.6)	58.7 (55.6, 61.8)	0.001
Physical activity readiness score %				<0.001
Little/none activity	7.4	3.7	5.4	
Occasional walks/exercise	14.9	10.6	10.8	
Regular mod 10-60mins/wk	23.3	19.4	15.0	
Regular mod >60mins/wk	34.4	34.9	30.4	

Regular heavy<30mins/week Regular heavy 30-60mins/wk Regular heavy 1-3hrs/wk Regular heavy >3hrs/wk	0.9 2.9 4.5 11.8	0.9 3.1 8.9 18.5	0.8 3.2 7.8 26.6	
P value generated from chi square for differences (Pearson) in dichotomous or categorical outcomes. P value generated from linear regression model for continuous outcomes.				