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Original article

Associations between sleep duration and sleep debt with insulin sensitivity and insulin secretion in the EGIR-RISC Study



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ABSTRACT

Aim. – Extremes in sleep duration play an important role in the development of type 2 diabetes. We examined the associations between sleep duration and sleep debt with estimates of insulin sensitivity and insulin secretion.

Methods. – Data were derived from the European multi-centre EGIR-RISC study. Sleep duration and sleep debt were derived from a sleep questionnaire asking about sleeping time during the week and during the weekend. Insulin sensitivity and insulin secretion were estimated from a 2-hour Oral Glucose Tolerance Test, with samples every 30 minutes. Associations between sleep duration and sleep debt with insulin sensitivity and insulin secretion, were analysed by multiple linear regression models corrected for possible confounders.

Results. – Sleep data were available in 1002 participants, 46% men, mean age 48 ± 8 years, who had an average sleep duration of 7 ± 1 hours [range 3–14] and an average sleep debt (absolute difference hours sleep weekend days minus weekdays) of 1 ± 1 hour [range 0–8]. With regard to insulin sensitivity, we observed an inverted U-shaped association between sleep duration and the Stumvoll MCR in (mL/kg/min), with a corrected β (95% CI) of 2.05 (0.8; 3.3) and for the quadratic term -0.2 (-0.3 ; -0.1). Similarly, a U-shaped association between sleep duration and log HOMA-IR in (μ U/mL), with a corrected β s of -0.83 (-1.4 ; -0.24) and 0.06 (0.02; 0.10) for the quadratic term. Confounders showed an attenuating effect on the associations, while BMI mediated 60 to 91% of the association between sleep duration and insulin sensitivity. No significant associations were observed between sleep duration with insulin secretion or between sleep debt with either insulin sensitivity or insulin secretion.

Conclusions. – Short and long sleep duration are associated with a lower insulin sensitivity, suggesting that sleep plays an important role in insulin resistance and may provide the link with development of type 2 diabetes.

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glucose sensitivity, beta cell rate sensitivity and the potentiation factor ratio. The assessment of insulin secretion by these three model-based parameters has been described earlier [16,17]:

- Beta cell glucose sensitivity (pmol/min/m²/mM): the mean slope of the β -cell dose response in the observed glucose range. This parameter represents the sensitivity of the β -cell to the glucose changes;
- Beta cell rate sensitivity (pmol/m²/mM): the parameter that determines the anticipated response when glucose is rising in the initial part of the OGTT. This parameter is a surrogate of first phase insulin secretion;
- potentiation factor ratio (dimensionless): the ratio of potentiation at 120 min to 0 min. The ratio is calculated by averaging the potentiation factor between 0 and 20 min and between 100 and 120 min. On average the ratio increases during the OGTT.

Covariates

In addition to age and gender, smoking habits (smoker, non-smoker, ex-smoker), alcohol intake (g/week) and family history of diabetes were derived from questionnaires. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Physical activity was assessed using the International Physical Activity Questionnaire [23] and participants were stratified as inactive, minimally active or health enhancing active. Depressive symptoms were assessed by the Centre for Epidemiologic Studies Depression scale (CES-D), a validated self-reported depression scale with 20 items; a score of ≥ 16 is used to describe depressive symptoms [24]. We correct for depressive symptoms as this often explains the association between long sleep duration and diabetes. The recruitment centre was also included as a covariate and it was analysed as a series of dummy variables.

Statistical analysis

First, we analysed differences between participants with and without sleep data at follow-up, using *t*- and Chi² tests. Second, descriptive analyses were presented per sleep group with normally distributed continuous variables shown as means (standard deviations), skewed continuous variables as medians [quartiles] and categorical variables in percentages. Additionally, we calculated *P*-values for trends across the sleep duration groups, by using Chi² tests for the dichotomous and categorical variables and ANOVA for continuous variables. Third, we used linear regression models with second order polynomials to assess potential U-shaped associations between sleep duration (continuous) with insulin sensitivity and insulin secretion. If the second order term was non-significant (*P* < 0.05), we report only the first order term. While there were non-linear associations between sleep debt with insulin sensitivity and insulin secretion, we reported the associations per tertiles of sleep debt. Potential confounders were added to the models in a stepwise approach. Data were log transformed (natural log) for positively skewed outcome variables: Matsuda, beta cell glucose sensitivity and beta cell rate sensitivity. Fourth, we assessed whether sex was an effect modifier, however no interaction effects for sex were observed (*P* > 0.3). All analyses described above were presented unadjusted, adjusted for age, sex, recruitment centre and depression score (model 2), model 2 plus smoking, alcohol use and physical activity (model 3). For sleep debt, we additionally adjusted models 2–3 for sleep duration. Finally, to quantify the mediating effect of BMI in the association between sleep duration and metabolic factors, we conducted mediation analysis, using the SPSS macros provided by Preacher and Hayes [25,26], corrected for the possible confounders from model 3. Bootstrapped confidence intervals (1000 resamples) were used to

interpret direct and indirect effects. Proportion mediated was used as a measure of effect size (indirect effect divided by total effect). No mediation analysis was conducted for the association between sleep duration and insulin secretion as well as for the association between sleep debt, insulin sensitivity and insulin secretion, as the total effects were not significant. IBM SPSS Statistics version 22 was used for data analysis and *P*-values < 0.05 were considered to be statistically significant. Mean imputation was performed for missing covariates. *P*-values < 0.10 were considered to be statistically significant with regard to effect modifiers.

Results

Sleep data were available in 1002 participants, 46% men, mean age 48 ± 8 years, who had an average sleep duration of 7 ± 1 hours [range 3 to 14] and an average sleep debt of 1 ± 1 hour [range 0–8]. There was a statistically significant difference in age between participants with and without sleep data: mean age 48 ± 8 years vs. mean age 50 ± 10 years, respectively, *P* = 0.01. Participants with sleep data were not only younger, they also had marginally (not significant) better clinical characteristics: higher OGIS (11.2 vs. 10.8 mL/min/kg_{FFM}) and Stumvoll values (9.0 vs. 8.3 mL/kg/min or μ mol/kg/min/pmol/L), and a lower BMI (25.8 vs. 25.9 kg/m²). This suggests that our study population was slightly healthier than those without sleep data at the three-year follow-up. Characteristics stratified by sleep duration group are presented in Table 1. We observed a significant difference between the groups for BMI, with those sleeping 3–5 h or ≥ 9 h having a higher BMI, compared to those sleeping 7 h (*P* < 0.001).

Sleep duration

With regard to insulin sensitivity (Tables 1, 2a, 2b), we observed an inverted U-shaped association between sleep duration and the Stumvoll MCR in (mL/kg/min), with a β (95% CI) of 2.05 (0.8; 3.3) and -0.2 (-0.3 ; -0.1) for the quadratic term, corrected for age, recruitment centre, depression score, smoking, alcohol and physical activity. Similarly, we observed inverted U-shaped associations between sleep duration and Stumvoll ICI (μ mol/kg/min/pmol/L) as well as for logMatsuda (μ mol/min/kg), with respectively confounder adjusted β s and β^2 s of 0.03 (0.01; 0.04) and -0.01 (-0.01 ; -0.01) as well as 0.47 (0.1; 0.8) and -0.03 (-0.06 ; -0.01). A U-shaped association between sleep duration and log HOMA-IR in (μ U/mL), with a corrected β s of 2–0.83 (-1.4 ; -0.24) and β^2 of 0.06 (0.02; 0.10). Overall, these results suggest that participants with short or long sleep duration were less insulin sensitive. Additionally, all confounders attenuated the associations. BMI mediated 60 to 91% of the association between sleep duration and insulin sensitivity. No significant association was observed for sleep duration and OGIS. Additionally, no associations were observed for sleep duration and insulin secretion parameters.

Sleep debt

We observed no significant associations between sleep debt with insulin sensitivity or insulin secretion (Tables 3a and 3b). These results suggest that sleep debt is not associated with insulin sensitivity or insulin secretion. No interactions with sex were observed.

Discussion

The aim of this study was to examine the associations between sleep duration and sleep debt with estimates of insulin sensitivity and insulin secretion. The data were derived from the cross-sectional data of the three-year follow-up of middle-aged

Table 1
Characteristics of the study population ($n = 1002$), stratified by average sleep duration: the EGIR-RISC study.

	Sleep 3–5 hours ($n = 45$)	Sleep 6 hours ($n = 159$)	Sleep 7 hours ($n = 440$)	Sleep 8 hours ($n = 294$)	Sleep ≥ 9 hours ($n = 64$)	P for trend
Sex (men, %)	42.2	52.8	51.8	38.1	29.7	0.001
Age (years)	49.7 (7.7)	48.5 (8.6)	47.3 (8.1)	46.9 (7.9)	47.4 (7.9)	0.42
BMI (kg/m^2)	27.3 (5.1)	26.4 (4.5)	25.6 (3.9)	25.1 (3.8)	26.9 (5.3)	0.001
Smoking status (non-smoker, %)	45.5	45.5	46.4	47.4	45.3	0.44
Alcohol (g/week)	35.0 [0.0–88.1]	40.3 [0.0–120.2]	54.2 [15.0–119.6]	54.2 [15.0–100.0]	35.0 [0.0–86.2]	0.16
Physical activity (IPAQ score, %)						0.86
Inactive	24.4	21.0	22.2	25.7	23.8	
Minimally active	33.3	38.2	41.2	36.6	33.3	
Health enhancing active	42.2	40.8	36.6	37.7	42.9	
Depression score (≥ 16 , %)	36.6	16.9	14.1	11.7	16.9	0.09
Sleep debt (hours)	0.0 [0.0–1.0]	1.0 [0.0–1.0]	1.0 [0.0–1.0]	1.0 [0.0–2.0]	2.0 [0.0–2.0]	0.002
Insulin sensitivity						
HOMA-IR ($\mu\text{U}/\text{mL}$)	1.2 [0.9–2.3]	1.2 [0.7–1.9]	1.1 [0.7–1.6]	1.4 [0.8–1.7]	1.2 [0.9–1.6]	0.06
Stumvoll MCR ($\text{mL}/\text{kg}/\text{min}$)	8.7 [7.2–9.8]	9.2 [7.6–10.2]	9.5 [8.3–10.4]	9.6 [8.1–10.4]	8.9 [7.2–10.4]	0.004
Stumvoll ISI ($\mu\text{mol}/\text{kg}/\text{min}/\text{pmol}/\text{L}$)	0.10 [0.08–0.12]	0.11 [0.09–0.12]	0.11 [0.10–0.12]	0.11 [0.10–0.12]	0.10 [0.08–0.12]	0.004
OGIS ($\text{mL}/\text{min}/\text{kg}_{\text{FFM}}$)	10.5 (2.2)	10.8 (2.8)	11.4 (2.9)	11.4 (2.8)	11.1 (2.8)	0.19
Matsuda ($\mu\text{mol}/\text{min}/\text{kg}$)	19.5 [24.1–25.0]	20.6 [13.7–31.6]	23.4 [17.2–33.8]	23.9 [15.8–33.7]	20.3 [13.8–32.3]	0.03
Insulin secretion						
Beta cell glucose sensitivity ($\text{pmol}/\text{min}/\text{m}^2/\text{mM}$)	101 [68–151]	108 [74–152]	112 [84–156]	113 [81–166]	113 [83–187]	0.43
Beta cell rate sensitivity ($\text{pmol}/\text{m}^2/\text{mM}$)	841 [127–1560]	900 [334–1495]	897 [461–1566]	904 [314–1599]	975 [393–1547]	0.79
Potentiation factor ratio	1.6 [1.1–2.3]	1.4 [1.1–2.2]	1.7 [1.2–2.6]	1.8 [1.2–2.4]	1.5 [1.1–2.3]	0.06

Normally distributed continuous data are presented as means (SD). Skewed variables are shown as medians [quartiles]. Categorical data are presented in percentages. P -values for trends across the sleep duration groups were calculated, by using Chi^2 tests for the dichotomous and categorical variables and ANOVA for continuous variables. BMI: body mass index; IPAQ: International Physical Activity Questionnaire; CES-D: Centre for Epidemiologic Studies Depression scale, score ≥ 16 ; significant depression; OGIS: oral glucose insulin sensitivity; FFM: fat free mass; HOMA-IR: homeostasis model assessment of insulin resistance; MCR: metabolic clearance rate; ISI: Insulin Sensitivity Index.

participants of the EGIR-RISC study. The results of this study showed a U-shaped association, with participants who sleep 6, 7 or 8 hours per night had a higher insulin sensitivity, compared to participants who slept 3 to 5 hours or ≥ 9 hours per night. This association was mediated by BMI. Additionally, we observed no association between sleep duration and estimates of insulin secretion. Finally, in our cohort we observed no significant association between sleep debt with insulin sensitivity and insulin secretion.

This study adds to the literature, as it investigates the association between sleep and several additional estimates of insulin sensitivity, such as the oral glucose insulin sensitivity (OGIS) index and the Matsuda index for insulin sensitivity and for estimates of insulin secretion derived from OGTT-data. Our findings on sleep

duration and insulin sensitivity are consistent with earlier studies that have shown extremes in sleep duration to be associated with insulin resistance [7–15]. In contrast to our previous study on sleep and insulin sensitivity in the EGIR-RISC cohort [15], we did not observe a significant interaction effect of sex nor an association between sleep duration and insulin secretion. This might be due to the smaller effect size in the current population, the more homogenous population (healthier), the smaller sample size as well as the different method of determining sleep duration: questionnaires versus accelerometer [20].

Additionally, our study adds to the literature as besides sleep duration, sleep debt was examined in relation to insulin sensitivity and secretion estimates. To the authors' knowledge, this is the first

Table 2a

Linear stepwise regression models of the associations between sleep duration, markers of insulin sensitivity and insulin secretion ($n = 1002$): the EGIR-RISC study. Beta estimates and 95% confidence estimates for insulin sensitivity.

Outcome	Model 1	Model 2	Model 3	Indirect effect BMI
OGIS ($\text{mL}/\text{min}/\text{kg}_{\text{FFM}}$)				
Linear	1.05 (–0.2; 2.2)	1.28 (–0.2; 2.8)	1.12 (–0.4; 2.6)	1.02 (0.4; 2.1)
Quadratic	ns	ns	ns	
Stumvoll MCR ($\text{mL}/\text{kg}/\text{min}$)				
Linear	1.95 (1.0; 2.9)	2.25 (1.0; 3.5)	2.05 (0.8; 3.3)	1.64 (0.6; 2.8)
Quadratic	–0.1 (–0.2; –0.1)	–0.2 (–0.3; –0.1)	–0.2 (–0.3; –0.1)	
Stumvoll ISI ($\mu\text{mol}/\text{kg}/\text{min}/\text{pmol}/\text{L}$)				
Linear	0.02 (0.01; 0.04)	0.03 (0.01; 0.04)	0.03 (0.01; 0.04)	0.02 (0.01; 0.03)
Quadratic	–0.01 (–0.01; –0.01)	–0.01 (–0.01; –0.01)	–0.01 (–0.01; –0.01)	
HOMA-IR ($\mu\text{U}/\text{mL}$) ^a				
Linear	–0.48 (–0.1; –0.05)	–0.86 (–1.5; –0.26)	–0.83 (–1.4; –0.24)	–0.50 (–0.9; –0.16)
Quadratic	0.03 (0.01; 0.06)	0.06 (0.02; 0.10)	0.06 (0.02; 0.10)	
Matsuda ($\mu\text{mol}/\text{min}/\text{kg}$) ^a				
Linear	0.37 (0.1; 0.6)	0.52 (0.2; 0.9)	0.47 (0.1; 0.8)	0.30 (0.1; 0.5)
Quadratic	–0.02 (–0.04; –0.01)	–0.04 (–0.06; –0.01)	–0.03 (–0.06; –0.01)	

Model 1: crude model.

Model 2: adjusted for age, recruitment centre and depression score.

Model 3: adjusted for age, recruitment centre, depression score, smoking, alcohol and physical activity.

OGIS: oral glucose insulin sensitivity; FFM: fat free mass; MCR: metabolic clearance rate; ISI: Insulin Sensitivity index.

$P < 0.05$ depicted in bold.

NS: second order term was non-significant ($P < 0.05$).

^a Natural Log of variable.

Table 2b

Linear stepwise regression models of the associations between sleep duration, markers of insulin sensitivity and insulin secretion ($n = 1002$); the EGIR-RISC study. Beta estimates and 95% confidence estimates for insulin secretion.

Outcome	Sleep duration in groups (hours)	Model 1	Model 2	Model 3
Beta cell glucose sensitivity (pmol/min/m ² /mM) ^a	Linear	0.27 (−0.7; 1.2)	−0.12 (−1.5; 1.3)	−0.19 (−1.6; 1.2)
	Quadratic	ns	ns	ns
Beta cell rate sensitivity (pmol/m ² /mM) ^a	Linear	0.03 (−5.2; 5.2)	0.05 (−7.3; 7.4)	0.59 (−6.9; 8.0)
	Quadratic	ns	ns	ns
Potentiation factor ratio	Linear	0.32 (−0.2; 0.8)	0.27 (−0.5; 1.0)	0.25 (−0.5; 1.0)
	Quadratic	ns	ns	ns

Model 1: crude model.

Model 2: adjusted for age, recruitment centre and depression score.

Model 3: adjusted for age, recruitment centre, depression score, smoking, alcohol and physical activity.

OGIS: oral glucose insulin sensitivity; FFM: fat free mass; MCR: metabolic clearance rate; ISI: Insulin Sensitivity index.

$P < 0.05$ depicted in bold.

NS: second order term was non-significant ($P < 0.05$).

^a Natural Log of variable.

Table 3a

Linear regression models of the associations between absolute sleep debt, markers of insulin sensitivity and insulin secretion ($n = 1002$); the EGIR-RISC study. Beta estimates and 95% confidence estimates for insulin sensitivity.

Outcome	Sleep debt (hours)	Model 1	Model 2	Model 3
Insulin sensitivity OGIS (mL/min/kg _{FFM})	0–1	Ref	Ref	Ref
	> 1–2	0.25 (−0.2; 0.7)	0.12 (−0.3; 0.5)	0.10 (−0.3; 0.5)
	> 2	0.38 (−0.1; 0.8)	−0.12 (−0.5; 0.3)	−0.1 (0.05; 0.3)
Stumvoll MCR (mL/kg/min)	0–1	Ref	Ref	Ref
	> 1–2	0.24 (−0.1; 0.6)	0.06 (−0.3; 0.4)	0.04 (−0.3; 0.4)
	> 2	0.11 (−0.2; 0.4)	−0.05 (−0.4; 0.3)	−0.02 (−0.3; 0.3)
Stumvoll ISI (μmol/kg/min/pmol/L)	0–1	Ref	Ref	Ref
	> 1–2	(−0.1; 0.1)	0.01 (−0.1; 0.1)	0.01 (−0.1; 0.1)
	> 2	(−0.1; 0.1)	(−0.1; 0.1)	(−0.1; 0.1)
HOMA-IR (μU/mL) ^a	0–1	Ref	Ref	Ref
	> 1–2	−0.09 (−0.2; 0.1)	−0.09 (−0.2; 0.1)	−0.09 (−0.2; 0.1)
	> 2	−0.07 (−0.2; 0.1)	−0.07 (−0.2; 0.1)	−0.09 (−0.2; 0.1)
Matsuda (μmol/min/kg) ^a	0–1	Ref	Ref	Ref
	> 1–2	0.07 (−0.1; 0.2)	0.04 (−0.1; 0.2)	0.04 (−0.1; 0.2)
	> 2	0.01 (−0.1; 0.1)	−0.02 (−0.1; 0.1)	−0.01 (−0.1; 0.1)

Model 1: crude model.

Model 2: adjusted for age, recruitment centre, sleep duration and depression score.

Model 3: adjusted for age, recruitment centre, sleep duration, depression score, smoking, alcohol and physical activity.

OGIS: oral glucose insulin sensitivity; FFM: fat free mass; MCR: metabolic clearance rate; ISI: Insulin sensitivity index.

$P < 0.05$ depicted in bold.

^a Natural Log of variable.

Table 3b

Linear regression models of the associations between absolute sleep debt, markers of insulin sensitivity and insulin secretion ($n = 1002$); the EGIR-RISC study. Beta estimates and 95% confidence estimates for insulin secretion.

Outcome	Sleep debt (hours)	Model 1	Model 2	Model 3
Insulin secretion Beta cell glucose sensitivity (pmol/min/m ² /mM) ^a	0–1	Ref	Ref	Ref
	> 1–2	−0.08 (−0.4; 0.3)	−0.13 (−0.5; 0.3)	−0.16 (−0.5; 0.2)
	> 2	0.19 (−0.2; 0.5)	0.17 (−0.2; 0.5)	0.14 (−0.2; 0.5)
Beta cell rate sensitivity (pmol/m ² /mM) ^a	0–1	Ref	Ref	Ref
	> 1–2	−1.05 (−2.9; 0.7)	−1.81 (−3.7; 0.1)	−1.83 (−3.7; 0.1)
	> 2	−1.21 (−3.1; 0.7)	−1.55 (−3.5; 0.5)	−1.37 (−3.4; 0.6)
Potentiation factor ratio	0–1	Ref	Ref	Ref
	> 1–2	0.13 (−0.1; 0.3)	0.12 (−0.1; 0.3)	0.12 (−0.1; 0.3)
	> 2	−0.03 (−0.2; 0.2)	−0.05 (−0.2; 0.2)	−0.05 (−0.2; 0.2)

Model 1: crude model.

Model 2: adjusted for age, recruitment centre, sleep duration and depression score.

Model 3: adjusted for age, recruitment centre, sleep duration, depression score, smoking, alcohol and physical activity.

OGIS: oral glucose insulin sensitivity; FFM: fat free mass; MCR: metabolic clearance rate; ISI: Insulin Sensitivity index.

$P < 0.05$ depicted in bold.

^a Natural Log of variable.

study to investigate these associations. In contrast to the study in people with type 2 diabetes, no association was observed between sleep debt, insulin sensitivity and secretion estimates [18]. These contradictory findings could be due to different population types, people with type 2 diabetes versus the general population or differences in outcome with HbA1c and HOMA-IR versus other insulin sensitivity and secretion indexes, such as OGIS measured from an OGTT. More research, in larger groups is needed to determine the role of sleep debt in the development of type 2 diabetes.

Several possible mechanisms could mediate the association between sleep, insulin sensitivity and secretion estimates. First, the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic activation have been suggested to play a role in the development of the metabolic syndrome. Activation of the HPA-axis and sympathetic activation can lead to sleeplessness and vice versa [27]. Hyperactivation of the HPA-axis or sympathetic activation leads to an increase in cortisol levels, which contribute to insulin resistance, dyslipidaemia and abdominal obesity [28]. Second, there is some evidence that reduced sleep duration is associated with activation of the inflammatory signalling pathway [28]. Overexpression of TNF- α in turn leads to insulin resistance and to higher fasting plasma glucose levels [29]. Finally, the hunger regulating hormones leptin and ghrelin are associated with sleep restriction. Sleep restriction causes an increase in ghrelin levels and a decrease in leptin levels, which regulate satiety and hunger, respectively. This leads to higher intake of food and subsequently weight gain and insulin resistance [30]. This pathway is supported by our current findings, with BMI mediating the association between sleep and insulin sensitivity.

This study has several limitations that need to be discussed. First, we were unable to use the baseline data of the EGIR-RISC cohort, to assess changes in sleep and changes in metabolic parameters, due to different sleep measures at the two time points. Second, the study was cross-sectional and therefore no causal inferences can be made. Future prospective studies are needed to further investigate the associations between sleep duration and sleep debt with insulin sensitivity and insulin secretion. Third, we lack information on the stability of the reported sleep pattern, which leaves us unable to determine if the measured sleep pattern i.e. 3–5 h sleep is a chronic condition or a temporary behaviour. Fourth, while we did not collect information the bedtime or waking up time, we were not able to measure sleep variability or social jetlag [31]. Finally, we used only self-reported sleeping times. To date, there is no gold standard for measures of sleep. Self-report measures of sleep are correlated with measures from diaries or accelerometer measures [20]. Associations found in other studies, might therefore be due to the different methods used to assess sleep duration.

This study also has several strengths. We used data from a large, well-phenotyped cohort, with elaborate measurements including an OGTT with 30 minute intervals between drawing blood, as well as several confounders. Second, we are the first study to examine the associations between sleep debt and estimates of insulin sensitivity and insulin secretion. Finally, we confirmed the results from Byberg et al. [13], however in contrast we used several markers for OGTT-derived insulin sensitivity, providing additional information on the association between sleep and insulin sensitivity.

Conclusion

Short and long sleep duration are associated with a lower insulin sensitivity, suggesting that sleep plays an important role in insulin resistance and may provide the link with development of type 2 diabetes.

Disclosure of interest

The RISC study received the European Union Grant QL1-CT-2001-01252 and AstraZeneca, Sweden provided additional finances. Merck, France supported the European Group for the study of Insulin Resistance (EGIR). The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2018.11.001>.

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