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Original Article

ORIGINAL ARTICLE

Habitual late sleep initiation is associated with increased incidence of type 2 diabetes mellitus in Korean adults: the Korean Genome and Epidemiology Study

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Abstract

Study Objectives: Although sleep duration and quality were significant risk factors of type 2 diabetes (T2D), the impact of sleep initiation time on the development of T2D has not been studied in large longitudinal studies.
Methods: A total of 3689 participants without diabetes aged 40–69 years at baseline were enrolled from the Korean Genome and Epidemiology Study and followed up for 12 years. Participants were categorized based on habitual sleep initiation time by questionnaire as follows: 20:00–22:59 (early sleepers, ES, n = 766), 23:00–00:59 (usual sleepers, US, n = 2407), and 1:00–5:59 (late sleepers, LS, n = 516). Incident T2D was identified biennially by fasting plasma glucose or 2-hour glucose after 75-g oral glucose loading or use of anti-diabetes medication.
Results: During follow-up, 820 cases of T2D were documented and the LS group showed the highest increase in insulin resistance. Hazard ratio (HR) (95% confidence interval) for T2D of LS compared to ES was 1.34 (1.04–1.74) after adjustment for covariates including sleep duration. The impact of late sleep on the development of T2D was more evident in older individuals (≥65 years at baseline) (HR = 4.24 [1.42–12.68] in older LS vs. older ES, HR = 1.27 [1.00–1.62] in younger LS vs. younger ES, $p_{interaction}$ = 0.002). In addition, LS with low insulin secretion and sensitivity showed an approximately fivefold increased risk for T2D compared to ES with high insulin secretion and sensitivity.
Conclusions/Interpretation: Habitual late sleep initiation is a significant risk factor for T2D in Koreans, especially in people with lower insulin sensitivity, lower β-cell function, and older age.

Statement of Significance

Sleep disorders are significant nontraditional risk factors for type 2 diabetes (T2D); however, previous studies have concentrated on the effects of sleep quantity and quality, and shift work on the risk of T2D and metabolic disturbances. This is the first prospective cohort study to examine the longitudinal effects of habitual sleep initiation time on the incidence of T2D independent of sleep duration, sleep quality, and unhealthy lifestyle. This study showed habitual late sleep is a significant risk factor for T2D independent of sleep duration in Koreans. Notably, this association is particularly strong in participants with lower insulin sensitivity, lower β-cell function, and older age. Further research is warranted to investigate whether behavioral intervention of sleep timing in high-risk individuals is effective to prevent T2D.

Key words: sleep; type 2 diabetes; insulin resistance

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Introduction

People usually spend a third of their lifetime sleeping. In modern society, however, bedtime is often curtailed by increasing social demands and the median sleep time in adults has gradually decreased from 8 to 7 hours per night over the past four decades [1]. Sleep restriction is a predictive factor for the development of type 2 diabetes (T2D) and obesity [2–4]. Sleep quality such as difficulty in initiating and maintaining sleep and sleep apnea also has a detrimental effect on T2D [2, 5], obesity, and metabolic syndrome [6]. Thus, sleep disorder is regarded as an emerging risk factor for various metabolic diseases.

Sleep timing is another aspect of sleep characteristic which is determined by endogenous circadian rhythm, affecting the sleep-wake cycle and energy metabolism, and also by environmental influences. Although later chronotype was significantly associated with worse metabolic features than earlier chronotype [7, 8], sleep timing in weekdays represents more than chronotype. It reflects an actual sleep pattern compromised by the individual's chronotype and lifestyle regardless of sleep duration and quality. It has been reported that people with later sleep time have less healthy dietary habits [9]. A recent study in a cohort of middle-aged women reported that bedtime delay was associated with a greater increase of homeostasis model assessment of insulin resistance index (HOMA-IR) over 5 years of follow-up; however, the authors could not examine the development of diabetes due to the small number of participants [10]. Another recent study with Hispanic/Latino adults found that later sleep timing was associated with higher estimated insulin resistance across individuals with and without diabetes, with this association being especially pronounced in the elderly group [11].

Until now, most studies have concentrated on the effects of sleep quantity and quality, and the impact of shift work, which is a chronic extreme circadian misalignment [12, 13]. To our knowledge, there have been no prospective studies examining the impact of more moderate shifts in sleep timing on the development of T2D. Therefore, this study aimed to examine the effect of sleep initiation time, independent of sleep duration and lifestyle, on the incidence of T2D in a longitudinal population-based cohort.

Methods

Study participants

All study participants were from the Ansan cohort of the Korean Genome Epidemiology Study (KoGES), an ongoing population-based, prospective cohort study that began in 2001. Details of KoGES and sampling method have been provided in previous reports [14]. Briefly, the cohort consisted of 5020 participants aged 40–69 years at baseline who were followed up biennially with a scheduled site visit for similar interviews, comprehensive health examination and collection procedures of biospecimens for assays at study site [15]. In particular, participants completed an interview-based questionnaire for demographic information, medical histories, health conditions, family disease history, lifestyles including smoking and alcohol drinking, dietary intakes and sleep habit. Of these 5020 participants, those who had diabetes at baseline examination (n = 578), missing information of diabetes (n = 20), sleep habit (n = 21), body mass index (BMI) or waist circumference (n = 8) at baseline, missing information or outliers of insulinogenic index (n = 122), and current shift workers (n = 50) were excluded. Also, among the participants who underwent a baseline examination, those who did not have at least one follow-up examination before 2014 (n = 532) were excluded. Finally, a total of 3689 participants were enrolled in this study, and were followed up biennially until 2014 or the development of T2D (Supplementary Figure S1). All participants participated in the study voluntarily, and informed consent was obtained in all cases. The study protocol was approved by the Ethics Committee of the Korean Health and Genomic Study of the Korea National Institute of Health.

Sleep measurements

Information on habitual sleep initiation time (HSIT), sleep duration and the presence of sleep apnea was taken from responses to the following questions: (1) "*What time do you usually go to sleep on an average week day?*" (HSIT), (2) "*How many hours did you usually sleep during the last month?*" (sleep duration) and (3) "*Has anyone who sleeps with you ever said that you stopped breathing while snoring?*" (witnessed sleep apnea). In this study population, the mean sleep initiation time was 23:29 and about half of the participants went to sleep between 23:00 and 00:59. This was a similar pattern with the previous report in Korean adults [16]. In addition, when the T2D hazard is checked at hourly intervals in this study population, an evident increase of T2D risk is observed after 01:00 (Supplementary Table S1). Therefore, study participants were classified into three groups based on HSIT as follows: 20:00–22:59 (early sleepers, ES, n = 766); 23:00–00:59 (usual sleepers, US, n = 2407); and 1:00–5:59 (late sleepers, LS, n = 516) [17].

To examine the long-term effect of a constant sleep initiation time, participants who belonged to the same HSIT group at the baseline and final visit were extracted and they were classified as persistent ES (n = 577), persistent US (n = 1765) and persistent LS (n = 237) groups (Supplementary Table S2).

Participants were asked to answer sleep-related questions with respect to usual weekdays and nights. In this report, participants who snored ≥4 days per week were defined as habitual snorers. A test-retest reliability study found substantial agreement for the question about snoring [18]. The presence of insomnia was determined if the participants often had any difficulty in initiating or maintaining sleep, or early morning awakening. Snack intake was defined if they ate snacks more than once a day. The average daily consumption of nutrients was calculated on the basis of the response to a semi-quantitative food frequency questionnaire (FFQ), which was developed and evaluated for validity by the Korea Centers for Disease Control and Prevention (Seoul, Korea) [19].

Definition of incident T2D

All study participants underwent a 2-hour 75-g oral glucose tolerance test (OGTT) at each follow-up visit. At baseline visit, fasting, 60 minutes, and 120 minutes post-OGTT glucose and insulin were measured. From the second visit, fasting and 120 minutes post-OGTT glucose and insulin were measured. Incident T2D was defined as a fasting glucose concentration ≥126 mg/dL or a post 2-hour glucose after the 75-g OGTT (2h-PG)

≥200 mg/dL based on the World Health Organization criteria [20]. Regardless of glucose values, participants who reported current therapy with antidiabetic medications were considered to have T2D. To analyze incident T2D, participants were followed up until the development of T2D or their last examination.

Measurement of anthropometric and biochemical parameters

Height, body weight, and waist circumference of participants wearing light clothes were measured using standard methods. BMI was calculated as weight divided by height squared (kg/m^2). Smoking status was divided into three categories: current smokers, ex-smokers, and never smokers. Alcohol intake was categorized as nondrinker or current drinker (alcohol consumption of ≥15 g per day for the previous 12 months). Exercise status was categorized as no exercise, light exercise (<3 times/week), or regular exercise (≥3 times/week, ≥30 minutes per session) during the previous month.

All blood samples were obtained in the morning after a 12-hour overnight fast and were immediately stored at −80°C for subsequent assays. Plasma concentrations of glucose, total cholesterol, triglycerides, and HDL cholesterol were measured enzymatically using a 747 Chemistry Analyzer (Hitachi, Tokyo, Japan). Plasma insulin concentrations were determined using a radioimmunoassay kit (Linco Research, St. Charles, MO). Glycated hemoglobin (A1c) level was measured by high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA).

Pancreatic β-cell function was estimated by 60-minute insulinogenic index (IGI_{60}) calculated with plasma insulin and glucose levels at 0 and 60 minutes of OGTT [21, 22]. Insulin sensitivity was measured by composite (Matsuda) insulin sensitivity index (ISI) and the HOMA-IR [22, 23]. High value of IGI_{60} and ISI means high insulin secretion and sensitivity status, whereas high HOMA-IR indicates low insulin sensitivity. All of the formula and meanings of these indices are presented in the Supplementary Table S3 [22, 23].

Statistical analysis

Demographic characteristics of the study participants were expressed as the mean ± *SD* or numbers and percentages, or as the median and interquartile ranges if the distributions were skewed. For continuous variables, one-way analysis of variance (ANOVA) with Tukey's post hoc test was used to assess differences in means according to HSIT groups. A chi-square test was used for categorical variables. Differences of changes in metabolic variables during follow-up period between HSIT groups were assessed by one-way analysis of covariance (ANCOVA) with Tukey's post hoc test.

Risk for incident T2D was compared among HSIT groups with ES as a control group using Cox proportional hazard models after adjusting for age, sex, body mass index, sleep duration, insomnia, habitual snoring (or presence of sleep apnea), exercise status, smoking status, alcohol intake, snack intake, amount of daily total energy intake, and presence of hypertension, dyslipidemia, and cardiovascular disease at baseline. Similarly, the impact of persistent HSIT on future development of T2D was also examined. To evaluate whether there was an interaction by pancreatic β-cell function and insulin sensitivity or age, the diabetic risk of each HSIT group was evaluated according to IGI_{60}/ISI status using cutoffs of the median values of IGI_{60} and ISI or by age subgroups (<65 years vs. ≥65 years at baseline). The time of development of T2D was estimated by the Kaplan–Meier method, and statistical differences among HSIT groups according to IGI_{60}/ISI or age stratifications were compared by the log-rank test. Assumptions of proportionality were tested using log follow-up time interaction terms for each baseline variable. Statistical analyses were conducted using SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC). All reported *p*-values were two-tailed. *p*-values less than 0.05 were considered statistically significant.

Results

During 8.9 ± 3.7 years of follow-up between 2002 and 2014, 820 cases of T2D (22.2% of study participants) developed. The baseline characteristics of study participants in the three HSIT groups are shown in Table 1. Of the 3689 participants, the proportion of ES, US, and LS was 20.8% (*n* = 766), 65.2% (*n* = 2407), and 14.0% (*n* = 516), respectively. At baseline, LS was the youngest among the three groups. LS had higher fasting insulin, HOMA-IR, and IGI_{60} levels, lower ISI, 2h-PG levels, and blood pressure than ES participants. However, a subgroup analysis with age, sex, and BMI-matched HSIT participants as many as possible (*n* = 394 in each group) revealed that blood pressure (*p* = 0.33) and prevalence of hypertension (*p* = 0.8) were not different among the HSIT groups. Compared to US, LS had higher BMI, waist circumference and triglycerides levels. (Table 1). Mean duration of sleep was shortest in LS, and LS participants had more insomnia than the other groups. Also, LS group had a less healthy lifestyle; their daily intake of total calories, fat, and snacks, and the proportion of current smokers and drinkers were higher than ES or US groups (Table 1).

The baseline characteristics of participants in the three persistent HSIT groups are shown in Supplementary Table S4, which were almost identical to those of the baseline HSIT groups.

Changes in metabolic parameters during follow-up in HSIT groups

During 12 years of follow-up, LS group showed the biggest decline of insulin sensitivity among the three groups (Table 2). After adjusting for age, sex, lifestyle factors and value of each variable at baseline visit, LS showed greater increase of fasting insulin (*p* = 0.002 than ES, *p* = 0.04 than US) and HOMA-IR (*p* = 0.001 than ES), greater decline in ISI (*p* = 0.02 than ES) over the follow-up period. The changes in BMI, waist circumference, IGI_{60}, and blood pressure were not different by HSIT group.

Development of T2D according to HSIT groups

The risk for development of T2D in the three HSIT groups was examined using a Cox proportional hazards model (Table 3). Compared to ES controls, participants in the LS group had a 1.3-fold increased risk for incident T2D in a model adjusted for age, sex, body mass index, sleep duration, habitual snoring, insomnia, smoking status, alcohol intake, exercise status, daily total energy intake, snack intake, and presence of hypertension, dyslipidemia, and cardiovascular disease at baseline. In contrast,

Table 1. Baseline characteristics of study participants by habitual sleep initiation time

	20:00–22:59 (ES) (*n* = 766)	23:00–00:59 (US) (*n* = 2407)	01:00–05:59 (LS) (*n* = 516)	
Habitual sleep initiation time	Mean ± *SD* (%)	Mean ± *SD* (%)	Mean ± *SD* (%)	*p*
Men (*n*, %)	392 (51.2)	1185 (49.2)	260 (50.4)	0.618
Age (years)	52.5 ± 8.6	47.6 ± 6.8†	45.8 ± 5.6‡	<0.0001
BMI (kg/m^2)	24.7 ± 2.9	24.5 ± 2.9	24.9 ± 3.1	0.029
Waist (cm)	80.9 ± 8.3	80.1 ± 8.2†	81.1 ± 9.0	0.006
Fasting glucose (mg/dL)	83.1 ± 8.6	83.2 ± 8.8	83.9 ± 9.1	0.185
Post 2-hour OGTT glucose (mg/dL)	122.4 ± 31.0	118.6 ± 30.0†	117.4 ± 30.3‡	0.004
Systolic blood pressure (mmHg)	119.7 ± 17.7	115.3 ± 16.6†	114.8 ± 16.2‡	<0.0001
HDL cholesterol (mg/dL)	45.0 ± 9.6	45.1 ± 10.1	44.3 ± 9.5	0.273
Triglyceride (mg/dL)*	135 (97–186)	129 (95–178)	141 (104–191)	0.007
Total cholesterol (mg/dL)	195.2 ± 33.2	194.2 ± 35.1	195.8 ± 33.2	0.575
HOMA-IR*	1.32 (0.98–1.73)	1.36 (0.99–1.86)	1.41 (1.05–1.88)‡	0.016
Fasting insulin (IU/L)*	6.4 (4.8–8.4)	6.8 (4.9–9.1)	6.9 (5.2–9.3)‡	0.025
Post 2-hour OGTT insulin (IU/L)*	22.3 (10.6–39.7)	22.8 (10.9–41.8)	23.5 (11.2–41.9)	0.232
IGI_{60}	6.8 ± 10.4	7.7 ± 11.2	8.8 ± 11.7‡	0.007
ISI*	9.7 (10.6–8.4)	9.4 (10.9–9.1)	9.2 (11.2–9.3)‡	0.013
Sleep duration (hours)	7.3 ± 1.3	6.5 ± 1.1†	5.8 ± 1.4‡,§	<0.0001
Habitual snoring (%)	143 (18.7)	362 (15.1)	91 (17.6)	0.039
Sleep apnea (%)	105 (13.7)	302 (12.6)	79 (15.4)	0.22
Insomnia (%)	99 (12.9)	223 (9.3)	71 (13.8)	0.001
Daily total energy intake				
Protein (g)	64.4 ± 21.7	65.8 ± 23.4	67.5 ± 22.1	0.063
Fat (g)	31.1 ± 15.4	32.8 ± 16.3†	35.4 ± 16.7‡,§	<0.0001
Carbohydrate (g)	317.2 ± 74.7	322.1 ± 77.1	318.9 ± 78.4	0.270
Three regular meals/day (%)	666 (87.5)	1985 (83.1)	343 (67.5)	<0.0001
Snack ≥ 1 time/day (%)	409 (53.4)	1399 (58.1)	328 (63.6)	0.001
Current smoker (%)	145 (19.0)	529 (22.0)	169 (32.8)	<0.0001
Current drinker (%)	380 (49.6)	1250 (52.0)	293 (56.8)	0.040
Physical activity (%)	157 (20.5)	549 (22.8)	102 (19.8)	0.181
Hypertension (%)	214 (27.9)	519 (21.6)	107 (20.7)	0.001

Values are presented as the mean ± *SD*, number (%), or median (interquartile range).
*Statistical significance was estimated after logarithmic transformation.
†ES vs. US; ‡ES vs. LS; §US vs. LS: *p* value < 0.05 in Tukey's post hoc analysis.

Table 2. Changes in metabolic variables over the follow-up period in each habitual sleep initiation time group

	Habitual sleep initiation time						
	20:00–22:59 (ES)		23:00–00:59 (US)		01:00–5:59 (LS)		
	LSM	SE	LSM	SE	LSM	SE	*p*
△BMI (kg/m^2)	–0.004	0.05	–0.07	0.03	0.07	0.06	0.081
△Waist (cm)	0.68	0.21	0.31	0.12	0.61	0.24	0.186
△Fasting glucose (mg/dl)	6.67	0.30	7.63†	0.18	7.59	0.34	0.011
△ Post 2-hour OGTT glucose (mg/dl)	11.35	1.16	13.40	0.68	11.70	1.33	0.175
△Triglyceride (mg/dl)	–5.21	2.95	–12.15	1.76	–5.08	3.41	0.028
△Systolic blood pressure (mmHg)	0.02	0.82	–0.58	0.49	0.54	0.95	0.481
△Fasting insulin (IU/L)	0.64	0.14	0.92	0.08	1.32‡,§	0.16	0.004
△HOMA-IR	0.26	0.03	0.35†	0.02	0.44‡	0.04	0.002
△IGI_{60}	7.36	1.80	6.21	1.06	6.94	2.06	0.822
△ISI	–3.46	0.21	–4.08†	0.12	–4.35‡	0.24	0.006

All of the models were adjusted for age, sex, smoking status, alcohol intake, exercise status and value of each variable at baseline visit.
†ES vs. US; ‡ES vs. LS; §US vs. LS: *p* value < 0.05 in Tukey's post hoc analysis.

the ES and US groups showed a similar risk for T2D. Since the LS group had lower insulin sensitivity at baseline, which is a power risk factor for T2D, the model was adjusted for age, sex, body mass index, and logISI to exclude the effect of lower insulin sensitivity. In this model, LS remained a significant risk factor for T2D compared with ES (hazard ratio [HR] 1.30, 95% confidence interval [CI]: 1.02–1.64).

Impact of HSIT groups on the development of T2D according to age group

Interestingly, the association between late sleep initiation and the development of T2D was more evident in elderly than younger participants. In younger participants (<65 years at baseline), LS group showed a 1.3-fold increased risk for T2D

Table 3. Adjusted hazard ratios (95% CI) of incident T2D over the follow-up period by habitual sleep initiation time

	Habitual sleep initiation time				
	20:00–22:59 (ES) (*n* = 766)	23:00–00:59 (US) (*n* = 2407)		01:00–05:59 (LS) (*n* = 516)	
T2D cases (*n*, (%))	180 (23.5%)	511 (21.2%)		129 (25.0%)	
	HR	HR	95% CI	HR	95% CI
Model 1	ref	1.02	0.86–1.22	1.34	1.06–1.70
Model 2	ref	1.03	0.86–1.24	1.33	1.04–1.72
Model 3	ref	1.03	0.85–1.24	1.34	1.04–1.74
Model 4	ref	1.04	0.86–1.25	1.34	1.04–1.74

Model 1: adjusted for age, sex, and body mass index at baseline. Model 2: further adjusted for sleep duration, habitual snoring, and insomnia at baseline in addition to the adjustment made for model 1. Model 3: further adjusted for smoking status, alcohol intake, exercise status, daily total energy intake, snack intake, presence of hypertension, dyslipidemia, or cardiovascular disease at baseline in addition to the adjustment made for model 2. Model 4: adjusted for sleep apnea instead of habitual snoring in model 3.

than ES group (HR [95% CI]: 1.27 [1.00–1.62]); however, in older participants (≥65 years at baseline), LS group had a greater than fourfold increased risk for T2D than ES group (HR: 4.24 [1.42–12.68]). There was a significant age interaction between HSIT groups and risk of T2D (*P* for interaction = 0.002, Figure 1).

Impact of HSIT groups on incident T2D according to insulin secretion and sensitivity status

When participants were further categorized by IGI_{60} and ISI level in the HSIT group, those with low IGI_{60} (low insulin secretion capacity) and low ISI (low insulin sensitivity) had the highest risk for T2D among four IGI_{60}/ISI groups in each HSIT groups (Figure 2). However, this finding was noticeable especially in LS group. The HR for T2D was about fivefold higher in the low IGI_{60}/low ISI group of LS compared to the high IGI_{60}/high ISI group of ES (Figure 2). Thus, the association between IGI_{60}/ISI status and diabetic risk was significantly affected by HSIT after adjustment for age and sex (*p* for interaction = 0.024).

Risk for T2D according to persistent HSIT groups

When the participants were classified by HSIT at their baseline and last follow-up visits, 52% of ES (*n* = 580), 82% of US (*n* = 1766), and 57% of LS (*n* = 237) belonged to the same HSIT group at baseline and last follow-up visit (Supplementary Table S2). Compared to persistent ES controls, participants with persistent LS had an approximately 1.8-fold increased risk for T2D (Table 4) in a fully adjusted model.

Discussion

The main findings of this study indicate that habitual LS developed T2D more frequently and showed more unfavorable metabolic changes than ES or US during 12 years of follow-up. The impact of late sleep on the development of T2D was more evident in older individuals and in participants with lower insulin sensitivity and lower beta cell function. To the best of our knowledge, this is the first prospective cohort study to examine the longitudinal effects of HSIT on the incidence of T2D independent of sleep duration, sleep quality, and unhealthy lifestyle.

Potential mechanisms between sleep timing and T2D

People sleep late for variable reasons, but the pattern can be simplified into two factors—voluntary (late chronotype) or

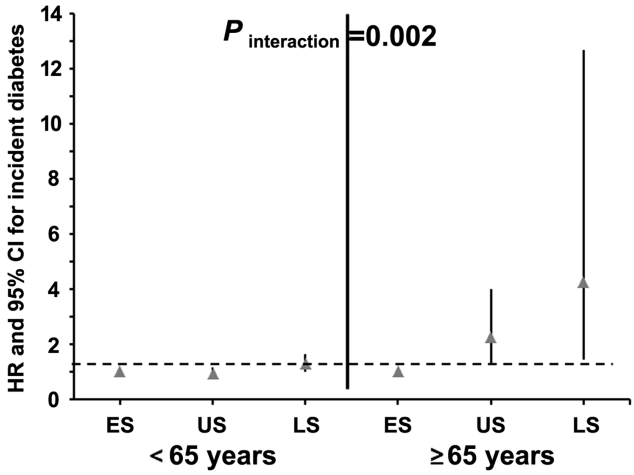

Figure 1. Adjusted hazard ratios (95% CI) for incident T2D over the follow-up period by habitual sleep initiation time for different age subgroups. All of the models were adjusted for age and sex.

involuntary (late worker). The mechanism of the effect of late sleep initiation on metabolic abnormality may be a mixture of this underlying pathophysiology. One possible explanation is chronic sleep loss in LS because lack of sleep exerts deleterious effects on metabolic pathways. Sleep restriction decreases glucose clearance and acute insulin response to glucose during glucose tolerance test [24]. Elevated level of nonesterified free fatty acids after sleep restriction is associated with insulin resistance in humans [25]. In addition, sleep restriction promotes a positive energy balance by affecting levels of hunger and appetite, with particular cravings for carbohydrate with a high glycemic index [26]. Therefore, lack of sleep is strongly associated with obesity and T2D. In the present study, LS slept less than other groups; however, the impact of late sleep initiation time on T2D development was retained even after adjusting for sleep duration. Interestingly, when we subdivided the study participants according to sleep duration and HSIT, a significantly increased risk of T2D in short sleep duration (≤5 hours) group was more evident in LS (Supplementary Table S5). It suggests that late and short sleep is the most harmful for T2D. Another possible explanation is circadian misalignment due to delayed sleep phase in LS. The higher prevalence of insomnia in LS in this study may be due to the circadian misalignment of the endogenous circadian rhythm and external environmental conditions. Disruption of the circadian system may affect

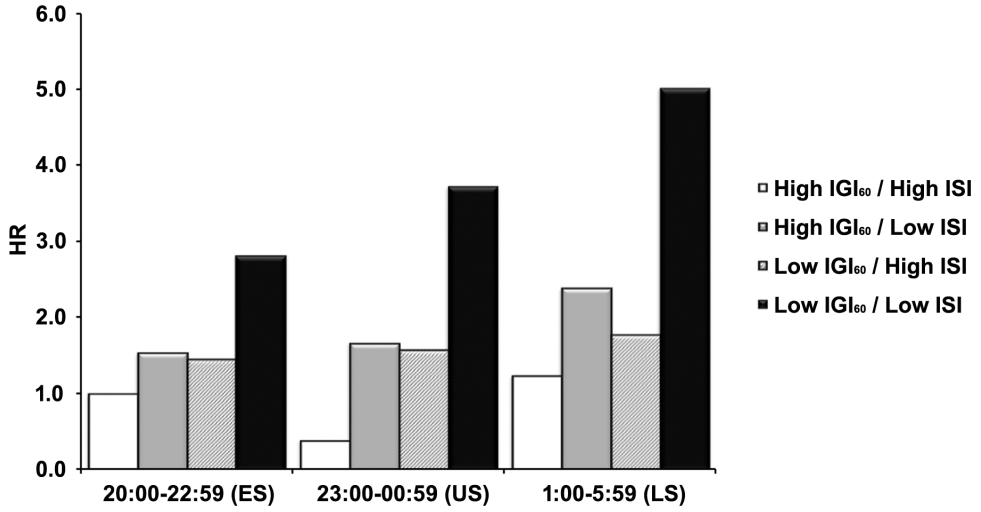

Figure 2. Adjusted hazard ratios of incident T2D over the follow-up period by habitual sleep initiation time and IGI_{60}/ISI status*. All of the models were adjusted for age and sex. *: high/ low IGI_{60}/ISI was classified by cut-off of median value.

Table 4. Adjusted hazard ratios (95% CI) of incident T2D over the follow-up period by persistent habitual sleep initiation time

	Persistent habitual sleep initiation time				
	20:00–22:59 (persistent ES) (*n* = 577)	23:00–00:59 (persistent US) (*n* = 1765)		01:00–05:59 (persistent LS) (*n* = 237)	
T2D cases (*n*, (%))	146 (25.3)	396 (22.4)		81 (34.2)	
	HR	HR	95% CI	HR	95% CI
Model 1	ref	1.11	0.90–1.36	2.17	1.63–2.90
Model 2	ref	1.11	0.90–1.38	2.11	1.55–2.87
Model 3	ref	1.08	0.85–1.37	1.82	1.29–2.57
Model 4	ref	1.08	0.85–1.37	1.82	1.28–2.57

Model 1: adjusted for age, sex, and body mass index at baseline. Model 2: further adjusted for sleep duration, habitual snoring, and insomnia at baseline in addition to the adjustment made for model 1. Model 3: further adjusted for smoking status, alcohol intake, exercise status, daily total energy intake, snack intake, presence of hypertension, dyslipidemia and cardiovascular disease, at baseline in addition to the adjustment made for model 2. Model 4: adjusted for sleep apnea instead of habitual snoring in model 3.

sleep, appetite, energy expenditure, and many possible determinants of obesity [27]. There is evidence of hormonal changes such as decreased leptin levels and inversed cortisol profile during a short-term circadian misalignment (~12-hour shift) in humans [28]. Previous studies in shift workers implicated that circadian sleep misalignment has adverse consequences for metabolic health such as T2D, hypertension, and cardiovascular disease, even after controlling for traditional risk factors [12, 29, 30]. Leproult et al. showed circadian misalignment decreases insulin sensitivity independently of sleep loss in healthy adults [31]. Shift workers had an increased risk of incident T2D of approximately 30%–50% in observational cohort studies [12, 13]. Noticeably, the present study demonstrated that only a few hours delay of bedtime increased the risk for T2D by approximately 34%. As shift workers were excluded, this study highlights the significance of bedtime delay for future metabolic risk in a typical non-shift working population. A recent previous study in a cohort of middle-aged women reported that bedtime delay was associated with greater increase of HOMA-IR over 5 years of follow-up [10], which is consistent with the result of ongoing impairment of insulin sensitivity in LS in this study. However, the previous study could not investigate incident T2D because of the small sample size and short follow-up period [10].

Effects of late sleep timing on lifestyle factors

People who sleep late may practice more detrimental health behaviors compared to ES. A previous study has found that evening chronotypes practice more unhealthy behaviors compared to other chronotypes, such as smoking more, consuming more caffeinated beverages at night, and eating heavy meals at bedtime [32]. These unhealthy behaviors may subsequently increase their risk for health problems and disease. The present study also indicated that the LS group had a significantly higher calorie and fat intake and snack frequency and a higher proportion of current smoking and drinking. However, the increased risk of T2D from late sleep was not offset by adjustment of these behavioral risk factors. Although the timing of snacks was not evaluated in this study, Baron et al. reported that later sleepers consume more calories after 8 pm, which is related to higher BMI [33]. Eating late not only decreases resting-energy expenditure and glucose tolerance, but also blunts the daily cortisol rhythm and thermal effect of food [34].

Taken together, these unhealthy behavior patterns might lead to metabolic dysregulation in LS.

Light exposure as a potential mechanism

Increased light exposure during nighttime may be another mechanism. It is likely that the LS are more frequently exposed to light at night than ES. Evening use of light-emitting technologies such as LEDs, computer screens or televisions and mobile phones can lead to a circadian phase delay and a slowing melatonin secretion [35]. Specifically, short-wavelength, blue-enriched light causes significantly more strong and sustained suppression of melatonin than standard light [36, 37]. Lower nocturnal melatonin secretion in humans is associated with increased insulin resistance and incident T2D [38]. Continuous exposure to light at night disrupts circadian clock function in islet cells, leading to diminished glucose-stimulated insulin secretion in rats [39]. Thus, light exposure at night may be associated with glucose intolerance via melatonin suppression and circadian disruption.

Effect of sleep timing according to age and insulin secretion and sensitivity

Interestingly, this study showed the effects of late sleep on diabetic risk were significantly higher in older (≥65 years of age at baseline) than younger participants even after adjusting for several confounders. Considering that the timing of sleep and the phase of the circadian melatonin rhythm are earlier in older participants [40], late sleep initiation could induce greater circadian misalignment or disruption in this population. A recent community-based, cross-sectional, cohort study in a Latino population reported that the association between sleep timing and metabolic measures might in part be age-dependent [11]. In that study, an increase in BMI, fasting glucose, and HbA1c in LS was evident in older participants (≥56 years), whereas the opposite (i.e. decrease in BMI, fasting glucose, HbA1c) was true for younger (18–35 years) participants [11]. However, there was no opposite finding between the age groups in the present study because study population was ranged from middle-aged to old.

The present study also showed that late sleep is especially harmful for people with higher risks for T2D, such as participants with low insulin secretion capacity and low insulin sensitivity. When the participants were categorized by the insulin secretion and sensitivity in each HSIT groups, the increased T2D risk in low insulin secretion and low insulin sensitivity groups was consistently evident in ES, US, and LS. The impact of these unfavorable glucose homeostasis markers was highest in the LS; fivefold increased risk for T2D compared to ES with high insulin secretion and high insulin sensitivity. Therefore, we can infer that late sleep initiation accentuates the potential metabolic risk, and can be a triggering factor for the development of T2D in this vulnerable population.

Study strength and limitations

The present study has several strengths. First, this study evaluated and confirmed the effect of late sleep on the incidence of T2D and changes in metabolism over long-term follow-up. Moreover, persistent late sleep initiation reinforced the effect. Second, by using an oral glucose tolerance test, the identification of T2D in the KoGES was fairly strict and insulin resistance and secretion could be evaluated, unlike most previous studies. Third, the large number of the participants allowed several subgroup analyses, such as age, insulin secretion, and sensitivity. In addition, in the regression model, a large number of potential confounders including sleep duration, snoring, and insomnia, as well as lifestyle habits and several co-morbidities, were controlled to minimize the bias of confounders.

This study also has several limitations. First, the information on HSIT was obtained from a questionnaire using a single question, and might be subject to recall bias. However, the subgroup analysis with persistent sleep initiation time demonstrated the association between late sleep and the increased risk of T2D more convincingly. Second, this study did not distinguish whether late sleep was voluntary or involuntary. Therefore, the exact effects of late chronotype and environmental influences on T2D could not be determined. Third, although the regression models were adjusted for several confounding factors, unknown confounders related to late sleep timing and outcome might be still present. Nevertheless, the result of this study is meaningful to public health since sleep timing is a potentially modifiable behavior that might be a focus of intervention for metabolic health [9].

Conclusion

Habitual late sleep was a risk factor of T2D independent of sleep duration or quality and other risk factors in a Korean adult population, especially in participants with insulin resistance, lower beta cell function, and old age. Further research is warranted to investigate whether behavioral intervention of sleep timing in high-risk individuals is effective to prevent T2D and improve metabolic health.

Supplementary material

Supplementary material is available at *SLEEP* online.

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