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ORIGINAL ARTICLE

Cross-sectional and prospective associations between sleep regularity and metabolic health in the Hispanic Community Health Study/Study of Latinos

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Abstract

Study Objectives: Sleep is an emergent, multi-dimensional risk factor for diabetes. Sleep duration, timing, quality, and insomnia have been associated with diabetes risk and glycemic biomarkers, but the role of sleep regularity in the development of metabolic disorders is less clear.

Methods: We analyzed data from 2107 adults, aged 19–64 years, from the Sueño ancillary study of the Hispanic Community Health Study/Study of Latinos, followed over a mean of 5.7 years. Multivariable-adjusted complex survey regression methods were used to model cross-sectional and prospective associations between the sleep regularity index (SRI) in quartiles (Q1-least regular, Q4-most regular) and diabetes (either laboratory-confirmed or self-reported antidiabetic medication use), baseline levels of insulin resistance (HOMA-IR), beta-cell function (HOMA-β), hemoglobin A1c (HbA1c), and their changes over time.

Results: Cross-sectionally, lower SRI was associated with higher odds of diabetes (odds ratio $[OR]_{Q1\ vs.\ Q4} = 1.64$, 95% CI: 0.98–2.74, $OR_{Q2\ vs.\ Q4} = 1.12$, 95% CI: 0.70–1.81, $OR_{Q3\ vs.\ Q4} = 1.00$, 95% CI: 0.62–1.62, $p_{trend} = 0.023$). The SRI effect was more pronounced in older (aged ≥ 45 years) adults ($OR_{Q1\ vs.\ Q4} = 1.88$, 95% CI: 1.14–3.12, $p_{interaction} = 0.060$) compared to younger ones. No statistically significant associations were found between SRI and diabetes incidence, as well as baseline HOMA-IR, HOMA-β, and HbA1c values, or their changes over time among adults not taking antidiabetic medication.

Conclusions: Our results suggest that sleep regularity represents another sleep dimension relevant for diabetes risk. Further research is needed to elucidate the relative contribution of sleep regularity to metabolic dysregulation and pathophysiology.

Statement of Significance

Inadequate sleep duration, later sleep timing, and reduced sleep quality are associated with poorer metabolic health. To date, less attention has been paid to sleep regularity and its effect on metabolic health. We examined the cross-sectional and prospective association between sleep regularity index and measures of metabolic health in a large sample of Hispanics/Latinos, a group disproportionately burdened by diabetes and adverse health outcomes. Our results indicate lower levels of sleep regularity are associated with higher prevalence of diabetes, particularly in older adults (≥45 years). Cross-sectional findings regarding insulin resistance, beta-cell function, and glycemic control, as well as all prospective findings were negative. Future prospective studies in populations with repeated, longer-term sleep assessments are warranted.

Key words: sleep; sleep regularity; sleep regularity index; metabolic disease; diabetes; glycemic biomarkers; cross-sectional; prospective; Hispanics; Latinos

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Introduction

Metabolic diseases, including diabetes, are major causes of disability and death in the United States and worldwide [1–4]. They significantly reduce quality of life, and generate a large burden for public health care systems [2]. Sleep is an emergent, multi-dimensional risk factor for metabolic disorders [5, 6]. Different aspects of sleep, such as sleep duration [3, 7], timing [8–10], quality [11], and insomnia [12, 13] have been associated with risk of diabetes and glucose metabolism disorders (GMDs). Less attention has been devoted to examining the role of sleep regularity in the development of metabolic disorders.

Exposure to rotating shift work schedules, which results in irregular sleep schedules and circadian disruption [14], increases the risk of diabetes and GMDs, suggesting regular sleep schedules may be important for metabolic health [15, 16]. However, the generalizability of these findings beyond shift workers is unclear. Studies performed in recent years have also confirmed the association of irregular sleep schedules with increased risk of metabolic disorders and cardiovascular events in non-shift workers [17–23]. In the Multi-Ethnic Study of Atherosclerosis (MESA), for example, sleep irregularity has been found to be cross-sectionally associated with higher risk of obesity, hypertension, fasting glucose, hemoglobin A1C (HbA1c), diabetes status [19], and metabolic syndrome [21]. Prospective associations with cardiovascular disease [23] have been reported, too. Some of these results have been replicated in other studies, such as the Rush Memory and Aging Project [17] and the Study of Women's Health Across the Nation (SWAN) Sleep Study [18]. However, the majority of these studies were performed in elderly individuals (mean age ≥ 65 years), examined cross-sectional associations, and/or did not have physiological measurements of metabolic health, such as insulin resistance (IR), pancreatic beta-cell function, or long-term glycemic control. Furthermore, Hispanics/Latinos, as well as individuals with a lower socioeconomic status (SES), were underrepresented in all of the aforementioned studies. Since metabolic diseases are disproportionately prevalent in these individuals [24–26], further studies are warranted in these populations. Lastly, different metrics of sleep regularity, often derived from self-reports on habitual sleeping habits, have been used, such as standard deviation (*SD*) of sleep duration, *SD* of sleep onset, or inter-daily stability [27], complicating comparisons across studies.

In our study, we used the sleep regularity index (SRI), a recently developed measure to quantify the regularity of individuals' sleep schedules [28], whose association with cardiometabolic risk has, to our knowledge, been validated only in one study of older participants in the MESA cohort [19]. The SRI is computed as a rescaled likelihood that any two timepoints 24 hours apart correspond to the same sleep/wake state, across the entire observation period, and ranges from 0 (sleep and wake times at random) to 100 (perfectly regular). In contrast to other measures, the SRI has two desirable properties: (1) it is sensitive to how rapidly sleep patterns change between consecutive days (other metrics of sleep regularity, e.g. those quantifying variability across days, are invariant under permutation of days); and (2) its calculation is straightforward even in the presence of naps or if there are multiple sleep periods across a day [28]. Furthermore, sleep fragmentation, another important dimension of sleep, and shift work might weigh in more in the calculation of SRI (due to the epoch-to-epoch comparison across days) than in the calculation of *SD* of sleep duration, *SD* of sleep onset, or inter-daily stability.

The aim of this study was to examine the association of SRI with diabetes and GMDs, both cross-sectionally and prospectively. Specifically, we tested the hypothesis that a lower SRI is associated with higher risk of diabetes and GMDs, using actigraphy-measured sleep data of Hispanic/Latino participants of the Sueño ancillary study of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) [29, 30].

Methods

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

The HCHS/SOL is a community-based cohort study of 16 415 Hispanic/Latino adults aged 18 to 74 years recruited from four large US cities (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA). Households were selected with a stratified two-stage probability sampling design. Further details about design and cohort selection have been previously described [29]. A baseline clinic examination took place between 2008 and 2011 and included comprehensive biological, behavioral, and socio-demographic assessments [29, 30]. In addition, sleep apnea severity was assessed using a home monitoring system, as previously described [31]. An average of 6 years after the completion of the baseline examination (retention rate 81%) [32], the originally recruited individuals were invited to attend a re-examination (Visit 2, between 2014 and 2017), with similar assessments as at the baseline examination. At both visits, participants were asked to fast and refrain from smoking in the morning before the visit. Venous blood samples were collected, processed, and frozen on site. Thereafter, participants with a fasting glucose <150 mg/dL (measured by in-clinic glucose meter testing) and without a self-reported history of diabetes mellitus completed a 2-hour glucose tolerance test that entailed administration of a 75 g glucose load and collection of a 2-hour blood specimen. Samples were analyzed at the HCHS/SOL Central Laboratory. Plasma glucose was assayed with a hexokinase enzymatic method (Roche Diagnostics Corp, Indianapolis, IN). Glycated hemoglobin was measured in EDTA whole blood with a Tosoh G7 automated high-performance liquid chromatography analyzer (Tosoh Bioscience Inc, San Francisco, CA). Fasting insulin was measured with two commercial immunoassays (ELISA, Mercodia AB, Uppsala, Sweden; and sandwich immunoassay on a Roche Elecsys 2010 Analyzer, Roche Diagnostics, Indianapolis, IN). Measures conducted with the Mercodia and Roche assay methods were calibrated so that they could be combined. Homeostatic model assessment of insulin resistance (HOMA-IR) was computed as fasting glucose [mg/dL] × fasting insulin [mU/L] / 405; and HOMA of beta-cell function (HOMA-β) as 360 × fasting insulin [mU/L] / (fasting glucose [mg/dL] – 63) [33]. The presence of diabetes (binary indicator yes/no) was determined according to the American Diabetes Association criteria [34]: fasting glucose ≥126 mg/dL if fasting time was more than 8 hours and ≥200 mg/dL if fasting time was 8 hours or less; 2-hour post-load glucose (2-hour oral glucose tolerance test) ≥200 mg/dL; HbA1c ≥6.5%; and/or self-reported antidiabetic medication use over the last 4 weeks.

The Sueño Ancillary Study

The Sueño Ancillary Study recruited a subset of 2252 HCHS/SOL participants who were within 30 months of their baseline HCHS/SOL examination between December 2010 and December 2013. Eligible participants were aged 18 to 64 years, and had no diagnosis of narcolepsy, were not treated for sleep apnea and had an apnea–hypopnea index (AHI) < 50 events per hour at baseline. Further details of recruitment into the Sueño Ancillary Study have been previously published [35]. A flowchart of the study design, selection of participants and time intervals between baseline examination, Sueño visit, and Visit 2 are shown in Supplementary Figure S1.

All participants were asked to wear an Actiwatch Spectrum (Philips Respironics, Murrysville, PA) device on their non-dominant wrist continuously for 7 days, recording activity and light data in 30-second epochs, and to complete a daily sleep diary. A centralized reading center at Brigham and Women's Hospital, Boston, MA, scored all records. Rest periods were identified following a standardized protocol that made use of event markers, sleep diaries, light exposure, and activity levels [35]. Sleep-wake state for each 30-second epoch within each rest period was computed using the Actiware 5.59 scoring algorithm [36] with sleep onset defined based on five immobile minutes, zero immobile minutes for sleep offset, and a wake threshold of 40 counts.

The SRI was calculated according to the published formula [28] using 30-second epochs:

$$NMEP = \sum_{i=1}^{N-2880} (1 - m_i) * (1 - m_{i+2880})$$

$$PrMatch = \frac{1}{NMEP} \sum_{i=1}^{N-2880} \delta(s_i, s_{i+2880})$$

$$SRI = \left[-\frac{1}{2} + PrMatch \right] * 200$$

where N is the number of epochs, all 30 seconds apart, during the observation period, s_i indicates the sleep/wake state at epoch i (either asleep or awake), m_i indicates missing values (i.e. $m_i = 1$ if the value of s_i is missing, and 0 if s_i is not missing), and $\delta(x,y)$ is the Kronecker delta function, taking the value 1 if $x = y$ and x and y are non-missing, and 0 otherwise. The term *NMEP*, that is the number of pairs of epochs 24 hours apart (2880 epochs with a length of 30 seconds each sum up to 24 hours) where sleep/wake state is available for both elements, ensures that only epoch pairs with complete sleep/wake information are used for calculation of the SRI. *PrMatch* gives the probability (ranging from 0 to 1) that, across all days of the observation period, any two 30-second intervals 24 hours apart are the same sleep/wake state, which is ultimately rescaled to the range of −100 to 100 to give the SRI. The rescaling was done in accordance with the original publication about the SRI [28], and gives a more intuitive range, where a value of 0 represents sleep and wake times occurring at random, and a value of 100 a perfectly 24-hour periodic sleep-wake rhythm. Values below 0 are theoretically possible, yet very unlikely [28], and were not observed in our study.

Both the HCHS/SOL study and the Sueño ancillary study were approved by the institutional review boards of all participating institutions, and all participants provided informed consent.

Statistical analysis

Of the 2252 SOL participants of the Sueño ancillary study, 96 participants were excluded due to incomplete actigraphy data (i.e. <5 valid days, where a day was defined to be valid if there were (1) ≤4 hours of missing data and (2) ≤2 min of missing data during a main rest interval [35]). Furthermore, 32 participants with <5 overlapping days of actigraphy data for the calculation of the SRI, and 17 participants with incomplete information on outcome variables (diabetes, HOMA, HbA1c) were excluded, resulting in a final sample size of 2107. Of these, 1851 attended Visit 2 and were eligible for the prospective analyses (Supplementary Figure S1).

Throughout all analyses, sampling weights were used to account for the study design and probability of participating in the study, and normalizing to age and sex distributions of the target population (i.e. all non-institutionalized Hispanic/Latino adults aged 18–74 years residing in the four sampled areas) from the 2010 US Census. Importantly, the sampling weights for the cross-sectional analyses accounted for non-response at the baseline examination and the Sueño visit, while the sampling weights for the prospective analyses additionally accounted for Visit 2 non-response, thus ensuring that the target population remains unaltered for cross-sectional and prospective analyses. Normalized means and frequencies were calculated for baseline characteristics, stratified by unweighted quartiles of SRI (Q1—least regular SRI quartile, Q4—most regular SRI quartile), and compared across SRI quartiles using Satterthwaite adjusted Wald tests and Rao-Scott second-order correction chi-square tests [37], respectively. Odds ratios (OR) for the cross-sectional association of SRI with diabetes were calculated using complex survey logistic regression models. For the prospective association of SRI with diabetes incidence, incidence rate ratios (IRRs) were calculated among adults free of diabetes at baseline using complex survey Poisson regression models with robust standard errors. Cross-sectional differences in mean, and prospective differences in mean changes of HOMA variables and HbA1c across SRI quartiles were calculated using complex survey linear regression models. Baseline HOMA and HbA1c variables were also dichotomized (using the cut-off values of 4.03 (i.e. the 75th percentile of the HOMA-IR distribution in our analysis population) for HOMA-IR, 76.4 (i.e. the 25th percentile) for HOMA-β, and 48 mmol/mol (this is equivalent to 6.5%) for HbA1c). An additional set of dichotomized variables capturing both the presence of glycemic markers in the most extreme quartile or the intake of antidiabetic medication was calculated as well. These variables were analyzed according to the methods already described for the dichotomous outcome variable diabetes. *p*-values for linear trends using continuous SRI values were computed; for the calculation of *p*-values, HOMA-IR, HOMA-β, and HbA1c were log-transformed due to the skewness of these variables for the cross-sectional analyses, but used on the original scale for prospective analyses, since the distribution of changes from the baseline examination to Visit 2 roughly followed a normal distribution (as determined by visual inspection of the histograms). For the association between SRI and diabetes incidence, a post hoc test for a quadratic trend in this association was performed since the primary analysis showed that parameter estimates were highest in quartiles Q2 and Q3, and lower in quartiles Q1 and Q4. This was done by including the

Table 1. Baseline characteristics of the HCHS/SOL Sueño Ancillary Study population, by sleep regularity index (SRI) in quartiles

			SRI				
		Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P**
	N	2107	526	526	529	526	
	Mean (*SD*) of SRI	69.4 (10.8)	54.8 (9.0)	68.0 (2.2)	74.2 (1.5)	80.7 (2.8)	
	Range of SRI	2.4 to 92.4	2.4 to 63.8	63.8 to 71.5	71.5 to 77.0	77.0 to 92.4	
Age, years		40.7 (0.4)	37.9 (0.8)	39.8 (0.8)	42.7 (0.8)	44.0 (0.9)	**<.001**
Sex	Male	749 (48.9%)	58.4%	48.3%	44.2%	40.8%	**<.001**
	Female	1358 (51.1%)	41.6%	51.7%	55.8%	59.2%	
Body mass index†, kg/m^2		29.8 (0.2)	29.5 (0.4)	29.7 (0.4)	30.1 (0.4)	29.9 (0.4)	.777
Hispanic/Latino background	Central American	287 (5.9%)	5.3%	5.6%	6.7%	6.2%	**<.001**
	Cuban	379 (20.4%)	18.2%	22.1%	19.9%	22.0%	
	Dominican	262 (12.9%)	17.7%	12.9%	9.8%	9.4%	
	Mexican	563 (36.9%)	29.0%	33.4%	44.3%	44.5%	
	Puerto Rican	442 (20.2%)	26.8%	22.2%	15.7%	13.1%	
	South American	174 (3.7%)	2.9%	3.8%	3.7%	4.8%	
Study site	Bronx	532 (29.7%)	40.2%	32.1%	23.0%	18.7%	**<.001**
	Chicago	575 (16.5%)	16.3%	15.1%	14.5%	20.8%	
	Miami	653 (27.9%)	24.7%	29.4%	28.3%	30.2%	
	San Diego	347 (26.0%)	18.8%	23.5%	34.3%	30.3%	
Nativity	Lived in United States <10 years	540 (28.1%)	22.5%	33.4%	29.7%	28.0%	**<.001**
	Lived 10 to 20 years in United States	492 (22.1%)	16.9%	19.9%	28.5%	25.2%	
	Lived in United States ≥20 years, but not US born	724 (25.1%)	24.6%	23.3%	24.5%	28.6%	
	US-born	344 (24.7%)	36.0%	23.3%	17.3%	18.3%	
Educational level†	No high school diploma	672 (29.4%)	33.0%	24.2%	29.5%	30.8%	**.040**
	At most a high school diploma	551 (30.0%)	31.8%	32.3%	24.3%	30.8%	
	Greater than high school	881 (40.6%)	35.2%	43.5%	46.2%	38.3%	
Household income†	Less than $20 000	954 (47.5%)	52.2%	50.5%	44.6%	40.5%	.163
	$20 000 to $50 000	810 (41.9%)	39.6%	38.5%	44.0%	47.0%	
	More than $50 000	185 (10.6%)	8.2%	11.0%	11.4%	12.6%	
Work schedule†	Non-working or retired	876 (41.6%)	49.0%	43.0%	35.7%	35.6%	**<.001**
	Non-shift workers	795 (35.7%)	27.0%	33.8%	39.7%	46.3%	
	Shift workers	434 (22.7%)	24.0%	23.2%	24.5%	18.1%	
Physical activity‡		221.1 (2.3)	223.1 (4.5)	218.3 (4.5)	220.1 (4.2)	222.7 (3.9)	.834
Average sleep duration, hours		7.60 (0.04)	7.58 (0.07)	7.73 (0.08)	7.59 (0.06)	7.49 (0.05)	.107
Average sleep onset		0:13 (0:04)	0:50 (0:07)	0:15 (0:07)	23:51 (0:05)	23:42 (0:07)	**<.001**
Average midsleep point		4:05 (0:03)	4:46 (0:07)	4:11 (0:06)	3:39 (0:04)	3:27 (0:06)	**<.001**
SD of sleep duration, minutes		85.01 (1.28)	117.21 (2.71)	83.63 (2.04)	71.01 (1.92)	55.10 (1.32)	**<.001**
SD of sleep onset, minutes		68.61 (1.45)	104.37 (3.37)	64.62 (1.76)	51.92 (1.22)	39.93 (0.99)	**<.001**
Inter-daily stability†, %		75.59 (0.50)	61.90 (0.92)	76.44 (0.64)	81.96 (0.50)	88.00 (0.27)	**<.001**
Sleep Medication use†	Less than once per week	1805 (86.3%)	84.2%	83.4%	88.5%	90.5%	.176
	1 to 4 times per week	164 (7.1%)	7.8%	8.3%	6.3%	5.5%	
	More than 5 times per week	135 (6.6%)	8.0%	8.3%	5.2%	4.0%	
Apnea-hypopnea index†, events per hour	<15	1891 (92.6%)	92.4%	92.1%	92.6%	94.0%	.806
	≥15	183 (7.4%)	7.6%	7.9%	7.4%	6.0%	
Depressive symptoms†,§		7.2 (0.2)	8.2 (0.4)	7.2 (0.3)	6.9 (0.4)	6.1 (0.3)	**<.001**

Values are presented as mean (standard error) or absolute counts and percentages. Values (except absolute counts and summary statistics for SRI) are weighted for survey design and non-response and normalized to the age and sex distribution of the 2010 US Census. Significant *p*-values are marked in bold. Quartile 1—least regular SRI, Quartile 4—most regular SRI.

*Satterthwaite adjusted Wald tests for continuous variables, and Rao-Scott second-order correction Chi-Square tests for categorical variables.

†Number of missing values: 22 for body mass index, 3 for educational level, 158 for household income, 2 for work schedule, 363 for inter-daily stability, 3 for sleep medication use, 33 for apnea-hypopnea index, and 1 for depressive symptoms; the other variables are complete.

‡Physical activity given as the average activity counts per minute in 24-hour periods over all days from actigraphy.

§Depressive symptoms measured via the 10-item version of the Center for Epidemiological Studies Depression (CES-D10) questionnaire (scale: 0–30).

Table 2. Cross-sectional associations of sleep regularity index (SRI) quartiles with diabetes prevalence and glycemic biomarkers, Sueño Ancillary Study

		SRI				
		Quartile 1 (2.4–63.8)	Quartile 2 (63.8–71.5)	Quartile 3 (71.5–77.0)	Quartile 4 (77.0–92.4)	p_{trend}*
Overall (*N* = 2107)		**Diabetes**				
Prevalence, %		14.0%	10.5%	11.7%	12.9%	
OR (95% CI)	Model 1	1.70 (1.02 to 2.83)	1.08 (0.68 to 1.72)	0.97 (0.62 to 1.53)	1.00 (ref)	**.018**
	Model 2	1.56 (0.95 to 2.58)	1.10 (0.68 to 1.78)	0.99 (0.61 to 1.60)	1.00 (ref)	**.028**
	Model 3	1.64 (0.98 to 2.74)	1.12 (0.70 to 1.81)	1.00 (0.62 to 1.62)	1.00 (ref)	**.023**
	Model 4	1.61 (0.96 to 2.70)	1.05 (0.65 to 1.70)	0.94 (0.58 to 1.52)	1.00 (ref)	**.043**
Not on antidiabetic medication† at baseline (*N* = 1889)		**HOMA-IR**				
Mean (*SE*)		3.03 (0.16)	2.90 (0.13)	2.99 (0.15)	3.01 (0.16)	
Difference in mean (95% CI)	Model 1	0.06 (–0.40 to 0.53)	–0.08 (–0.48 to 0.31)	–0.01 (–0.45 to 0.42)	0.00 (ref)	.945
	Model 2	0.03 (–0.45 to 0.51)	–0.09 (–0.48 to 0.31)	–0.03 (–0.47 to 0.40)	0.00 (ref)	.814
	Model 3	0.08 (–0.40 to 0.57)	–0.05 (–0.45 to 0.35)	–0.03 (–0.46 to 0.41)	0.00 (ref)	.937
	Model 4	0.19 (–0.22 to 0.59)	–0.03 (–0.36 to 0.30)	–0.04 (–0.40 to 0.31)	0.00 (ref)	.874
Not on antidiabetic medication† at baseline (*N* = 1889)		**HOMA-β**				
Mean (*SE*)		162.10 (10.91)	163.94 (10.40)	150.77 (6.80)	144.33 (5.87)	
Difference in mean (95% CI)	Model 1	15.75 (–10.68 to 42.17)	17.06 (–5.30 to 39.41)	5.91 (–11.73 to 23.54)	0.00 (ref)	.957
	Model 2	14.05 (–11.18 to 39.27)	15.10 (–6.95 to 37.15)	4.59 (–12.71 to 21.90)	0.00 (ref)	.929
	Model 3	19.12 (–8.15 to 46.39)	18.98 (–4.18 to 42.14)	5.57 (–11.71 to 22.85)	0.00 (ref)	.924
	Model 4	23.32 (–2.94 to 49.59)	20.08 (–0.98 to 41.14)	4.85 (–9.47 to 19.17)	0.00 (ref)	.982
Not on antidiabetic medication† at baseline (*N* = 1889)		**HbA1c** [mmol/mol]				
Mean (*SE*)		36.34 (0.43)	35.81 (0.42)	36.37 (0.40)	36.97 (0.48)	
Difference in mean (95% CI)	Model 1	0.51 (–0.83 to 1.86)	–0.34 (–1.67 to 0.98)	–0.32 (–1.54 to 0.90)	0.00 (ref)	.297
	Model 2	0.70 (–0.66 to 2.07)	–0.11 (–1.36 to 1.13)	–0.16 (–1.34 to 1.01)	0.00 (ref)	.204
	Model 3	0.82 (–0.60 to 2.24)	–0.07 (–1.30 to 1.16)	–0.18 (–1.38 to 1.02)	0.00 (ref)	.156
	Model 4	0.87 (–0.51 to 2.25)	–0.10 (–1.29 to 1.10)	–0.23 (–1.39 to 0.94)	0.00 (ref)	.165

Means, standard errors (SEs) and percentages are weighted for survey design. Significant *p*-values are marked in bold. Quartile 1—least regular SRI, Quartile 4—most regular SRI. CI, confidence interval; OR, odds ratio; SE, standard error. Model 1: adjusted for age and sex. Model 2: adjusted for the covariates of Model 1, plus additionally Hispanic/Latino background, study site, work schedule, income, education, and depressive symptoms. Model 3: adjusted for the covariates of Model 2, plus additionally midsleep point, sleep duration, and sleep medication use. Model 4: adjusted for the covariates of Model 3, plus additionally body mass index, physical activity and apnea-hypopnea index.

*HOMA-IR, HOMA-β, and HbA1c were log-transformed for calculation of p_{trend}.

†Including 9 participants for whom information on self-reported antidiabetic medication use during the last 4 weeks was missing at the baseline examination.

quartile number (i.e. 1, 2, 3, 4) together with its square (i.e. 1, 4, 9, 16) as a numerical variable in the regression model, which was otherwise adjusted for the same variables as the main model. Since HOMA-IR, HOMA-β, and HbA1c are strongly affected by antidiabetic medication use, analyses regarding these parameters were restricted to participants who reported not to have taken antidiabetic medication during the last 4 weeks. If the question on antidiabetic medication was not answered (n = 9 participants at the baseline examination, and n = 26 for Visit 2), we assumed the participant not to have taken antidiabetic medications at the respective visit. All models were adjusted for different sets of covariates, with our primary model including age, sex, Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, or South American), study site, work schedule, income, education, depressive symptoms (measured via the 10-item version of the Center for Epidemiological Studies Depression (CES-D10) questionnaire [38, 39]), midsleep point, sleep duration, sleep medication use, and—for prospective analyses—follow-up time (i.e. time between baseline examination and Visit 2) (as an offset in the Poisson regressions). Levels of the categorical variables are shown in Table 1. In all regression models, the missing indicator method was used to accommodate for missing covariate values (proportions of missingness were low for all variables; numbers given in footnote of Table 1) and to guarantee consistent sample sizes across different analyses. We assessed for effect modification of obesity (body mass index [BMI] < 30 kg/m^2 vs. ≥ 30 kg/m^2), work schedule (non-working or retired vs. non-shift workers vs. shift workers), age (<45 years vs. ≥45 years), and sex, and computed *p*-values for interaction between SRI quartiles and the modifying variable using likelihood ratio tests. Furthermore, we performed a subgroup analysis restricting to participants without other prevalent diseases than possibly diabetes at baseline (i.e. free of self-reported coronary heart disease, stroke, cancer, and chronic kidney disease). Finally, we replaced SRI, our main exposure variable, by other actigraphy-derived measures of sleep irregularity, including *SD* of sleep duration, *SD* of sleep onset, and inter-daily stability. For definition and calculation details of the inter-daily stability we refer to HCHS/SOL publications where this index was previously used [40, 41]. *SD* of sleep duration has been previously used in HCHS/SOL as well [35, 42]. All statistical tests were two-sided at a significance level of 0.05. Analyses were conducted in R, version 3.5.1 [43], using the R package *survey*, version 3.34, for all complex survey procedures.

Table 3. Associations of sleep regularity index (SRI) quartiles with diabetes prevalence and diabetes incidence stratified by obesity, employment, age group, sex, and among those without other prevalent diseases*, Sueño Ancillary Study

	SRI					
	Quartile 1 (2.4–63.8)	Quartile 2 (63.8–71.5)	Quartile 3 (71.5–77.0)	Quartile 4 (77.0–92.4)	p_{trend}	$p_{interaction}$ †
Diabetes prevalence	OR (95% CI)					
BMI < 30 kg/m² (*N* = 1177)	1.99 (0.90 to 4.38)	0.89 (0.42 to 1.87)	1.03 (0.53 to 2.01)	1.00 (ref)	.070	.486
BMI ≥ 30 kg/m² (*N* = 908)	1.29 (0.66 to 2.51)	1.32 (0.70 to 2.50)	0.92 (0.47 to 1.78)	1.00 (ref)	.290	
Non-working or retired (*N* = 876)	3.16 (1.56 to 6.40)	2.08 (1.04 to 4.17)	1.72 (0.90 to 3.28)	1.00 (ref)	**.001**	.273
Non-shift workers (*N* = 795)	0.77 (0.34 to 1.76)	0.63 (0.28 to 1.44)	0.56 (0.26 to 1.21)	1.00 (ref)	.517	
Shift workers (*N* = 434)	1.71 (0.49 to 5.98)	1.35 (0.45 to 4.03)	1.53 (0.47 to 4.97)	1.00 (ref)	.987	
<45 years (*N* = 731)	0.75 (0.26 to 2.15)	0.29 (0.09 to 0.92)	0.18 (0.05 to 0.71)	1.00 (ref)	.250	.060
≥45 years (*N* = 1376)	1.88 (1.14 to 3.12)	1.53 (0.97 to 2.42)	1.42 (0.90 to 2.26)	1.00 (ref)	**.031**	
Males (*N* = 749)	1.49 (0.64 to 3.44)	0.63 (0.26 to 1.52)	0.85 (0.34 to 2.14)	1.00 (ref)	.087	.187
Females (*N* = 1358)	1.64 (0.90 to 2.98)	1.75 (1.02 to 3.00)	1.09 (0.65 to 1.80)	1.00 (ref)	**.030**	
Without other prevalent diseases* (*N* = 1862)	1.90 (1.04 to 3.46)	1.13 (0.66 to 1.91)	0.98 (0.56 to 1.71)	1.00 (ref)	**.011**	
Diabetes incidence	IRR (95% CI)					
BMI < 30 kg/m² (*N* = 899)	1.33 (0.54 to 3.30)	2.38 (1.20 to 4.73)	1.30 (0.67 to 2.50)	1.00 (ref)	.067	.589
BMI ≥ 30 kg/m² (*N* = 618)	1.29 (0.62 to 2.65)	1.56 (0.66 to 3.71)	1.86 (0.88 to 3.95)	1.00 (ref)	.989	
Non-working or retired (*N* = 573)	1.42 (0.75 to 2.69)	1.37 (0.64 to 2.96)	1.50 (0.74 to 3.06)	1.00 (ref)	.182	.150
Non-shift workers (*N* = 629)	0.96 (0.32 to 2.90)	2.30 (1.03 to 5.14)	2.83 (1.36 to 5.89)	1.00 (ref)	.979	
Shift-workers (*N* = 328)	0.32 (0.09 to 1.16)	1.10 (0.18 to 6.67)	0.41 (0.09 to 1.89)	1.00 (ref)	.472	
<45 years (*N* = 555)	1.37 (0.36 to 5.29)	2.85 (0.64 to 12.70)	1.36 (0.35 to 5.30)	1.00 (ref)	.759	.799
≥45 years (*N* = 977)	1.33 (0.80 to 2.21)	1.69 (1.05 to 2.72)	1.42 (0.83 to 2.41)	1.00 (ref)	.057	
Males (*N* = 510)	1.93 (0.87 to 4.30)	2.47 (1.04 to 5.85)	1.18 (0.47 to 3.01)	1.00 (ref)	**.005**	.175
Females (*N* = 1022)	0.87 (0.40 to 1.90)	1.51 (0.78 to 2.90)	1.93 (1.07 to 3.46)	1.00 (ref)	.386	
Without other prevalent diseases* (*N* = 1379)	1.02 (0.52 to 1.97)	1.91 (1.09 to 3.33)	1.62 (0.94 to 2.81)	1.00 (ref)	.755	

All complex survey regression models are adjusted for age, sex, Hispanic/Latino background, study site, work schedule, income, education, depressive symptoms, midsleep point, sleep duration, sleep medication use, and, for the diabetes incidence analysis, follow-up time as an offset. Significant *p*-values are marked in bold. Quartile 1—least regular SRI, Quartile 4—most regular SRI. BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio.
*Prevalent diseases considered in this analysis were self-reported coronary heart disease, stroke, cancer, and chronic kidney disease.
†*p*-values for interaction from likelihood ratio tests.

Results

Table 1 presents weighted descriptive statistics of baseline characteristics, overall and stratified by SRI quartiles. The mean baseline age was 40.7 years, and mean baseline BMI was 29.8 kg/m². Baseline age, sex, Hispanic/Latino background, study site, nativity, educational level, work schedule, midsleep point, and depressive symptoms were significantly associated with SRI quartile. SRI values ranged from 2.4 to 92.4, with a median value of 71.5 (Q1 = 63.8, Q3 = 77.0).

In multivariable-adjusted, cross-sectional analyses with 352 prevalent diabetes cases, lower sleep regularity was significantly associated with higher diabetes odds ($OR_{Q1\ (least\ regular\ quartile)\ vs.\ Q4\ (most\ regular\ quartile)}$ = 1.64, 95% confidence interval [CI]: 0.98 to 2.74, $OR_{Q2\ vs.\ Q4}$ = 1.12, 95% CI: 0.70 to 1.81, $OR_{Q3\ vs.\ Q4}$ = 1.00, 95% CI: 0.62 to 1.62, p_{trend} = 0.023) (Table 2). There was a trend towards effect modification by age ($p_{interaction}$ = 0.060), with the SRI effect being more pronounced in older (aged ≥45 years) adults ($OR_{Q1\ vs.\ Q4}$ = 1.88, 95% CI: 1.14 to 3.12) than in younger (<45 years) adults ($OR_{Q1\ vs.\ Q4}$ = 0.75, 95% CI: 0.26 to 2.15). The association between SRI and diabetes was particularly marked for non-working or retired adults ($OR_{Q1\ vs.\ Q4}$ = 3.16, 95% CI: 1.56 to 6.40, $OR_{Q2\ vs.\ Q4}$ = 2.08, 95% CI: 1.04 to 4.17, $OR_{Q3\ vs.\ Q4}$ = 1.72, 95% CI: 0.90 to 3.28, p_{trend} = 0.001). However, the interaction term for work schedule was not statistically significant (*p* = 0.273) (Table 3).

No cross-sectional associations were found between SRI and baseline values of HOMA-IR (p_{trend} = 0.937), HOMA-β (p_{trend} = 0.924), and HbA1c (p_{trend} = 0.156) (Table 2) among individuals not currently taking antidiabetic medication. Associations were also not statistically significant between SRI and elevated HOMA-IR, reduced HOMA-β, and elevated HbA1c values as dichotomous variables among individuals not currently taking antidiabetic medication (Supplementary Table S1). Subgroup analyses did not reveal significant results, either, with the exception of the BMI < 30 kg/m² group, where baseline HbA1c values showed a significant negative association with SRI (adjusted mean $difference_{Q1\ vs.\ Q4}$ = 1.35 mmol/mol, 95% CI: 0.18 to 2.52, p_{trend} = 0.039). HbA1c values also showed a borderline significant negative association with SRI among non-working or retired adults (adjusted mean $difference_{Q1\ vs.\ Q4}$ = 2.03 mmol/mol, 95% CI: −0.23 to 4.29, p_{trend} = 0.051; Supplementary Table S2).

When combing antidiabetic medication use and elevated HbA1c into a single metric (i.e. elevated HbA1c or current antidiabetic medication use), there was a significant association with SRI ($OR_{Q1\ vs.\ Q4}$ = 1.57, 95% CI: 0.90 to 2.74, $OR_{Q2\ vs.\ Q4}$ = 1.18, 95% CI: 0.72 to 1.93, $OR_{Q3\ vs.\ Q4}$ = 0.93, 95% CI: 0.56 to 1.53, p_{trend} = 0.038). However, for the combinations HOMA-IR/antidiabetic medication use and HOMA-β/antidiabetic medication use, associations with SRI were not statistically significant (p_{trend} = 0.228 and p_{trend} = 0.258, respectively) (Supplementary Table S1).

In prospective analyses of 1532 participants with a mean follow-up time of 5.7 years and 164 incident diabetes cases (319

Table 4. Prospective associations of sleep regularity index (SRI) quartiles with diabetes incidence and changes in glycemic biomarkers, Sueño Ancillary Study

		SRI				
		Quartile 1 (2.4–63.8)	Quartile 2 (63.8–71.5)	Quartile 3 (71.5–77.0)	Quartile 4 (77.0–92.4)	p_{trend}*
Adults without prevalent diabetes (*N* = 1532)			**Diabetes**			
Cumulative incidence†, %		5.8%	7.5%	8.3%	6.5%	
IRR (95% CI)	Model 1	1.31 (0.75 to 2.28)	1.66 (0.94 to 2.91)	1.46 (0.90 to 2.39)	1.00 (ref)	.340
	Model 2	1.18 (0.69 to 2.02)	1.73 (1.03 to 2.92)	1.47 (0.88 to 2.44)	1.00 (ref)	.505
	Model 3	1.27 (0.74 to 2.18)	1.96 (1.17 to 3.29)	1.61 (0.97 to 2.67)	1.00 (ref)	.385
	Model 4	1.18 (0.70 to 1.97)	1.91 (1.14 to 3.21)	1.52 (0.92 to 2.52)	1.00 (ref)	.575
Not on antidiabetic medication‡ at baseline and Visit 2 (*N* = 1536)			**HOMA-IR**			
Mean change (*SE*) †		0.77 (0.26)	0.98 (0.21)	1.11 (0.16)	0.36 (0.16)	
Difference in mean change (95% CI)	Model 1	0.47 (–0.04 to 0.99)	0.63 (0.08 to 1.17)	0.73 (0.30 to 1.15)	0.00 (ref)	.290
	Model 2	0.39 (–0.11 to 0.88)	0.61 (0.11 to 1.10)	0.69 (0.28 to 1.09)	0.00 (ref)	.444
	Model 3	0.41 (–0.09 to 0.91)	0.65 (0.14 to 1.15)	0.68 (0.28 to 1.07)	0.00 (ref)	.440
	Model 4	0.48 (0.01 to 0.95)	0.67 (0.16 to 1.18)	0.68 (0.27 to 1.08)	0.00 (ref)	.547
Not on antidiabetic medication‡ at baseline and Visit 2 (*N* = 1536)			**HOMA-β**			
Mean change (*SE*) †		18.85 (13.26)	7.72 (8.96)	17.05 (6.18)	–3.76 (5.16)	
Difference in mean change (95% CI)	Model 1	26.27 (0.84 to 51.71)	14.90 (–3.17 to 32.96)	21.07 (6.50 to 35.64)	0.00 (ref)	.087
	Model 2	13.65 (–8.10 to 35.41)	6.33 (–10.55 to 23.20)	15.24 (0.84 to 29.64)	0.00 (ref)	.673
	Model 3	15.42 (–9.00 to 39.84)	7.10 (–9.59 to 23.80)	13.76 (–1.21 to 28.73)	0.00 (ref)	.535
	Model 4	18.18 (–4.80 to 41.16)	9.65 (–7.29 to 26.58)	14.22 (–1.14 to 29.58)	0.00 (ref)	.632
Not on antidiabetic medication‡ at baseline and Visit 2 (*N* = 1536)			**HbA1c** (mmol/mol)			
Mean change (*SE*) †		1.24 (0.25)	1.36 (0.22)	2.27 (0.25)	1.79 (0.25)	
Difference in mean change (95% CI)	Model 1	–0.32 (–1.07 to 0.43)	–0.26 (–0.91 to 0.39)	0.53 (–0.15 to 1.21)	0.00 (ref)	.888
	Model 2	–0.27 (–1.04 to 0.50)	–0.22 (–0.89 to 0.46)	0.56 (–0.12 to 1.24)	0.00 (ref)	.992
	Model 3	–0.27 (–1.05 to 0.51)	–0.18 (–0.84 to 0.48)	0.59 (–0.08 to 1.25)	0.00 (ref)	.960
	Model 4	–0.27 (–1.04 to 0.50)	–0.16 (–0.82 to 0.51)	0.60 (–0.06 to 1.27)	0.00 (ref)	.827

Means, standard errors (*SE*s) and percentages are weighted for survey design. Quartile 1—least regular SRI, Quartile 4—most regular SRI. CI, confidence interval; IRR, incidence rate ratio. Model 1: adjusted for age and sex. Model 2: adjusted for the covariates of Model 1, plus additionally Hispanic/Latino background, study site, work schedule, income, education, depressive symptoms, and follow-up time (as an offset in the Poisson regressions). Model 3: adjusted for the covariates of Model 2, plus additionally midsleep point, sleep duration, and sleep medication use. Model 4: adjusted for the covariates of Model 3, plus additionally body mass index, physical activity, and apnea-hypopnea index.

*HOMA-IR, HOMA-β, and HbA1c were used on the original scale for calculation of p_{trend}.

†During a mean follow-up time of 5.7 years.

‡Including 30 participants for whom information on self-reported antidiabetic medication use during the last 4 weeks was missing either at the baseline examination or at Visit 2.

participants were excluded because of prevalent diabetes), we did not observe a linear relationship between lower SRI and higher diabetes incidence. Diabetes incidence rates were numerically higher for SRI middle quartiles Q2 ($IRR_{Q2\ vs.\ Q4}$ = 1.96, 95% CI: 1.17 to 3.29) and Q3 ($IRR_{Q3\ vs.\ Q4}$ = 1.61, 95% CI: 0.97 to 2.67) compared to the most regular SRI quartile (Q4) and the least regular SRI quartile (Q1; $IRR_{Q1\ vs.\ Q4}$ = 1.27, 95% CI: 0.74 to 2.18) (Table 4). However, testing for a quadratic trend in this association gave a non-significant result ($p_{quadratic\ trend}$ = 0.193). In *post hoc* subgroup analyses, the majority of the IRRs were >1 as compared to the reference group Q4; however, 95% CIs were generally wide (Table 3).

Among individuals not taking antidiabetic medication at either baseline or Visit 2 (1536 out of 1851 participants who were eligible for the prospective analyses), no statistically significant associations were found between SRI and changes (from baseline examination to Visit 2) in HOMA-IR, HOMA-β, and HbA1c, either overall (Table 4), or in subgroups (Supplementary Table S3).

When analyzing our data with *SD* of sleep duration (Supplementary Table S4), *SD* of sleep onset (Supplementary Table S5), and inter-daily stability (Supplementary Table S6) as the exposure (instead of our main exposure SRI), we did not see the cross-sectional associations with diabetes which we had seen for SRI (p_{trend} = 0.894 for *SD* of sleep duration, p_{trend} = 0.434 for *SD* of sleep onset, and p_{trend} = 0.186 for inter-daily stability), and there were also no associations with HOMA-IR, HOMA-β, and HbA1c.

Discussion

In this prospective study of US Hispanic/Latino individuals with objective, actigraphy assessed sleep data, lower SRI, a measure of individual sleep regularity, was associated with an increased likelihood of prevalent diabetes, particularly in older adults. Diabetes incidence rates were lowest among individuals with highly regular sleep; however, the association was not statistically significant. Results regarding glycemic biomarkers (HOMA-IR, HOMA-β, HbA1c) were negative.

Our cross-sectional results are in line with the few prior reports of sleep regularity being associated with diabetes status [17–19, 21] in the general population as well as studies in shiftworkers [15, 44], with stronger associations present in older individuals. Metrics used to capture sleep regularity were inconsistent across previous studies, comprising the *SD* of sleep duration, *SD* of sleep

onset, and inter-daily stability [27]. Comparing *SD* of sleep duration, *SD* of sleep onset, and inter-daily stability (as derived from the actigraphy data) with the SRI in our 2107 participants, we saw high correlations (Pearson correlation coefficients were $\rho = -0.64$, $\rho = -0.66$, and $\rho = 0.83$, respectively). Unlike in our SRI analyses, we did not observe cross-sectional associations between these alternative measures of sleep irregularity. These findings are in line with studies of hypertension as an outcome in the MESA cohort, where lower SRI, but not higher *SD* of sleep duration or higher *SD* of sleep onset, were associated with increased risk of hypertension [19, 21, 22]. In general, estimated differences across quartiles were more alike between SRI and inter-daily stability, than with *SD* of sleep duration/sleep onset, which is not surprising as SRI and inter-daily stability correlated the strongest ($\rho = 0.83$). A possible explanation for the differences in results might be that, in contrast to other more global measures of regularity and variability such as *SD*s, the SRI captures regularity on a 24-hour timescale, since it always compares the sleep/wake state of two epochs exactly 24 hours apart, rather than comparing each individual day to an average day. It is thus more sensitive to for example sleep fragmentation and effects of shift work on sleep.

We did not see the expected cross-sectional associations of SRI with glycemic biomarkers. There might be several explanations for this. First, diabetes and glycemic biomarkers were assessed up to 30 months (median 27 months) prior to the time of actigraphy. Because SRI is hypothesized to precede the development of adverse health effects, this could have led to an underestimation of the magnitude of the association. Secondly, in our study population, the prevalence of overweight (36.3%) and obesity (41.8%), as well as other comorbidities, was high. BMI is a strong predictor of diabetes and related glycemic biomarkers [45], and could therefore mask and/or modify effects of SRI on these glycemic biomarkers. It is conceivable that obesity, as one of the most potent predictors of diabetes, overrules the comparatively small effects of sleep irregularity on diabetes and glycemic biomarkers, so that its full effect would be easier to detect in the absence of obesity. Thirdly, HOMA-IR, HOMA-β, and HbA1c are strongly affected by the application of antidiabetic medication. Since we did not have detailed information about antidiabetic medication to adequately control for, we decided to exclude participants on antidiabetic medication from these analyses. However, this might introduce collider stratification bias, because the excluded participants are exactly those who would have observed the worst outcomes had they not been taking the medication. This probably biased the tested associations towards the null. Indeed, in analyses where we avoided the exclusion of participants on antidiabetic medication by creating a dichotomous variables indicating either a glycemic biomarker value in the most extreme quartile or the intake of antidiabetic medication, and testing their associations with SRI (Supplementary Table S1), we generally saw slight increases in estimates away from the null effect, as compared to our original analyses. For the combination of elevated HbA1c values and/or intake of antidiabetic medication, the association with SRI even became statistically significant. Considering that an HbA1c value ≥ 6.5% is one of four qualifying criteria in our definition of diabetes and that SRI and prevalent diabetes were shown to be associated in our analyses, this result makes sense. Lastly, we did not have information on past sleep habits, nor did we have continuous or repeated measures of SRI. Instead, SRI was determined at a single point in time, about 5 years prior to the second metabolic assessment, over the period of only 7 days, which is likely to be too short to give a representative picture of the long-term sleeping behavior. The effect of sleep on health outcomes is cumulative, and our approach likely introduces variability, and thus underestimates the true effects.

Our prospective analyses yielded nonsignificant results about the relationship between SRI, diabetes, and glycemic biomarkers. The only two studies which, to our knowledge, tried to elucidate similar research questions to date [18, 21] found evidence of prospective associations between sleep regularity and metabolic health. However, the study populations—only non-shift working women in one study [18], and an elderly cohort in the other [21]—were distinctly different from our cohort. The HCHS/SOL Sueño Ancillary study is the first study investigating the relationship of sleep regularity in Hispanic/Latino individuals and it has a higher prevalence of low income and low SES, a higher proportion of unemployment and shift work, and a higher prevalence of comorbidities, obesity, and other risk factors. One explanation why we found a relationship between SRI and diabetes in prevalence but not incidence analyses is reverse causation. Diabetes might be causing sleep irregularity by fragmenting sleep through nocturia [46], neuropathic pain [47], or fatigue causing napping [48]. Alternatively, considering that the presence of risk factors such as overweight, obesity, and unfavorable sleep habits may accelerate the development of diabetes, it is possible that in the group with the lowest SRI, more individuals may already have developed the disease at baseline then in the groups with higher SRI (in fact, in our population, diabetes prevalence is highest with 14.0% in the lowest SRI group; see Table 2). This may leave a selected group of individuals for incidence analysis, possibly also explaining why, in our analyses, diabetes incidence rates were numerically smaller in the least regular SRI quartile compared to the SRI middle quartiles Q2 and Q3. It is conceivable that, in a younger, healthier population, prospective associations of SRI with glycemic biomarkers might be more clear-cut with a more linear dose-response curve. Moreover, 5 to 7 days of actigraphy measured at one single point in time does not capture long-term trajectories and changes in sleeping behavior over time, likely leading to an underestimation of the true effects of long-term sleep irregularity on metabolic health. Finally, sample sizes are smaller in incidence than prevalence analyses, possibly leading to insufficient power to detect effects, especially in the case of diabetes, where the cumulative incidence was only 7%. Lastly, when interpreting our findings, it has to be considered that blood samples were obtained at a single time point, and were not taken with respect to endogenous circadian phase, although it is known that there is diurnal variation in glucose and insulin [49, 50]. Since circadian phase might also systematically vary across SRI groups, this might be another source of bias.

We also investigated the possibility of differential effects of SRI on diabetes and glycemic markers based on age, work schedule, sex, and BMI. Although the interaction terms did not reach statistical significance in our models, we think a further discussion of potential subgroup differences may be warranted; we might have been limited by insufficient sample size to detect statistically significant effects. Indeed, our results show a trend towards a stronger effect of SRI in older (aged ≥ 45 years), as compared to younger (aged < 45 years) adults ($p = 0.060$), which is in line with the existing literature where the observed effects were, in general, more pronounced in older cohorts [17–19, 21].

For other dimensions of sleep, such as sleep timing, similar age effects have already been reported [10]. Older individuals might be more susceptible to the adverse effects of irregular sleep, but it is also conceivable that the effects of irregular sleep accumulate over the lifetime and are thus more pronounced in older adults. The observation that the SRI effect on diabetes was more pronounced in non-working or retired adults in our cohort might be attributable to their higher age compared to working adults, which might be the reason why the interaction term from the full model, which was also adjusted for age was not statistically significant. Another phenomenon that could explain this observation—at least in part—is a healthy worker effect [51]. The healthy worker effect stipulates that unhealthy individuals are more likely to have dropped out of the workforce. These unhealthier individuals might be more susceptible to the negative effects of irregular sleep than their healthy, working counterparts. The potential effect modification of SRI on diabetes by sex is less clear. However, there are a couple of independent studies showing that the effects of various sleep metrics on health outcomes might be more pronounced in women compared to men (e.g. sleep maintenance efficiency and HbA1c concentrations [20]; sleep duration and sleep continuity with bodyweight and distribution of body fat [52]). In our analyses, in line with these reports, we found significant effects of SRI on reduced beta-cell function and higher levels of glycated hemoglobin when also including antidiabetic medication use in our analysis for women, but not for men (Supplementary Table S2), although the *p*-value for interaction was nonsignificant. These potential sex differences require further investigation. Finally, more pronounced associations between SRI and diabetes risk in participants with lower BMI have been reported previously in a similar context to ours, as for example, in the case of the association of inter-daily stability with metabolic syndrome [17]. Indeed, although not statistically significant, effect estimates of SRI on prevalent diabetes risk are numerically higher for non-obese ($OR_{Q1\ vs.\ Q4}$ = 1.99, 95% CI: 0.90 to 4.38) than for obese adults ($OR_{Q1\ vs.\ Q4}$ = 1.29, 95% CI: 0.66 to 2.51) in our cohort. A possible explanation why a lower BMI increases the adverse effects of irregular sleep might be that obesity as one of the most potent predictors of diabetes [53] overrules the effect of sleep irregularity which is comparatively small in relation to obesity. However, additional experimental work is needed to clarify whether this is indeed the case, and to gain more insights into the underlying mechanisms. Together, if true, this body of evidence would suggest that individuals with the lowest BMI, the elderly and female may benefit the most from interventions to improve the regularity of sleep.The biological mechanisms underlying the relationship between sleep regularity and glycemic health are not fully understood [54]. Sleep habits probably affect diabetes and glycemic biomarkers in different ways, by triggering changes to hormones, contributing to weight gain and obesity, and causing changes to behavior and lifestyle [55, 56]. Irregular sleeping behavior leads to variable exposure to light cues [19, 28], and thus inconsistent circadian signaling, which can ultimately lead to misalignment among circadian clocks in multiple peripheral tissues related to glucose metabolism [18, 57]. Downstream, this could result in mistimed and/or attenuated rhythms in circadian-regulated hormones, such as melatonin, cortisol, leptin, and ghrelin [54, 55]. These hormones also have important roles in maintaining metabolic health, which might be impaired by circadian disruption [55]. Melatonin rhythms modulate insulin secretion, glucose homeostasis [58–61], and cortisol, which can make cells more resistant to insulin [62], promoting the development of diabetes. At the behavioral level, less regular sleep may further result in irregularities in eating frequencies, meal timing, and higher caloric intake, which have been associated with weight gain and diabetes risk [56, 63–65]. Physical activity could also play a role in explaining the association between sleep irregularity and metabolic outcomes [66], although in analyses adjusted for physical activity results did not substantially change (model 4 in our tables). However, direct mechanistic evidence of most of these effects is scarce in the concrete context of sleep regularity, and more studies are needed to elucidate these relationships and the interrelationships and effect modification between different pathways. This is an especially important question, since sleep irregularity and the behavioral consequences are modifiable and could therefore present a novel target for interventions to promote metabolic health.

A limitation of our study is that it did not differentiate between type 1 or type 2 diabetes, and that information on antidiabetic medication is self-reported and only available for the last 4 weeks. However, given the age structure of our cohort (age range 19 to 64 years), with only 1.3% of those younger than 30 years having diabetes at the baseline examination, one can surmise that the overwhelming percentage of participants with diabetes in the HCHS/SOL have type 2 diabetes [26].

In summary, our study provides information regarding sleep regularity and diabetes-related outcomes in a population of Hispanics/Latinos, with higher prevalence of low SES, unemployment, shift work, and comorbidities as compared to the general population, limiting the generalizability of our findings. Our results suggest that sleep regularity represents another dimension of sleep relevant for diabetes risk and potentially glycemic biomarkers HOMA-IR, HOMA-β, and HbA1c. Further research is warranted to elucidate the relative contribution of sleep regularity to metabolic dysregulation and pathophysiology, in particular since sleep regularity is, like other dimensions of sleep, a modifiable behavioral factor, and targeted interventions to optimize the sleep-wake cycle might help in preventing and/or managing diabetes and metabolic disorders.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Data accessibility

The study website http://www.cscc.unc.edu/hchs/ provides detailed information on data accessibility.

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