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Lack of association between self-reported insomnia symptoms and clamp-derived insulin sensitivity in elderly men

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ABSTRACT

Insomnia-related sleep disruptions, such as short and disturbed sleep, have been tied to systemic insulin resistance in young adult populations. We therefore sought to confirm these findings in a cohort of elderly men. To this aim, we utilized variables from 980 men who participated in the investigation at age 70 of the Uppsala Longitudinal Study of Adult Men. Self-reported insomnia symptoms were assessed by questions about difficulty initiating sleep, early final awakening, and regular use of hypnotics. All participants also underwent the gold-standard hyperinsulinemic-euglycemic clamp technique to assess the insulin sensitivity index (M/I). Finally, fasting blood was collected to measure free fatty acids (FFAs) and adiponectin. Differences in blood parameters between men with and those without insomnia were determined by ANCOVA, and were adjusted for lifestyle and cardio-metabolic risk factors. Our analysis yielded no differences in M/I, FFAs, and adiponectin between men with and those without insomnia symptoms. Analyses in non-diabetic and diabetic subsamples confirmed these negative findings. Our cross-sectional results therefore suggest that insomnia symptoms may have a minimal effect, if any, on measures of insulin sensitivity in elderly men. Given the observational design of our study, future studies are needed to determine whether experimental sleep manipulations influence systemic insulin sensitivity in elderly humans, as has previously been shown in young adult populations.

1. Introduction

Insomnia symptoms including difficulties in initiating and maintaining sleep, thereby leading to curtailed and non-restorative sleep, as well as the long-term use of pharmacological sleep aids have all been associated with a greater risk of type 2 diabetes (Cappuccio et al., 2010; Tan et al., 2018a). All-night suppression of slow-wave sleep, a sleep stage that is often disrupted in patients with insomnia, results in marked decreases in systemic insulin sensitivity in young metabolically healthy subjects (Tasali et al., 2008). Similar adverse effects on systemic insulin sensitivity have been observed upon either experimental fragmentation or curtailment of sleep in healthy young volunteers (Stamatakis and Punjabi, 2010; Buxton et al., 2010). Finally, 15-day oral administration of the sleep aid zolpidem (Z drug) enlarged the glucose delta area under curve response to oral glucose tolerance testing by about 86% in healthy young adults (Gramaglia et al., 2014). Collectively, these experimental data suggest a causative role of sleep problems associated with insomnia symptoms in the development of type 2 diabetes.

Whether reports of insomnia symptoms or the regular use of pharmacological sleep aids are associated with greater insulin resistance in older subjects is, however, less well-studied. Accumulating evidence suggests that the association between sleep and metabolic health may be age-specific. For instance, in a Swedish cohort of about 20,000 subjects aged between 45 and 75 years, short sleep duration (defined as $\leq$6 h sleep per day) was associated with an increased prevalence of the metabolic syndrome in middle-aged but not older subjects (aged $\geq$65 years) (Titova et al., 2018). With this in mind, the aim of our cross-sectional study involving 980 men aged 70 years was to investigate whether insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp technique would differ between men with and those without reports of insomnia symptoms. The hyperinsulinemic-euglycemic clamp technique is the gold standard for assessing insulin sensitivity in humans (DeFronzo et al., 1979). We also measured fasting blood concentrations of free fatty acids (FFAs) and adiponectin. FFAs are known to impair insulin-stimulated muscle uptake of glucose which results in systemic insulin resistance (Roden et al., 1996). In contrast, administration of the adipokine adiponectin increases insulin sensitivity

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in murine models of insulin resistance (Yamauchi et al., 2001), and high blood levels of this adipokine positively predict insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp technique in non-diabetic subjects (Tschritter et al., 2013). We hypothesized that reports of insomnia symptoms would be associated with lower insulin sensitivity, lower serum levels of adiponectin, and higher circulating concentration of FFAs.

2. Materials and methods

2.1. Population and study design

The present study utilized variables from the age-70 investigation of the Uppsala Longitudinal Study of Adult Men (ULSAM; http://www.pubcare.uu.se/ulsam/). When started in 1970, the main objective of ULSAM was to identify metabolic risk factors for cardiovascular disease in middle-aged men. For this purpose, a total of 2322 men living in Uppsala, Sweden (response rate: 82% of those invited) participated in the baseline investigation at age 50. Although participants attended several consecutive follow-up investigations, assessments relevant for the present study occurred only at the age-70 follow-up investigation. Specifically, insomnia symptoms and insulin sensitivity were assessed in 1069 participants at age 70 (from a total of 1221 men). An additional 89 participants were excluded due to missing covariate data. Thus, 980 men were available for the final analysis. All participants gave written informed consent and the study was approved by the regional ethical review board in Uppsala.

2.2. Variables of insomnia symptoms

Participants answered the three following questions: *1) Do you have difficulties falling asleep at night?* (referring to difficulty initiating sleep); *2) Do you often wake up in early hours, unable to get back to sleep?* (referring to early final awakening); and *3) Do you take sleeping pills more than three times per week?* (referring to frequent use of hypnotics). Participants could either answer 'yes', 'no', or "I don't know" to each of the three questions. Answering 'yes' to a minimum of one of the three questions was defined as insomnia in the present study.

2.3. Hyperinsulinemic-euglycemic clamp procedure

The euglycemic-hyperinsulinemic clamp technique with a slight modification to suppress hepatic glucose production was used for estimation of in vivo sensitivity to insulin (DeFronzo et al., 1979). The clamp procedure and other measurements (including sleep variables and oral glucose tolerance test) in the present study took place on separate days within one week. A 2-h insulin (Actrapid Human; Novo, Copenhagen, Denmark) infusion was implemented with a primary dose for the first 10 min and then a continuous infusion (56 mU/min per m^2) for 110 min to maintain steady-state hyperinsulinemia. The target plasma glucose level was 5.1 mmol/L, which was maintained by measuring plasma glucose every 5 min. The glucose infusion rate during the last 60 min was used as a measure of insulin sensitivity (M, in mg/kg body weight/min). The insulin sensitivity index (M/I) was calculated by dividing M by the mean insulin concentration during the same period of the clamp. M/I thus represent the amount of glucose metabolized per unit of plasma insulin (100 × mg/kg_{bw}/min/mU/L).

Plasma glucose was measured by the glucose dehydrogenase method (Gluc-DH; Merck, Darmstadt, Germany). Plasma insulin was assayed using an enzymatic-immunological assay (Enzymmun, Boehringer Mannheim, Germany) performed in an ES300 automatic analyser (Boehringer Mannheim) and was given in mU/l. For conversion to pmol/L, it was multiplied by 6.0.

2.4. Determination of free fatty acids (FFAs) and adiponectin

Blood samples were obtained in the morning after overnight fast. Serum FFAs were measured by an enzymatic colorimetric method (Wako Chemicals, Neuss, Germany). Serum adiponectin was analyzed using a validated in-house time-resolved immunofluorometric assay (TR-IFMA) based on commercial reagents from R & D Systems (Abingdon, UK). Within assay coefficients of variability of standards and unknown samples averaged less than 5%.

2.5. Covariates

All covariates were measured at age 70, unless otherwise stated. A detailed description of the methods that were used to assess covariates can be found here: http://www.pubcare.uu.se/ulsam/. Briefly, the presence of diabetes (treated as binary variable) was either confirmed by reviewing medical records, fasting plasma glucose ≥ 7.0 mmol/L, or when the 2 h oral glucose tolerance test (OGTT) blood glucose value and one or more of the 30–90 min OGTT plasma glucose values were ≥ 11.1 mmol/L. Family history of diabetes was assessed at the age-50 baseline investigation (treated as binary variable). Specifically, participants were asked to indicate whether the following relatives had been diagnosed any type of diabetes: father, mother, siblings, or children.

Exact age (y) at the age-70 follow-up investigation was used as covariate (continuous). Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2) (continuous). Waist circumference (cm), systolic blood pressure (mm Hg), and diastolic blood pressure (mm Hg) were measured by conventional methods, and entered as continuous variables into the analysis. Participants' current smoking status (yes/no) and level of physical activity during leisure time ('*Do you do any active sport or heavy gardening for at least* 3 h *every week?*'; yes/no/unknown) were assessed by questionnaires. Finally, alcohol consumption (entered into the analysis as average % of total energy intake per day) was estimated by using a 7-day pre-coded food diary.

2.6. Statistical analysis

Analyses were performed with Stata 15.1 (StataCorp LLC, College Station, TX, USA). The distributions of the variables were examined by Shapiro-Wilk's test. Variables with skewed distributions (fasting glucose, fasting insulin, free fatty acids, and adiponectin) were log-transformed before analyses. One-way analyses of variance (ANOVA), Pearson's chi-square test, and analyses of covariance (adjusted for different covariates) were used to test the differences of the dependent variables between men with and those without insomnia. Overall, a two-sided P value of less than 0.05 was regarded as statistically significant.

3. Results

Numbers of participants stratified by insomnia symptoms are displayed in Table 1a. Characteristics of the study population, stratified by the presence of insomnia symptoms, are summarized in Table 1b. BMI and waist circumference differed between men with and those without insomnia symptoms (all $P < 0.05$, one-way ANOVA). No other significant differences were observed between the two groups.

No significant differences in the insulin sensitivity index (M/I) were detected between men with and those without insomnia symptoms, neither in crude nor in multivariate adjusted models (Table 2a). Subsample analyses among non-diabetic and diabetic men confirmed these findings. Separate analyses either utilizing single insomnia symptoms or the number of self-reported insomnia symptoms as predictor of interest confirmed the main findings, i.e., no association between these sleep variables and clamp-derived insulin sensitivity was found ($P > 0.05$; data not shown). Finally, as shown in Table 2b, the blood levels of FFA

Table 1a
Prevalence of insomnia symptoms in the study cohort (n = 980).

	No/I don't know Number of participants (%)	Yes Number of participants (%)
Difficulty initiating sleep	877 (89.5)	103 (10.5)
Early final awakening	793 (80.9)	187 (19.1)
Frequent use of hypnotics (> 3 times/wk)	940 (95.9)	40 (4.1)
Any of the symptoms above	750 (76.5)	230 (23.5)
One of the symptoms above	833 (85.0)	147 (15.0)
Two of the symptoms above	914 (93.3)	66 (6.7)
All three symptoms above	963 (98.3)	17 (1.7)

and adiponectin did not differ between men with and those without insomnia symptoms.

4. Discussion

The present cross-sectional study involving 980 men at age 70 did not find a significant association between self-reported insomnia symptoms and clamp-derived insulin sensitivity, neither in the full cohort nor in subsamples stratified by diabetes status. Furthermore, circulating levels of adiponectin and FFA, two key regulators of insulin sensitivity, did not differ between men with and those without insomnia symptoms. Collectively, our cross-sectional results therefore suggest that insomnia symptoms may have a minimal effect, if any, on measures of insulin sensitivity in elderly men.

Previous findings in younger adults have shown that insomnia-related sleep disturbances, including short and non-restorative sleep, adversely affect insulin sensitivity. For instance, in one experiment involving 9 healthy young men and women (mean age: 44.6 years; and mean BMI: 23.8 kg/m^2), a single night of 4-h sleep restriction was sufficient to lower glucose infusion rate during a hyperinsulinemic-euglycemic clamp by approximately 25% (Donga et al., 2010). A lower glucose infusion during the hyperinsulinemic-euglycemic clamp indicates reduced systemic insulin sensitivity (DeFronzo et al., 1979). Similar adverse effects on insulin sensitivity were found in 20 healthy young men (mean age: 26.8 years; BMI 23.3 kg/m^2) after 1 week of partial sleep restriction (5 h of sleep per night) (Buxton et al., 2010).

With the above-mentioned findings in younger adults in mind, the lack of association between insomnia and clamp-derived insulin sensitivity in elderly men we observed run counter to expectation. However, our results are in good agreement with results in the literature, which suggest that the association between disturbed sleep and metabolic perturbations may vary by age. It has, for instance, been demonstrated in a Korean study involving ˜5000 subjects that adults aged between 19–64 years who regularly slept less than 6 h per day had increased odds of hypertension, compared to those who slept 7 h per day. This association was not found among those aged ≥65 years (Kim and Jo, 2010). Noteworthy, similar to our results, no consistent associations between insomnia symptoms and glucose metabolism (OGTT response and fasting plasma glucose) or incident type 2 diabetes were found in the Cardiovascular Health Study involving 5888 participants ≥65 years of age from four U.S. communities (Strand et al., 2015). In contrast, a previous meta-analysis found increased risks of type 2 diabetes for sleep initiation and sleep maintenance problems (Capuccio et al., 2010). Importantly, this meta-analysis included participants with a wide age range, but was unable to stratify studies by age-groups because of the inconsistent reporting of age in the original studies. With all these conflicting results in mind, future studies are needed to determine whether experimental sleep manipulations influence systemic insulin sensitivity in elderly humans, as has previously been shown in young adult populations. One possible explanation for why variance in insulin sensitivity may be less explained by insomnia symptoms in older subjects than it does in younger adults could relate to the overall impaired metabolic status of elderly humans. Aging is associated with obesity, sarcopenia, insulin resistance, and reduced β-cell function (Kahn et al., 1992; Schwartz et al., 1990; Chen et al., 1985).

Some study limitations should be taken into account when interpreting the negative results of this cross-sectional study. First, some insomnia symptoms were not assessed in the ULSAM cohort, such as sleep maintenance problems. Second, no information was available on duration and frequency of insomnia symptoms. With these two limitations in mind, it cannot be ruled out that some participants might have been wrongly assigned to the group with insomnia symptoms, or vice

Table 1b
Cohort characteristics split by status of insomnia symptoms.

Variable	Total cohort	No insomnia symptom	Self-reported insomnia symptoms	P*
Number of participants	980	750	230	–
Age (y)	71.0 ± 0.6	71.0 ± 0.6	71.0 ± 0.5	0.97
BMI (kg/m^2)	26.2 ± 3.4	26.1 ± 3.2	26.7 ± 4.0	0.02
Waist circumference (cm)	94.4 ± 9.5	94.1 ± 8.9	95.5 ± 11.2	0.05
Systolic BP (mm Hg)	138.9 ± 16.3	138.7 ± 16.6	139.4 ± 15.5	0.57
Diastolic BP (mm Hg)	78.6 ± 8.3	78.4 ± 8.2	79.1 ± 8.5	0.23
Diabetes diagnosis (% group)	14.0	12.7	18.3	0.10†
Family history of diabetes (% group) [b]	15.6	14.3	16.0	0.55
Current smoking (% group)	20.2	20.1	20.4	0.92
Alcohol intake (average % of total daily energy intake)	2.7 ± 3.1	2.7 ± 3.1	2.6 ± 3.3	0.61
Leisure time physical activity ≥3 h/wk (% group)	61.5	63.2	56.1	0.08
Fasting glucose (mmol/L)	5.8 (5.7, 5.8)	5.7 (5.6, 5.8)	5.9 (5.7, 6.1)	0.08#
Fasting insulin (pmol/L)	12.9 (12.3, 13.4)	12.9 (12.3, 13.5)	12.7 (11.7, 13.8)	0.51#
M/I (100 × mg/kg_{bw}/min/mU/L)	5.1 ± 2.5	5.2 ± 2.5	4.9 ± 2.6	0.19
Free fatty acids (mmol/L)[c]	0.52 (0.51, 0.53)	0.52 (0.50, 0.53)	0.53 (0.50, 0.56)	0.58#
Adiponectin (ng/L)[d]	10.3 (10.0, 10.5)	10.4 (10.1, 10.7)	9.9 (9.3, 10.5)	0.08#

Abbreviations: BMI, body mass index; BP, blood pressure; M/I, insulin sensitivity index (derived from the hyperinsulinemic-euglycemic clamp).
Data are shown as mean ± SD or mean (95% CI).

* One-way ANOVA or Pearson's chi-squared test.

\# Comparison under log-transformed data.

† P = 0.104 as derived from logistic regression, adjusted for adjusted for age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, family history of diabetes, smoking, alcohol intake, and level of leisure time physical activity.

[b] Diabetes in any first-degree relatives.

[c] Total cohort, n = 967; non-sleep disturbance, n = 739; sleep disturbances, n = 228.

[d] Total cohort, n = 970; non-sleep disturbance, n = 743; sleep disturbances, n = 227.

Table 2a
Mean difference in the insulin sensitivity index (M/I) between men with and those without insomnia: P values derive from one-way ANOVA (crude model) or analysis of covariance (model 1–3). Model 1: adjusted for age, BMI, and waist circumference; Model 2: additionally adjusted for systolic blood pressure, diastolic blood pressure, diabetes status (only in total cohort), and family history of diabetes; Model 3: additionally adjusted for smoking, alcohol intake, and level of leisure time physical activity. Mean difference (MD): Mean insulin sensitivity index (M/I) of participants without insomnia minus mean M/I of participants with insomnia. [a]655 without sleep disturbance, 188 with sleep disturbances; [b]95 without sleep disturbance, 42 with sleep disturbances.

	Total cohort			Non-diabetic participants[a]			Diabetic participants[b]		
	MD	95% CI	P	MD	95% CI	P	MD	95% CI	P
Crude model	0.25	−0.12, 0.62	0.19	0.03	−0.37, 0.43	0.88	0.52	−0.07, 1.10	0.09
Model 1	0.19	−0.29, 0.33	0.91	−0.04	−0.37, 0.30	0.84	0.01	−0.53, 0.55	0.98
Model 2	−0.40	−0.91, 0.11	0.12	−0.13	−0.61, 0.35	0.60	−0.44	−1.10, 0.22	0.19
Model 3	−0.20	−0.92, 0.53	0.59	−0.01	−0.84, 0.81	0.97	−0.31	−1.25, 0.62	0.51

Table 2b
Mean difference in blood concentration of free fatty acids and adiponectin levels between men with and those without insomnia: # One-way ANOVA for log-transformed data. * One-way analysis of covariance adjusted for age, BMI, and waist circumference. Mean difference (MD): Mean blood concentration of free fatty acids/adiponectin in participants without insomnia minus mean blood concentration of free fatty acids/adiponectin in participants with insomnia. [a]647 without sleep disturbance, 186 with sleep disturbances; [b]92 without sleep disturbance, 42 with sleep disturbances.c649 without sleep disturbance, 185 with sleep disturbances; d94 without sleep disturbance, 42 with sleep disturbances.

	Total cohort			Non-diabetic participants			Diabetic participants		
Free fatty acids (mmol/L)	n = 967			n = 833[a]			n = 134[b]		
	MD	**95% CI**	**P#**	**MD**	**95% CI**	**P#**	**MD**	**95% CI**	**P#**
Crude	−0.01	−0.05, 0.02	0.58	−0.01	−0.04, 0.03	0.98	−0.00	−0.08, 0.08	0.94
Adjusted*	−0.01	−0.04, 0.02	0.73	−0.00	−0.04, 0.03	0.90	−0.00	−0.09, 0.08	0.94
Adiponectin (ng/L)	n = 970			n = 834[c]			n = 136[d]		
	MD	**95% CI**	**P#**	**MD**	**95% CI**	**P#**	**MD**	**95% CI**	**P#**
Crude	0.44	−0.20, 1.08	0.08	0.31	−0.40, 1.02	0.23	0.24	−0.94, 1.41	0.68
Adjusted*	0.22	−0.39, 0.82	0.29	0.24	−0.44, 0.91	0.29	−0.08	−1.32, 1.16	0.83

versa. It is therefore important that future studies investigating the link between insomnia symptoms and metabolic parameters should implement validated insomnia questionnaires (e.g. the insomnia severity index). A third limitation is that primary and secondary insomnia could not be discriminated. Fourth, hyperinsulinemic clamp-derived insulin sensitivity and the remaining variables were measured within a seven-day interval but on separate days. Hence, it cannot be ruled out that significant associations between insomnia symptoms and insulin sensitivity may have occurred when these parameters would have been collected on the same day. Since insomnia symptoms were the only sleep variables collected in ULSAM, caution is also warranted before concluding that short and long sleep duration, sleep-disordered breathing (e.g. obstructive sleep apnea), and mistimed sleep (e.g. daytime vs. nighttime sleep) do not correlate with insulin sensitivity in older men. These sleep parameters have all been linked to impaired insulin sensitivity (Tan et al., 2018b; Cedernaes et al., 2018; Cedernaes et al., 2015; Strand et al., 2015). The observation that insomnia combined with objective short sleep duration has been linked to hypertension (Bathgate et al., 2016) further highlights the complexity of the relationship between sleep and metabolism. Finally, the majority of individuals with insomnia symptoms only endorsed one symptom. This suggests that the insomnia symptoms in the present study might in fact be quite mild and that the relationship between insomnia and insulin sensitivity may exist when insomnia is more severe. To conclude, more research is needed to investigate the generalizability of our results (eg. no elderly women were included).

Author contributions

All authors of this manuscript fulfill the criteria of authorship.

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Conflict of interests

All authors declare that they have no conflicts of interest.

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