Sleep Architecture and Glucose and Insulin Homeostasis in Obese Adolescents

Dorit Koren, md[1]
Lorraine E. Levitt Katz, md[1]
Preneet C. Brar, md[2]
Paul R. Gallagher, ma[3]
Robert I. Berkowitz, md[4]
Lee J. Brooks, md[5]

OBJECTIVE—Sleep deprivation is associated with increased risk of adult type 2 diabetes mellitus (T2DM). It is uncertain whether sleep deprivation and/or altered sleep architecture affects glycemic regulation or insulin sensitivity or secretion. We hypothesized that in obese adolescents, sleep disturbances would associate with altered glucose and insulin homeostasis.

RESEARCH DESIGN AND METHODS—This cross-sectional observational study of 62 obese adolescents took place at the Clinical and Translational Research Center and Sleep Laboratory in a tertiary care children's hospital. Subjects underwent oral glucose tolerance test (OGTT), anthropometric measurements, overnight polysomnography, and frequently sampled intravenous glucose tolerance test (FSIGT). Hemoglobin A_{1c} (HbA_{1c}) and serial insulin and glucose levels were obtained, indices of insulin sensitivity and secretion were calculated, and sleep architecture was assessed. Correlation and regression analyses were performed to assess the association of total sleep and sleep stages with measures of insulin and glucose homeostasis, adjusted for confounding variables.

RESULTS—We found significant U-shaped (quadratic) associations between sleep duration and both HbA_{1c} and serial glucose levels on OGTT and positive associations between slow-wave sleep (N3) duration and insulin secretory measures, independent of degree of obesity, pubertal stage, sex, and obstructive sleep apnea measures.

CONCLUSIONS—Insufficient and excessive sleep was associated with short-term and long-term hyperglycemia in our obese adolescents. Decreased N3 was associated with decreased insulin secretion. These effects may be related, with reduced insulin secretory capacity leading to hyperglycemia. We speculate that optimizing sleep may stave off the development of T2DM in obese adolescents.

Diabetes Care 34:2442–2447, 2011

Sleep deprivation is endemic; 9.3% of U.S. adults sleep <6 h per night (1), and 75% of high-school seniors report getting insufficient sleep (2). This cumulative societal sleep curtailment is significant, as sleep deprivation is associated with a number of metabolic consequences: increased predisposition to obesity (3) and insulin resistance (IR) (4) in both adults and children, increased risk of type 2 diabetes mellitus (T2DM) in adults (5), and higher fasting glucose in young adults with preexisting diabetes (6). The metabolic consequences of insufficient sleep may be the result of a lack of total sleep or insufficiency of a certain sleep component. The American Academy of Sleep Medicine recognizes four different sleep stages indicated as follows: stage 1 (N1), a brief transition between wake and sleep; stage 2 (N2); stage 3 (N3), "slow-wave" or "deep" sleep; and rapid eye movement (REM) (dream) sleep. In adult studies, cerebral glucose utilization declines (7) and plasma glucose rises (8) in N3 sleep. One pediatric study found a negative association between REM sleep duration and obesity (9), but there is little pediatric data on sleep architecture and glucose and insulin homeostasis. A potential confounding factor is obstructive sleep apnea (OSA), a syndrome more common in obesity in which upper airway obstruction leads to sleep fragmentation and desaturation (10). OSA has been associated with T2DM risk in adults (10) and with IR in children (11,12). We hypothesized that in obese adolescents (who are at risk for T2DM), altered sleep architecture is associated with abnormalities of insulin secretion and sensitivity and of glucose homeostasis independently of confounding factors (e.g., degree of obesity, presence of OSA, sex, and pubertal stage). Therefore, the aim of our study was to investigate the relationship between sleep architecture and insulin secretion and sensitivity and overall glycemia in this population.

RESEARCH DESIGN AND METHODS

—This was a cross-sectional study of obese (BMI, >95th percentile for age and sex) pubertal adolescents recruited from an obesity clinic in The Children's Hospital of Philadelphia. Exclusion criteria included having previously diagnosed diabetes or sleep disorders, genetic syndromes affecting glucose tolerance or sleep, or major organ system illness, or taking medications affecting insulin or glucose metabolism. The protocol was approved by The Children's Hospital of Philadelphia Institutional Review Board; informed consent was obtained from the parents or guardians, and assent was obtained from the participants.

From the [1]Division of Pediatric Endocrinology and Diabetes, The Children's Hospital of Philadelphia, and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; the [2]Division of Pediatric Endocrinology, New York University Langhorne Medical Center, and Department of Pediatrics, New York University School of Medicine, New York, New York; the [3]Biostatistics Core, Clinical and Translational Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; the [4]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; and the [5]Division of Pediatric Pulmonary Medicine, The Children's Hospital of Philadelphia, and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania.
Corresponding author: Dorit Koren, koren@email.chop.edu.
Received 20 June 2011 and accepted 28 July 2011.
DOI: 10.2337/dc11-1093
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1093/-/DC1.
The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Anthropometrics

Demographic data and medical history were obtained from guardians and participants. Physical examination, including pubertal (Tanner) staging, was performed by a study investigator. Weight was measured using a digital scale (Scaletronix, White Plains, NY). Height was measured using a wall-mounted stadiometer (Holtain Inc., Crymych, U.K.). BMI was calculated as weight (kilograms) divided by height (meters) squared. BMI percentiles and *z* scores were assessed using age- and sex-specific reference data (13).

Glucose and metabolic testing

After a 12-h overnight fast, an oral glucose tolerance test (OGTT) was performed: subjects ingested oral glucose solution (1.75 g/kg, maximum 75 g), and blood samples for glucose and insulin were obtained at –10, 0, 10, 30, 60, 90, 12, 150, and 180 min. Hemoglobin A_{1c} (HbA_{1c}) was also measured. The following morning, after an overnight fast, subjects underwent a frequently sampled intravenous glucose tolerance test (FSIGT): infusion of 0.25 g/kg of 25% dextrose intravenously over 30 s, infusion of regular human insulin (0.015 units/kg i.v.) over 5 min at t = 20 min, and drawing of blood samples for glucose and insulin at $t = -5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100$, and 180 min. Plasma glucose levels were measured by the glucose dehydrogenase method (Hemocue Analyzer; Hemocue Inc., Cypress, CA). Plasma insulin levels were measured by radioimmunoassay (LINCO, St. Charles, MO). The MINMOD Millenium software program (14) was used to estimate indices of glucose and insulin dynamics from the FSIGT.

Calculated insulin sensitivity and secretion parameters

A. OGTT.

1. Homeostasis model assessment of IR (HOMA-IR) is a validated measure of insulin sensitivity (15):

$$\text{HOMA-IR} = [\text{fasting plasma insulin } (\mu\text{IU/mol}) \times \text{fasting plasma glucose (mmol/L)}]/22.5$$

2. Insulinogenic index (IGI) is a measure of insulin secretion that has been validated in children against the hyperglycemic clamp (16):

$$\text{IGI} = [\text{30-min insulin} - \text{FPI } (\mu\text{IU/mL})]/[\text{30-min glucose} - \text{FPG (mg/dL)}]$$

3. Whole-body insulin sensitivity index (WBISI) is an insulin sensitivity measure that has been validated in obese children and adolescents (15):

$$\text{WBISI} = \frac{10{,}000}{\sqrt{(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})}}$$

Higher WBISI levels indicate greater insulin sensitivity.

B. FSIGT.

1. Acute insulin response to glucose (AIRg) is a parameter of early pancreatic response to glucose, calculated as the mean incremental plasma insulin concentration over baseline in the first 8 min of the FSIGT (14).
2. Sensitivity to insulin (S_I) is a parameter calculated from serial insulin and glucose values during the FSIGT (14).

Overnight polysomnography

Overnight polysomnography (PSG) was performed the night between the OGTT and FSIGT. Signals were recorded on a computerized system (Rembrandt; Rescare, Buffalo, NY). The following parameters were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2, and O2/A1); right and left electro-oculograms; submental electromyogram; tibial electromyogram; electrocardiogram; chest and abdominal wall motion by inductance plethysmography; oronasal pressure/airflow (nasal pressure cannula with oral thermistor bead; Pro-Tech, Woodinville, WA); end-tidal PCO_2, measured at the nose by infrared capnometry (Nellcor *N*-1000); arterial oxygen saturation (SaO_2) by pulse oximetry, and oximeter pulse waveform. Studies were reviewed by a single sleep Board-certified investigator (L.J.B.), who had no knowledge of subjects' metabolic status. Sleep architecture (N1, N2, N3, and REM sleep stages) and respiratory disturbances (including the apnea-hypopnea index [AHI], arousal index, and lowest oxyhemoglobin saturation [lowest SaO_2]) were scored using standard pediatric criteria (17).

Statistical analysis

Statistical analysis was performed using SPSS Statistics 17.0 analysis software. Histograms and one-sample Kolmogorov-Smirnov tests were used to assess normality of distribution of continuous variables. Distributions of seriously skewed variables were normalized via logarithmic transformation. Pearson or Spearman correlations were used to examine associations between sleep architecture or OSA measures and parameters of glucose homeostasis and insulin secretion and sensitivity. Hierarchical linear regression procedures were used to evaluate the aforementioned relationships while controlling for potential confounding variables (e.g., degree of obesity and OSA). Covariate selection for the stepwise regression stages was guided by correlation analyses. Assumptions of linearity were tested by examining plots of

Table 1—*Subject characteristics*

Characteristic	Mean ± SD (range) or number (%)
Age (years)	14.4 ± 2.1 (8–17.5)
Sex	
Male	28 (45%)
Female	34 (55%)
Race	
White	23 (37.1%)
African American	34 (54.8%)
Asian American	1 (1.6%)
>1 race or other	4 (6.4%)
Ethnicity	
Hispanic	8 (17.7%)
Non-Hispanic	54 (82.3%)
Tanner stage (breast or genitalia)	
Tanner 2	5 (8.1%)
Tanner 3	12 (19.4%)
Tanner 4	14 (22.6%)
Tanner 5	31 (50%)
BMI (kg/m^2)	36.76 ± 6.82 (26.84–56.33)
BMI *z* score	2.37 ± 0.38 (1.53–3.21)

Table 2—*Glucose tolerance testing and PSG results*

Characteristic	Mean ± SD (range)
Insulin and glucose measures	
Fasting plasma glucose (mg/dL)	92 ± 10 (74–130)
Fasting plasma insulin (μIU/mL)	26.7 ± 16.1 (6.6–66)
2-h plasma glucose (mg/dL)	130 ± 31 (90–237)
2-h plasma insulin (μIU/mL)	194.4 ± 250.6 (6.5–1,541.5)
HbA_{1c} (%)	5.4 ± 0.4 (4.6–6.4)
HOMA-IR	6.1 ± 4.0 (1.4–17.6)
IGI	3.89 ± 3.08 (0.38–12.32)
AIRg	1,787.48 ± 1,635.72 (30.33–7,433.40)
WBISI	2.54 ± 1.57 (0.42–7.37)
S_I	2.01 ± 1.39 (0.031–6.29)
Sleep architecture and OSA measures	
Sleep latency (minutes)	20.9 ± 18.7 (0.5–91.0)
TST (minutes)	424.6 ± 57.8 (291.5–552)
%TST in N1 (%)	9.2 ± 5.7 (1.5–32.4)
%TST in N2 (%)	49.2 ± 7.2 (31.2–62.5)
%TST in N3 (%)	21.2 ± 4.9 (10.4–32.5)
%TST in REM (%)	20.3 ± 5.2 (8.4–31.3)
AHI	4.7 ± 10.7 (0.0–68.5)
Distribution	
AHI <5	*N* = 49
AHI 5–10	*N* = 7
AHI >10	*N* = 6
Arousal index (%)	14.8 ± 9.7 (6.8–72.4)
Lowest SaO_2 (%)	92 ± 4 (82–100)

Sleep architecture (durations are given in minutes; percentages are denoted as %). %TST in N = percentage of total sleep time spent in a given sleep stage (e.g., %TST in N1 = % total sleep time in N1).

the standardized residuals as a function of standardized predicted values. Where curve estimation procedures uncovered curvilinear relationships, polynomial regressions were conducted. Analysis of covariance (ANCOVA) models were used to examine differences in the outcome variables between sexes and among different pubertal stages, controlling for covariates. As we tested three underlying hypotheses relating to the relationship between sleep architecture and insulin secretion and sensitivity and overall glycemia, we used an adjusted *P* value of <0.017 (0.05/3) for statistical significance.

RESULTS

Study subjects

Seventy obese adolescents were screened for participation; seven cancelled prior to the study date and one did not undergo PSG, leaving 62 participants for analysis. Baseline subject characteristics are presented in Table 1. Insulin and glucose values, calculated indices, and PSG results are presented in Table 2.

Sleep and glucose homeostasis

Total sleep time (TST) was significantly or near-significantly associated with both short- and long-term measures of glucose homeostasis (Table 3). Curve estimation modeling and regression statistics showed that these relationships were U shaped (quadratic) (Fig. 1*A–C*). There was no association between any measure of OSA and measures of glucose homeostasis (Supplementary Table 1).

On regression analysis, TST was the most significant predictor of glucose homeostasis measures. Individual sleep stages, pubertal stage, and sex were not significant predictors of any glucose homeostasis measure; BMI *z* score was a significant contributor, and Tanner stage was a marginal contributor, to the overall 2-h glucose model only (not to the overall fasting glucose or HbA_{1c} models). Sex did not contribute significantly to any glucose model.

For the overall regression models mentioned above, adjusted R^2 and *P* values were as follows: 0.201 ($P = 0.002$) for fasting glucose, 0.442 ($P < 0.0005$) for 2-h glucose, and 0.200 ($P = 0.002$) for HbA_{1c}.

Sleep and insulin secretory measures

N3 sleep, both total duration and the percentage of total sleep time in N3 (%TST in N3), correlated significantly or with marginal significance (*P* value between 0.017 and 0.05) with several insulin secretory measures (Table 4) in bivariate analysis. Curve estimation modeling uncovered a cubic relationship between N3 and AIRg ($r^2 = 0.286$; $P = 0.001$), with inflection points at approximately 65 and 98 min. OSA measures did not associate significantly with any measure of insulin secretion (Supplementary Table 2). A marginally significant negative association was seen between pubertal stage and both N3 duration ($r = -0.282$; $P = 0.028$) and %TST in N3 ($r = -0.252$; $P = 0.050$), but there was no association between pubertal stage and any of the insulin secretory measures examined, or between sex and insulin secretory measures.

Table 3—*Correlations of sleep architecture with measures of glucose homeostasis*

	TST	N1 duration‡	N1 (%TST)‡	N2 duration	N2 (%TST)	N3 duration	N3 (%TST)	REM duration	REM (%TST)
Fasting plasma glucose (mg/dL)	*−0.291**	0.129	0.195	−0.105	0.130	**−0.328†**	−0.160	**−0.305‖**	−0.233
Glu 1 h (mg/dL)	*−0.293**	−0.169	−0.082	−0.205	−0.009	−0.084	0.041	−0.106	0.000
Glu 2 h (mg/dL)‡	**−0.366†**	0.054	0.172	−0.236	0.086	**−0.313‖**	−0.103	−0.221	−0.071
HbA_{1c} (%)	**−0.357†**	0.146	0.225	−0.185	0.050	−0.235	−0.037	**−0.350†**	*−0.279**

All numbers represent correlation coefficients. Glu 1 h, glucose level 1 h after oral glucose ingestion on OGTT; Glu 2 h, glucose level 2 h after oral glucose ingestion on OGTT. Sleep durations are given in minutes (percentages are denoted as %). Numbers in boldface indicate significant association, and numbers in italics indicate near-significant association (*P* value between 0.017 and 0.05). *$P < 0.05$. ‡Spearman correlation analysis. †$P < 0.01$. ‖$P < 0.017$.

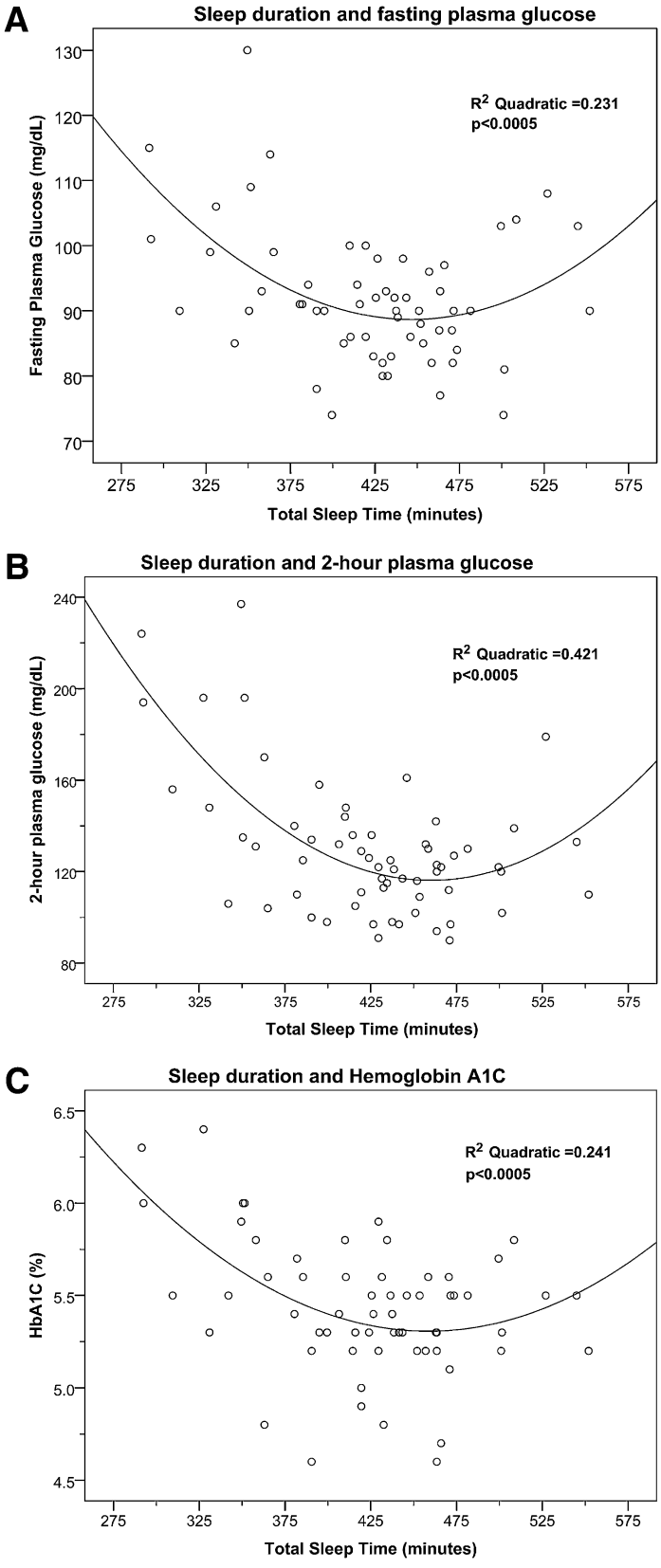

Figure 1—*Sleep duration and glucose homeostasis measures. A: Association between sleep duration and fasting plasma glucose levels on OGTT. B: Association between 2-h glucose level on OGTT and total sleep duration (minutes) that evening. C: Association between HbA_{1c} and total sleep duration (minutes) that evening. In all three panels, the U-shaped relationships suggest that a sleep duration of 420–510 min (7–8.5 h) is associated with optimal glucose homeostasis.*

N3 duration remained the strongest predictor of insulin secretory measures on stepwise regression analysis. Other sleep stages, TST, OSA measures, and sex were not significant predictors of insulin secretory measures in the final regression model. BMI *z* score contributed significantly to the AIRg final model but not to the IGI model, and pubertal stage contributed significantly to the final IGI model but not the AIRg model. Adjusted R^2 and *P* values for the overall models were 0.161 ($P = 0.002$) for IGI and 0.383 ($P < 0.0005$) for AIRg.

Sleep and insulin sensitivity

Correlation analysis showed a marginally significant negative association between N2 sleep and several insulin sensitivity measures (Table 4). A marginally significant negative correlation was seen between AHI and S_I ($r = -0.338$; $P = 0.025$; see Supplementary Table 3). Pubertal stage and sex did not associate significantly with any insulin sensitivity measure. However, on regression analysis, no strong associations were seen between sleep architecture or OSA and OGTT-derived insulin sensitivity measures. We found a marginal relationship between N2 duration and HOMA-IR (overall $R^2 = 0.088$; $P = 0.040$), and although the relationship between %TST in N2 and S_I was stronger, BMI *z* score (i.e., degree of obesity) was the strongest predictor in that model (overall model $R^2 = 0.400$; $P < 0.0005$).

CONCLUSIONS—In this multiethnic group of obese adolescents, we found strong relationships between sleep, hyperglycemia, and insulin secretion. Specifically, we found U-shaped relationships between total sleep duration and measures of both short- and long-term glycemia, and positive or cubic associations between N3 and insulin secretory measures, even after adjusting for potential confounders such as degree of obesity, OSA, sex, and pubertal stage. Our sleep duration data suggest that glucose metabolism is optimal when 7.5–8.5 h of sleep is achieved. This is consistent with adult data noting U-shaped associations between self-reported sleep duration and T2DM risk (5).

Adults with T2DM have also been reported to have shorter N3 duration than nondiabetic adults (18). Although one postulated mechanism suggests that N3 loss increases IR (19), our results instead demonstrated a relationship between N3 and insulin secretion. This relationship, which appeared to be a function of N3 itself rather than of total sleep duration,

Table 4—*Correlation of sleep architecture with measures of insulin secretion and sensitivity*

	TST	N1 duration (min)‡	N1 (%TST)‡	N2 duration (min)	N2 (%TST)	N3 duration (min)	N3 (%TST)	REM duration (min)	REM (%TST)
Sleep architecture and measures of insulin secretion									
1-h insulin (μIU/mL)‡	−0.063	−0.143	−0.116	−0.170	−0.201	*0.277**	*0.288**	0.055	0.110
2-h insulin (μIU/mL)‡	−0.039	−0.082	−0.034	−0.214	*−0.280**	0.246 (P = 0.058)	**0.348†**	0.046	0.107
IGI‡	0.179	−0.10	−0.042	0.007	−0.185	*0.288**	*0.265**	0.041	−0.060
AIRg‡	0.180	−0.117	−0.144	−0.104	−0.272 (P = 0.051)	**0.367†**	**0.375†**	0.137	0.081
Sleep architecture and measures of insulin sensitivity									
Fasting insulin (μIU/mL)‡	−0.005	0.115	0.137	*−0.267**	−0.235	0.130	0.172	0.055	0.077
HOMA-IR‡	−0.056	0.137	0.170	*−0.282**	−0.202	0.083	0.148	−0.008	0.021
WBISI	0.157	−0.101	−0.152	0.178	0.124	0.016	−0.096	0.094	0.054
S_I	0.139	−0.101	−0.139	*0.321**	*0.337**	−0.146	−0.213	−0.028	−0.070

Sleep architecture (durations are given in minutes; percentages are denoted as %). %TST in N = percentage of total sleep time spent in a given sleep stage. All numbers represent correlation coefficients. Numbers in boldface indicate significant association, and numbers in italics indicate near-significant association (P value between 0.017 and 0.05). ‡Spearman correlation analysis. *$P < 0.05$. †$P < 0.01$.

suggested that an absolute N3 duration of 1 h may be needed to achieve a stable amount of insulin secretion, and that increasing N3 might greatly improve insulin secretion. Our results may help explain the aforementioned association between N3 lack and T2DM, as a loss in first-phase insulin secretion is both an early marker of T2DM and part of its pathogenesis (20). Parasympathetic activity, which is increased in N3 sleep (21), stimulates glucose-induced insulin secretion (22); we speculate that increased parasympathetic activity may be responsible for our observed associations. Although growth hormone (GH) secretion occurs largely during the N3 sleep (23), GH is unlikely to be a factor in the associations, as GH increases insulin resistance (24) rather than insulin secretion. In addition, insulin-like growth factor-1 levels in our subjects did not correlate significantly with either sleep duration or any individual sleep stage, further corroborating that GH secretion is unlikely to explain the observed associations.

Finally, we found a positive association between N2 sleep and insulin sensitivity, with varying contribution from degree of obesity. Although N2 duration was also negatively associated with at least one marker of OSA, the AHI, indicating possible confounding, the AHI did not consistently associate with insulin sensitivity measures; thus, the observed association may represent an intrinsic relationship between N2 sleep and insulin sensitivity.

A night in the sleep laboratory does not necessarily reflect sleep at home, a possible limitation of our study. However, in our study, the OGTT *preceded* the PSG. Thus, any observed associations between sleep parameters and OGTT-derived measures could not have been short-term effects of a night in the laboratory. The association between TST and HbA_{1c}, which reflects long-term glycemia, also supported our findings. Also, families completed post-PSG surveys asking whether sleep in the laboratory was typical of home sleep. Only 32% indicated worse sleep in the laboratory; these subjects had no significant demographic, anthropometric, or glucose/insulin parameter differences compared with the remaining subjects, and of the sleep parameters, the only difference seen was a lower absolute REM duration in the "poorer sleep" group.

Our subjects' mean TST of 7.1 h was similar to the mean 7.2-h sleep duration reported in the 2006 National Sleep

Foundation adolescent poll (2). A recent study showed an association between short sleep on actigraphy and metabolic dysregulation in school-age children (25). Although home-based actigraphy studies could be useful, actigraphy is less precise and cannot discriminate between sleep stages.

In conclusion, we found significant relationships between sleep duration and sleep architecture and measures of glucose homeostasis and insulin secretion. To our knowledge, this is the first report of an association between N3 sleep and changes in β-cell function and of a U-shaped association between sleep duration and glucose levels in a pediatric population. We speculate that inadequate sleep duration and altered sleep architecture (relative suppression of N3 sleep) may play a role in T2DM development. Ensuring adequate sleep might reduce the risk of T2DM in at-risk obese adolescents.

Acknowledgments—This study was funded by the Pennsylvania State Tobacco Settlement Fund and Grant UL1-RR-24134 from the National Center for Research Resources (support for the University of Pennsylvania Clinical and Translational Research Center).

No potential conflicts of interest relevant to this article were reported.

D.K. and L.E.L.K. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. P.C.B. researched data, contributed to discussion, and reviewed and edited the manuscript. P.R.G. contributed to discussion, wrote the manuscript (statistician), and reviewed and edited the manuscript. R.I.B. contributed to discussion and reviewed and edited the manuscript. L.J.B. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript.

The authors would like to acknowledge the contributions of Carole Marcus (Division of Pediatric Pulmonary Medicine, The Children's Hospital of Philadelphia, and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania), Andrea Kelly (Division of Pediatric Endocrinology and Diabetes, The Children's Hospital of Philadelphia, and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania), and Diva D. De Leon-Crutchlow (Division of Pediatric Endocrinology and Diabetes, The Children's Hospital of Philadelphia, and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania).

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