

# High Baseline Insulin Levels Associated With 6-Year Incident Observed Sleep Apnea

BEVERLEY BALKAU, PHD<sup>1,2</sup>  
 SYLVIANE VOL, MSc<sup>3</sup>  
 SANDRINE LOKO, MD<sup>1,2</sup>  
 TIANA ANDRIAMBOAVONJY, MD<sup>1,2</sup>  
 OLIVIER LANTIERI, MD, MPH<sup>3</sup>  
 GAELLE GUSTO, PHD<sup>3</sup>

NICOLE MESLIER, MD<sup>4</sup>  
 JEAN-LOUIS RACINEUX, MD<sup>4</sup>  
 JEAN TICHET, MD<sup>3</sup>  
 AND THE DATA FROM AN EPIDEMIOLOGIC  
 STUDY ON THE INSULIN RESISTANCE  
 SYNDROME (D.E.S.I.R.) STUDY GROUP\*

**OBJECTIVE** — Obstructive sleep apnea is common in patients with type 2 diabetes, and its association with insulin and insulin resistance has been examined in cross-sectional studies. We evaluate risk factors for incident observed sleep apnea in a general population not selected for sleep disturbances.

**RESEARCH DESIGN AND METHODS** — A total of 1,780 men and 1,785 women, aged 33 to 68 years, from the cohort Data from an Epidemiologic Study on the Insulin Resistance Syndrome (D.E.S.I.R.) responded to the question, “Has someone said to you that you stop breathing during your sleep?” at baseline and 6 years. Anthropometric, clinical, and biological factors were recorded at both time points.

**RESULTS** — At baseline, 14% of men and 7% of women reported having observed sleep apnea (positive response to question); 6-year incidences were 14 and 6%, respectively. Age, anthropometric parameters, blood pressure, and sleep characteristics were all associated with prevalent, observed apnea episodes, in both sexes. Baseline waist circumference was the strongest predictor of incident apnea: standardized odds ratio (OR), adjusted for age and sex, 1.34 (95% CI 1.19–1.52). After adjustment for age, sex, and waist circumference, the standardized ORs for incident observed apnea were identical for fasting insulin and the homeostasis model assessment of insulin resistance: 1.31 (1.13–1.51) and 1.24 (1.09–1.41) for triglycerides and 1.52 (1.12–2.05) for smoking. Observed apnea at baseline was not associated with changes in anthropometric or biological parameters over the 6-year follow-up.

**CONCLUSIONS** — The most important baseline risk factor for incident apnea was adiposity. After accounting for adiposity, other risk factors were high insulin, insulin resistance, high triglycerides, and smoking, factors amenable to lifestyle intervention.

*Diabetes Care* 33:1044–1049, 2010

Obstructive sleep apnea is becoming more and more recognized as a health condition because it affects a considerable proportion of the population, in particular those with cardiovascular diseases, diabetes, and other chronic diseases (1). Sleep apnea can be classified as central if there is no effort or airflow (central apnea has a <1% frequency of all apnea), obstructive if the respiratory effort is preserved and increased in the presence of partial or complete occlusion on the upper airway, and mixed if there is a combination of both central and ob-

structive apnea. Apnea results in intermittent hypoxia, recurrent arousals, changes in intrathoracic pressure, and changes in sleep architecture (reduction in rapid eye movement and deep sleep and an excess in stage 2 sleep). In some cases it is accompanied by excessive daytime sleepiness and disturbed sleep. It is diagnosed by an apnea-hypopnea index (AHI) of  $\geq 5$  episodes per hour during polysomnography; apnea is present in  $\sim 1$  in 4 individuals in the general adult population (1). Sleep apnea is associated with diabetes, hypertension, and cardiovascular disease. In recognition of this association, the International Diabetes Federation and the American Heart Association have both provided leadership in issuing recommendations for identifying and treating this condition (2,3). The interrelation between sleep and the metabolic system is being increasingly recognized (4,5).

Most of the studies on the epidemiology of sleep apnea are either cross-sectional or case-control studies. The prospective or longitudinal studies come from the 4-year follow-up of the Wisconsin Sleep Cohort Study (6) and the 5-year follow-up of two cohorts, the Cleveland Family Study (7) and the Sleep Heart Health Study (8). These three studies all used polysomnography to quantify sleep apnea, but the cohorts had an oversampling of individuals likely to have sleep apnea. In the 1981 Australian Busselton Health Survey of a general population (9), the incidence of snoring was studied over a 13-year follow-up; the risk factors were sex, obesity, and weight gain.

The main interest in the above studies was adiposity, and they showed that age, sex, and adiposity at baseline and anthropometric changes over follow-up are related to incident sleep apnea. Among other factors related to incident sleep-disordered breathing studied by Tishler et al. (7), only cholesterol levels were found to show a marginal association.

A recent cross-sectional study showed that both insulin sensitivity and insulin secretion were related to sleep-disordered breathing, as evaluated by the AHI during polysomnography, and the authors suggested that sleep-disordered

From the <sup>1</sup>Institut Nationale de la Santé et de la Recherche Médicale, CESP Centre for research in Epidemiology and Population Health, Unité 1018, Epidemiology of diabetes, obesity and chronic kidney disease over the lifecourse, Villejuif, France; <sup>2</sup>University Paris Sud 11, Unité Mixte de Recherche en Santé 1018, Villejuif, France; the <sup>3</sup>Institut inter Régional pour la Santé, La Riche, France; and the <sup>4</sup>Department of Pneumology, Center Hospitalier Universitaire d'Angers, Angers, France.

Corresponding author: Beverley Balkau, [beverley.balkau@inserm.fr](mailto:beverley.balkau@inserm.fr).

Received 13 October 2009 and accepted 7 February 2010. Published ahead of print at <http://care.diabetesjournals.org> on 25 February 2010. DOI: 10.2337/dc09-1901.

\*A complete list of the members of the Data from an Epidemiologic Study on the Insulin Resistance Syndrome (D.E.S.I.R.) Study Group can be found in the APPENDIX.

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

breathing may lead to insulin resistance (10). In this report, we study, after accounting for adiposity, risk factors for incident observed sleep apnea in a population leaner than that in of most published reports with mean  $\pm$  SD for BMI of  $25.0 \pm 3.8$  kg/m<sup>2</sup>.

## RESEARCH DESIGN AND METHODS

— Participants were recruited into the study Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.) between 1994 and 1996. They were 30 to 65 years of age at recruitment and were consultants at Social Security Health Examination centers in the central western part of France.

We studied the 1,780 men and 1,785 women who were present at both the 3-year and the 9-year follow-up examinations and who, at both examinations, had BMI and waist circumference measured and responded to a question on whether they had observed sleep apnea, "Has someone said to you that you stop breathing during your sleep?" (11). The complete sleep questionnaire is shown in the online appendix (available at <http://care.diabetesjournals.org/cgi/content/full/dc09-1901/DC1>). Baseline date for this analysis is 1997–1999, 3 years after inclusion into the D.E.S.I.R. study.

At baseline and 6 years later, the clinical examinations followed the same protocol, with examinations by trained physicians and nurses. Two measures of blood pressure, using a mercury sphygmomanometer were taken with the participant in a supine position after a 5-min rest; mean values were used. Weight and height were measured in lightly clad participants, and BMI was calculated. The waist circumference, the smallest circumference between the lower ribs and the iliac crests, was also measured, as well as the neck circumference.

Smoking habits (current smoker or not), alcohol consumption (glasses per day of wine, beer, cider, and spirits, all transformed to grams per day), and degree of physical activity (people with little activity at home, at work, and in sporting activities were classified as physically inactive) were assessed using a self-administered questionnaire. All medications taken by participants were recorded.

We have defined observed apnea by a positive response to the question, "Has someone said to you that you stop breathing during your sleep?" The sleep ques-

tionnaire (11), as shown in the online appendix, included the Epworth Sleepiness Scale, which provides a measure of daytime sleepiness, that we study with the reference threshold of 10 or higher, which was derived in a general population (12).

All biochemical measurements were from one of four health center laboratories located in France at Blois, Chartres, La Riche, and Orléans. The interlaboratory variability for normal and pathological values was assessed monthly. Fasting plasma glucose, measured by the glucose-oxidase method, was applied to fluoroxalated plasma using a Technicon RA100 analyzer (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta device (Konelab, Evry, France). Total cholesterol, HDL cholesterol, and triglycerides were assayed with a DAX 24 (Bayer Diagnostics) or KONE analyzer (Konelab). LDL cholesterol was calculated from the Friedewald equation. A1C was determined by high-performance liquid chromatography (L9100 ion-exchange analyzer; Hitachi/Merck-VWR, Fontenay-sous-Bois, France) or an immunoassay (DCA 2000; Bayer Diagnostics). Insulin was quantified by microparticle enzyme immunoassay with an automated analyzer (IMX; Abbott, Rungis, France).

Diabetes was defined to include individuals treated for diabetes and those with a fasting plasma glucose  $\geq 7.0$  mmol/l. The homeostasis model assessment of insulin resistance (HOMA-IR) index was used as a surrogate measure of insulin resistance (13).

## Statistical analysis

Logarithms of triglycerides and insulin concentrations and of the HOMA-IR index have been used in statistical analyses. All data were analyzed using SAS (version 9.1; SAS Institute, Cary, NC). Data are presented as means  $\pm$  SD and as percentages. Characteristics of those with and without observed apnea at baseline were compared by *t* or  $\chi^2$  tests, stratified by sex.

Anthropometric characteristics of those with and without incident observed apnea at 6 years were compared by ANCOVA, with adjustment for baseline age, in participants without observed apnea at baseline. Factors measured at baseline were analyzed according to incident observed apnea by logistic regression, after verifying that the relations were linear, by including squared terms in the regression analyses; continuous variables were standardized according to sex, and rela-

tions were adjusted for age and waist circumference. Sex interactions were tested for each of these risk factors, and a combined analysis is presented, adjusted for age, waist, and sex. Results are presented as standardized odds ratios (ORs). Further, to test the homogeneity of the relation of insulin and the HOMA-IR index with incident observed apnea, interactions were tested across BMI classes:  $<25$ ,  $25\text{--}30$ , and  $\geq 30$  kg/m<sup>2</sup>.

## RESULTS

— At baseline, the prevalence of reported, observed apnea was 14% in men and 7% in women. Apnea was associated with aging and with higher BMI, waist circumference, and neck circumference (Table 1). After adjustment for age, all three anthropometric parameters—BMI, waist circumference, and neck circumference—were higher in those with observed apnea; the strongest relation was with waist circumference. There was no interaction between age and these anthropometric parameters. In both men and women, observed sleep apnea was associated with other sleep disorders, particularly snoring (Table 1). The Epworth Sleepiness Scale was associated with observed apnea only in men ( $P < 0.01$ ), with an average score of 6.9 in men with observed apnea and 6.2 in those without; there was no relation for women. Fasting glucose, A1C, insulin, the HOMA-IR index, and triglycerides were all significantly and positively associated with observed apnea in men (all  $P < 0.006$ ), whereas in women, there were fewer associations, and those significant were with total and LDL cholesterol and triglyceride concentrations (all  $P < 0.04$ ). Blood pressures were higher in those with apnea (all  $P < 0.002$ ). Neither smoking nor alcohol consumption showed a significant relation with observed apnea; men and women with observed apnea were more physically inactive than those without observed apnea (both  $P < 0.007$ ). Finally, in women 7.1% of those with observed apnea used hypnotics in contrast with 2.8% of those without observed apnea ( $P < 0.01$ ). All results were homogeneous across men and women, except for total and LDL cholesterol, for which the interactions with sex were significant.

The incidence of observed apnea was 14% in men and 6% in women, and men with incident observed apnea were 1 year older than those without; women were 4 years older (Table 2). In both men and women, higher baseline BMI and waist

Table 1—Characteristics of participants at baseline, according to the presence of observed apnea during sleep: the D.E.S.I.R. study

	Men			Women		
	No observed apnea	Observed apnea	<i>P</i> value	No observed apnea	Observed apnea	<i>P</i> value
<i>n</i> (%)	1,524 (86)	256 (14)		1,659 (93)	126 (7)	
Age (years)	50 ± 10	53 ± 10	0.0001	50 ± 10	54 ± 9	0.0001
Diabetes	4.7	11.7	0.0001	2.4	2.4	0.9
Anthropometry						
BMI (kg/m <sup>2</sup> )	25.5 ± 3.1	26.6 ± 3.6	0.0001	24.3 ± 4.2	25.8 ± 4.5	0.0003
Waist circumference (cm)	90 ± 9	93 ± 10	0.0001	78 ± 11	82 ± 12	0.0001
Neck circumference (cm)	40 ± 2	41 ± 3	0.0007	34 ± 2	35 ± 3	0.0001
Sleep characteristics						
Agitated sleep	16	29	0.0001	23	40	0.0001
Difficulty to wake up	25	38	0.0001	42	60	0.0001
Chronic unexplained fatigue	10	18	0.0002	19	31	0.002
Frequent waking at night	34	45	0.001	46	59	0.006
Snoring	66	89	0.0001	44	71	0.0001
Epworth Sleepiness Scale score	6.2 ± 4.0	6.9 ± 4.1	0.01	5.9 ± 4.2	5.7 ± 4.2	0.6
Epworth Sleepiness Scale score ≥10	20	27	0.02	20	21	0.8
Biological parameters						
Fasting glucose (mmol/l)	5.6 ± 0.9	5.8 ± 1.1	0.006	5.2 ± 0.7	5.2 ± 0.8	0.7
A1C (%)	5.5 ± 0.6	5.6 ± 0.6	0.002	5.4 ± 0.5	5.5 ± 0.6	0.07
Insulin (pmol/l)*	52 ± 32	62 ± 49	0.002	50 ± 34	52 ± 32	0.3
HOMA-IR index*	13.1 ± 9.9	16.9 ± 17.1	0.0006	11.9 ± 10.2	12.6 ± 8.2	0.2
Total cholesterol (mmol/l)	5.8 ± 0.9	5.7 ± 1.0	0.6	5.6 ± 0.9	5.8 ± 1.0	0.04
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.4 ± 0.4	0.4	1.7 ± 0.4	1.6 ± 0.4	0.5
LDL cholesterol (mmol/l)	3.8 ± 0.8	3.7 ± 0.8	0.4	3.5 ± 0.9	3.6 ± 1.0	0.04
Triglycerides (mmol/l)*	1.4 ± 1.2	1.5 ± 1.0	0.006	1.0 ± 0.5	1.1 ± 0.6	0.04
Blood pressure						
Systolic (mmHg)	133 ± 15	137 ± 16	0.0002	126 ± 16	133 ± 18	0.0001
Diastolic (mmHg)	80 ± 9	83 ± 10	0.0001	76 ± 9	77 ± 10	0.002
Lifestyle factors						
Smoking	21	22	0.7	13	12	0.8
Alcohol (g/day)						
0	11	12		32	35	
0–20 g/day	26	25	0.8	44	37	0.2
>20 g/day	63	64		23	28	
Physically inactive	27	36	0.001	26	37	0.007
Drug treatments						
Treatment by hypnotics	1.6	2.3	0.4	2.8	7.1	0.01

Data are means ± SD or %. \*Logarithms taken for analysis.

circumference were associated with incident apnea (all  $P < 0.006$ ), and in women only baseline neck circumference was also related with incident observed apnea, with a significant 0.6 cm larger neck circumference ( $P < 0.01$ ), in comparison to only 0.3 cm in men ( $P < 0.1$ ). Increases in BMI were associated with incident observed apnea in both men and women (both  $P < 0.05$ ), and an increase in neck circumference was also associated in women ( $P < 0.0001$ ).

Risk factors for incident apnea were studied separately in men and women (Table 3), but because there was no significant sex interaction for most of the risk factors (data not shown), men and

women were combined for reporting the relation between cardiometabolic risk factors and incident observed apnea, after adjustment for age, waist circumference, and sex (Table 3). For total cholesterol and for alcohol intake, there was a sex interaction, with total cholesterol being predictive of apnea only in men ( $P < 0.002$ ); for alcohol, there was only a marginal relation in either sex. Combining men and women, insulin ( $P < 0.0001$ ), the HOMA-IR ( $P < 0.0001$ ) index and triglycerides ( $P < 0.0009$ ), smoking ( $P < 0.006$ ), and treatment by hypnotics ( $P < 0.02$ ) were related with incident observed apnea; diastolic blood pressure was close to showing statistical significance ( $P < 0.06$ ). In men,

treatment by hypnotics was associated with a threefold increase in incident observed apnea.

The relation between insulin and the HOMA-IR index with incident observed apnea was homogeneous across BMI classes for both men and women. Thus, the observed relation does not seem to be the result of adiposity (data not shown).

The presence of observed apnea at baseline was not associated with an increase in adiposity over 6 years. The changes in waist circumference were 2.0 cm in men with baseline observed apnea and 2.2 cm in those without ( $P = 0.5$ ); for women the corresponding changes were 1.6 and 2.8 cm ( $P = 0.4$ ). Similarly, the

**Table 2—Anthropometric characteristics in those without observed apnea at baseline, according to 6-year incident observed apnea, after adjustment for age at baseline: the D.E.S.I.R. study**

	No observed apnea at 6 years	Observed apnea at 6 years	P value
<b>Men</b>			
n (%)	1,310 (86)	214 (14)	
Baseline age (years)	50	51	
Baseline BMI (kg/m <sup>2</sup> )	25.4	26.0	0.006
Baseline waist (cm)	89.3	91.2	0.004
Baseline neck (cm)	39.8	40.1	0.1
Change in BMI (kg/m <sup>2</sup> )	0.57	0.83	0.02
Change in waist (cm)	2.41	2.75	0.4
Change in neck (cm)	0.42	0.58	0.2
<b>Women</b>			
n (%)	1,554 (14)	105 (6)	
Baseline age (years)	50	54	
Baseline BMI (kg/m <sup>2</sup> )	24.1	26.2	0.0001
Baseline waist (cm)	77.4	81.8	0.0001
Baseline neck (cm)	34.3	34.9	0.01
Change in BMI (kg/m <sup>2</sup> )	0.86	1.21	0.05
Change in waist (cm)	3.01	4.16	0.06
Change in neck (cm)	0.40	1.23	0.0001

Data are means unless indicated otherwise.

changes in insulin were 4.8 and 11.4 pmol/l for men with and without baseline observed apnea ( $P = 0.6$ ), and for women the changes were 5.1 and 7.2 pmol/l, respectively ( $P = 0.6$ ). These results did not

change after adjustment for age and waist circumference.

**CONCLUSIONS**— As in other studies, this study also shows that adiposity

was related to prevalent and incident apnea, and increases in adiposity over time were related to incident apnea. Our results pertain only to observed apnea. Other factors preceding incident observed apnea, after adjustment for age, waist circumference, and sex, were insulin, the HOMA-IR index, and triglyceride concentrations with standardized ORs of 1.31, 1.31, and 1.24, respectively; smoking also increased the risk of incident observed apnea by 50%. Whereas the use of hypnotics by women at baseline was related cross-sectionally with observed apnea, with no relation for men, the reverse was the case for incident observed apnea: use of baseline hypnotics had an OR of 3.54 in men, despite the fact that fewer than 2% of the men were treated with them.

The adverse effect of gaining weight on sleep-disordered breathing was clear from the 4-year Wisconsin Sleep Cohort Study (6): a 10% increase in weight, in comparison with a stable weight, was associated with a 32% higher increase in AHI and a sixfold risk of developing moderate to severe obstructive sleep apnea; a 10% decrease in weight was associated with a 26% decrease in the AHI. However, as indicated by Newman et al. (8), sleep

**Table 3—Baseline cardiometabolic risk factors and their standardized ORs (95% CI) for incident observed apnea: the D.E.S.I.R. study**

	Men	P value	Women	P value	Men and women combined	P value
Number of incident cases (n)/total participants studied (N)	214/1,524 (14)		105/1,659 (6)		319/3,183 (10)	
Age*	1.12 (0.96–1.31)	0.1	1.32 (1.06–1.64)	0.01	1.18 (1.04–1.34)	0.008
Waist circumference†	1.25 (1.07–1.46)	0.004	1.50 (1.24–1.80)	0.0001	1.34 (1.19–1.52)	0.0001
Glucose	1.01 (0.87–1.17)	0.8	1.14 (0.97–1.34)	0.1	1.07 (0.96–1.19)	0.2
A1C	1.04 (0.90–1.20)	0.6	1.04 (0.85–1.27)	0.7	1.05 (0.93–1.18)	0.4
Insulin‡	1.38 (1.15–1.65)	0.0004	1.19 (0.94–1.50)	0.1	1.31 (1.13–1.51)	0.0002
HOMA-IR index‡	1.35 (1.13–1.63)	0.0008	1.23 (0.97–1.54)	0.08	1.31 (1.13–1.51)	0.0002
Diabetes§	0.64 (0.30–1.35)	0.2	1.43 (0.56–3.64)	0.4	0.81 (0.45–1.46)	0.5
Total cholesterol	1.26 (1.08–1.46)	0.002	0.90 (0.72–1.12)	0.3	—	
HDL cholesterol	0.93 (0.79–1.10)	0.4	0.86 (0.68–1.09)	0.2	0.90 (0.79–1.03)	0.1
LDL cholesterol	1.18 (1.01–1.37)	0.03	0.91 (0.73–1.12)	0.4	1.10 (0.97–1.24)	0.1
Triglycerides‡	1.25 (1.07–1.47)	0.004	1.18 (0.94–1.47)	0.1	1.24 (1.09–1.41)	0.0009
Systolic blood pressure	1.06 (0.90–1.24)	0.5	1.02 (0.81–1.28)	0.8	1.05 (0.91–1.19)	0.5
Diastolic blood pressure	1.18 (1.01–1.38)	0.04	1.03 (0.83–1.29)	0.8	1.13 (0.99–1.28)	0.06
Smoking	1.53 (1.08–2.16)	0.02	1.48 (0.79–2.75)	0.2	1.52 (1.12–2.05)	0.006
Alcohol					—	
0–20 vs. 0 g/day	0.58 (0.32–1.02)	0.06	1.01 (0.64–1.61)	0.9		
>20 vs. 0 g/day	0.92 (0.57–1.47)	0.07	0.62 (0.36–1.07)	0.1		
Physical inactivity	1.17 (1.84–1.63)	0.3	1.03 (1.00–1.05)	0.7	1.11 (0.85–1.44)	0.4
Treatment by hypnotics	3.54 (1.51–8.25)	0.003	1.11 (0.38–3.24)	0.8	2.13 (1.13–4.02)	0.02

Data are ORs (95% CI) unless indicated otherwise. Data are adjusted for age and waist circumference at baseline. The combined analyses have been also adjusted for sex. \*Adjusted for waist circumference only. †Adjusted for age only. ‡Logarithms taken for analysis. §Diabetes defined by medication and/or fasting plasma glucose  $\geq 7.0$  mmol/l. —, not reported as significant interaction between men and women.

apnea increases with aging, even in the weight-stable population. The Busselton Health Survey in Australia is one of the few studies in a general population in which sleep disorders have been prospectively examined over 15 years. In the 967 men and women, risk factors associated with the development of snoring were sex, baseline obesity, and weight gain (9); no biochemical measures were studied.

Other authors have shown cross-sectional relations between sleep-disordered breathing and glucose or diabetes (14,15); however, to our knowledge, there are no other prospective studies with insulin, glucose, and diabetes as putative risk factors. In our study, neither baseline fasting glucose, nor A1C, nor the presence of diabetes was a risk factor for incident observed apnea. High insulin levels and high HOMA-IR index values were strongly related to incident observed apnea, particularly in men. This result was independent of the effects of the main risk factors for observed apnea (a large waist circumference, age, and sex).

We were not able to show the reverse relations, that the presence of observed apnea at baseline was associated with higher insulin levels or greater adiposity 6 years later. Thus, we believe that the high insulin levels seen with observed sleep apnea, precede this condition, rather than being caused by it. This analysis partly answers “the chicken or the egg” question posed with regard to abdominal fat and sleep apnea (16). It has been reported that women with polycystic ovary syndrome have a 30 times higher risk of having sleep-disordered breathing (17); insulin resistance seems to be the primary defect in these women, which is then followed by sleep-disordered breathing. There have been suggestions in the literature that the improvement in insulin sensitivity after treatment with continuous positive airway pressure is evidence that sleep-disordered breathing may be a causative risk factor for insulin resistance. However, there are as many positive as negative results on this relation in clinical investigations (15).

A possible mechanism for our observation that hyperinsulinemia and insulin resistance precede observed apnea is that in obesity, the level of pharyngeal dilator muscle activity may be diminished in the presence of insulin or insulin resistance, just as the alteration in arterial muscle tone that is well recognized in vascular disease (18). An alternative or additional

mechanism may be the inflammation associated with hyperinsulinemia, insulin resistance, and abdominal adiposity, preceding sleep apnea (15).

The cross-sectional associations that have been shown in the literature among apnea, cigarette smoking, and alcohol consumption (14) were not seen in our study, but we found that smokers had a 50% higher risk of incident observed apnea than nonsmokers and that there was a trend for higher alcohol intake in men only. Physical inactivity has been little studied in relation to apnea; in our cross-sectional study, physical inactivity was more frequent in men and women with than without observed apnea at baseline, but it was not associated with incident observed apnea.

The strength of our study is the large cohort, drawn from a general population, with 6 years of follow-up. However, we must acknowledge the main limitation of our study: the lack of recorded polysomnographic data. Our measure of “observed apnea,” as reported by the participants in our study, is a crude and nonobjective measure. A polysomnographic recording was performed in 225 men and women from this cohort: 8 men and 2 women reported that they had observed apnea; 6 of these men and both women had an AHI  $\geq 15$  and all had an AHI  $\geq 10$  (data not published). Furthermore, an argument for the use of observed apnea is the observation that in obese individuals presenting for obesity surgery, reported observed apnea was the only symptom related to obstructive sleep apnea (19). These two elements provide some support for the use of our question on observed apnea. Reported apnea, observed by another person, is probably the information that a general practitioner would have to make a referral, and thus it is a simple method to screen people requiring further investigation. Another limitation for the interpretation of our study is that an individual must have a sleeping partner for apnea to be observed; thus, our estimates may be underestimated of the actual frequency, as only individuals with severe apnea would be able to report their own. However, the frequency of apnea in those living or not as a couple was 11 and 9%, i.e., almost identical, and their characteristics were similar except that there were more women who reported that they were living alone. We do not have a direct measure of insulin resistance, and we have used both insulin and the HOMA-IR index as surrogate

measures. However, hyperinsulinemia and insulin resistance do not always occur together (20,21), and the HOMA-IR index and insulin have similar correlations with clamp-measured insulin sensitivity in a nondiabetic population (Spearman correlation coefficients;  $-0.505$  and  $0.525$ , respectively, from the Relationship between Insulin Sensitivity and Cardiovascular Disease [RISC] study) (20,21).

Adiposity was strongly related to incident apnea, but after accounting for this relation, the risk of observed apnea also increased with increasing insulin levels and with an increasing HOMA-IR index. This is the first report that has been able to show that hyperinsulinemia and an insulin resistance index are predictive of later apnea, albeit observed apnea, after accounting for adiposity and changes in adiposity. Limiting weight gain is the simplest but probably the hardest-to-achieve preventive strategy for sleep apnea. Increasing physical activity and limiting sedentary behavior could play a role in increasing insulin sensitivity (22) and decreasing the risk for apnea.

**Acknowledgments**— The D.E.S.I.R. study is supported by Institut National de la Santé et de la Recherche Médicale (INSERM) contracts with Caisse Nationale d'Assurance Maladie des Travailleurs Salari, Lilly, Novartis Pharma, and sanofi-aventis and by INSERM (Réseaux en Santé Publique, Interactions entre les déterminants de la santé, Cohortes Santé TGIR 2008), the Association Diabète Risque Vasculaire, the Fédération Française de Cardiologie, La Fondation de France, l'Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques, Office National Interprofessionnel des Vins, Ardix Medical, Bayer Diagnostics, Becton Dickinson, Cardionics, Merck Santé, Novo Nordisk, Pierre Fabre, Roche, and Topcon.

No potential conflicts of interest relevant to this article were reported.

**APPENDIX**— Members of the D.E.S.I.R. Study Group are the following: INSERM U1018: B. Balkau, M.A. Charles, P. Ducimetière, and E. Eschwège; INSERM U367: F. Alhenc-Gelas; Center Hospitalier Universitaire d'Angers: Y. Gallois and A. Girault; Bichat Hospital: F. Fumeron and M. Marre; Center Hospitalier Universitaire de Rennes: F. Bonnet; Unité Mixte de Recherche 8090, Lille: P. Froguel; Centres d'Examens de Santé: Alençon, Angers, Caen, Chateauroux, Cholet, Le Mans, Tours, Institute de Recherche Médecine Générale: J. Cogneau and general practitioners of the region;

Institute Inter-Regional pour la Santé: C. Born, E. Caces, M. Cailleau, J.G. Moreau, O. Lantieri, F. Rakotozafy, J. Tichet, and S. Vol-

## References

1. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003; 290:1906–1914
2. Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ, International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2–12
3. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, American Heart Association Stroke Council, American Heart Association Council on Cardiovascular Nursing, American College of Cardiology Foundation. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008;118:1080–1111
4. Trenell MI, Marshall NS, Rogers NL. Sleep and metabolic control: waking to a problem? *Clin Exp Pharmacol Physiol* 2007; 34:1–9
5. Martins RC, Andersen ML, Tufik S. The reciprocal interaction between sleep and type 2 diabetes mellitus: facts and perspectives. *Braz J Med Biol Res* 2008;41: 180–187
6. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284:3015–3021
7. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA* 2003;289:2230–2237
8. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med* 2005;165: 2408–2413
9. Knuiman M, James A, Divitini M, Bartholomew H. Longitudinal study of risk factors for habitual snoring in a general adult population: the Busselton Health Study. *Chest* 2006;130:1779–1783
10. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. *Am J Resp Crit Care Med* 2009; 179:235–240
11. Meslier N, Vol S, Balkau B, Gagnadoux F, Cailleau M, Petrella A, Racineux JL, Tichet J, Groupe D'étude D.E.S.I.R.. Prevalence of symptoms of sleep apnea syndrome. Study of a French middle-aged population. *Rev Mal Respir* 2007;24:305–313
12. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419
14. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136–143
15. Lévy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J*. 2009;34:243–260
16. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care* 2008;31(Suppl. 2):S303–S309
17. Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. *J Intern Med* 2003;254:32–44
18. Yki-Järvinen H, Westerbacka J. Vascular actions of insulin in obesity. *Int J Obes Relat Metab Disord* 2000;24(Suppl. 2): S25–S28
19. Dixon JB, Schachter LM, O'Brien PE. Predicting sleep apnea and excessive day sleepiness in the severely obese: indicators for polysomnography. *Chest* 2003; 123:1134–1141
20. Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, Walker M, Natali A, Beck-Nielsen H, RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. *J Clin Endocrinol Metab* 2007;92: 2885–2892
21. de Rooij SR, Dekker JM, Kozakova M, Mitrakou A, Melander O, Gabriel R, Guidone C, Højlund K, Murphy MS, Nijpels G, RISC Group Investigators. Fasting insulin has a stronger association with an adverse cardiometabolic risk profile than insulin resistance: the RISC study. *Eur J Endocrinol* 2009;161:223–230
22. Balkau B, Mhamdi L, Oppert JM, Nolan J, Golay A, Porcellati F, Laakso M, Ferrannini E, EGIR-RISC Study Group. Physical activity and insulin sensitivity: the RISC study. *Diabetes* 2008;57:2613–2618