Sleep Duration, Diet Quality and Type 2 Diabetes

SLEEP DURATION, DIET QUALITY AND TYPE 2 DIABETES

ELIZABETH M CESPEDES

A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Science

in the Departments of Nutrition and Epidemiology

Harvard University

Boston, Massachusetts.

May 2015

Dissertation advisor: Frank B Hu Elizabeth M Cespedes

SLEEP DURATION, DIET QUALITY AND TYPE 2 DIABETES

Type 2 diabetes has reached epidemic proportions globally, and accumulating evidence suggests extremes of sleep duration increase risk. Diet may be an important mechanism, yet few studies examine prospective relationships of sleep duration and diet quality or whether diet explains associations of sleep duration with childhood obesity or diabetes in adults. In Chapter One, we report a moderate correlation between self-reported sleep duration and actigraphy in Sueño, the sleep ancillary study to the Hispanic Community Health Study/Study of Latinos. Chapter Two identifies associations of chronic insufficient sleep duration since infancy with lower diet quality in mid-childhood in Project Viva: children with the least favorable diet and sleep have the highest body mass index z-scores in mid-childhood, but diet does not explain associations with adiposity. In Chapter Three, adherence to healthful dietary patterns reduces risk of diabetes in the Women's Health Initiative; high quality diets are protective in all groups, but race/ethnicity modifies associations. In Chapter Four, we find that changes in sleep duration, increases in particular , are associated with diabetes and concomitant changes in diet quality, physical activity and weight in the Nurses' Health Study. Each of these studies contributes new knowledge: Sueño represents the largest sleep validation to date, the only validation among Hispanic/Latinos and allows researchers to better understand the information contained in (and the limitations of) self-reported measures of sleep duration within subgroups. In the Women's Health Initiative, we address limitations of the current literature on dietary patterns by calculating four dietary indices within the same cohort, standardizing the scores for comparison and examining associations across racial/ethnic groups. Project Viva is the first study to examine

the influence of chronic insufficient sleep on diet quality in childhood when health behaviors and dietary preferences are being formed. Finally, examining changes in sleep duration and changes in diet quality, physical activity and weight in the Nurses' Health Study represents a novel way to leverage repeated assessments. Results of this dissertation may help build the case for policy and intervention efforts to prevent and treat obesity and diabetes, particularly those that seek to improve both sleep and diet.

Table of Contents

Signature Page

Title Page i

Abstract ii

List of Figures v

List of Tables vi

Acknowledgements vii

Introduction 1

Chapter 1
Comparison of Self-Reported Sleep Duration with Actigraphy: Results from the Hispanic Community Health Study/ Study of Latinos Sueño Ancillary Study 4

Chapter 2
Chronic Insufficient Sleep and Diet Quality: Contributors to Childhood Obesity 41

Chapter 3
Multiple Healthful Dietary Patterns are Associated with Reduced Risk of Type 2 Diabetes in the Women's Health Initiative 70

Chapter 4
Long-Term Changes in Sleep Duration, Energy Balance and Risk of Type 2 Diabetes in the Nurses' Health Study 98

Conclusion 124

List of Figures

Chapter 1: Comparison of Self-Reported Sleep Duration with Actigraphy: Results from the Hispanic Community Health Study/ Study of Latinos Sueño Ancillary Study

- Figure 1.1: Mean actigraphy-assessed time asleep and time in bed by hour/day of self-Reported sleep duration 22
- Figure 1.S1: Prediction of tertiles of actigraphy-assessed sleep duration given tertiles of self-reported sleep duration 40

Chapter 2: Chronic Insufficient Sleep and Diet Quality: Contributors to Childhood Obesity

- Figure 2.1: Association of sleep curtailment score with BMI z-score in mid-childhood does not attenuate with adjustment for mid-childhood dietary factors 55
- Figure 2.S1: Dietary factors as predictors of BMI z-score mid-childhood 68
- Figure 2.S2: Joint associations of sleep curtailment and diet quality with BMI z-score in mid-childhood 69

Chapter 3: Multiple Healthful Dietary Patterns are Associated with Reduced Risk of Type 2 Diabetes in the Women's Health Initiative

- Figure 3.1: Multivariate hazard ratios of diabetes per standard deviation higher score on diet quality indices in the Women's Health Initiative 82

Chapter 4: Long-Term Changes in Sleep Duration, Energy Balance and Risk of Type 2 Diabetes in the Nurses' Health Study

- Figure 4.S1. Joint associations of sleep duration in 1986 and change in sleep duration from 1986 - 2000 with subsequent risk of type 2 diabetes 123

List of Tables

Chapter 1: Comparison of Self-Reported Sleep Duration with Actigraphy: Results from the Hispanic Community Health Study/ Study of Latinos Sueño Ancillary Study

- Table 1.1. Characteristics of the sample by self-reported sleep duration at the Sueño visit 13
- Table 1.2. Mean (SD), correlations and bivariate regression coefficients: actigraphy measurements predicted by self-report 16
- Table 1.3. Actigraphy-assessed time asleep predicted by self-reported sleep duration: mean (SD), correlations and bivariate regression coefficients by participant characteristic 18
- Table 1.4. Actigraphy-assessed sleep predicted by self-reported sleep and participant characteristics 24
- Table 1.5. Coefficients and R^2 for predictors of actigraphy-assessed time asleep and time in bed 27
- Table 1.6. Conditional probabilities of low, medium or high actigraphy-assessed time asleep and in bed given self-reported sleep duration categorization 29
- Table 1.S1. Characteristics of the Sueño sample compared to HCHS/SOL 39

Chapter 2: Chronic Insufficient Sleep and Diet Quality: Contributors to Childhood Obesity

- Table 2.1. Participant characteristics by sleep curtailment category 51
- Table 2.2. Sleep curtailment score as a predictor of dietary intake in mid-childhood 53
- Table 2.S1: Dietary Factors at Mid-Childhood Visit 67

Chapter 3:Multiple Healthful Dietary Patterns are Associated with Reduced Risk of Type 2 Diabetes in the Women's Health Initiative

- Table 3.1. Participant characteristics by category of standardized diet quality scores, Women's Health Initiative 80
- Table 3.2. Association of diabetes per quintile and standard deviation higher diet quality in Women's Health Initiative 83
- Table 3.3. Association of diabetes per category and standard deviation higher diet quality: results by race/ethnicity in Women's Health Initiative 85
- Table 3.S1. Scoring criteria for diet quality indices using MyPyramid Equivalents in the Women's Health Initiative OS-CT 96

Chapter 4: Long-term Changes in Sleep Duration, Energy Balance and Risk of Type 2 Diabetes in the Nurses' Health Study

- Table 4.1 Baseline characteristics by change in sleep in the Nurses' Health Study 107
- Table 4.2. Change in sleep duration and change in energy balance factors 109
- Table 4.3. Change in sleep duration and subsequent risk of type 2 diabetes 111
- Table 4.S1. Change in sleep duration and subsequent risk of type 2 diabetes 122

ACKNOWLEDGEMENTS

Sincere thanks to my advisor, Dr. Frank Hu, who has provided me with invaluable opportunities to develop as a scientist, to learn and to advance professionally. I express my deepest gratitude: his help and guidance have been the most important features of my doctorate.

Other dissertation committee members were also instrumental. Dr. Bernard Rosner made time to discuss with me individually each of the papers presented here. He not only strengthened the statistical aspects, but brought thoughtful insight to the substantive areas addressed. Dr. Susan Redline was encouraging and supportive while providing irreplaceable expertise in the biology and epidemiology of sleep. In addition to their contributions to this dissertation, I have had the privilege of learning from both of these outstanding scientists through the Harvard Center of Transdisciplinary Research in Energetics and Cancer.

Thank you to the all the other co-authors of this research and to the many mentors who have taken me under their wings during my studies. In particular, Drs. Matthew Gillman and Elsie Taveras have been generous and nurturing mentors since the beginning. Working at the Obesity Prevention Program at Harvard Pilgrim Health Care was the defining experience of my Masters, enabled me to apply for doctoral programs, led directly to the content of my dissertation work in Project Viva, and has provided countless opportunities since.

When I sought out Dr. Sanjay Patel at the Brigham and Women's Hospital, he was not only open to sharing data, but also served as a patient teacher. Working with him has deepened my understanding of sleep’s contribution to metabolic health and how to measure it. I am grateful for the time he has taken to provide feedback on the projects we have pursued together.

More recently, Drs. Marian Neuhouser and Lesley Tinker have become valued mentors, first through their kindness in enabling collaborations at the Fred Hutchinson Cancer Research Center, and second through guiding my research on dietary patterns Women's Health Initiative.

Institutional funding from the National Institute of Diabetes and Digestive and Kidney Diseases T32 DK007703 enabled my doctoral research.

Many generous colleagues in Nutrition, Epidemiology and other departments have also provided professional and personal support throughout, in particular, Brittany: thank you for being the understanding friend and generous colleague I needed to navigate this world.

My partner and my parents have helped bolster my confidence and cultivate optimism at critical times. I am always grateful for their patience and love.

_____

Elizabeth M. Cespedes

INTRODUCTION

Type 2 diabetes has reached epidemic proportions in the United States and globally. By 2035, 592 million diabetes cases are projected worldwide. (1) An estimated 29.1 million Americans were living with diabetes in 2014, with African Americans and Hispanic/Latinos experiencing a greater burden than non-Hispanic whites and developing diabetes at younger ages. (2) The estimated national cost of diabetes in 2012 totaled $245 billion, $176 billion in direct health care expenditure and $69 billion in lost or reduced productivity, unemployment from chronic disability, and premature mortality. (3)

Lifestyle factors – in particular, diet quality and, more recently sleep duration – are recognized contributors to diabetes and potentially to disparities in disease burden. (4) Accumulating evidence suggests that extremes of sleep duration increase risk of obesity and diabetes in adults and that short sleep duration is an obesity risk factor in children. Lower diet quality may be one mechanism underlying these associations: experimental research indicates that sleep restriction can induce a hormonal state predisposed to over eating, and both experimental and observational research point towards short sleep increasing caloric intake and consumption of fats and carbohydrates. (5-11) Yet, few studies have assessed prospective relationships of sleep duration with diet quality or examined whether diet quality can explain associations of sleep duration with childhood obesity or diabetes in adults.

The goal of this dissertation is to advance knowledge of these two behavioral risk factors and their interplay: diet quality and sleep duration. To accomplish this, we draw on diverse datasets from different racial/ethnic populations encompassing different periods of the life course. In Chapter One, we validate self-reported sleep duration against actigraphy in Sueño, the sleep ancillary study to the Hispanic Community Health Study/Study of Latinos. In Chapter Two, we

examine whether chronic insufficient sleep duration from infancy on predicts diet quality in mid-childhood, and whether diet quality mediates associations with child adiposity in Project Viva. In Chapter Three, we examine dietary patterns associated with risk of diabetes in post-menopausal women, and whether race/ethnicity modifies these associations, using data from the Women's Health Initiative. Finally, in Chapter Four, we examine whether changes in sleep duration predict subsequent risk of diabetes or concomitant changes in diet quality, physical activity or weight in middle-aged and older women in the Nurses' Health Study. We hope the results of these studies may help build the case for policy and intervention efforts to prevent and treat obesity and diabetes, particularly those that seek to improve both sleep and diet.

REFERENCES

1. International Diabetes Federation. Version 6th. Internet: http://www.idf.org/diabetesatlas (accessed November 5 2014).
2. Centers for Disease Control and Prevention. Internet: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes care 2013;36(4):1033-46. doi: 10.2337/dc12-2625.
4. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. Endocrine 2014;47(1):107-16. doi: 10.1007/s12020-014-0264-4.
5. Chaput JP. Sleep patterns, diet quality and energy balance. Physiology & behavior 2013. doi: 10.1016/j.physbeh.2013.09.006.
6. Chaput JP, St-Onge MP. Increased food intake by insufficient sleep in humans: are we jumping the gun on the hormonal explanation? Frontiers in endocrinology 2014;5:116. doi: 10.3389/fendo.2014.00116.
7. Klingenberg L, Sjodin A, Holmback U, Astrup A, Chaput JP. Short sleep duration and its association with energy metabolism. Obesity reviews : an official journal of the International Association for the Study of Obesity 2012;13(7):565-77. doi: 10.1111/j.1467-789X.2012.00991.x.
8. Schmid SM, Hallschmid M, Schultes B. The metabolic burden of sleep loss. The lancet Diabetes & endocrinology 2014. doi: 10.1016/s2213-8587(14)70012-9.
9. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Annals of internal medicine 2004;141(11):846-50.
10. St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJ. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. The American journal of clinical nutrition 2011;94(2):410-6. doi: 10.3945/ajcn.111.013904.
11. Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. Sleep 2010;33(9):1201-9.

Chapter 1: Comparison of Self-Reported Sleep Duration with Actigraphy: Results from the Hispanic Community Health Study/ Study of Latinos Sueño Ancillary Study

---

Elizabeth M Cespedes, Frank B Hu, Susan Redline, Bernard Rosner,

Carmela Alcantara, Jianwen Cai, Martica H Hall, Jose S. Loredo,

Yasmin Mossavar-Rahmani, Alberto R Ramos, Kathryn J Reid, Neomi A Shah,

Daniela Sotres-Alvarez, Phyllis C Zee, Rui Wang, Sanjay R Patel

ABSTRACT

Background/objective: Measurement error limits research on health effects of sleep. Most studies rely on self-reported sleep duration, although correlation with objective measures is poor. We define socio-demographic and sleep characteristics associated with misreporting and assess whether accounting for these factors improves prediction of objective sleep duration.

Methods: We evaluated 2,086 participants in the Sueño Ancillary Study to the Hispanic Community Health Study who completed ≥5 nights of wrist actigraphy and reported habitual bed/wake-times on weekdays/weekends. Using linear regression, we assessed the accuracy of self-report as a predictor of actigraphy-assessed sleep duration.

Results: Mean (SD) actigraphy-assessed time asleep was 6.74 (1.02) hours, self-reported sleep averaged 7.85 (1.12) hours and their correlation was 0.43. For each additional hour of self-reported sleep, time asleep increased by 20 minutes (95% CI: 19, 22). Correlations between self-report and actigraphy-assessed time asleep were lower among men, younger subjects, and those with the greatest night-to-night variability in sleep duration. Adding socio-demographic and sleep factors to self-reported sleep duration increased the proportion of variance explained in actigraphy-assessed sleep only moderately, from 18% to 25%.

Conclusions: In the largest study to date, we confirm the presence of systematic bias and identify predictors of actigraphy-assessed time asleep to aid in measurement error correction of self-reported sleep duration.

INTRODUCTION

Accumulating evidence links habitual short sleep duration with chronic diseases including hypertension, obesity, diabetes, and cancer. (1-3) The majority of epidemiologic studies use questionnaires to assess sleep duration, yet little research examines the validity of self-report against objective measurements of sleep. Even fewer studies have had sufficient participants to explore sources of systematic bias or to validate measures within subgroups defined by participant socio-demographic or sleep characteristics. (4, 5)

Although polysomnography is regarded as the gold standard for measuring sleep, it is impractical in large epidemiologic studies for multiple nights due to participant burden and expense. (6) Wrist actigraphy, which imputes sleep/wake status by measuring movement, is a less expensive, less invasive alternative that allows for data collection over multiple days while participants sleep in their typical surroundings. Though actigraphy is not itself a gold standard, total sleep time measured by actigraphy and polysomnography have good agreement (r=0.90). (7, 8) Thus, actigraphy is the method of choice for objective sleep measurement over multiple nights, and provides a standard for validating self-reported sleep duration in epidemiologic studies.

A recent validation by Girschik et al. in which 56 Australian women ages 18-80 years wore a wrist actigraph for 7 nights found poor agreement between a three-item sleep questionnaire and actigraphy-recorded sleep duration. (9) Larger studies in American populations have found moderate correlations of self-reported and actigraphy-assessed sleep duration, and suggested the presence of both random error and systematic bias. For example, the sleep ancillary study of the Coronary Artery Risk Development in Young Adults Study (CARDIA) found a correlation of 0.47 between self-reported sleep duration and 3 days of wrist actigraphy among 669 African American and non-Hispanic white participants (mean age 43

years). (5) The Osteoporotic Fractures in Men Study included 2,006 older men (mean age 76 years) with concurrently measured polysomnography and actigraphy and found a modest correlation of self-reported sleep duration with total sleep time as assessed by actigraphy (r = 0.31). (4)

To our knowledge no prior study has examined the validity of self-reported sleep duration among Hispanic/Latinos, the largest racial/ethnic minority group in the U.S. and a population particularly burdened by obesity, diabetes and other diseases linked to sleep duration. With 2,086 participants, ours is the largest study to compare self-reported sleep duration against wrist actigraphy. This large sample enables examination of how well self-report and actigraphy correlate within subgroups defined by sleep and socio-demographic characteristics, and which characteristics contribute to the difference between self-reported and objective measures. Additionally, we identify predictors of actigraphy-assessed time asleep and time in bed to assess the possibility of developing calibration equations to correct for measurement error in self-reported sleep duration.

METHODS

Study Population

The Hispanic Community Health Study/ Study of Latinos (HCHS/SOL) enrolled 16,415 self-identified Hispanic/Latino persons aged 18-74 years between March 2008 and June 2011. Participants were recruited from randomly selected households in four US communities (Bronx, New York; Chicago, Illinois; Miami, Florida; San Diego, California) representing first, second and third generation Hispanic/Latinos, including individuals from Cuban, Dominican, Mexican, Puerto Rican, Central American, and South American backgrounds. The study was approved by

review boards at each participating institution and written informed consent was obtained from all participants. Details of the study design and procedures are described elsewhere. (10, 11)

Sueño, a sleep ancillary study, enrolled 2,252 HCHS/SOL participants between October 2010 and December 2013. Participants were <65 years of age, not pregnant and had no severe sleep disorder (narcolepsy or severe obstructive sleep apnea defined as an apnea hypopnea index [AHI] >50 events/hour or use of positive airway pressure therapy). All Sueño participants were interviewed within 30 months of their baseline HCHS/SOL visit. The present analysis included 2,086 individuals meeting eligibility criteria with available objective and subjective sleep measures.

Self-reported sleep duration was assessed at the Sueño visit through participant-report of habitual bed/wake times on weekends/weekdays, from which we calculated a weighted average of sleep duration (2/7*weekends+5/7*weekdays) as in other sleep publications. (12) Self-reported sleep duration was examined continuously and categorized in tertiles and also into a priori groupings (<7 hours, 7-≤9 hours and >9 hours) based on the published literature.

Actigraphy measurements

At the Sueño visit, participants were instructed to wear an Actiwatch Spectrum actigraph (Philips Respironics, Murrysville, PA) on the non-dominant wrist for 7 days and complete sleep diaries upon awakening. Time in bed was based on four inputs in order of importance: event markers, sleep diary, white light intensity and activity. The Actiware 5.59 algorithm was applied to generate sleep/wake status for each 30-second epoch during the time in bed; this algorithm has been validated on an epoch-by-epoch basis against polysomnography. (13, 14) The settings used for this analysis were 5 immobile minutes to define sleep onset, 0 immobile minutes to define sleep offset, and a wake-threshold activity count of 40.

Only subjects with a minimum of 5 days of actigraphy were included in this analysis. Among those included, the mean (standard deviation, SD) number of valid nights of actigraphy was 7 (1), ranging 5–17 days. From actigraphy, we calculated a weighted average (2/7*weekends+5/7*weekdays) of time in bed (duration of time between getting in/out of bed) and time asleep (duration of time within the in-bed interval scored as sleep). Time asleep and time in bed were treated continuously, in tertiles, and in a priori groupings: <7 hours, 7-≤9 hours and >9 hours. Variability in nightly sleep was defined as the SD of time asleep across all recorded days. Participants in the top quartile (SD >1.5 hours) were considered to have "high" variability in nightly sleep.

Covariate Assessment

As part of the HCHS/SOL baseline exam, participants underwent home sleep apnea monitoring using the ARES Unicorder 5.2 (B-Alert, Carlsbad, CA) to compute the AHI, defined above. (15) Use of this device and the centralized scoring process are described elsewhere. (16) Sleep apnea severity was classified as none (<5 events/hour), mild (5-15 events/hour) or moderate (15-50 events/hour). The HCHS/SOL baseline examination included interviewer-administered questionnaires in the participant's preferred language (Spanish or English), and other measurements decribed previously. (10, 11) Information was obtained on demographics (Hispanic/Latino background [Cuban, Dominican, Mexican, Puerto Rican, Central American, or South American], nativity [in/out of the mainland US]), socioeconomic status (educational attainment [<high school, high school diploma, or >high school] and annual household income [<$30k, ≥$30k, or not reported]), cigarette and alcohol use (current or non-current use), and physical activity (via the Global Physical Activity Questionnaire, participants self-reported

days/week of recreational, transportation or work activity; corresponding metabolic equivalent units were categorized as high, moderate or low). (17)

As part of the Sueño visit, interviewers administered questionnaires about socio-demographics, mental health and sleep behaviors. Sleep-related symptoms were assessed using the Sleep Heart Health Study Sleep Habits Questionnaire, (18) the Epworth Sleepiness Scale (ESS), (19) and the Insomnia Severity Index (ISI). (20) Excessive daytime sleepiness was dichotomized as ESS≥10 and ISI was categorized into: No clinically significant insomnia, ISI 0-7; Sub-threshold insomnia: 8-14; Moderate clinical insomnia: 15-21; and Severe clinical insomnia: 22- 28. Depressive symptoms were evaluated using the 10-item Center for Epidemiological Studies – Depression (CES-D10) questionnaire, dichotomized as CES-D10≥10). (21, 22) Questionnaire-measured frequency of sleep medication usage was categorized as < /≥ than once/week. Participants were asked about current employment, and typical work schedule. Night, irregular, on-call or rotating shifts that included late nights or early mornings were considered shift work. Caffeine intake (daily consumption of caffeinated coffee, tea, soda and energy drinks) was categorized as < /≥ 3 cups/day. Age was categorized into 18-44 and 45-64 years. Body mass index (BMI) was calculated as measured weight in kilograms divided by the square of measured height in meters and categorized into underweight/normal weight (≤25), overweight (>25-<=30), and obesity (class I: >30-≤35, II: >35-≤40 or III: ≥40).

Statistical Analysis

We computed descriptive statistics of the HCHS/SOL cohort and of the Sueño sub-sample by category of self-reported sleep duration. Next, we calculated Pearson correlation coefficients of self-reported sleep duration with actigraphy-assessed time asleep, overall and in subgroups defined by participant characteristics. We estimated unadjusted beta coefficients and

95% confidence intervals for self-reported sleep duration as a predictor of actigraphy-assessed time asleep using linear regression.

To examine predictors of actigraphy-assessed time asleep, we used multivariable linear regression with actigraphy outcomes predicted by self-reported sleep duration and participant characteristics: age, sex, BMI, insomnia, sleep apnea, sleepiness, sleep medication, employment, education, ethnicity, nativity, language, depressive symptoms, caffeine, smoking, alcohol, and physical activity. We also considered interaction terms of each participant characteristic and self-reported sleep duration. To identify predictors of actigraphy-measurements using self-report and participant characteristics, we used stepwise regression with 10-fold cross validation. Candidate variables introduced into this selection procedure included each of the above characteristics and their interactions with self-reported sleep duration. Interaction terms entered the model only with the corresponding main effect.

Self-reported sleep duration is often treated categorically due to an observed U-shaped relationship between sleep duration and many disease outcomes. Thus, we assessed the accuracy of ranking by calculating proportion of participants correctly classified in low, medium or high tertiles of actigraphy-measurements based on tertiles of self-reported sleep duration. We also report the area under the receiver operating characteristics curve (AUC) for logistic models using self-reported sleep duration tertiles to predict measured actigraphy-assessed short sleep (excluding 'long sleep,' i.e. those in the top tertile of sleep time) and actigraphy-assessed long sleep (excluding 'short sleep,' i.e. those in the bottom tertile of sleep time) with/without additional covariates.

In sensitivity analyses, we excluded participants in the top quartile of nightly variability in sleep. We compared goodness of fit for models with/without non-linear relationships, adding

quadratic and cubic terms for self-reported sleep to models, and testing linear and cubic splines. In order to understand whether differences between self-report and actigraphy were due to the fact that self-report asked about time spent in bed rather than asleep per se, we repeated all analyses with actigraphy-assessed time in bed as the outcome.

A p value <0.05 was used to indicate statistical significance in all analyses.

RESULTS

Table 1.1 shows Sueño sample characteristics by category of self-reported sleep duration. Overall, Sueño characteristics were similar to the HCHS/SOL parent cohort with respect to key demographic/health variables such as BMI, education, income, and employment (Supplemental Table 1). Mean (SD) age at Sueño was 47.1 (11.5) years and mean (SD, range) time between the HCHS/SOL baseline examination and Sueño was 24 (5, 4 - 30) months. Mean (SD) self-reported sleep duration was 7.86 (1.28) hours; actigraphy-assessed time asleep was more than one hour shorter (6.74 [1.02] hours). Participants reporting short sleep were slightly older, with slightly higher scores for depression, sleepiness, insomnia, sleep apnea, and adiposity, and were more likely to consume $\geq$3 caffeinated beverages/day. Those reporting long sleep were younger, more likely to have incomes <$30k/year, to be unemployed and to have no or low physical activity.

Table 1.1. Characteristics of the sample by self-reported sleep duration at the Sueño visit (n=2,086)

	Self-Reported Sleep Duration at Sueño Visit		
	Short, < 7h N=460	Intermediate, 7-9h N=1292	Long, >9h N=334
Age, years, mean (SD)	48.1 (10.6)	46.9 (11.5)	46.5 (12.7)
Women, n (%)	283 (62)	849 (66)	219 (66)
BMI, kg/m^2	31.1 (6.8)	29.8 (6.0)	29.7 (6.6)
Center for Epidemiologic Studies Depression Scale	8.2 (6.3)	7.2 (6.1)	7.5 (5.8)
Educational attainment, n (%) *			
No High school	137 (30)	387 (30)	140 (42)
≤ High school graduate	115 (25)	349 (27)	75 (22)
> High school graduate	208 (45)	553 (43)	119 (36)
Annual household income, n (%) *			
< $30,000	309 (67)	846 (65)	245 (73)
≥ $30,000	132 (29)	393 (30)	68 (20)
Did not report	19 (4)	53 (4)	21 (6)
Employment status, n (%)			
Employed, Non-Shift Worker	227 (49)	614 (48)	102 (31)
Shift Worker	79 (17)	157 (12)	44 (13)
Unemployed or retired	154 (33)	521 (40)	188 (56)
Ethnic heritage, n (%) *			
Cuban	86 (19)	233 (18)	57 (17)
Dominican	66 (14)	160 (12)	35 (10)
Mexican	102 (22)	366 (28)	93 (28)
Puerto Rican	97 (21)	241 (19)	90 (27)
Central American	67 (15)	172 (13)	45 (13)
South American	42 (9)	120 (9)	14 (4)
US Born Status, n (%)			
Born in mainland US	68 (20)	202 (16)	73 (16)
Born outside, lived in US ≥10 years	198 (59)	742 (58)	257 (56)
Born outside, lived in US< 10 years	67 (20)	343 (27)	129 (28)
English-language preference, n (%)	100 (22)	242 (19)	82 (25)
Current drinker, n (%)	212 (46)	579 (45)	147 (44)
Current smoker, n (%)	102 (22)	229 (18)	71 (21)
Physical activity status, n (%) *			
High	45 (10)	119 (9)	20 (6)
Moderate	201 (44)	575 (45)	144 (43)
Low	214 (47)	595 (46)	169 (51)
Apnea Hypopnea Index; median (25th, 75th quantiles) *	2.4 (0.4, 6.9)	1.5 (0.4, 5.1)	1.8 (0.4, 6.3)
Epworth Sleepiness Scale	6.9 (5.0)	5.4 (4.3)	5.0 (4.0)
Insomnia Severity, n (%)			
None	254 (55)	814 (63)	190 (57)

Table 1.1 continued

	Self-Reported Sleep Duration at Sueño Visit		
	Short, < 7h	Intermediate, 7-9h	Long, >9h
	N=460	N=1292	N=334
Sub-threshold	103 (22)	288 (22)	80 (24)
Moderate	77 (17)	143 (11)	45 (14)
Severe	26 (6)	45 (3)	18 (5)
Caffeine Intake ≥3 servings/day, n (%)	192 (42)	441 (34)	118 (35)
Sleep Medication ≥once/week, n (%)	66 (14)	170 (13)	57 (17)
Self-reported sleep duration, minutes, mean (SD) [1]	368 (41)	478 (36)	587 (33)
Standard deviation of actigraphy-assessed time asleep >1.5 h/day, n (%)	112 (34)	285 (22)	124 (27)
Actigraphy-assessed time asleep, minutes, mean (SD) [2]	366 (58)	408 (54)	442 (62)
Difference between self-report and actigraphy-assessed time asleep, minutes, mean (SD)	2 (62)	70 (59)	145 (65)
Actigraphy-assessed Time in bed, minutes, mean (SD) [3]	425 (65)	474 (58)	521 (65)
Difference between self-report and actigraphy-assessed time in bed, minutes, mean (SD)	-57 (70)	4 (60)	66 (66)

* Characteristic measured at the HCHS/SOL baseline visit, and not at the Sueño Visit

[1] Sleep duration is the weighted average of weekend and weekday self-reported habitual bed minus wake time measured at the Sueño visit

[2] Actigraph-measured time asleep is the weighted average time spent asleep during the main rest period, excluding periods of wakefulness, over weekends and weekdays

[3] Actigraph-measured time in bed is the weighted average duration of the main rest period, including periods of wakefulness, over weekends and weekdays

Table 1.2 shows descriptive statistics for self-reported sleep duration, actigraphy-assessed time asleep, their difference, correlation, and bivariate associations. Overall, the correlation of self-reported sleep duration with time asleep was 0.43 (95% CI: 0.39, 0.46), with higher correlations for weekdays (0.44) versus weekends (0.27).

Table 1.2. Mean (SD), correlations and bivariate regression coefficients: actigraphy measurements predicted by self-report (n=2,086)

	Self-Report	Actigraphy	Difference	Correlation	Self-Report as a Predictor of Actigraphy Time in Bed or Asleep	
		Minutes, Mean (SD)		ρ (95% CI)	480 min. Intercept	β (95% CI)
Time in Bed	472 (77)	471 (67)	1 (74)	0.48 (0.45, 0.52)	475	0.42 (0.39, 0.46)
Weekday	459 (85)	466 (73)	-8 (80)	0.49 (0.46, 0.53)	475	0.42 (0.39, 0.45)
Weekend	503 (99)	482 (92)	21 (114)	0.29 (0.25, 0.33)	476	0.27 (0.23, 0.31)
Time Asleep	472 (77)	404 (61)	67 (75)	0.43 (0.39, 0.46)	407	0.34 (0.31, 0.37)
Weekday	459 (85)	400 (65)	59 (81)	0.44 (0.40, 0.47)	407	0.34 (0.31, 0.37)
Weekend	503 (99)	415 (84)	88 (111)	0.27 (0.23, 0.31)	410	0.23 (0.19, 0.26)

Before multivariable adjustment, actigraphy-assessed time asleep increased by 20 minutes (95% CI: 19, 22) for each additional hour of self-reported sleep duration. When stratified by socio-demographic, sleep, and health characteristics (Table 1.3), the association of self-reported sleep duration with measured time asleep differed significantly by sex ($p=0.02$), age ($p=0.04$), nightly sleep variability ($p<0.0001$), and education ($p=0.01$)), with weaker associations among males, younger participants, those with nightly variability >1.5 hours or with higher education levels.

Table 1.3. Actigraphy-assessed time asleep predicted by self-reported sleep duration: mean (SD), correlations and bivariate regression coefficients by participant characteristic (n=2,086)

	N	Self-Report	Actigraphy	Difference	Correlation	Self-Report as a Predictor of Actigraphy Time Asleep		Interaction P-Value
		Minutes, Mean (SD)			ρ (95% CI)	480 min.	β (95% CI)	F-Test[4]
Sex								0.02*
Male	735	468 (77)	391 (64)	77 (81)	0.35 (0.28, 0.41)	395	0.29 (0.23, 0.34)	
Female	1351	473 (76)	412 (59)	62 (71)	0.47 (0.43, 0.51)	414	0.36 (0.33, 0.40)	
Age								0.04*
18-44 years	724	481 (75)	403 (59)	78 (76)	0.38 (0.31, 0.44)	403	0.30 (0.25, 0.35)	
45-64 years	1362	467 (73)	405 (62)	61 (74)	0.45 (0.41, 0.49)	410	0.37 (0.33, 0.40)	
BMI Category								0. 63
≥ Normal	405	477 (76)	408 (66)	69 (78)	0.40 (0.31, 0.48)	409	0.35 (0.27, 0.42)	
Overweight	791	477 (72)	409 (60)	68 (72)	0.42 (0.36, 0.48)	410	0.36 (0.30, 0.41)	
Obese I, >30-≤35	506	462 (80)	401 (58)	61 (77)	0.42 (0.34, 0.49)	408	0.30 (0.24, 0.36)	
Obese II, >35-≤40	249	470 (78)	398 (61)	72 (71)	0.49 (0.39, 0.58)	402	0.38 (0.30, 0.47)	
Obese III, ≥40	135	465 (89)	394 (63)	71 (84)	0.43 (0.28, 0.56)	399	0.30 (0.20, 0.41)	
Insomnia Severity Index								0.16
Severe Insomnia	89	460 (100)	418 (77)	42 (87)	0.54 (0.38, 0.67)	426	0.42 (0.28, 0.55)	
Moderate Insomnia	265	456 (87)	403 (68)	55 (88)	0.37 (0.26, 0.47)	409	0.29 (0.21, 0.38)	
Sub-threshold insomnia	471	474 (76)	410 (62)	64 (72)	0.48 (0.40, 0.54)	412	0.39 (0.32, 0.45)	
No insomnia	1258	474 (72)	402 (58)	72 (71)	0.41 (0.37, 0.46)	404	0.33 (0.29, 0.37)	
Apnea Hypopnea Index								0.30
0-5, no sleep apnea	1516	474 (75)	407 (61)	66 (75)	0.40 (0.36, 0.44)	409	0.32 (0.29, 0.36)	
5-15, mild sleep apnea	388	462 (79)	395 (60)	66 (73)	0.48 (0.40, 0.55)	402	0.36 (0.30, 0.43)	
≥15, moderate/severe	182	474 (84)	400 (68)	75 (78)	0.49 (0.37, 0.59)	402	0.39 (0.29, 0.50)	
Epworth Sleepiness Scale								0.27
ESS ≥10	386	453 (78)	383 (65)	70 (82)	0.35 (0.26, 0.44)	391	0.29 (0.22, 0.37)	
ESS <10	1700	476 (76)	409 (59)	66 (73)	0.43 (0.39, 0.47)	411	0.34 (0.30, 0.37)	

[4] Interaction p-value for the product term of the participant characteristic with self-reported habitual sleep duration.

Table 1.3 continued

Table 1.3. Actigraphy-assessed time asleep predicted by self-reported sleep duration: mean (SD), correlations and bivariate regression coefficients by participant characteristic (n=2,086)

	N	Self-Report	Actigraphy	Difference	Correlation	Self-Report as a Predictor of Actigraphy Time Asleep		Interaction P-Value
		Minutes, Mean (SD)			ρ (95% CI)	480 min.	β (95% CI)	F-Test[4]
Day to Day Variability								<.0001*
<1.5 hour/day	1565	470 (73)	408 (59)	62 (68)	0.48 (0.44, 0.52)	412	0.39 (0.35, 0.42)	
≥1.5 hour/day	521	476 (86)	395 (67)	81 (91)	0.32 (0.24, 0.39)	396	0.25 (0.18, 0.31)	
Employment Status								0.25
Employed, Non-Shift	943	463 (67)	401 (54)	62 (65)	0.44 (0.38, 0.49)	407	0.36 (0.31, 0.40)	
Shift Worker	280	456 (83)	387 (66)	72 (86)	0.35 (0.24, 0.44)	393	0.28 (0.19, 0.37)	
Unemployed/retired	863	485 (83)	414 (65)	71 (81)	0.42 (0.36, 0.47)	412	0.33 (0.28, 0.38)	
Educational Attainment								0.01*
<GED or high school	664	478 (82)	410 (65)	68 (75)	0.50 (0.44, 0.56)	410	0.40 (0.35, 0.45)	
GED or high school	539	471 (76)	404 (58)	67 (75)	0.40 (0.32, 0.47)	407	0.31 (0.25, 0.37)	
>GED or high school	880	467 (73)	401 (60)	67 (75)	0.37 (0.31, 0.43)	404	0.30 (0.25, 0.35)	
Hispanic Background								0.25
Cuban	376	468 (78)	403 (64)	65 (76)	0.44 (0.35, 0.51)	407	0.36 (0.28, 0.43)	
Dominican	261	464 (78)	405 (58)	59 (78)	0.37 (0.26, 0.47)	409	0.27 (0.19, 0.36)	
Mexican	561	480 (69)	414 (57)	66 (66)	0.46 (0.39, 0.52)	414	0.38 (0.32, 0.44)	
Puerto Rican	428	476 (87)	401 (71)	75 (85)	0.44 (0.36, 0.51)	402	0.36 (0.29, 0.43)	
Central American	284	469 (74)	400 (52)	69 (72)	0.38 (0.28, 0.48)	403	0.27 (0.19, 0.35)	
South American	176	459 (67)	393 (60)	65 (72)	0.36 (0.23, 0.49)	400	0.32 (0.20, 0.45)	
US Born Status								0.12
Born in mainland US	343	476 (83)	398 (67)	79 (87)	0.34 (0.25, 0.43)	399	0.28 (0.20, 0.36)	
Born outside, US≥10yr	539	473 (76)	408 (61)	65 (73)	0.44 (0.37, 0.51)	406	0.35 (0.29, 0.41)	
Born outside, US<10yr	1197	466 (73)	401 (58)	65 (70)	0.45 (0.40, 0.49)	410	0.36 (0.32, 0.40)	
Language Preference								0.12
English	424	475 (85)	399 (68)	76 (87)	0.37 (0.28, 0.45)	400	0.30 (0.23, 0.37)	
Spanish	1662	471 (74)	406 (59)	65 (72)	0.45 (0.41, 0.48)	409	0.36 (0.32, 0.39)	
Depressive symptoms								0.56

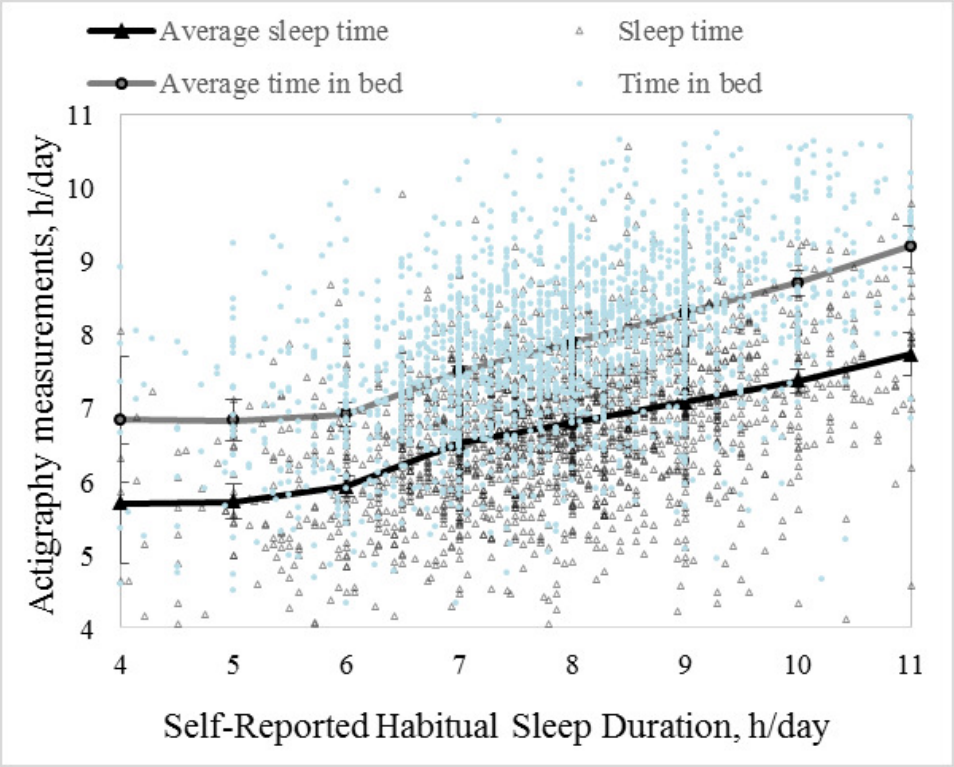
Table 1.3 continued

Table 1.3. Actigraphy-assessed time asleep predicted by self-reported sleep duration: mean (SD), correlations and bivariate regression coefficients by participant characteristic (n=2,086)

	N	Self-Report	Actigraphy	Difference	Correlation	Self-Report as a Predictor of Actigraphy Time Asleep		Interaction P-Value
		Minutes, Mean (SD)			ρ (95% CI)	480 min.	β (95% CI)	F-Test[4]
CESD≥10	643	473 (75)	403 (58)	70 (72)	0.42 (0.36, 0.48)	411	0.35 (0.29, 0.41)	
CESD<10	1443	468 (81)	407 (68)	61 (81)	0.43 (0.39, 0.47)	406	0.33 (0.30, 0.37)	
Sleep Medication Use								0.19
≥once/week	293	471 (75)	402 (60)	69 (73)	0.38 (0.28, 0.47)	419	0.29 (0.21, 0.38)	
<once/week	1793	473 (85)	417 (66)	55 (86)	0.44 (0.40, 0.47)	405	0.35 (0.32, 0.38)	
Current Smoker								0.34
Yes	402	467 (84)	394 (72)	74 (88)	0.36 (0.27, 0.44)	398	0.31 (0.23, 0.39)	
No	1683	473 (75)	407 (58)	66 (71)	0.45 (0.41, 0.48)	410	0.35 (0.31, 0.38)	

Self-reported measures did not uniformly overestimate actigraphy-assessed time asleep; self-report under-estimated actigraphy-assessed time asleep for 17% of participants. On average, self-reports <6 hours were under-estimates of actigraphy-assessed time asleep while self-reports >6 hours were over-estimates (Figure 1.1). However, in sensitivity analyses we found no evidence of non-linear associations of self-reported duration with actigraphy measurements (all likelihood ratio test p-values > 0.05).

Figure 1.1. Mean actigraphy-assessed time asleep and time in bed by hour/day of self-Reported sleep duration (n=2086)



Dots represent individual data points for the observed values of actigraphy-assessed time asleep and in bed (Y-axis) versus self-reported sleep duration (X-axis). Lines represent mean values of actigraphy-assessed time asleep and in bed within one hour buckets of self-reported habitual sleep duration. All units are hours/day.

Table 1.4 shows separate multivariable-adjusted regression models for actigraphy-assessed time asleep. Self-reported sleep duration made the largest contribution to the overall model R^2 (partial R^2 0.18) with only minimal additional variance explained by socio-demographic, health and sleep characteristics (R^2 rising to 0.25). Bias (the intercept) for those with self-reported sleep duration of 8 hours (the mean self-reported sleep duration) was almost one hour for time asleep. Holding self-reported sleep duration and other characteristics constant, males, participants with daytime sleepiness, mild sleep apnea/hypopnea, BMI>35, shift workers and current smokers spent 5-18 fewer minutes/night asleep. Adults with insomnia or who used sleep medication $\geq$once/week spent 12-15 more minutes/night asleep.

Table 1.4. Actigraphy-assessed sleep predicted by self-reported sleep and participant characteristics (n=2086) [¥,¥]

Characteristic	Time Asleep (min/day) [1] Partial R^2	Time Asleep (min/day) [1] β (SE)	Time in Bed (min/day) [2] Partial R^2	Time in Bed (min/day) [2] β (SE)
Intercept	.	426.81 (5.24)	.	473.63 (5.6)
Self-reported sleep centered at 480	0.18	0.31 (0.02)*	0.23	0.4 (0.02)
Male	0.02	-15.59 (2.67)*	0	-5.86 (2.85)*
Age 45-64	0	-5.25 (2.73)*	0	-1.55 (2.92)
BMI category				
Overweight	0	-0.44 (3.32)	0	-3.43 (3.54)
Obese I, >30-≤35	0	-2.46 (3.66)	0	-3.75 (3.91)
Obese II, >35-≤40	0	-9.57 (4.45)*	0	-12.6 (4.76)*
Obese III, ≥40	0	-11.11 (5.52)*	0	-15.92 (5.89)*
Insomnia Severity Index				
Sub-threshold insomnia	0	6.86 (3.01)*	0	13.62 (3.22)*
Moderate Insomnia	0	3.61 (4.05)	0	10.97 (4.33)*
Severe Insomnia	0	15.35 (6.42)*	0.01	31.32 (6.86)*
Apnea Hypopnea Index [3]				
5-15, mild sleep apnea	0	-7.87 (3.19)*	0	-4.45 (3.41)
≥ 15, moderate or more severe	0	-4.49 (4.43)	0	3.10 (4.73)
Epworth Sleepiness Scale ≥ 10	0.02	-18.48 (3.12)*	0.01	-19.03 (3.34)*
Sleep Medication ≥ once/week	0	12.43 (3.66)*	0	11.38 (3.91)*
Employment Status				
Shift Worker	0	-11.10 (3.67)*	0	-9.54 (3.92)*
Unemployed	0	4.63 (2.73)	0.01	10.79 (2.92)*
Educational Attainment [3]				
< GED or high school	0	2.15 (2.90)	0	3.31 (3.10)
GED or high school	0	2.41 (2.95)	0	3.00 (3.16)
Ethnic Background				
Cuban	0	-7.86 (3.96)	0	-2.89 (4.23)
Dominican	0	-7.60 (4.10)	0	0.98 (4.38)
Puerto Rican	0	-10.10 (3.92)*	0	-1.33 (4.19)
Central American	0	-12.81 (4.02)*	0	-5.28 (4.29)
South American	0	-13.34 (4.79)*	0	-7.48 (5.12)
US Born Status [3]				
Born in mainland US	0	-4.19 (4.91)	0	0.69 (5.24)
Born outside, lived in US ≥10	0	2.02 (3.05)	0	4.20 (3.25)
English Language Preference [3]	0	-1.76 (3.97)	0	1.64 (4.24)
Depression symptoms, CESD ≥ 10	0	0.12 (2.93)	0	2.91 (3.13)
Caffeine Intake ≥ 3 cups/day	0	-0.03 (2.54)	0	-0.9 (2.72)
Current Smoker	0	-10.62 (3.22)*	0	-7.49 (3.44)*
Current Drinker	0	-5.90 (2.56)*	0	-5.20 (2.73)
Physical Activity Level [3]				
High	0	4.45 (4.50)	0	5.12 (4.81)
Moderate	0	0.20 (2.50)	0	2.15 (2.67)
Full Model R^2	0.25		0.30	

Table 1.4 continued

* Asterisks indicates statistically significant predictors of actigraphy-assessed sleep time at the $p<0.05$ level.

[¥] Each column (time asleep and time in bed) represents a separate statistical model, adjusted for all variables in the column.

[¥] Reference categories are: female; 18-44 years; Normal or underweight; no clinical insomnia; AHI 0-5, no sleep apnea; ESS <10; sleep medication use < once/week; employed non-shift worker; > GED or high school; Mexican; Born outside, lived in US< 10 years; Spanish language preference; CESD < 10, no clinical depressive symptoms; < 3 cups/day caffeinated beverages; current non-smoker; current non-drinker; and low physical activity level.

[1] "Time asleep" indicates that the time spent asleep during the main rest period is the actigraphy-assessed outcome for the model.

[2] "Time in bed" indicates that total duration of the main rest period is the actigraphy-assessed outcome for the model.

[3] Variable was measured at baseline study visit rather than at the Sueño ancillary study visit.

Table 1.5 shows results of a stepwise selection procedure using internal cross-validation to identify predictors of actigraphy-assessed time asleep. From the full list of candidate variables shown in Table 4 as well as their interactions with self-reported sleep duration, only self-reported sleep duration, sex and daytime sleepiness were selected as predictors of time asleep. No interactions of any predictors with self-reported sleep duration were selected. As in Table 1.4, results indicate that little information is added in addition to self-reported sleep duration when models adjust for socio-demographic, health and sleep characteristics, precluding the development of calibration models.

Table 1.5. Coefficients and R^2 for predictors of actigraphy-assessed time asleep and time in bed (n=2086) [¥, ¥]

	Partial R^2	Time Asleep (min/day) β (SE)	Partial R^2	Time in Bed (min/day) β (SE)
Intercept	.	418.03 (2.62)*	.	466.66 (2.14)*
Self-reported sleep centered at 480 minutes/day	0.18	0.27 (0.02)*	0.23	0.40 (0.02)*
Sex				
Male	0.02	-17.33 (3.62)*		
Epworth Sleepiness				
ESS ≥10	0.01	-25.20 (4.66)*	0.01	-19.13 (3.34)*
Insomnia Severity				
Sub-threshold			0	14.61 (3.17)*
Moderate Insomnia			0	11.53 (4.15)*
Severe Insomnia			0.01	34.58 (6.54)*
Employment Status				
Shift Worker			0	-10.02 (3.93)*
Unemployed			0	11.40 (2.79)*
Sleep Medication ≥once/week			0	11.64 (3.90)
Full Model R^2	0.22		0.28	
Root Mean Squared	54.28		57.16	

* Indicates statistical significance at the $p<0.05$ level.

¥ Each column (time asleep and time in bed) represents a separate statistical model adjusted for all the variables in the column. The coefficients were estimated through a stepwise selection with the full list of candidate variables plus the interaction of each with self-reported sleep duration.

¥ Reference categories for selected variables were: female sex; ESS <10; no clinical insomnia; and employed non-shift worker.

Table 1.6 shows proportion of participants appropriately ranked in low, medium or high tertiles of actigraphy-assessed time asleep given the participant's tertile of self-reported sleep duration without covariate adjustment (which did not change results). For time asleep, the proportion of participants correctly classified were 0.54, 0.40 and 0.53 for low, medium and high self-reported sleep duration. Results were similar for a priori sleep categories in sensitivity analyses.

Table 1.6. Proportion of participants correctly classified as low, medium or high actigraphy-assessed time asleep and in bed given self-reported sleep categorization (n=2086)

		Actigraphy-assessed Time Asleep			**Actigraphy-assessed** Time in Bed		
		Low	Medium	High	Low	Medium	High
Self-Reported Sleep Duration *	Mean (SD), min/day	Proportion of Participants			Proportion of Participants		
Low	388 (44)	0.54	0.31	0.15	0.56	0.29	0.14
Medium	471 (18)	0.29	0.40	0.31	0.30	0.42	0.29
High	554 (40)	0.17	0.30	0.53	0.14	0.29	0.56
		Mean (SD) of tertile, minutes/day					
		338 (38)	407 (14)	468 (33)	399 (39)	472 (15)	534 (39)

* Self-reported sleep duration is calculated as the weighted average of weekday and weekend habitual bed minus wake time.

Supplemental Figure 1.S1 shows the receiver operating characteristics (ROC) curves predicting the tertile of actigraphy-assessed duration from tertile of self-reported sleep duration, with/without adjustment for covariates. When the AUC was calculated, the probability that a randomly selected individual would be correctly classified as having an actigraphy-assessed sleep time in the lowest tertile (short sleep) based on tertile of self-reported sleep duration was 0.62. The corresponding probability for actigraphy-assessed sleep time in the highest tertile (long sleep) was 0.64. Both probabilities increased slightly, to 0.68, with the addition of the covariates shown in Table 3.

Though time asleep is often of biologic interest in epidemiologic studies, in Sueño sleep duration was reported as bed minus wake time. Thus, secondary analyses examined time in bed and found similar results to those with time asleep. As anticipated, mean (SD) actigraphy-assessed time in bed was longer than time asleep and similar to self-reported sleep duration at 7.85 (1.12) hours/day (Table 1). However, the correlation with self-reported sleep duration was only slightly higher than for time asleep at r=0.48 (95% CI: 0.45, 0.52), and for each additional hour of self-reported sleep duration, time in bed increased by 25 minutes (95% CI: 24, 27); Table 2. The addition of covariates to self-reported sleep duration did little to improve the overall model R^2, which rose from 0.23 to 0.30 (Table 4). In the stepwise selection procedure, at the same level of self-reported sleep duration, shift workers and participants with daytime sleepiness spent less time in bed, while those with insomnia, who used sleep medication weekly or were unemployed spent more time in bed (Table 5).

DISCUSSION

In this diverse cohort of US Hispanic/Latinos, we found moderate correlations between self-reported habitual sleep duration and actigraphy-assessed time asleep (r=0.43). Ours is the

largest study to date and the only study we know of to identify predictors of actigraphy-measurements from self-reported sleep duration in Hispanics/Latinos. Other studies have also observed moderate correlations between reported and actigraphy-assessed sleep, ranging from 0.31 to 0.47, but with few exceptions (5, 23) have recruited older, European, Australian, or US non-Hispanic white populations. (9, 24, 25) Habitual bed and wake times are commonly used to measure sleep duration in epidemiologic studies because participants may more accurately report these habits than the hours of actual sleep on a typical night. However, not all time in bed is spent asleep. Consistent with this, the unadjusted difference between measured time asleep and self-reported sleep duration in our study exceeded one hour, while the difference between objectively measured time in bed and self-reported sleep duration was only 1 minute (though with substantial variation). Yet, correlations of actigraphy-assessed time asleep and time in bed with self-reported sleep duration were close (0.43 and 0.48), indicating the measurement approach for self-reported sleep duration did not fully explain discrepancies between self-report and actigraphy assessments.

We observed higher correlations for weekdays versus weekends, perhaps in part due to consistent weekday routines enabling more accurate reporting. However, fewer nights of actigraphy recording were collected on weekends, which weakens the correlation with self-reported sleep duration (median of 5 weekday versus 2 weekend nights of actigraphy).

Self-reported sleep duration made the largest contribution to the overall variance in actigraphy-assessed time asleep, but only accounted for 18% of this variance; the model R^2 rose to 25% with the addition of socio-demographic, sleep and health characteristics. Thus, the addition of covariates to self-reported habitual sleep duration did not result in a model that explained sufficient variation in actigraphy to justify the development of calibration equations.

When prior research in nutrition attempted to improve the accuracy of self-reported measures of diet (compared to an objective measure such as a biomarker), often the addition of participant characteristics to the model substantially increased the R^2. For example, in the Women's Health Initiative, the addition of characteristics such as BMI and age increased the model R^2 for total energy intake from 4% for the food frequency questionnaire alone to 42%. (26) Similar improvements with the addition of covariates were observed in the HCHS/SOL when calibrating dietary intake; the addition of BMI, age, Hispanic/Latino background, income and sex increased the model R^2 for total energy intake from 24 hour dietary recalls from 8% to 54%. (27) One possibility to explain this difference is that the skills needed to report diet (e.g. portion estimation) are more complex compared to reporting habitual bed/wake times. In the case of sleep, difficulty in estimating habitual sleep duration may arise, in part, from night-to-night variability. In keeping with this hypothesis, the correlation of self-reported and actigraphy-assessed sleep duration was lower among those in the highest quartile of night-to-night variability (0.32) while -participants in the lowest variability quartile (<0.8 hours) had the highest correlation (0.54). However, when those with high nightly variability participants were excluded in sensitivity analyses, self-report was still only able to explain 31% of the variation in time asleep.

The association of self-reported sleep duration with actigraphy-assessed time asleep varied by socio-demographic, health and sleep characteristics. In particular, we found most individuals over-report sleep duration relative to actigraphy, with greater discrepancies among men and those with poor sleep quality. Similar findings have been reported in other populations. (5, 23, 24) In our study, there were no statistically significant differences in the discrepancy between measured time asleep and self-reported sleep duration by sleep apnea severity or BMI.

In contrast, there were differences identified by age, sex, nightly variability, sleep medication use and smoking.

Other studies have noted that individuals with higher BMI, education, apnea risk, sleepiness and depression report shorter sleep duration, which reduces the discrepancy self-reported and actigraphy-assessed sleep duration (as self-reported sleep duration increases, so does the discrepancy between self-reported sleep duration and actigraphy-assessed time asleep). (5, 25) In keeping with this, we found that, controlling for self-reported sleep duration, males, shift workers, those with sleep apnea and excessive daytime sleepiness and current smokers slept fewer minutes, while those with insomnia or those using sleep medication weekly slept a greater number of minutes.

Strengths and limitations

No prior study has validated self-reported sleep duration in such a large sample. The inclusion of ≥5 days of actigraphy for each participant and the measurement of sleep characteristics including insomnia, sleep apnea severity and sleep medication use are additional strengths. Compared with other validation studies of self-reported sleep duration, strengths of the present study include active exclusion of participants with severe sleep apnea and the use of a state-of-science actigraphy device with a light sensor and off-wrist detection to increase accuracy. (5) The study population is comprised of a diverse group of US Hispanic/Latinos, addressing an important gap in sleep research; however, this could limit generalizability to other ethnic groups if cultural attitudes or home or neighborhood environments modify reporting of sleep duration relative to actigraphy. A key limitation is that actigraphy, while a commonly used objective measurement, is not itself a gold standard and may overestimate total sleep time relative to polysomnography (inactivity during wake may be interpreted as sleep, or vice versa). Additionally, we used an average of 7 nights of actigraphy to estimate habitual sleep duration.

Though 7 nights is considered to have reasonable reliability, nightly variation in sleep or episodic variation in sleep duration (e.g. ‘good weeks’ and ‘bad weeks’) undoubtedly weakens the correlation with self-reported habitual sleep duration. (28) Finally, we asked participants to report habitual bed/wake times but did not ask them to estimate the actual number of hours of sleep obtained on a typical night, as done in other cohort studies such as CARDIA. This difference may limit the comparability of our results to those of other studies.

CONCLUSIONS

In this cohort of US Hispanic/Latinos, the correlation between self-reported and actigraphy-assessed sleep duration was moderate. We confirm the presence of systematic bias in self-reported sleep duration. Our results indicate that the addition of socio-demographic, health and sleep characteristics to models provides little additional information to explain the variation in actigraphy-assessed sleep. Use of actigraphy as a primary measure of sleep duration or in a subset to correct for measurement error may increase statistical power. Where there is systematic bias in self-reported sleep duration, the influence of characteristics on objectively measured sleep duration cannot be assessed with self-report alone if those characteristics influence reporting. Additionally, actigraphy provides information about other aspects of sleep (e.g. efficiency) not captured by self-report that are associated with health outcomes independent of duration.

REFERENCES

1. Zhao H, Yin JY, Yang WS, Qin Q, Li TT, Shi Y, Deng Q, Wei S, Liu L, Wang X, et al. Sleep duration and cancer risk: a systematic review and meta-analysis of prospective studies. Asian Pacific journal of cancer prevention : APJCP 2013;14(12):7509-15.
2. Schmid SM, Hallschmid M, Schultes B. The metabolic burden of sleep loss. The lancet Diabetes & endocrinology 2014. doi: 10.1016/s2213-8587(14)70012-9.
3. Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. Annals of epidemiology 2013;23(6):361-70. doi: 10.1016/j.annepidem.2013.03.015.
4. Patel SR, Blackwell T, Ancoli-Israel S, Stone KL. Sleep characteristics of self-reported long sleepers. Sleep 2012;35(5):641-8. doi: 10.5665/sleep.1822.
5. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology (Cambridge, Mass) 2008;19(6):838-45. doi: 10.1097/EDE.0b013e318187a7b0.
6. Curcio G, Ferrara M, Piergianni A, Fratello F, De Gennaro L. Paradoxes of the first-night effect: a quantitative analysis of antero-posterior EEG topography. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2004;115(5):1178-88. doi: 10.1016/j.clinph.2003.12.018.
7. Sadeh A, Acebo C. The role of actigraphy in sleep medicine. Sleep medicine reviews 2002;6(2):113-24.
8. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26(3):342-92.
9. Girschik J, Fritschi L, Heyworth J, Waters F. Validation of self-reported sleep against actigraphy. Journal of epidemiology / Japan Epidemiological Association 2012;22(5):462-8.
10. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, Schneiderman N, Raij L, Talavera G, Allison M, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Annals of epidemiology 2010;20(8):629-41. doi: 10.1016/j.annepidem.2010.03.015.
11. Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, Liu K, Giachello A, Lee DJ, Ryan J, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Annals of epidemiology 2010;20(8):642-9. doi: 10.1016/j.annepidem.2010.05.006.
12. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, Punjabi NM. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep 2006;29(8):1009-14.
13. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep medicine 2001;2(5):389-96.
14. Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM, Dulin H, Berkman LF, Buxton OM. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 2013;36(11):1747-55. doi: 10.5665/sleep.3142.
15. Westbrook PR, Levendowski DJ, Cvetinovic M, Zavora T, Velimirovic V, Henninger D, Nicholson D. Description and validation of the apnea risk evaluation system: a novel

method to diagnose sleep apnea-hypopnea in the home. Chest 2005;128(4):2166-75. doi: 10.1378/chest.128.4.2166.
16. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, et al. Sleep-disordered Breathing in Hispanic/Latino Individuals of Diverse Backgrounds. The Hispanic Community Health Study/Study of Latinos. American journal of respiratory and critical care medicine 2014;189(3):335-44. doi: 10.1164/rccm.201309-1735OC.
17. Hoos T, Espinoza N, Marshall S, Arredondo EM. Validity of the Global Physical Activity Questionnaire (GPAQ) in adult Latinas. Journal of physical activity & health 2012;9(5):698-705.
18. Lind BK, Goodwin JL, Hill JG, Ali T, Redline S, Quan SF. Recruitment of healthy adults into a study of overnight sleep monitoring in the home: experience of the Sleep Heart Health Study. Sleep Breath 2003;7(1):13-24. doi: 10.1007/s11325-003-0013-z.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540-5.
20. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine 2001;2(4):297-307.
21. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Measure 1977;1:385-401.
22. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77-84.
23. Lemola S, Ledermann T, Friedman EM. Variability of sleep duration is related to subjective sleep quality and subjective well-being: an actigraphy study. PloS one 2013;8(8):e71292. doi: 10.1371/journal.pone.0071292.
24. Van Den Berg JF, Van Rooij FJ, Vos H, Tulen JH, Hofman A, Miedema HM, Neven AK, Tiemeier H. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. Journal of sleep research 2008;17(3):295-302. doi: 10.1111/j.1365-2869.2008.00638.x.
25. Silva GE, Goodwin JL, Sherrill DL, Arnold JL, Bootzin RR, Smith T, Walsleben JA, Baldwin CM, Quan SF. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 2007;3(6):622-30.
26. Prentice RL, Mossavar-Rahmani Y, Huang Y, Van Horn L, Beresford SA, Caan B, Tinker L, Schoeller D, Bingham S, Eaton CB, et al. Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. American journal of epidemiology 2011;174(5):591-603. doi: 10.1093/aje/kwr140.
27. Mossavar-Rahmani Y, Shaw PA, Wong WW, Sotres-Alvarez D, Gellman MD, Van Horn L, Stoutenberg M, Daviglus ML, Wylie-Rosett J, Siega-Riz AM, et al. Applying recovery biomarkers to calibrate self-report measures of energy and protein in the Hispanic Community Health Study/Study of Latinos. Amer J Epidemiol 2015;In Press.
28. EJ VANS. Improving actigraphic sleep estimates in insomnia and dementia: how many nights? Journal of sleep research 2007;16(3):269-75. doi: 10.1111/j.1365-2869.2007.00592.x.

ACKNOWLEDGEMENTS

Author affiliations

Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (EM Cespedes and FB Hu); Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA (S Redline, R Wang and SR Patel); Channing Division of Network Medicine, Harvard Medical School and Department of Biostatistics, Harvard School of Public Health, Boston, MA (B Rosner); Department of Medicine, Columbia University Medical Center, New York, NY (C Alcantara); Collaborative Studies Coordinating Center, Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC (J Cai and D Sotres-Alvarez); Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA (MH Hall); Division of Pulmonary and Critical Care Medicine, Sleep Medicine Center and VA Pulmonary Sleep Disorders Laboratory, University of California San Diego (J Loredo); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY (Y Mossavar-Rahmani); Department of Neurology, University of Miami Miller School of Medicine, Miami, FL (AR Ramos); Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL (KJ Reid); Albert Einstein College of Medicine, Montefiore Medical Center, Yeshiva University, Bronx, NY (NA Shah); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, and Institute for Minority Health Research, University of Illinois at Chicago, Chicago, IL (PC Zee)

Funding

Sueño was supported by the National Heart, Lung, and Blood Institute (NHLBI) grant to the Brigham and Women’s Hospital (HL098297). The Hispanic Community Health Study/Study of Latinos was carried out as a collaborative study supported by contracts from the NHLBI to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The following Institutes/Centers/Offices contribute to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements. Elizabeth M. Cespedes is supported by NIDDK T32 DK007703.

Conflicts of interest

The authors have no conflicts of interest to disclose.

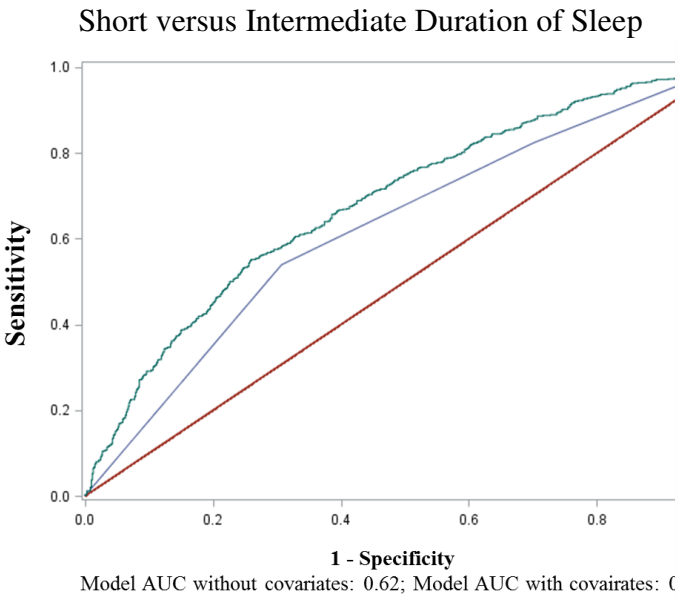
APPENDIX

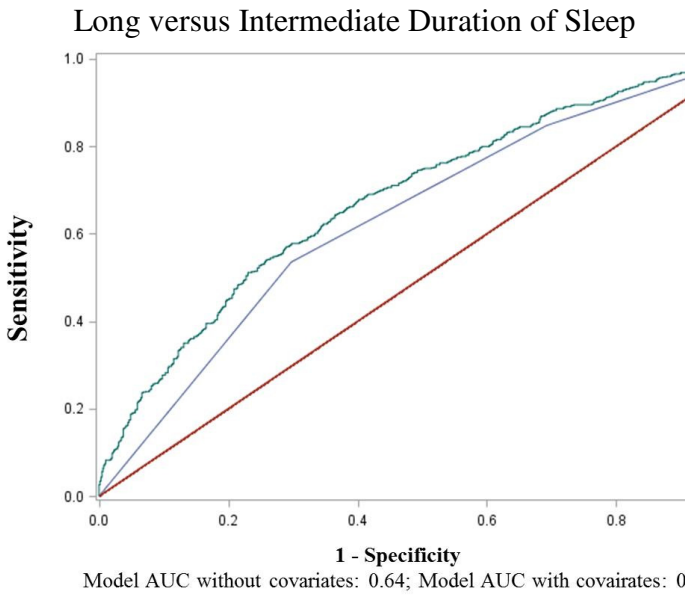
Supplemental Table 1.S1. Characteristics of the Sueño sample compared to HCHS/SOL *

Characteristics measured at baseline HCHS/SOL visit	HCHS/SOL N=16415	Sueño N=2086
Age, y; mean (SD)	45.9 (13.9)	45.0 (11.5)
Women; n (%)	9835 (60)	1351 (65)
Self-reported sleep duration, hours/day; mean (SD)	7.93 (1.42)	7.82 (1.40)
BMI, kg/m^2; mean (SD)	29.8 (6.1)	29.9 (6.1)
Center for Epidemiologic Studies Depression Scale; mean (SD)	7.3 (6.1)	7.23 (6.16)
Apnea Hypopnea Index; median (interquartile range)	1.9 (6.0)	1.7 (5.2)
Epworth Sleepiness Scale; mean (SD)	5.7 (4.8)	5.7 (4.9)
Educational attainment; n (%)		
No High school	6207 (38)	664 (32)
≤High school graduate	4180 (26)	540 (26)
>High school graduate	5937 (36)	879 (42)
Annual household income; n (%)		
<$30,000	10516 (64)	1401 (67)
≥$30,000	4877 (30)	5923 (28)
Did not report	1022 (6)	93 (4)
Employment status; n (%)		
Employed, Non-Shift Worker	6640 (41)	874 (42)
Shift Worker	1516 (9)	186 (9)
Unemployed	7953 (49)	1012 (49)
Hispanic background; n (%)		
Cuban	2348 (14)	376 (18)
Dominican	1473 (9)	261 (13)
Mexican	6472 (40)	561 (27)
Puerto Rican	2728 (17)	428 (21)
Central American	1732 (11)	284 (14)
South American	1072 (7)	176 (8)
Other/More than one heritage	503 (3)	
US Born Status		
Born in mainland US	2863 (18)	343 (17)
Born outside, lived in US ≥10 years	9626 (59)	1197 (58)
Born outside, lived in US< 10 years	3805 (23)	539 (26)
English-language preference at baseline interview; n (%)	3296 (20)	424 (20)
Current drinker; n (%)	7750 (47)	937 (45)
Current smoker; n (%)	3166 (19)	402 (19)
Physical Activity Status		
High	1771 (11)	184 (9)
Moderate	7203 (44)	919 (44)
Low	7301 (45)	979 (47)

* Participants with AHI ≥50 or age >65 were not eligible to participate in the Sueño ancillary study.

Supplemental Figure 1.S1:
Prediction of tertiles of actigraphy-assessed sleep duration given tertiles of self-reported sleep duration: ROC curves with/without covariate adjustment





Chapter 2: Chronic insufficient sleep and diet quality: contributors to childhood obesity

---

Elizabeth M Cespedes, Frank B Hu, Susan Redline, Bernard Rosner,

Matthew W Gillman, Sheryl L Rifas-Shiman, Elsie M Taveras

ABSTRACT

Background/objective: Diet is one hypothesized mechanism underlying the association of shorter sleep duration with childhood obesity, but prospective studies examining diet quality as a mediator are lacking. To examine associations of chronic insufficient sleep with diet, and whether diet explains the sleep-adiposity relationship.

Methods: In Project Viva, 1,046 parents reported children's sleep duration at 6m and annually until mid-childhood (7y). The main exposure was a sleep curtailment score (6m-7y) ranging from 0 (maximal curtailment) to 13 (adequate sleep). In mid-childhood, parents reported children's diet; researchers measured height/weight. Multivariable linear regression assessed associations of sleep with diet (Youth Healthy Eating Index [YHEI]); sleep with BMI z-score adjusting for YHEI; and, secondarily, joint associations of sleep and YHEI with BMI.

Results: Mean (SD) sleep and YHEI scores were 10.21 (2.71) and 58.76 (10.37). Longer sleep duration was associated with higher YHEI in mid-childhood (0.59 points/unit sleep score; 95%CI: 0.32, 0.86). Though higher YHEI was associated with lower BMI z-score (-0.07 units/10-point increase; 95%CI: -0.13, -0.01), adjustment for YHEI did not attenuate sleep-BMI associations. Children with sleep and YHEI scores below the median (<11 and <60) had BMI z-scores 0.34 units higher (95%CI: 0.16, 0.51) than children with sleep and YHEI scores above the median.

Conclusions: While parent-reported diet did not explain inverse associations of sleep with adiposity, both sufficient sleep and high-quality diets are important to obesity prevention.

INTRODUCTION

Early childhood is a critical period for obesity prevention: dietary behaviors and weight trajectories established in early childhood often carry forward into later years. (1-3) One influential behavior may be sleep: many studies support an association of shorter sleep duration (4-6) and chronic insufficient sleep (7) with risk of childhood obesity in diverse populations with parent-reported and actigraph-measured sleep. (8-11) Yet, the underlying mechanisms remain unclear.

Lower diet quality is one proposed pathway through which inadequate sleep may lead to adiposity. In adults, experimentally restricting sleep alters appetite hormones (decreased leptin and increased ghrelin) and changes in hunger ratings, energy intake and food preferences. (12, 13) Recently, functional magnetic resonance imaging studies measuring brain responses to food stimuli suggest disinhibited eating and altered food selection in a sleep-deprived state. (14, 15) Outside the laboratory, epidemiologic evidence supports a cross-sectional relationship of shorter sleep with lower diet quality and altered appetite hormones in children (16) and adults. (17) However, since children often have less autonomy in food choice, (18) findings in older populations may not apply. A recent prospective study found that compared to parent-reported sleep duration of 11-<12-hours/day at 16 months, children sleeping <10-hours/day consumed 50 kcal/day more at 21 months. (19) However, the authors could not examine mediation by diet since the relationship of insufficient sleep with adiposity was not yet apparent among their young participants. Regardless of its possible role as a mediator, poor diet quality may have effects in combination with chronic sleep insufficiency that further increase risk of childhood obesity.

This study examines chronic insufficient sleep as a predictor of diet quality in mid-childhood and whether diet explains previously observed associations of chronic insufficient

sleep with mid-childhood BMI z-score. (7) As a secondary aim, we examine the joint association of low quality diet and chronic insufficient sleep with mid-childhood BMI z-score.

METHODS

Subjects and study design

We studied participants in Project Viva, a prospective cohort that recruited women during early pregnancy from Harvard Vanguard Medical Associates, a multi-specialty practice in eastern Massachusetts. Details of recruitment/retention procedures are available elsewhere. (20) Of the 2,128 live infants delivered, 1,116 attended a mid-childhood in-person visit. Our main exposure was chronic sleep curtailment from age 6-months to 7-years; thus, we excluded 70 participants without sleep data for these time points for a final sample of n=1,046. Nonparticipants were less likely to have college-educated mothers (59% vs 71%) and annual household incomes exceeding $70,000 (52% vs 63%). Maternal age at enrollment was similar for participants excluded vs included (31 vs 32 years).

After obtaining informed consent, we performed in-person study visits with the mother at the end of the first and second trimesters of pregnancy, and with mother and child in the first days after delivery and in infancy (median child age 6 months), early childhood (median age 3.1 years) and mid-childhood (median age 7.7 years). Mothers completed mailed questionnaires at 1, 2, 4, 5, and 6 years after birth. The Institutional Review Board of Harvard Pilgrim Health Care approved the study.

MEASUREMENTS

Sleep measurements

At 6 months and in annual questionnaires (1-7 years), mothers reported children's 24-hour sleep duration. At 6-months, we asked mothers to report separately in hours/minutes their

baby's average length of morning nap, afternoon nap and nighttime sleep in the past month. At 1-year, mothers reported in hours/minutes the child's usual 24-hour sleep duration in the past month including morning naps, afternoon naps, and nighttime sleep. Between 2-7 years, mothers reported number of hours the child slept in a usual 24-hour period in the past month, separating weekends and weekdays. Response categories included, "< 9, 9, 10, 11, 12, 13, and >14-hours/day"; at the 7-year visit response options were in hours/minutes. In a recent validation, parental report of sleep duration in children 4-6 years correlated well with actigraphy among healthy controls (ρ=0.85). (21)

Our primary exposure was chronic insufficient sleep as quantified by a sleep score tallying the adequacy of parent-reported sleep duration from infancy to mid-childhood. As described previously, (7, 22) the score was derived from mean sleep duration at each of 8 measurements (6 months and 1-7 years). Using sleep durations associated with elevated BMI ($\geq$ 95th percentile), (23) and the age-specific recommendations available in 2014 from the National Sleep Foundation (24) and the National Heart, Lung and Blood Institute, (25) we scored sleep duration as follows: from 6-months to 2-years, the score was 0 for <12-hours/day and 1 for ≥12-hours/day; from 3 to 4-years, <10-hours/day = 0, 10-<11-hours/day = 1, and ≥ 11-hours/day = 2; at 5 and 7-years, <9-hours/day = 0, 9-<10-hours/day = 1, and ≥ 10-hours/day = 2. The range of the total score was 0-13, where 0 indicated maximal sleep curtailment and 13 indicated never having curtailed sleep. We grouped scores into five categories, collapsing scores of 0-4, 5-7 and 8-9 due to small frequencies and also 10-11 and 12-13 due to comparable results. (7, 26)

The National Sleep Foundation updated age-specific recommendations for sleep duration in 2015, after the initial development and use of the sleep curtailment score. In sensitivity analyses, re-derived the sleep score to align with the current recommendations but with the same

range (0-13) as the original score described above by awarding 1.625 points if children's sleep duration fell within the recommended ranges: 6-months, 12-15 hours 1-2 years, 11-14 hours; 3-5 years, 10-13 hours; 6-7 years, 9-11 hours.

Diet measurements

In mid-childhood, parents reported children's dietary behaviors (times/week eating dinner with family, skipping breakfast, and consuming fast food outside the home). Parents reported children's dietary intake through a Prime-Screen composed of 18 Food Frequency Questionnaire (FFQ) items asking about consumption of specific food groups, with examples. These included servings/day of fruits/vegetables, dairy, whole grains, snacks, and lean, red or processed meat. The questionnaire also asked about drinks with added sugar (soda/fruit drinks). The Prime-Screen has not been validated for parent-report of children's intake; in adults, the average correlation with estimates from a full FFQ over 18 food groups was 0.6. (27)

Our primary outcome was the Youth Healthy Eating Index (YHEI), a summary measure of diet developed in adolescents. (28) In addition to food groupings (whole grains, vegetables, fruits, dairy, lean:fatty meat ratio and sugary drinks), the YHEI also includes multivitamins, margarine/butter, and incorporates behaviors including fried foods outside the home, eating breakfast, and family dinner. The original YHEI included 5-points for removing visible animal fat; this information was not available for a theoretical range of 0-95 rather than 0-100 points. The YHEI awards up to 10-points for favorable consumption of whole grains, vegetables, fruits, dairy, lean:fatty meat ratio, less consumption of sweet/salty snack foods and soda/drinks, and up to 5-points for multivitamins, eating breakfast and family dinner and less consumption of

margarine/butter and fried foods outside the home. Further description of the YHEI and components is in Table S1.

Demographic and anthropometric measurements

At enrollment, we collected information about maternal age, educational attainment, and household income. In early childhood, parents reported the child's race/ethnicity. In mid-childhood, we measured height/weight using a calibrated stadiometer (Shorr Productions, Olney, MD) and scale (Seca model 881, Seca Corporation, Hanover, MD). We calculated children's age/sex-specific BMI z-scores using national reference data.

STATISTICAL ANALYSIS

Multiple imputation

Confounding variables were not available for all subjects; we used multiple imputations to generate plausible values for each missing value. We used a chained equations approach with predictive mean matching based on linear regressions for ~continuous variables and logistic or generalized logistic regression for dichotomous or categorical variables. The "completed" dataset comprises the observed data and one imputed value for each missing value. We replicated analyses across 50 completed datasets and combined multivariable modeling results from the 50 datasets (Proc MI ANALYZE) in SAS version 9.3 (SAS Institute, Cary NC), which recovers information in partially observed subjects erroneously presuming imputed values are known true values.

Primary analyses

Our primary analysis examined associations of the sleep curtailment score as a predictor of mid-childhood dietary factors. All multivariable linear regression models adjusted for socio-

demographic factors (child race/ethnicity, age and sex, maternal education and household income). Models with a mid-childhood dietary factor as the main outcome were adjusted for all other dietary factors in mid-childhood, except for our summary measure of diet, YHEI.

Prior research in Project Viva demonstrated associations of the sleep score with mid-childhood BMI z-score. (7) To assess whether diet plays a mediating role, we examined the sleep score as a predictor of mid-childhood BMI z-score in multivariable linear regression models, with/without adjustment for mid-childhood dietary factors; the degree of attenuation in the sleep score coefficient was inferred as mediation by diet.

Supplemental analyses

In supplemental analyses, we assessed joint associations of chronic insufficient sleep and diet quality with BMI z-score. We cross-classified participants into according to their sleep ($\geq$ versus $<$ 11, the median score), and diet quality in mid-childhood (YHEI: $\geq$ 60 versus $<$ 60, the median score), and entered these four categories as predictors of BMI z-score in multivariable-adjusted models; children above the median score for both sleep and diet were the reference. We also examined mutually-adjusted associations of mid-childhood dietary factors as predictors of mid-childhood BMI z-score. All models adjusted for socio-demographic factors.

Sensitivity analyses

In sensitivity analyses, we restricted to non-Hispanic white children with college-educated mothers and considered additional adjustment for maternal pre-pregnancy BMI. Neither sensitivity analysis materially altered point estimates for the sleep score's association with mid-childhood BMI z-score or diet quality.

RESULTS

The mean (SD, range) was for the sleep score 10.21 (2.71, 0 - 13) and for the YHEI score was 58.76 (10.37, 30 - 91). Table 2.1 shows characteristics by category of sleep curtailment. Children with longer duration of sleep during childhood (higher sleep scores), were more likely to be non-Hispanic white, have college-educated mothers and live in households with incomes $\geq$ $70,000/year. In mid-childhood, children with higher sleep scores had lower BMI z-scores and higher YHEI diet quality scores.

Table 2.1. Participant characteristics by sleep curtailment category (N=1,046)

Characteristic	Sleep curtailment score: 0=maximal curtailed sleep to 13=never curtailed sleep				
	0 to 4	5 to 7	8 to 9	10 to 11	12 to 13
	41 (4%)	129 (12%)	151 (15%)	306 (29%)	419 (40%)
	Mean (SD) or N (%)				
Sleep curtailment score	3.20 (1.30)	6.09 (1.02)	8.61 (0.65)	10.59 (0.62)	12.46 (0.54)
Maternal/Household Characteristics					
College, %	14 (34)	62 (49)	95 (62)	233 (76)	337 (81)
Household income >70k/year, %	11 (27)	60 (47)	81 (54)	205 (67)	311 (74)
Child Characteristics					
Race/ethnicity, %					
Asian	2 (4)	7 (5)	6 (4)	10 (3)	10 (2)
Black	15 (36)	43 (33)	42 (28)	39 (13)	17 (4)
Hispanic	4 (9)	11 (8)	6 (4)	6 (2)	10 (2)
Other	12 (29)	19 (15)	17 (11)	38 (12)	39 (9)
Non-Hispanic White	9 (21)	49 (38)	81 (54)	213 (70)	343 (82)
Female, %	23 (57)	51 (39)	74 (49)	151 (49)	226 (54)
Sleep duration, hours/day					
6 months	10.17 (2.42)	11.00 (2.17)	11.46 (2.47)	12.17 (1.96)	13.09 (1.65)
1 year	10.64 (2.31)	11.63 (2.19)	12.20 (1.90)	12.73 (1.67)	13.47 (1.24)
2 years	10.12 (1.44)	10.71 (1.39)	11.43 (1.38)	12.02 (1.14)	12.61 (0.84)
3 years	9.53 (1.26)	9.97 (1.24)	10.67 (1.40)	11.18 (1.12)	11.82 (0.83)
4 years	9.37 (0.96)	9.85 (1.14)	10.37 (1.12)	10.78 (1.06)	11.36 (0.83)
5 years	8.88 (1.42)	9.82 (1.58)	10.24 (1.27)	10.63 (1.06)	11.03 (0.96)
6 years	8.85 (1.33)	9.47 (1.28)	9.98 (1.11)	10.31 (1.06)	10.65 (0.78)
7 years	8.26 (1.04)	8.99 (1.13)	9.44 (1.04)	9.93 (0.81)	10.32 (0.59)
Mid-Childhood, 7-Year Visit					
BMI z-score	0.98 (1.03)	0.57 (1.03)	0.49 (0.96)	0.36 (1.00)	0.21 (0.93)
Television, hours/day	2.35 (1.43)	2.00 (1.36)	1.70 (1.20)	1.52 (1.02)	1.28 (0.83)
Family dinner per week	4.93 (2.46)	5.01 (2.41)	5.48 (2.29)	5.52 (2.06)	5.78 (1.73)
Skipping breakfast per week	0.61 (1.22)	0.54 (1.45)	0.32 (1.09)	0.25 (0.97)	0.19 (0.77)
Fast food, servings/week	0.82 (0.91)	0.88 (1.13)	0.72 (0.90)	0.70 (0.87)	0.62 (0.72)
Youth Healthy Eating Index	54.39 (13.63)	54.49 (11.23)	57.5 (11.12)	58.81 (10.08)	60.92 (10.80)
Fruit, servings/day	1.20 (1.14)	1.29 (1.32)	1.60 (1.58)	1.69 (1.45)	1.70 (1.32)
Vegetables, servings/day	1.22 (1.26)	1.18 (1.08)	1.29 (1.02)	1.35 (0.90)	1.35 (0.94)
Whole grains, servings/day	0.55 (0.65)	0.66 (0.86)	0.76 (0.95)	0.79 (0.90)	0.97 (0.98)
Total dairy, servings/day	1.97 (1.63)	1.92 (1.66)	2.12 (1.73)	2.47 (1.74)	2.40 (1.54)
Red/processed meats, servings/day	0.50 (0.64)	0.54 (0.67)	0.47 (0.44)	0.55 (0.48)	0.49 (0.44)
Sweet/salty snacks, servings/day	0.26 (0.38)	0.38 (0.50)	0.29 (0.36)	0.38 (0.39)	0.37 (0.34)
Sugary drinks, servings/day	0.68 (1.18)	0.57 (1.09)	0.43 (0.96)	0.34 (0.67)	0.25 (0.51)

Table 2.2 shows the primary results: chronic insufficient sleep from infancy to mid-childhood is associated with dietary factors in mid-childhood. Each incremental increase in the sleep score (indicating more adequate sleep duration) was associated with more favorable dietary intake (indicated by the YHEI). The mean difference in the YHEI per 1-unit increase in the sleep score was 0.59 points; 95% Confidence Interval [95%CI]: 0.32, 0.86. Components of the YHEI were modestly associated with the sleep score, as follows: whole grains (0.02 more servings/day; 95%CI: 0.00, 0.05); sugary drinks (-0.02 fewer servings/week; 95%CI: -0.04, 0.00); family dinner (0.05 more times/week; 95%CI: 0.00, 0.10); and skipping breakfast (-0.03 fewer times/week; 95%CI: -0.05, 0.00). Intake of fast food, dairy and fruits and vegetables were not associated with the sleep score.

Table 2.2. Sleep curtailment score as a predictor of dietary intake in mid-childhood (N=1,046)[1]

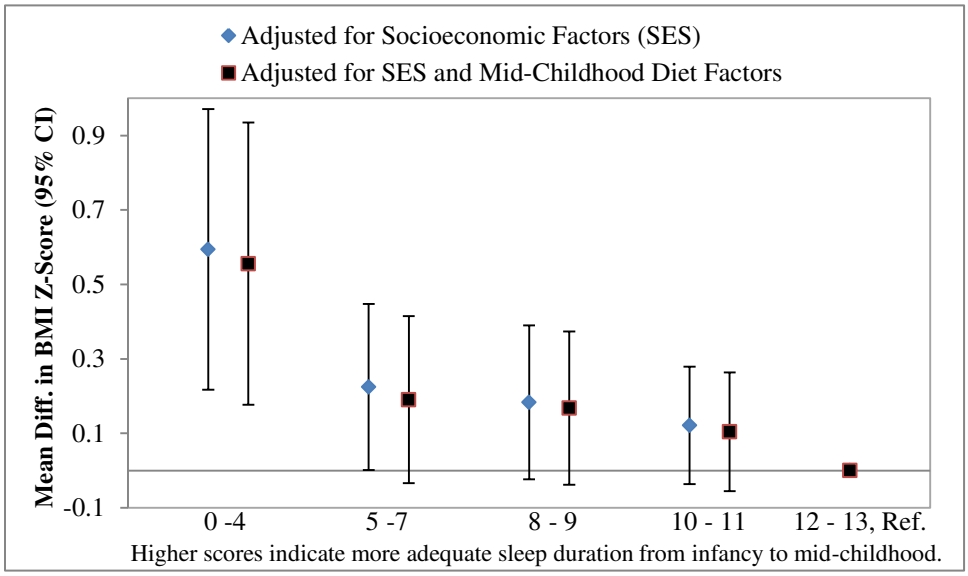
	Mean difference in mid-childhood dietary factor (95%CI) Sleep Curtailment Score[2]					
	0 to 4 4%	5 to 7 12%	8 to 9 15%	10 to 11 29%	12 to 13 40%	Continuous Score
YHEI score[3]	-4.17 (-8.29,-0.04)	-4.51 (-6.84,-2.18)	-2.16 (-4.29,-0.03)	-1.66 (-3.24,-0.08)	0.0 (ref)	**0.59 (0.32, 0.86)**
Whole grains, servings/day	-0.20 (-0.50, 0.09)	-0.14 (-0.33, 0.06)	-0.11 (-0.28, 0.06)	-0.16 (-0.30,-0.03)	0.0 (ref)	**0.02 (0.00, 0.05)**
Sugary drinks, servings/week	0.18 (-0.10, 0.46)	0.11 (-0.07, 0.28)	0.09 (-0.05, 0.23)	0.04 (-0.06, 0.14)	0.0 (ref)	**-0.02 (-0.04, 0.00)**
Family dinner per week	-0.48 (-1.18, 0.21)	-0.39 (-0.83, 0.05)	-0.08 (-0.48, 0.31)	-0.15 (-0.45, 0.15)	0.0 (ref)	**0.05 (0.00, 0.10)**
Total dairy, servings/day	-0.03 (-0.58, 0.52)	-0.21 (-0.55, 0.14)	-0.03 (-0.34, 0.27)	0.19 (-0.05, 0.43)	0.0 (ref)	0.02 (-0.02, 0.06)
Fruits and vegetables, servings/day	-0.10 (-0.77, 0.57)	-0.11 (-0.51, 0.29)	0.09 (-0.28, 0.46)	0.12 (-0.15, 0.39)	0.0 (ref)	0.01 (-0.04, 0.06)
Fast food, servings/week	-0.01 (-0.30, 0.27)	0.06 (-0.13, 0.25)	0.03 (-0.13, 0.19)	0.01 (-0.11, 0.13)	0.0 (ref)	-0.01 (-0.03, 0.01)
Skipping breakfast per week	0.23 (-0.13, 0.59)	0.18 (-0.03, 0.40)	0.04 (-0.16, 0.24)	0.03 (-0.12, 0.17)	0.0 (ref)	**-0.03 (-0.05, 0.00)**

Boldface indicates statistical significance at the $p \leq 0.05$ level for the continuous score outcome

[1.] Models adjust for child sex, age in days and race/ethnicity; maternal college graduate (yes/no); and household income (>/≤ 70k)
[2.] Higher sleep scores indicate more often meeting the recommended sleep for age, i.e., children with higher sleep scores had more adequate sleep duration over childhood.
[3.] Youth Healthy Eating Index (YHEI) score is not adjusted for other mid-childhood dietary factors.

Figure 2.1 shows previously examined associations of chronic insufficient sleep with mid-childhood BMI z-score, (7) which were not explained by mid-childhood dietary factors. Comparing children with the least adequate sleep (scores 0-4) from infancy to mid-childhood to children with the most adequate sleep (scores 12-13), the mean difference in mid-childhood BMI z-score was 0.59 SD (95%CI: 0.22, 0.97), attenuating only slightly (~5% to 0.56 SD [95%CI: 0.18, 0.93]) with the addition of all YHEI dietary factors to multivariable models. Considering the score continuously, the mean difference in mid-childhood BMI z-score per 1-unit increase in the sleep score was -0.05 SD (95%CI: -0.08, -0.03). This protective association did not attenuate when YHEI components were added to multivariable models (-0.05 SD; 95%CI: -0.07, -0.02).

Figure 2.1. Association of sleep curtailment score with BMI z-score in mid-childhood does not attenuate with adjustment for mid-childhood dietary factors (N=1,046) [1, 2]



[1.] Results from linear regression models adjusted for maternal education, household income, age in days at mid-childhood visit, sex, and race/ethnicity. The sleep curtailment score is shown categorically, with and without adjustment for all dietary factors other than YHEI in mid-childhood.
[2.] Higher sleep scores indicate more often meeting the recommended sleep for age, i.e., children with higher sleep scores had more adequate sleep duration over childhood.

In supplemental analyses, we examined mutually-adjusted associations of mid-childhood dietary factors with mid-childhood BMI z-score (Figure 2.S1). Though most associations were in the expected direction, the dietary factors that were significantly associated with BMI z-score were overall diet quality (-0.07 SD per 10-point increase in YHEI; 95%CI: -0.13, -0.01); whole grain intake (-0.12 SD per servings/day; 95%CI: -0.19, -0.04); and skipping breakfast (0.07 SD per skipped meal/week; 95%CI: 0.01, 0.14). Sugary drinks and family dinner were not associated with mid-childhood BMI z-score.

Our supplemental analyses assessing joint associations of chronic insufficient sleep and dietary factors found that children in the least favorable category of sleep and diet had the highest estimated mid-childhood BMI z-scores. The mean difference in BMI z-score was 0.34 standard deviation units higher (95%CI: 0.16, 0.51) comparing children with sleep and diet scores below median values (sleep score <11; YHEI <60) to those with sleep and diet scores above median values (Figure 2.S2). However, the interaction term of continuous sleep and YHEI score was not statistically significant (p=0.53).

In sensitivity analyses updating the sleep curtailment score to align with 2015 sleep recommendations, results were similar. Associations per unit increase in the revised sleep score with BMI z-score in mid-childhood (-0.05 SD [95%CI: -0.08, -0.02]), YHEI score (0.61 points [95%CI: 0.34 0.88]), sugary drink intake (-0.02 servings/day [95%CI: -0.04, -0.01]) and frequency of skipping breakfast (-0.04 times/week [95%CI:-0.06, -0.01]) were nearly identical. However, the revised sleep score was not associated with other dietary factors (e.g. whole grain intake or frequency of family dinner).

DISCUSSION

In this cohort of 1,046 children followed from infancy to mid-childhood, we found that chronic insufficient sleep predicted less favorable diet quality in mid-childhood adjusting for child age, sex and race/ethnicity, maternal education and household income. While mid-childhood dietary factors were associated with mid-childhood BMI z-score, diet quality did not explain associations of chronic insufficient sleep with BMI z-score. Dietary assessment in young children is challenging, and typically relies on parental report. Random measurement error could be one explanation for why children's diet quality did not mediate the sleep score's association with BMI z-score. Further, total energy intake was not examined (it is not well-measured through dietary questionnaires on habitual intake). Another possibility is that sleep influences energy balance through pathways other than diet quality; e.g., experimental data show timing of feeding impacts metabolic processes and satiety responses independent of calories, reflecting the importance of circadian alignment of eating behaviors with metabolism. (29) Though the impact of chronic insufficient sleep on other aspects of diet (e.g. meal timing) warrant exploration, our finding that chronic insufficient sleep is associated with diet quality plus the previously observed associations of chronic insufficient sleep with BMI z-score (7) both support the need to consider sleep as a relevant behavior in pediatric obesity.

Sleep and diet quality

We found that chronic sleep curtailment is associated with less favorable overall diet quality as measured by the YHEI, and with less frequent family dinner and consumption of whole grains and more frequent consumption of sugary drinks. To our knowledge, ours is the first study to examine associations of chronic insufficient sleep with diet quality in mid-childhood; few studies are directly comparable. Our findings extend prior cross-sectional research, primarily in older

children and adolescents, in two important ways: first we assess chronic insufficient sleep over the course of childhood and habitual dietary intake, and second we assess this in young children still establishing dietary habits and preferences. Key examples of prior cross-sectional research include that of Westerlund et al., who found that questionnaire-measured shorter sleep in Finish schoolchildren (n=1,265) was associated with greater consumption of energy-dense foods including pizza, pasta and refined sugars. (30) With respect to macronutrient composition, Weiss et al found in American adolescents (n=240) that compared to actigraphy-measured sleep of $\geq$ 8-hours on weekdays, sleeping < 8-hours was associated with a higher proportion of calories from fats. (31)

In the present study, we found no association of chronic insufficient sleep with consumption of fast food or fruits and vegetables in mid-childhood; in contrast, data from the National Longitudinal Study of Adolescent Health (Add Health, n=13,284) found that self-reported short sleep duration (< 7-hours/night compared to >8-hours/night) was associated with reduced odds of vegetable/fruit consumption and increased odds of fast food consumption. However, Add Health data were cross-sectional, from older children, and dietary factors were not mutually adjusted. (32) One possibility is that there is a cross-sectional relationship of shorter sleep duration with fast food and vegetables/fruits but chronic insufficient sleep duration does not influence consumption. Another possibility is that results do not extend to a study population as young as ours (e.g. adolescents have more autonomy over food choice), or, as mentioned previously, measurement error in parent-report of children's intake attenuates associations.

Prospective studies are few, and provide inconsistent evidence for an association of shorter sleep duration in childhood with lower diet quality; e.g., the United Kingdom's Gemini cohort (n=1,303) reported that shorter (<10-hours/day) versus longer sleep duration (11-<12-hours/day)

at 16 months predicted slightly higher energy intake at 21 months, but found no differences in macronutrient composition. (19) Similar to our findings that shorter sleep duration was associated with sugary drink intake, a recent prospective study with shorter follow-up (200 days) and smaller size (n= 441 Danish 8-11-year-olds) found that each 1-hour decline in accelerometer-measured sleep duration was associated with higher intake of added sugar and sugar-sweetened beverages. (33) Our study extends this literature by showing that chronic insufficient sleep from infancy to mid-childhood is associated with less favorable overall diet quality in mid-childhood as measured by the YHEI and selected components.

Diet quality*'s* role in the relationship of sleep to adiposity

Diet quality did not explain associations of chronic insufficient sleep duration with adiposity in young children. Results from experimental studies are inconsistent, short-term, and in small samples; e.g., a recent intervention assigned (n=37) children 8-11 years to 1.5-hour increased (versus decreased) time in bed and reported lower food intake, fasting leptin and weight at 3-weeks. (16) By contrast, in a crossover trial of Danish adolescents (n=21) short-term sleep restriction was not associated greater ad libitum intake or positive energy balance. (34) In free-living adults, one of the only observational studies examining this question was conducted among Japanese workmen; the authors concluded that diet adjustment (e.g. fatty food preference, skipping breakfast, snacking, and eating out) only partially explained associations of short sleep with obesity. (35)

Longitudinal research in children examining diet as a mediator is limited to one prior study, the Quebec Longitudinal Study of Child Development (n=1,106), which found associations of shorter sleep patterns from birth through mid-childhood with lower diet quality, irregular eating and eating too much too fast at 6 years. Consistent with our finding that dietary

quality did not play a strong mediating role in the relationship of chronic insufficient sleep to adiposity, the Quebec study found that irregular eating and eating too much too fast, and not dietary intake, mediated the inverse association between sleep duration and overweight/obesity. (36) These findings are echoed by a small study of Canadian 5-12 year olds (n=56) that found shorter actigraphy-measured sleep duration was associated with emotional eating, greater response to food stimuli, and less dietary restraint. (37) Altered eating behaviors, not just the composition of diet, may play important mediating roles in the associations of sleep duration with adiposity in early childhood when children often have less autonomy in food selection.

We found that children scoring below the median for both the sleep and diet scores had higher BMI z-scores than children scoring below the median on either alone, suggesting that both sufficient sleep and diet quality may aid in childhood obesity prevention. No other study has examined the joint associations of chronic insufficient sleep duration and diet with mid-childhood BMI z-score.

Strengths and limitations

Ours is one of the first studies examining the relationship of chronic insufficient sleep to diet quality in young children. Strengths include repeated parental report of sleep duration over time and research measures of height/weight. Additionally, prior studies examining sleep duration in relation to single dietary factors or behaviors have not adjusted for other aspects of diet to show independent associations as we did in this study.

This study has limitations. Parental report of children's sleep duration and diet almost certainly contain error. While this error is likely random, null bias could mask diet's mediating role in sleep-adiposity relationship. Additionally, our measure of overall diet quality –YHEI –

was developed in older children; neither this index nor other common dietary indices are used widely in young children. (38) Future prospective research should examine additional aspects of children's sleep and diet not measured here, including sleep quality (e.g. nighttime awakenings or difficulty falling asleep), night-to-night variation in sleep duration and eating behaviors (e.g. emotional/disinhibited eating). Further work including meal timing may further clarify the inter-relationships among sleep, eating behaviors and energy balance.

CONCLUSION

Our results demonstrate that chronic insufficient sleep duration as measured from longitudinal data from infancy to mid-childhood is associated with lower quality diet in children. This association is not explained by measured confounders such as sex, age, race/ethnicity, education or income. With questionnaire data, we did not identify an appreciable mediating role of diet in the sleep-adiposity association. That children with the least favorable diets and sleep duration throughout childhood had the highest estimated BMI z-scores suggests that consideration of sleep duration and diet quality is necessary for childhood obesity prevention.

REFERENCES

1. Ambrosini GL, Emmett PM, Northstone K, Jebb SA. Tracking a dietary pattern associated with increased adiposity in childhood and adolescence. Obesity (Silver Spring, Md) 2014;22(2):458-65. doi: 10.1002/oby.20542.
2. Bjelland M, Brantsaeter AL, Haugen M, Meltzer HM, Nystad W, Andersen LF. Changes and tracking of fruit, vegetables and sugar-sweetened beverages intake from 18 months to 7 years in the Norwegian Mother and Child Cohort Study. BMC public health 2013;13:793. doi: 10.1186/1471-2458-13-793.
3. Cunningham SA, Kramer MR, Narayan KMV. Incidence of Childhood Obesity in the United States. New England Journal of Medicine 2014;370(5):403-11.
4. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 2008;31(5):619-26.
5. Padez C, Mourao I, Moreira P, Rosado V. Long sleep duration and childhood overweight/obesity and body fat. American journal of human biology : the official journal of the Human Biology Council 2009;21(3):371-6. doi: 10.1002/ajhb.20884.
6. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A. Early life risk factors for obesity in childhood: cohort study. BMJ (Clinical research ed) 2005;330(7504):1357. doi: 10.1136/bmj.38470.670903.E0.
7. Taveras EM GM, Peña MM, Redline S, Rifas-Shiman SL. Chronic Sleep Curtailment and Adiposity. Pediatrics 2014;133(6):1013-22. doi: 10.1542/peds.2013-3065.
8. Spruyt K, Molfese DL, Gozal D. Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. Pediatrics 2011;127(2):e345-52. doi: 10.1542/peds.2010-0497.
9. Matthews KA, Dahl RE, Owens JF, Lee L, Hall M. Sleep duration and insulin resistance in healthy black and white adolescents. Sleep 2012;35(10):1353-8. doi: 10.5665/sleep.2112.
10. Kong AP, Wing YK, Choi KC, Li AM, Ko GT, Ma RC, Tong PC, Ho CS, Chan MH, Ng MH, et al. Associations of sleep duration with obesity and serum lipid profile in children and adolescents. Sleep medicine 2011;12(7):659-65. doi: 10.1016/j.sleep.2010.12.015.
11. Kjeldsen JS, Hjorth MF, Andersen R, Michaelsen KF, Tetens I, Astrup A, Chaput JP, Sjodin A. Short sleep duration and large variability in sleep duration are independently associated with dietary risk factors for obesity in Danish school children. International journal of obesity (2005) 2014;38(1):32-9. doi: 10.1038/ijo.2013.147.
12. Morselli L, Leproult R, Balbo M, Spiegel K. Role of sleep duration in the regulation of glucose metabolism and appetite. Best practice & research Clinical endocrinology & metabolism 2010;24(5):687-702. doi: 10.1016/j.beem.2010.07.005.
13. Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. Annals of the New York Academy of Sciences 2008;1129:287-304. doi: 10.1196/annals.1417.033.
14. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. International journal of obesity (2005) 2014;38(3):411-6. doi: 10.1038/ijo.2013.114.
15. Benedict C, Brooks SJ, O'Daly OG, Almen MS, Morell A, Aberg K, Gingnell M, Schultes B, Hallschmid M, Broman JE, et al. Acute sleep deprivation enhances the brain's

response to hedonic food stimuli: an fMRI study. The Journal of clinical endocrinology and metabolism 2012;97(3):E443-7. doi: 10.1210/jc.2011-2759.
16. Hart CN, Carskadon MA, Considine RV, Fava JL, Lawton J, Raynor HA, Jelalian E, Owens J, Wing R. Changes in children's sleep duration on food intake, weight, and leptin. Pediatrics 2013;132(6):e1473-80. doi: 10.1542/peds.2013-1274.
17. Chaput JP. Sleep patterns, diet quality and energy balance. Physiology & behavior 2014;134:86-91. doi: 10.1016/j.physbeh.2013.09.006.
18. Ventura AK, Birch LL. Does parenting affect children's eating and weight status? The international journal of behavioral nutrition and physical activity 2008;5:15. doi: 10.1186/1479-5868-5-15.
19. Fisher A, McDonald L, van Jaarsveld CH, Llewellyn C, Fildes A, Schrempft S, Wardle J. Sleep and energy intake in early childhood. International journal of obesity (2005) 2014;38(7):926-9. doi: 10.1038/ijo.2014.50.
20. Oken E, Baccarelli AA, Gold DR, Kleinman KP, Litonjua AA, De Meo D, Rich-Edwards JW, Rifas-Shiman SL, Sagiv S, Taveras EM, et al. Cohort Profile: Project Viva. International journal of epidemiology 2014. doi: 10.1093/ije/dyu008.
21. Kushnir J, Sadeh A. Correspondence between reported and actigraphic sleep measures in preschool children: the role of a clinical context. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 2013;9(11):1147-51. doi: 10.5664/jcsm.3154.
22. Cespedes EM, Rifas-Shiman SL, Redline S, Gillman MW, Pena MM, Taveras EM. Longitudinal associations of sleep curtailment with metabolic risk in mid-childhood. Obesity (Silver Spring, Md) 2014. doi: 10.1002/oby.20894.
23. Hart CN, Cairns A, Jelalian E. Sleep and obesity in children and adolescents. Pediatr Clin North Am 2011;58(3):715-33. doi: 10.1016/j.pcl.2011.03.007.
24. National Sleep Foundation. Internet: http://sleepfoundation.org/ (accessed April 9 2014).
25. National Heart Lung and Blood Institute. Internet: http://www.nhlbi.nih.gov/health/health-topics/topics/sdd/howmuch (accessed April 9 2014).
26. Taveras E, Rifas-Shiman S, Redline S, Gillman M. Short Sleep Duration in Infancy and Chronic Sleep Curtailment from Infancy to Mid-Childhood Are Associated with Higher Adiposity at Age 7 Years. Boston, Mass: Pediatric Academic Societies' Annual Meeting, April 28-May 1, 2012.
27. Rifas-Shiman SL, Willett WC, Lobb R, Kotch J, Dart C, Gillman MW. PrimeScreen, a brief dietary screening tool: reproducibility and comparability with both a longer food frequency questionnaire and biomarkers. Public health nutrition 2001;4(2):249-54.
28. Feskanich D, Rockett HR, Colditz GA. Modifying the Healthy Eating Index to assess diet quality in children and adolescents. Journal of the American Dietetic Association 2004;104(9):1375-83. doi: 10.1016/j.jada.2004.06.020.
29. McHill AW, Melanson EL, Higgins J, Connick E, Moehlman TM, Stothard ER, Wright KP, Jr. Impact of circadian misalignment on energy metabolism during simulated nightshift work. Proceedings of the National Academy of Sciences of the United States of America 2014;111(48):17302-7. doi: 10.1073/pnas.1412021111.
30. Westerlund L, Ray C, Roos E. Associations between sleeping habits and food consumption patterns among 10-11-year-old children in Finland. The British journal of nutrition 2009;102(10):1531-7. doi: 10.1017/s0007114509990730.

31. Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. Sleep 2010;33(9):1201-9.
32. Kruger AK, Reither EN, Peppard PE, Krueger PM, Hale L. Do sleep-deprived adolescents make less-healthy food choices? The British journal of nutrition 2014;111(10):1898-904. doi: 10.1017/s0007114514000130.
33. Hjorth MF, Quist JS, Andersen R, Michaelsen KF, Tetens I, Astrup A, Chaput JP, Sjodin A. Change in sleep duration and proposed dietary risk factors for obesity in Danish school children. Pediatric obesity 2014. doi: 10.1111/ijpo.264.
34. Klingenberg L, Chaput JP, Holmback U, Jennum P, Astrup A, Sjodin A. Sleep restriction is not associated with a positive energy balance in adolescent boys. The American journal of clinical nutrition 2012;96(2):240-8. doi: 10.3945/ajcn.112.038638.
35. Nishiura C, Noguchi J, Hashimoto H. Dietary patterns only partially explain the effect of short sleep duration on the incidence of obesity. Sleep 2010;33(6):753-7.
36. Tatone-Tokuda F, Dubois L, Ramsay T, Girard M, Touchette E, Petit D, Montplaisir JY. Sex differences in the association between sleep duration, diet and body mass index: a birth cohort study. Journal of sleep research 2012;21(4):448-60. doi: 10.1111/j.1365-2869.2011.00989.x.
37. Burt J, Dube L, Thibault L, Gruber R. Sleep and eating in childhood: a potential behavioral mechanism underlying the relationship between poor sleep and obesity. Sleep medicine 2014;15(1):71-5. doi: 10.1016/j.sleep.2013.07.015.
38. Marshall S, Burrows T, Collins CE. Systematic review of diet quality indices and their associations with health-related outcomes in children and adolescents. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 2014. doi: 10.1111/jhn.12208.

ACKNOWLEDGEMENTS

Author affiliations

Department of Nutrition, Harvard School of Public Health, Boston, MA (Elizabeth M. Cespedes, Frank B. Hu, Matthew W. Gillman, Elsie M. Taveras); Department of Epidemiology, Harvard School of Public Health, Boston, MA (Elizabeth M. Cespedes, Frank B. Hu); Channing Division of Network Medicine, Harvard Medical School and Department of Biostatistics, Harvard School of Public Health, Boston, MA (Bernard Rosner); Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA (Susan Redline); Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA (Elizabeth M Cespedes, Matthew W Gillman, Sheryl L. Rifas-Shiman); Division of General Academic Pediatrics, Department of Pediatrics, Massachusetts General Hospital for Children, Boston, MA (Elsie M. Taveras)

Funding

This work was supported by the National Cancer Institute's Centers for Transdisciplinary Research on Energetics and Cancer (TREC) (U54CA116847) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R37HD034568). Elizabeth Cespedes is supported by the National Institute of Diabetes and Digestive and Kidney Diseases T32 DK007703.

Conflicts of Interest

The authors have no conflict of interest to disclose

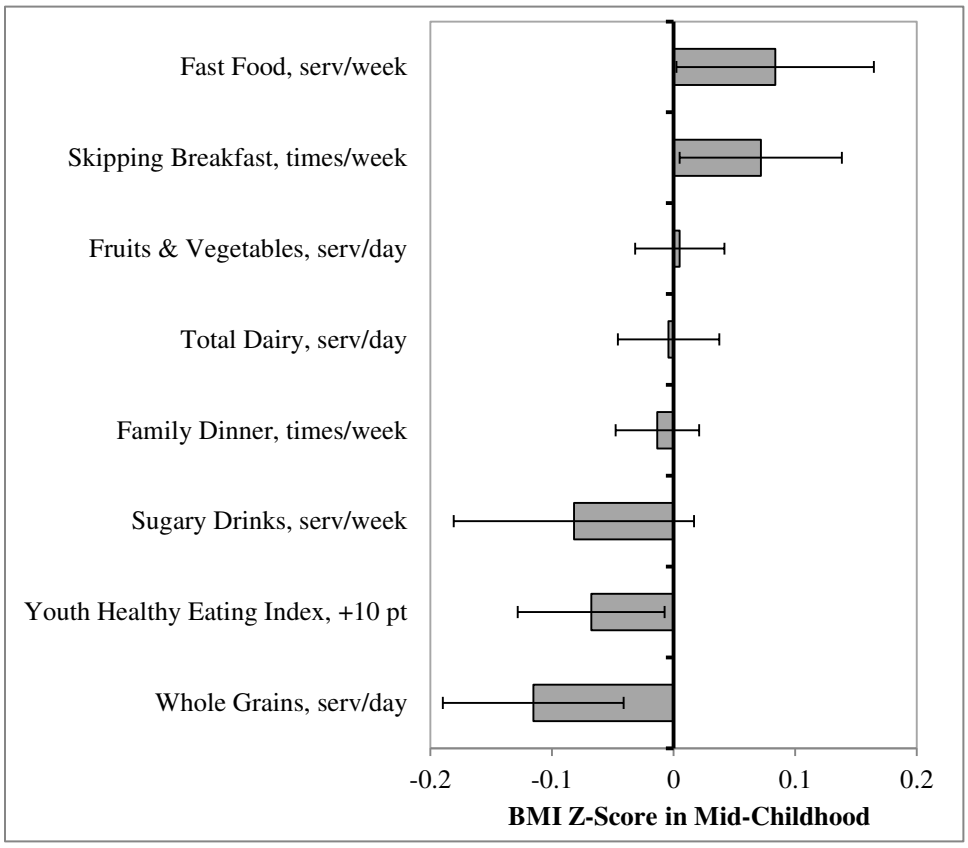
APPENDIX

Supplemental Table 2.S1: Dietary Factors at Mid-Childhood Visit

Dietary Factor	Component Variables	Responses/Derivation
Youth Healthy Eating Index[1]	1. Whole grains, 2. Vegetables, 3. Fruits, 4, Dairy, 5. Meat ratio (servings/day of chicken, fish, eggs, nuts, seeds, soy/tofu, and beans, divided by servings/day of beef, pork, lamb, and liver), 6. Sweet and salty snack foods, 7. Soda and drinks, 8. Multivitamin use, 9. Margarine and butter, 10. Fried foods outside the home (see Fast Food), 11. Eating breakfast (skipping breakfast reverse coded), 12. Family dinner.	Theoretical Range: 0-95; components 1 to 7 awarded up to 10 points and components 8 to 12 awarded up to 5 points. Study Mean (Observed Range): 59 (29-92)
Fast Food	In the past month, on average, how often did your child eat something from a fast food restaurant (McDonald's, Burger King, Taco Bell, etc)	"Never/less than once per month" (coded as 0/week); "1–3 times per month" (0.5), "once per week" (1), "2–4 times per week" (3), '5–6 times per week" (5.5), and "once per day or more" (7)
Sugary drinks	Sum of: (1) Soda and (3) Fruit drinks	"Never" (coded as 0/day); "Less than once per week" (0.07); "once per week" (0.14); "2 – 4 times per week" (0.43); "Nearly daily or daily" (1); "2 –4 times per day" (3); "5 or more times per day" (5).
Snacks	Baked Products (donuts, cookies, muffins, crackers, cakes, sweet rolls, pastries)	
Whole Grains	Whole grain foods (e.g., whole grain breads, brown rice)	
Total Dairy	Sum of: (1) Whole Milk Dairy Foods (e.g., whole milk, hard cheese, butter, ice cream) and (2) Low-fat Milk Products (e.g., low fat/skim milk, yogurt, cottage cheese)	
Lean Meats	Sum of: (1) Fish/Seafood (not fried, but broiled, baked, poached, canned) and (2) Whole eggs	"Never" (coded as 0/day); "Less than once per week" (0.07); "once per week" (0.14); "2 – 4 times per week" (0.43); "Nearly daily or daily" (1); "2 or more times per day" (3)
Fatty Meats	Sum of: (1) Beef, pork or lamb as main dish and (2) Processed meats (sausages, salami, bologna, hot dogs, bacon)	
Fruits and Vegetables	Sum of: (1) Dark green leafy vegetables (spinach, romaine lettuce, greens/kale), (2) Broccoli, Cauliflower, Cabbage, Brussels Sprouts, (3) Carrots, (4) Other Vegetables (e.g., peas, corn, green beans, tomatoes, squash) , (5) Citrus Fruits (e.g., orange juice or grapefruit juice, oranges, grapefruit)and (6) Other Fruits (e.g., fresh apples or pears, bananas, berries, grapes, melons)	
Skipping Breakfast	In the past month, on average, how often does your child skip eating breakfast?	"Never/less than once per week" (coded as 0); "Once per week" (1); "2 – 4 times per week" (3); "5 – 6 times per week" (5.5); "Every day" (7)
Family Dinner	In the past month, on average, how often does your child eat supper or dinner together with family members?	

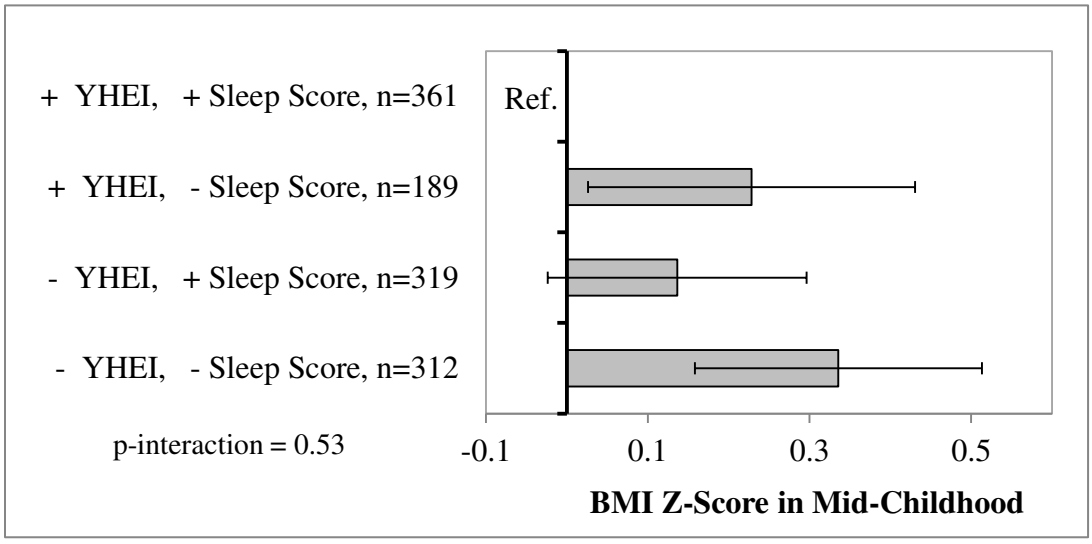
[1] The original YHEI included 5 points for removing visible animal fat from food. This information was not available and thus excluded for a theoretical range of 0-95 rather than 0-100. Additionally, information on nuts/seeds was not available and was excluded from calculations.

Figure 2.S1. Dietary factors as predictors of BMI z-score mid-childhood [1]



[1.] Results from linear regression models adjusted for maternal education, household income, age in days at mid-childhood visit, sex, and race/ethnicity. With the exception of YHEI, all dietary predictors are adjusted for other dietary factors in mid-childhood.

Figure 2.S2. Joint associations of sleep curtailment and diet quality with BMI z-score in mid-childhood [1]



+ Sleep score = sleep curtailment score ≥ median score of 11
- Sleep score = sleep curtailment score < median score of 11
+ YHEI = Youth Healthy Eating Index score ≥ median score of 60
- YHEI = Youth Healthy Eating Index score < median score of 60

[1.] Results from linear regression models adjusted for maternal education, household income, age in days at mid-childhood visit, sex, and race/ethnicity. The sleep score ranges from 0 (maximal sleep curtailment) to 13 (never having curtailed sleep); p-interaction calculated from the product of the continuous sleep score with the continuous YHEI score.

Chapter 3: Multiple healthful dietary patterns are associated with reduced risk of type 2 diabetes in the Women's Health Initiative

---

Elizabeth M Cespedes, Frank B Hu, Lesley tinker, Bernard Rosner, Susan Redline,

Lorena Garcia, Melanie Hingle, Linda Van Horn, Barbara V Howard,

Emily B Levitan, Wenjun Li, JoAnn E Manson, Lawrence Phillips,

Jinnie J Rhee, Molly E Waring, Marian L Neuhouser

ABSTRACT

Background/objective: The relationship between various diet quality indexes and risk of type 2 diabetes (T2D) remains unsettled. We compare associations of four indices–Alternate Mediterranean Diet (aMED), Healthy Eating Index-2010 (HEI-2010), Alternate Healthy Eating Index-2010 (AHEI-2010), and Dietary Approaches to Stop Hypertension (DASH) –with reported T2D among participants in the Women's Health Initiative.

Methods: This prospective cohort included (n=101,504) postmenopausal women without T2D who completed a baseline food frequency questionnaire. Higher scores indicated higher diet quality. Cox regression was used to estimate multivariate hazard ratios and 95% confidence intervals for incident T2D.

Results: Pearson correlation coefficients among the scores ranged from 0.55 (aMED-HEI-2010) to 0.74 (DASH-HEI-2010). During a median 15 years follow-up, 10,815 incident cases of T2D occurred. Across indices, 1 standard deviation higher score was associated with 10%–14% lower risk of T2D ($p < 0.001$). Adjusting for overweight/obesity at enrollment (a potential mediator) attenuated but did not eliminate associations to 5%-10% lower risk per standard deviation higher score ($p < 0.001$). Associations were dependent on race/ethnicity: stronger associations were observed among Hispanic/Latinas compared to non-Hispanic Caucasians (LRT p-interaction < 0.05).

Conclusions: Multiple forms of a healthful diet are associated with lower risk of T2D in post-menopausal women in all racial/ethnic groups.

INTRODUCTION

Type 2 diabetes (T2D) has reached epidemic proportions with 592 million diabetes cases projected worldwide by 2035. (1) Since diet and lifestyle factors contribute to risk of T2D and potentially also to racial/ethnic disparities in disease burden, identifying the optimal diet (or diets) for prevention of T2D is a public health priority. (2) Though much nutrition research focuses on single nutrients or specific foods, the combinations and quantities in which foods and nutrients are consumed have synergistic and cumulative effects. Moreover, isolating individual dietary exposures may not provide a realistic picture of dietary patterns or health impact since typically when one component of diet changes it is substituted by another. (3) Numerical indices measuring adherence to a dietary pattern pre-defined based on scientific evidence offer a method to examine the totality of diet. Dietary pattern analysis of this sort may lead more easily to public health recommendations as noted in the 2010 Dietary Guidelines for Americans. (4)

An important obstacle to summarizing the evidence on dietary patterns and T2D is the ability to compare associations of various scores due to differences in modeling approaches and scores based on median population intakes versus fixed cut-offs for recommended intakes. The Women's Health Initiative (WHI) offers the opportunity to calculate multiple, standardized dietary indices in the same cohort, thus addressing an important limitation to the present evidence highlighted in a recent systematic review by the USDA's National Evidence Library. (5) Further, the ethnic diversity of WHI offers a complement to existing prospective research on dietary patterns, which has been primarily among European and European-descent populations, with few exceptions. (6-8) This is particularly important since African Americans and Hispanic/Latinos experience a greater burden than non-Hispanic whites and develop T2D at younger ages. (9)

The present study extends research by Qiao et al examining associations of the AHEI with T2D in the Women's Health Initiative. (7) Here we calculate the updated AHEI-2010 and newly present results for three additional indices. Further, we strengthen the Qiao et al approach by excluding women in the dietary intervention trial, who likely changed diets after the baseline assessment and had high energy intake from fat (>32%) due to the trial eligibility criteria. In sum, the present study examines four commonly used dietary indices associated with lower risk of T2D in prospective cohort studies: the alternate Mediterranean Diet Score (aMED), (6, 10, 11) the Healthy Eating Index-2010 (HEI-2010), (12) the Alternate Healthy Eating Index-2010 (AHEI-2010), (12, 13) and Dietary Approaches to Stop Hypertension Score (DASH). (14, 15) We present associations for each index, standardized for comparability, with T2D. Importantly, we examine whether race/ethnicity modifies associations of dietary indices with T2D in this diverse cohort of postmenopausal women.

METHODS

Study population

The design, recruitment and assessment methods of WHI have been previously described. (16-18) From 1993-1998, postmenopausal women 50–79 years of age were recruited into the clinical trials (CT) or the observational study (OS). The ended their first phase in 2004–2005, and participants were invited to participate in the 2005–2010 WHI Extension Study 1. Participants consenting to join the Extension Study 2 (2010-2015) continue to be followed for outcomes data collection, including T2D. The present study includes follow-up through September 20, 2013.

Written informed consent was obtained from all study participants. Procedures and protocols were approved by institutional review boards at all participating institutions. A standardized written protocol, centralized training of staff, and quality assurance visits by the clinical coordinating center were used to ensure uniformity of data collection. The present sample was drawn from women participating in WHI OS and calcium, vitamin D and hormone therapy (HT) trials. We excluded women in both arms of the dietary modification trial due to the systematically higher fat intake that was part of the eligibility criteria (>32% energy from fat) and because intervention participants likely changed their diets after baseline. Of these 112,129, we additionally excluded those with prior diagnosis of diabetes outside of pregnancy (n=6,585) and implausible energy intakes of less than 600 kcals/day or more than 5,000 kcals/day (n=4,040). Our sample for analysis was 101,504 women.

At enrollment, participants reported demographic characteristics, health behaviors, and medical histories using self-administered questionnaires. We categorized risk factors as follows: age at screening (50-54, 55-59, 60-69, and 70-79 years); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other race/ethnicity, or missing [n=275]); educational level (high school or below, some college, college, postgraduate, or missing [n=798]); and smoking status (never, past, current or missing [n=1,355]). Self-reported physical activity was measured using WHI brief physical activity inventory, which has been shown to be reliable (weighted κ ranging from 0.67 to 0.71) and valid when compared with accelerometer data (r = 0.73). (18) For each participant, we calculated metabolic equivalent (MET)-hours per week of recreational physical activity categorized level into quintiles (0-<2, 2-<7, 7-13, >13-23, >23 MET-hours/week, or missing [n= 2,132]). The use of postmenopausal hormone therapies (unopposed estrogen and/or estrogen plus progesterone) via pills or patches was self-reported, and we classified women as

never, past, current users or missing (n=2119). At the clinic visit, trained staff measured each participant's weight and height using a standardized protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, categorized as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0-39.9, ≥40 kg/m^2 or missing (n=1,070). Also at the clinic visit, trained staff measured each participant's waist circumference during expiration at the narrowest section of the torso, which we considered as a continuous variable in sensitivity analyses.

Diet assessment

Diet was measured at enrollment using a self-administered food frequency questionnaire (FFQ) developed and validated specifically for WHI and adapted from the Health Habits and Lifestyle Questionnaire. (19, 20) The 3 sections of the WHI FFQ included 122 composite and single-food line items asking about frequency of consumption and portion size, 19 adjustment questions about the type of fat intake, and 4 summary questions about the usual intakes of fruits and vegetables and added fats for comparison with information gathered from line items. The WHI FFQ was designed to capture foods relevant for multiethnic and geographically diverse population groups, and it has been shown to produce reliable and comparable estimates to 8 days of dietary intake from four 24-hour dietary recalls and 4-day food records. (20) The nutrient database used to analyze the WHI FFQ was derived from the Nutrition Data Systems for Research, version 2005 (University of Minnesota, Minneapolis, Minnesota). (21) The Nutrition Data Systems for Research provides nutrient information for more than 140 nutrients and compounds, including energy, saturated fat, and sodium.

We measured diet quality with the following indices: 1) the aMED, which reflects a Mediterranean-style dietary pattern characterized by high consumption of minimally processed

plant-based foods; olive oil as the principal fat source; low-to-moderate consumption of dairy products, fish, and poultry; low consumption of red meat; and low-to-moderate consumption of wine; (22, 23) 2) the HEI -2010, created by the US Department of Agriculture (Washington, DC) and the National Cancer Institute to align with the 2010 US Dietary Guidelines for Americans; (24-26) 3) the aHEI-2010, which adapted from recommended intakes from the Dietary Guidelines to incorporate foods and nutrients predictive of chronic disease risk, including greater intake of vegetables and fruits, whole grains, nuts and legumes, long-chain omega-3 fatty acids, and polyunsaturated fatty acids (PUFAs); lower intake of sugar-sweetened beverages and fruit juice, red/processed meat, trans-fat, sodium; and moderate alcohol consumption; (12) and 4) the DASH index, based on the DASH controlled-feeding studies, (27, 28) which administered a diet rich in vegetables, fruits, and low-fat dairy products, includes whole grains, poultry, fish, and nuts and tends to be lower in saturated fat, red meat, sweets, and sugar containing beverages and reduced in sodium. (29, 30) Further details of the components of each diet quality index, their contributions to total scores and study-specific cut-points are shown in Supplemental Table 3.S1. We calculated index scores using diet data in units of MyPyramid equivalents by establishing a customized link (31) between Nutrition Data Systems for Research and the MyPyramid Equivalents Database, version 2.0 (US Department of Agriculture). (32) MyPyramid equivalents translate foods, as eaten, into standardized quantities of dietary components of interest; for example, an equivalent is an amount considered nutritionally equal to 1 cup in the vegetable, fruit, and dairy components or 1 ounce (1 ounce = 28.35 g) in the grains or protein foods components. We classified the scores into quintiles, and standardized the scores to one standard deviation units for comparability.

Diabetes ascertainment

Participants were asked at baseline whether a physician had ever told them that they had 'sugar diabetes' or 'high blood sugar' when they were not pregnant. Women who self-reported 'yes' to this question at baseline were excluded from this study. At each semi-annual (WHI-CT) or annual contact (WHI-OS), all participants were asked, 'Since the date given on the front of this form, has a doctor prescribed for the first time any of the following pills or treatments?' Choices included 'pills for diabetes' and 'insulin shots for diabetes.' Thus, only incident treated diabetes was ascertained, and this was defined as a self-report of a new physician diagnosis of diabetes treated with oral drugs or insulin. (33, 34) The accuracy of self-reported diabetes in WHI trials has been assessed using medication and laboratory data, and self-reported diabetes was found to be valid. (35)

Statistical analysis

Participants were followed from study enrollment until death, loss to follow-up, or the most recent follow-up for the previously described WHI Extension Study 2 on September 20, 2013. Data from participants who did not consent to either extension study but were alive at study closeout were censored on those dates, September 12, 2005 and September 30, 2010, respectively. Means, standard deviations, and frequencies of demographic and lifestyle characteristics of the study sample were calculated by category of the standardized index scores (<-1, -1 to 1 and >1 standard deviation unit). We calculated Pearson correlations between index scores.

Cox proportional hazards models were fit using person-days since enrollment as the underlying time metric. We estimated multivariable-adjusted hazard ratios and 95% confidence intervals for T2D per standard deviation unit increase in index scores. To examine potential non-linear associations, we also categorized the scores in quintiles. The proportional hazards

assumption was assessed by examining plots of weighted Schoenfeld residuals with log person-months, and no evidence of violation was found for any of the dietary indices. Models adjusted for age at screening, educational attainment, race/ethnicity, smoking status, family history of diabetes, HT status, total daily energy intake, physical activity quintile, and study arm (Calcium and Vitamin D Trial, intervention or placebo, and HT Trial arm: estrogen only, estrogen placebo, estrogen and progestin, or estrogen and progestin placebo).

Given obesity's potential role as a mediator of the relationships we examined, we subsequently added BMI categories to the adjusted models (18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0-39.9, $\geq$40 kg/m^2 or missing) and assessed mediation by examining the change in the multivariable-adjusted hazard ratios with/without BMI category as a covariate.

We also conducted analyses stratified by race/ethnicity, tertile of physical activity and baseline overweight or obesity (<25.0, 25.0–29.9, or $\geq$30.0 kg/m^2); we tested for interaction by race/ethnicity, physical activity and BMI category using likelihood ratio tests and Wald χ2 tests.

In sensitivity analyses we considered modeling age as continuous in years and stratifying on age; and adding hypertension status, waist circumference, waist:hip ratio, coffee intake (which has a protective association with T2D (36)), geographic region and neighborhood socioeconomic status (NSES) to models. NSES is a composite measure based on census tract data regarding adult high school education rates, male unemployment, neighborhood poverty, female-headed households with children, and median household income. (37)

All statistical analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). All tests were 2-sided with statistical significance set at P<0.05.

RESULTS

Univariate correlations between the 4 diet quality indices were moderate to strong, ranging from 0.55 to 0.74 (all $P < 0.001$), with the weakest correlation between HEI-2010 and aMED and the strongest between HEI-2010 and DASH. Across diet quality indices, compared with women with poor-quality diets (standard deviation of diet score < -1), women with better-quality diets (standard deviation of diet score > +1) were older, had lower BMI values, engaged in more physical activity, and were more likely to be college educated, non-Hispanic white, and current users of HT; they were also less likely to have a family history of diabetes (Table 3.1).

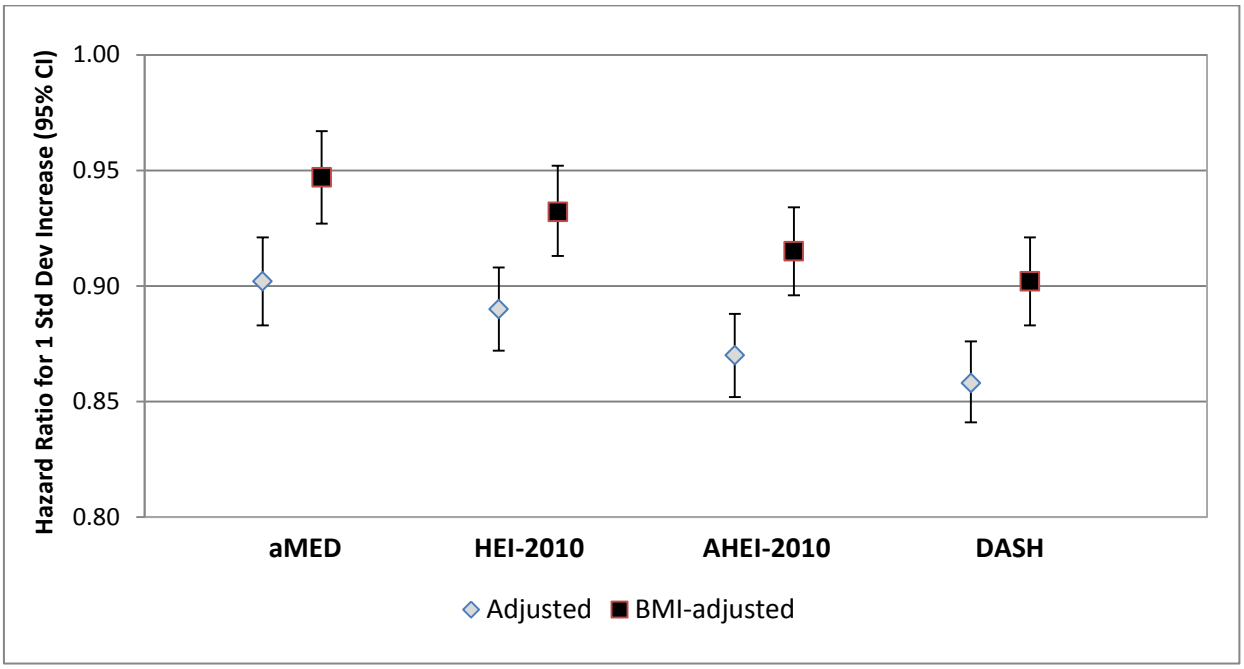
Table 3.1. Participant characteristics by category of standardized diet quality scores, Women's Health Initiative, 1993 – 2013, n=101,504

	USDA Healthy Eating Index 2010			Alternate Healthy Eating Index 2010			Alternate Mediterranean Diet Score			Dietary Approaches to Stop Hypertension		
	SD < -1	SD -1 to 1	SD > 1	SD < -1	SD -1 to 1	SD > 1	SD < -1	SD -1 to 1	SD > 1	SD < -1	SD -1 to 1	SD > 1
	N=16,617	N=68,716	N=16,171	N=16,824	N=67,872	N=16,808	N=18,912	N=71,680	N=10,912	N=18,376	N=65,216	N=17,912
Median (min-max)	50 (18-55)	68 (55-77)	80 (77-95)	35 (13-39)	50 (39-61)	66 (61-94)	2 (0-2)	4 (3-6)	7 (7-9)	17 (8-19)	24 (20-28)	30 (29-38)
						Mean (SD) or %						
Age, years	62 (7)	64 (7)	65 (7)	63 (7)	64 (7)	64 (7)	63 (7)	64 (7)	64 (7)	62 (7)	64 (7)	64 (7)
BMI, kg/m^2	29 (7)	27 (6)	26 (5)	29 (6)	27 (6)	26 (5)	28 (6)	27 (6)	26 (5)	29 (6)	27 (6)	26 (5)
METS/week	8 (12)	14 (14)	18 (15)	8 (11)	13 (14)	20 (16)	9 (12)	14 (14)	19 (16)	8 (11)	14 (14)	20 (16)
Total energy, kcal	1818 (766)	1550 (567)	1427 (455)	1718 (627)	1552 (603)	1520 (537)	1350 (534)	1596 (603)	1826 (561)	1596 (638)	1551 (607)	1637 (529)
Alcohol, beverage/week	0.38 (1.08)	0.44 (0.81)	0.41 (0.65)	0.32 (0.99)	0.43 (0.84)	0.52 (0.63)	0.36 (0.9)	0.43 (0.84)	0.49 (0.68)	0.38 (0.88)	0.45 (0.85)	0.38 (0.71)
Neighborhood SES Index	74 (9)	76 (8)	77 (8)	74 (9)	76 (8)	78 (8)	75 (9)	76 (8)	78 (7)	73 (10)	76 (8)	78 (7)
HRT												
Current	34	43	46	34	42	48	36	42	47	34	43	46
Past	26	23	23	26	24	22	25	23	22	26	23	22
Never	38	34	31	38	34	30	37	35	31	38	34	32
Smoking Status												
Current	15	6	3	12	6	3	12	6	3	14	6	2
Past	38	43	44	35	42	50	38	43	46	37	43	45
Never	46	50	52	52	50	45	49	50	49	47	50	52
Race/Ethnicity												
Caucasian	78	86	89	80	85	89	83	85	89	75	87	91
Black	12	6	6	12	6	4	8	7	5	14	6	4
Hispanic/Latina	7	3	2	5	4	2	6	3	1	7	3	2
Asian	2	3	2	1	3	3	2	3	3	3	3	2
Other	2	1	1	1	1	1	1	1	1	2	1	1
College graduate	27	42	52	26	41	56	28	42	58	25	42	56
Family History of T2D	33	30	27	33	30	27	31	30	27	33	30	27

BMI = Body Mass Index; METS = Metabolic Equivalents; SES = Socioeconomic Status; T2D = Type 2 Diabetes

During a median 14.9 years of follow-up, 10,815 incident cases of T2D occurred. As shown in Figure 3.1, in multivariable-adjusted models, across indices, having a better-quality diet was associated with lower risk of T2D: A one standard deviation higher score on a given dietary index, wherein higher scored indicates better quality diet, was associated with a 10%–14% lower risk of T2D ($p<0.001$). Additional adjustment for BMI category at enrollment attenuated but did not eliminate these associations (5%-10% lower risk [$p<0.001$]). As shown in Table 3.2, when comparing the top to the bottom quintile of diet quality the protective associations with T2D ranged from reductions of 26% (aMed, 95% CI: 21, 30) to 36% (DASH, 95% CI: 32, 40).

Figure 3.1. Multivariate hazard ratios of diabetes per standard deviation higher score on diet quality indices in the Women's Health Initiative, 1993 – 2013, n=101,504



[1]Hazard ratio of incident type 2 diabetes and 95% confidence limits shown per unit standard deviation for each diet adjusted for covariates measured at the screening visit, including age [50-54, 55-59, 60-69, and 70-79 years], educational attainment [<GED/High School, some college or vocational training, college graduate, or post-graduate education (ref)], quintiles of MET-hours/week of recreational physical activity, post-menopausal hormone use (current, former or never [ref]), family history of diabetes (yes/no), smoking status [current, former or never (ref)], study arm [randomization status for CaD, HRT or no assignment (ref.)], and dietary energy intake. Additionally adjusted for BMI category where indicated ("BMI-Adjusted").
aMED = Alternate Mediterranean Diet Score; HEI-2010 = Healthy Eating Index 2010; aHEI-2010 = Alternate Healthy Eating Index 2010; DASH = Dietary Approaches to Stop Hypertension; BMI = Body Mass Index; MET = Metabolic Equivalents; GED = General Education Development Test; CaD = Calcium and Vitamin D; HRT = Hormone Replacement Therapy

Table 3.2. Association of diabetes per quintile and standard deviation higher diet quality in Women's Health Initiative, n= 101,504

Index Quintile (Q) (Min-Max Score)	n (cases) / n (total)	Cases: 10,815; 8.26 cases/1,000 p-y	Age-Adjusted Hazard Ratio	95% CI	Multivariable-Adjusted Hazard Ratio	95% CI	Multivariable & BMI Hazard Ratio	95% CI
Alternate Mediterranean Index		Per SD increase	0.84	0.83, 0.86	0.90	0.88, 0.92	0.95	0.93, 0.97
		Per 10% increase	0.91	0.90, 0.92	0.94	0.93, 0.96	0.97	0.96, 0.98
Q1 (0-2)	2,305/ 18,936	Q1	Ref.		Ref.		Ref.	
Q2 (3-3)	1,953 / 18,129	Q2	0.82	0.77, 0.87	0.87	0.82, 0.92	0.90	0.85, 0.96
Q3 (4-4)	2,245 / 20,301	Q3	0.81	0.77, 0.86	0.90	0.85, 0.95	0.95	0.90, 1.01
Q4 (5-5)	1,961 / 18,869	Q4	0.74	0.69, 0.78	0.85	0.80, 0.91	0.92	0.87, 0.98
Q5 (6-9)	2,366 / 25,392	Q5	0.61	0.58, 0.65	0.74	0.70, 0.79	0.85	0.80, 0.90
USDA Healthy Eating Index 2010		Per SD increase	0.77	0.76, 0.79	0.89	0.87, 0.91	0.93	0.92, 0.95
		Per 10% increase	0.79	0.78, 0.80	0.90	0.88, 0.92	0.94	0.92, 0.96
Q1 (18 - 57)	2,777 / 20,325	Q1	Ref.		Ref.		Ref.	
Q2 (57 - 65)	2,267 / 20,326	Q2	0.74	0.70, 0.78	0.88	0.83, 0.93	0.92	0.87, 0.97
Q3 (65 - 70)	2,115 / 20,325	Q3	0.65	0.61, 0.68	0.84	0.79, 0.89	0.90	0.85, 0.95
Q4 (70 - 76)	1,925 / 20,326	Q4	0.56	0.53, 0.59	0.77	0.73, 0.82	0.85	0.80, 0.91
Q5 (76 - 95)	1,746 / 20,325	Q5	0.49	0.46, 0.52	0.72	0.67, 0.76	0.83	0.78, 0.89
Alternate Healthy Eating Index 2010		Per SD increase	0.77	0.75, 0.78	0.87	0.85, 0.89	0.92	0.90, 0.94
		Per 10% increase	0.77	0.75, 0.78	0.87	0.85, 0.89	0.92	0.90, 0.94
Q1 (13 - 41)	2,786 / 20,325	Q1	Ref.		Ref.		Ref.	
Q2 (41 - 47)	2,348 / 20,326	Q2	0.79	0.75, 0.83	0.90	0.85, 0.95	0.93	0.88, 0.99
Q3 (47 - 53)	2,107 / 20,325	Q3	0.67	0.63, 0.71	0.82	0.77, 0.87	0.87	0.82, 0.92
Q4 (53 - 60)	1,923 / 20,326	Q4	0.58	0.55, 0.62	0.77	0.72, 0.81	0.84	0.79, 0.90
Q5 (60 - 94)	1,666 / 20,325	Q5	0.48	0.45, 0.51	0.68	0.64, 0.72	0.78	0.73, 0.83
Dietary Approaches to Stop Hypertension		Per SD increase	0.75	0.73, 0.76	0.86	0.84, 0.88	0.90	0.89, 0.92
		Per 10% increase	0.82	0.81, 0.83	0.90	0.89, 0.92	0.93	0.92, 0.95
Q1 (8 - 19)	2,623 / 18,402	Q1	Ref.		Ref.		Ref.	
Q2 (20 - 22)	2,219 / 19,781	Q2	0.71	0.67, 0.75	0.84	0.79, 0.89	0.87	0.82, 0.92
Q3 (23 - 25)	2,499 / 24,094	Q3	0.60	0.57, 0.63	0.77	0.73, 0.82	0.83	0.78, 0.88
Q4 (26 - 28)	2,013 / 21,418	Q4	0.51	0.48, 0.54	0.70	0.66, 0.75	0.77	0.72, 0.82
Q5 (29 - 38)	1,476 / 17,932	Q5	0.43	0.40, 0.46	0.64	0.60, 0.68	0.74	0.69, 0.80

[1] Adjusted for age [50-54, 55-59, 60-69, and 70-79 years], and where indicated covariates measured at the screening visit, including educational attainment [<GED/High School, some college or vocational training, college graduate, or post-graduate education (ref)], quintiles of MET-hours/week of recreational physical activity, post-menopausal hormone use (current, former or never [ref]), family history of diabetes (yes/no), smoking status [current, former or never (ref)], study arm [randomization status for CaD, HRT or no assignment (ref.)], and dietary energy intake. Additionally adjusted for BMI category where indicated [<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0-39.9, >40 kg/m^2].

Risk reductions were comparable across categories of BMI and tertile of physical activity at baseline, with no evidence that the association of any diet index with T2D varied by level of physical activity or whether the participant was normal, underweight, overweight or obese at baseline. However, the magnitude of T2D risk reduction associated with higher diet quality varied by race/ethnicity (LRT p-value <0.01 for interaction of race/ethnicity and dietary index in all models, Table 3.3). Non-Hispanic white and Asian women had the highest median scores on all diet indices and the lowest crude rates of T2D, while Hispanic/Latina women and black women had the lowest median scores and highest crude rates of T2D. Though higher quality diets were associated with lower risk of T2D among all women, compared to non-Hispanic white women (8 to 13% reduction in risk of T2D per standard deviation higher dietary index score), we observed stronger associations among Hispanic/Latina women for all indices (18 to 25% reduction, p-interaction <0.05). The association of diet quality with T2D did not differ significantly between non-Hispanic white and black (9 to 11% lower risk of T2D per standard deviation higher dietary index score) and Asian women (16 to 18% lower risk), but there were few cases among Asian women (p-interaction >0.05).

Sensitivity analyses, adding alternate and additional measures of adiposity, hypertension, geographic region, NSES or coffee intake to models and excluding participants with baseline cardiovascular disease and cancer did not materially alter the results overall or when stratified by race/ethnicity.

Table 3.3. Association of diabetes per category and standard deviation higher diet quality: results by race/ethnicity in Women's Health Initiative, 1993 - 2013.

	Non-Hispanic White	Black	Hispanic/Latina	Asian
	N= 86,442; Cases: 8,549 7.49 cases/1,000 p-y	N= 7,021; Cases: 1,208 15.56 cases/1,000 p-y	N= 3,675; Cases: 549 13.95 cases/1,000 p-y	N= 2,621; Cases: 282 9.58 cases/1,000 p-y
	Multivariable-Adjusted Hazard Ratio, 95% Confidence Interval			
aMED	Mean (SD) aMED; z-score 4 (2); 0.02 (1)	Mean (SD) aMED; z-score 4 (2); -0.16 (0.97)	Mean (SD) aMED; z-score 4 (2); -0.36 (0.91)	Mean (SD) aMED; z-score 5 (2); 0.23 (0.94)
Per SD	0.92 0.90, 0.94	0.90 0.85, 0.96	0.75 0.67, 0.83	0.83 0.72, 0.95
Q5 v. Q1	0.78 0.73, 0.83	0.76 0.63, 0.92	0.33 0.23, 0.49	0.61 0.40, 0.93
P-Trend	<0.001	0.01	<0.001	0.01
p-interaction	Ref.	0.56	<0.001	0.60
HEI-2010	Mean (SD) HEI; z-score 67 (11); 0.05 (0.98)	Mean (SD) HEI; z-score 63 (12); -0.33 (1.13)	Mean (SD) HEI; z-score 62 (11); -0.44 (1.05)	Mean (SD) HEI; z-score 67 (10); 0.06 (0.91)
Per SD	0.90 0.88, 0.92	0.91 0.86, 0.97	0.82 0.75, 0.90	0.84 0.73, 0.97
Q5 v. Q1	0.74 0.69, 0.79	0.68 0.56, 0.83	0.63 0.45, 0.88	0.66 0.43, 1.02
P-Trend	<0.001	0.001	<0.001	0.02
p-interaction	Ref.	0.10	0.008	0.77
aHEI-2010	Mean (SD) aHEI; z-score 51 (11); 0.03 (1)	Mean (SD) aHEI; z-score 46 (11); -0.36 (0.99)	Mean (SD) aHEI; z-score 48 (10); -0.26 (0.93)	Mean (SD) aHEI; z-score 53 (10); 0.27 (0.91)
Per SD	0.87 0.85, 0.89	0.91 0.85, 0.97	0.75 0.68, 0.84	0.84 0.73, 0.96
Q5 v. Q1	0.69 0.64, 0.74	0.73 0.59, 0.91	0.40 0.28, 0.58	0.66 0.43, 1.01
P-Trend	<0.001	0.04	<0.001	0.004
p-interaction	Ref.	0.04	0.0005	0.88
DASH	Mean (SD) DASH; z-score 24 (5); 0.07 (0.98)	Mean (SD) DASH; z-score 21 (5); -0.53 (1.06)	Mean (SD) DASH; z-score 22 (5); -0.44 (1)	Mean (SD) DASH; z-score 24 (4); -0.08 (0.96)
Per SD	0.87 0.85, 0.89	0.89 0.84, 0.95	0.78 0.71, 0.86	0.82 0.71, 0.93
Q5 v. Q1	0.66 0.61, 0.71	0.64 0.50, 0.82	0.45 0.31, 0.66	0.56 0.35, 0.88
P-Trend	<0.001	0.0002	<0.001	0.01
p-interaction	Ref.	0.08	0.001	0.94

Restricted to the racial/ethnic group specified and adjusted for covariates measured at the screening visit: age [50-54, 55-59, 60-69, and 70-79 years], educational attainment [<GED/High School, some college or vocational training, college graduate, or post-graduate education (ref)], quintiles of MET-hours/week of recreational physical activity, post-menopausal hormone use (current, former or never [ref]), family history of diabetes (yes/no), smoking status [current, former or never (ref)], study arm [randomization status for CaD, HRT or no assignment (ref.)], and dietary energy intake. All p-trend, computed using the median of the quintile as a continuous variable, <0.001

DISCUSSION

A one standard deviation higher score on any of the four of the dietary patterns examined was associated with 10% to 14% lower risk of T2D, suggesting each index captures important characteristics of a healthful dietary pattern. There are multiple ways to achieve high scores on each of these indices. For example, a 10-point increase in the AHEI-2010 could be achieved by eliminating sugar-sweetened beverages or by reducing intake of red and processed meat <2.5 ounces/day. However, several defining characteristics are shared across multiple indices, including high intake of fruits, vegetables, whole grains, nuts, legumes, and unsaturated fats; and low intake of red and processed meat, sodium, sugar-sweetened beverages, and trans fat. Adjusting for overweight/obesity status at enrollment attenuated but did not eliminate these associations to a 5% to 10% lower risk, suggesting that adiposity does not entirely explain the impact of diet on T2D risk. The magnitude of the estimated protective association with T2D was lowest for aMED and highest for DASH. One reason that higher scores for the aMED dietary pattern may confer less protection than DASH is that in a US population such as WHI, most mono-unsaturated fat comes from intake of meat. Thus, the potential benefits of plant-source mono-unsaturated fat intake (a signature component of a Mediterranean diet) may be confounded by meat intake. Consistent with this, omission the MUFA:SFA ratio strengthened rather than attenuated the score's association with T2D.

While high-quality diets were associated with lower T2D risk in all groups examined, Hispanic/Latina women appeared to benefit most from higher quality diets compared to non-Hispanic white women. Other studies have also detected racial/ethnic differences in the association of dietary patterns with T2D. As previously mentioned, research by Qiao et al found AHEI to be associated with reduced risk of T2D only among white and Hispanic/Latina women in WHI. However, Qiao et al used the original AHEI (here we use the AHEI-2010) and did not

exclude participants in the WHI dietary modification trial, which could bias results due to the eligibility requirements (>32% energy from fat, a key component of the AHEI) and participants randomized to intervention changing their diet after the baseline assessment. (7) Similar to our findings, a recent analysis of the Multiethnic Cohort (MEC) observed significant inverse associations between higher DASH scores and T2D in non-Hispanic whites adjusting for BMI category and other covariates, as well as in Japanese-American women and Native Hawaiian men. However, in MEC higher scores on the AHEI-2010 and aMED indices were protective only among non-Hispanic whites and the HEI-2010 did not show protection in any group. (6) By contrast, in our study all indices showed protective associations with T2D in all racial/ethnic groups before adjusting for BMI category at baseline; after adjustment for BMI, all indices other than the aMED maintained a statistically significant benefit, and the aMED was non-significant only in black and Asian women.

Racial/ethnic differences could reflect biologic differences, e.g. clinical studies have suggested differences between African American and Hispanic/Latina women compared to non-Hispanic white women with respect to insulin sensitivity and β-cell responsiveness according to level of body fat, and also location of body fat depots. (38-41) However, differing associations of dietary indices with T2D by race/ethnicity may also reflect differing influence of incremental improvements (i.e. black and Hispanic/Latina women had the lowest mean scores) as well as differing patterns of consumption in the foods making up the dietary indices; the Multi-Ethnic Study of Atherosclerosis (MESA) study reported significant ethnic differences for all nutrients except saturated fat when intakes based on the DASH guidelines were compared between white, Chinese-American, African-American and Hispanic adults. (42)

Our study has several strengths: the prospective design of WHI and large, ethnically diverse sample strengthen the internal and external validity of the findings and allowed for subgroup analyses by race/ethnicity. Additionally, we had research measures of BMI. Our study also has limitations. T2D was self-reported rather than adjudicated. Self-reported diabetes in this cohort has been shown to be valid, (35) however our definition of T2D did not include those treated with diet and exercise alone. Additionally, since ~28% cases of diabetes are un-diagnosed in the United States, (9) it is possible some participants living with T2D were misclassified as non-cases. Further, the indices as well as the FFQs used to measure their components were developed initially in majority European and European-descent populations; it is possible that culturally-specific foods are not completely captured. The most likely impact of this misclassification of diet would be to underestimate associations among racial/ethnic minorities. Additionally, though a strength of this study was adequate sample size to present results stratified by race/ethnicity, in relative terms we had few participants in racial/ethnic minority groups, especially Asian women (n = 2,621; events=281). As in any observational study, the possibility residual confounding by health consciousness remains even after careful control for many possible confounders of the relationship between dietary patterns and T2D. However, our results were robust to additional adjustment for NSES and other measured confounders.

CONCLUSION

Higher quality diets as described by all four diet-quality scores were associated with lower incidence of T2D in all racial/ethnic groups. While multiple factors overlap in these dietary scores, the features emphasized also differed. This suggests that while overall diet quality

is beneficial for prevention of T2D, preventive dietary interventions may be tailored to individual tastes, preferences, customs or cultures.

REFERENCES

1. International Diabetes Federation. Version 6th. Internet: http://www.idf.org/diabetesatlas (accessed November 5 2014).
2. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. Endocrine 2014;47(1):107-16. doi: 10.1007/s12020-014-0264-4.
3. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Current opinion in lipidology 2002;13(1):3-9.
4. US Department of Agriculture and US Department of Health and Human Services. Internet: www.cnpp.usda.gov/dietaryguidelines.htm (accessed November 5 2014).
5. USDA National Evidence Library. Internet: http://www.nel.gov/vault/2440/web/files/DietaryPatterns/DPRptFullFinal.pdf (accessed November 5 2014).
6. Jacobs S, Harmon BE, Boushey CJ, Morimoto Y, Wilkens LR, Le Marchand L, Kroger J, Schulze MB, Kolonel LN, Maskarinec G. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. Diabetologia 2014. doi: 10.1007/s00125-014-3404-8.
7. Qiao Y, Tinker L, Olendzki BC, Hebert JR, Balasubramanian R, Rosal MC, Hingle M, Song Y, Schneider KL, Liu S, et al. Racial/ethnic disparities in association between dietary quality and incident diabetes in postmenopausal women in the United States: the Women's Health Initiative 1993-2005. Ethnicity & health 2014;19(3):328-47. doi: 10.1080/13557858.2013.797322.
8. Zamora D, Gordon-Larsen P, He K, Jacobs DR, Jr., Shikany JM, Popkin BM. Are the 2005 Dietary Guidelines for Americans Associated With reduced risk of type 2 diabetes and cardiometabolic risk factors? Twenty-year findings from the CARDIA study. Diabetes care 2011;34(5):1183-5. doi: 10.2337/dc10-2041.
9. Centers for Disease Control and Prevention. Internet: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
10. Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, Benito S, Tortosa A, Bes-Rastrollo M. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ (Clinical research ed) 2008;336(7657):1348-51. doi: 10.1136/bmj.39561.501007.BE.
11. Rossi M, Turati F, Lagiou P, Trichopoulos D, Augustin LS, La Vecchia C, Trichopoulou A. Mediterranean diet and glycaemic load in relation to incidence of type 2 diabetes: results from the Greek cohort of the population-based European Prospective Investigation into Cancer and Nutrition (EPIC). Diabetologia 2013;56(11):2405-13. doi: 10.1007/s00125-013-3013-y.
12. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. The Journal of nutrition 2012;142(6):1009-18. doi: 10.3945/jn.111.157222.
13. Fung TT, McCullough M, van Dam RM, Hu FB. A prospective study of overall diet quality and risk of type 2 diabetes in women. Diabetes care 2007;30(7):1753-7. doi: 10.2337/dc06-2581.

14. de Koning L, Chiuve SE, Fung TT, Willett WC, Rimm EB, Hu FB. Diet-quality scores and the risk of type 2 diabetes in men. Diabetes care 2011;34(5):1150-6. doi: 10.2337/dc10-2352.
15. Liese AD, Nichols M, Sun X, D'Agostino RB, Jr., Haffner SM. Adherence to the DASH Diet is inversely associated with incidence of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes care 2009;32(8):1434-6. doi: 10.2337/dc09-0228.
16. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Controlled clinical trials 1998;19(1):61-109.
17. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE. The Women's Health Initiative recruitment methods and results. Annals of epidemiology 2003;13(9 Suppl):S18-77.
18. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Annals of epidemiology 2003;13(9 Suppl):S107-21.
19. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. American journal of epidemiology 1986;124(3):453-69.
20. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Annals of epidemiology 1999;9(3):178-87.
21. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. Journal of the American Dietetic Association 1988;88(10):1268-71.
22. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. The New England journal of medicine 2003;348(26):2599-608. doi: 10.1056/NEJMoa025039.
23. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. The American journal of clinical nutrition 2005;82(1):163-73.
24. Guenther PM, Reedy J, Krebs-Smith SM. Development of the Healthy Eating Index-2005. Journal of the American Dietetic Association 2008;108(11):1896-901. doi: 10.1016/j.jada.2008.08.016.
25. Guenther PM, Casavale KO, Reedy J, Kirkpatrick SI, Hiza HA, Kuczynski KJ, Kahle LL, Krebs-Smith SM. Update of the Healthy Eating Index: HEI-2010. Journal of the Academy of Nutrition and Dietetics 2013;113(4):569-80. doi: 10.1016/j.jand.2012.12.016.
26. US Department of Agriculture and US Department of Health and Human Services. Version 7th. Internet: www.cnpp.usda.gov/dietaryguidelines.htm (accessed November 3 2014).
27. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England journal of medicine 1997;336(16):1117-24. doi: 10.1056/nejm199704173361601.
28. Sacks FM, Obarzanek E, Windhauser MM, Svetkey LP, Vollmer WM, McCullough M, Karanja N, Lin PH, Steele P, Proschan MA, et al. Rationale and design of the Dietary

Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. Annals of epidemiology 1995;5(2):108-18.
29. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Archives of internal medicine 2008;168(7):713-20. doi: 10.1001/archinte.168.7.713.
30. National Institutes of Health and Human Services. Internet: www.nhlbi.nih.gov/health/resources/heart/hbp-dash-index.htm (accessed November 3 2014).
31. George SM, Irwin ML, Smith AW, Neuhouser ML, Reedy J, McTiernan A, Alfano CM, Bernstein L, Ulrich CM, Baumgartner KB, et al. Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer. Cancer causes & control : CCC 2011;22(4):589-98. doi: 10.1007/s10552-011-9732-9.
32. Bowman SA, Friday JE, A M. Internet: http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/mped/mped2_doc.pdf (accessed November 5 2014).
33. de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, Larson JC, Manson JE, Margolis KL, Siscovick DS, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. Diabetes care 2008;31(4):701-7. doi: 10.2337/dc07-1829.
34. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SA, Robinson JG, Rodriguez B, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Archives of internal medicine 2008;168(14):1500-11. doi: 10.1001/archinte.168.14.1500.
35. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, Simin L, Robinson JG, Safford MM, Tinker LT, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clinical trials (London, England) 2008;5(3):240-7. doi: 10.1177/1740774508091749.
36. Jiang X, Zhang D, Jiang W. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. European journal of nutrition 2014;53(1):25-38. doi: 10.1007/s00394-013-0603-x.
37. Shih RA, Ghosh-Dastidar B, Margolis KL, Slaughter ME, Jewell A, Bird CE, Eibner C, Denburg NL, Ockene J, Messina CR, et al. Neighborhood socioeconomic status and cognitive function in women. American journal of public health 2011;101(9):1721-8. doi: 10.2105/ajph.2011.300169.
38. Chandler-Laney PC, Phadke RP, Granger WM, Munoz JA, Man CD, Cobelli C, Ovalle F, Fernandez JR, Gower BA. Adiposity and beta-cell function: relationships differ with ethnicity and age. Obesity (Silver Spring, Md) 2010;18(11):2086-92. doi: 10.1038/oby.2010.44.
39. Ingram KH, Lara-Castro C, Gower BA, Makowsky R, Allison DB, Newcomer BR, Munoz AJ, Beasley TM, Lawrence JC, Lopez-Ben R, et al. Intramyocellular lipid and insulin resistance: differential relationships in European and African Americans. Obesity (Silver Spring, Md) 2011;19(7):1469-75. doi: 10.1038/oby.2011.45.

40. Lawrence JC, Newcomer BR, Buchthal SD, Sirikul B, Oster RA, Hunter GR, Gower BA. Relationship of intramyocellular lipid to insulin sensitivity may differ with ethnicity in healthy girls and women. Obesity (Silver Spring, Md) 2011;19(1):43-8. doi: 10.1038/oby.2010.148.
41. Weiss R, Dziura JD, Burgert TS, Taksali SE, Tamborlane WV, Caprio S. Ethnic differences in beta cell adaptation to insulin resistance in obese children and adolescents. Diabetologia 2006;49(3):571-9. doi: 10.1007/s00125-005-0109-z.
42. Gao SK, Fitzpatrick AL, Psaty B, Jiang R, Post W, Cutler J, Maciejewski ML. Suboptimal nutritional intake for hypertension control in 4 ethnic groups. Archives of internal medicine 2009;169(7):702-7. doi: 10.1001/archinternmed.2009.17.

ACKNOWLEDGEMENTS

Author affiliations

Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (Elizabeth M. Cespedes, Frank B. Hu); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (Lesley Tinker, Marian L. Neuhouser); Channing Division of Network Medicine, Harvard Medical School and Department of Biostatistics, Harvard School of Public Health, Boston, MA (Bernard Rosner); Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA (Susan Redline); Department of Public Health Sciences, University of California Davis, Davis, CA (Lorena Garcia); Department of Nutritional Sciences, University of Arizona, Tucson, AZ (Melanie Hingle); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, University of Illinois at Chicago, Chicago, IL (Linda Van Horn); MedStar Health Research Insititute, Hyattsville, MD (Barbara V. Howard); Department of Epidemiology, University of Alabama School of Public Health, Birmingham, AL (Emily B. Levitan); Department of Medicine, University of Massachusetts Medical School, Amherst, MA (Wenjun Li); Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (JoAnn E. Manson); Atlanta VA Medical Center, Decatur, GA and Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, GA (Lawrence Phillips); Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA (Jinnie J. Rhee); Departments of Quantitative Health Sciences and Obstetrics & Gynecology, University of Massachusetts Medical School, Worcester, MA (Molly E. Waring)

Funding

This work is supported by NIDDK T32 DK007703 (EMC) and KL2TR000160 (MEW). The Women's Health Initiative is funded by the National Heart, Lung, and Blood Institute (contracts HHSN268201100046C, HHSN 268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN26820110004C, and HHSN271201100004C). Additional support from FDA award RO1FD003527(LSP), VA award HSR&D IIR 07-138(LSP), NIH awards R21DK099716, DK066204 (LSP), U01 DK091958(LSP), U01 DK098246 (LSP), and a Cystic Fibrosis Foundation award PHILLI12A0 (LSP).

Conflicts of Interest

With regard to potential conflicts of interest, within the past several years, Dr. Emily Levitan has received research support from Amgen, though this activity was unrelated to this project. Dr. Phillips has served on Scientific Advisory Boards for Boehringer Ingelheim and Janssen, and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the last several years. He is also a co-founder of a company, Diasyst LLC, which aims to develop and commercialize diabetes management software programs. These activities involve diabetes, but have nothing to do with this manuscript.

APPENDIX

Supplementary Table 3.S1. Scoring criteria for diet quality indices using MyPyramid Equivalents in the Women's Health Initiative OS-CT [1]

	USDA Healthy Eating Index 2010 0-100 points 12 components, each 5–20 points				Alternate Healthy Eating Index 2010 0-110 points 11 components, each 10 points				Dietary Approaches to Stop Hypertension[2] 8–40 points 8 components, each 5 points				Alternate Mediterranean Diet Score 0–9 points 9 components, each 1 point			
	Min/Max Criteria and Score															
Fruit	0 cups	0	≥0.8 cup total fruit; ≥0.4 cup whole fruit/1,000 kcal	5	0 cups	0	≥ 2 cups, excl. juices	10	Low Quintile 0.46 cups	1	High Quintile 3 cups	5	< median	0	≥ median 1.51 cups/day	1
Vegetables	0 cups	0	≥1.1 cup total; ≥0.2 cup greens/beans	5	0 cups	0	≥ 2.5 cups	10	Low Quintile 0.44 cups	1	High Quintile 2 cups	5	< median	0	≥ median 1.05 cups/day	1
Dairy	0 cups	0	≥1.3 cup/1,000 kcal, includes high fat	10		0		10	Low Quintile 0.09 cups	1	High Quintile 3 cups	5				
Nuts and legumes			Allocated to total or plant proteins or vegetables		0 oz	0	≥ 1oz	10	High Quintile 0.09 oz	1	Low Quintile 2 oz	5	< median	0	≥ median 0.25 cups/day legumes, 0.15 oz/day nuts	1
Fish	0 oz	0	≥0.8 oz/1,000 kcal (Seafood/ plant proteins)										< median	0	≥ median 0.45 oz/day	1
Oils/Fats			Ratio (PUFA+MUFA): SFA		≥4% Trans; 0 mg EPA+DHA; ≤ 2% PUFA	0	≤0.5% Trans; 250 mg EPA+DHA; ≥10% PUFA	10					< median	0	≥ median ratio MUFA:SFA 1.14	1
Total Protein Foods	0 oz	0	≥ 2.5oz/1,000 kcal	10												

[1] Adapted from George et al 2014

[2] Mean of high and low quintile are shown

Table 3.S1 continued

Supplementary Table 3.S1. Scoring criteria for diet quality indices using MyPyramid Equivalents in the Women's Health Initiative OS-CT [1]

	USDA Healthy Eating Index 2010 0-100 points 12 components, each 5–20 points				Alternate Healthy Eating Index 2010 0-110 points 11 components, each 10 points				Dietary Approaches to Stop Hypertension[2] 8–40 points 8 components, each 5 points				Alternate Mediterranean Diet Score 0–9 points 9 components, each 1 point			
Whole Grains	0 oz	0	≥ 1.5oz/1,000 kcal	10	0 oz	0	≥ 5oz	10	Low Quintile 0.22 oz	1	High Quintile 3 oz	5	< median	0	≥ median 1.00 oz/day	1
Refined Grains	≥4.3 oz	0	≤1.8 oz/1,000 kcal	10												
Sugar-Sweetened Beverages					≥1 serving incl. juice	0	0 serv	10	High Quintile 1 serv/day	1	Low Quintile 0 serv/day	5				
Red and Processed Meats					≥ 2.5oz	0	0 oz	10	High Quintile 0.34 oz	1	Low Quintile 4 oz	5	≥ median	0	< median 1. oz/day	1
Sodium	≥2.0 g	0	≤1.1g per 1,000 kcal	10	High Decile 1177 mg	0	Low Decile 4941 mg	10	High Quintile 1382 mg	1	Low Quintile 4314 mg	5				
Empty Calories	≥50 % kcal	0	≤19% kcal from solid fat, added sugars, alcohol													
Alcohol			> 2 drinks/day towards empty kcal		< 0.5 or >1.5 drinks; non-drinker 2.5 pts	0	0.5-1.5 drinks	10					<5 or >15g	0	5-15g	1

Chapter 4: Long-term changes in sleep duration, energy balance and risk of type 2 diabetes

---

Elizabeth M Cespedes, Yanping Li, Shilpa N Bhupathiraju,

Bernard Rosner, Susan Redline, Frank B Hu

ABSTRACT

Background/objective: Baseline sleep duration has a U-shaped relationship with type 2 diabetes (T2D) in prospective studies; changes have not been examined. We examine associations of long-term changes in sleep duration with concomitant changes in diet quality, physical activity, weight and subsequent T2D.

Methods: We followed 59,031 women 55-83-years in Nurses' Health Study without diabetes in 2000. We derived change in sleep duration as the difference between self-reported 24-hour sleep duration in 1986 and 2000. Diet, physical activity and covariates were updated every 2-4 years. Self-reported T2D was confirmed via validated questionnaire. Cox regression models adjusted for 1986 sleep and for baseline (2000) and updated (2000-2012) values of diabetes risk factors, including body mass index (BMI).

Results: We documented 3,513 incident type 2 diabetes cases from 2000-2012. Compared with no change, decreases in sleep duration were adversely associated with changes in diet quality and physical activity, while increases were associated with greater weight gain. After adjustment for baseline covariates, hazard ratios (95% confidence intervals) for $\leq$-2, -1, 1 or $\geq$2 hour/day changes in sleep duration (v. no change) were 1.05 (0.89-1.23), 1.09 (0.99-1.19), 1.05 (0.96-1.14), and 1.14 (1.01-1.30), respectively. Additional adjustment for diet and physical activity did not appreciably alter the results. Increases in sleep duration $\geq$2 hours/day remained adversely associated with T2D (HR [95%CI]: 1.18 [1.04-1.33]) after adjustment for updated covariates including BMI.

Conclusions: Increases in sleep duration among middle-aged and older women were associated with risk of T2D; changes in diet, physical activity and BMI did not explain associations.

INTRODUCTION

Type 2 diabetes (T2D) has reached epidemic proportions with 592 million diabetes cases projected worldwide by 2035. (1) Identifying modifiable risk factors is of urgent public health importance and sleep duration has emerged as a novel prevention target. (2) A recent dose-response meta-analysis of prospective studies illustrated a U-shaped relationship between sleep duration and risk of T2D, with the lowest risk at 7–8 hours per day. (3) In experimental and observational studies, shortened sleep has been related to glucose intolerance, insulin resistance, and reduced acute insulin response to glucose thus predisposing individuals to T2D. (4-7) With respect to longer sleep duration, some authors suggest excessive time in bed has detrimental effects on health, (8) while others argue that associations with long sleep are confounded by mood disorders, sleep apnea, and other chronic illnesses. (9) However, in an actigraphy study of healthy adolescents, long sleep remained associated with insulin resistance after adjustment for BMI, suggesting that chronic illness does not explain all associations of long sleep with metabolic dysregulation. (10)

Extremes of sleep duration are hypothesized to influence both sides of the energy balance equation –intake and expenditure. (11) In observational studies, both short and long sleep duration are associated with less favorable diet and physical activity, (12, 13) and experimental research suggests that short sleep can induce a hormonal state predisposed to over eating. (14-16). Decreases in leptin and increases in ghrelin follow experimental sleep restriction, and a dominant hypothesis has been that alternations in appetite-regulating hormones lead to increases in hunger and thus energy intake. (15) Others suggest decreased self-regulation and greater sensitivity to food reward play a role in increasing vulnerability to an obesogenic environment and promoting over-eating, (17, 18) supported by recent functional magnetic resonance imaging studies showing disinhibited eating and altered food selection in a sleep-deprived state. (19, 20) With respect to energy expenditure,

results are inconsistent: limited experimental evidence does not support a substantial impact of sleep restriction on daily energy expenditure, (21) despite short sleep duration leading to increased fatigue and in some observational studies to reduced physical activity. (11)

Whether long-term changes in sleep duration predict concomitant changes in diet quality, physical activity, and weight or subsequent risk of T2D has not been examined. The present study assesses whether fourteen-year changes in self-reported sleep duration in the Nurses' Health Study (NHS) are predictive of concomitant changes in energy balance factors (diet quality, physical activity and weight) as well as subsequent risk of T2D.

METHODS

Study population

The NHS was initiated in 1976 when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire. The cohort has been followed by means of biennial mailed questionnaires about lifestyle practices and other exposures of interest, as well as the incidence of disease, as described previously. (22, 23) Habitual sleep duration was derived from answers by participants who were actively participating in the NHS surveys after our study's baseline in 2000. We excluded participants with diabetes at baseline (n=11,729), or who did not respond to the questions on sleep duration in 1986 (n=34,479) or 2000 (n=13,903), leaving 59,031 women in our primary analysis. The Institutional Review Boards at the Harvard School of Public Health and Brigham and Women's Hospital approved the study protocol.

Ascertainment of type 2 diabetes (T2D)

T2D cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire. For cases before 1998, we used the National Diabetes Data Group criteria to define

T2D. We used the American Diabetes Association diagnostic criteria for T2D diagnosis from 1998 onward. The validity of self-reported T2D diagnosis in our cohorts has been previously documented in detail. Briefly, 97-98% cases were reconfirmed against blinded physician medical record review. (24)

Assessment of other covariates

Information on potential confounders, such as age, race and ethnicity, smoking status, weight, height, menopausal status and postmenopausal hormone therapy, regular use of medications (e.g., antidepressant [first measured in 1996] and antihypertensive drugs), and physician diagnoses (e.g., hypertension and high cholesterol) was collected via biennial questionnaires. Information on food and alcohol consumption was collected every 4 years via a validated semi-quantitative food frequency questionnaire. Body mass index (BMI) was calculated as weight (kg)/height (m). Hypertension and high cholesterol were considered as either a professionally diagnosis or use of related medications. A participant was considered as having depression symptoms if she reported physician diagnosed depression or use of antidepressant medications.

Diet quality was assessed by the alternate healthy eating index (AHEI-2010), based on a high consumption of vegetables, fruit, nuts and legumes, whole grain, long-chain fats, polyunsaturated fatty acid, and a low level of sugar-sweetened beverages and fruit juice, red/processed meat, trans fat, and sodium. (25) Physical activity was defined from work and leisure activities as weekly energy expenditure in metabolic equivalent (MET)-hours; vigorous activity was defined as$\geq$6 METs. (26) In a previous validation study (27), the correlation of physical activity reported on questionnaires was 0.79 when compared to prospectively collected 1-week recalls and 0.62 when compared to prospectively collected physical activity diaries.

Sleep duration was asked in the 1986 and 2000 questionnaires, corresponding to the hours of sleep in a typical 24-hour period. Seven options were provided (≤5, 6, 7, 8, 9, 10, ≥11 hours). Sleep duration was treated continuously with values assigned to the nearest integer (≤5= 5 hours;; ≥11 = 11 hours). Information on rotating night shifts was collected from the 1988 questionnaire. Participants were asked for their total number of years of rotating night shifts, which was characterized as "at least three nights per month in addition to working days or evenings in that month". Eight categories were provided (in years): never, 1-2, 3-5, 6-9, 10-14, 15-19, 20-29, 30 or more. Given prior evidence, we categorized this variable into <5 years or ≥5 years of rotating shift work. (23)

Statistical Analysis

Our main exposure was fourteen-year change in sleep duration computed as the difference in hours/day between 2000 and 1986 sleep duration. This continuous change was then categorized into a priori groupings: decreases in sleep duration (≤-2 hours/day or >-2 to <0 hours/day), no change in sleep between time-points (reference), and increases in sleep duration (≥2 hours/day or <2 to >0 hours/day). We computed age-adjusted descriptive statistics by category of change in habitual sleep duration from 1986 to 2000 (Table 4.1).

To examine the associations of changes in sleep duration with the intermediate outcomes of concomitant changes in energy balance factors (AHEI-2010 [change in score from 1986 to 1998, the nearest food frequency questionnaire to 2000], METS [change in hours/week from 1986 to 2000] and weight [change in pounds from 1986 to 2000]) we used multivariable linear regression. Models adjusted for race/ethnicity (non-Hispanic white, yes/no) and 1986 values of sleep duration and covariates: age in years, menopausal status (premenopausal or use of hormone therapy [never user, past user, or current user]), alcohol intake in quartiles, smoking status (never smoker, past smoker,

current smoker [1-14, 15-24, or 25+ cigarettes per week]), diabetes family history (yes/no), frequency of snoring (most nights, some nights or never), use of anti-depressants (yes/no), shift work history (shift work history ≥ 5 years), BMI and high blood pressure or high cholesterol. Subsequent models adjusted for changes in these covariates (1986-2000).

To examine the primary outcome of T2D, we used multivariable Cox proportional hazards models jointly stratified by age in months at the start of follow-up and calendar year of the current questionnaire cycle to estimate hazard ratios (HR) and 95% confidence intervals (CIs) according to category of change in sleep duration from 1986 to 2000. Individuals contributed person-time from the return of the 2000 questionnaire until the date of diagnosis of T2D, death, loss to follow-up, or the end of the follow-up period (June 30, 2012), whichever came first. Models adjusted for the same variables listed above at baseline (2000) and updated throughout follow-up (2000-2012).

Sensitivity analyses

In order to test the robustness of our findings, we did several sensitivity analyses. We considered excluding women over the median age of 66 years in 2000 (n=30,243), who had conducted shift work for >5 years (n=9,503) and excluding women with chronic disease in 2000 (ever diagnosis of cancer and/or cardiovascular disease [n=11,186]). Since covariates measured in 2000 or updated thereafter could plausibly serve as intermediates in the association between change in sleep duration and risk of T2D, we conducted secondary Cox regression analyses in which we controlled for the values of the covariates at the start of the change period in 1986 and subsequently for the change in covariates between 1986 and 2000, shown in a supplemental table. Additionally, we varied our approach to modeling changes in sleep duration by using two additional a priori categories. In the first approach, we compared cross-classified participants according to change in sleep duration (increase, decrease or no change) and sleep duration in 1986 (short [≤6 hours/day], long [≥9

hours/day], and normative [7-8 hours/day]), with women reporting 7-8 hours/day at both time-points as the reference group (Supplemental Figure 4.S1). In the second approach we compared normative sleep duration at both time-points (7-8 hours/day) to chronic short sleep, ≤6 hours/day, and short sleep increasing to normative sleep. Results are described in the text.

Data were analyzed using a commercially available software program (SAS, version 9.3; SAS Institute, Inc.), and statistical significance was set at a 2-tailed <0.05.

RESULTS

Average sleep duration remained constant between 1986 and 2000, with participants reporting a mean (SD) of 7 (1) hours at both time-points. The mean (SD, range) change in sleep duration was 0 (1, -6 to 5) hours/day. The Pearson correlation coefficients between sleep measurements in 1986 and 2000 was r=0.42. Approximately half of women (49%) reported normative sleep duration (7-8 hours/night) at both time-points, while 15% were consistently short (≤6 hours) sleep duration and 2% reported consistently long (≥9 hours) sleep duration. The mean (SD) change in AHEI-2010 over this period was an increase of 3 (10) points, from 46 to 49; the mean (SD) change in MET hours/week was an increase of 3 (26) hours/week, from 15 to 18; and the mean (SD) change in weight was an increase of 9 (17) pounds. BMI increased from a mean (SD) of 25 (4) in 1986 to 26 (5) kg/m^2 in 2000. Mean (SD, range) age at the start of follow-up in 2000 was 66 (7, 53-82) years.

Table 4.1 shows age-adjusted descriptive characteristics by our main exposure: category of change in sleep duration from 1986 to 2000. Relatively few women reported dramatic decreases (5%) or increases (7%) in sleep duration of ≥2 hours/day. Most women reported no change (41%) in sleep duration or decreases (21%) or increases (25%) of one hour/day. Compared to women with lesser or no changes in sleep duration, at baseline in 2000 women reporting increases or decreases of ≥2

hours/day had higher indices of body mass, lower indices of physical activity and diet quality, were more likely to snore frequently, to smoke, to have high blood pressure, high cholesterol or a family history of diabetes, to take anti-depressant medications or to have a history of rotating shift work ≥5 years. Women who reported ≥2 hour/day increases in sleep duration from 1986 to 2000 were slightly older and gained more weight over this period. Notably, average sleep duration in 1986 among women reporting increases of ≥2 hours/day was 6 hours/day ~1 hour below average) while average sleep duration in 2000 was 8 hours/day (~1 hour above average), and vice versa among women reporting decreases of ≤-2 hours/day.

Table 4.1 Baseline characteristics by change in sleep (1986-2000) in the Nurses' Health Study, n=59,839

	Decrease		No	Increase	
	-2 h/day	-1 h/day	0 h/day	+1 h/day	+2 h/day
	5%	21%	41%	25%	7%
	(n=3,170)	(n=12,626)	(n=24,349)	(n=14,494)	(n=4,392)
age86*	51.6 (7.5)	51.7 (7.4)	51.8 (7.0)	52.4 (6.7)	53.1 (6.6)
age00*	65.6 (7.6)	65.7 (7.4)	65.8 (7.1)	66.4 (6.8)	67.1 (6.6)
BMI 86	25.1 (4.6)	24.8 (4.3)	24.6 (4.2)	24.9 (4.3)	25.4 (4.7)
BMI 2000	26.6 (5.4)	26.2 (4.9)	26.1 (4.9)	26.5 (5.1)	27.3 (5.5)
Alcohol gm, 1986	6.7 (11.7)	6.3 (10.6)	6.4 (10.4)	6.4 (10.6)	6.3 (11.0)
Alcohol gm, 2000	5.1 (9.1)	5.1 (9.0)	5.4 (9.2)	5.3 (9.3)	5.1 (10.0)
Sleep duration, hours/day, 1986	8.1 (0.8)	7.3 (1.0)	7.1 (0.8)	6.6 (0.8)	6.2 (0.8)
Sleep duration, hours/day, 2000	5.8 (0.9)	6.2 (1.0)	7.1 (0.8)	7.6 (0.8)	8.4 (0.8)
AHEI-2010, 1986	45.5	46.0 (10.4)	46.2 (10.3)	46.0 (10.4)	45.7
AHEI-2010, 1998	48.6	49.2 (10.1)	49.5 (10.0)	49.2 (9.8)	49.1
Total Activity Mets/week, 1986	14.0	14.5 (21.5)	15.0 (21.4)	14.7 (21.0)	14.1
Total activity Mets/week, 2000	15.8	17.4 (21.0)	18.4 (21.3)	18.0 (22.9)	16.3
Shift work $\geq$ 5 years, %	18.5	15.6	14.9	16.6	20.3
Premenopausal in 1986, %	35.9	35.3	35.3	34.0	32.1
Premenopausal in 2000, %	1.0	1.3	1.2	1.2	1.0
Current smoker in 1986, %	18.9	18.1	17.9	19.9	24.7
Current smoker in 2000, %	8.2	8.0	8.3	8.8	11.3
Quit smoking, 1986-2000, %	11.2	10.7	10.1	11.5	14.1
Non-Hispanic white, %	98.3	97.7	98.3	98.0	97.5
Family history of diabetes, %	27.9	27.3	27.0	27.6	28.8
High blood pressure 2000, %	49.9	45.3	44.0	46.9	52.1
High cholesterol 2000, %	63.6	60.3	58.8	59.6	62.1
Anti-depressant use 2000, %	11.0	8.2	7.6	10.3	18.4
<6 hours/day in 1986, %	0.0	17.3	23.6	44.1	67.7
<6 hours/day in 2000, %	81.8	57.2	23.6	6.7	0.0
$\geq$9 hours/day in 1986, %	25.6	7.3	2.7	1.1	0.0
$\geq$9 hours/day in 2000, %	0.2	0.7	2.7	11.2	42.2
Lost >5 lbs, '00-'86, %	19.6	17.8	16.5	16.1	17.3
Gained >5 lbs, '00-'86, %	61.5	60.2	61.5	63.5	65.1
Weight change, lbs, '86-'00, %	9.1 (18.8)	8.7 (17.5)	9.0 (16.5)	9.9 (17.2)	11.0
AHEI-2010 change, '86-'98	2.9 (10.1)	2.9 (9.8)	3.2 (9.5)	3.1 (9.5)	3.2 (10.1)
MET hours/week change, '86-'00	1.8 (25.9)	2.9 (25.1)	3.4 (24.9)	3.3 (26.5)	2.2 (28.5)
Frequent snoring, '00, %	18.8	17.8	16.7	17.7	21.0

Table 4.1 continued: Values are means (SD) or percentages and are standardized to the age distribution of the study population.

*Values are not age-adjusted.

Change in Sleep Duration and Changes in Energy Balance Factors

We examined the association of changes in sleep duration from 1986 to 2000 with concurrent changes in diet quality (AHEI-2010), physical activity (MET hours/week) and weight in pounds (Table 4.2). Overall, changes in sleep duration did not have a profound impact on change in these factors. Associations were small in magnitude after adjustment for 1986 values of confounding variables (including BMI and sleep duration in 1986) and for change in confounding variables between 1986 and 2000. For example, decreases of -1 hour/day had an adverse association with changes in AHEI-2010 scores; the mean difference (95% CI) in change in AHEI-2010 score compared to women reporting no change in sleep duration was -0.25 (-0.48, -0.03) points. Compared to women reporting no change in sleep duration, both decreases of $\leq$-2 and -1 hours/day and increases of $\geq$2 hours/day were adversely associated with change (95% CI) in physical activity, with mean differences of -1.47 (-2.40, -0.55), -0.65 (-1.16, -0.13), and -1.29 (-2.08, -0.50) MET hours/week, respectively. Increases in sleep duration, but not decreases, were associated with greater weight gain: women reporting increases of one or $\geq$2 hours/day gained 0.51 (0.16, 0.86) and 0.70 (0.13, 1.26) additional pounds from 1986 to 2000.

Table 4.2. Change in sleep duration and change in energy balance factors, 1986 – 2000

	-2 hours/day	-1 hours/day	0 hours/day	+1 hours/day	+2 hours/day
	Mean Difference in Change in AHEI-2010: 1986 – 1998 (95% Confidence Interval), n=50,462				
Age-adjusted	-0.30 (-0.68, 0.09)	**-0.27 (-0.49, -0.05)**	0.00 (Ref)	-0.05 (-0.27, 0.16)	0.07 (-0.27, 0.40)
Multivariable-adj. [1]	-0.33 (-0.74, 0.07)	**-0.29 (-0.51, -0.06)**	0.00 (Ref)	-0.07 (-0.29, 0.15)	0.03 (-0.32, 0.38)
+ Change in covariates [2]	-0.26 (-0.67, 0.14)	**-0.25 (-0.48, -0.02)**	0.00 (Ref)	-0.07 (-0.28, 0.15)	0.05 (-0.29, 0.40)
+ Change in BMI [3]	-0.25 (-0.65, 0.16)	**-0.25 (-0.48, -0.03)**	0.00 (Ref)	-0.05 (-0.27, 0.16)	0.08 (-0.27, 0.43)
	Mean Difference in Change in MET hours/week: 1986 – 2002 (95% Confidence Interval), n=58,885				
Age-adjusted	**-1.59 (-2.53, -0.64)**	**-0.56 (-1.11, -0.01)**	0.00 (Ref)	0.06 (-0.47, 0.58)	**-1.21 (-2.03, -0.39)**
Multivariable-adj. [1]	**-1.80 (-2.72, -0.87)**	**-0.75 (-1.27, -0.23)**	0.00 (Ref)	-0.18 (-0.68, 0.32)	**-1.63 (-2.43, -0.84)**
+ Change in covariates [2]	**-1.58 (-2.50, -0.65)**	**-0.65 (-1.17, -0.13)**	0.00 (Ref)	-0.10 (-0.60, 0.40)	**-1.42 (-2.21, -0.62)**
+ Change in BMI [3]	**-1.47 (-2.40, -0.55)**	**-0.65 (-1.16, -0.13)**	0.00 (Ref)	-0.04 (-0.54, 0.45)	**-1.29 (-2.08, -0.50)**
	Mean Difference in Change in Weight, pounds: 1986 – 2002 (95% Confidence Interval), n=56,758				
Age-adjusted	0.32 (-0.30, 0.94)	-0.25 (-0.61, 0.11)	0.00 (Ref)	**1.00 (0.65, 1.34)**	**1.96 (1.42, 2.50)**
Multivariable-adj. [1]	0.53 (-0.14, 1.20)	-0.16 (-0.54, 0.21)	0.00 (Ref)	**0.75 (0.39, 1.11)**	**1.33 (0.75, 1.90)**
+ Change in covariates [2]	0.12 (-0.54, 0.77)	-0.37 (-0.74, -0.01)	0.00 (Ref)	**0.51 (0.16, 0.86)**	**0.70 (0.13, 1.26)**

Boldface indicates findings are statistically significant at the $p<0.05$ level.

[1] Models adjust for race/ethnicity, diabetes family history, shiftwork history 1986 values of sleep duration, age, BMI category, high cholesterol or high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, alcohol use, diet quality and/or physical activity.

[2] Models additionally adjust for change in high cholesterol or high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, alcohol use, diet quality and/or physical activity from 1986-2000.

[3] Models additionally adjust for change in BMI category from 1986-2000.

Sleep Duration and Risk of Type 2 Diabetes

We observed 3,513 cases of T2D among 59,031 participants over 612,409 person-years of follow-up. In initial Cox regression models stratified on age and calendar time, there was a U-shaped relationship of changes in sleep duration with T2D in which both decreases and increases were associated with increased risk (Table 4.3): after adjusting for sleep duration in 1986, the hazard ratios (95% CI) for participants reporting -2, -1, 1 or 2 hour/day changes in sleep duration were 1.18 (1.01-1.39), 1.13 (1.03-1.08), 1.09 (1.00-1.10), and 1.40 (1.23-1.58), respectively. However, after additional multivariable adjustment (race/ethnicity, diabetes family history, shiftwork history and 2000 values of high cholesterol, high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, alcohol use, diet quality, physical activity and BMI category), all associations were attenuated and only increases in sleep duration remained adversely associated with T2D (1.14 [1.01, 1.30]). Adjusting for AHEI-2010 and MET hours/week did not appreciably alter the results, nor did subsequent adjustment for updated covariates and BMI over follow-up (2000-2012).

Table 4.3. Change in sleep duration and subsequent risk of type 2 diabetes, 1986 - 2000, n=59,031

	-2 hours/day	-1 hours/day	0 hours/day	+1 hours/day	+2 hours/day
	Hazard Ratio for Type 2 Diabetes (95% Confidence Interval)				
Cases	190	759	1334	889	341
Person-Years	32,306	131,534	255,889	149,769	42,912
Age+ Sleep in 1986 [1]-adjusted	**1.18 (1.01, 1.39)**	**1.13 (1.03, 1.24)**	1.00 Ref	**1.09 (1.00, 1.19)**	**1.40 (1.23, 1.58)**
+ Covariates in 2000 [2]	1.07 (0.91, 1.26)	**1.09 (1.00, 1.19)**	1.00 Ref	1.06 (0.97, 1.16)	**1.25 (1.10, 1.41)**
+ AHEI-2010 score and METS/week in 2000 [3]	1.05 (0.89, 1.23)	1.08 (0.98, 1.18)	1.00 Ref	1.06 (0.97, 1.15)	**1.21 (1.06, 1.37)**
+ BMI in 2000 [4]	1.05 (0.89, 1.23)	1.09 (0.99, 1.19)	1.00 Ref	1.05 (0.96, 1.14)	**1.14 (1.01, 1.30)**
+ Updated covariates [5]	1.07 (0.91, 1.25)	1.09 (1.00, 1.20)	1.00 Ref	1.05 (0.96, 1.14)	**1.16 (1.03, 1.32)**
+ Updated covariates and BMI [6]	1.06 (0.90, 1.25)	**1.10 (1.00, 1.20)**	1.00 Ref	1.05 (0.96, 1.14)	**1.18 (1.04, 1.33)**

Boldface indicates findings are statistically significant at the $p<0.05$ level.

[1] Models adjust for categorical sleep duration in 1986 ($\leq$5, 6, 7, 8, 9, or $\geq$10 hours/day).

[2] Models adjust for race/ethnicity, diabetes family history, shiftwork history and 2000 values of high cholesterol or high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, and alcohol use.

[3] Models additionally adjust for diet quality (AHEI-2010) and physical activity (MET h/week) in 2000.

[4] Models additionally adjust for BMI category in 2000.

[5] Models additionally adjust for updated covariates from 2000 - 2012.

[6] Models additionally adjust for updated BMI from 2000 - 2012.

Sensitivity Analyses

In sensitivity analyses excluding participants who conducted shift work for ≥5 years or with cancer or cardiovascular disease in 2000 did not alter results. Excluding participants over the median age of 66 years in 2000 did not alter point estimates for decreases or ≥2 hour/day increases in sleep duration. However, the point estimate for 1 hour/day increases in sleep duration was attenuated and non-significant. Interaction terms of age > 66 years and change in sleep duration were non-significant. After adjusting for 1986 values of covariates and subsequent change in covariates, results were similar to our main analysis adjusting for 2000 and updated values of covariates: only increases of ≥2 hours/day were associated with risk of T2D (Supplemental Table 4.S1).

When we considered cross-classifying women according to sleep duration in 1986 (≤6, 7-8 or ≥9 hours/day) and category of change from 1986 to 2000 (decrease, increase or no change), women with chronic short sleep ≤6 hours/day, or who initially reported 7-8 hour/day but then increased or decreased sleep duration, had an elevated risk of T2D compared to women maintaining a normative sleep duration of 7-8 hour/day. These associations remained statistically significant after adjustment for BMI and other diabetes risk factors (Supplemental Figure 4.S1). However, interaction terms were not statistically significant and there were not many women (or cases) with sleep durations ≥9 hours/day in 1986.

DISCUSSION

This study of 59,031 women is the first to assess the relationship of long-term changes in self-reported sleep duration with energy balance and subsequent risk of T2D. We detected modest, adverse associations of fourteen-year changes in sleep duration with changes in diet quality and physical activity; however, diet quality and physical activity did not appear to mediate the

association of increases in sleep duration with T2D. The suggestion of a U-shaped relationship with T2D in age-adjusted models attenuated with multivariable adjustment, and only extreme increases in sleep duration of ≥2 hours/day maintained a significant adverse association with T2D.

Epidemiologic evidence supports a cross-sectional relationship of shorter sleep duration with lower diet quality, but prospective evidence is limited and whether long-term changes in sleep duration are accompanied by changes in diet quality has not been studied previously. (28) Consistent with our results, in studies that have examined mediation, differences in diet and physical activity did not explain or attenuate the magnitude of associations between baseline sleep duration and weight gain or diabetes. (11)

Most prior longitudinal studies assess whether a single baseline measure of sleep duration predicts future risk. Assessing changes in sleep duration is appealing; if achieving a more adequate sleep duration prevented weight gain or T2D, the corresponding public health message would be to improve sleep duration (e.g. from <6 hours/day to 7-8 hours per day) to benefit health. However, our results are not consistent with the hypothesis that short or long sleepers who achieve normative sleep durations will experience benefits for metabolic health. Instead, we found that extreme increases (and not decreases) in sleep duration were associated with weight gain and increased risk of T2D, independent of prior sleep duration. The Whitehall Study is one of few studies to examine long-term changes in sleep duration (over ~7 years, in relation to mortality among office workers aged 35-55 years). Decreases among 6-8 hour sleepers were associated with cardiovascular mortality, while increases among 7-8 hour sleepers were associated with non-cardiovascular mortality. (29) That increases and decreases were associated with different cause-specific mortality underscores the possibility that different extremes of sleep duration may operate through different mechanisms or reflect different underlying disease processes.

Another explanation for our finding that increases in sleep duration are adversely associated with T2D is that the age of the study population modifies the associations of change in sleep with metabolic outcomes. Our study included middle-aged and older women; in the younger population of the Quebec family cohort (n=216 adults 18-64 years), short sleepers (<6 hour/day) who reported sleeping 7–8 hours/day 6 years later were less likely to gain weight compared with those who maintained short-sleep-duration. (30) When we conducted a similar analysis, we too found that chronic short sleepers (≤6 hour/day at both time-points) gained more weight and had elevated risk of T2D compared to women who maintained a normative sleep duration (7–8 hours/day). However, in contrast to the Quebec study, short sleepers who increased sleep duration to 7–8 hours/day had even greater weight gain and stronger adverse associations with T2D than those with chronic short sleep, while consistently long sleep durations of ≥9 hours had no association with T2D (though there were very few participants in this category). These findings are consistent with prior literature on the detrimental impacts of chronic insufficient sleep duration on metabolic health.

We did not have information on why changes in sleep duration occurred; changes could reflect voluntary alterations in lifestyle; be mediated through changes in other metabolic, hormonal, or behavioral factors associated with T2D; or represent a distress signal indicating pre-clinical illness. We controlled for many of these indicators of poor health status (e.g. diet, physical activity, anti-depressant use, high cholesterol, high blood pressure, etc.), thus, changes in sleep duration may have a truly bi-directional relationship with changes in weight and metabolic health. For example, increases in sleep duration may result from or induce an inflammatory state: pro-inflammatory cytokines, abundant in obesity, can induce sleepiness. (31) The pilot showed that extended time in bed can also increase inflammation: the study randomized 14 healthy, average duration sleepers (mean age 32 years) to 3 additional hours in bed over two weeks and found adverse effects on mood

and inflammation compared to time in bed fixed to the individual's median time in bed at enrollment. (32) Additionally, while older adults reporting longer sleep durations do sleep longer by objective measures, they also spend substantially more time in bed than those reporting shorter sleep durations. Longer time in bed is associated with next-day lethargy and daytime sleepiness. As time asleep and time in bed increase, sleep becomes increasingly fragmented and the total amount of slow wave sleep (particularly restorative) does not increase proportionally. (33) Further, increases in sleep duration are accompanied by longer time periods in the dark, which some researchers argue could be interpreted physiologically as a shorter day-length, which is associated with increased mortality. (34)

Our study has several strengths and limitations. The sample size, longitudinal design and long duration of follow-up enabled examination of T2D and represent important strengths. We controlled for underlying illness more robustly than prior studies by adjusting for anti-depressant use, diet quality, and physical activity and baseline high cholesterol and high blood pressure, as well as by excluding participants with cancer and cardiovascular disease in sensitivity analyses. However, observational cohort studies cannot establish causality. Additionally, sleep duration was self-reported and assessed at two time points. Thus, fluctuations in sleep duration over follow-up would not be captured in our data. Further, random error in self-reported sleep duration, diet or physical activity is magnified when computing a change and could have attenuated observed associations towards the null. Though self-reported sleep duration in NHS was validated among 260 participants in 2002 and found to correlate well (spearman $\rho = 0.79$) with six days of sleep diaries and have good reproducibility over a two year span, (35) no objective sleep measurements capable of distinguishing time in bed from time asleep were taken. Finally, we examined overall diet quality and weekly physical activity; the circadian timing of meals and physical activity - not measured in this study - may contribute to weight gain and risk of T2D.

CONCLUSION

Though adequate sleep has many positive benefits, increasing sleep duration did not improve risk of T2D in middle-aged and older women. Long-term decreases in sleep duration have modest adverse associations with diet quality and physical activity, while long-term increases in sleep duration have modest adverse associations with weight gain. Ongoing trials will provide further insight as to whether changes in sleep duration influence energy balance: the results of a sleep extension among chronically short sleeping obese adults could provide insight about the potential benefits of intentionally improving sleep duration from inadequate to adequate durations. (36) Another study will test whether chronic moderate sleep restriction in long and average sleeping older adults improves glucose tolerance and inflammation, among other endpoints. (8) The results of the present study assessing long term changes in sleep compliment forthcoming results from intervention trials with shorter follow-up. However, further research is needed to determine whether optimizing sleep duration is an effective strategy to promote metabolic health.

REFERENCES

1. International Diabetes Federation. Version 6th. Internet: http://www.idf.org/diabetesatlas (accessed November 5 2014).
2. Schmid SM, Hallschmid M, Schultes B. The metabolic burden of sleep loss. The lancet Diabetes & endocrinology 2014. doi: 10.1016/s2213-8587(14)70012-9.
3. Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson CL, Hu FB, Liu L. Sleep Duration and Risk of Type 2 Diabetes: A Meta-analysis of Prospective Studies. Diabetes care 2015;38(3):529-37. doi: 10.2337/dc14-2073.
4. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes care 2006;29(3):657-61.
5. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354(9188):1435-9. doi: 10.1016/s0140-6736(99)01376-8.
6. Lucassen EA, Rother KI, Cizza G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. Annals of the New York Academy of Sciences 2012;1264:110-34. doi: 10.1111/j.1749-6632.2012.06655.x.
7. Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Archives of internal medicine 2005;165(8):863-7. doi: 10.1001/archinte.165.8.863.
8. Youngstedt SD, Jean-Louis G, Bootzin RR, Kripke DF, Cooper J, Dean LR, Catao F, James S, Vining C, Williams NJ, et al. Chronic moderate sleep restriction in older long sleepers and older average duration sleepers: a randomized controlled trial. Contemporary clinical trials 2013;36(1):175-86. doi: 10.1016/j.cct.2013.06.014.
9. Bliwise DL, Young TB. The parable of parabola: what the U-shaped curve can and cannot tell us about sleep. Sleep 2007;30(12):1614-5.
10. Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Association of short and long sleep durations with insulin sensitivity in adolescents. The Journal of pediatrics 2011;158(4):617-23. doi: 10.1016/j.jpeds.2010.09.080.
11. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity (Silver Spring, Md) 2008;16(3):643-53. doi: 10.1038/oby.2007.118.
12. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep 2006;29(7):881-9.
13. Stranges S, Dorn JM, Shipley MJ, Kandala NB, Trevisan M, Miller MA, Donahue RP, Hovey KM, Ferrie JE, Marmot MG, et al. Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States: the Whitehall II Study and the Western New York Health Study. American journal of epidemiology 2008;168(12):1353-64. doi: 10.1093/aje/kwn337.
14. Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. The Journal of clinical endocrinology and metabolism 2004;89(11):5762-71. doi: 10.1210/jc.2004-1003.
15. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Annals of internal medicine 2004;141(11):846-50.
16. St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJ. Short sleep duration increases energy intakes but does not change energy expenditure in

normal-weight individuals. The American journal of clinical nutrition 2011;94(2):410-6. doi: 10.3945/ajcn.111.013904.
17. Chaput JP. Sleep patterns, diet quality and energy balance. Physiology & behavior 2013. doi: 10.1016/j.physbeh.2013.09.006.
18. Chaput JP, St-Onge MP. Increased food intake by insufficient sleep in humans: are we jumping the gun on the hormonal explanation? Frontiers in endocrinology 2014;5:116. doi: 10.3389/fendo.2014.00116.
19. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. International journal of obesity (2005) 2014;38(3):411-6. doi: 10.1038/ijo.2013.114.
20. Benedict C, Brooks SJ, O'Daly OG, Almen MS, Morell A, Aberg K, Gingnell M, Schultes B, Hallschmid M, Broman JE, et al. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. The Journal of clinical endocrinology and metabolism 2012;97(3):E443-7. doi: 10.1210/jc.2011-2759.
21. Klingenberg L, Sjodin A, Holmback U, Astrup A, Chaput JP. Short sleep duration and its association with energy metabolism. Obesity reviews : an official journal of the International Association for the Study of Obesity 2012;13(7):565-77. doi: 10.1111/j.1467-789X.2012.00991.x.
22. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. American journal of epidemiology 2002;155(5):387-93.
23. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS medicine 2011;8(12):e1001141. doi: 10.1371/journal.pmed.1001141.
24. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338(8770):774-8.
25. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. The Journal of nutrition 2012;142(6):1009-18. doi: 10.3945/jn.111.157222.
26. Zhang C, Solomon CG, Manson JE, Hu FB. A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus. Arch Intern Med 2006;166(5):543-8. doi: 10.1001/archinte.166.5.543.
27. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23(5):991-9.
28. Chaput JP. Sleep patterns, diet quality and energy balance. Physiology & behavior 2014;134:86-91. doi: 10.1016/j.physbeh.2013.09.006.
29. Ferrie JE, Shipley MJ, Cappuccio FP, Brunner E, Miller MA, Kumari M, Marmot MG. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. Sleep 2007;30(12):1659-66.
30. Chaput JP, Despres JP, Bouchard C, Tremblay A. Longer sleep duration associates with lower adiposity gain in adult short sleepers. International journal of obesity (2005) 2012;36(5):752-6. doi: 10.1038/ijo.2011.110.
31. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Annals of internal medicine 1998;128(2):127-37.

32. Reynold AM, Bowles ER, Saxena A, Fayad R, Youngstedt SD. Negative Effects of Time in Bed Extension: A Pilot Study. Journal of sleep medicine and disorders 2014;1(1).
33. Webb WB, Agnew HW, Jr. Sleep stage characteristics of long and short sleepers. Science (New York, NY) 1970;168(3927):146-7.
34. Youngstedt SD, Kripke DF. Long sleep and mortality: rationale for sleep restriction. Sleep medicine reviews 2004;8(3):159-74. doi: 10.1016/j.smrv.2003.10.002.
35. Patel SR, Ayas NT, Malhotra MR, White DP, Schernhammer ES, Speizer FE, Stampfer MJ, Hu FB. A prospective study of sleep duration and mortality risk in women. Sleep 2004;27(3):440-4.
36. Cizza G, Marincola P, Mattingly M, Williams L, Mitler M, Skarulis M, Csako G. Treatment of obesity with extension of sleep duration: a randomized, prospective, controlled trial. Clinical trials (London, England) 2010;7(3):274-85. doi: 10.1177/1740774510368298.

ACKNOWLEDGEMENTS

Author affiliations

Department of Nutrition, Harvard School of Public Health, Boston, MA (Elizabeth M. Cespedes, Frank B. Hu, Yanping Li, Shilpa N Bhupathiraju); Department of Epidemiology, Harvard School of Public Health, Boston, MA (Elizabeth M. Cespedes, Frank B. Hu); Channing Division of Network Medicine, Harvard Medical School and Department of Biostatistics, Harvard School of Public Health, Boston, MA (Bernard Rosner); Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA (Susan Redline)

Funding

This work is supported by NIDDK T32 DK007703 and NCI Centers for Transdisciplinary Research on Energetics and Cancer U54CA116847 (EMC).

Conflicts of Interest

The authors have no conflicts of interest to declare.

APPENDIX

Supplemental Table 4.S1. Change in sleep duration and subsequent risk of type 2 diabetes, 1986 - 2000, n=59,031

	-2 hours/day	-1 hours/day	0 hours/day	+1 hours/day	+2 hours/day
	Hazard Ratio for Type 2 Diabetes (95% Confidence Interval)				
Cases	190	759	1334	889	341
Person-Years	32,306	131,534	255,889	149,769	42,912
Age+ Sleep in 1986 [1]-adjusted	**1.18 (1.01, 1.39)**	**1.13 (1.03, 1.24)**	1.00 Ref	**1.09 (1.00, 1.19)**	**1.40 (1.23, 1.58)**
+ Covariates in 1986 [2]	1.07 (0.92, 1.25)	1.09 (0.99, 1.19)	1.00 Ref	**1.11 (1.02, 1.21)**	**1.37 (1.22, 1.55)**
+ AHEI-2010 score and METS/week in 1986 [3]	1.03 (0.89, 1.20)	1.07 (0.97, 1.17)	1.00 Ref	1.08 (0.99, 1.18)	**1.26 (1.12, 1.42)**
+ BMI in 1986 [4]	1.04 (0.89, 1.21)	1.07 (0.98, 1.17)	1.00 Ref	1.08 (0.99, 1.18)	**1.26 (1.12, 1.42)**
+ Change in covariates [5]	0.99 (0.85, 1.16)	1.06 (0.97, 1.15)	1.00 Ref	1.06 (0.97, 1.16)	**1.20 (1.07, 1.36)**
+ Change in BMI [6]	0.99 (0.85, 1.16)	1.06 (0.97, 1.16)	1.00 Ref	1.04 (0.96, 1.14)	**1.17 (1.04, 1.32)**

Boldface indicates findings are statistically significant at the $p<0.05$ level.

[1] Models adjust for categorical sleep duration in 1986 ($\leq$5, 6, 7, 8, 9, or $\geq$10 hours/day).

[2] Models adjust for race/ethnicity, diabetes family history, shiftwork history and 1986 values of high cholesterol or high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, alcohol use, diet quality (AHEI-2010) and physical activity (MET h/week).

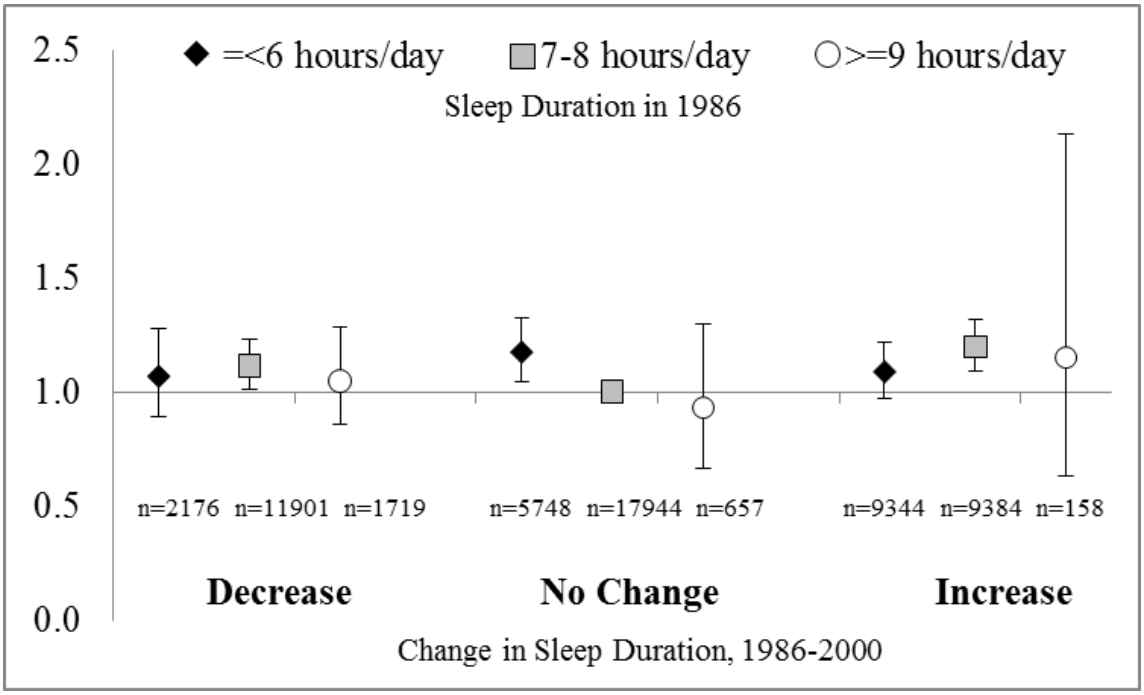
[3] Models additionally adjust for quintile of change in AHEI-2010 and MET h/week in 1986.

[4] Models additionally adjust for BMI category in 1986

[5] Models additionally adjust for change in high cholesterol or high blood pressure, menopausal status, snoring frequency, anti-depressant use, smoking status and quintile of change in alcohol use, AHEI-2010 and MET h/week from 1986 – 2000.

[6] Models additionally adjust for quintile of change in body mass index from 1986 – 2000.

Supplemental Figure 4.S1. Joint associations of sleep duration in 1986 and change in sleep duration from 1986 - 2000 with subsequent risk of type 2 diabetes, n=59,031



* Models adjust for race/ethnicity, diabetes family history, shiftwork history and 2000 values of high cholesterol or high blood pressure, menopausal status, snoring, anti-depressant use, smoking status, alcohol use and BMI category.

CONCLUSION

Taken together, these studies contribute new knowledge on sleep duration and metabolic health. Our validation in Sueño represents the largest study to date to examine the correlation of self-reported sleep duration with actigraphy and the only study to do so among Hispanic/Latinos. The large sample size and rich data on sleep and socio-demographic characteristics enables examination of the validity of self-report within subgroups to better understand the information contained in (and the limitations of) self-reported measures of sleep duration. In the Women's Health Initiative, we address a limitation of the current literature on dietary patterns by calculating four different dietary indices within the same cohort and standardizing them for comparison. Additionally, since the a priori numerical indices measuring dietary patterns were originally developed and tested in European and European-descended populations, the racial/ethnic diversity of Women's Health Initiative helps make the case for the generalizability of these dietary patterns to populations particularly burdened by T2D. Our study in Project Viva is the first to examine whether chronic insufficient sleep over the course of childhood influences diet quality or to examine the joint associations of inadequate sleep and low quality diets on childhood adiposity. This work is of interest because associations of short sleep with obesity appear to be stronger in children than in adults, and childhood is a time when health behaviors and dietary habits and preferences are being formed. Finally, the examination of changes in sleep duration in middle and later life in the Nurses' Health Study highlights the difficulty of isolating voluntary changes in lifestyle behaviors from observational data.

Future research directions include examining long-term changes in sleep duration at different periods of the life course; assessing the influence of the circadian timing of meals and physical activity on sleep duration, sleep quality and metabolic health; identifying the optimal number of

days of actigraphy to represent true habitual sleep duration (e.g., how many repeated measurements to take, and at what intervals); and investigating the bi-directional relationship of sleep duration with weight and chronic illness.