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ORIGINAL ARTICLE

Sleep and Metabolic Health

Sleep duration and timing are prospectively linked with insulin resistance during late adolescence

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Abstract

Objective: The aim of this study was to evaluate whether short sleep duration or later sleep timing is a risk factor for insulin resistance (IR) in late adolescence.

Methods: Mexico City adolescents enrolled in a longitudinal birth cohort (ELEMENT) took part in two study visits during peri-puberty that occurred approximately 2 years apart. IR was assessed with serum glucose and insulin. Four groups were defined using puberty-specific cut points: no IR over the follow-up period, transition from normal to IR, transition from IR to normal, and IR at both time points. Baseline sleep assessments were measured with 7-day wrist actigraphy. Multinomial logistic regression models were used to evaluate associations between sleep duration and timing with homeostatic model assessment of insulin resistance categories, adjusting for age, sex, and baseline pubertal status.

Results: Adolescents who were ≥ 1 hour below the sleep duration recommendations-for-age were 2.74 times more likely to develop IR (95% CI: 1.0-7.4). Similarly, adolescents who were in the latest category of sleep midpoint (>4:33 a.m.) were more likely than those with earliest midpoints (1 a.m.–3 a.m.) to develop IR (odds ratio = 2.63, 95% CI: 1.0-6.7). Changes in adiposity over follow-up did not mediate sleep and IR.

Conclusions: Insufficient sleep duration and late sleep timing were associated with development of IR over a 2-year period in late adolescence.

INTRODUCTION

Type 2 diabetes (T2D), characterized by insulin resistance (IR), is one of the leading causes of death and morbidity worldwide [1, 2], and Mexico is no exception. The prevalence of diabetes in the Mexican adult population is 14%, and in 2016, the disease was declared a public health emergency [3, 4]. Although the disease typically is detected during adulthood, the origins may be traced back to earlier life. Indeed, literature on the Developmental Origins of Health and Disease (DOHaD) has revealed that gestational diabetes and excessive weight gain during pregnancy can predispose offspring to the development of T2D in adulthood [5] [6]. During childhood, unhealthy dietary patterns [7] and higher body size [8] have been related to later T2D.

The late pubertal and emerging adulthood stage may be another sensitive period for development of T2D later in life. During puberty, adolescents experience transient IR that typically normalizes upon full maturation [9]. Specifically, IR begins to increase early in puberty (Tanner stage 2, on the pubertal Tanner scale that delineates the stages of puberty from 1 [prepubertal] to 5 [fully mature]), reaches a peak in midpuberty (Tanner stage 3 and 4), and declines again by full maturation (Tanner stage 5) [10]. Mechanisms remain unclear but they could involve altered fuel metabolism meant to preserve lean muscle mass and maximize fat as a fuel source [11, 12]. Of relevance for adolescent health, IR may continue to remain high or even rise for some adolescents [9]. Although persistent postpubertal IR has not been studied extensively in large-scale longitudinal studies, prior work suggests that weight status is one important indicator [13]. Specifically, adolescents who enter puberty with obesity were more likely to remain insulin resistant and to develop other metabolic complications [9]. Other lifestyle factors including diet (e.g., high-glycemic-index diets [14]) and low physical activity during puberty have also been related to diabetes and cardiovascular disease risk in adulthood (vegetable consumption and physical activity [15]). In addition to diet and physical activity, poor sleep is emerging as an important risk factor for IR during adolescence. Short sleep duration, delayed sleep timing, and poor sleep quality have each been related to higher IR among adolescents, primarily in cross-sectional investigations [16–20]. In Mexican adolescents who were 14 years of age on average, we recently showed that both delayed and short sleep duration were associated cross-sectionally with higher IR, an association that was stronger in girls [21]. Variability in sleep duration and timing has also been related to other markers of metabolic health among adolescents (e.g., triglycerides [22] and adiposity [23]), although associations with IR are unclear. Furthermore, the influence of sleep on IR has been rarely examined in longitudinal studies, i.e., whether sleep predicts persistent or emerging IR in the late adolescence period.

Thus, the aim of our study was to assess whether sleep characteristics including short sleep duration, sleep duration variability, later sleep timing, and social jet lag (>2 hour difference between weekend and weekday sleep timing) were associated with persistent or increasing IR in late adolescence in a Mexican cohort. Furthermore, given that we found some evidence of mediation by higher adiposity (body mass index [BMI] *z* scores) in our cross-sectional study, we sought to evaluate the extent to which changes in adiposity over the follow-up period mediated relationships between sleep characteristics and IR.

Study Importance

What is already known?

- Sleep has emerged as a possible risk factor for insulin resistance (IR) among adolescents, but longitudinal investigations that consider the multidimensionality of sleep are lacking.

What does this study add?

- Both short sleep duration and later sleep timing were related to higher odds of developing IR over a 2-year period during late adolescence.

How might these results change the direction of research?

- Whether intervening to improve both sleep timing and duration can reduce risk for IR in late adolescence deserves further investigation.

METHODS

Study population

The study sample included adolescent participants from 2 of 3 sequentially enrolled cohorts of the Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) study [24]. Between 1997 and 2004, 1012 mother/child dyads were recruited from prenatal clinics of the Mexican Social Security Institute in Mexico City, which serves low- to middle-income populations formally employed in the private sector. At baseline, mothers reported sociodemographic and health information. In 2015, a subset of 554 adolescents from the original birth cohorts 2 and 3 between the ages of 9 and 17 years were selected to participate in a follow-up visit (called time 1 [T1] in the present study). Participants from cohort 1 were not included in this follow-up visit because they were older and most were postpubertal. Starting in 2017, 519 (94%) of the same adolescents participated in an additional follow-up visit that was identical to the 2015 visit when they were between 11 and 19 years (time 2 [T2]). Among these, there were 362 adolescents who had wrist actigraphy data at T1 as well as insulin and glucose measurements at both T1 and T2 (flowchart provided in Supporting Information Figure S1). Compared with the full sample of 519 adolescents, the analytic sample was younger (−2.4 years with 95% CI: −2.7 to −2.0; $p < 0.0001$) and reported less screen time (−1.4 h/d with 95% CI: −2.1 to −0.8; $p < 0.0001$). The institutional review boards at the Mexico National Institute of Public Health and the University of Michigan approved the research protocols (CI 599 and HUM00034344). Informed

consent was obtained from participants aged ≥ 18 years. For those aged < 18 years, both participant assent and parental informed consent were obtained.

Sleep measures

During the in-person follow-up visits, adolescents were given an ActiGraph GT3X-BT to wear on their nondominant wrist continuously for 7 days and provided with a sleep diary to record bedtimes and wake times. For this analysis, we used sleep data from T1 participants who provided ≥ 4 days of valid wear days (a valid wear day was defined as < 4 hours of non-wear time); of those who agreed to wear the actigraph at this time, 96% wore it for 7 days. Nightly sleep measures were estimated from the actigraphy data with 60-second epoch lengths using a pruned dynamic programming (PDP) algorithm developed in R (R Foundation for Statistical Computing) [25]. This method has been evaluated against polysomnography, the gold standard for sleep assessment, and compared with manual detection of sleep/wake times in the present cohort with > 95% correlation [25]. The algorithm incorporated the self-reported bedtimes and wake times to improve accuracy and it was used to calculate weekday (Sunday through Thursday night) and weekend (Friday and Saturday) sleep duration (minutes) and weekday and weekend sleep midpoint (the midpoint of sleep onset and wake time; reported in decimal hours). Naps were not included as one of the sleep parameters because the algorithm could not differentiate between naps and daytime sedentary behavior. The primary sleep exposures included weekday sleep duration and weekday sleep midpoint at T1 (i.e., averaged across the weekdays), variability in sleep duration (represented by the standard deviation [SD] of the 7 days), and the difference between weekend sleep midpoint and weekday sleep midpoint, a marker of circadian misalignment known as social jet lag [26]. Sleep duration was categorized as meeting the age-specific duration recommendations defined by the American Academy of Sleep Medicine [27], being within 1 hour below the recommendation, or being ≥ 1 hour below the recommendation. Sleep duration variability was categorized as < 1 hour SD, 1 to 2 hour SD, or > 2 hour SD. Weekday sleep midpoint was divided evenly into tertiles (as there are currently no specific guidelines for optimal sleep midpoints for adolescents), and social jet lag was divided into a difference of ≤ 1 hour from weekend to weekdays, >1 hour later to 2 hours later on the weekend, or >2 hours later on the weekend.

HOMA-IR

At both T1 and T2, venous whole blood was taken during the clinic visit after an overnight fast (at least 8 hours) and immediately separated and stored at −80 °C. Serum glucose and insulin were measured at the Michigan Diabetes Research Center (P30DK020572). The insulin assay is a double-antibody radioimmunoassay (RIA) that uses ^{125}I-human insulin tracer (Millipore Sigma), a guinea pig anti-porcine insulin first antibody (MDRTC, 68.5% cross-reaction to human proinsulin), and a goat anti-guinea pig gamma globulin (Antibodies Inc.)-polyethylene glycol second antibody. It was standardized against the Human Insulin International Reference Preparation (NIBSC) and run in duplicate. The glucose assay was run singularly on our automated chemistry analyzer (Randox). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from the product of the fasting serum insulin and fasting serum glucose divided by 405 [28]. A cut point developed in Chilean adolescents that accounted for pubertal stage was used to define IR [29]. A HOMA-IR >2.1 is considered insulin resistant among adolescents with Tanner stages 1 and 2 (Tanner breast development for girls and Tanner genital development for boys), whereas HOMA-IR >3.3 is considered insulin resistant among adolescents in Tanner stage 3 or higher. Tanner staging was assessed by a trained clinician during a physical examination [30]. Four groups were defined using the cut points: normal HOMA-IR over the follow-up period, transition from normal to IR, transition from IR to normal, and IR at both time points.

Covariates

Possible baseline confounders, which were selected a priori, included sex, age, pubertal status, maternal education, physical activity, total energy intake, screen time, and smoking status (ever/never). For descriptive statistics, age at T1 was divided into 9 to 12 years and ≥ 13 years in accordance with the American Academy of Sleep Medicine sleep recommendation age cut points [27]. In addition to the Tanner staging (described previously), pubertal status was assessed through questions about menstruation (girls) and estimation of testicular volume in boys [30]. Because the IR categories already incorporated adjustment for Tanner stages, we examined other indicators of puberty as potential residual confounders, given that pubertal indicators are not always aligned within individuals and that there may be measurement error. Specifically, pubertal status was considered dichotomously as either being in late puberty or postpuberty versus earlier puberty based on menarche and testicular volume. For girls, late puberty or postpuberty was considered as already having experienced menarche. For boys, late puberty or postpuberty was considered a physician-assessed testicular volume ≥ 15 mL. Intensity and duration of physical activity were obtained from the actigraphs and classified as moderate or vigorous and as minutes per day [31]. Total energy intake was estimated by a food frequency questionnaire regarding the previous week's intake as described in detail elsewhere [32]. Total screen time was assessed with a questionnaire adapted for and validated in Mexican adolescents [33] and was divided into quartiles. Smoking behavior was self-reported with a single question, "Have you ever tried smoking?" and was categorized dichotomously. Maternal education was reported by mothers at the original cohort enrollment visit and was classified into 4 categories: < 9 years (attended primary or secondary school only), 9 to 11 years (completed secondary or completed secondary and at least some high school), 12 years (completed high school), and >12 years (posthigh school).

TABLE 1 Sleep characteristics at baseline, stratified by sex and age

Baseline sleep characteristic	*n*	Boys, %	Girls, %	Younger age group, 9–12, %	Older age group, 13+, %
Weekday sleep duration[a]					
Recommended sleep duration	196	54.5	53.8	38.0	65.6
Within 1 hour below recommendation	103	29.8	27.2	35.3	23.6
≥1 Hour below recommendation	63	15.7	19.0	26.7	10.8
Sleep duration variability over 7 days					
<1 Hour SD	97	28.65	25.00	36.67	19.81
1–2 Hour SD	190	51.69	53.26	49.33	54.72
>2 Hour SD	75	19.66	21.74	14.00	25.47
Weekday sleep midpoint					
Tertile 1, 12:55–2:58 a.m.	127	38.20	32.07	44.00	28.77
Tertile 2, 2:59–4:33 a.m.	128	30.34	40.22	36.67	34.43
Tertile 3, 4:34–7:59 a.m.	107	31.46	27.72	19.33	36.79
Social jet lag					
Within 1 hour, weekend to weekday	193	56.82	50.54	53.33	53.81
>1 Hour later on weekend	96	26.14	27.17	28.00	25.71
>2 Hours later on weekend	71	17.05	22.28	18.67	20.48

[a]Recommended sleep duration for ages 6–12 is 9–12 hours per 24 hours, although recommended sleep duration for 13–18 is 8–10 hours per 24 hours.

Potential mediators of fat mass or distribution included changes in BMI, body fat percentage, waist circumference, and triceps skinfolds, measured at T1 and T2 by trained research assistants using standard protocols described previously [34]. Duplicate height was measured to the nearest 0.1 cm (Tonelli E120 A), weight to the nearest 0.1 kg (InBody270), waist circumference to the nearest 0.1 cm (QM2000; QuickMedical), triceps skinfold in millimeters (Lange calipers, Beta Technology), and body fat percentage with bioelectrical impedance (InBody270). All height measures were averaged, and BMI was computed as weight in kilograms divided by height in meters squared. Changes in BMI and other adiposity measures were computed by subtracting the T2 measure from T1.

Statistical analysis

To assess potential confounding, we examined associations between covariates and HOMA-IR outcomes by computing the percentages of adolescents in each category of change in HOMA-IR across covariates. Next, bivariate associations between sleep variables and HOMA-IR outcomes were evaluated by estimating the percentages of adolescents in each HOMA-IR category according to sleep variables. *P* values in all categorical analyses were obtained with $\chi 2$ tests. In multivariable complete-case analysis, multinomial logistic regression models were run with HOMA-IR change categories as the outcome ("normal HOMA-IR at T1 and T2" was the reference group) and categorical T1 sleep characteristics as the exposure, adjusting for age, sex, and pubertal status. Additional adjustment for physical activity and total energy intake did not alter the estimates and thus these variables were not retained. Because of a positive correlation ($r = 0.46$), sleep duration and sleep midpoint were run in the same model, whereas sleep duration variability and social jet lag were run in separate models (the latter variables were not strongly correlated with other sleep characteristics). *P* values for trend (*p*, trend) were obtained by running the exact same models but with a variable representing ordinal categories of each sleep category. Age and sex were evaluated as possible effect modifiers by including interaction terms for these variables along with each sleep measure. To investigate mediation of sleep and IR by adiposity changes, we fitted linear regression models with change in waist circumference, change in BMI, change in body fat percentage, and change in triceps skinfolds as the outcomes and sleep characteristics as predictors. A formal mediation model based on the methods of Vanderweele [35, 36] was run on a subsample, in which IR was considered as a dichotomous outcome (1 for those who became insulin resistant at T2 among those who did not have IR at T1 and 0 for those who were never insulin resistant). All analyses were conducted in Stata 14.0 (StataCorp LP), and a p value < 0.05 was considered statistically significant.

RESULTS

At the T1 visit, the average age was 14.4 ± 2.1 years; 79% of the sample had reached the latter stages of puberty (menarche for girls and ≥ 15 mL testicular volume for boys). Within the younger participants (9–12 years old), 38% met the sleep duration recommendations for this age group, and 53% had < 1 hour of difference between weekdays and weekends (i.e., no social jet lag) (Table 1). Among the adolescents who were 13 years or older at T1, 6% met the sleep duration recommendations, and 54% had no social jet lag.

TABLE 2 Associations between baseline sociodemographic or lifestyle characteristics and categories for changes in IR during the 2 years between baseline (T1) and follow-up (T2) assessments

	N (row total)	Normal HOMA-IR at T1 and T2, *N* = 115	Transition from normal to IR, *N* = 61	Transition from IR to normal, *N* = 40	IR at T1 and T2, *N* = 146
Sex					
Male	178	41.4[a]	12.9	11.8	34.8
Female	184	23.4	20.7	10.3	45.7
p value		0.002			
Age group					
9–< 12 years	82	23.2	15.9	9.8	51.2
12–< 14 years	136	31.6	11.8	11.0	45.6
14–18 years	144	36.8	22.2	11.8	29.2
p value		0.02			
Testicular volume (boys only)					
< 15 mL	35	31.4	14.3	11.4	42.9
≥ 15 mL (latter stages of puberty)	132	43.2	13.6	10.6	32.6
p value		0.61			
Menarche status (girls only)					
Had not experienced	38	15.8	13.2	7.9	63.2
Had experienced	147	25.2	21.1	11.6	42.2
p value		0.15			
Maternal education					
≤ 8 Years or less (secondary or primary)	39	28.2	25.6	15.4	30.8
9–11 Years (some high school)	145	26.9	20.7	9.0	43.5
12 Years (completed high school)	121	36.4	11.6	12.4	39.7
>12 Years	54	37.0	11.1	9.3	42.6
p value		0.24			
Moderate/vigorous physical activity, min/d					
Q1, 15–60.22	89	25.8	23.6	11.2	39.3
Q2, 60.23–77.13	88	39.8	15.9	13.6	39.7
Q3, 77.14–97.9	88	33.0	13.6	13.6	39.8
Q4, 98.7–174	88	26.1	14.8	6.8	52.3
p value		0.11			
Screen time, h/wk					
Q1, 2–20.5	92	28.3	16.3	12.0	43.5
Q2, 21–30.5	90	30.0	15.6	11.1	43.3
Q3, 31–40.5	88	37.5	19.3	6.8	36.4
Q4, 41–104	90	31.1	16.7	13.3	38.9
p value		0.87			
Ever smoked cigarettes					
No	298	30.9	14.8	10.1	44.3
Yes	59	35.6	27.1	15.3	22.0
p value		0.007			
Average calorie intake, kcal					
Q1, 663–1688	89	23.6	14.6	9.0	52.8
Q2, 1690–2169	91	31.9	14.3	17.6	36.3
Q3, 2173–2812	89	38.2	16.9	7.9	37.1
Q4, 2817–5964	89	31.5	22.5	9.0	37.1
p value		0.10			

(Continues)

TABLE 2 (Continued)

	N (row total)	Normal HOMA-IR at T1 and T2, *N* = 115	Transition from normal to IR, *N* = 61	Transition from IR to normal, *N* = 40	IR at T1 and T2, *N* = 146
Change in waist circumference, cm					
Q1, median = −14.9 to 2.8	92	39.1	7.6	16.3	37.0
Q2, median = 3–6.25	90	37.8	14.4	13.3	34.4
Q3, median = 6.3–9.34	91	30.8	13.2	7.7	48.4
Q4, median = 9.35–25.1	89	19.1	32.6	6.7	41.6
p value		<0.0001			
Change in BMI, kg/m^2					
Q1, median = −6.3 to 0.26	92	44.6	8.7	13.0	33.7
Q2, median = 0.27–1.1931	91	34.1	13.2	16.5	36.3
Q3, median = 1.1933–2.20	91	28.6	19.8	8.8	42.9
Q4, median = 2.21–9.79	88	19.3	26.1	5.7	48.9
p value		0.001			
Change in body fat percentage					
Q1, median = −22 to −1.8	91	34.1	6.6	16.5	42.9
Q2, median = −1.79–1.19	90	34.4	12.2	13.3	40.0
Q3, median = 1.20–3.80	89	33.7	18.0	9.0	39.3
Q4, median = 3.90–20	89	25.8	30.3	5.6	38.2
p value		0.005			
Change in triceps skinfold, mm					
Q1, median = −16 to − 1	101	42.6	9.9	14.9	32.7
Q2, median = −0.7–1.5	87	34.5	16.1	12.6	36.8
Q3, median = 2–5	89	25.8	18.0	4.5	51.7
Q4, median = 5.5–21	84	22.6	25.0	10.7	41.7
p value		0.006			

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; Q, quartile.
[a]Values represent row percentages.

None of the younger adolescents exceeded the sleep duration recommendations, whereas 3% of the older adolescents slept longer than recommended.

The median (Q25, Q75) HOMA-IR at T1 was 3.0 (2.2, 4.5), and 51% were considered insulin resistant. At the T2 follow-up visit approximately 2 years later (± 0.4 years), 98% of the sample were in late or postpuberty based on menarche or testicular volume, and the median (Q25, Q75) HOMA-IR was 3.4 (2.6, 4.8), with 57% considered insulin resistant. Forty percent of participants were insulin resistant at both time points, 17% became insulin resistant from T1 to T2, 11% changed from insulin resistant to normal, and 32% were non–insulin resistant at both time points. Males were more likely to be have normal IR at both time points, whereas females were more likely to transition into and out of IR (Table 2). Participants who were younger at T1 were more likely to transition from IR to normal over the follow-up period. Those who reported to have ever tried smoking and those who had higher increases in adiposity were more likely to become insulin resistant.

In unadjusted analyses, there were no statistically significant associations between sleep characteristics and categories of IR (Table 3). However, in adjusted multinomial models, there were associations between sleep duration and timing with transitions to IR (Table 4). Specifically, adolescents who were ≥ 1 hour below the sleep duration recommendation in comparison to those who met it had 2.74 higher odds of becoming insulin resistant over follow-up (95% CI: 1.01-7.43; *p*, trend = 0.05). Considered as a continuous variable, each additional hour of sleep was related to 0.71 (95% CI: 0.52-0.96; $p = 0.02$) lower odds of developing IR, as well as 0.76 (95% CI: 0.59-0.97; $p = 0.04$) lower odds of being insulin resistant at both T1 and T2 and 0.70 (95% CI: 0.49- 0.99; $p = 0.03$) lower odds of transitioning from insulin resistant to normal compared with normal HOMA-IR at both T1 and T2 (Supporting Information Table S1). Those with a sleep midpoint later than 4:33 a.m. had 2.63 higher odds of becoming insulin resistant (95% CI: 1.03-6.72; *p*, trend = 0.04). As a continuous variable, each hour later sleep midpoint was related to 1.31 (95% CI: 0.97-1.75) higher odds of becoming insulin resistant,

TABLE 3 Unadjusted associations between baseline sleep characteristics and 2-year changes in HOMA-IR from baseline (T1) to follow-up (T2)

Baseline sleep characteristic	Normal HOMA-IR at T1 and T2, $N = 115$	Transition from normal to IR, $N = 61$	Transition from IR to normal, $N = 40$	IR at T1 and T2, $N = 146$
Sleep duration				
Recommended sleep duration	34.7[a]	16.8	11.2	37.2
Within 1 hour below recommendation	33.0	15.5	7.8	43.7
≥ 1 Hour below recommendation	20.6	19.1	15.9	44.4
p value	0.35			
Sleep duration variability over 7 days				
< 1 Hour SD	32.0	12.4	11.3	44.3
1–2 Hour SD	28.4	18.4	10.5	42.6
> 2 Hour SD	40.0	18.7	12.0	29.3
p value	0.34			
Sleep midpoint				
Tertile 1, 12:55 a.m.–2:58 a.m.	36.2	12.6	11.0	40.2
Tertile 2, 2:59 a.m.–4:33 a.m.	27.3	17.2	10.2	45.3
Tertile 3, 4:34 a.m.–7:59 a.m.	31.8	21.5	12.2	34.6
p value	0.40			
Social jet lag				
Within 1 hour, weekend to weekday	30.1	18.1	13.0	38.9
>1 Hour later on weekend	31.3	13.5	8.3	46.9
>2 Hours later on weekend	36.6	18.3	9.9	35.2
p value	0.60			

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; Q, quartile.
[a]Values represent row percentages.

although this was not a statistically significant association ($p = 0.08$). Interaction analysis showed no evidence of interaction by sex or age. There were no associations between sleep duration variability or social jet lag with changes in IR.

We next evaluated whether changes in adiposity mediated the relationships between sleep duration and timing with IR categories. As a first step, we examined associations between sleep duration and timing with continuous adiposity changes, but all were null. In formal mediation models, there was no evidence of mediation by adiposity changes for either sleep duration or timing with development of IR (e.g., $p = 0.9$ for the natural indirect effect of sleep duration and odds of developing IR through changes in waist circumference and $p = 0.8$ for sleep midpoint; data not shown). Finally, sensitivity analyses evaluating whether changes in sleep characteristics from T1 to T2 were related to IR revealed no evidence of associations (not shown).

DISCUSSION

Within this cohort of Mexican adolescents, shorter sleep duration and later sleep timing at baseline (T1) were each associated with developing IR during late adolescence. Specifically, adolescents who were ≥ 1 hour below the sleep duration recommendation or who had later sleep midpoints than their peers at T1 had 2.74 and 2.63 higher odds, respectively, of becoming insulin resistant over the next 2 years. In contrast, neither social jet lag nor sleep duration variability were associated with IR categories. Although larger changes in adiposity were associated with higher likelihood of developing IR and persistent IR across 2 years of follow-up, adiposity change was not a mediator in the sleep timing or duration and IR pathways.

Longitudinal investigations of actigraphy-based sleep and IR during adolescence are rare. Previous cross-sectional work, including ours, has linked insufficient sleep duration with IR among adolescents [16–20]. Delayed sleep timing has also been related IR independently of sleep duration in a few cross-sectional studies [18, 21]. Existing longitudinal studies were conducted in children and focused on sleep duration. Among 8– to 11-year-old Danish children, declines in sleep duration over a period of approximately 200 days were associated with increases in HOMA-IR after accounting for physical activity and sedentary time [37]. Another study of 3900 European children who were between 2 and 11 years old at baseline found that shorter self-reported sleep duration was associated with higher HOMA-IR measured 4 years later, and this was mediated by waist circumference [20]. Our study is an extension to the literature with regard to the focus on late adolescence. Puberty is a unique period for sleep because it marks the beginning of a circadian phase delay that continues into the young adult period [38]. Increased independence and new social or academic activities during this time period could also

TABLE 4 Adjusted associations between baseline sleep characteristics and 2-year changes in HOMA-IR from baseline (T1) to follow-up (T2)

Baseline sleep characteristic	Transition to IR compared with normal HOMA-IR at both,[a] OR (95% CI)	Transition from IR to normal compared with normal HOMA-IR at both,[a] OR (95% CI)	IR at both time points compared with normal HOMA-IR at both,[a] OR (95% CI)
Sleep duration			
Recommended sleep duration	Reference	Reference	Reference
Within 1 hour below recommendation	1.43 (0.64, 3.20)	0.87 (0.33, 2.33)	1.20 (0.65, 2.24)
≥ 1 Hour below recommendation	2.74 (1.01, 7.43)	2.83 (0.98, 8.22)	2.00 (0.90, 4.47)
p, trend[b]	0.05	0.10	0.11
Sleep duration variability over 7 days			
< 1 Hour SD	Reference	Reference	Reference
1–2 Hour SD	1.49 (0.6, 3.37)	0.98 (0.41, 2.35)	1.17 (0.4, 2.14)
> 2 Hour SD	1.02 (0.39, 2.8)	0.68 (0.23, 2.00)	0.62 (0.29, 1.33)
p, trend[b]	0.99	0.48	0.28
Sleep midpoint			
Tertile 1, 12:55 a.m.-2:58 a.m.	Reference	Reference	Reference
Tertile 2, 2:59 a.m.-4:33 a.m.	1.82 (0.80, 4.17)	1.24 (0.49, 3.10)	1.64 (0.89, 3.05)
Tertile 3, 4:34 a.m.-7:59 a.m.	2.63 (1.03, 6.72)	1.54 (0.54, 4.44)	1.64 (0.79, 3.41)
p, trend[b]	0.04	0.42	0.15
Social jet lag			
Within 1 hour, weekend to weekday	Reference	Reference	Reference
> 1 hour later on weekend	0.69 (0.31, 1.52)	0.62 (0.25, 1.56)	1.13 (0.62, 2.04)
> 2 hours later on weekend	0.77 (0.34, 1.73)	0.62 (0.24, 1.65)	0.73 (0.37, 1.43)
p, trend[b]	0.43	0.26	0.50

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; OR, odds ratio.
[a]From a multinomial logistic regression model adjusted for age, sex, and baseline puberty status; sleep duration and midpoint were mutually adjusted.
[b]Obtained by replacing the categorical predictor with a variable representing ordinal categories of each sleep category.

contribute to shorter sleep duration. Moreover, our evidence suggests that sleep duration and timing during puberty may contribute to IR that persists beyond the typical transient increase in IR. During typical development, as adolescents progress through the Tanner stages, IR rises (it may or may not reach the threshold for "insulin resistant") but then falls again by Tanner stage 5 [9]. Within our sample, 11% of adolescents who started out as insulin resistant at the first visit became non–insulin resistant by the T2 visit. Nonetheless, there was a substantial number of adolescents in our sample who either remained insulin resistant or became insulin resistant over follow-up. Because the majority of these participants were classified as late puberty or fully mature by the follow-up visit, the fact that they continued as insulin resistant likely signals increased risk for cardiometabolic complications as they enter young adulthood. From a clinical viewpoint, our results may suggest that more extreme challenges to healthy sleep during late puberty could serve as an early indicator for later cardiometabolic risk, suggesting the need for sleep intervention.

Although we were underpowered to examine sex differences in sleep and IR relationships, we did not find statistical evidence that associations were stronger in females. This is in contrast to our earlier findings whereby sleep timing and duration were associated cross-sectionally with HOMA-IR in females but not males [21]. Although the literature is somewhat mixed [17], one other pediatric study suggested similar associations between sleep duration or timing with IR in girls but not boys [16]. These dissimilar findings within this same cohort may suggest that relationships vary across the pubertal transition.

The fact that changes in measures of fat mass and distribution over the follow-up period were not statistical mediators also suggests that the potential mechanisms to explain a relationship between baseline sleep and development of IR could be independent of body size and composition, at least over this relatively short-term period of 2 years. Diet and physical activity are 2 potential behavioral mediators. A large body of evidence now shows that insufficient sleep duration and late sleep timing among children and adolescents are associated with higher caloric intake [39, 40], especially calories from carbohydrates [41, 42] and sugar-sweetened beverages [39–42]. These sleep characteristics have also been associated with lower fruit and vegetable intake [41]. Moreover, each of these dietary factors has been associated with IR [43–46]. Insufficient sleep also has been related to declines in moderate and vigorous activity and higher sedentary behavior [47, 48], factors that are also independent predictors of IR [49]. It is worth pointing out that in the present analysis, moderate/vigorous physical activity and total energy intake were related to development of IR (although not statistically significantly), but the addition of these variables to the sleep and IR model did not alter

estimates. This suggests that the quantity of food and physical activity may not play a strong mediating role in the sleep and IR relationship, although further examination of potential modifying roles for these factors is warranted. However, it is important to highlight the likely role of circadian disruption for the observed relationship between sleep timing and IR. Circadian disruption can refer to differences between the circadian rhythms of the central brain clock (the suprachiasmatic nucleus) and the peripheral clocks in tissues such as liver, muscle, adipose tissue, and the pancreas or between the central brain clock and behavioral sleep/wake patterns [50]. These differences can arise from delayed sleep patterns, as well as delayed eating [51] and mistimed physical activity [52], and they may contribute directly to IR by altering daily rhythms of glucose metabolism [50].

A primary strength of this study is the repeated measures of IR over late adolescence. Additional studies that follow these participants into young adulthood will provide further insights into potential cardiometabolic ramifications associated with persistent IR in late adolescence. The fact that sleep duration and timing were measured with wrist actigraphy rather than self-report is another strength. There are also limitations to consider. HOMA-IR is not the gold standard to measure IR, although it is a feasible measure in the context of a large cohort study and it has been shown to be highly correlated with euglycemic-hyperinsulinemic clamp measurements [53]. Furthermore, clear consensus does not exist on which HOMA-IR value should demarcate IR among adolescents. We used cut points from a Chilean study [29] that accounted for pubertal status, but we acknowledge there may be limitations in this approach. In particular, the cut points were not validated against euglycemic-hyperinsulinemic clamps, although they had a sensitivity of 0.65 and specificity of 0.69 for metabolic syndrome [54]. Of note, these cut points were more conservative than others reported in the literature among healthy populations of adolescents [55], suggesting that we may be underestimating IR in the present study. In addition, even though sex-stratified analyses of sleep and IR were warranted based on prior literature, the study was not adequately powered to detect these differences. Furthermore, because sleep was not a primary exposure of interest for the original grant, we did not have self-reported information on sleep quality, which could be an independent predictor of IR and an unmeasured confounder in this analysis. Finally, study findings may not be generalizable to adolescents in other populations, especially in settings where cultural norms and customs regarding sleep may differ. On a related note, findings may not be generalizable to adolescents who exceed sleep duration recommendations; there were too few adolescents in our cohort to examine relationships between excessive sleep duration and IR.

In summary, within a cohort of Mexican adolescents, we found that insufficient sleep duration and later sleep timing were each associated with more than 2.5 times higher odds of developing IR over a 2-year follow-up period. These associations were independent of changes in adiposity over the follow-up period. This prospective, longitudinal study raises the possibility of causal relationships but it cannot prove them. Whether intervening to improve sleep specifically around the time of pubertal transition can reduce risk for IR in late adolescence deserves further investigation.O

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CONFLICT OF INTEREST

Dr. Chervin reports patents and copyrighted material for the assessment and treatment of patients with obstructive sleep apnea, has received consulting fees from Eli Lilly and Company, and acts as treasurer and board member for the International Pediatric Sleep Association and as an Advisory Board member for the nonprofit Pajama Program. Dr. Lee reports support from the Elizabeth Weiser Caswell Diabetes Institute, has received consulting fees from Tandem Diabetes Care, and is on the Medical Advisory Board for GoodRx. Dr. Burgess serves on the scientific advisory board for Natrol, LLC, and is a consultant for F. Hoffmann-La Roche Ltd. None of these disclosures played a role in the analysis, interpretation, decision to publish, or preparation of this manuscript. The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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