The Association Between Sleep Duration, Insulin Sensitivity, and β-Cell Function: The EGIR-RISC Study

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Context: In the past decade, over 3 dozen studies reported a relationship between self-reported short sleep and disturbed glucose metabolism. A study with insulin sensitivity assessed according to the gold standard hyperinsulinemic-euglycemic clamp is, however, still missing.

Objective: To evaluate the cross-sectional association of sleep duration with insulin sensitivity and β-cell function in the European group for the study of insulin resistance (EGIR-RISC) study cohort.

Design, Setting, Participants, and Measures: We used data from the baseline measurements of the European, multicentre EGIR-RISC study that included 1319 clinically healthy participants. Sleep and physical activity were measured using a single-axis accelerometer. Insulin sensitivity and β-cell function were estimated by hyperinsulinemic-euglycemic clamp and from the oral glucose insulin sensitivity index model, using an oral glucose tolerance test. Associations of sleep duration with insulin sensitivity and β-cell function were analyzed by multiple linear regression, stratified by sex.

Results: In our current analysis, we included 788 participants (57% women, age 44 ± 8 y), who had an average sleep duration of 7.3 ± 1.5 hours. In men, we observed an inverted U-shaped association between sleep duration categorized per hour and M/I (in μmol/min per kg_{FFM}/nM per hour) (β-estimate [95% confidence intervals] 41 [2, 80]; $P = .04$ and β^2-estimate −3 [−6, −0.2], $P = .04$) as well as a trend for the oral glucose insulin sensitivity index (in mL/min per kg_{FFM}) (β-estimate [95% confidence intervals] 0.8 [−0.4, 2]; $P = .17$). In women, we observed a U-shaped association between sleep duration and β-cell function (in pmol/min per m^2/mM per hour) (β-estimate −45 [−86, −3]; $P = .04$ and β^2-estimate 3 [0.2, 6]; $P = .04$).

Conclusions: Sleep duration is associated with insulin sensitivity and β-cell function in a sex-specific manner in clinically healthy people. **(*J Clin Endocrinol Metab* 101: 3272–3280, 2016)**

In the last 50 years, the average self-reported sleep duration has decreased by 1.5–2 hours, whereas the prevalence of diabetes has doubled in the same time period (1). Although this evidence is circumstantial, recent meta-analyses indeed support the role of sleep curtailment in the development of diabetes (2–5). Data from over a dozen experimental studies showed decreases in insulin sensitivity and β-cell function after sleep deprivation, including

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Abbreviations: BMI, body mass index; BP, blood pressure; EGIR-RISC, European group for the study of insulin resistance; HDL, high-density lipoprotein; M/I, the amount of glucose metabolized per unit of plasma insulin; OGIS, oral glucose insulin sensitivity; OGTT, oral glucose tolerance test; SWS, slow wave sleep.

studies using the gold standard, a hyperinsulinemic-euglycemic clamp (6–16). One experimental study even showed that 1 night without sleep is sufficient to induce insulin resistance in healthy participants (6).

Data from over 30 epidemiological studies showed a negative or U-shaped relationship between self-reported sleep duration and incident diabetes or impaired glucose metabolism, with both short and long sleep being associated with an increased risk (3–5). The strength of the observed associations was variable, with the relative risk of incident diabetes ranging from 0.97 (0.8, 1.1) to 2.8 (1.1, 7.2) (3–5). A study on the relationship between sleep duration, insulin sensitivity, and β-cell function, with insulin sensitivity assessed according to the gold standard hyperinsulinemic-euglycemic clamp, is, however, still missing.

In this study, we evaluated the cross-sectional association of sleep duration with insulin sensitivity and β-cell function in the European group for the study of insulin resistance (EGIR-RISC) study cohort (17).

Materials and Methods

The rationale and design of the EGIR-RISC study have been described previously (17). In brief, clinically healthy study participants aged 30–60 years were recruited from 19 study centers in 14 European countries. Exclusion criteria for participation included prevalent cardiovascular disease and treatment for obesity, arterial hypertension, lipid disorders, or diabetes. Further exclusion criteria were systolic/diastolic blood pressure (BP) more than or equal to 140/90 mm Hg, fasting plasma glucose more than or equal to 7.0 mmol/L, 2-hour plasma glucose more than or equal to 11.1 mmol/L, total cholesterol more than or equal to 7.8 mmol/L, or triglyceride levels more than or equal to 4.6 mmol/L.

Using a standardized protocol, the baseline assessments included anthropometrics, BP measurements, fasting blood sampling, an oral glucose tolerance test (OGTT), a hyperinsulinemic-euglycemic clamp, lifestyle, and medical history questionnaires as well as assessment of physical activity and sleep with an accelerometer. In total, between 2002 and 2004, more than 1500 study participants were examined, and 1319 participants had a 2-hour hyperinsulinemic-euglycemic clamp. A total of 847 participants wore the accelerometer; however, only 788 had worn it for at least 3 days. The 59 participants without correct sleep and activity measures were excluded from the study. The EGIR-RISC study complies with the Declaration of Helsinki and ethical approval was obtained from the local ethics committees. All participants gave written informed consent before study inclusion.

Sleep duration

Sleep and physical activity were measured objectively by a small single-axis accelerometer (Actigraph, AM7164-2.2; Computer Science and Applications) (18). The acceleration signal was digitized with 10 samples per second, registered as counts over 1-minute intervals. The accelerometer was worn for up to 8 days on a belt in the small of the back, from waking to bedtime except during water-based activities. We analyzed participants with at least 3 days of data, including days when the device was worn more than 12 hours and less than 23 hours.

Accelerometer data were processed with custom software developed for this project using SAS version 9, as described earlier by other EGIR-RISC researchers (19–21). Data were checked for spurious recording: high counts more than 20 000 counts per minute and repeated counts. For each day with valid data as defined above, our software computed the following:

-daily sedentary time (min) with less than 100 counts per minute worn,

-daily moderate physical activity (min) with 1952–5724 counts per minute worn,

-daily vigorous physical activity (min) with more than 5724 counts per minutes-worn, and

-daily light physical activity (min) with 100–1952 counts per minute worn (19–21).

We estimated daily sleep duration (min) based on the time the device was not worn for more than 60 consecutive minutes. This assumption may, however, include some water-based activities for which the accelerometer was not worn. To assess the validity of our assumption, we determined the correlation between the accelerometer data at baseline and a sleep questionnaire completed at the 3-year follow-up. The sleep questionnaire assessed the average sleep duration (h) on weekdays and weekend days, from which average sleep duration was calculated (sleep weekday × 5 + sleep weekend × 2)/7 (22). Questionnaire data were available in 603 participants and we observed a significant association between the 2 measures ($r = 0.31$, $P < .05$), which is similar to data published by Kripke et al (23), who showed a correlation coefficient of $r = 0.35$ between sleep duration assessed with an accelerometer and sleep duration assessed with a questionnaire, at the same point in time. While we observed a mean difference of +0.8 hours (range, 5.9 h) between the accelerometer data and questionnaire data, we corrected for this difference (23). The uncorrected data showed very similar associations with insulin sensitivity and β-cell function (data not shown). Overall, sleep duration was categorized per hour.

Two-hour hyperinsulinemic-euglycemic clamp

We conducted a 2-hour hyperinsulinemic-euglycemic clamp with a primed-continuous infusion rate of 240 pmol/min per m^2 and a variable dextrose infusion adjusted every 5–10 minutes to maintain the plasma glucose level within 0.8 mmol/L (±15%) of target glucose (4.5–5.5 mmol/L). The procedure was standardized across centers using a written protocol and a video demonstration, and data from the clamp were quality controlled centrally. Insulin sensitivity calculated from the clamp results was expressed the ratio of the M value calculated during the final 40 minutes of the clamp and normalized to the mean plasma insulin (I) in the same period and to fat-free mass (M/I, in μmol/min per kg_{FFM}/nM) (24). Plasma glucose was measured by the glucose oxidase technique (Cobas Integra; Roche). Plasma insulin and C-peptide were measured by a 2-site time-resolved immunofluorometric assays (AutoDELFIA Insulin kit; Wallac Oy), using monoclonal antibodies.

Oral glucose tolerance test

At least 1 week before the 2-hour hyperinsulinemic-euglycemic clamp, participants underwent a 75-g OGTT after an overnight fast. Blood samples were taken before and during the test

at 0, 30, 60, 90, and 120 minutes. Insulin sensitivity calculated from the OGTT results was expressed as the oral glucose insulin sensitivity (OGIS) index (mL/min per kg_{FFM}), using glucose and insulin levels at 0, 90, and 120 minutes of the OGTT (25). β-Cell function calculated from the OGTT results (26, 27) was expressed as 3 model-based insulin secretion parameters (28); β-cell glucose sensitivity, the potentiation factor ratio and β-cell rate sensitivity (26, 27). In the model, insulin secretion depends on absolute glucose concentration through a dose-response function. β-cell glucose sensitivity is defined as the mean dose-response slope over the observed glucose range. The potentiation factor modulates the dose-response relationship, which accounts for higher insulin secretion during the descending phase of hyperglycaemia compared with the ascending phase with the same glucose concentration during acute stimulation. The potentiation factor is set as a positive function of time and to average 1 during the OGTT. Therefore, it represents the relative potentiation of the insulin secretion response to glucose. The potentiation parameter used in the present analysis is the ratio of the potentiation factor at the end of the 2-hour OGTT to the one at the start. Finally, β-cell rate sensitivity represents the dynamic dependence of insulin secretion on the rate of change in glucose concentration and represents early insulin release.

Metabolic syndrome markers

We measured body weight and fat mass by bioelectric impedance (TBF 300; Tanita), height with a stadiometer and waist circumference with a horizontally placed tailor's tape measure midway between the lower costal margin and the iliac crest on lightly clad participants. The body mass index (BMI) was calculated as weight/height squared (kg/m^2). Secondly, sitting BP (mm Hg) was measured 3 times (OMRON 705 cp; OMRON Healthcare Europe); median values were used in the analyses. Plasma high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were measured by Roche enzymatic colorimetric methods for Modular Systems (Hoffmann La-Roche). Low-density lipoprotein concentration was calculated by the Friedewald formula (29).

Other variables

Smoking habits (current or previous smoking vs no smoking: yes/no), daily alcohol intake (g/d), and family history of diabetes were assessed using questionnaires.

Statistical analysis

Normally distributed continuous data were presented as means (SD), skewed continuous data as medians (quartiles), and categorical data were presented as percentages. We used linear regression models with second order polynomials to assess the (U-shaped) association between sleep duration and markers of insulin sensitivity, β-cell function, and the metabolic syndrome. The results were presented with one or 2 coefficients (βs) depending on the significance of the first or second order polynomial. If the second order term was significant in the crude model, we reported it in the following adjusted models, even when it was not significant. Because we observed interaction effects for sex, all analyses were stratified by sex. Models were sequentially adjusted for age, recruitment center, BMI, smoking, and physical activity. When necessary data were log^{10} transformed, and data were presented transformed to the original units. Statistical analyses used SPSS version 20.0 (SPSS, Inc), and $P \leq .05$ was considered to be statistically significant.

Results

Data were available in 788 participants (57% women, age 44 ± 8 y), who had an average sleep duration of 7.3 ± 1.5 hours. There were no significant differences in age or sex between study participants with and without sleep measurements. Participants with sleep data, however, had better clinical characteristics; higher M/I and OGIS values, a lower BMI, and lower triglyceride levels (data not shown), suggesting our current study population is somewhat healthier compared with the total EGIR-RISC population. Table 1 shows the characteristics of our current study population, for men and women.

With regard to insulin sensitivity (Figure 1, A and B, and Table 2), in men, we observed an inverted U-shaped association between sleep duration categorized per hour and M/I (in μmol/min per kg_{FFM}/nM per hour; β-estimate

Table 1. Population Characteristics at Baseline Stratified by Sex (n = 788): The EGIR-RISC Study

	Men	Women
Number	341	447
Age (y)	44 ± 9	45 ± 8
BMI (kg/m^2)	26 ± 3	25 ± 4
Waist circumference (cm)	93 ± 10	81 ± 11
Fat mass (kg)	18 ± 7	22 ± 9
Systolic BP (mm Hg)	123 ± 11	114 ± 13
Diastolic BP (mm Hg)	77 ± 8	73 ± 8
Low-density lipoprotein cholesterol (mmol/L)	3.1 ± 0.8	2.8 ± 0.8
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.6 ± 0.4
Triglycerides (mmol/L)	1.0 (0.7–1.4)	0.8 (0.6–1.1)
Alcohol intake (g/d)	72 (30–142)	35 (11–68)
Smoking (current and previous %)	50	55
Family history diabetes (%)	24	28
Fasting glucose (mmol/L)	5.2 ± 0.5	5.0 ± 0.5
Fasting insulin (pmol/L)	27 (19–38)	24 (17–35)
Fasting C-peptide (pmol/L)	512 (399–685)	515 (352–628)
M/I (μmol/min per kg_{FFM}/nM)	130 ± 62	163 ± 64
OGIS (mL/min per kg_{FFM})	10 ± 2	13 ± 3
β-Cell glucose sensitivity (pmol/min per m^2/mM)	111 ± 58	139 ± 83
β-Cell rate sensitivity (pmol/m^2 per mM)	998 (282–1372)	989 (80–1233)
Potentiation factor ratio	2 ± 1	2 ± 1
Average daily physical activity (counts/min)	343 (274–448)	348 (261–427)
Average time spent in moderate/vigorous activity (%)	1.5 ± 2	1.2 ± 2
Average sleep duration (h)	7.2 ± 1	7.4 ± 2

Continuous data are presented as mean ± SD or as median (quartiles), categorical data as percentages.

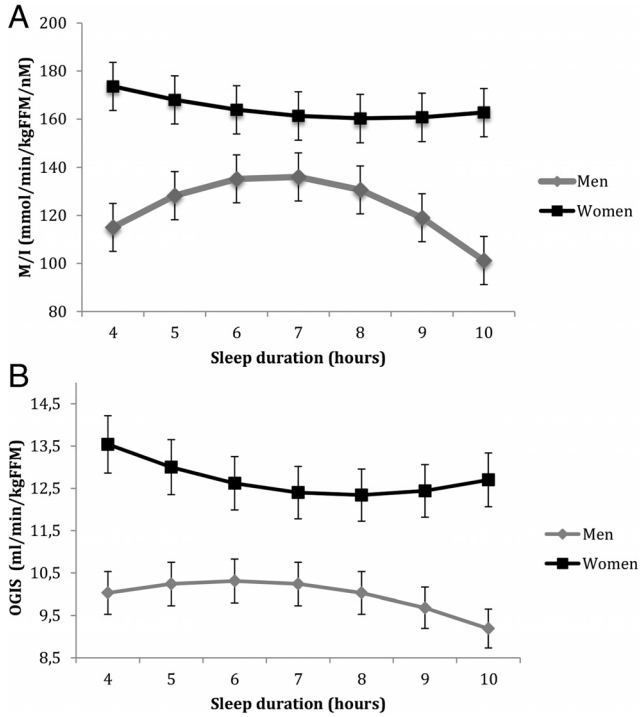

Figure 1. A, Mean and SE of insulin sensitivity expressed as M/I, according to sleep duration, stratified by sex, men (n = 314) and women (n = 447). The EGIR-RISC study. B, Mean and SE of insulin sensitivity expressed as OGIS, according to sleep duration, stratified by sex, men (n = 314) and women (n = 447). The EGIR-RISC study.

[95% confidence intervals] 41 [2, 80]; $P = .04$ and β^2-estimate −3 [−6, −0.2]; $P = .04$) as well as trend for OGIS (in (mL/min per kg_{FFM}; β-estimate [95% confidence intervals] 0.8 [−0.4, 2]; $P = .17$). These results suggest that men with short or long sleep duration are less insulin sensitive, compared with those with average sleep duration. The association with M/I became nonsignificant, *P* value between 0.06 and 0.08, after correction for potential confounders. With regard to insulin sensitivity, in women, we observed the opposite: sleep duration was not significantly related to M/I, but a U-shaped association was observed between sleep duration and OGIS (in (mL/min per kg_{FFM}; β-estimate (95% confidence intervals) −1.3 [−2, 0)]; $P = .06$ and β^2-estimate 0.1 [−0.1, 0.2]; $P = .09$), which became significant after correction for age and recruitment center (mL/min per kg_{FFM}; β-estimate −1.4 [−3, −0.1]; $P = .03$ and β^2-estimate 0.1 [0.1, 0.2]; $P = .04$). These results suggest that women with short or long sleep duration are more insulin sensitive, compared with those with average sleep duration. The association was not confounded by age, recruitment center, BMI, smoking, or physical activity.

With regard to markers of β-cell function (Figure 2 and Table 2), in women we observed a U-shaped association between sleep duration and β-cell glucose sensitivity (in pmol/min per m^2/mM per hour β-estimate −45 [−86, −3]; $P = .04$ and β^2-estimate 3 [0.2, 6]; $P = .04$). These results suggest that women with short or long sleep duration have a better β-cell function, compared with those with average sleep duration. The association was not confounded by age, recruitment center, or BMI and became stronger after correction for smoking and physical activity. In women, no significant associations were observed for the potentiation factor ratio or β-cell rate sensitivity, whereas in men, no significant associations were observed with any of the β-cell function markers.

With regard to markers of the metabolic syndrome (Table 3), in men, we observed a U-shaped association between sleep duration and fasting glucose levels (in mmol/L, β-estimate −0.3 [−0.5, 0.0)]; $P = .05$ and β^2-estimate 0.02 [0.0, 0.1]; $P = .05$). These results suggest that men with short or long sleep duration have higher baseline glucose levels, compared with those with average sleep duration. The association was not confounded by age, recruitment center, BMI, smoking, or physical activity. No significant associations were observed for BMI, systolic BP, or levels of HDL cholesterol and triglycerides.

In contrast, in women (Table 3), we observed an inverted U-shaped association between sleep duration and fasting glucose levels (in mmol/L, β-estimate 0.3 [0.1, 0.5]; $P = .02$ and β^2-estimate −0.02 [−0.1, 0.0]; $P = .05$) as well a U-shaped association between sleep duration and HDL levels (in mmol/L, β-estimate −0.2 [−0.4, −0.1]; $P = .02$ and β^2-estimate 0.02 [0.0, 0.1]; $P = .02$). These results suggest that women with short or long sleep duration have lower glucose levels and higher HDL levels, compared with those with average sleep duration. The association for glucose was not confounded by age, recruitment center, BMI, smoking, or physical activity; however, the association for HDL was. No significant associations were observed for BMI, systolic BP, or levels of triglycerides.

Discussion

The aim of our current study was to evaluate the cross-sectional association of sleep duration with insulin sensitivity and β-cell function in the EGIR-RISC study. The study was conducted in a large, middle-aged, and clinically healthy group of men and women. We observed sex-specific associations: when compared with average sleep duration, in men, short and long sleep duration were associated with worse insulin sensitivity, whereas in women, short and long sleep duration were associated with a better insulin sensitivity as well as better β-cell function. These findings were supported by the fasting glucose levels: when compared with average sleep duration, in men, the fasting glucose levels were higher for short and long sleep duration, in contrast to women, who had lower

Table 2. Associations of Sleep Duration With Measures of Insulin Sensitivity and β-Cell Function (β-Estimates, 95% Confidence Intervals, *P* Values) in Men (n = 341) and Women (n = 447): The EGIR-RISC Study

	Men			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Insulin sensitivity				
M/I (μmol/min per kg_{FFM}/nM)				
Linear	41 (2, 80) 0.04	35 (−4, 74) 0.07	33 (−4, 69) 0.08	38 (−2, 79) 0.06
Quadratic	−3 (−6, −0.2) 0.04	−3 (−6, 0.3) 0.07	−2 (−5, 0.4) 0.08	−3 (−6, −0.1) 0.06
OGIS (mL/min per kg_{FFM})				
Linear	0.8 (−0.4, 2) 0.17	0.7 (−0.5, 2) 0.23	0.7 (−0.4, 2) 0.21	0.9 (−0.2) 0.15
Quadratic	ns	ns	ns	ns
β-Cell function				
β-Cell glucose sensitivity (pmol/min per m^2/mM)				
Linear	−8 (−43, 27) 0.65	−12 (−48, 22) 0.48	−13 (−49, 23) 0.48	−13 (−49, 23) 0.47
Quadratic	ns	ns	ns	ns
β-Cell rate sensitivity (pmol/m^2 per mM)[a]				
Linear	67 (−15, 148) 0.51	54 (−28, 136) 0.73	57 (−26, 139) 0.74	40 (−39, 120) 0.68
Quadratic	ns	ns	ns	ns
Potentiation factor ratio				
Linear	0.02 (−0.1, 0.1) 0.88	0.03 (−0.1, 0.1) 0.85	0.04 (−0.1, 0.1) 0.88	0.04 (−0.1, 0.1) 0.91
Quadratic	ns	ns	ns	ns
β-Cell rate sensitivity (pmol/m^2 per mM)[a]				
Linear	67 (−15, 148) 0.51	54 (−28, 136) 0.73	57 (−26, 139) 0.74	40 (−39, 120) 0.68
Quadratic	ns	ns	ns	ns
Potentiation factor ratio				
Linear	0.02 (−0.1, 0.1) 0.88	0.03 (−0.1, 0.1) 0.85	0.04 (−0.1, 0.1) 0.88	0.04 (−0.1, 0.1) 0.91
Quadratic	ns	ns	ns	ns

Model 1, crude; model 2, corrected for age and recruitment center; model 3, corrected for age, recruitment center and BMI; model 4, corrected for age, recruitment center, smoking, and percentage of time spent in moderate and vigorous activity measured by accelerometer.

M/I, insulin sensitivity calculated from clamp; FFM, fat-free mass; ns, not significant.

[a] Log^{10} of variable.

levels. Our results suggest that compared with average sleep duration, short or long sleep duration have deleterious effects in healthy men, whereas in women, short and long sleep duration are associated with better glucose metabolism.

When comparing our results to the literature, it is striking that most studies that use diabetes or markers of diabetes as endpoints, did not test for interaction effects of sex or included only men or only women (3–5). Our sex-specific findings are consistent with earlier experimental and epidemiological studies that did stratify by sex (7, 15, 16, 30–34), showing a stronger effect of short sleep in men, compared with women. We are, however, the first to show opposite effects in men and women. This might be due to the type of cohort studied: we investigated healthy adults, whereas previous studies included population-based cohorts or cohorts of people at risk for diabetes. The only other cohort that studied healthy participants, however, showed no effect of sex on the association between sleep duration and glucose and did not study insulin sensitivity or β-cell function (32). A second explanation for these differences is that we measured insulin sensitivity using a standard hyperinsulinemic-euglycemic clamp and OGTT, which has not been done before in a large cohort. Third, we measured sleep duration using an accelerometer, whereas most studies used self-reported data. Although there is an association between these measures of sleep duration, the 2 measures are not interchangeable (23).

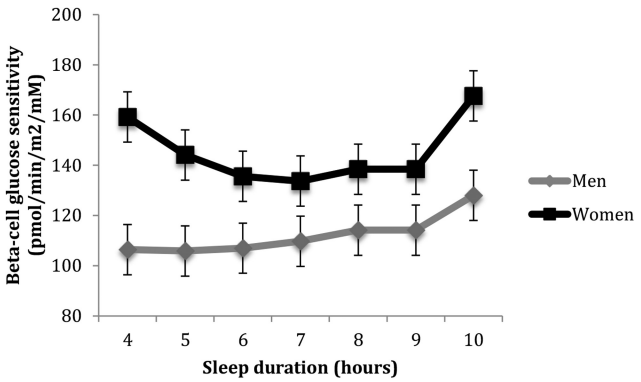

Figure 2. Mean and standard error of β-cell glucose sensitivity, according to sleep duration, stratified by sex, men (n = 314) and women (n = 447). The EGIR-RISC study.

In contrast to studies on diabetes or markers of diabetes as endpoints, studies with other endpoints did show sex-specific effects of sleep curtailment. For example, Knutson (35) showed a negative effect of short sleep on BMI in men, but not in women. Additionally, an intervention study showed sleep loss to result in differential effects on inflammatory factors between the sexes (36). The mecha-

Table 2. Continued

	Women			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Insulin sensitivity				
M/I (μmol/min per kg_{FFM}/nM)				
Linear	−2 (−7, 2) 0.45	−2 (−6, 3) 0.68	−3 (−8, 1) 0.95	−3 (−6, 3) 0.71
Quadratic	ns	ns	ns	ns
OGIS (mL/min per kg_{FFM})				
Linear	−1.3 (−2, 0) 0.06	−1.4 (−3, −0,1) 0.03	−1.2 (−2, 0) 0.05	−1.2 (−2, 0.1) 0.08
Quadratic	0.1 (−0.1, −0.2) 0.09	0.1 (0.1, −0.2) 0.04	0.1 (−0.1, −0.2) 0.10	0.1 (−0.1, −0.2) 0.10
β-Cell function				
β-Cell rate sensitivity (pmol/m^2 per mM)[a]				
Linear	−45 (−86, −3) 0.04	−44 (−86, −9) 0.04	−42 (−84, 1) 0.05	−49 (−93, −4) 0.03
Quadratic	3 (0.2, 6) 0.04	3 (0.1, 6) 0.04	3 (−0.1, 6) 0.05	4 (0.3, 7) 0.03
β-Cell rate sensitivity (pmol/m^2 per mM)[a]				
Linear	71 (−11, 153) 0.26	77 (−6, 160) 0.23	81 (−2, 166) 0.25	61 (−24, 148) 0.23
Quadratic	ns	ns	ns	ns
Potentiation factor ratio				
Linear	0.01 (−0.1, 0.1) 0.78	0.03 (−0.1, 0.1) 0.65	0.01 (−0.1, 0.1) 0.52	0.04 (−0.1, 0.1) 0.89
Quadratic	ns	ns	ns	ns
β-Cell rate sensitivity (pmol/m^2 per mM)[a]				
Linear	71 (−11, 153) 0.26	77 (−6, 160) 0.23	81 (−2, 166) 0.25	61 (−24, 148) 0.23
Quadratic	ns	ns	ns	ns
Potentiation factor ratio				
Linear	0.01 (−0.1, 0.1) 0.78	0.03 (−0.1, 0.1) 0.65	0.01 (−0.1, 0.1) 0.52	0.04 (−0.1, 0.1) 0.89
Quadratic	ns	ns	ns	ns

nisms behind these sex differences are unknown but could entail differences in sleep apnoea, slow wave sleep (SWS) (the deeper substage of the sleep cycle), or circadian clocks. Men are more often affected by sleep apnoea, reducing sleep quantity and quality, including SWS. SWS is thought to be the most "restorative" sleep stage and deprivation of SWS results in insulin resistance and reduced glucose tolerance (37). Women have a larger percentage of SWS per hour of sleep when compared with men (38), which might explain why sleep curtailment is more deleterious in men.

Table 3. Associations of Sleep Duration With Markers of the Metabolic Syndrome (β-Estimates, 95% Confidence Intervals, *P* Values) in Men (n = 341) and Women (n = 447): The EGIR-RISC Study

	Men			
	Model 1	**Model 2**	**Model 3**	**Model 4**
BMI (kg/m^2)				
Linear	0.2 (−0.1, 0.4) 0.23	0.2 (−0.1, 0.4) 0.14	—	0.2 (−0.1, 0.5) 0.10
Quadratic	ns	ns		ns
Systolic BP (mm Hg)				
Linear	−0.7 (−2, 0.2) 0.12	−0.5 (−1, 0.4) 0.28	−0.6 (−2, 0.3) 0.16	−0.6 (−1, 0.3) 0.19
Quadratic	ns	ns	ns	ns
Fasting glucose (mmol/L)				
Linear	−0.3 (−0.5, 0.0) 0.05	−0.3 (−0.5, −0.1) 0.05	−0.3 (−0.5, 0.0) 0.05	−0.3 (−0.6, −0.1) 0.04
Quadratic	0.02 (0.0, 0.1) 0.05	0.02 (0.0, 0.1) 0.03	0.02 (0.0, 0.1) 0.04	0.03 (0.0, 0.1) 0.03
HDL cholesterol (mmol/L)				
Linear	0.01 (−0.1, 0.1) 0.93	0.01 (−0.1, 0.1) 0.91	0.01 (−0.1, 0.1) 0.97	0.03 (−0.2, 0.2) 0.72
Quadratic	ns	ns	ns	ns
Triglycerides (mmol/L)[a]				
Linear	0.01 (−0.1, 0.1) 0.67	0.01 (−0.1, 0.1) 0.38	0.01 (−0.1, 0.1) 0.69	0.01 (−0.1, 0.1) 0.31
Quadratic	ns	ns	ns	ns

Model 1, crude; model 2, corrected for age and recruitment center; model 3; corrected for age, recruitment center and BMI; model 4, corrected for age, recruitment center and percentage of time spent in moderate and vigorous activity measured by accelerometer.

[a] Log^{10} of variable.

Additionally, central and peripheral circadian clocks coordinate the temporal relationships between sleep-wake behaviors, feeding cycles and metabolic rhythms, including glucose homeostasis. Disruption of the circadian clock impairs glucose metabolism (39) and women have a phase-advanced rhythm (40). This makes women less prone to disturbance of the circadian rhythm and therefore it may protect them against the sex dependent deleterious effects of sleep curtailment. Overall, these results suggest that women are protected against the negative effect of sleep curtailment on insulin sensitivity and β-cell function. However, more research is needed to elucidate these potential mechanisms.

Although our data are cross-sectional, we propose that the current findings contribute to the knowledge on the role of sleep duration in the development of diabetes, namely via loss of insulin sensitivity and β-cell function. In the literature, several other pathways mediating this association have been proposed, first sleep curtailment deregulates appetite and physical activity (9). Aside from alterations in health behaviors, curtailed sleep could also affect glucose metabolism via several physiologic pathways, such as the hyperactivation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system (2). Unfortunately, we do not have data to study this; however, proxy measurements of these systems (ie, BP) were not associated with sleep duration. Finally, a recent experimental study by Rao et al showed a role for nonesterified fatty acid levels in the decrease of whole body insulin sensitivity after sleep restriction (16). In general, it is believed that all these different pathways add up to in insulin insensitivity and loss of β-cell function. However, future studies need to include measures of these potential pathways.

Our study has several limitations that need to be discussed. First, no information was available on other sleep related measures that could affect insulin sensitivity and β-cell function, such as shift work, low sleep quality, use of sleep medication, or sleep apnoea, although we correct for a proxy of sleep apnoea, namely BMI. Second, we estimated sleep duration based on the time the accelerometer was not worn for 1 hour, and although this is not a standard method, we validated this using questionnaire data (23). Third, the proportion of healthier participants was higher among the participants with sleep data compared with those without, thus, selection bias might be present, indicating a potential underestimation of the effect of sleep duration on insulin sensitivity and β-cell function. Fourth, in women, we observed an association between sleep duration and insulin sensitivity derived from sampling during an OGTT, but not with the hyperinsulinemic-euglycemic clamp. This might be due to the fact the OGTT derived measures are likely to combine measures of both hepatic and muscle insulin sensitivity as well as incretin effects, compared with the clamp only measuring muscle insulin sensitivity. Finally, our data were cross-sectional, and thus, no causal inferences could be made. Future longitudinal studies are warranted to further explore the associations between sleep duration, insulin sensitivity, and β-cell function.

Our study also had several strengths. First, the assessment of sleep duration in relation to several different indicators of insulin sensitivity and β-cell function, including insulin sensitivity assessed according to the gold standard, the hyperinsulinemic-euglycemic clamp, which was conducted in a large group of participants. Second,

Table 3. Continued

	Women			
	Model 1	**Model 2**	**Model 3**	**Model 4**
BMI (kg/m^2)				
Linear	−0.3 (−0.5, 0.1) 0.08	−0.3 (−0.6, −0.1) 0.02	—	−0.4 (−0.7, −0.1) 0.01
Quadratic	ns	ns		ns
Systolic BP (mm Hg)				
Linear	−0.5 (−1, 0.3) 0.24	−0.7 (−2, 0.2) 0.12	−0.4 (−1, 0.4) 0.29	−0.7 (−2, 0.2) 0.13
Quadratic	ns	ns	ns	ns
Fasting glucose (mmol/L)				
Linear	0.3 (0.1, 0.5) 0.02	0.3 (0.1, 0.5) 0.01	0.3 (0.1, 0.6) 0.01	0.3 (0.1, 0.5) 0.05
Quadratic	−0.02 (−0.1, 0.0) 0.05	−0.02 (−0.1, 0.0) 0.02	−0.02 (−0.1, 0.0) 0.02	−0.02 (−0.1, 0.1) 0.07
HDL cholesterol (mmol/L)				
Linear	−0.2 (−0.4, 0.1) 0.02	−0.2 (−0.4, 0.0) 0.05	−0.1 (−0.4, 0.1) 0.09	−0.2 (−0.4, 0.1) 0.07
Quadratic	0.02 (0.0, 0.1) 0.02	0.02 (0.0, 0.1) 0.04	0.02 (−0.1, 0.1) 0.09	0.02 (0.0, 0.1) 0.05
Triglycerides (mmol/L)[a]				
Linear	0.01 (−0.1, 0.1) 0.35	0.01 (−0.1, 0.1) 0.26	0.01 (−0.1, 0.1) 0.09	0.01 (−0.1, 0.1) 0.24
Quadratic	ns	ns	ns	ns

the inclusion of only healthy participants: although data on such populations are scarce, they are of interest because they show the association without potential confounding from comorbidities. Third, we used linear models to explore the aforementioned associations. This is in contrast to most studies where arbitrary thresholds were assigned to define short and long sleep duration. Finally, sleep duration was assessed with an accelerometer and therefore less prone to bias, compared with self-reported measures (41). Overall, our current findings contribute to the knowledge on the role of sleep duration in the development of diabetes, namely via disturbances of insulin sensitivity and β-cell function.

From our current study, we conclude that sleep duration is associated with insulin sensitivity and β-cell function in a sex-specific manner in clinically healthy people. Prospective studies are needed to study the temporal associations.

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