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Sleep Duration Patterns from Adolescence to Young Adulthood and their Impact on Asthma and Inflammation

Chighaf Bakour
University of South Florida, chbak70@gmail.com

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Sleep Duration Patterns from Adolescence to Young Adulthood

and their Impact on Asthma and Inflammation

by

Chighaf Bakour

A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Public Health
Department of Epidemiology and Biostatistics
College of Public Health
University of South Florida

Major Professor: Kathleen O’Rourke, Ph.D.
Skai Schwartz, Ph.D.
William Sappenfield, MD, MPH
Wei Wang, Ph.D.
Marisa Couluris, DO

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June 3, 2016

Keywords: Sleep duration, asthma, adolescents, inflammation, longitudinal, young adults

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DEDICATION

This dissertation is dedicated to my soul mate, my husband, Mohammad Ayman Joud. It is through his unwavering support and encouragement that I am able to reach this point.

To my sons, Hadi and Bilal, who tolerated my erratic schedule and cheered me all the way.

To my parents, Yahia and Fatima, for all they have done for me all my life.

To my sister Rawan, who has always been by my side, even when she is thousands of miles away, lending an ear or a helping hand whenever I needed one.

To my brother, Firas, my inspiration. To my aunt Najat, and all my family and friends. Thank you all for your support.

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This project also used data from the Florida Youth Risk Behavior Survey (YRBS), obtained through a contract with the Florida Department of Health (FDOH) Bureau of Epidemiology (BOE).
### TABLE OF CONTENTS

List of Tables ......................................................................................................................... iv

List of Figures ......................................................................................................................... vi

Abstract ................................................................................................................................... vii

Section One: Introduction ...................................................................................................... 1

Section Two: Sleep Duration, Obesity, and Asthma in Florida Adolescents: Analysis of
Data from the Florida Youth Risk Behavior Survey (2009-2013) .......................................... 7
  Abstract ................................................................................................................................. 7
  Introduction ............................................................................................................................. 7
  Methods .................................................................................................................................. 9
    Population ............................................................................................................................. 9
    Measures .............................................................................................................................. 10
      Sleep duration ................................................................................................................... 10
      Asthma .............................................................................................................................. 10
      BMI .................................................................................................................................. 10
    Covariates ............................................................................................................................ 11
  Data Analysis .......................................................................................................................... 11
  Results .................................................................................................................................... 12
  Discussion ............................................................................................................................... 14
  Conclusions ............................................................................................................................ 16
  Tables and Figures .................................................................................................................. 17

Section Three: Sleep Duration trajectories and Asthma From Adolescence to Young
Adulthood ............................................................................................................................... 20
  Abstract ................................................................................................................................. 20
  Introduction ............................................................................................................................. 21
  Methods .................................................................................................................................. 22
    Design .................................................................................................................................. 22
    Measures .............................................................................................................................. 23
      Sleep duration ................................................................................................................... 23
      Asthma .............................................................................................................................. 23
      Race/ethnicity .................................................................................................................... 24
      BMI .................................................................................................................................. 24
      Family income ................................................................................................................... 24
      Parental education ............................................................................................................ 24
      Physical activity ............................................................................................................... 24
Appendix A: Review of Literature

Asthma ............................................................................................................. 73

Obesity and asthma ................................................................................. 73
Systemic inflammation and asthma ......................................................... 74
Adolescents and young adults with asthma ........................................... 75
Sleep disorders and their consequences ................................................. 77
Sleep and asthma ....................................................................................... 82

Sleep disturbances in asthma ............................................................... 82
Sleep duration and asthma ..................................................................... 83
The impact of sleep quality on patients with asthma ....................... 85

References ................................................................................................. 60

Appendix A: Review of Literature .......................................................... 73

Asthma ............................................................................................................. 73

Obesity and asthma ................................................................................. 73
Systemic inflammation and asthma ......................................................... 74
Adolescents and young adults with asthma ........................................... 75
Sleep disorders and their consequences ................................................. 77
Sleep and asthma ....................................................................................... 82

Sleep disturbances in asthma ............................................................... 82
Sleep duration and asthma ..................................................................... 83
The impact of sleep quality on patients with asthma ....................... 85

Section Four: Sleep Duration Trajectories and Systemic Inflammation in Young Adults:
Results from the National Longitudinal Study of Adolescent to Adult Health (Add Health) ................................................................. 39
Abstract .................................................................................................. 39
Introduction ............................................................................................. 40
Methods .................................................................................................. 40
Design ...................................................................................................... 40
Measures .................................................................................................. 41
High-sensitivity CRP (hs-CRP) ............................................................... 41
Sleep duration ......................................................................................... 41
Body Mass Index (BMI) ........................................................................... 42
Demographic variables ........................................................................... 42
Measures of socioeconomic status ....................................................... 42
Behavioral factors .................................................................................. 42
Illnesses and medications ..................................................................... 43
Statistical Analysis .................................................................................. 44
Results .................................................................................................... 45
Discussion ............................................................................................... 47
Conclusion ............................................................................................... 50
Tables and Figures ................................................................................... 51

Section Five: Conclusions and Recommendations .................................. 56

Results .................................................................................................... 26
Sleep duration and the risk of new-onset asthma .................................. 26
Sleep duration and the persistence of asthma ........................................ 27
Discussion ............................................................................................... 28
Conclusions ............................................................................................. 32
Tables and Figures ................................................................................... 33
## LIST OF TABLES

| Table 2.1 | Select Characteristics of adolescents participating in the Florida Youth Risk Behavior Survey (YRBS, 2009 – 2013) | 17 |
| Table 2.2 | Results of logistic regression analysis: Association between asthma and selected variables in the Florida Youth Risk Behavior Survey (YRBS, 2009-2013) | 19 |
| Table 2.3 | Results of the interaction analysis between sleep duration and BMI and their effect on asthma in the Florida Youth Risk Behavior Survey (YRBS, 2009 – 2013) | 19 |
| Table 3.1 | Characteristics of adolescents participating in the Add Health study, who were free of asthma in wave I, in total, and by sleep duration trajectory group | 34 |
| Table 3.2 | Results of the regression analysis examining the association between sleep duration trajectories from adolescents into young adulthood and the risk of new-onset asthma. Analysis of data from the Add Health study | 35 |
| Table 3.3 | Characteristics of participants in wave III of the ADD health study who had asthma in wave I | 37 |
| Table 3.4 | Association between short sleep duration trajectories and persistence of asthma into wave III in participants who had asthma at wave I of the add health study | 38 |
| Table 4.1 | Selected characteristics of participants in waves 3 & 4 of the National Longitudinal Study of Adolescent to Adult Health, in total and stratified by sleep duration trajectory group | 52 |
| Table 4.2 | Results of multivariate linear regression analysis for natural logarithm of CRP and sleep duration in waves 3 & 4 in the Add Health study (Regression coefficients and P-values) | 53 |
| Table 4.3 | Association between sleep in waves 3 & 4 and CRP levels greater than 3 mg/dl in the Add Health study (Odds ratios and 95% C.I.) | 54 |
| Table 4.4 | Results of sex-stratified regression analysis examining the association of sleep trajectory groups and continuous log hs-CRP as well as categorized CRP in the Add health study | 55 |
Table B.1 Sleep duration statistics by trajectory group in participants of waves 3 & 4 of the Add Health study .................................................................95

Table B.2 Results of multivariate linear regression analysis for natural logarithm of CRP and sleep duration in waves 3 & 4 in the Add Health study (Regression coefficients and P-values), after including CRP values greater than 10 mg/l ..........95

Table B.3 Association between sleep in waves 3 & 4 and CRP levels greater than 3 mg/dl in the Add Health study (Odds ratios and 95% C.I.) after inclusion of CRP values >10 mg/l........................................................................................................95
LIST OF FIGURES

Figure 2.1 Prevalence of asthma in each sleep duration category in adolescents Participating in the Florida Youth Risk Behavior Survey (YRBS) ......................18

Figure 3.1 Trajectories of sleep duration from adolescence into young adulthood, in participants without asthma at baseline. The Add Health study .........................33

Figure 3.2 Trajectories of sleep duration from waves I to III of the Add Health study, among participants with asthma in wave I ........................................36

Figure 4.1 Trajectories of sleep duration between waves 3 and 4 of the Add Health study ........51

Figure A.1 Asthma and comorbid conditions ........................................................................................................90

Figure B.1 Add health study design .....................................................................................................................94
ABSTRACT

This dissertation includes three studies that examined the impact of inadequate sleep duration in adolescents and young adults on asthma and systemic inflammation. We used data from the Florida Youth Risk Behavior Survey (YRBS), years 2009-2013, and from the National Longitudinal Study of Adolescent to Adult Health (Add health), which was conducted between 1994 and 2008.

The first study used data from 16,738 high school students participating in the Florida YRBS. We examined the cross-sectional association between sleep duration and asthma, and the interactive effects of sleep duration and BMI. We found that short and long sleep durations were associated with increased odds of current asthma. Compared with 7-8 hours of sleep per night, sleeping for <7 hours had an OR (95% CI) of 1.22 (1.07, 1.40), while sleeping for ≥ 9 hours had and OR of 1.31 (1.06, 1.63). We found a significant effect modification by BMI, with the associations between sleep duration and asthma mostly limited to overweight adolescents. Compared with normal weight students who sleep for 7-8 hours per night, those who are overweight and sleep for <7 hours or ≥ 9 hours have approximately twice the odds of having current asthma [OR= 1.75 (1.45, 2.11), and OR=2.00 (1.32, 3.02) respectively]. No significant associations were found in normal-weight adolescents.

The second study used data from 12,633 adolescents (age 13-19) participating in the National Longitudinal Study of Adolescent to Adult Health (Add health), and followed through 4 waves of interviews through their young adulthood (age 24-32). We constructed trajectories of
sleep duration through 4 waves of data for participants without asthma at wave I (n=11,016), and examined the association between sleep duration and the risk of asthma by young adulthood. Similarly, we constructed trajectories of sleep duration for participants with asthma at wave I (n=1,395) through 3 waves of data, and examined the association between sleep duration and persistence of asthma into young adulthood. Sleep trajectories in non-asthmatic participants showed that 13.8% of them had persistent short sleep duration, while 80.7% had adequate sleep durations from adolescence though young adulthood. Those with consistently short sleep had 1.59 times the risk of new onset asthma by age 32 (95% CI 1.12, 2.26), compared with consistently adequate sleepers. Among adolescents with asthma, 10.2% had consistently short sleep through age 24, while 81.2% had adequate sleep. Short sleepers were 2.35 times more likely than adequate sleepers to have their asthma symptoms persist into young adulthood (95% CI 1.12, 4.96).

The third study used data from waves III and IV of the Add health study, and examined the association between sleep trajectories over a 6-year follow-up in young adulthood, and the risk of elevated high sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation. Short sleep trajectories were associated with a significant increase in log-transformed hs-CRP (coefficient=0.11, p-value 0.03), and with a significant increase in the odds of having hs-CRP levels >3 mg/dl (OR=1.85, 95% CI 1.29, 2.67). The association was modified by sex, with the association between short sleep duration and hs-CRP limited to males. In males, both the continuous (coefficient 0.117, p-value=0.0362) and the categorized hs-CRP (OR= 2.21, 95% CI 1.48, 3.30) were significantly increased with short sleep durations, while no significant associations were seen in females with short sleep durations. By contrast, there was a significant increase in log hs-CRP in females with long sleep durations (coefficient=0.232, p-value=0.0296),
and a non-significant increase in the odds of having hs-CRP levels greater than 3 mg/dl (OR=1.48, 95% CI 0.75, 2.93), while there were no associations with long sleep duration in males.

The results of this dissertation research point to the detrimental effects of sleep loss on the bodies of adolescents and young adults. We found sleep loss to be associated with the incidence of asthma and its persistence, in addition to heightened systemic inflammation, which is a likely pathway that links sleep duration with the above outcomes. Our findings indicate that males are more susceptible to the effect of insufficient sleep on the risk of heightened inflammation, while females are more susceptible to the effects of long sleep durations. Interestingly, adolescents in the more recent YRBS study had shorter sleep durations than those who participated in the earlier Add health study. The prevalence of sleeping less than 7 hours was 16.5% in the Add health study (years 1994-1995), compared with 47.2% in the YRBS study (years 2009-2013), indicating a progressive decrease in the average sleep duration of adolescents.
SECTION 1
INTRODUCTION

“What people need to know is that asthma isn't a minor 'wheeze-disease.' It kills over five thousand people in America every year, and I could've been one of them.”

-Jackie Joyner-Kersee

Indeed, asthma is not a minor condition; it is common cause of morbidity and mortality in the United States and around the world. The prevalence of asthma has been increasing in the past few decades, as has the prevalence of obesity and both are causing significant morbidity. Modern lifestyle is at least partially responsible for the increase in prevalence of many chronic diseases. A life filled with stimulation as a result of technological advancements has a side effect of sleep deprivation, which was recently found to be associated with negative health outcomes. Although studies show that asthma leads to sleep disruption and poor sleep quality, few studies examined the impact of poor sleep quality or quantity on asthma, and their results were inconclusive. Sleep loss was found to be associated with systemic inflammation in cross-sectional and some longitudinal studies, which is likely to explain the relationship between sleep and many health conditions. However, this pathway is yet to be explored in terms of the association between sleep duration and asthma.

In this study, we propose to examine the association between sleep duration and asthma using two population-based data sets. We will utilize the Florida Youth Risk Behavior Survey (YRBS) to examine the association between sleep duration and asthma in Florida teenagers, and
whether BMI modifies this association. Using the National Longitudinal Study of Adolescent to Adult Health (Add Health), we will examine the association between trajectories of sleep duration from adolescence into young adulthood and the incidence and persistence of asthma, and the prevalence of heightened systemic inflammation in young adults, as well as the role of BMI and sex-related differences in these associations. The results of this study will pave the way for future recommendations and interventions that target sleep duration and quality, in order to reduce the impact and morbidity of asthma.

BACKGROUND AND SIGNIFICANCE

The prevalence of asthma has been increasing in recent decades, leading to a significant impact on the health and well-being of affected individuals, as well as the nation as a whole. In 2009—in the USA alone—asthma was responsible for 3,388 deaths; 479,300 hospitalizations; 14.4 million lost school days in children and 14.2 million lost workdays in adults; and an annual cost of $56.0 million. Asthma is the most common chronic disease in childhood, affecting approximately seven million children in USA. The prevalence of asthma has been on the rise. In USA, the number of persons with asthma increased between 2001 and 2010 by 2.9% each year, from 20.3 million persons in 2001 to 25.7 million persons in 2010. Current asthma prevalence increased at a rate of 1.5% per year, to a prevalence of 8.4% in 2010. However, the number of deaths from asthma declined from 2001 (4,269) to 2009 (3,388) at a rate of 3.3% per year. The increase in asthma prevalence and its morbidity prompted many studies of the risk factors as well as preventive measures that may reduce its morbidity and impact. Studies show that asthma is the result of interaction of host and environmental factors that contribute to the development of the disease as well as aggravation of its symptoms. Obesity recently received much attention as potential risk factors for many chronic diseases, including asthma, as it is associated with an
increased risk of asthma and with poor asthma control. Many mechanisms were proposed to explain this association, most prominently through the inflammatory pathway. This pathway has also gained a lot of attention recently as a possible explanation of the association between sleep loss and obesity, heart disease, and other chronic illnesses.

Chronic sleep loss is a prevalent public health problem that, along with other sleep disorders, affect as many as 70 million Americans, leading to an annual cost of $16 billion in healthcare expenses and $50 billion in lost productivity. Healthy People 2020 includes an objective to increase proportion of students in grades 9 through 12 who get sufficient sleep to 33.1%, from a baseline of 30.9%, and increase the proportion of adults who obtain sufficient sleep from 69.6% to 70.8%. Chronic sleep loss is linked with an increased risk of obesity, cardiovascular diseases, metabolic syndrome, poor cognitive function, and mortality. Systemic inflammation is one of the pathways proposed to explain these associations. However, the majority of studies examining the association between sleep loss and inflammation have been cross sectional, with few longitudinal studies with inconsistent findings.

Asthma is associated with poor sleep quality, mainly due to nocturnal symptoms. However, even those who do not have nocturnal symptoms still suffer from sleep disturbances, and those disturbances are associated with worse subsequent symptoms and quality of life suggesting that the association between sleep loss and asthma is in fact bi-directional. Experimental evidence of the impact of improved sleep duration on asthma morbidity came from a pilot study by Meltzer et al. who found that sleep extension in teens with asthma led to an improvement in symptoms and lung function. Likewise, Mastronade et al. found that improved sleep quality correlated with improvements in asthma control and quality of life. Longitudinal studies provided clues into the possible association between sleep loss and asthma, however
their methods and results were inconsistent. No longitudinal study to date has examined the impact of sleep trajectories from adolescence into young adulthood on the risk or persistence of asthma or on the risk of systemic inflammation in young adulthood.

Adolescents with asthma are a unique population. Adolescence is a period of physical and psychosocial changes that affect the health and well-being of teenagers. Overall, adolescents with asthma are at increased risk for asthma morbidity and death as the adolescent becomes more independent and takes control of his/her asthma management. Non-adherence to medical regimens as well as lifestyle factors contribute to the increase in asthma morbidity.\(^{27}\) Moreover, adolescents frequently report insufficient sleep.\(^ {11}\) Unfortunately, studies of the association between sleep and asthma in adolescents and young adults are lacking, and none has looked at the longitudinal effects of cumulative sleep loss in adolescence and young adulthood on subsequent systemic inflammation and asthma incidence and prevalence in young adulthood.

This dissertation encompasses three studies that will use different populations and data, and aim to shed the light on the association of sleep loss, inflammation, and asthma. The findings of this research may pave the way for future studies on sleep-related interventions that may help reduce the morbidity of asthma as well as the economic burden associated with it.

**SPECIFIC AIMS AND OBJECTIVES**

The purpose of this study is to evaluate the association between sleep loss and asthma as well as inflammation, accounting for the roles of BMI and sex. We plan to attain this goal by pursuing the following specific aims:

**Aim 1. To examine the association between sleep duration and asthma in adolescents, and whether BMI modifies this association**
**Objective 1.1:** To explore the association between sleep duration and the presence of asthma in high school students in Florida.

**Hypothesis 1.1:** Our hypothesis is that inappropriate sleep duration in adolescents is associated with a higher prevalence of asthma than is optimal sleep duration.

**Objective 1.2:** To examine whether BMI modifies the above association between sleep duration and asthma.

**Hypothesis 1.2:** We hypothesize a synergistic interaction between inappropriate sleep duration and BMI in explaining prevalent asthma.

**Aim 2. To determine the impact of sleep duration trajectories from adolescence to young adulthood on the risk and persistence of asthma in young adulthood.**

**Objective 2.1:** To examine the association between inappropriate sleep duration trajectories from adolescence to young adulthood on the incidence of asthma by age 24-32 in non-asthmatic adolescents.

**Hypothesis 2.1:** Non-asthmatic Adolescents who have persistent short or long sleep durations are more likely to develop asthma by young adulthood (age 24-32) than those with optimal sleep duration.

**Objective 2.2:** To examine the association between sleep duration trajectories from adolescence into young adulthood and persistence of asthma into young adulthood, in adolescents who have asthma.

**Hypothesis 2.2:** Asthmatic adolescents with persistent short or long sleep duration are more likely to have their asthma persist into young adulthood (age 18-24) compared with adolescents with optimal sleep duration.
Aim 3. To examine the association between sleep duration trajectories and systemic inflammation in young adulthood, and the potential interaction with sex.

Objective 3.1: To quantify the association between sleep duration trajectories throughout young adulthood and hs-CRP in young adulthood.

Hypothesis 3.1: Young adults with short or long sleep duration are more likely to have elevated hs-CRP, compared with young adults with optimal sleep duration.

Objective 3.2: To examine the effect of sex on the association between young adult sleep duration trajectories and elevated hs-CRP.

Hypothesis 3.2: Female young adults with short or long sleep duration are more likely than their male counterparts to have elevated hs-CRP in their young adulthood.
SECTION 2
SLEEP DURATION, OBESITY, AND ASTHMA, IN FLORIDA ADOLESCENTS: ANALYSIS OF DATA FROM THE FLORIDA YOUTH RISK BEHAVIOR SURVEY (2009-2013)

ABSTRACT

Purpose: To examine the association between sleep duration and asthma among Florida high school students, and determine whether body mass index (BMI) is an effect modifier of this association.

Methods: This is a cross-sectional analysis that included 16,728 high school students, participating in the Florida Youth Risk Behavior Survey (2009, 2011, and 2013). We used logistic regression to obtain odds ratios (OR) and 95% confidence intervals (CI) of the association between sleep duration and current asthma, after controlling for potential confounders, followed by analyzing the interaction between sleep duration and BMI.

Results: Both short and long sleep durations were associated with increased odds of current asthma. Compared with 7-8 hours of sleep per night, sleeping for <7 hours had an OR (95% CI) of 1.22 (1.07, 1.40), while sleeping for ≥ 9 hours had an OR of 1.31 (1.06, 1.63). We found a significant effect modification by BMI, with the associations between sleep duration and asthma mostly limited to overweight adolescents. Compared with normal weight students who sleep for 7-8 hours per night, those who are overweight and sleep for <7 hours or ≥ 9 hours have approximately twice the odds of having current asthma [OR= 1.75 (1.45, 2.11), and OR=2.00 (1.32, 3.02) respectively]. No significant associations were found in normal-weight adolescents.
Conclusion: Sleep durations that are too short or too long are associated with asthma in adolescents. However, these associations are modified by BMI. Both associations of short and long sleep durations with asthma are statistically significant in overweight adolescents but weaker and statistically non-significant in those with normal BMI.

INTRODUCTION

The prevalence of asthma has been increasing in recent decades, leading to a significant morbidity, mortality, and economic impact.1 Meanwhile, the average sleep duration of Americans has declined by 20% in the past century.28 Half of high school students participating in the 2007 National Youth Risk Behavior Survey reporting short sleep duration (6-7 hours per night), and another 14.8% of males and 16.9% of females reporting very short sleep durations (5 hours or less).29

Asthma is known to be associated with poor quality sleep, mainly due to nocturnal symptoms.30 However, its association with sleep duration is less clear. Some studies have found that sleep durations among asthmatic adults,31–33 and children34,35 are generally shorter than sleep durations in those without asthma, while other studies have not found such differences in adolescents22 or children.36,37 Some of these studies relied on parental report of adolescent sleep duration, which may not accurately reflect actual sleep duration, as parents tend to report earlier bed times and give an idealized version of their adolescents’ sleep habits.38

Short or long sleep durations may increase the risk of obesity, which in turn is associated with an increase in risk of asthma as well as with poor asthma control. Different mechanisms have been proposed to explain these associations including neuroendocrine and hormonal mechanisms, as well as activation of chronic inflammatory responses.8 It is therefore possible, at least in theory, that inadequate sleep durations may affect the risk and/or outcomes of asthma through the
inflammatory pathway. It is also possible that inadequate sleep will interact with obesity to cause an even greater increase in the risk of asthma. With the increasing prevalence of overweight and obesity, knowing whether those affected are more susceptible to the effects of sleep loss will help target interventions and channel resources efficiently. No studies to date have examined the effect of sleep duration on asthma and the potential effect modification by BMI.

The purpose of this study is to examine the association between sleep duration and asthma among Florida high school students, and determine whether body mass index (BMI) is an effect modifier of this association.

METHODS

Population

The Florida Youth Risk Behavior Survey (YRBS) is statewide, school-based confidential survey of Florida’s public high school students, and is administered on odd years with the purpose of monitoring priority health-risk behaviors that contribute substantially to the leading causes of death, disability, and social problems among youth, which contribute to patterns in adulthood. A detailed description of the survey design and instruments can be found at Florida Department of Health’s website. YRBS uses a two-stage cluster probability sampling design. First, a random sample of public high schools is selected for participation in the survey. Second, within each selected school, a random sample of classrooms is selected, and all students in those classes are invited to participate in the survey. The responses of the survey participants are weighted to be representative of all Florida public high school students. This analysis uses data from three years of YRBS, 2009; 2011; and 2013

The 2009 survey was completed by 5,664 students with an overall response rate of 71%, the 2011 survey was completed by 6,212 students with an overall response rate of 75%, and the
2013 survey was completed by 6,089 students, with an overall response rate of 69%. For this analysis, we included all participants in the survey, excluding those who had missing values for sleep duration or asthma (N=16,626)

**Measures**

YRBS collects data by administering a survey to students. The survey includes demographic questions as well as self-reported height and weight, and questions on a variety of behavioral, physical activity, dietary, health and sleep topics. For the purpose of this analysis we will include the following measures:

*Sleep duration:* Students were asked: “On an average school night, how many hours of sleep do you get?” Answer choices included 4 hours or less, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, and 10 hours or more. We categorized the responses based on the recommendations of the National Sleep Foundation for this age group,\(^{40}\) into short duration (less than 7 hours), normal duration (7-8 hours) and long duration (9 hours or more). Our choice of a lower cutoff for long sleep duration (9 hours or more) was based on the low prevalence of long sleepers in our study sample (2.1% slept more than 9 hours).

*Asthma:* Students were asked two questions related to asthma. “Has a doctor or nurse ever told you that you have asthma?” (Yes/No/Not sure), and “Do you still have asthma?” (Yes/No/Not sure). For the purpose of this analysis, students who answered “Yes” to both questions were considered to have current asthma.

*BMI:* The datasets included pre-calculated BMI percentiles based on self-reported height and weight. They also included two dichotomous (yes/no) variables labeled “overweight” and “obese” for students who meet the cutoff according to the CDC guidelines (overweight: at or above 85\(^{th}\) percentile for age and sex but less than the 95\(^{th}\) percentile, Obese: at or above the 95\(^{th}\)
percentiles). For the purpose of this analysis, we considered students labeled as “overweight” or “obese” to be overweight. We classified students who were neither overweight nor obese to be of normal weight. This category also includes underweight teenagers, which account for 3.5% of the study population.

Covariates:

- Demographic variables: Age (in years), sex, race/ethnicity (Hispanic or Latino, Asian, Black or African American, White, Other)
- Behavioral variables: Smoking (on one or more days in the past 30 days), alcohol use (on one or more days in the past 30 days), marijuana use (on one or more days in the past 30 days), and physical activity (Active=60 or more minutes per day at least five days a week).

Data analysis

Statistical analysis was carried out using SAS 9.4 software, using procedures that accommodate the weighted sampling design of YRBS. We combined the three datasets according to the CDC guidelines: (http://www.cdc.gov/healthyyouth/yrbs/pdf/yrbs_combining_data.pdf), then checked for missing data. We calculated baseline statistics for the whole sample and separately for adolescents with current asthma and those without asthma, and used chi-square to test for the difference. Logistic regression was used to estimate the strength of association between sleep duration and asthma, first with bivariate model, then with multivariate analysis controlling for potential confounders. The first model included age, gender, and race. The second model included, in addition to the variables included in model 1, behavioral factors (smoking and marijuana). The third model included variables in model 2 in addition to BMI and physical activity, as these may be
intervening variables. Model four was similar to model 3 with the addition of the interaction term (sleep duration*BMI category) to check for significant interaction. From this model we will report odds ratios for each combination of sleep duration and BMI, compared with the reference category of normal sleep duration-normal weight.

RESULTS

The analysis included 16,626 High school students, 1668 (9.86%) of whom had current asthma (Table 2.1). Compared with adolescents without asthma, those with current asthma were generally younger, more likely to be female, less likely to be white (42.6% vs. 45.3%, P=0.0175), and more likely to use marijuana and drink alcohol. They were also significantly more likely to be overweight (30.9% vs. 24.9%, P<0.0001).

The distribution of sleep duration (Table 2.1) showed that 47% of participants slept for 6 hours or less per night, while only 25% got the recommended 8 hours or more of sleep. Sleep duration differed significantly between asthmatic and non-asthmatic teenagers (P<0.0001), with asthmatics more likely to sleep for less than seven hours per night compared with non-asthmatics (51.3% vs. 46.6%)

Figure 1 shows the prevalence of asthma in each sleep duration category. Short sleep durations (less than 6 hours) and long durations (more than 8 hours) show an increase in the prevalence of asthma compared with 6-8 hours of sleep per night. The lowest prevalence of asthma (8.8%) was seen in those who sleep for 7 hours per night on average, while the highest prevalence (13.1%) was in those who sleep for 4 hours or less.

We performed bivariate followed by multivariate logistic regression using SAS 9.4, PROC SURVEYLOGISTIC, which takes into account the complex sampling design. We used the categorized sleep duration as a main exposure and current asthma as the outcome. Results of the
multivariate analysis are presented in Table 2.2. Both short (6 hours or less) and long (9 hours or more) sleep durations were significantly associated with current asthma, compared with 7-8 hours of sleep, and the associations remained significant after controlling for potential confounders (OR for short sleep duration=1.22, 95% CI 1.06, 1.38, OR for long sleep duration = 1.31, 95% CI 1.06, 1.62).

Other variables that were significantly associated with asthma in the study population include being overweight, Black race, and female gender. The interaction term for short sleep and overweight was statistically significant (coefficient=0.34, P-value= 0.0172). Interaction term for long sleep and BMI was not significant.

Interaction analysis (Table 2.3) shows that, compared with normal weight teens who sleep for 7-8 hours per night, those who were overweight and slept for less than 7 hours had 1.75 times the odds of having asthma (95% CI 1.45, 2.11), while those who slept for 9 hours or more had OR of 2.00 (95% CI 1.32, 3.02). Relative Excess Risk due to Interaction (RERI) for short sleep and overweight was 0.52 (95% CI 0.07, 0.98), and for long sleep and overweight=0.70 (95% CI -0.10, 1.50), suggesting a statistically-significant positive additive interaction for short sleep duration and overweight, and a positive additive interaction for long sleep duration and overweight, that did not reach statistical significance.

DISCUSSION

In this large cross-sectional survey of high school students in Florida (N=16,626), the prevalence of asthma was 9.9%, which is very close to the prevalence reported by CDC (2013) for the 15-17 year age group in the US (10.2%, 95% CI 9.1% - 11.3%). Our results demonstrated the association between sleep duration that are too short or too long and the increased prevalence of current asthma. Effect modification by BMI was observed in the interaction analysis. The
associations between short and long sleep durations and asthma were only significant when combined with being overweight. Relative Excess Risk due to Interaction (RERI) was statistically significant only for the short sleep duration and overweight, while it was non-significant in the long duration-overweight group, despite this group having the largest odds ratio. The non-significant RERI may be due in part to the small sample size in the long sleep duration-overweight group (n=229).

Our findings on the association between short sleep duration and asthma are consistent with those found by Jensen at el.\textsuperscript{35} in children and by Fitzpatrick et al. and Vir et al. in adults.\textsuperscript{31,32} Our results on long sleep duration were matched by Chugh et al., who found that sleep duration in asthmatics is significantly longer than it is in non-asthmatics.\textsuperscript{42}

The combination of asthma, sleep duration, and BMI has been studied previously by Teodorescu et al. and by Fedele et al. However, the former examined the combined effect of asthma and short sleep duration on obesity,\textsuperscript{43} while the latter examined the combined effect of obesity and asthma on sleep duration.\textsuperscript{44} Our study sought to complete the triangle by examining the combined effect of obesity and short sleep duration on asthma. Additionally, we also examined the role of long sleep duration, alone and combined with obesity. We have not been able to find another study that examined this combination of interactions and associations.

The National Sleep Foundation recommends that teenagers aged 14-17 sleep for 8-10 hours per night, with 7 hours considered appropriate for some teenagers. However, in our study population only 25% slept for 8 hours or more and 53% slept for 7 hours or more. We selected our cut-off values for short sleep duration based on the lower recommendation, and our long sleep cutoff based on the distribution of sleep duration in our sample.
Major limitations of this study include the reliance of self-report of all relevant measures. Although the asthma question in YRBS has not been validated, the CDC has conducted reliability tests on the national YRBS survey as a whole, and found that three fourths of the questions had substantial or higher reliability (kappa > 0.6). Furthermore, a study of adult self-report of asthma found a substantial agreement (kappa > 0.6) between self-report of asthma diagnosis and medical records.\textsuperscript{45} Moreover, a systematic review by Toren et. al. found that self-report of asthma diagnosis has a mean sensitivity of 68\% (range 48-100) and a mean specificity of 94\% (range 78-100).\textsuperscript{46} As for self-report of BMI, the CDC has tested the validity and reliability of the height and weight questions on the national YRBS, which are identical to the questions on Florida YRBS. They found the self-reported values to be substantially reliable, but compared with measured height and weight, students over-reported their height by 2.7 inches on average, and underreported their weight by 3.5 pounds on average, which indicates the possibility of an underestimation of overweight and obesity in the study population.\textsuperscript{47} Studies of sleep duration found self-report to be valid for large-scale studies of habitual sleep duration, and correspond well to objective measures such as actigraphy.\textsuperscript{48–50}

The second limitation is that the survey included only public school children. Therefore, we may not be able to generalize the results to high-school aged youth who are not enrolled in schools, or to private school students (around 11\%). An additional limitation is our inability to control for socioeconomic status, which was not measured in the YRBS. Lastly, the cross-sectional nature of this study does not allow for determination of direction of association or for inference regarding causality. Nevertheless, it constitutes a stepping stone that will lead further longitudinal studies into the path of exploring the complex relationships among sleep duration, BMI, and asthma.
Our study has many strengths, including the large sample size, the cluster sampling design that makes for a representative sample, and the standardized survey instruments. Sleep duration was self-reported by the adolescents, which is more accurate than parental reports used in other studies.\(^5\) Furthermore, the research topic is innovative given that very few studies have examined the complex association among sleep duration, obesity, and asthma in adolescents.

**CONCLUSION**

The current study shows that a large proportion of adolescents sleep less than the recommended amount for their age. It also suggests that sleep durations that are too short or too long are associated with an increased prevalence of asthma in teenagers and that those who are overweight are more susceptible to this effect. Sufficient sleep is important for the health and well-being of teenagers. Moreover, it is known to be associated with increased risk of obesity. Sleep interventions may help decrease the risk of persistent asthma in adolescents in addition to improving their weight status. Our results indicate that special attention and customized interventions must be directed at overweight adolescents, who may benefit for sleep interventions. Further studies are needed to validate the results of this study and to establish the direction of the above associations.
### Table 2.1: Select Characteristics of adolescents participating in the Florida Youth Risk Behavior Survey (YRBS, 2009 – 2013)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample (N=16626)</th>
<th>With current asthma (N=1668, 9.86%)</th>
<th>Without current asthma (N=15060, 90.14%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>10.2%</td>
<td>10.8%</td>
<td>10.0%</td>
<td>0.5329</td>
</tr>
<tr>
<td>15-16</td>
<td>50.1%</td>
<td>49.9%</td>
<td>49.9%</td>
<td></td>
</tr>
<tr>
<td>&gt;16</td>
<td>39.7%</td>
<td>39.3%</td>
<td>39.3%</td>
<td></td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>49.7%</td>
<td>53.1%</td>
<td>49.3%</td>
<td>P=0.0020</td>
</tr>
<tr>
<td>Race/Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45.8%</td>
<td>43.6%</td>
<td>46.7%</td>
<td>P=0.0426</td>
</tr>
<tr>
<td>Black</td>
<td>22.8%</td>
<td>24.8%</td>
<td>21.9%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>25.8%</td>
<td>25.6%</td>
<td>25.8%</td>
<td></td>
</tr>
<tr>
<td>Other or Multiple</td>
<td>5.6%</td>
<td>6%</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Sleep duration</td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>&lt;=4 hours</td>
<td>9%</td>
<td>12.3%</td>
<td>8.6%</td>
<td></td>
</tr>
<tr>
<td>5 hours</td>
<td>14.1%</td>
<td>16.4%</td>
<td>13.8%</td>
<td></td>
</tr>
<tr>
<td>6 hours</td>
<td>24.1%</td>
<td>22.6%</td>
<td>24.2%</td>
<td></td>
</tr>
<tr>
<td>7 hours</td>
<td>27.7%</td>
<td>24.4%</td>
<td>28.1%</td>
<td></td>
</tr>
<tr>
<td>8 hours</td>
<td>18.5%</td>
<td>17.0%</td>
<td>18.7%</td>
<td></td>
</tr>
<tr>
<td>9 hours</td>
<td>4.5%</td>
<td>5.1%</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 hours</td>
<td>2.1%</td>
<td>2.3%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>13.5%</td>
<td>14.8%</td>
<td>13.3%</td>
<td>P=0.0995</td>
</tr>
<tr>
<td>Alcohol</td>
<td>35.9%</td>
<td>38.6%</td>
<td>35.6%</td>
<td>P=0.0208</td>
</tr>
<tr>
<td>Marijuana</td>
<td>36.6%</td>
<td>40.3%</td>
<td>36.2%</td>
<td>P=0.0002</td>
</tr>
<tr>
<td>Physically active</td>
<td>42.4%</td>
<td>41.7%</td>
<td>42.5%</td>
<td>P=0.6086</td>
</tr>
<tr>
<td>BMI (% Overweight)</td>
<td>25.5%</td>
<td>30.9%</td>
<td>24.9%</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure 2.1: Prevalence of asthma in each sleep duration category in adolescents participating in the Florida Youth Risk Behavior Survey (YRBS)
Table 2.2: Results of logistic regression analysis: Association between asthma and selected variables in the Florida Youth Risk Behavior Survey (YRBS, 2009-2013)

<table>
<thead>
<tr>
<th>Sleep duration categories</th>
<th>Unadjusted OR (95% CI)</th>
<th>Fully adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (≤ 6 hours)</td>
<td>1.24 (1.12, 1.38)</td>
<td>1.22 (1.07, 1.40)</td>
</tr>
<tr>
<td>Good (7-8 hours)</td>
<td>Ref</td>
<td>1.31 (1.06, 1.63)</td>
</tr>
<tr>
<td>Long (≥ 9 hours)</td>
<td>1.26 (1.01, 1.57)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>1.20 (1.05, 1.35)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td></td>
<td>1.16 (0.87, 1.53)</td>
</tr>
<tr>
<td>15-17</td>
<td></td>
<td>1.05 (0.89, 1.23)</td>
</tr>
<tr>
<td>&gt;17</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>1.19 (1.00, 1.40)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>0.84 (0.66, 1.05)</td>
</tr>
<tr>
<td>Other or multiple</td>
<td></td>
<td>1.11 (0.94, 1.31)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>marijuana</td>
<td></td>
<td>1.08 (0.95, 1.21)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td>1.41 (1.22, 1.62)</td>
</tr>
</tbody>
</table>

*Bolded odds ratios are statistically significant at the 95% confidence level

Table 2.3: Results of the interaction analysis between sleep duration and BMI and their effect on asthma in the Florida Youth Risk Behavior Survey (YRBS, 2009 – 2013)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Normal weight Adjusted OR* (95% CI)</th>
<th>Overweight Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 hours</td>
<td>1.09 (0.94, 1.28)</td>
<td>1.75 (1.45, 2.11)</td>
</tr>
<tr>
<td>7-8 hours</td>
<td>1.00 (REF)</td>
<td>1.14 (0.92, 1.42)</td>
</tr>
<tr>
<td>≥9 hours</td>
<td>1.16 (0.88, 1.53)</td>
<td>2.00 (1.32, 3.02)</td>
</tr>
</tbody>
</table>

Measure of effect modification on additive scale between short sleep and overweight (95% CI): **RERI = 0.52 (0.07, 0.98)**

Measure of effect modification on additive scale between long sleep and overweight (95% CI): **RERI = 0.70 (-0.10, 1.50)**

*ORs adjusted for age, sex, race-ethnicity, smoking, alcohol, marijuana, physical activity

Bolded numbers are statistically significant at the 95% confidence level
SECTION 3
SLEEP DURATION TRAJECTORIES AND ASTHMA
FROM ADOLESCENCE TO YOUNG ADULTHOOD

ABSTRACT

Objectives: This study aims to examine the impact of sleep duration trajectories from adolescence into young adulthood on the risk and persistence of asthma into young adulthood.

Methods: Using data from 12,633 participants in the National Longitudinal Study of Adolescent to Adult Health (Add Health), we constructed trajectories of sleep duration for participants starting in adolescence (age 13-18) to young adulthood (age 24-32). We constructed separate trajectories for participants with asthma and for those without asthma and used them to examine the impact of sleep duration patterns on the risk of new-onset asthma, and persistence of asthma into young adulthood, respectively, after adjusting for potential confounders.

Results: Sleep trajectories in non-asthmatic participants showed that 13.8% of them had persistent short sleep duration, while 80.7% had adequate sleep durations from adolescence though young adulthood. Those with consistently short sleep had 1.59 times the risk of new onset asthma by age 32 (95% CI 1.12, 2.26), compared with consistently adequate sleepers. Among adolescents with asthma, 10.2% had consistently short sleep through age 24, while 81.2% had adequate sleep. Short sleepers were 2.35 times more likely than adequate sleepers to have their asthma symptoms persist into young adulthood (95% CI 1.12, 4.96).
**Conclusion:** Persistent short sleep duration increases the risk of new-onset asthma in non-asthmatic adolescents, and the likelihood that those will asthma will continue to suffer from asthma symptoms into their young adulthood.

**INTRODUCTION**

The prevalence of asthma has been increasing in recent decades, leading to significant morbidity, mortality, and economic impact. In 2009, in the USA alone, asthma was responsible for 3,388 deaths; 479,300 hospitalizations; 14.4 million lost school days in children and 14.2 million lost workdays in adults; and an annual cost of $56.0 million.¹ The prevalence of current asthma in USA increased between 2001 and 2010 at a rate of 1.5% per year, to a prevalence of 8.4% in 2010³ Despite many studies seeking to identify risk factors and effective interventions, the prevalence of asthma is yet to decline. What makes asthma particularly challenging, is its multifactorial nature, with many risk factors, including heredity; obesity; and environmental exposures, playing a role in its pathogenesis.⁵² It is important to identify modifiable risk factors that may impact the risk or burden of asthma. Sleep duration is one such factor that deserves attention. Growing evidence suggest that lack of sleep, is linked to many deleterious health conditions, such as obesity, cardiovascular diseases, and diabetes.¹¹ The most likely mechanisms for these associations is through activation of systemic inflammation.⁸,⁵³,⁵⁴ Asthma is a chronic disease with a underlying inflammatory component, therefore it is possible, at least in theory, that chronic sleep deprivation may influence the risk of asthma through the same pathway.

Asthma is known to cause sleep disruption, leading to reduced quality of sleep,³⁴,⁵⁵ and some cross sectional studies found it to be associated with shorter duration of sleep.³³–³⁵ However, it is unclear whether the association is bidirectional, or whether sleep quantity may play a role in the pathogenesis of asthma. The few longitudinal studies that examined the
association between sleep and asthma mostly focused on sleep quality rather than duration, with some of them finding an association with the risk or morbidity of asthma.\textsuperscript{13,23,24} The only study we found that examined the impact of sleep duration in childhood on the risk of asthma in adolescence, with non-significant results, measured sleep duration by parental perception that the child sleeps less than other children, rather than the actual duration of sleep.\textsuperscript{26} More recently, a pilot clinical trial by Meltzer et al. found that a two-week experimental sleep extension in adolescents with asthma lead to an improvement in their asthma symptoms, indicating that sleep duration can affect asthma morbidity and control.\textsuperscript{56}

This study examines the impact of sleep duration trajectories from adolescence to young adulthood on the diagnosis of asthma in adulthood and on the persistence of asthma from adolescence into young adulthood.

METHODS

Design

We used data from the National Longitudinal Study of Adolescent to Adult Health (ADD Health), which is a nationally representative school-based, longitudinal study that used clustered sampling design to enroll and follow participants from adolescence through young adulthood. During the first wave of interviews, between April 1995 and December 1995, a total 20,745 adolescents in in grades 7-12 completed in-home interviews and 17,713 parents completed the parent questionnaires. The second follow up period (Waves II, April 1996 -August 1996) included 14,738 adolescent in-home interviews, while the third follow-up period (wave III, July 2001–April 2002) included 15,197 young adult (age 18-24) in-home Interviews. The fourth follow-up period (wave IV, January 2008–February 2009) consisted of 15,701 adult (age 24-32)
in-home interviews and biomarker collections. More details regarding the design can be found at the add health website.\textsuperscript{57}

This analysis included all subjects enrolled in the study who have answered the questions about sleep duration and asthma, and who completed interviews in all four waves. Subjects whose parents said they were “mentally retarded” were excluded (n= 196). We also excluded participants under 13 years of age as the sleep needs of this age group differ than older adolescents. Our final analysis sample included 12,633 participants who had complete data for sleep and asthma.

**Measures**

*Sleep durations* in waves I & II were measured by the respondent’s answer to the question “How many hours of sleep do you usually get”. In wave III the respondents were asked about the time they go to bed and the time they get up on work/school days and non-work days. We calculated the average sleep duration by assigning weights of 5/7 to work nights and 2/7 to non-work night.

*Asthma* at baseline was measured by the parents’ response to the question “does (your child) have asthma?” In wave III respondents were asked “have you ever been diagnosed with asthma?”, and in wave IV they were asked “have you ever been diagnosed with: Asthma, emphysema, or chronic bronchitis?” Those whose parents answered “no” at baseline and who answered “yes” in wave III or in wave IV were considered to have new-onset asthma by wave IV. Persistence of asthma was measured by the use of prescription medications for asthma in the 12 months prior to the wave III interview, in a participant who (1) answered “yes” to the question “have you ever been diagnosed with asthma” in wave III, and (2) whose parents indicated that he/she had current asthma at wave I.
Covariates included in the analysis were age, sex, race, parental income, pubertal development, BMI, smoking, alcohol, family history of asthma, and physical activity.

Race/ethnicity was categorized as Hispanic, Non-Hispanic White, Non-Hispanic Black, and other.

BMI was calculated from self-reported height and weight. We calculated BMI percentiles and categorized participants as Underweight: BMI < 5%; Normal weight: 5 ≤ BMI < 85%; Overweight: 85% ≤ BMI < 95%; and Obese: BMI ≥95%. For adults aged 20 or above, BMI categories were Underweight: BMI < 18.5; Normal weight: 18.5 ≤ BMI ≤ 24.9; Overweight: 25 ≤ BMI ≤ 29.9; and Obese: BMI ≥ 30. For the purpose of the analysis, we combined the underweight and normal weight into one category called “normal” and combined the overweight and obese into one category called “overweight”.

Family income: After considering family size, we categorized family income as (1) less than 150% of the poverty threshold; (2) from 150% to under 250% of the poverty threshold; (3) from 250% to under 400% of the poverty threshold; and (4) more than 400% of the poverty threshold.

Parental education was measured as the highest education level of any of the two parents. We categorized the education variable as: (1) less than high school; (2) high school degree or equivalent; (3) some post-secondary education; (4) college degree; and (5) post-graduate degree.

Physical activity: We constructed an activity variable as the sum of times per week the participant engaged in certain activities (roller-blading, roller-skating, skateboarding, bicycling, active sports, and different types of exercise). Participants who received a score of 5-9 were considered physically active. We constructed measures of physical activity for each of the four waves.
A Puberty index was constructed for males and another for female. Each index is the sum of scores of each of the five questions the adolescent answered regarding their physical development. A median score was calculated for males and females, and each participant was categorized as “below the median” and “at or above the median” at baseline.

Smoking was measured based on the participant’s response to the question “During the past 30 days, on how many days did you smoke cigarettes?” Those who smoked on one or more days were considered smokers, as per the definition of the National Survey on Drug Use and Health (NSDUH)

Alcohol was measured by the participant’s response to the question “During the past 12 months, on how many days did you drink alcohol?” Those who said they drank once a month or more were considered drinkers, according to the definition of the NSDUH.

Statistical Analysis

All analyses were performed using SAS 9.4 software. We divided the sample into two groups based on asthma diagnosis at wave I, then we identified trajectories of sleep duration separately for each group using PROC TRAJ, which uses the semiparametric group-based mixture model described by Nagin. This model estimates sleep trajectories for each individual and classifies individuals with similar sleep duration patterns into different trajectory groups. We tried a number of models identifying two to six trajectory groups, and selected the optimal number of groups based on the best fitting model for the data that produced the lowest value for the Bayesian Information Criterion (BIC), while preserving parsimony. Additionally, we used entropy to ensure classification accuracy, for the selected trajectories. Consequently, we identified four groups of sleep duration trajectories from waves I to IV for the asthma-free sample, and four groups of sleep trajectories from waves I to III for the asthma sample. Each
participant was assigned into the group to which he or she had the highest probability of belonging.

We performed descriptive analysis using SAS procedures SURVEYFREQ and SUREVEYMEAN that take into account the complex sampling design. Then we used SAS GENMOD procedure for the longitudinal regression analysis, for the new-onset asthma in asthma-free participants, and for the persistence of asthma in participants with current asthma. We started with an unadjusted model for each outcome, and progressed into the multivariate model, calculating relative risk and 95% confidence intervals for each outcome.

RESULTS

The study population included 12,633 adolescents, 12.8% of whom had current asthma. The asthma group included 1,617 adolescents and the asthma-free group was made up of 11,016 adolescents.

Sleep duration and the risk of new-onset asthma

Trajectories of sleep duration from wave I-IV in the asthma-free group are shown in figure 3.1. The sleep trajectories model with the best fit included four groups: Consistently short, consistently adequate, initially short-adequate but increasing, and initially adequate but decreasing. Out of all participants, 13.8% had consistently short sleep duration (mean sleep duration in the 4 waves ranged from 5.9 – 6.4, median duration 5.4-6.5), while 80.7% had consistently adequate sleep duration (mean durations in the four waves ranged from 7.7- 8.0 hours, median duration 7.3-7.9). Confidence intervals for mean and median durations in these two groups did not overlap in any wave. The four trajectory model had an entropy of 0.76, and the mean posterior probability for each group ranged from 74% to 89%.
There were significant differences among adolescents belonging into different trajectory groups in terms of a number of key variables (Table 3.1). Compared with adolescents in the consistently adequate group, those in the consistently short group were older, more likely to Black, overweight, and to smoke, drink, be physically active, and at a more advanced puberty stage (Table 3.1). Those in the initially short but increasing duration group were the youngest, most likely to be Black, female, overweight, and have low SES, and a family history of asthma. However, they were the least likely to smoke or drink. The long-decreasing duration group had the most females (almost the same as the short-increasing group), and had the lowest parental education levels. (Table 3.1)

During the study period, 935 new cases of asthma were diagnosed among participants who did not have asthma in wave I (incidence rate=1.04% per year). Table 3.2 shows the results of the longitudinal association between sleep trajectory groups and risk of new-onset asthma. Compared with the consistently adequate sleep group, the group with consistently short sleep had an increased risk for asthma (RR=1.40, 95% CI 1.06, 1.86) which persisted after adjusting for all relevant covariates (RR= 1.59, 95% CI 1.12, 2.26). The long-decreasing sleep group showed a non-significant increase in risk (adjusted RR=1.53, 95% CI 0.90-2.62), while the short-increasing sleep group did not show an association with asthma. Other predictors of asthma risk included female sex (RR=1.56, 95% CI 1.24, 1.92); family history of asthma (RR=2.02, 95% CI 1.53, 2.66); smoking (RR=1.25, 95% CI 1.03, 1.53); as well as the “other” racial-ethnic groups.

**Sleep duration and the persistence of asthma into young adulthood**

We identified four distinct sleep duration trajectories in asthmatic adolescents from wave I to III (age 18-24) Figure 3.2. People in the first trajectory group (10.2% of the sample) had consistently short sleep duration (mean duration in waves I – III: 5.6, 5.4, 5.9 hours respectively).
The second group included 3.6% of the sample and had initially short sleep duration that increased until wave III (mean durations of 6.8, 7.5, and 11.5 hours respectively). The third group included the majority of participants (81.2%) and had consistently adequate sleep durations throughout the three waves (mean duration 7.9, 7.7, and 7.9 hours respectively), and the fourth group had 4.9% of the population with generally long sleep duration throughout (mean durations 10.4, 10.3, and 8.6 hours respectively). There was no overlap in confidence intervals of mean durations of groups at any of the three waves. This model had an average posterior probability for each group that ranged from 75% to 89%, and an entropy of 0.75.

Young adults who had asthma in wave I and were interviewed in wave III (n=1,395) were 48.7% female, 68.3% white, and had an average age of 21.8 years at wave III interview (Table 3.3). The prevalence of overweight in both waves I and III was 24.3%, while 30.9% were considered overweight in wave I or III, but not both.

Logistic regression analysis (Table 3.4) shows that the adolescents with consistently short sleep duration had an increased risk of having their asthma persist into young adulthood, when compared with adolescents with consistently adequate sleep duration (Adjusted RR=2.35, 95% 1.12, 4.96). The short-increasing and the long trajectory groups showed a non-significant increase in risk of asthma persistence. No other variables in our analysis were significantly associated with persistence of asthma.

DISCUSSION

This is the first study to examine the impact of changes in sleep duration from adolescence into adulthood on the incidence of asthma, as well as its persistence into young adulthood. Results of this large longitudinal study indicate that adolescents who are free of asthma and consistently sleep for durations through their young adulthood have an increased risk
of new-onset asthma by age 32. Likewise, consistently short sleep durations is associated with increased likelihood of asthma persistence into young adulthood among adolescent with current asthma.

Sleep trajectories provide a means of more clearly defining sleep patterns in adolescents transitioning into young adulthood, compared with the single measurement of sleep duration commonly used in cross-sectional and some longitudinal studies. With the use of group-based trajectory models, we were able to identify a distinct group of adolescents with persistent short sleep duration through young adulthood, which enabled us to study the cumulative effects of long-term exposure to short sleep duration on the risk and persistence of asthma. Our sleep trajectories from adolescence to young adulthood were not very different from those found by Hayley et al., who found 16.5% of adolescents in their data to have sustained short sleep duration from ages 15 to 30. Similarly, Gilmour et al. found 11.1% of adults (18+) had consistently short sleep duration while 87% had short-normal or long-normal sleep trajectories.

The findings of this research may pave the way for future studies on sleep-related interventions that may help reduce the morbidity of asthma as well as the economic burden associated with it. Given the recent clinical trial by Meltzer et al., which showed teenagers with asthma may benefit from more adequate sleep durations, and the results of our current study, it seems likely that interventions targeting sleep duration may help reduce the incidence of asthma in non-asthmatic, as well as reduce the long-term morbidity and persistence of asthma symptoms in asthmatics.

It is important to note however, that our data were collected starting in 1994. We recognize that current sleep habits of adolescents and young adults may be significantly different, especially given the widespread use of smartphones, tablets, and other internet-
connected devices that may engage users and delay their sleep time, effectively shortening their sleep durations. A recent study we conducted using data from the Florida Youth Risk Behavior Survey (YRBS), years 2009-2013 showed that nearly 47.2% of adolescents aged 13-19 slept less than 7 hours per night, while in the population of the current study, only 16.8% of 13-19 year olds slept under 7 hours (in progress). This decline in sleep duration is likely to cause an even greater impact on the incidence and persistence of asthma, however, we need to replicate the analysis with more recent data to validate the results and verify this impact in our current times in order to plan the appropriate interventions.

Our study has several limitations, starting with the reliance on self-report of sleep durations in all four waves. Although some researchers found subjective sleep duration to be in poor agreement with objectively measured duration, and to over-estimate actigraphy-measured sleep duration, other studies found self-report to be valid for large-scale studies of habitual sleep duration, and corresponds well to objective measures such as actigraphy.

There were some changes noted in the wording of sleep durations questions at different waves. In the first two waves, participants were asked “how many hours of sleep do you usually get?” while in the third and fourth waves, they were asked what time they went to sleep and what time they got up on nights when they had work or school the next day and on nights when they didn’t (weekdays and weekends). We were unable to analyze weekday and weekend sleep separately since they were not reported in the first two waves. Therefore, we calculated a weighted average for the last two waves in order to obtain a measure that was as consistent as possible given the available data.

There were also some consistencies in measurement of asthma, which was based on parental-report in wave I and self-report in waves III & IV. This type of inconsistency is difficult
to avoid in longitudinal studies involving adolescents. Moreover, studies show that parental reports of the diagnosis and symptoms of asthma agree well with adolescent reports.\textsuperscript{51,65}

Another limitation related to asthma measurement was the wording of the questions. In wave I, parents were asked whether their child has “asthma or emphysema”, and in wave IV, respondents were asked whether they were ever diagnosed with “asthma, chronic bronchitis, or emphysema”, which carries the possibility that a fraction of respondents who answer “yes” actually have chronic bronchitis or emphysema rather than asthma. It is unlikely for this misclassification to cause bias, as most young adults diagnosed with chronic bronchitis actually have asthma, or an overlap of asthma and chronic bronchitis.\textsuperscript{66} Furthermore, emphysema is rare in adolescents and young adults, and not known to be associated with sleep duration.\textsuperscript{67} Therefore, any possible misclassification is unlikely to be large enough to bias our results.

Finally, the association between sleep trajectories and the persistence of asthma may have been partially explained by severity of asthma in adolescents. It is possible that those with more severe asthma had shorter sleep durations that persisted into their adulthood, and were also more likely to have their asthma persist into young adulthood. We cannot rule this out given that we have no measure of asthma severity at baseline. However, a clinical trial by Meltzer et. Al. mentioned above,\textsuperscript{56} supports our hypothesis that sleep duration may impact asthma symptoms. As for the incidence analysis, one might think that the onset of asthma symptoms may have affected subsequent sleep trajectories. We do not have a measure of time of onset of asthma to rule this out, but it is unlikely that this would have biased our results, given that it is not known whether asthma may affect sleep duration, and 34\% of new cases were still free of asthma in wave III.
The major strengths of our study include the longitudinal design and the long follow-up period with a response rate of over 77% at each wave. The large representative sample of adolescents is another major strength, as is the clustered probability sampling methods. Our use of sleep trajectories is an innovative method of studying the impact of sleep duration on the incidence of asthma. Furthermore, we created sleep trajectories separately for adolescents with asthma and those without asthma, which eliminates the possibility of asthma affecting sleep duration trajectories. Finally, the young adult age group that is included is usually under-represented in epidemiologic studies, and our study may help shed the light on the characteristics of this group.

CONCLUSIONS

This is the first study to explore the association between sleep trajectories from adolescence into adulthood and the risk of adult-onset asthma. The results of this study of a nationally representative sample of adolescents indicate that cumulative exposure to short sleep duration can increase the risk of developing asthma in non-asthmatics and increase the morbidity of asthma in asthmatics. These results raise the question of the long-term impact of persistent sleep loss on the risk of asthma later in adulthood. Further studies are needed using more current data that reflect the widespread decline in the average sleep duration, and with longer follow-up duration into adulthood.
Figure 3.1: Trajectories of sleep duration from adolescence into young adulthood, in participants without asthma at baseline of the Add Health study.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N=11016</th>
<th>Group 1 (^1) N=1520</th>
<th>Group 2 (^2) N=143</th>
<th>Group 3 (^3) N=8890</th>
<th>Group 4 (^4) N=463</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% Female)</td>
<td>50.0%</td>
<td>48%</td>
<td>56.5%</td>
<td>49.9</td>
<td>56.6%</td>
<td>0.3697</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>15.5±0.2</td>
<td>15.6±0.2</td>
<td>14.7±0.6</td>
<td>15.1±0.2</td>
<td>15.2±0.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>• White</td>
<td>67.4%</td>
<td>61.2%</td>
<td>44.2%</td>
<td>68.4%</td>
<td>63.3%</td>
<td></td>
</tr>
<tr>
<td>• Black</td>
<td>15.1%</td>
<td>21.4%</td>
<td>40.0%</td>
<td>13.9%</td>
<td>22.2%</td>
<td></td>
</tr>
<tr>
<td>• Hispanic</td>
<td>11.7%</td>
<td>10.4%</td>
<td>14.0%</td>
<td>11.9%</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>5.8%</td>
<td>7.0%</td>
<td>1.8%</td>
<td>5.8%</td>
<td>5.9%</td>
<td></td>
</tr>
<tr>
<td>Overweight or obese (%)</td>
<td>23.3%</td>
<td>29.8%</td>
<td>47.4%</td>
<td>22.5%</td>
<td>21.2%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Family income (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt;150% of poverty threshold</td>
<td>27.2%</td>
<td>27.2%</td>
<td>53.5%</td>
<td>26.4%</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>• 150% - &lt; 250% of threshold</td>
<td>22.0%</td>
<td>23.5%</td>
<td>22.3%</td>
<td>21.8%</td>
<td>22.6%</td>
<td></td>
</tr>
<tr>
<td>• 250% - 400% of threshold</td>
<td>28.3%</td>
<td>28.2%</td>
<td>6.9%</td>
<td>28.7%</td>
<td>23.1%</td>
<td></td>
</tr>
<tr>
<td>• &gt;400% of threshold</td>
<td>22.6%</td>
<td>21.2%</td>
<td>17.2%</td>
<td>23.1%</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>Parental education (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0053</td>
</tr>
<tr>
<td>• Less than high school</td>
<td>11.0%</td>
<td>10.2%</td>
<td>17.7%</td>
<td>10.8%</td>
<td>18.0%</td>
<td></td>
</tr>
<tr>
<td>• High school or equivalent</td>
<td>32.1%</td>
<td>34.3%</td>
<td>34.6%</td>
<td>31.5%</td>
<td>41.4%</td>
<td></td>
</tr>
<tr>
<td>• Some post-sec education</td>
<td>21.0%</td>
<td>20.2%</td>
<td>36.3%</td>
<td>21.3%</td>
<td>11.5%</td>
<td></td>
</tr>
<tr>
<td>• College degree</td>
<td>24.6%</td>
<td>24.9%</td>
<td>9.5%</td>
<td>24.8%</td>
<td>21.7%</td>
<td></td>
</tr>
<tr>
<td>• Post-graduate degree</td>
<td>11.4%</td>
<td>10.5%</td>
<td>1.8%</td>
<td>11.7%</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Family history of asthma (%)</td>
<td>10.9%</td>
<td>11.2%</td>
<td>18.2%</td>
<td>10.7%</td>
<td>13.1%</td>
<td>0.0874</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>24.3%</td>
<td>27.6%</td>
<td>24.5%</td>
<td>24.0%</td>
<td>23.7%</td>
<td>0.5814</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>25.7%</td>
<td>37.0%</td>
<td>15.3%</td>
<td>24.6%</td>
<td>25.5%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>15.5%</td>
<td>24.1%</td>
<td>8.4%</td>
<td>14.8%</td>
<td>13.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Above median puberty level</td>
<td>57.5%</td>
<td>64.4%</td>
<td>40.4%</td>
<td>57.2%</td>
<td>49.8%</td>
<td>0.0082</td>
</tr>
</tbody>
</table>

\(^1\) Group 1: Consistently short.  
\(^2\) Group 2: initially short, increasing.  
\(^3\) Group 3: Consistently adequate.  
\(^4\) Group 4: Initially long, decreasing  

*Bolded p-values indicate statistically significant differences among sleep duration groups.
Table 3.2: Results of the regression analysis examining the association between sleep duration trajectories from adolescents into young adulthood and the risk of new-onset asthma. Analysis of data from the Add Health study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted RR (95% CI)</th>
<th>Fully Adjusted Model* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep duration trajectory groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Group 1: Consistently short</td>
<td>1.40 (1.06, 1.86)</td>
<td>1.59 (1.12, 2.26)</td>
</tr>
<tr>
<td>• Group 2: Increasing</td>
<td>1.32 (0.49, 3.54)</td>
<td>1.04 (0.30, 3.69)</td>
</tr>
<tr>
<td>• Group 3: Consistently normal</td>
<td>Ref</td>
<td>1.53 (0.90, 2.62)</td>
</tr>
<tr>
<td>• Group 4: Decreasing</td>
<td>1.35 (0.85, 2.14)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.94 (0.88, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.54 (1.24, 1.92)</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>2.02 (1.53, 2.66)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hispanic</td>
<td>1.38 (0.99, 1.91)</td>
<td></td>
</tr>
<tr>
<td>• Black</td>
<td>1.14 (0.84, 1.50)</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>1.55 (1.02, 2.36)</td>
<td>Ref</td>
</tr>
<tr>
<td>Household income (&lt;250% of poverty threshold vs. &gt;= 250% of threshold)</td>
<td>0.99 (0.79, 1.26)</td>
<td></td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Less than high school</td>
<td>0.81 (0.55, 1.18)</td>
<td></td>
</tr>
<tr>
<td>• High school or equivalent</td>
<td>1.03 (0.75, 1.40)</td>
<td></td>
</tr>
<tr>
<td>• Some post-secondary education</td>
<td>1.03 (0.73, 1.46)</td>
<td></td>
</tr>
<tr>
<td>• College degree</td>
<td>1.02 (0.72, 1.44)</td>
<td>Ref</td>
</tr>
<tr>
<td>• Post-graduate degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.25 (1.03, 1.53)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.86 (0.64, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Physically active</td>
<td>0.99 (0.76, 1.29)</td>
<td></td>
</tr>
<tr>
<td>Pubertal category</td>
<td>1.16 (0.95, 1.21)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.09 (0.83, 1.44)</td>
<td></td>
</tr>
</tbody>
</table>

* Bolded numbers indicate statistically significant associations
Figure 3.2: Trajectories of sleep duration from waves I to III of the Add Health study, among participants with asthma in wave I.
Table 3.3 Characteristics of participants in wave III of the ADD health study who had asthma in wave I

<table>
<thead>
<tr>
<th>Variable</th>
<th>% of Total (N=1,395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% Female)</td>
<td>48.7%</td>
</tr>
<tr>
<td>Age at wave III (mean, 95% CI)</td>
<td>21.8 (21.5-22.0)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>• White</td>
<td>68.3%</td>
</tr>
<tr>
<td>• Black</td>
<td>15.9%</td>
</tr>
<tr>
<td>• Hispanic</td>
<td>5.4%</td>
</tr>
<tr>
<td>• Other</td>
<td>68.3%</td>
</tr>
<tr>
<td>• Overweight in both waves</td>
<td>24.3%</td>
</tr>
<tr>
<td>• Overweight in wave I or III</td>
<td>30.9%</td>
</tr>
<tr>
<td>• Normal weight in both waves</td>
<td>44.8%</td>
</tr>
<tr>
<td>Family income (%)</td>
<td></td>
</tr>
<tr>
<td>• &lt;150% of poverty threshold</td>
<td>26.5%</td>
</tr>
<tr>
<td>• 150% - &lt; 250% of threshold</td>
<td>24.8%</td>
</tr>
<tr>
<td>• 250% - 400% of threshold</td>
<td>25.1%</td>
</tr>
<tr>
<td>• &gt;400% of threshold</td>
<td>23.6%</td>
</tr>
<tr>
<td>Parental education (%)</td>
<td></td>
</tr>
<tr>
<td>• Less than high school</td>
<td>8.9%</td>
</tr>
<tr>
<td>• High school or equivalent</td>
<td>31.6%</td>
</tr>
<tr>
<td>• Some post-secondary education</td>
<td>25.3%</td>
</tr>
<tr>
<td>• College degree</td>
<td>22.4%</td>
</tr>
<tr>
<td>• Post-graduate degree</td>
<td>11.8%</td>
</tr>
<tr>
<td>Family history of asthma (%)</td>
<td>35.9%</td>
</tr>
<tr>
<td>Physically active at wave III (%)</td>
<td>21.2%</td>
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<tr>
<td>Smoking at wave III (%)</td>
<td>36.4%</td>
</tr>
<tr>
<td>Alcohol at wave III (%)</td>
<td>11.2%</td>
</tr>
<tr>
<td>Above median puberty level at w I</td>
<td>62.4%</td>
</tr>
</tbody>
</table>
Table 3.4: Association between short sleep durations trajectories and persistence of asthma into wave III in participants who had asthma at wave I of the add health study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Fully adjusted model* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep duration trajectory groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1: Consistently short</td>
<td>1.66 (0.90, 3.10)</td>
<td><strong>2.35 (1.12, 4.96)</strong></td>
</tr>
<tr>
<td>Group 2: Increasing</td>
<td>1.06 (0.43, 2.71)</td>
<td>1.22 (0.47, 4.02)</td>
</tr>
<tr>
<td>Group 3: Consistently normal</td>
<td>Ref</td>
<td>1.10 (0.48, 2.78)</td>
</tr>
<tr>
<td>Group 4: Long</td>
<td>0.92 (0.41, 2.11)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>0.98 (0.86, 1.13)</td>
</tr>
<tr>
<td><strong>Sex (female)</strong></td>
<td></td>
<td>1.43 (0.97, 2.10)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.91 (0.62, 1.62)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.20 (0.70, 2.02)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.15 (0.68, 2.22)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td><strong>household income (&lt;250% of poverty threshold vs. &gt;= 250% of threshold)</strong></td>
<td>1.39 (0.90, 2.17)</td>
<td></td>
</tr>
<tr>
<td><strong>Parental education</strong></td>
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</tr>
<tr>
<td>Less than high school</td>
<td>0.69 (0.29, 1.76)</td>
<td></td>
</tr>
<tr>
<td>High school or equivalent</td>
<td>0.89 (0.56, 1.60)</td>
<td></td>
</tr>
<tr>
<td>Some post-secondary education</td>
<td>1.15 (0.68, 1.85)</td>
<td></td>
</tr>
<tr>
<td>College degree</td>
<td>1.05 (0.57, 1.87)</td>
<td></td>
</tr>
<tr>
<td>Post-graduate degree</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td><strong>Pubertal status w1 (less than median vs. median or above)</strong></td>
<td>1.24 (0.84, 1.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>0.78 (0.52, 1.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>1.10 (0.48, 1.73)</td>
<td></td>
</tr>
<tr>
<td><strong>Overweight in both waves</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight in wave I or III</td>
<td>1.24 (0.80, 1.90)</td>
<td></td>
</tr>
<tr>
<td>Normal weight in both waves</td>
<td>1.32 (0.86, 2.05)</td>
<td></td>
</tr>
<tr>
<td><strong>Physically active</strong></td>
<td>0.96 (0.66, 1.40)</td>
<td></td>
</tr>
</tbody>
</table>

* Bolded numbers indicate statistically significant findings
SECTION 4

SLEEP DURATION TRAJECTORIES AND SYSTEMIC INFLAMMATION IN YOUNG ADULTS: RESULTS FROM THE NATIONAL LONGITUDINAL STUDY OF ADOLESCENT TO ADULT HEALTH (ADD HEALTH)

ABSTRACT

This study examines the effects of consistently short and consistently long sleep durations in young adults on the levels of CRP, as well as the potential effect modification by sex. Using data from waves III (age 18-26) and IV (age 24-32) of the National Longitudinal study of adolescent to adult health, we examined the association between sleep trajectories in young adults, and the risk of elevated high sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation. Short sleep trajectories were associated with a significant increase in log-transformed hs-CRP (coefficient=0.11, p-value 0.03), and with a significant increase in the odds of having hs-CRP levels >3 mg/dl (OR=1.86, 95% CI 1.29, 2.67). The association was modified by sex, with the association between short sleep duration and hs-CRP limited to males. Both the continuous (coefficient 0.117, p-value=0.0362) and the categorized hs-CRP (OR= 2.21, 95% CI 1.48, 3.30) were significantly increased with short sleep durations in males, while no significant associations were seen in females with short sleep durations. By contrast, there was a significant increase in log hs-CRP in females with long sleep durations (coefficient=0.232, p-value=0.0296), and a non-significant increase in the odds of having hs-CRP levels greater than 3 mg/dl (OR=1.48, 95% CI 0.75, 2.93), while there were no associations with long sleep duration in males.
INTRODUCTION

Sleep loss is an increasingly prevalent public health problem with more than 35% of US adults sleeping less than the recommended 7 hours per night. Sleep durations that are very short or very long have been implicated in the risks of obesity, cardiovascular diseases, and depression, among other conditions. Recent studies pointed to the production of pro-inflammatory cytokines, including C-reactive protein (CRP), an acute phase reactant, as a possible pathway that explains these associations. While experimental sleep deprivation studies found an association between acute sleep loss and CRP levels, population-based studies had inconsistent results, with some finding a significant association between short or long sleep durations and CRP, while others found no significant associations. Some studies found the association to be limited to women or men. The majority of these studies were cross-sectional. In order to confirm whether systemic inflammation is indeed the mediating factor in the association between sleep duration and negative health outcomes, it is imperative to determine first whether sleep duration is associated with systemic inflammation, using large population-based longitudinal studies. These studies are lacking, especially in young adults, and none to our knowledge has used trajectories of sleep duration to examine the association between sleep and inflammation in young adults.

This study examines the effects of consistently short and consistently long sleep durations in young adults on the levels of CRP, as well as the potential effect modification by sex.

METHODS

Design

This study uses data from waves III and IV of the National Longitudinal Study of Adolescent to Adult Health (Add health), which is a nationally representative study of adolescent
health and behavior in the USA that used clustered sampling design to select adolescents in
grades 7-12, and followed them through 4 waves of interviews into early adulthood (age 24-32). Of the 17,670 participants who had completed in-home and parental interviews at wave I (1994–1995), 15,197 completed interviews in wave III and 15,701 were interviewed in Wave IV, with a response rate of 80% in wave IV. This analysis includes participants who were seen at waves III and IV and have a valid measurement of CRP (N=10,744).

Measures

*High-sensitivity CRP (hs-CRP)* was collected during wave IV interview using capillary blood spots that were dried, frozen, and assayed using an adapted DBS (Dried Blood Spot) sandwich ELISA procedure cross-validated with paired plasma samples ($r = 0.98; N = 80$ matched serum samples). More details are available online (see “Add Health IV Documentation: Measures of Inflammation and Immune Function”).

Because the distribution of hs-CRP was right-skewed, we used natural log-transformation prior to the analysis. We analyzed log-transformed hs-CRP as a continuous variable, and hs-CRP as a categorical variable, using values $\leq 3$ mg/L (low-to-average risk) as the reference value, and $>3$ mg/L as the main outcome value. For the main analysis, we excluded values of hs-CRP $> 10$ mg/dl, as they are known to be associated with acute infectious or inflammatory conditions, and were present in 12.4% of the study sample. We later performed sensitivity analysis including values of hs-CRP $> 10$ mg/dl to check their impact on the results.

*Sleep duration* was measured in waves III & IV by the participant’s answers to questions about bed-time and wake-up times on work/school nights and non-work nights. We calculated a weighted average sleep duration for each participant at each wave by assigning weights of 5/7 to work nights and 2/7 to non-work night.
Body Mass Index (BMI) calculated from measured height and weight in waves III & IV. A participant was considered overweight if he/she had a BMI > 25.0 kg/m². In order to capture effects of long-standing overweight, we constructed a variable that combined waves III & IV BMIs into one variable with 3 categories: (0) if normal weight in both waves, (1) if overweight in one of the two waves, (2) if overweight in both waves.

Demographic variables included age, sex, & race-ethnicity

Measures of socioeconomic status in wave IV included

- Total household income in wave IV before taxes and deductions. We categorized the income variable as follows: (1) less than $50,000 per year, (2) $50,000 – $99,999 per year, and (3) more than $100,000 per year.
- Educational level: Participants were asked about their highest level of education, with choices ranging from (1) 8th grade or less, to (13) completed post baccalaureate professional education. We categorized the education variable into (1) less than high school graduate, (2) high school graduate to some post-secondary education, and (3) college degree or more.

Behavioral factors included:

- Smoking: Participants were asked, “During the past 30 days, on how many days did you smoke cigarettes?” Those who smoked on one or more days were considered current smokers, as per the definition from the National Survey on Drug Use and Health (NSDUH)⁵⁸
- Alcohol: Participants were asked, “During the past 12 months, on how many days did you drink alcohol?” Those who said they drank once a month or more were considered drinkers, according to the definition of the NSDUH.
• Physical activity measure was constructed from a series of seven questions about the 
frequency of engaging in certain physical activities. The binary measure included in the 
data set was coded as 0=bouts of physical activity, 1=no bouts of physical activity.

**Illnesses and Medications:** Hs-CRP is sensitive to many illnesses and medications; therefore, we adjusted for these conditions in the analysis using the following variables:

• **Subclinical symptoms:** A count of the number of symptoms the participants reported, 
  including cold or flu symptoms, fever, night sweats, nausea, vomiting, or diarrhea, blood 
  in stool or urine, frequent urination, and skin rash or abscess in the past two weeks. 
  Counts range from 0 to ≥3

• **Infectious or inflammatory diseases:** A count of lifetime diagnoses of conditions including 
  asthma / chronic bronchitis / emphysema, lifetime diagnosis of hepatitis C, in addition to 
  gum disease, active infection, injury, acute illness, surgery, and active seasonal allergies in 
  the past 4 weeks. Counts range from 0 to ≥3

• **Other illnesses or conditions:** Hypertension, depression, and snoring (indicative of 
  obstructive sleep apnea)

• **Medications that may affect hs-CRP:** NSAID/Salicylate, Cox-2 inhibitors, inhaled 
  corticosteroids, corticotropin/glucocorticoids, antirheumatic/antipsoriatic, 
  immunosuppressive, and anti-inflammatory medications

**Data analysis**

We identified trajectories of sleep duration using PROC TRAJ in SAS 9.4®, which uses 
the semiparametric group-based mixed model described by Nagin.60 This model estimates sleep 
trajectories for each individual and classifies individuals with similar sleep duration patterns into 
trajectory groups. We tried a number of models identifying two to five trajectory groups.
Selection of the optimal number of groups was based on the best fitting model for the data that produced the lowest value for the adjusted Bayesian Information Criterion (BIC),\textsuperscript{82} while preserving parsimony and facilitating interpretability. Additionally, we used entropy as a measure of classification accuracy.\textsuperscript{82} Consequently, we identified three groups of sleep duration trajectories from waves III to IV. Each participant was assigned into the group into which he or she had the highest probability of belonging.

Descriptive analyses included calculation of means and confidence intervals for continuous variables and frequencies of categorical variables. It was performed using SAS 9.4 procedures SURVEYMEANS and SURVEYFREQ, which take into account the complex sampling design.

Using SURVEYREG procedure in SAS, we ran regression analysis models examining the association between sleep duration trajectories and the natural logarithm of hs-CRP, first unadjusted, then after adjusting for covariates, obtaining coefficients and p-values. We examined interaction with sex by adding an interaction term to the model, and obtaining coefficients and p-values. We then performed the same analysis stratified by sex.

We examined the association with hs-CRP categories using SAS procedure SURVEYLOGISTIC, starting with an unadjusted model, then adding covariates to obtain adjusted odds ratios and 95% confidence intervals. We examined interactions between sleep duration and sex by adding an interaction term to the model. Then we performed the same analysis above, stratified by sex.

**RESULTS**

Figure 1 shows the sleep duration trajectories from wave III to wave IV by average age at each wave. The three distinct trajectories represent participant with short sleep durations in
both waves (group 1), those with good duration in both waves (group 2), and those with long
duration in both waves (group 3). Our model had an entropy of 0.75, and the mean posterior
probability for belonging into each of three groups was between 73% and 91%, with a minimum
above 50%. Group 1 participants had median sleep durations in waves III & IV of 5.5 and 5.8
hours, respectively. Group 2 had median durations of 7.9 & 7.8 hours, and group 3 had median
durations of 10.7 & 10.6 hours in waves III & IV respectively (Table B.1).

Characteristics of the study population are presented in Table 1. The analytic sample
consisted of 10,744 participants, 50.4% of whom were females, 66.4% white, and the mean age
at wave IV was 28.4 years. Short sleep duration trajectory included 10.6% and long sleep was
present in 2.7%. There were significant differences among people belonging into different
trajectory groups in terms of several key variables. Compared with good sleepers, those with
short sleep trajectories were significantly more likely to have hs-CRP>3 mg/dl (40.9% vs.
31.4%). They were also more likely to be Male (69.3% vs. 49.7%), Black (23.6% vs. 14.5%),
overweight in both waves (52.6% vs. 46.5%), of lower education and income, and to smoke,
have hypertension, depression, or snoring. Long sleepers were the most likely to be female
(64.5%), Black (41.2%), have income below $50,000, high school degree or less, and to have
no bouts physical activity. However, they were the least likely to smoke, drink, snore, or have
trouble sleeping (Table 1). Both the short and the long sleep duration groups had higher mean
Log-transformed hs-CRP (1.13, 1.21 respectively) compared with the good sleep duration group
(1.05), however the differences were not statistically significant. (Table 1)

Regression analysis results (Table 2) show that hs-CRP increases significantly with
consistently short sleep duration compared with good sleep durations, after adjusting for relevant
covariates (coefficient=0.111, p-value=0.0327). Long duration trajectories were also significant
in the unadjusted model (coefficient= 0.154, P-values=0.0244), and in the fully adjusted model (coefficient=0.200, P-value=0.0145). Other significant variables included female sex (P <.0001), overweight in one or both waves (P<.0001), low educational level, lack of physical activity, hypertension, and snoring. There was a borderline significant interaction between female sex and short sleep duration (P=0.0494), and a significant interaction between long sleep duration and being overweight in both waves (P=0.0130).

Logistic regression examining categorical hs-CRP as an outcome (Table 3) shows that, similar to linear regression on Ln hs-CRP, short sleep duration raised the odds of having hs-CRP>3 mg/dl in the unadjusted model, and the effect persisted and became more pronounced after adjusting for relevant covariates (OR=1.86, 95% CI 1.29, 2.67). Long sleep duration was not significantly associated with categorical hs-CRP in any of the models.

Other variables that were significantly associated with hs-CRP>3 mg/dl included female sex (adjusted OR=2.44, 95% CI 2.09-2.85), overweight in one wave OR=3.36 (2.82, 4.02), and overweight in both waves OR=1.97 (1.62, 2.39), in addition to low education level (high school degree, compared with college degree or more), hypertension, snoring, and lack of physical activity. Medications and symptoms of infection were not significantly associated with increased CRP, but subclinical symptoms of inflammatory diseases did produce a statistically significant OR with 1, 2, and 3 or more symptoms. Race, smoking, drinking, and trouble sleeping were not significantly associated with CRP in the adjusted model.

Interaction term sex*sleep duration groups was significant for short sleep and female sex, compared with good sleep and male sex (P= 0.0380). Stratified analysis by sex (Table 4) revealed that the association between short sleep duration and hs-CRP is limited to males. Both the continuous and the categorical hs-CRP were significantly increased in males who had short
sleep durations, while no association was found in females. By contrast, there was a significant increase in log hs-CRP in females with long sleep durations, and a non-significant increase in the odds of having hs-CRP levels greater than 3 mg/dl, while there were no associations in males.

**Sensitivity analysis:** Results of multivariate regression including hs-CRP values greater than 10 were not very different. In logistic regression (Table B.2), short sleep trajectory group produced an adjusted OR of 1.74 (1.26, 2.39), which is slightly lower than the one we had while excluding extremely high hs-CRP values. Similar to the original analysis, long sleep trajectories were not significantly associated with hs-CRP > 3mg/dl. Furthermore, in the linear regression, short sleep trajectories were associated with had an adjusted coefficient of 0.10 and P-value=0.0492. Long sleep trajectories were not significant in the adjusted model (Table B.1).

**DISCUSSION**

This prospective analysis of a nationally representative sample of US young adults revealed different relationships between sleep duration and hs-CRP levels among men and women. Men who consistently sleepless than the recommended seven hours per night have a significant increase in systemic inflammation, measured by hs-CRP, while no association is detected in females. By contrast, women appear to be more sensitive to long sleep durations, which are associated with an increase in hs-CRP in young women but not young men.

Long sleep duration was significantly associated with the increase in hs-CRP in women, which is consistent with previous studies, but it was not statically significant when hs-CRP was used as a categorized variable. This may be due to lack of power due to the small number of participants in the long trajectory group (n=106 females), or may reflect an association with the increase in hs-CRP, rather than with the probability of having hs-CRP >3 mg/dl, compared with values ≤3 mg/dl. Further studies using hs-CRP categories are needed to clarify.
Our results are somewhat consistent with those found by Ferrie et al. in their longitudinal analysis from the Whitehall II study of middle-aged men and women, using two measures of sleep duration 5 years apart. They found the decrease in sleep duration to be significantly associated with the increase in hs-CRP, but the association was no longer significant after adjusting for BMI, hypertension, and diabetes. Unlike Ferrie et al., we adjusted for medication use, symptoms of infectious and inflammatory diseases, and sleep problems. Similarly, the Coronary Artery Risk Development in Young Adults (CARDIA) study found a significant association between sleep duration at baseline and CRP levels 5 years later, but similar to Ferrie et al.’s study above, the association was attenuated to non-significant after adjusting for covariates. This study used CRP as a continuous variable and unlike our analysis, had only one measurement of sleep duration at baseline, categorized as short (<6 hours) or usual (6 h or more). Both of the studies above had older cohorts than ours, and smaller sample sizes (5003, 2679, respectively), that may explain the non-significant results. Neither of the two studies examined the interaction between sleep duration and sex.

Our finding of significant effect modification by sex requires further study. We found short sleep in men and long sleep in women to be associated with increased hs-CRP. In contrast, Miller et. al.’s analysis from the Whitehall II study found the association between short sleep duration and hs-CRP to be limited to females. Furthermore, they found an increase in hs-CRP in women who slept for more than 8 hours, but unlike our results, it was not statistically significant. Miller et. al.’s analysis was cross-sectional, with an older cohort and a smaller sample size (n = 4677) than ours, which may explain the non-significant results. Our findings of an association between long sleep duration and log-transformed hs-CRP that is limited to women is consistent
with the Nurses’ Health Study\textsuperscript{75}, that included 935 women aged 43-69 years, and found an association between long sleep duration and hs-CRP (as a continuous variable) in women.

In a recent study using data from Add health, Mantua & Spencer\textsuperscript{85} examined the interactive effects of nocturnal sleep and daytime naps in relation to hs-CRP. This study included 2147 participants, and measured sleep duration in wave III only. They found that short sleepers had the highest hs-CRP, but did not find a significant effect of sleep duration on hs-CRP in their regression model. The smaller sample size may be responsible for the lack of significant results.

This is the first study to our knowledge that used sleep trajectories to examine the association between sleep duration and CRP. Our sleep trajectories matched those found by Gilmour et. al.\textsuperscript{62} in a study of Canadians during the same time period as our study. Their short duration trajectory included 11.1\% of the population, and the long duration trajectory included 2.1\%. In comparison, our short and long trajectories included 10.6\% and 2.7\% of our population respectively.

The main limitation of this analysis was the reliance on self-reported sleep durations in waves III & IV, which raises the question of agreement between subjectively and objectively measured sleep duration. Self-report was found by Lauderdale et. al. to over-estimate actigraphy-measured sleep duration.\textsuperscript{64} By contrast, several studies found self-report to be valid for large-scale studies of habitual sleep duration, and correspond well to objective measures such as actigraphy.\textsuperscript{48–50}

Another limitation is the lack of measurement of CRP prior to wave IV, which does not allow for determination of temporality. As with many chronic health outcomes that produce no symptoms, it is very difficult to capture the onset of systemic inflammation. We are cautious in
interpreting the results of our analysis, and realize the need for further longitudinal studies with multiple measurements of CRP.

Major strengths of this study include the large cohort of US young adults, an under-represented group in epidemiologic research, and the complex sampling design that insures the sample is representative of US population. Additional strengths include the longitudinal design, and utilization of group-based trajectory modeling to predict the impact of sleep duration patterns on levels of hs-CRP.

CONCLUSION

Accumulating evidence point to sleep loss, as well as excess sleep as modifiable risk factors for many acute and chronic diseases, resulting in significant public health burden. It is therefore very important to understand the mechanism of these associations. The present study supports previous research indicating a link between sleep duration and inflammation, which partially explains the detrimental effects of inadequate sleep. It also indicates that the impact of inadequate sleep duration differs between males and females, which will help guide public health interventions and sleep education efforts. More prospective studies are needed to understand the mediating effect of inflammation on the risk.
Tables and Figures

Figure 4.1: Trajectories of sleep duration between waves 3 and 4 of the Add Health study
Table 4.1: Selected characteristics of participants in waves 3 & 4 of the National Longitudinal Study of Adolescent to Adult Health, in total and stratified by sleep duration trajectory group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=10741)</th>
<th>Short (10.6%)</th>
<th>Good (86.7%)</th>
<th>long (2.7%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in wave 4 (mean) (95% CI)</td>
<td>28.4 (28.2 - 28.6)</td>
<td>28.6 (28.3 - 29.0)</td>
<td>28.4 (28.2 - 28.6)</td>
<td>28.6 (28.1 – 29.1)</td>
<td>0.1790</td>
</tr>
<tr>
<td>Log-transformed CRP (mean) (95% CI)</td>
<td>1.06 (1.04 - 1.08)</td>
<td>1.13 (1.04 - 1.22)</td>
<td>1.05 (1.03 - 1.07)</td>
<td>1.21 (1.07 – 1.34)</td>
<td>0.5637</td>
</tr>
<tr>
<td>CRP &gt; 3 mg/dl (%)</td>
<td>32.0%</td>
<td>40.9%</td>
<td>31.4%</td>
<td>35.9%</td>
<td>0.0055</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>50.4%</td>
<td>30.7%</td>
<td>51.3%</td>
<td>64.5%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66.4%</td>
<td>57.7%</td>
<td>67.2%</td>
<td>46.1%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Black</td>
<td>15.3%</td>
<td>23.6%</td>
<td>14.5%</td>
<td>41.2%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11.8%</td>
<td>11.4%</td>
<td>11.8%</td>
<td>10.9%</td>
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</tr>
<tr>
<td>Other</td>
<td>6.4%</td>
<td>7.3%</td>
<td>6.5%</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In one wave (%)</td>
<td>24.7%</td>
<td>25.8%</td>
<td>24.5%</td>
<td>38.9%</td>
<td>0.0390</td>
</tr>
<tr>
<td>- In both waves (%)</td>
<td>46.8%</td>
<td>52.6%</td>
<td>46.5%</td>
<td>47.2%</td>
<td></td>
</tr>
<tr>
<td>Household income (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $50,000</td>
<td>49.5%</td>
<td>52.6%</td>
<td>48.9%</td>
<td>72.4%</td>
<td>0.0002</td>
</tr>
<tr>
<td>$ 50,000 - $100,000</td>
<td>36.8%</td>
<td>36.3%</td>
<td>37.0%</td>
<td>23.9%</td>
<td></td>
</tr>
<tr>
<td>&gt; $100,000</td>
<td>13.7%</td>
<td>11.1%</td>
<td>14.1%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Less than high school</td>
<td>8.5%</td>
<td>10.9%</td>
<td>8.3%</td>
<td>10.7%</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>17.3%</td>
<td>19.8%</td>
<td>16.8%</td>
<td>44.4%</td>
<td></td>
</tr>
<tr>
<td>Some post-secondary education</td>
<td>43.8%</td>
<td>49.0%</td>
<td>43.5%</td>
<td>41.6%</td>
<td></td>
</tr>
<tr>
<td>College degree or higher</td>
<td>30.4%</td>
<td>20.2%</td>
<td>31.5%</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>No Physical activity (%)</td>
<td>15.0%</td>
<td>12.7%</td>
<td>14.8%</td>
<td>30.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>31.0%</td>
<td>43.7%</td>
<td>30.4%</td>
<td>25.8%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>58.9%</td>
<td>58.5%</td>
<td>59.1%</td>
<td>39.7%</td>
<td>0.0246</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.3%</td>
<td>32.3%</td>
<td>24.8%</td>
<td>31.6%</td>
<td>0.0084</td>
</tr>
<tr>
<td>snoring</td>
<td>49.7%</td>
<td>60.5%</td>
<td>49.2%</td>
<td>42.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>depression</td>
<td>20.7%</td>
<td>24.2%</td>
<td>20.4%</td>
<td>23.3%</td>
<td>0.2662</td>
</tr>
<tr>
<td>Trouble sleeping or staying asleep (1 or more per week)</td>
<td>67.8%</td>
<td>64.3%</td>
<td>68.3%</td>
<td>50.6%</td>
<td>0.0016</td>
</tr>
</tbody>
</table>
Table 4.2: Results of multivariate linear regression analysis for natural logarithm of CRP and sleep duration in waves 3 & 4 in the Add Health study (Regression coefficients and P-values)

<table>
<thead>
<tr>
<th>Sleep duration trajectory group</th>
<th>UNADJUSTED COEFFICIENT (P-VALUE)</th>
<th>FULLY ADJUSTED$^\S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>0.08 (0.0875) Ref</td>
<td>0.10 (0.0327) Ref</td>
</tr>
<tr>
<td>Good</td>
<td>0.15 (0.0244) Ref</td>
<td>0.20 (0.0145)</td>
</tr>
<tr>
<td>Long</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sex (female)
0.27 (<.0001)

Race/ethnicity
- Black -0.02 (0.3580)
- Hispanic -0.0001 (0.9862)
- Other - 0.06 (0.1051) Ref
- White

Overweight in both waves 0.42 (<.0001)
Overweight in one wave 0.25 (<.0001) Ref
Normal weight in both waves

Education
- Less than high school 0.09 (0.0291)
- High school diploma 0.12 (<.0001)
- Some post-secondary education 0.08 (0.0005) Ref
- College degree or higher

Income
- < $50,000 0.02 (0.4805)
- $ 50,000 - $100,000 0.004 (0.8563) Ref
- > $100,000

Alcohol use -0.08 (0.0519)

Smoking 0.01 (0.7227)

Lack of physical activity 0.06 (0.0150)

Hypertension 0.10 (0.0001)

Depression 0.01 (0.5726)

Snoring 0.08 (<.0001)

Trouble sleeping 0.01 (0.2614)

$^\S$Fully adjusted model also included symptoms of infection, subclinical symptoms of inflammatory disease, & medication use (not shown in table)
### Table 4.3: Association between sleep in waves 3 & 4 and CRP levels greater than 3 mg/dl in the Add Health study (Odds ratios and 95% C.I.)

<table>
<thead>
<tr>
<th>Sleep duration trajectory group</th>
<th>Unadjusted</th>
<th>Fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short</td>
<td>1.51 (1.12, 2.04)</td>
<td>1.86 (1.29, 2.67)</td>
</tr>
<tr>
<td>• Good</td>
<td>1.22 (0.82, 1.84)</td>
<td>1.25 (0.67, 2.35)</td>
</tr>
<tr>
<td>• Long</td>
<td>Ref</td>
<td>1.86</td>
</tr>
</tbody>
</table>

| Sex (female)                    | 2.44 (2.09, 2.85) |

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Black</td>
<td>0.95 (0.74, 1.22)</td>
</tr>
<tr>
<td>• Hispanic</td>
<td>0.98 (0.80, 1.21)</td>
</tr>
<tr>
<td>• Other</td>
<td>0.78 (0.57, 1.06)</td>
</tr>
<tr>
<td>• White</td>
<td>Ref</td>
</tr>
</tbody>
</table>

| • Overweight in both waves      | 3.36 (2.82, 4.02) |
| • Overweight in one wave        | 1.97 (1.62, 2.39) |
| • Normal weight in both waves   | Ref             |

<table>
<thead>
<tr>
<th>Education</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less than high school</td>
<td>1.13 (0.85, 1.52)</td>
</tr>
<tr>
<td>• High school diploma</td>
<td>1.30 (1.03, 1.66)</td>
</tr>
<tr>
<td>• Some post-secondary education</td>
<td>1.13 (0.95, 1.36)</td>
</tr>
<tr>
<td>• College degree or higher</td>
<td>Ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Income</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt; $50,000</td>
<td>1.14 (0.91, 1.43)</td>
</tr>
<tr>
<td>• $50,000 - $100,000</td>
<td>1.05 (0.85, 1.29)</td>
</tr>
<tr>
<td>• &gt; $100,000</td>
<td>Ref</td>
</tr>
</tbody>
</table>

| Alcohol use                     | 0.86 (0.74, 1.01) |

| Smoking                         | 1.03 (0.88, 1.20) |

| Lack of physical activity      | 1.32 (1.08, 1.61) |

| Hypertension                   | 1.40 (1.17, 1.68) |

| Depression                     | 1.05 (0.85, 1.29) |

| Snoring                        | 1.30 (1.13, 1.49) |

| Trouble sleeping               | 1.01 (0.98, 1.04) |

*Fully adjusted model also included symptoms of infection, subclinical symptoms of inflammatory disease, & medication use (not shown in table)*
Table 4.4: Results of sex-stratified regression analysis examining the association of sleep trajectory groups and continuous log hs-CRP as well as categorical CRP in the Add health study:

<table>
<thead>
<tr>
<th></th>
<th>Sleep duration trajectory groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>CRP &gt;3 mg/dl (OR, 95% CI) vs. ≤ 3 mg/dl</td>
<td>2.21 (1.48, 3.30)</td>
</tr>
<tr>
<td>Ln hs-CRP (coefficient, p-value)</td>
<td>0.117 (0.0362)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>CRP &gt;3 mg/dl (OR, 95% CI) vs. ≤ 3 mg/dl</td>
<td>0.998 (0.54, 1.86)</td>
</tr>
<tr>
<td>Ln hs-CRP (coefficient, p-value)</td>
<td>-0.004 (0.9544)</td>
</tr>
</tbody>
</table>

Results shown are of the fully adjusted models, which included Race, BMI, education, income, smoking, alcohol, physical activity, depression, hypertension, trouble sleeping, symptoms of infection, subclinical symptoms of inflammatory disease, & medication use.
SECTION 5

CONCLUSIONS AND RECOMMENDATIONS

The results of this dissertation research point to the detrimental effects of sleep loss on the bodies of adolescents and young adults. Sleep duration has previously been linked with a range of conditions, from obesity to cardiovascular disease, metabolic syndrome, and other negative health outcomes. In our research, we found sleep loss to be associated with the incidence of asthma and its persistence, in addition to heightened systemic inflammation, which is a likely pathway that links sleep duration with the above outcomes.

In our first study, using the Florida YRBS, we examined the cross-sectional association between sleep duration and the prevalence of current asthma in adolescents. We found that adolescents with short or long sleep duration were more likely to have current asthma than those with adequate sleep durations. Overweight adolescents were more susceptible to the effects of short sleep duration on asthma.

The second study, using data from Add health examined the association between longitudinal trajectories of sleep duration from adolescence to young adulthood and the risk and persistence of asthma. Our results indicated that non-asthmatic adolescents who sleep for short durations consistently through their young adulthood are at a higher risk of developing asthma by age 32. Adolescents with asthma who consistently sleep for short durations are at a higher risk of having their asthma symptoms persist into young adulthood (age 18-24).

In our third study, using Add health data, we found that young adults who consistently sleep for short durations are more likely to have increased levels of C-reactive protein (CRP), a
marker of systemic inflammation. The association was mostly limited to males, while females had a more significant association between long sleep duration and CRP.

We used innovative measures of sleep duration in our longitudinal studies. Using trajectories of sleep durations from adolescence into young adulthood, we classified participants according to their patterns of sleep. In all the models we used, there was always a group of participants who consistently slept less than the recommended amount for their age. Another group, usually the largest, consistently slept for an adequate amount through the follow-up period of Add health study. The use of trajectories enabled us to examine the impact of consistently short sleep duration from adolescence through young adulthood, which is informative than a single measure of self-reported sleep commonly used in cross-sectional and many longitudinal studies.

Our cross-sectional analysis was the first step that revealed the association between sleep duration and asthma, and it acted as a stepping stone towards the more extensive longitudinal analysis. The cross-sectional analysis used more recent data (2009-2013), while the adolescent stage of the longitudinal data were collected between 1994-1996. The time difference helped shed the light on the change in average sleep duration in adolescents over the past 20 year. The proportion of adolescents sleeping less 7 hours per night changed dramatically between the two studies. In the Add health study, 16.5% of adolescents slept less than 7 hours in 1994-1995, while 47.2% of participants in Florida YRBS (2009-2013) slept less than 7 hours. This decrease in sleep duration, likely to be caused by the widespread use of mobile phones and other internet-connected devices, highlights the need to determine the effects of sleep loss on the growing bodies of adolescents, and to design effective interventions that address this public health problem.
Although our third study could not answer the question whether the association between sleep duration and asthma was mediated by systemic inflammation, it solved a piece of the puzzle, and paved the way to further studies that will answer this question. Before we can determine whether the association is indeed through the inflammatory pathway, we need to confirm the longitudinal association between consistently short sleep duration and systemic inflammation. The effect-modification by sex is an important, yet unexpected findings that needs further examination.

This research was limited by the use of self-reported sleep duration and asthma diagnoses, and the lack of a measure of asthma severity. Given the cost associated with objective measures of sleep duration, it is not feasible to use them in large population-based longitudinal studies. Nevertheless, several studies found self-report to be valid for large-scale studies of habitual sleep duration, and correspond well to objective measures such as actigraphy.\textsuperscript{48–50} The lack of measure of asthma severity is a cause for concern, particularly in the study of asthma persistence, as it is possible, in theory, that adolescents with more severe asthma had shorter sleep durations, and were also more likely to have their asthma symptoms persist into young adulthood. We are planning future studies that will verify the results of this analysis while taking into account the severity of asthma.

Strengths of this research include the use of large representative samples of the population, and the focus on adolescents and young adults, which are usually under-represented in epidemiologic research. The longitudinal analyses, use of sleep duration trajectories, and the novel questions that were addressed in this research are among the major strengths.

Our future research plans include a follow-up study using wave V of the Add health study, currently under collection, to examine the effects of sleep duration trajectories on the risk
of asthma by age 32-40, and the potential mediation by hs-CRP levels in wave IV (age 24-32) (figure B.1). We will also examine the effects of sleep duration trajectories in males and females on the change in hs-CRP levels between waves IV and V.

The results of this study have significant public health implications. Given the increase in the incidence and prevalence of asthma, and given the progressive decrease in average sleep duration in adolescents, it is likely that behavior-modification interventions that aim at increasing sleep durations in adolescents will have a significant impact on the incidence and prevalence of asthma, along with the associated morbidity, mortality, and economic burden.
REFERENCES


APPENDIX A

REVIEW OF CURRENT LITERATURE

ASTHMA

Asthma is one of the most common chronic diseases in children and adults worldwide and is the most common chronic diseases in childhood, affecting 7 million children in the US.\textsuperscript{4} Asthma is an inflammatory lung disease, with a complex pathophysiology that involves airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness. It is characterized by episodes of airway obstruction leading to symptoms of cough, wheezing, shortness of breath, and chest tightness.\textsuperscript{86} There are two general types of asthma: Allergic and non-allergic (or atopic and non-atopic),\textsuperscript{87} which differ little in terms of manifestations, but have different risk factors and triggers.\textsuperscript{88}

The prevalence of asthma has been increasing in recent years, at a rate of 1.5\% per year, to a prevalence of 8.4\% in 2010, and the number of persons with asthma has increased between 2001 and 2010 by 2.9\% each year, from 20.3 million persons in 2001 to 25.7 million persons in 2010. Current asthma prevalence is higher in children than in adults, and in females than in males.\textsuperscript{3} According to findings from the Asthma Call Back Survey (2006-2008), incidence among youth aged 12-17 years was 4.4/1000 and in adults 3.8/1000.\textsuperscript{89}

Asthma is a significant cause of morbidity and mortality, leading to an estimated 14.4 million lost school days in children and 14.2 million lost workdays in adults in 2008.\textsuperscript{90} Asthma is also a leading cause of activity limitation and costs our nation $56.0 billion in health care costs.
annually.\textsuperscript{90} The death rate per 1,000 persons with asthma was 0.15 for the period of 2007–2009, and it is more than 30\% higher for females than males, 75\% higher for black persons than it is for white persons, and almost seven times higher for adults than children. \textsuperscript{1}

Risk factors for asthma include family history and prenatal risk factors such as maternal smoking, diet and nutrition, and delivery by cesarean section. Childhood risk factors for asthma may include allergic sensitization, environmental tobacco smoke, obesity, gastroesophageal reflux; decreased lung function in infancy; family size and structure; socio-economic status; antibiotics; and infections, while breastfeeding may have a protective effect against the development of asthma. Occupational exposures, smoking, and obesity constitute common risk factors for adult asthma. Triggers of asthma exacerbations commonly include infections, exposure to allergens or other irritants, exercise, and stress.\textsuperscript{52}

\textbf{Obesity and asthma.} The prevalence of obesity has been on the rise in USA for the past decades, from 23.0\% of adults in 1988–1994 to approximately 36.0\% in 2009–2010.\textsuperscript{91} Similarly, the prevalence of obesity in adolescents aged 12-19 increased from 5\% in 1980 to nearly 21\% in 2012.\textsuperscript{92} Obesity is a risk factor for many chronic diseases including cardiovascular disease, diabetes, stroke, and sleep apnea.\textsuperscript{92} The association between obesity and asthma has been studied extensively, with many studies finding an increased risk of asthma in obese children and adults.\textsuperscript{5,93–96} Obesity is also associated with poor asthma control and quality of life, and more asthma-related hospitalizations.\textsuperscript{97–99} However, these associations may be modified by gender. Kattan et al.\textsuperscript{100} found that increased BMI in female adolescents was associated with worse asthma control, more exacerbations, and worse pulmonary function, while these effects were not observed in males. On the other hand, adiponectin had a protective effect in males but not in females.\textsuperscript{100}
Several mechanisms were proposed to explain association between obesity and asthma including cardio-respiratory deconditioning, physiological restriction of the chest wall by excess adipose tissue, common genetic predisposition, and co-morbidities such as gastroesophageal reflux disease and sleep disordered breathing (SDB). Additionally, the inflammatory pathway is now considered a plausible explanation, given that obesity is associated with chronic low grade systemic inflammation. In particular, Leptin (a proinflammatory adipokine) and adiponectin (an anti-inflammatory adipokine) were the focus of many research studies. Leptin, which is markedly increased in obesity, may play a role in asthmatic inflammation and may be a key modulator of airway remodeling. Leptin increases production of Tumor Necrosis Factor (TNF)-alpha, and Interleukin 6 (IL 6), both of which are increased in asthma. The role of gender in the association between Leptin and asthma is not clear. Abdul Wahab et al. found that higher Leptin levels were strongly associated with female gender in asthmatic children. By contrast, Guler et al. found the difference in Leptin concentration to be confined to boys.

Another marker of systemic inflammation in C-Reactive Protein (CRP), Which is found to be elevated in individuals with asthma and negatively correlated with pulmonary function indices. High sensitivity CRP (hs-CRP) is also correlated with the numbers of sputum eosinophils, suggesting that serum hs-CRP can indirectly indicate the degree of airway inflammation. However, studies of the role of hs-CRP in the association between obesity and asthma have been inconsistent. Several studies found that hs-CRP is more elevated in obese asthmatics compared with non-obese asthmatics. Additionally, a study by Michelson et al. even showed that some of the seeming association between obesity and asthma is significantly mitigated after controlling for serum CRP levels. By contrast, a study by Bekkers et al. concluded that hs-CRP did not play a role in the association between BMI and asthma symptoms, and Huang
et al. found no significant difference in CRP levels between obese and non-obese asthmatics.\textsuperscript{110} Although the latter study was limited by its sample size. Furthermore, studies conducted by Kattan et al., Bekkers et al., and Dixon et al. revealed that hs-CRP levels did not correlate with asthma severity or symptoms in obese individuals.\textsuperscript{96,100,111} The discrepancy in results is likely due to the existence of a distinct obesity-related phenotype of asthma, which is different from atopic asthma.\textsuperscript{101} Obese asthma is likely to be the result of mechanical restriction of breathing, and is not associated with increased airway or systemic inflammation (measured by exhaled nitric oxide, sputum eosinophils, blood CRP, and IL-6).\textsuperscript{54} However, obesity itself is associated with systemic inflammation and may increase the risk of atopic or non-atopic asthma through different pathways.\textsuperscript{54} The variability in prevalence of each phenotype in different study populations may explain the difference in results.

Concerning the effect of obesity on airway inflammation, animal studies as well as some observational ones suggested that obesity-induced systemic inflammation might influence pulmonary inflammatory mechanisms.\textsuperscript{6,93,103} However, other studies failed to find a link between obesity and markers of airway inflammation such as exhaled Nitric Oxide (eNo), and sputum eosinophils in asthmatic subjects,\textsuperscript{5,94,112} while BMI was found to be associated with eNo in healthy individuals.\textsuperscript{113} These two markers are usually elevated in atopic asthma, which may indicate that obesity is associated with non-atopic asthma only, or that asthma in obese individuals is a separate phenotype that needs special treatment considerations. The association between obesity and asthma is complex and multifactorial, and cannot be explained by inflammation alone.

**Systemic inflammation and asthma.** A few longitudinal studies examined the link between systemic inflammation and subsequent asthma. Ahmadi-Abhari and colleagues conducted a longitudinal study that included 18,110 men and women aged 40–79 years.\textsuperscript{114} Results of the
study revealed that a 1-standard deviation increase in log_{e}-CRP over 13 years was associated with a decline in FEV1 ($-64.0\text{ mL}, 95\%\text{ C.I.: }-72.1, -55.8$) and a decline in FVC over the same period, regardless of baseline CRP. Similarly, Shaaban et al. found an inverse association between change in CRP and change in FEV1 over time, while no association was found between baseline FEV1 and subsequent change in CRP.\textsuperscript{115} Furthermore, Fogarty et al. and Hancox et al. also found serum CRP levels to be inversely related to FEV1 and FVC. However, they found no significance association between baseline CRP and rate of decline in lung function in young adults.\textsuperscript{116,117} By contrast, Rasmussen et al. conducted a study of 1,134 young adults aged 20 years and found lower pulmonary function indices at age 29 and a greater decline in FEV1 and FVC in persons with higher baseline CRP, as well as with the increase in CRP between the ages of 20 and 29.\textsuperscript{54} Similarly, in the Coronary Artery Risk Development in Young Adults (CARDIA) Study Kalhan et al. found a greater decline in FVC and FEV1 in young adults with higher baseline CRP.\textsuperscript{118} These studies indicate that systemic inflammation has a negative impact on lung function in healthy young adults, which raises the question of its impact on the lung function of asthmatics.

**Adolescents and young adults with asthma** are a unique population, given the physical and psychological changes that occur during this period and affect the health and well-being of teenagers.\textsuperscript{27} Adolescents are at increased risk of asthma morbidity and mortality as a result of their new independence and the shift in responsibility for asthma management from parents to adolescents. Non-adherence to treatment, lifestyle factors, and comorbid depression are among the contributing factors to increased morbidity.\textsuperscript{27} Similarly, young adults may be uninsured and lack access to health care as they transition from pediatric to adult health care, which puts them at risk for poor asthma control. They also frequently have unhealthy life styles that negatively affect their
asthma, and are prone to non-compliance with their maintenance medications. Yet, few asthma research studies include these age groups.

**SLEEP DISORDERS AND THEIR CONSEQUENCES**

Sleep is a fundamental human need, yet the quantity and quality of sleep in modern society have been declining steadily for the past decades. A 1994 Report of the National Commission on Sleep Disorders Research estimated that total sleep time for the US population has decreased by 20% over the past century. This reduction is related to the availability of electric lighting as well as other changes in environmental and social conditions, such as extended shift work and round-the-clock activities. Disorders of sleep and wakefulness are widespread in modern society; with an estimated 50 to 70 million Americans suffering from one or more of over 90 distinct sleep disorders, which may result in an annual cost of $16 billion in health care and $50 billion in lost productivity. Symptoms of most sleep disorders include excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep. These disorders affect daily functioning and can adversely affect health and longevity.

Sleep loss in adults generally refers to sleep of shorter duration than the average basal need of 7 to 8 hours per night. Sleep loss is a prevalent problem with at least 18% of adults reporting insufficient sleep. Adolescents also frequently report insufficient sleep, with half of high school students participating in the 2007 National Youth Risk Behavior Survey reporting short sleep duration (6-7 hours per night), and another 14.8% of males and 16.9% of females reporting very short sleep durations (5 hours or less). Contrary to popular belief, adolescents need as much sleep as pre-teens, with an optimal sleep duration of about 9 hours per night. Insomnia is the most commonly reported sleep disorder, which affects approximately 10 per cent of US adults. It is defined as “difficulty falling asleep, difficulty maintaining sleep, or by
short sleep duration despite adequate opportunity for a full night’s sleep”. The prevalence of insomnia is higher in women and it increases with age in both sexes.

Sleep loss is associated with many deleterious health consequences such as obesity, diabetes and impaired glucose tolerance, cardiovascular disease and hypertension, anxiety symptoms, depressed mood, and alcohol use. These associations were mostly observed in observational studies, many of which are cross-sectional, therefore we cannot make assumptions of causality. Some of these diseases may be the cause of sleep loss, rather than the inverse.

A number of possible biological mechanisms were proposed to explain the between sleep loss and obesity. These mechanisms include neuroendocrine changes; chronic inflammation; and hormonal changes that result from loss of sleep. An experimental case-crossover study by Spiegel et al. found that sleep loss is associated with a decrease in Leptin and an increase in Ghrelin, both are appetite-regulating hormones, leading to increased subjective hunger and a greater desire for calorie-dense foods. Similarly, Boeke et al. found shorter sleep duration to be associated with lower levels of leptin in young girls and in male adolescents, suggesting a sex-specific effect. However, the Nurse’s Health Study suggested that the association between sleep loss and weight gain is not necessarily due to an increase in appetite, but rather due to changes in energy metabolism. Furthermore, a review by Knutson et al, suggested that sleep problems may be associated with reduced energy expenditure, which may explain the increased risk of obesity.

Dysregulated inflammatory mechanisms may occur as a result of primary sleep disorders such as insomnia and obstructive sleep apnea, manifesting as an increase in serum pro-inflammatory C-reactive protein; IL-6; and TNF-α. Moreover, experimental studies found that acute sleep deprivation resulted in an increase un IL-6 and/or hs-CRP. However, observational studies on the association between chronic sleep loss and systemic inflammation had
inconsistent results. Martinez-Gomez et al. found short sleep to be associated with an elevated CRP in adolescent.\textsuperscript{69} By contrast, Taheri et al found no association between short sleep duration and CRP levels in adult men and women participating in the Wisconsin Sleep Cohort Study,\textsuperscript{131} while Okun et al. found that poor sleep quality, but not duration, was associated with an increase in hs-CRP.\textsuperscript{76} On the other hand, a number of studies (Suarez et al.\textsuperscript{79} as well as Miller et al.\textsuperscript{77} and Liu et al.\textsuperscript{120}) found an association between sleep duration and hs-CRP that is limited to women, which suggests that Taheri’s insignificant results may be due to an insufficient number of women in the study. By contrast, Liukkonen found an association between sleep disturbances and CRP that is significant in men but not in women.\textsuperscript{80} This latter study was cross-sectional and included premenopausal women at the age of 31. By contrast, the studies by Liu et al. and Miller et al. included a population with an average age of 48 years, which includes pre- and post-menopausal women. Hormonal changes may explain the discrepancy in results of these studies. Longitudinal studies included the one conducted by Ferrie et al.,\textsuperscript{70} which found that each hour per night decrease in sleep duration between 1991/1994 and 1997/1999 was associated with higher levels of C-reactive protein (8.1\%) and interleukin-6 (4.5\%). However, the association with CRP was no longer significant after adjustment for cardiometabolic risk factors (hypertension, BMI, cholesterol, and diabetes), while IL6 remained significant. Patel et al also found a significant linear association between sleep duration and both hs-CRP and IL6, where each additional hour of sleep led to an 8\% increase in CRP and 7\% increase in IL6.\textsuperscript{74} Whereas Miller et al. found no trend, linear or non-linear, between sleep duration and IL-6. They did however, find that levels of IL-6 were lower in women with longer sleep duration (8 hours compared with 7 hours).\textsuperscript{77} Furthermore, Dowd et al. found that longer sleep duration (more than 8 hours) was associated with elevated levels of CRP and IL-6.\textsuperscript{72} Grandner et al.\textsuperscript{71} also found extreme sleep durations (very short and very long) to
be associated with elevated CRP. However, similar to the study by Ferrie et al., the association between short sleep and CRP was no longer significance after adjusting for comorbid illnesses and concurrent sleep disorders. By contrast, long sleep duration remained significant in all models. This U-shaped association between sleep duration and inflammatory markers mirrors that of sleep duration and mortality, where both short and long sleep durations were associated with higher risk of death, suggesting that there is an optimum duration of sleep that is associated with good health and well-being.

Persistent inflammation is associated with many diseases, such as Type 2 diabetes, cardiovascular disease and asthma. Inflammatory mechanisms contribute to the association between sleep loss and many chronic illnesses. Yet, there is still considerable uncertainty as to whether sleep duration is simply an associated risk marker or a causal risk factor in any disease process. The discrepancy in results is likely to be due to variability in defining sleep quality and categorizing sleep duration, which makes different studies difficult to compare or generalize.

Insufficient sleep in adolescents has been linked to depression, anxiety, inattention and conduct problems, drug and alcohol use, impaired academic performance, and suicidal thoughts and behaviors. Adolescent short sleepers have also been reported to have more fatigue, less energy, worse perceived health and symptoms such as headaches; stomachaches and backaches, and more respiratory infections. Similarly, college students and young adults frequently suffer from poor sleep quality and insufficient sleep. Lund et al. reported that nearly 60% of college students have of poor sleep quality and frequently depend on alcohol and medications to manage their sleep. Sleep deprivation has negative effects on cognitive performance in young adults, and is associated with drug and alcohol use, depression, and obesity, among other negative health consequences.
SLEEP AND ASTHMA

Sleep disturbances in asthma: Asthma is frequently associated with poor sleep quality, thought to be mainly due to nocturnal symptoms experienced at least once a month by as many as 74% of asthmatics. Nocturnal worsening of asthma symptoms occur as a result of circadian rhythms of circulating hormones (such as epinephrine, cortisol, and melatonin), sleep-related variation in airway caliber, and the increase in upper airway resistance, especially in those with uncontrolled asthma. Nocturnal asthma is marked by a decrease in FEV1 of at least 15% between sleep onset and wake up time in asthmatic patients. In addition to variation in FEV1, the airways become hyper-reactive and under-responsive to bronchodilators during sleep in individuals who have nocturnal asthma. Consequently, asthmatics have more frequent sleep disturbances, including difficulty initiating and maintaining sleep, and shorter sleep duration. Asthmatic children and adults were also found to have longer sleep latency and reduced duration of sleep. However Jansen et al found the increase in sleep latency to be limited to females, suggesting gender-related differences.

In addition to nocturnal symptoms, medications used to treat asthma may have a role in some sleep disturbances. Bronchodilators (beta-agonists) act as stimulants and may cause sleep disturbances when given in high doses, corticosteroids in high doses decrease slow wave sleep and REM sleep, and Aminophylline decreases sleep efficiency and REM sleep and increases sleep latency. However, Garrison et al reported that controller medications, especially leukotriene
inhibitors, might be effective in reducing sleep problems through their effect in controlling symptoms.\textsuperscript{147}

Nocturnal symptoms and medications do not fully explain sleep disturbances in asthmatics. Even clinically stable asthmatics appear to have more frequent sleep disturbances.\textsuperscript{11,42} In a study by Luyster et al, the majority (88–100\%) of participants with non-severe asthma (NSA) or severe asthma (SA), who did not report nighttime asthma disturbances, still reported having poor sleep quality.\textsuperscript{148} In both asthma categories, poor sleep quality was associated with worse asthma control and quality of life after controlling for GERD and other covariates.\textsuperscript{148} Similarly, in a study of asthmatic adults by Mastronarde et al., Global Pittsburgh Sleep Quality Index (PSQI) scores correlated with asthma control, quality of life, and marginally with FEV1\%, but Epworth Sleepiness Scale (ESS) did not correlate with FEV1\% or with asthma control. Furthermore, neither PSQI nor ESS were associated with asthma exacerbations, and neither were affected by treatment with theophylline or Montelukast.\textsuperscript{14} Moreover, Stores et al. conducted a study of asthmatic children using Polysomnography, and found that children with asthma had more sleep disruption, nighttime awakenings, and reduced sleep efficiency, than non-asthmatic children, although actual sleep time and REM/NREM sleep did not differ between asthmatics and non-asthmatics. Additionally, subjective impairment and daytime sleepiness were much higher in asthmatic children.\textsuperscript{36} Furthermore, a study by Chugh et al that included 40 children with clinically stable asthma and 30 age and gender matched, healthy children, children with asthma were found to have significantly worse quality of sleep and longer sleep latency.\textsuperscript{42}

**Sleep duration and asthma:** Several studies showed that sleep duration is generally shorter in children and adults with asthma. In a community-based study of 1,478 subjects, those with asthma had a higher prevalence of ‘too little sleep’ (39\% compared with 29\% for non-
asthmatics) and a higher risk (OR=2) of unrefreshing sleep, after adjusting for age, gender, and snoring.\textsuperscript{145} Similarly, two studies by Janson et al. and Vir et al. using sleep diaries, also found that asthmatics recorded shorter sleep time compared with controls.\textsuperscript{32,33} Interestingly, a study of children 5-17 years of age using polysomnography, found that male asthmatics had significantly shorter sleep duration (425.9 (5.4) vs 441.8 (5.4) min, \( p < 0.05 \)) than male controls, while females did not display a significant difference.\textsuperscript{35} By contrast, in the study by Stores et al. mentioned earlier, using Polysomnography, actual sleep time did not differ significantly between children with asthma and their healthy counterparts.\textsuperscript{36} However, the study had a small sample size (15 children, aged 6-15) that may have been responsible for the non-significant results. Furthermore, Desager et al, using a sleep questionnaire completed by parents, did not find a significant difference in total sleep time between asthmatic and non-asthmatic schoolchildren, while they did find significant differences in nocturnal awakenings, restless sleep, daytime sleepiness, and tiredness.\textsuperscript{37} Similarly, Meltzer et al., found no significant difference in sleep duration between asthmatic and non-asthmatic adolescents, using an online survey completed by the adolescent.\textsuperscript{22} However, more adolescents with severe asthma reported insufficient weekday sleep (44\%) versus adolescents without asthma (31\%).\textsuperscript{22} Moreover, a study of adults by Teodoruscru et al. suggested that the association between sleep duration and asthma might be related to asthma severity, as they found that sleep duration was inversely associated with the severity of asthma. Interestingly, a case-control study by Chugh et al. found that children with clinically stable asthma slept longer on average than healthy controls, despite having poorer sleep quality.\textsuperscript{42}

The studies cited above used different study designs, assessment instruments, and age groups, which may explain the discrepancy in results. Using subjective versus objective measures of sleep duration may cause systematic bias\textsuperscript{133} that makes these studies incomparable. In addition,
questionnaires completed by parents of adolescents (like the study by Desager et al. mentioned above) may not accurately reflect sleep duration, as parents tend to report earlier bed times and give an idealized version of their adolescents’ sleep habits.\textsuperscript{38}

**The impact of sleep quality on patients with asthma:** While there are many studies of the impact of asthma on sleep quality, studies exploring the reverse are very limited. Most of those who examined the impact of sleep quality looked at quality of life and daily functioning as the outcomes of interest. For example, Daniel et al. studied the association between missed sleep and asthma morbidity in children, and found that higher reports of missed sleep were associated with more frequent school absences, more activity limitations, and lower quality of life scores.\textsuperscript{18} Diette et al. found that children who awoke from asthma had greater odds of missed school days, compared with those who did not awake, with the odds being higher with awakenings that are more frequent. In addition, parents of children who awoke from asthma also had higher odds of missing work, indicating that quality of life of both children and parents was affected by nocturnal symptoms.\textsuperscript{19} Furthermore, during a 6-month prospective clinical trial, Mastronade et al. found that improved PSQI and Epworth Sleepiness Scale (ESS) scores correlated with improvements in asthma control and Asthma-related Quality Of Life (AQOL).\textsuperscript{14} Moreover, Matheson et al. studied quality of life in people with asthma or wheezing, and found that wheezing in the past 12 months was associated with decreased quality of life, while having current asthma, or a doctor’s diagnosis of asthma, were not significantly associated with QOL. The authors’ conclusion was that symptoms, not the epidemiological definition of asthma, are what affects quality of life.\textsuperscript{20} Similarly, in a cross-sectional study of college students with asthma, Molzon et al. found that poorer sleep quality in asthmatic college students was related to lower HRQOL.\textsuperscript{21} However, as the authors pointed out, the cross-sectional design of this study does not permit the conclusion of
causality. The above-mentioned studies indicate that quality of sleep affects quality of life in asthmatics, and that nocturnal symptoms are the most likely cause for sleep disruption.

As for the effect of sleep quality on asthma control and severity, a few studies suggested that the association between sleep and asthma might be bi-directional. In a study conducted by Becker et al. and presented at the European Respiratory Society Annual Congress 2013, the authors examined the association between sleep and asthma outcomes, and concluded that there is probably a bidirectional relation between asthma control and poor quality of sleep. However, the associations were marginally significant. In a study of 38 youth with asthma (aged 9-19), Hanson and colleagues found that poorer self-reported sleep quality predicted more severe symptoms, lower cortisol output, and lower PEF% the next day, while PEF and symptoms did not predict sleep quality or quantity the next night. The results suggest that sleep may affect subsequent health outcomes, rather than asthma affecting subsequent sleep. Despite the small sample size, this study offers a very important indication of the effect of sleep on asthma symptoms and pulmonary function, as well as the role of cortisol. Furthermore, in a review sleep abnormalities and chronic inflammatory conditions, Ranjbaran et al. concluded that “sleep disturbances are one of the major modifiers of asthma that can affect the course and the severity of the disease”. The mechanisms they cited included physiologic changes as a result of sleep disturbances that adversely affect respiration, arousal responses, and airway clearance of asthmatics. Similarly, Diette and colleagues found that children who experienced nocturnal awakenings had increased symptom severity, and an increased use of reliever medications.

Experimental evidence supporting the impact of sleep on asthma came from a recent pilot study by Meltzer et al. This pilot sleep-extension study included 12 teens with asthma, and found that teenagers who got more sleep during the 2-week program had significantly fewer nocturnal
asthma symptoms (P=0.001) and less variability in objective daily lung function (P=0.05). The authors explained the findings by the decrease in inflammation as a result of increased sleep duration, which in turn improved asthma expression. Further evidence came from a 6-month prospective clinical trial by Mastronarde et al, who found a correlation between asthma control scores (and marginally FEV1%) and global Pittsburgh Sleep Quality Index (PSQI). Moreover, they found that the improvement in PSQI and Epworth Sleepiness Scale (ESS) scores during the study period correlated with improvements in asthma control and Asthma-related Quality Of Life (AQOL), even in individuals who have no history of nocturnal awakenings. This study was limited to adult (mean age 40±15 years), who had mild-moderate symptomatic asthma.

A few longitudinal studies provided further clues into the effect of sleep disturbances on asthma morbidity. Leander et al. conducted a 13-year longitudinal study of 391 adolescents and adults, and found that those who developed asthma during the study period were more likely to have had sleep disturbances at baseline (30% vs. 10%). Furthermore, Kozyrskij et al followed 2398 children from birth until age 14, and found that persistent nocturnal awakening in early life was associated with an increased risk of non-atopic asthma at age 6 and 14 (at age 14 years: OR 2.18, 95% CI 1.15–4.13). This study provides the strongest evidence to date of the association between sleep disturbances and the development of non-atopic asthma. On the other hand, Zhang et al. studied 1534 Chinese adolescent twins age 12–21 years and found a dose-response relationship between sleep duration and sensitization to food and aeroallergens. Twins with shorter sleep durations were more likely to be sensitized to food and aeroallergens than those in the highest tertile of sleep. Although they did not study asthma as an outcome, the association between sensitization (especially to aeroallergens) and asthma is well-established, therefore, this study provides further evidence into an (probably indirect) association between sleep duration and
asthma. Likewise, Jernelov et al. studied 1480 twin pairs and found that being overtired at age 8 was associated with an increased risk of allergic rhinitis and asthma at age 13. However, the association with asthma was no longer significant after controlling for the presence of asthma at age 8, while allergic rhinitis remained significant. However, short sleep at age 8 was not associated with allergic rhinitis or asthma at age 13. Unlike Zhang et al., the authors of this study did not measure sleep duration. They used parental perception instead, with a question that states, “Child sleep less than other kids”, with answers of “often true, sometimes true, not true”. This question does not measure sleep duration accurately, which makes the comparison with other studies very difficult. The studies mentioned above used different age groups and different measure of sleep, which explains the discrepancy in some of their results.

**Possible Mechanisms:** Many mechanisms have been suggested to explain the impact of sleep disturbances on the development as well as the morbidity of asthma. These mechanisms include:

1. **Comorbid conditions:** Certain comorbid conditions that are associated with sleep disturbances as well as poor asthma outcomes were thought to explain the sleep-asthma association at least partially. These conditions also interact with one another as shown in Figure 1. They include: (1) *Obesity*, which is known to be associated with both asthma and short sleep duration, although the mechanisms of these associations are not clear. It is possible that short sleep duration leads to an increase in BMI, which in turn is associated with increased airway inflammation and worse asthma morbidity. However, some studies showed an association between sleep duration and asthma that is independent of BMI, indicating that BMI cannot entirely explain the sleep-asthma association, although it can exacerbate sleep problems in asthmatics. Furthermore, many asthmatics have normal BMI, including those who
have less than optimal sleep duration. (2) *Obstructive sleep apnea (OSA)* is another comorbid condition associated with both sleep and asthma.\(^{146,152}\) OSA is strongly associated with obesity, and often leads to sleep disruption and daytime sleepiness, as well as increased systemic and airway inflammation.\(^{153,154}\) However, OSA is not usually associated with shorter duration of sleep; therefore, it does not explain the association between sleep duration and asthma. It is possible though, that the combined effect of OSA and short sleep duration may lead to poorer asthma outcomes.\(^{155}\) (3) *Allergic rhinitis (AR)* is significantly associated with atopic asthma and with impaired quality of sleep.\(^{152}\) The strong correlation between asthma and AR makes it difficult to study the association between sleep and asthma, independent of allergic rhinitis. Furthermore, the disease processes in AR and asthma are very similar; therefore, AR needs to be taken into consideration when studying asthma as an outcome. (4) *Gastroesophageal reflux disease (GERD)* aggravates asthma and is associated with poor sleep quality.\(^{105}\) However, sleep duration is not usually affected by GERD. Furthermore, Luyster et al. found that poor sleep was associated with worse asthma control, independent of GERD.\(^{148}\) Additionally, there is no evidence that GERD treatment improves nocturnal asthma or asthma control.\(^{13}\) (5) *Depression and anxiety* are both associated with sleep disturbances as well as asthma severity. A study based on the Israeli health survey found that depressive symptoms were common in asthmatic individuals and were associated with less hours of sleep.\(^{156}\) Similarly, a study of US adults, based on the 2006 Behavioral Risk Factor Surveillance System (BRFSS), found that asthmatic adults who have current depression were more likely than those without current depression to report insufficient sleep, in addition to other HRQOL measures.\(^{157}\) The mechanism of these association may lie in the hormonal pathway (see below). Depression, anxiety, and stress are likely to be
contributing factors to the sleep-asthma association. However, they may be the cause of insufficient sleep, or may also occur as a result of the sleep disturbances.

2. Hormonal pathways: Sleep restriction affects the hypothalamic pituitary adrenocortical (HPA) axis, which leads to an increase in secretion of the stress hormone, Cortisol. As mentioned above, Ising&Ising found that sleep disruption as a result of traffic noise leads to an increase in cortisol secretion in the first half of the night and a disruption in circadian rhythm of cortisol secretion. They suggested that this disruption is associated with an aggravation in bronchitis and asthma in children.\textsuperscript{158,159} By contrast, Hanson et al. studied 38 youth with asthma (age 9-19) and found that greater reported sleep quantity predicted lower cortisol output and lower PEF\% the following day.\textsuperscript{16} Similarly, Capaldi et al. conducted a pilot study of the association between sleep and cortisol responses to stress in children and adolescents, and found that greater sleep-wake

![Figure A.1: Asthma and comorbid conditions.](Source: Catherine Kier, Stephanie Hom, and Faiza Qureshi (2012). Asthma and Sleep. Journal of Asthma & Allergy Educators. Vol 3:No. 3, pp: 99-105)

behavior problems were associated with decreased cortisol responses, while no association was found between sleep quantity and cortisol.\textsuperscript{160} Although the authors did not study the impact on asthmatics, the study provides evidence of the effect of sleep disruption on cortisol secretion. The
association between cortisol levels and asthma is further clarified through studies by Priftis et al., Buske-Kirchbaum et al., and Wamboldt et al., which showed that children with asthma have an attenuated cortisol response to stress. Priftis et al. suggested a model that explains the pathway through which stress may influence asthma in children. Stress leads to an increase in proinflammatory cytokines, which in turn attenuate cortisol response, leading to airway hyperactivity and inflammation. This points out to the possibility that poor sleep quality and insufficient sleep alters cortisol response to stress as suggested by Capaldi, leading to an increase in airway inflammation and asthma exacerbations through the mechanism suggested by Priftis.

3. Effect on the immune system: Another mechanism through which sleep deprivation can affect asthma is through its alteration of the immune response to a viral illnesses, and increased susceptibility to infections and allergy. Orzech et al. found that adolescents with shorter sleep time suffered more frequent bouts of acute infections. Viral infections are common triggers of asthma exacerbations; mostly due to inflammation that accompanies these infections. Therefore, susceptibility to infections because of sleep deprivation can have a negative impact on asthma.

4. Inflammation: As mentioned above, sleep loss is associated with systemic inflammation, which in turn was found to be associated with asthma severity in cross-sectional analyses. Furthermore, Kalhan et al. and Ahmadi-Abhari et al. found that systemic inflammation is longitudinally associated with a decline in lung function, with a potential negative effect on asthmatics. In the CARDIA study of healthy young adults, Kalhan et al. found that higher CRP in year 7 was associated with greater 15-year decline in both FVC and FEV1. Similarly, Ahamadi-Abhari and colleagues studied the longitudinal association between CRP and lung function over a 13-year period. They found that a one SD increase in baseline log$_e$-CRP was
associated with a reduction in FEV1 (-86.3 mL, 95% CI: -93.9, -78.6). In addition, a one SD increase in log-CRP over 13 years was associated with a decline in FEV1 over the same period (-64.0 mL, 95% CI: -72.1, -55.8). These findings may explain the association between sleep disturbances and asthma through the inflammatory pathway. Furthermore, Majde and Krueger conducted a review of the link between the innate immune system and sleep, and concluded that the role inflammatory cytokines play in asthma partially explains why sleep disorders exacerbate asthma. Moreover, Axelsson et al. found that sleep restriction results in a shift of the immune system toward the response of helper T cells, type Th2, which are associated with allergic diseases and asthma. Additionally, sleep disturbances are associated with an increase in IL-8 and TNF-α. The latter has been implicated in asthma exacerbations, airway inflammation associated with severe asthma in adults; and was also found to be elevated in children with viral wheeze or bronchial hyperactivity.

Sleep deprivation is also associated with airway inflammation, manifesting by elevated FeNO. Malish et al. found that medical residents who engaged in regular in house calls, leading to sleep deprivation had elevated FeNo levels compared with their non-call counterparts. Similarly, Oberg et al. found that male medical residents had higher FeNo levels when post-call than when not on-call. These studies point to the effect of sleep loss in young healthy individuals on airway inflammation, which raises the question of the effect would be even more pronounced in asthma patients, and what impact it would have on their symptoms.

**SUMMARY**

The literature review presented above highlights several gaps and issues that limit our understanding of the association between sleep duration and asthma. Very few studies attempted to examine this association, and most of those had very small sample sizes, or were limited to the
examination of quality of life in asthmatics. Longitudinal studies mostly examined the risk of allergic sensitization in children, rather than measures of asthma morbidity. Studies of adolescents and young adults are severely lacking, as are studies of the role of the interactions of sleep duration, asthma, and gender and their association with inflammation. There is a need for adequately powered studies that examine the association between sleep duration and asthma morbidity in adolescents and young adults, while accounting for the role of inflammation.
APPENDIX B

ADDITIONAL TABLES AND FIGURES

Figure B.1: Add Health study design
Tables B.1: Sleep duration statistics by trajectory group in participants of waves 3 & 4 of the Add Health study

<table>
<thead>
<tr>
<th>TRAJECTORY GROUP</th>
<th>WAVE 3 MEAN SLEEP DURATION (95% CI)</th>
<th>WAVE 4 MEAN SLEEP DURATION (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1</td>
<td>5.47 (5.3-5.6)</td>
<td>5.75 (5.6-5.9)</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>7.95 (7.9 – 8.0)</td>
<td>7.82 (7.79 – 7.86)</td>
</tr>
<tr>
<td>GROUP 3</td>
<td>10.7 (10.4- 11.0)</td>
<td>10.6 (10.2 – 10.7)</td>
</tr>
</tbody>
</table>

Table B.2: Results of multivariate linear regression analysis for natural logarithm of CRP and sleep duration in waves 3 & 4 in the Add Health study (Regression coefficients and P-values), after including CRP values greater than 10 mg/l

<table>
<thead>
<tr>
<th>Sleep duration trajectory group</th>
<th>UNADJUSTED COEFFICIENT (P-VALUE)</th>
<th>FULLY ADJUSTED§</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short</td>
<td>0.065 (0.1539)</td>
<td>0.091 (0.0492)</td>
</tr>
<tr>
<td>• Good</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>• Long</td>
<td>0.151 (0.0735)</td>
<td>0.109 (0.1837)</td>
</tr>
</tbody>
</table>

§ Fully adjusted model included sex, race, income, education, smoking, alcohol, physical activity, trouble sleeping, snoring, hypertension, depression, symptoms of infection, subclinical symptoms of inflammatory disease, & medication use

Table B.3: Association between sleep in waves 3 & 4 and CRP levels greater than 3 mg/dl in the Add Health study (Odds ratios and 95% C.I.) after including CRP values > 10 mg/l

<table>
<thead>
<tr>
<th>Sleep duration trajectory group</th>
<th>Unadjusted</th>
<th>Fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short</td>
<td>1.41 (1.09, 1.82)</td>
<td>1.74 (1.26, 2.38)</td>
</tr>
<tr>
<td>• Good</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>• Long</td>
<td>1.23 (0.85, 1.80)</td>
<td>1.14 (0.64, 2.03)</td>
</tr>
</tbody>
</table>

§ Fully adjusted model included sex, race, income, education, smoking, alcohol, physical activity, trouble sleeping, snoring, hypertension, depression, symptoms of infection, subclinical symptoms of inflammatory disease, & medication use
ABOUT THE AUTHOR

Chighaf Bakour was born in Damascus, Syria in 1970. She received her Doctor of Medicine degree from Damascus University in 1994, and followed it with training in ophthalmology. She earned a master of public health degree from Independence University in 2006, and joined USF College of public health to pursue her doctorate in Fall 2009. Her research interests include maternal and child health, asthma, obesity, and sleep epidemiology. She presented her research at many local, state, and national conferences. In addition to research, Chighaf worked as a teaching assistant for many classes, and taught an undergraduate course in epidemiology. She received many awards and scholarships, including the Greg Alexander scholarship, and the Maternal and Child Health Epidemiology Traineeship.