

# Subjective Sleep Complaints Are Associated With Insulin Resistance in Individuals Without Diabetes

## The PPP-Botnia Study

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**OBJECTIVE**—Sleep disorders and subjective sleep complaints have been associated with increased risk of type 2 diabetes. The evidence with respect to insulin resistance (IR) and insulin secretion in individuals without type 2 diabetes has been scarce and elusive. We examined if subjective sleep complaints and their co-occurrence were associated with IR and insulin secretion in adult women and men without diabetes.

**RESEARCH DESIGN AND METHODS**—Women ( $n = 442$ ) and men ( $n = 354$ ) 18–75 years of age without type 2 diabetes underwent an oral glucose tolerance test (OGTT), with insulin and glucose measured at fasting and at 30 and 120 min. Complaints related to sleep apnea, insomnia, and daytime sleepiness were self-rated with the Basic Nordic Sleep Questionnaire.

**RESULTS**—In comparison with individuals with no or minor sleep complaints, those with more frequent complaints of sleep apnea, insomnia, and daytime sleepiness were more insulin resistant, as evidenced by higher fasting insulin concentrations and insulin and glucose responses to OGTT, and more frequently had high homeostasis model assessment of IR and low insulin sensitivity index values. The likelihood of being insulin resistant increased significantly and linearly according to the accumulation of co-occurring sleep complaints. These associations changed only a little when adjusted for mediating and confounding factors and for depressive symptoms. Sleep complaints were not associated with indices of deficiency in insulin secretion.

**CONCLUSIONS**—Subjective sleep complaints were associated with IR. The likelihood of being insulin resistant increased according to accumulation of co-occurring sleep complaints. Sleep complaints were not associated with deficiency in insulin secretion.

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In several cross-sectional and prospective studies, sleep apnea, sleep disordered breathing, habitual snoring, insomnia, difficulties in initiating and maintaining sleep, and daytime sleepiness have been associated with the

prevalence and the incidence of type 2 diabetes (1–6). Although these findings suggest that sleep disorders and subjective sleep complaints may carry an increased risk for type 2 diabetes, the evidence with respect to insulin resistance

(IR) and insulin secretion, two major features of type 2 diabetes, in individuals without type 2 diabetes has been scarce and elusive.

In individuals without a history of or concurrently diagnosed type 2 diabetes, polysomnography-based sleep disordered breathing was associated with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (2), a higher degree of IR (7,8), and a decreased degree of insulin sensitivity and pancreatic  $\beta$ -cell function during a frequently sampled intravenous glucose tolerance test (9). However, subjective complaints of sleep apnea, habitual snoring, and daytime sleepiness were not associated with IFG, IGT, and IR (10). Finally, a recent study has reported that subjective complaints of frequent snoring were not associated with fasting insulin, glucose, and IR, whereas insomnia, a combined measure of actigraphy-based sleep latency and fragmentation, and subjective complaints were associated with lower fasting insulin values and a lower likelihood of being insulin resistant (4).

We studied whether subjective complaints of sleep apnea (habitual snoring and sleep disordered breathing), insomnia (difficulties in initiating and/or maintaining sleep), and daytime sleepiness were associated with IR and insulin secretion in a population-based sample of 18–75-year-old Finnish women and men without a history of or concurrently diagnosed type 2 diabetes. Our study contributes to previous studies in two ways. First, we tested if the degree of glycemia and IR increased according to accumulation of subjective sleep complaints that often co-occur together (11,12). Second, we tested if symptoms of depression accounted for the associations. The latter was seen as relevant since sleep complaints may indicate the presence of depression (13), and symptoms of depression have been linked with the prevalence and the incidence of type 2 diabetes (14,15), and with IR in populations without type 2 diabetes (16).

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## RESEARCH DESIGN AND METHODS

### Participants

The population-based Prevalence, Prediction, and Prevention of Diabetes (PPP)–Botnia Study has been described in detail elsewhere (16–19). Of the 9,518 invited individuals, 5,208 (2,443 men and 2,765 women, 55%) participated. A psychological survey including questions on sleep complaints was added later to the study protocol and administered to 1,335 consecutive individuals (59.8% of 2,232) recruited from the Vasa area. A total of 1,066 (79.9%) individuals returned the questionnaire, with 949 (535 women and 414 men) providing complete data on subjective sleep complaints. Of these, we excluded 47 with previously and 24 with newly diagnosed diabetes. An additional 82 individuals had missing oral glucose tolerance test (OGTT) values of insulin/glucose. In total, 796 participants (442 women and 354 men) without type 2 diabetes had complete data available on all study variables. The included participants differed from the entire PPP–Botnia sample without type 2 diabetes ( $n = 3,885$  after excluding 257 with history of/new diabetes) by being older, more frequently retired, consuming more alcohol, reporting regular exercise more frequently, and having higher fasting and 120-min glucose. All participants gave their written informed consent, and the study protocol was approved by the Ethics Committee of the Helsinki University Central Hospital, Finland.

### Insulin resistance and insulin secretion

The subjects participated in an OGTT by ingesting 75 g of glucose after a 12-h overnight fast. During the OGTT, venous samples for plasma glucose and serum insulin were drawn at 0, 30, and 120 min. The homeostasis model assessment of IR method (HOMA-IR) (20), insulin sensitivity index (ISI) (21), corrected insulin response (CIR) (22), and disposition index (DI) (23) were used as indices of IR and insulin secretion. The following formulas were used to calculate these variables:  $\text{HOMA-IR} = (\text{fasting plasma insulin [mU/L]} \times \text{fasting plasma glucose level [mmol/L]})/22.5$ ;  $\text{ISI} = 10,000/\sqrt{(\text{fasting plasma glucose level [mmol/L]} \times \text{fasting insulin [mU/L]})}$ ;  $\text{CIR} = (100 \times \text{insulin [mU/L]} \text{ at } 30 \text{ min})/\text{glucose [mmol/L]} \text{ at } 30 \text{ min} \times (\text{glucose [mmol/L]} \text{ at } 30 \text{ min} - 3.89 \text{ mmol/L})$ ; and

$\text{DI} = \text{CIR} \times \text{ISI}$ . Area under the curve (AUC) of insulin and AUC glucose were calculated as follows:  $\text{AUC insulin} = 15 \times \text{fasting plasma insulin (mU/L)} + 15 \times \text{insulin (mU/L)} \text{ at } 30 \text{ min} + 45 \times \text{insulin (mU/L)} \text{ at } 120 \text{ min}$ ;  $\text{AUC glucose} = 15 \times \text{fasting plasma glucose (mmol/L)} + 15 \times \text{glucose (mmol/L)} \text{ at } 30 \text{ min} + 45 \times \text{glucose (mmol/L)} \text{ at } 120 \text{ min}$ .

### Assays

Plasma glucose was measured with a glucose dehydrogenase method (HemoCue, Ångelholm, Sweden) and serum insulin by a fluoroimmunoassay (Delphia; Perkin-Elmer Finland, Turku, Finland).

### Sleep complaints

Self-reported complaints of sleep apnea, insomnia, and daytime sleepiness the previous 3 months were assessed with the Basic Nordic Sleep Questionnaire (24). Complaints of sleep apnea (frequency and quality of snoring and frequency of breathing pauses), insomnia (frequency of difficulties in falling asleep and maintaining sleep and frequency of awakenings per night), and daytime sleepiness (frequency of feeling excessively sleepy in the morning after awakening, during daytime, and napping) were rated on a scale ranging from never or less than once per month (1) to every day/night or almost every day/night per week (5); the quality of snoring was assessed using a scale ranging from “I don’t snore” (1) to “I snore very loud and intermittently (there are silent breathing pauses when snoring is not heard and at times very loud snorts with gasping)” (5), and frequency of awakenings during one night was assessed using a scale ranging from “I do not wake up at night” (1) to at least five times per night (5).

Answers to questions on sleep apnea, insomnia, and daytime sleepiness were summed, and the top quartile was used as a cutoff for identifying individuals with more frequent/severe complaints. The group whose complaints of sleep apnea, insomnia, and daytime sleepiness fell below the top quartile and who also reported using no sleeping pills (9.4%,  $n = 75$ , reported using sleeping pills) was used as the reference group (from here on referred to as “no or minor sleep complaints”).

### Mediating and confounding factors

The subjects self-reported their weekly alcohol consumption (g/week), current

smoking status (yes vs. no or former smoker), occupational status (categorized according to the classification system of Statistics Finland: manual workers, junior clericals, senior clericals, students, and retirees), and family history of known diabetes (yes vs. no) in at least one first-degree relative (father, mother, sibling, or child). In addition, frequency and intensity of current physical activity and physical activity during the past 12 months were assessed using the validated Kuopio Ischemic Heart Disease Questionnaire (25). This questionnaire provides detailed information on common lifestyle, commuting, and leisure-time physical activity and enables assessment of total physical activity as metabolic equivalent (MET) hours per week ( $\text{MET} \times \text{hours/week}$ ). Based upon leisure-time activity, the participants were assigned into two groups: the regularly exercising group performed >30 min physical activity three or more times per week with intensity resulting in breathlessness and/or sweating and the less/no exercising group performed less or no physical activity. Body weight and height were measured, BMI was calculated, and depressive symptoms were self-rated using the Beck Depression Inventory II (26).

### Statistical analyses

Multiple linear regression analyses, unstandardized regression coefficients, and 95% CIs were computed to examine associations between sleep complaints and fasting, 120-min, and AUC glucose and insulin. Logistic regression analyses, odds ratios (ORs), and 95% CIs were computed to examine if sleep complaints were associated with HOMA-IR, ISI, CIR, and DI indices of IR and insulin secretion dichotomized such that the top quartile in the HOMA-IR was contrasted with the lower three quartiles, and the bottom quartiles in the ISI, CIR, and DI were contrasted with the upper three quartiles. Variables were log transformed where appropriate, and the associations were adjusted for mediating and confounding factors.

**RESULTS**—Of the individuals who during the previous 3 months reported more frequent/severe complaints of sleep apnea ( $n = 162$ ), 143 (88%) reported snoring at least three nights per week, 47 (29%) reported at least very loud and intermittent snoring, and 34 (21%) reported breathing pauses at least three nights per week. Of those with more frequent/severe insomnia ( $n = 163$ ),

39 (24%) reported having problems in initiating sleep at least three nights per week, 120 (74%) reported waking up every night or almost every night per week, and 52 (32%) reported waking up at least three times per night. Of those with more frequent/severe daytime sleepiness ( $n = 202$ ), 95 (47%) reported feeling sleepy in the morning at least three days per week, 103 (51%) reported feeling sleepy during daytime at least three days per week, and 94 (47%) reported having had naps at least three days per week.

Of the sleep complaints, daytime sleepiness occurred most frequently

alone ( $n = 104$ , 40%), followed by sleep apnea ( $n = 81$ , 31%) and insomnia ( $n = 77$ , 29%). The most common combination of two co-occurring complaints was insomnia–daytime sleepiness ( $n = 38$ , 41%), followed by sleep apnea–daytime sleepiness ( $n = 33$ , 36%) and sleep apnea–insomnia ( $n = 21$ , 23%). All three sleep complaints were present in only 27 individuals and thus were not separately analyzed.

Table 1 shows that individuals with more frequent complaints of sleep apnea, insomnia, and daytime sleepiness were older, heavier, more frequently manual

workers/retired, and more depressed, and those with sleep apnea were additionally more frequently men, current smokers, more frequent alcohol users, and those who exercised regularly less frequently. Further, complaints of sleep apnea and insomnia were more frequent in post- than premenopausal women.

### Sleep complaints and IR and insulin secretion

Those with more frequent sleep complaints (sleep apnea, insomnia, or daytime sleepiness) were significantly more insulin resistant than individuals with no

**Table 1—Characteristics of the subjects with no or minor complaints and more frequent subjective sleep complaints**

	More frequent subjective sleep complaints						
	No or minor complaints	Sleep apnea	P vs. no or minor complaints	Insomnia	P vs. no or minor complaints	Daytime sleepiness	P vs. no or minor complaints
	$n = 395$	$n = 162$		$n = 163$		$n = 202$	
Sex, men/women (%)	44.6/55.4	68.5/31.5	0.001	36.8/63.2	0.092	39.6/60.4	0.247
Age (years)	48.3 ± 14.1	54.3 ± 13.9	0.001	55.7 ± 15.9	0.001	50.8 ± 15.8	0.049
BMI (kg/m <sup>2</sup> )	25.9 ± 3.7	27.7 ± 4.1	0.001	27.2 ± 4.8	0.001	26.7 ± 4.9	0.011
Current smoker, $n$ (%)	42 (10.7)	33 (20.8)	0.002	15 (9.3)	0.614	28 (14.0)	0.237
Regular exercise, $n$ (%)	254 (64.5)	81 (51.9)	0.007	95 (59.4)	0.261	118 (58.7)	0.170
Alcohol consumption, * $n$ (%)							
None	83 (21.4)	34 (21.4)	0.002	47 (29.4)	0.055	44 (22.1)	0.428
12–48 g/week	194 (50.0)	56 (35.2)		80 (50.0)		89 (44.7)	
60 ≥ g/week	111 (28.6)	69 (43.4)		33 (20.6)		66 (33.2)	
Occupational status, $n$ (%)							
Senior clerical	101 (25.9)	38 (23.8)	0.001	19 (11.9)	0.001	39 (19.7)	0.027
Junior clerical	147 (37.7)	34 (21.3)		41 (25.8)		59 (29.8)	
Manual worker	47 (12.1)	33 (20.6)		18 (11.3)		31 (15.7)	
Retired	89 (22.8)	53 (33.1)		76 (47.8)		64 (32.3)	
Student	6 (1.5)	2 (1.3)		5 (3.1)		5 (2.5)	
Post-menopause, women, $n$ (%)	82 (38.7)	34 (66.7)	0.001	61 (59.8)	0.001	50 (41.7)	0.593
First-degree family history of diabetes, $n$ (%)	112 (28.4)	42 (25.9)	0.561	48 (29.4)	0.795	52 (25.7)	0.499
Beck depression inventory score (0–63)	4.0 ± 4.4	6.6 ± 6.7	0.001	9.4 ± 7.1	0.001	9.3 ± 7.5	0.001
Insulin (mU/L), median (25–75%)							
Fasting	5.2 (3.6–7.3)	6.6 (4.2–10.4)	0.003	6.0 (4.2–9.1)	0.045	6.0 (3.9–8.7)	0.041
120 min	20.9 (12.4–32.8)	27.7 (17.7–54.0)	0.001	31.7 (17.9–50.3)	0.001	26.7 (16.1–44.9)	0.001
AUC mU/L/120 min	4,366 ± 2,885	5,807 ± 4,168	0.001	5,552 ± 3,115	0.001	5,360 ± 3,283	0.001
Glucose (mmol/L)							
Fasting	5.5 ± 0.5	5.6 ± 0.5	0.340	5.6 ± 0.5	0.121	5.5 ± 0.5	0.844
120 min	5.2 ± 1.4	5.8 ± 1.7	0.001	5.7 ± 1.6	0.001	5.6 ± 1.6	0.001
AUC mmol/L/120 min	818 ± 121	883 ± 148	0.001	859 ± 130	0.001	857 ± 136	0.001
IFG, $n$ (%)	56 (14.9)	26 (16.0)	0.740	25 (15.3)	0.904	26 (12.9)	0.494
IGT, $n$ (%)	17 (4.3)	21 (13.0)	0.001	15 (9.2)	0.024	22 (10.9)	0.002
HOMA-IR, top quartile $n$ (%)	78 (19.7)	65 (40.1)	0.001	55 (33.7)	0.001	64 (31.7)	0.001
ISI, bottom quartile $n$ (%)	74 (18.7)	64 (39.5)	0.001	60 (36.8)	0.001	65 (32.2)	0.001
CIR, bottom quartile $n$ (%)	106 (26.8)	44 (27.2)	0.937	35 (21.5)	0.185	44 (21.8)	0.178
DI, bottom quartile $n$ (%)	84 (21.3)	62 (38.3)	0.001	43 (26.4)	0.190	57 (28.2)	0.058

Data are mean ± SD, unless otherwise indicated. \*Self-reported alcohol dose per week was converted into g/week.

or minor subjective sleep complaints, as evidenced by higher fasting and 120-min insulin, higher 120-min glucose concentrations, and higher AUC for insulin and glucose, as well as a higher likelihood to have high HOMA-IR and low ISI (Table 1). In addition, sleep apnea was associated with lower DI (Table 1). When adjustments were made for sex and age, and further for all mediating and confounding factors, the associations of sleep apnea with fasting insulin and DI, and of insomnia with fasting insulin, 120-min glucose, AUC for glucose, and HOMA-IR and ISI were rendered nonsignificant (Table 2).

**Co-occurrence of sleep complaints and IR and insulin secretion**

The likelihood of being insulin resistant, as evidenced by higher fasting and 120-min insulin and 120-min glucose concentrations and higher AUC for insulin and glucose, and higher likelihood of having high HOMA-IR and low ISI, increased according to the accumulation of co-occurring sleep complaints (Table 3). Figure 1 displays graphically the significant linearly increasing trends of AUC insulin and AUC glucose, and the percentage of individuals with high HOMA-IR and low ISI according to the accumulation of co-occurring sleep

complaints. These associations remained significant in the fully adjusted models (Table 3). These associations changed only a little when we made further adjustments for depressive symptoms (see footnotes in Tables 2 and 3).

Finally, we tested if the associations were driven by IFG- and/or IGT-associated abnormalities in insulin and glucose concentrations. We reran all the analyses, first after excluding individuals with IGT (*n* = 55) and then after excluding individuals with IFG or IGT (*n* = 166). In the first set of analyses, the following associations were rendered nonsignificant: sleep apnea and daytime sleepiness with 120-min

**Table 2—Associations between subjective sleep complaints and insulin and glucose values during an OGTT, and indices of IR and insulin secretion**

	Sleep complaints, no or minor complaints ( <i>n</i> = 395) vs. more frequent					
	Sleep apnea ( <i>n</i> = 162)		Insomnia ( <i>n</i> = 163)		Daytime sleepiness ( <i>n</i> = 202)	
	Mean difference, %/OR (95% CI)	<i>P</i>	Mean difference, %/OR (95% CI)	<i>P</i>	Mean difference, %/OR (95% CI)	<i>P</i>
<b>Insulin</b>						
Fasting						
Sex and age adjusted	18.6 (7.3–29.9)	0.001	14.0 (3.3–24.7)	0.011	14.9 (5.0–24.8)	0.003
Fully adjusted	8.6 (–1.9–19.2)	0.110	4.2 (–5.4–13.8)	0.286	10.4 (1.4–19.3)	0.023
120 min						
Sex and age adjusted	33.1 (17.9–48.3)	0.001	23.5 (9.3–37.7)	0.001	25.2 (11.9–38.5)	0.001
Fully adjusted	22.7 (7.4–37.9)	0.004	15.4 (1.2–29.5)	0.034*	22.4 (9.3–35.4)	0.001
AUC						
Sex and age adjusted	22.0 (11.5–32.6)	0.001	20.2 (10.2–30.2)	0.001	19.7 (10.5–28.9)	0.001
Fully adjusted	13.6 (3.4–23.7)	0.009	12.6 (3.2–22.0)	0.009	16.4 (7.8–25.1)	0.001
<b>Glucose</b>						
Fasting						
Sex and age adjusted	–0.1 (–1.9–1.6)	0.894	0.5 (–1.2–2.2)	0.553	–0.2 (–1.7–1.4)	0.809
Fully adjusted	–0.6 (–2.5–1.2)	0.506	0.2 (–1.6–1.9)	0.830	–0.4 (–2.0–1.2)	0.601
120 min						
Sex and age adjusted	8.7 (3.2–14.3)	0.002	4.4 (–0.7–9.5)	0.093	7.0 (2.2–11.8)	0.005
Fully adjusted	7.6 (1.7–13.4)	0.011	2.9 (–2.5–8.2)	0.291	6.6 (1.7–11.5)	0.008
AUC						
Sex and age adjusted	4.6 (1.8–7.3)	0.001	2.5 (–0.1–5.1)	0.056	3.9 (1.5–6.3)	0.001
Fully adjusted	2.8 (0.0–5.7)	0.052†	1.5 (–1.2–4.2)	0.269	3.3 (0.9–5.8)	0.007
<b>HOMA-IR</b>						
Sex and age adjusted	2.49 (1.63–3.80)	0.001	1.68 (1.09–2.58)	0.018	1.80 (1.22–2.66)	0.003
Fully adjusted	2.18 (1.33–3.59)	0.002	1.24 (0.74–2.09)	0.417	1.75 (1.10–2.77)	0.017
<b>ISI</b>						
Sex and age adjusted	2.55 (1.67–3.89)	0.001	2.04 (1.33–3.13)	0.001	1.95 (1.31–2.89)	0.001
Fully adjusted	2.13 (1.28–3.55)	0.004	1.58 (0.94–2.65)	0.082†	1.89 (1.18–3.02)	0.008
<b>CIR</b>						
Sex and age adjusted	0.82 (0.53–1.27)	0.373	0.72 (0.46–1.14)	0.158	0.76 (0.50–1.14)	0.179
Fully adjusted	0.86 (0.54–1.38)	0.526	0.76 (0.47–1.23)	0.261	0.75 (0.49–1.15)	0.184
<b>DI</b>						
Sex and age adjusted	1.67 (1.09–2.58)	0.019	0.87 (0.54–1.39)	0.560	1.32 (0.88–2.00)	0.184
Fully adjusted	1.24 (0.77–1.99)	0.373	0.69 (0.41–1.14)	0.145	1.16 (0.75–1.81)	0.501

Fully adjusted refers to a model adjusting for sex, age, alcohol consumption, current smoking status, regular exercise, occupational status, BMI, and family history of diabetes. \*Association is not statistically significant when further adjusted for depressive symptoms. †Association becomes statistically significant when further adjusted for depressive symptoms.

**Table 3—Associations between accumulation of co-occurring subjective sleep complaints and insulin and glucose values during an OGTT, and indices of IR and insulin secretion**

	Sleep complaints, no or minor complaints (n = 395) vs. more frequent				
	One complaint (n = 262)		Two to three complaints (n = 119)		P for linear trend
	Mean difference, %/OR (95% CI)	P	Mean difference, %/OR (95% CI)	P	
<b>Insulin</b>					
Fasting					
Sex and age adjusted	6.5 (−2.6–15.5)	0.163	25.5 (13.4–37.7)	0.001	
Fully adjusted	1.1 (−7.1–9.3)	0.789	15.6 (4.5–26.6)	0.006	0.002
120 min					
Sex and age adjusted	18.7 (6.3–31.1)	0.003	34.6 (18.5–50.8)	0.001	
Fully adjusted	15.4 (3.1–27.8)	0.014	24.9 (8.8–40.9)	0.002	0.001
AUC					
Sex and age adjusted	14.5 (6.0–23.1)	0.001	26.5 (15.2–37.8)	0.001	
Fully adjusted	11.0 (2.9–19.2)	0.008	18.0 (7.4–28.7)	0.001	0.001
<b>Glucose</b>					
Fasting					
Sex and age adjusted	0.0 (−1.4–1.4)	0.998	0.0 (−1.9–1.9)	0.999	
Fully adjusted	−0.1 (−1.5–1.4)	0.901	−0.6 (−2.6–1.4)	0.557	0.965
120 min					
Sex and age adjusted	4.2 (−0.2–8.7)	0.063	8.1 (2.2–14.0)	0.007	
Fully adjusted	4.5 (−0.1–9.1)	0.056*	6.1 (0.0–12.2)	0.049	0.024
AUC					
Sex and age adjusted	2.1 (0.0–4.3)	0.054	5.2 (2.2–8.3)	0.001	
Fully adjusted	1.9 (−0.4–4.1)	0.100	3.6 (0.5–6.7)	0.023	0.006
<b>HOMA-IR</b>					
Sex and age adjusted	1.35 (0.92–1.96)	0.121	2.62 (1.66–4.12)	0.001	
Fully adjusted	1.23 (0.80–1.91)	0.347	2.17 (1.26–3.71)	0.005	0.001
<b>ISI</b>					
Sex and age adjusted	1.52 (1.04–2.21)	0.030	2.87 (1.82–4.52)	0.001	
Fully adjusted	1.39 (0.89–2.18)	0.147	2.42 (1.40–4.16)	0.001	0.001
<b>CIR</b>					
Sex and age adjusted	0.75 (0.52–1.09)	0.133	0.85 (0.53–1.38)	0.508	
Fully adjusted	0.76 (0.52–1.13)	0.175	0.90 (0.54–1.50)	0.675	0.647
<b>DI</b>					
Sex and age adjusted	1.14 (0.77–1.68)	0.508	1.49 (0.92–2.42)	0.105	
Fully adjusted	0.97 (0.64–1.48)	0.971	1.18 (0.70–1.97)	0.541	0.224

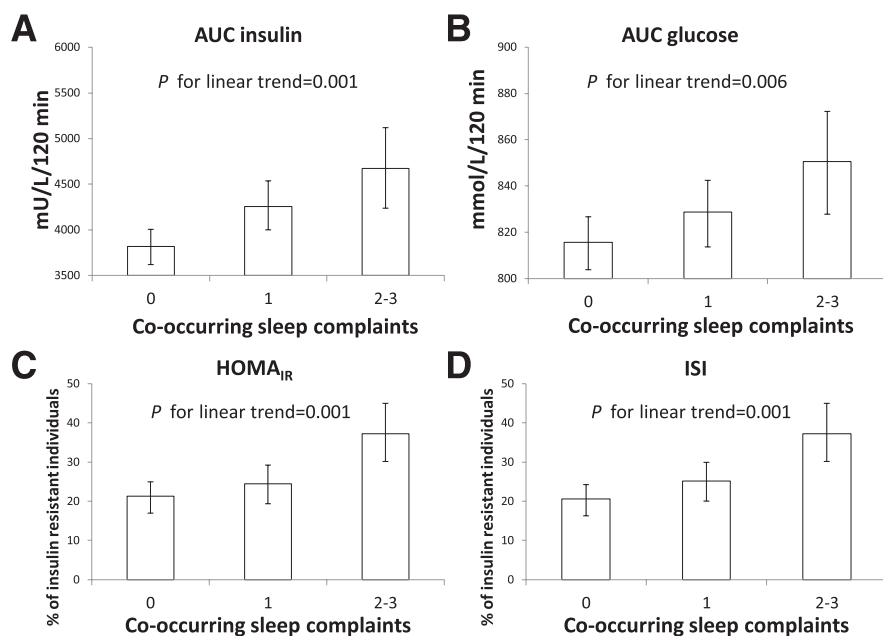
Fully adjusted refers to a model adjusting for sex, age, alcohol consumption, current smoking status, regular exercise, occupational status, BMI, and family history of diabetes. \*Association becomes statistically significant when further adjusting for depressive symptoms.

glucose, insomnia with 120-min insulin, and accumulation of co-occurring sleep complaints with 120-min and AUC glucose. In the second set of analyses, the following additional associations were rendered nonsignificant: sleep apnea with 120-min and AUC insulin and ISI. The other associations remained significant (all P values <0.05; data not shown).

**CONCLUSIONS**—We examined associations between subjective sleep complaints and their co-occurrence with IR and insulin secretion in individuals without a history of or concurrently diagnosed type 2 diabetes. Our findings

showed that in comparison with individuals with no or minor sleep complaints, those with more frequent complaints of sleep apnea, insomnia, and daytime sleepiness were significantly more insulin resistant. Further, our findings showed that the likelihood of being insulin resistant increased significantly and linearly according to co-occurring sleep complaints. Although the associations were somewhat attenuated when we excluded individuals with IFG and/or IGT, sleep complaints and their co-occurrence significantly increased the likelihood of being insulin resistant. These associations changed only a little when we made adjustments for sex, age, BMI, lifestyle, occupation, and

family history of diabetes. Nor did the associations change when adjustments were made for depressive symptoms. Complaints of sleep apnea were associated with deficiency in insulin secretion (DI), but this association was rendered nonsignificant when adjusted for mediating and confounding factors. Our findings thus suggest that IR, rather than deficiency in insulin secretion, is a characteristic of individuals reporting more frequent sleep complaints. These associations do not merely characterize individuals without diabetes who display abnormalities in insulin and glucose concentrations as a consequence of IFG and/or IGT but also appear to characterize individuals whose



**Figure 1**—Geometric means of AUC of insulin (A) and glucose (B) and adjusted percentage of insulin-resistant individuals (percentage of individuals in the top quartile of HOMA-IR [C] and in the bottom quartile of ISI [D], adjusted for sex, age, alcohol consumption, current smoking status, regular exercise, occupational status, BMI, and family history of diabetes) and 95% CIs (error bars) according to accumulation of co-occurring sleep complaints.

OGTT values fall within the normoglycemic range.

Our findings agree with the previous research suggesting that those who suffer from sleep disordered breathing by displaying a more severe apnea-hypopnea index in polysomnography were more likely to be insulin resistant (2,7,9). Our findings, however, disagree with a report (9) showing that sleep apnea was associated with impairments in pancreatic  $\beta$ -cell function (DI) (9). In the current study, sleep apnea and DI were associated in an unadjusted model, but when we made adjustments for mediating and confounding factors, this association was rendered nonsignificant. Our findings also disagree with the null associations found between subjective complaints of sleep apnea/snoring and IR (4,10). Nor do our findings confirm either the null associations of complaints of daytime sleepiness with IR (10) or the association of actigraphy- and complaint-based measures of insomnia with a lower likelihood of being insulin resistant (4).

The discrepant findings may rise from methodological differences. Our participants underwent an OGTT, providing us with the opportunity to exclude individuals with new type 2 diabetes based on fasting and 2-h values for type 2 diabetes.

Except for Seicean et al. (2) and Renko et al. (10), individuals with new type 2 diabetes have, in the previous studies, been excluded based on fasting values for type 2 diabetes only (4,8), even if an OGTT (7) or an intravenous glucose tolerance test (9) has identified additional responses characteristic of type 2 diabetes. It should also be kept in mind that we measured subjective sleep complaints, although with a validated questionnaire (24), which, as a methodology, is different from polysomnography and actigraphy. Nevertheless, epidemiological evidence points to an increased risk of type 2 diabetes also for individuals with subjective sleep complaints (1–6). Further, different self-reported questionnaires have been used in different studies, and therefore the findings are not directly comparable. The questions to capture sleep apnea, insomnia, and/or daytime sleepiness in questionnaires, such as the Basic Nordic Sleep Questionnaire (24), the Pittsburgh Sleep Quality Index (27), and the Berlin Sleep Apnea Questionnaire (28), are, however, similar, although the time frame and quantitative and qualitative measurement scales vary slightly. The questionnaires also vary in the degree to which input from a roommate/bed partner is requested in questions capturing sleep

apnea. Finally, a majority of the existing studies has focused on sleep disordered breathing, and in only two of the studies has more than one sleep disorder/complaint been measured. Even though sleep disorders and complaints co-occur (11,12), no previous study has tested if the likelihood of being insulin resistant increases according to co-occurring sleep complaints.

Due to the cross-sectional study design, we cannot draw causal inferences from the associations, and hence, we cannot rule out that the associations are reciprocal. A recent longitudinal study suggests that higher insulin, but not glucose, values may increase the risk of sleep apnea (29), and insomnia and daytime sleepiness may result from hyperglycemia. Nor can we unravel the mechanisms underlying these associations. We did adjust the association for BMI, lifestyle, occupation, family history of diabetes, and depression, suggesting that these may not explain the associations. Yet, we found that individuals with sleep complaints were heavier, older, more frequently manual workers or retired, and more depressed, and those with sleep apnea were additionally more frequently men, current smokers, more frequent alcohol users, and those who exercised regularly less frequently, a finding in general agreement with earlier reports (2–5,10,12,29). Therefore, the role of these factors cannot be entirely ruled out when interpreting the findings, as they all contribute to a higher likelihood of being insulin resistant. The mechanisms may relate to physical and psychological stresses that accompany complaints of sleep apnea, insomnia, and daytime sleepiness, such as hypoxia, sleep fragmentation, nonrestorative sleep, irritable mood, and problems in cognitive performance. These stresses may result in sympathetic arousal (12,30–34), hypothalamic-pituitary-adrenal axis dysfunction (35,36), and inflammatory response (37). Finally, a common genetic basis may underlie these findings. This basis may arise from genetic variants that participate in the regulation of the human sleep-wake cycle and are implicated in diabetes, such as *MTNR1B* (melatonin receptor 1B) on chromosome 11 (38). A further study limitation relates to the generalizability of our findings beyond Caucasians. Our findings suggest that strategies aimed at improving sleep quality in individuals without type 2 diabetes may be an additional tool in diabetes prevention.

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