High baseline insulin levels associated with 6-year incident observed sleep apnea.

Beverley Balkau, Sylviane Vol, Sandrine Loko, Tiana Andriamboavonjy, Olivier Lantieri, Gaelle Gusto, Nicole Meslier, Jean-Louis Racineux, Jean Tichet, The D.E.S.I.R Study Group

High baseline insulin levels associated with 6-year incident observed sleep apnea

Beverley Balkau [1 *] **, Sylviane Vol** [2] **, Sandrine Loko** [1] **, Tiana Andriamboavonjy** [1] **, Olivier Lantieri** [2] **, Gaelle Gusto** [2] **, Nicole Meslier** [3] **, Jean-Louis Racineux** [3] **, Jean Tichet** [2] **, The D.E.S.I.R Study Group** [2]

[1] *CESP, Centre de recherche en épidémiologie et santé des populations INSERM : U1018 , Université Paris Sud - Paris XI , Université de Versailles-Saint Quentin en Yvelines , INED , FR*

[2] *IRSA, Institut Inter Regional pour la santé IRSA , La Riche,FR*

[3] *Département de pneumologie CHU Angers , FR*

* Correspondence should be adressed to: Beverley Balkau <beverley.balkau@inserm.fr >

Abstract

OBJECTIVE

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

METHODS

1780 men, 1785 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, clinic and biologic factors were recorded at both time-points.

RESULTS

At baseline, 14% of men and 7% of women reported to have observed sleep apnea (positive response to question); six-year incidences were 14% and 6% respectively. Age, anthropometric parameters, blood pressure and sleep characteristics were all associated with prevalent, observed apneas, in both genders. Baseline waist circumference was the strongest predictor of incident apnea: standardized odds ratio (OR) (95% Confidence Interval), adjusted for age and sex, 1.34(1.19–1.52). After adjusting 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), 1.24(1.09–1.41) for triglycerides, 1.52(1.12–2.05) for smoking. Observed apnea at baseline was not associated with changes in anthropometric or biologic 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.

Author Keywords abdominal obesity ; apnea ; epidemiology ; hyperinsulinaemia ; insulin resistance ; obesity ; prospective ; sleep

Obstructive sleep apnea is becoming more and more recognized as a health condition as it affects a considerable proportion of the population, in particular those with cardiovascular diseases, diabetes and other chronic diseases (1). Sleep apnea can be classed 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 obstructive apnea. Apnea results in intermittent hypoxia, recurrent arousals, changes in intrathoracic pressure, 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) ≥ 5 episodes per hour during a polysomnography; apnea is present in approximately 1 in 4 in the general adult population (1). Sleep apnea is associated with diabetes, hypertension and cardiovascular disease. In recognition of this, 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 inter-relation 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 four-year follow-up of the Wisconsin Sleep Cohort Study (6), and the five 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 they were cohorts with an over-sampling 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 gender, obesity and weight gain.

The main interest of the above studies was adiposity, and they show that age, gender and adiposity, at baseline and anthropometric changes over follow-up, are related with incident sleep apnea. Among other factors related with incident sleep-disordered breathing studied by Tishler (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 with sleep-disordered breathing, evaluated by the AHI during polysomnography, and the authors suggested that sleep-disordered 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 in most published reports, with a mean (SD) for body mass index (BMI) of 25.0 (3.8) kg/m^2 .

RESEARCH DESIGN AND METHODS

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

We study the 1780 men and 1785 women present at both the three year and the nine year follow-up examinations and who, at both examinations, had BMI and waist circumference measured and who responded to a question on whether or not they had an observed sleep apnea: “has someone said to you that you stop breathing during your sleep” (11). The complete sleep questionnaire is shown in the on-line Appendix . Baseline date for this analysis is 1997–1999, three years after inclusion into the D.E.S.I.R. study.

At baseline and six 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 in a supine position after a 5 minute rest; mean values were used. Weight and height were measured in lightly clad participants, and BMI 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, 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 questionnaire (11) is shown in the on-line Appendix; this questionnaire 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-centre laboratories located in France at Blois, Chartres, La Riche or Orléans. The inter-laboratory variability was assessed monthly on normal and pathological values. Fasting plasma glucose, measured by the glucose-oxidase method, was applied to fluoro-oxalated plasma using a Technicon RA100 (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta device (Konelab, Evry, France). Total cholesterol, HDL-cholesterol, triglycerides, were assayed by DAX 24 (Bayer Diagnostics, Puteaux, France) or KONE (Evry, France). LDL-cholesterol was calculated from the Friedewald equation. HbA1c was determined by High Performance Liquid Chromatography (L9100 HPLC ion-exchange analyser, Hitachi/Merck-VWR, Fontenay-sous-Bois, France) or an Immunoassay (DCA 2000 Bayer Diagnostics, Puteaux, France.) Insulin was quantified by micro particle 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 ≥ 7.0 mmol/l. The HOmeostatisis Model of Assessment of insulin resistance index (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 have been analyzed using SAS version 9.1. Data are presented as means (SD) and as percentages. Characteristics of those with and without observed apnea at baseline were compared by t- or χ^2 -tests, stratified by sex.

Anthropometric characteristics of those with and without incident observed apnea at six-years, were compared by analysis of covariance, adjusting 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 gender, and relations were adjusted for age and waist circumference. Gender interactions were tested for each of these risk factors, and a combined analysis is presented, adjusted for age, waist and gender. Results are presented as standardized odds ratios. 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, 25–30 and ≥ 30 kg/m^2 .

RESULTS

At baseline, the prevalence of reported, observed apnea was 14% in men and 7% in women. Apnea was associated with ageing, and with higher BMI, waist and neck circumferences (Table 1). After adjusting for age, all three anthropometric parameters, BMI, waist and neck circumferences were higher in those with observed apnea and 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 only associated with observed apnea in men ($P < 0.01$) with an average score of 6.9 in men with observed apnea, 6.2 in those without; there was no relation for women. Fasting glucose, HbA1c, 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 to 2.8% of those without observed apnea ($P < 0.01$). All results were homogenous across men and women, excepting for total and LDL-cholesterol, where 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 one year older than those without, women four years older (Table 2). In both men and women, higher baseline BMI and waist 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 as there was no significant gender interaction for most of the risk factors (data not shown), men and women were combined for reporting the relation between cardio-metabolic risk factors related with incident observed apnea, after adjusting for age, waist circumference and gender (Table 3). For total-cholesterol and for alcohol intake, there was a sex interaction, with total-cholesterol 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 three-fold 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 appear 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 six years: the changes in waist circumference were 2.0 cm in men with baseline observed apnea, 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 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 5.1 and 7.2 pmol/l respectively ($P = 0.6$) and 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 with prevalent and incident apnea and increases in adiposity over time were related with incident apnea. Our results pertain only to observed apnea. Other factors preceding incident observed apnea, after adjusting on age, waist circumference and sex, were insulin, the HOMA-IR index and triglycerides concentrations with standardized odds ratios of 1.31, 1.31 and 1.24 respectively; smoking also increased the risk of incident observed apnea, by 50%. While hypnotics taken by the women at baseline was related cross-sectionally with observed apnea, with no relation for men, the reverse was the case for incident

observed apnea: baseline hypnotics carried an odds ratio of 3.54 in men, despite the fact that fewer than 2% of the men were treated by them.

The adverse effects 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 to a stable weight, was associated with a 32% higher increase in AHI and a six-fold 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 apnea increases with ageing, even in the weight stable population. The Busselton Study in Australia, is one of the few studies in a general population, which has prospectively studied sleep disorders over 15 years; in the 967 men and women, risk factors associated with the development of snoring, were gender, 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); 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 HbA1c, nor the presence of diabetes were risk factors for incident observed apnea. High insulin levels and high HOMA-IR index values were strongly related with 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 six 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 goes some way to answering ”the chicken or the egg” question posed, with regards 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 would appear 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 following treatment with continuous positive airway pressure (CPAP), 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 hyperinsulinaemia and insulin resistance precede observed apnea could be 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 hyperinsulinaemia, insulin resistance and abdominal adiposity, preceding sleep apnea (15).

The cross-sectional associations which have been shown in the literature between apnea, cigarette smoking and alcohol consumption (14) were not seen in our study, but we found that smokers had a 50% higher risk of an incident observed apnea than non-smokers, and that there was a trend for higher alcohol intake in men only. Physical inactivity has been little studied in relation with 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 six 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 non-objective measure. A polysomnographic recording was carried out in 225 men and women from this cohort: eight men and two women reported that they had observed apnea; six of these men and both women had an AHI ≥ 15, and all had an AHI ≥ 10 (data not published). Further, 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 with 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 an apnea to be observed, thus our estimates may be underestimates of the actual frequency, as only severe cases would be able to report their own apnea. However, the frequency of apnea in those living or not as a couple were 11% and 9%, almost identical, and their characteristics were similar, excepting 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, hyperinsulinaemia 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 non-diabetic population (Spearman correlation coefficients; −0.505 and 0.525 respectively, from the RISC study (20.21)).

Adiposity was strongly related with incident apnea, but after accounting for this, the risk of observed apnea also increased with increasing insulin levels and with an increasing HOMA-IR index. This is the first report which has been able to show that hyperinsulinaemia 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 sedentarity, could play a role in increasing insulin sensitivity (22) and decreasing the risk for apnea.

Ackowledgements:

The D.E.S.I.R. Study Group. INSERM U1018: B. Balkau, M.A. Charles, P. Ducimetière, E. Eschwège; INSERM U367: F. Alhenc-Gelas; CHU D'Angers: Y. Gallois, A. Girault; Bichat Hospital: F. Fumeron, M. Marre; CHU de Rennes: F. Bonnet; UMR8090, Lille: P. Froguel; Centres d'Examens de Santé: Alençon, Angers, Caen, Chateauroux, Cholet, Le Mans, Tours; Institute de Recherche Médecine Générale: J. Cogneau; 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, S. Vol.

Funding : The D.E.S.I.R. study has been supported by INSERM contracts with CNAMTS, Lilly, Novartis Pharma and Sanofi-Aventis; 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, ALFEDIAM, ONIVINS, Ardix Medical, Bayer Diagnostics, Becton Dickinson, Cardionics, Merck Santé, Novo Nordisk, Pierre Fabre, Roche, Topcon.

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 . Le Groupe d'étude DESIR . 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 : 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 - 28
- 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

TABLE 1

Characteristics of participants at baseline (mean (SD) or precentages), according to the presence of observed apnea during sleep. The D.E.S.I.R. Study

	Men			Women		
	No observed apnea	Observed apnea	P	No observed apnea	Observed apnea	P
	n=1524 (86%)	n=256 (14%)		n=1659 (93%)	n=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^2)	25.5 (3.1)	26.6 (3.6)	0.0001	24.3 (4.2)	25.8 (4.5)	0.0003
Waist (cm)	90 (9)	93 (10)	0.0001	78 (11)	82 (12)	0.0001
Neck (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 wakening at night	34%	45%	0.001	46%	59%	0.006
Snoring	66%	89%	0.0001	44%	71%	0.0001
Epworth Score	6.2 (4.0)	6.9 (4.1)	0.01	5.9 (4.2)	5.7 (4.2)	0.6
Epworth ≥ 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
HbA1c (%)	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 BP (mmHg)	133 (15)	137 (16)	0.0002	126 (16)	133 (18)	0.0001
Diastolic BP (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)						
zero	11%	12%		32%	35%	
< 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

* logarithms taken for analysis

TABLE 2

Anthropometric characteristics (mean) in those without observed apnea at baseline, according to 6-year incident observed apnea, after adjusting for age at baseline. The D.E.S.I.R. Study

	No observed apnea at 6 years	**Observed apnea at 6 years**	**P**
Men	n=1310 (86%)	n=214 (14%)	
Baseline age (years)	50	51	
Baseline BMI (kg/m^2)	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^2)	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
Women	n=1554 (14%)	n=105 (6%)	
Baseline age (years)	50	54	
Baseline BMI (kg/m^2)	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^2)	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

TABLE 3

Basline cardio-metabolic risk factors and their standardized Odds Ratios (95% confidence intervals) for incident observed apnea. Odds ratios are adjusted for age and waist circumference at baseline. The combined analyses have been also adjusted for sex. The D.E.S.I.R. Study.

	Men	P	Women	P	Men and women combined	P
Cases/n = %	214/1524 = 14%		105/1659 = 6%		319/3183 = 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
HbA1c	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 BP	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 BP	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					--	
0–20g/d vs zero	0.58 (0.32–1.02)	0.06	1.01 (0.64–1.61)	0.9		
> 20 g/d vs zero	0.92 (0.57–1.47)	0.7	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

* adjusted for waist circumference, only

** adjusted for age, only

*** logarithms taken for analysis

**** diabetes defined by medication and/or fasting plasma glucose ≥ 7.0 mmol/l

-- not reported, as significant interaction between men and women