Biological risk factors and sleep-related risk factors of type 2 diabetes mellitus

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Chapter 6

The association between multiple sleep-related characteristics and the metabolic syndrome in the general population: the New Hoorn study.

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ABSTRACT

Background: Previous studies have investigated the association between sleep duration, insomnia, day-time napping and metabolic syndrome individually, but never conjointly and the association with sleep medication use has yet to be investigated. Our aim was to examine the associations between these sleep-related characteristics and the metabolic syndrome in a population-based cohort, individually and conjointly.

Material and methods: We used cross-sectional data of 1679 participants from the New Hoorn study, 52.6% women and age 60.8±6.4y. Sleep duration, insomnia and day-time napping were measured using validated questionnaires. Use of sleep medication was measured by registration of dispensing labels. Metabolic syndrome was defined according to ATP III. Linear and Poisson regression were used and all analyses were adjusted for age, sex, education level, job status, smoking, physical activity, depression and BMI.

Results: In our population-based cohort, 447 (26.6%) persons had the metabolic syndrome. The individual associations showed that after correction, day-time napping for ≤30 minutes and >30 minutes was associated with a prevalence ratio for the metabolic syndrome of 1.28 (95% CI: 1.1-1.5) and 1.74 (95% CI: 1.4-2.2), respectively, compared to participants who did not nap. Sleep duration, insomnia, and sleep medication use were not associated with the metabolic syndrome individually. The conjoint analysis, showed after correction that having ≥2 sleep-related characteristics was associated with a PR of 1.36 (95% CI: 1.0-1.8) of having the metabolic syndrome, compared to having no sleep-related characteristics.

Conclusion: Sleep-related characteristics were associated with a higher prevalence of the metabolic syndrome in the general population.

INTRODUCTION

The metabolic syndrome refers to a cluster of metabolic and cardiovascular abnormalities, including visceral obesity, insulin resistance, hypertension and altered lipoprotein profiles [1]. The metabolic syndrome is an increasing problem in developed countries, with recent studies showing that worldwide about a quarter of the population is affected [2]. It is well known that the risk of the metabolic syndrome increases with age, higher Body Mass Index (BMI) as well as the presence of an inactive lifestyle and an unhealthy diet [3]. Besides these frequently studied risk factors, a less obvious risk factor for the metabolic syndrome is sleep. Experimental and observational studies have shown that disturbance of sleep, comprising both duration and quality, increased the risk of metabolic disturbance, the metabolic syndrome and type 2 diabetes mellitus (T2DM) [4–6]. A recent meta-analysis based on data from 12 cross-sectional studies, confirmed that in the general population short sleep duration was associated with an 27% increased risk of having the metabolic syndrome (OR = 1.27, 95% CI: 1.01-1.5) [7].

However, these previous studies were mostly conducted in only men or women and, more importantly, data on the associations between other sleep-related characteristics besides sleep duration and quality, such as insomnia (difficulty falling asleep, waking up in the middle of the night, or self-reported low quality of sleep) and day-time napping, and the metabolic syndrome is scarce. With regards to insomnia, one study has shown a higher risk of the metabolic syndrome in participants that suffer from difficulty falling asleep [8], and two other studies showed such an association with T2DM [9,10]. For day-time napping, two Asian population-based cohort studies have shown a higher prevalence of metabolic syndrome in those who nap [11,12], compared to those who do not. While experimental work suggests effects of fragmented sleep on metabolic parameters [13], more population-based research is needed to show the metabolic effect of these sleep disturbances in the general population.

The sleep-related problems described above are treated often with sleep medication. As sleep problems are highly prevalent, sleep medication is one of the most widely used drug classes worldwide [14]. Recent figures showed that 1 in 10 Dutch adults take sleeping pills to alleviate sleep problems [15]. In addition, the prevalence of sleep medication use is higher in women and the use steadily increases with age [14]. Sleep medication has previously been associated with metabolic disturbances, such as insulin insensitivity [16]. However, up until now the role of sleep medication in the development of metabolic diseases has been ignored. Additionally, previous studies showed that sleep-related characteristics cluster [17,18]. It is likely that clustering sleep-related characteristics provides an even bigger risk of having the metabolic syndrome, and therefore we should assess the conjoint effect of such sleep-related characteristics. Therefore, the first aim of this study was to examine the individual association between sleep duration, insomnia, day-

time napping and sleep medication use, and metabolic syndrome in a population-based cohort. The second aim of this study was to examine the joint association of multiple sleep-related characteristic.

MATERIALS AND METHODS

Design and study population

The New Hoorn Study is a population-based cohort. The study was carried out from 2006 to 2007 in the Dutch city of Hoorn, a city of 70.000 inhabitants in the province of West-Friesland. The eligible population of the Hoorn Study consisted of 6180 men and women, aged 40–75 years, who were randomly selected from the municipal registry. Of the eligible participants, 45% agreed to participate, resulting in the New Hoorn Study cohort of 2807 participants.

From 2013-2015, a follow-up examination was performed. Of the original cohort, 2576 participants could be invited. A total of 1815 participants agreed to participate of which 1734 participants actually took part in the follow-up measurements (67%). For the present study, only data from the follow-up measurement were used, since sleep-related characteristics were only assessed at that visit. Participants without information regarding sleep-related characteristics and metabolic syndrome were excluded (n=55). Thus, from the analytical sample consisted of 1679 participants (Figure 1). The Ethics Committee of the VU University Medical Centre approved the New Hoorn Study and written informed consent was obtained from all participants.

Measurements

Participants were asked to refrain from eating and drinking (except drinking water) from 10:00 P.M. the night before the visit and from drinking alcohol from 5:00 P.M. the day before the visit. The participants were asked not to smoke from 10:00 P.M. the night before the visit. Participants who had not been following these instructions were asked to reschedule their visit [19]. Before the visit, participants were asked to complete questionnaires on their medical history, depressive symptoms, diet, physical activity and sleep-related characteristics. During the visit, metabolic syndrome parameters as well as other physical measures were determined.

Sleep-related characteristics

Sleep duration (hours): was assessed by questionnaire by asking the 4 following questions: 1) at what time do you go to bed on weekdays? 2) at what time do you get up on weekdays? 3) at what time do you go to bed on weekend days? 4) at what time do you get up on weekend days? Sleep duration was calculated as the average duration between time

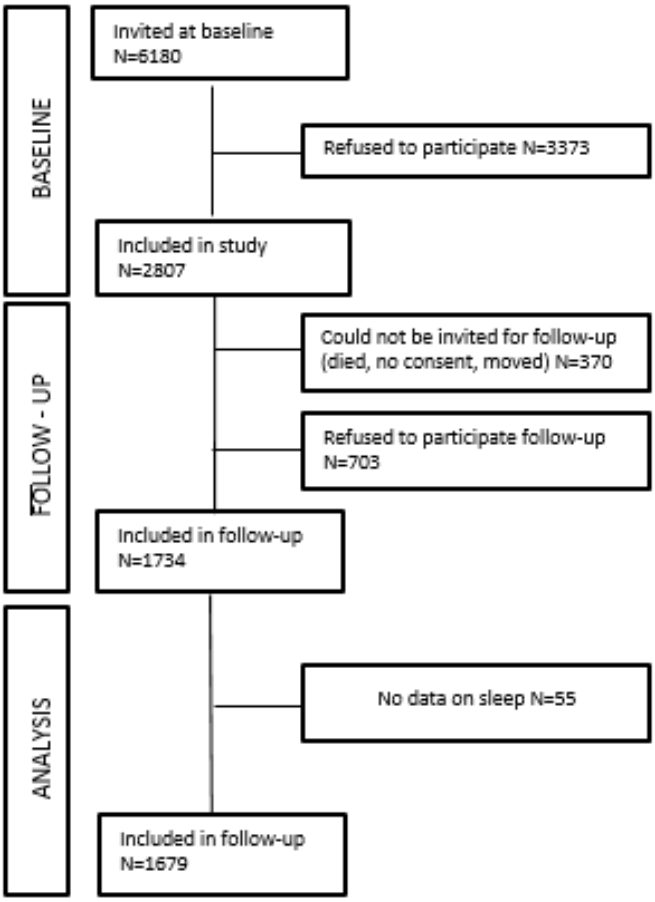

Figure 1: flow chart study population New Hoorn Study cohort

of going to bed and getting up on weekdays and weekend days (5*sleep duration week days + 2*sleep duration weekend days/7) [20,21]. Sleep duration was stratified into those who slept less than 7 hours, 7 to less than 8 hours, 8 to less than 9 hours and 9 hours or more. We conjoined the groups with less than 6 hours of sleep and 6 to less than 7 hours, due to the limited number of participants who slept less than 6 hours. Furthermore, we used the group who slept 7 to less than 8 hours on average as the reference group and participants who slept less than 7 hours were defined as short sleepers and those who slept more than 9 hours were defined as long sleepers.

Insomnia (yes/no): Participants were considered to have insomnia if three out of four of the following statements were true: 1) participant reported not falling asleep within 30 minutes after going to bed, 2) waking up in the middle of the night three or more times,

3) self-reported low quality of sleep, defined as yes or no, 4) scores of ≥10 on the Epworth Sleepiness Scale (ESS).

Day-time napping (min): was self-reported based on the question 'When possible do you try to incorporate a nap during the day?' and 'If yes, how many hours/minutes per day do you nap?'. Day-time napping time was stratified into no napping, napping 30 minutes or less or napping more than 30 minutes.

Sleep medication use (yes/no): participants were asked to bring their current prescribed medication to the visit, which were used to note the prescription labels. The Anatomical Therapeutic Chemical (ATC) Classification System was used for the classification of drugs. Anxiolytics, hypnotics and sedatives were defined as sleep medication, including ATC codes N05B and N05C.

Metabolic syndrome

Metabolic syndrome status was defined according to the ATP III of the National Cholesterol Education Program, i.e. participants had to meet three or more of the following criteria: fasting plasma glucose (FPG) levels ≥ 6.1 mmol/l or the presence of T2DM, high-density lipoprotein (HDL) cholesterol levels < 1.0 mmol/l in men or < 1.3 mmol/l in women, triglyceride levels ≥ 1.7 mmol/l or use of lipid medication, waist circumference ≥ 102 cm in men or ≥ 88 cm in women or ≥ 130/85 mmHg or use of antihypertensive medication [22].

Fasting plasma glucose levels (mmol/l) were determined using the glucose dehydrogenase method (Merck, Darmstad, Germany). Triglycerides and HDL levels (mmol/l) were determined in the fasting blood sample, using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Waist circumference (cm) was measured according to a standardised procedure, as described earlier [23]. Sitting systolic and diastolic blood pressure (mmHG) was measured twice on the right arm with a random-zero sphygmomanometer (Hawksley–Gelman, Lancing, UK) and the average was used in the analyses.

Possible confounders and effect modifiers

Age, sex, education level and job status were self-reported. Education level was stratified into 3 groups: low (no education, primary school), average (high school, secondary vocational education), and high (higher professional education, university). Job status was also stratified into three groups: having a paid job, being unemployed or being retired. Smoking was self-reported and dichotomized as smoking, including current smoking and former smoking, versus non-smoking. Finally, physical activity was self-reported (min) and was dichotomized into a sufficient amount of physical activity or an insufficient amount. A sufficient amount of physical activity was defined according to the Dutch physical activity guideline as at least 30 minutes, 5 days a week [24]. Depression was measured using the CES-D questionnaire and dichotomized at ≥ 16 score [25]. Finally, weight and height were

measured with participants wearing light clothes only, and BMI was calculated as weight/height squared (kg/m^2).

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD), percentages or median and IQR and were log-transformed in case of a skewed distribution. First, participant characteristics stratified for sleep duration were presented. Second, Poisson regression analyses were performed to estimate the prevalence ratios of the metabolic syndrome per sleep-related characteristic, individually. Poisson regression was used here since the metabolic syndrome was a prevalent outcome in our study. Since odds ratios from logistic regression may overestimate the association when the outcome is prevalent, the use of Poisson regression is suggested for these cases [26]. Next, we used linear regression analyses to estimate the beta coefficients per sleep-related characteristic and as a sensitivity analysis per parameter of the metabolic syndrome. Fourth, Poisson regression analyses were performed to estimate the conjoint association of the sleep-related characteristics with the prevalence ratios of the metabolic syndrome, in which we assessed the association of each additional sleep-related characteristic, comparing none versus 1 or $\geq$ 2 sleep-related characteristics. We defined the sum score by adding having either short sleep duration, long sleep duration, insomnia, day-time napping, and/or sleep medication use as the different sleep-related characteristics. Finally, we calculated the P for trend for the association between additional sleep-related characteristics and metabolic syndrome by using a Chi-Square test.

We tested whether age, sex and the sleep-related characteristics were effect modifiers, however we did not observe significant interaction effects (all $P > 0.31$). All analyses described above were presented unadjusted, adjusted for age, sex, education and job status (model 2), model 2 plus smoking, physical activity, and depression (model 3). We adjusted for the factors in model 2 plus BMI (model 4) to assess for possible mediation of the association by BMI. Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL) and a two-sided p-value below 0.05 was considered statistically significant.

RESULTS

Of the 1679 participants, 52.6% were women and the average age (SD) was 60.8 (±6.4) years. No significant differences were observed with regard to age and metabolic syndrome factors between those with and without sleep information (data not shown). Table 1 shows the participant characteristics stratified for average sleep duration. Participants with the longest sleep duration had the highest percentage of metabolic syndrome, compared to those in the average sleep duration group (7-8 h), namely 30.5% versus 24.5%. With regard to the other sleep-related characteristics, we observed that participants with the shortest average sleep duration had the highest prevalence of insomnia and the longest day-time napping duration and the highest sleep medication use rates.

Table 2 shows the prevalence ratios (PR) of the individual sleep-related characteristics and the metabolic syndrome. We report on the third model, as this is adjusted most completely. Model 3 showed that day-time napping for 30 minutes or less and day-time napping for more than 30 minutes were associated with an increased prevalence of the metabolic syndrome, PR = 1.28 (95% CI: 1.1; 1.5) and 1.74 (95% CI: 1.4; 2.2), respectively, compared to no day-time napping. Including BMI in the model attenuated the association by 7% and 22%, suggesting mediation of the association by BMI. Finally, sleep medication use was associated with a higher prevalence of having the metabolic syndrome in the crude model, PR = 1.41 (95%-CI: 1.0; 1.9). However, this association attenuated to non-significant after multivariable adjustment in model 3, namely PR = 1.21 (95%-CI: 0.8; 1.7).

Supplementary Table 1 shows the beta coefficients of the individual sleep-related characteristics and the parameters of the metabolic syndrome. Participants who reported to nap regularly had significantly higher fasting plasma glucose levels (0.15 mmol/l (95% CI: 0.1;0.3) for those who napped 30 minutes or less, and 0.34 mmol/l (95% CI: 0.2;0.5) for those napping longer), compared to no day-time napping. Short and longer day-time nappers also had a significantly larger waist circumference (1.50 cm (95% CI: -0.3;3.3), and 3.29 cm (95% CI: 0.6;6.0), respectively). Sleep medication use was associated with higher levels of fasting plasma glucose, 0.40 mmol/l (95% CI: 0.2;0.6) as well as log triglyceride levels, 0.14 mmol/l (95% CI: 0.0;0.3), compared to participants who did not use sleep medication.

Table 3 shows the association per additional sleep-related characteristics and the metabolic syndrome. We observed that after correction for multiple confounders (model 3), having ≥2 sleep-related measures was associated with 1.36 (95% CI: 1.0-1.8) higher PRs of having the metabolic syndrome, compared to having no sleep-related characteristics. The association attenuated to non-significant when adjusted for BMI (model 4), which suggests mediation by BMI. The P for trend for these associations were 0.001.

Table 1. Participants characteristics stratified by sleep duration (N=1679).

	Total	**<7 hours**	**7-8 hours**	**8-9 hours**	**>=9 hours**
N	1679	593	212	635	239
Age (years)	60.8 ±6.4	59.1 ±6.4	59.8 ±6.1	61.8 ±6.4	62.2 ±6.3
Sex (% women)	52.6	41.5	47.7	56.4	64.4
Education (%low/middle/high)	6/64/30	9/59/32	4/60/36	5/67/28	12/72/16
Job status (%paid/retired/unemployed)	59/37/4	74/23/3	68/28/4	50/46/5	49/48/3
Metabolic syndrome factors					
Fasting plasma glucose (mmol/l)	5.9 ±0.9	5.9 ±1.1	5.9 ±1.0	5.8 ±0.8	5.9 ±1.0
HDL (mmol/l)	1.6 ±0.4	1.6 ±0.4	1.6 ±0.5	1.6 ±0.4	1.5 ±0.4
Triglycerides (mmol/l)	1.3 [0.9; 1.6]	1.4 [0.9; 1.2]	1.3 [0.8; 1.6]	1.3 [0.9; 1.6]	1.4 [0.9; 1.7]
Waist circumference (cm)	91.6 ±16.0	93.3 ±12.2	92.4 ±22.2	90.5 ±10.7	91.4 ±12.1
Systolic blood pressure (mmHg)	131 ±18.8	131 ±19	130 ±18	131 ±19	134 ±19;
Diastolic blood pressure (mmHg)	79 ±8.4	80 ±9	79 ±8	78 ±8	80 ±8
Metabolic syndrome (%)	26.6	27.8	24.5	26.8	30.5
Other sleep characteristics					
Insomnia (%)	5.2	11.6	6.4	2.8	3.1
Day-time napping (minutes)	13.7 ±21.2	17.1 ±25.2	12.4 ±19.5	12.9 ±19.8	15.6 ±24.3
No day-time napping (%)	57.0	53.3	58.5	56.7	57.3
<=30 minutes (%)	31.4	30.2	32.0	32.0	29.3
>30 minutes (%)	11.6	16.5	9.4	11.3	13.4
Sleep medication use (%)	4.5	8.0	2.7	3.6	8.4
Other co-variants and confounders					
BMI (kg/m^2)	26.5 ±4.2	27.2 ±4.6	26.5 ±4.2	26.2 ±3.9	26.8 ±4.6
Depression >= 16 CESD (%)	11.0	14.1	9.0	10.4	15.2
Smokers (%)	58.7	60.7	60.0	56.8	58.9
Sufficient physical activity (%)	65.5	56.0	63.8	70.6	64.3

HDL: high-density lipoprotein; BMI: Body Mass Index. Data are presented as numbers (%) or mean (±SD). Differences between the different sleep duration groups were calculated with the Independent-Samples T Test and the Chi Square Test.

Table 2. Crude and adjusted prevalence ratios (95% confidence interval) of the metabolic syndrome for sleep-related characteristics (N=1679).

	Model 1	Model 2	Model 3	Model 4
<7 hours	1.14 (0.9; 1.5)	1.14 (0.9; 1.5)	1.04 (0.8; 1.2)	0.96 (0.7; 1.3)
>=7 to <8 hours	[Reference]	[Reference]	[Reference]	[Reference]
>=8 to <9 hours	1.10 (0.9; 1.3)	0.99 (0.8; 1.2)	0.99 (0.8; 1.2)	1.07 (0.9; 1.3)
>=9 hours	1.25 (0.99; 1.6)	1.07 (0.8; 1.4)	1.05 (0.8; 1.4)	1.06 (0.8; 1.3)
Insomnia	0.94 (0.6; 1.4)	0.90 (0.6; 1.4)	0.81 (0.5; 1.3)	0.85 (0.6; 1.2)
No nap	[Reference]	[Reference]	[Reference]	[Reference]
=<30 minutes	**1.27 (1.1; 1.5)**	**1.30 (1.1; 1.6)**	**1.28 (1.1; 1.5)**	**1.19 (1.0; 1.4)**
>30 minutes	**1.76 (1.4; 2.2)**	**1.86 (1.5; 2.3)**	**1.74 (1.4; 2.2)**	**1.38 (1.1; 1.7)**
Sleep medication	**1.41 (1.0; 1.9)**	1.34 (0.98; 1.8)	1.21 (0.8; 1.7)	1.25 (0.96; 1.6)

Model 1: unadjusted
Model 2: adjusted for age, sex, education, job status
Model 3: as model 2, plus smoking, physical activity, and depression
Model 4: as model 2, plus BMI
p<0.05 in bold

Table 3. Crude and adjusted prevalence ratios (95% confidence interval) of the metabolic syndrome for sleep-related characteristics (N=1679).

		Metabolic syndrome			
Number sleep related measures	*N*	Model 1	Model 2	Model 3	Model 4
0	288	[Reference]	[Reference]	[Reference]	[Reference]
1	733	1.11 (0.9; 1.4)	1.06 (0.8; 1.4)	1.09 (0.8; 1.4)	1.03 (0.8; 1.3)
2-4	487	**1.54 (1.2; 2.0)**	**1.43 (1.1; 1.8)**	**1.36 (1.0; 1.8)**	1.22 (0.9; 1.6)

Model 1: unadjusted
Model 2: adjusted for age, sex, education, job status
Model 3: as model 2, plus smoking, physical activity, and depression
Model 4: as model 2, plus BMI
p<0.05 in bold

DISCUSSION

We examined the individual and conjoint associations of multiple sleep-related characteristics and the metabolic syndrome in a population-based cohort. We showed that day-time napping was associated with the metabolic syndrome, such that participants who napped 30 minutes or more had a 30% higher chance of having the metabolic syndrome, compared to those who did not nap. The association with day-time napping and the metabolic syndrome was mainly due to the higher fasting glucose concentrations and waist circumference components of the metabolic syndrome. For sleep duration, insomnia, and sleep medication use we did not observe significant associations. Second, we observed a dose-response association, such that two or more sleep-related characteristics were associated with a 40% higher chance of the metabolic syndrome, compared to the absence of sleep-related characteristics.

In contrast with previous studies [7,27], we did not observe a significant association between sleep duration and metabolic syndrome. The majority of previous studies showed 27-62% higher risks of having the metabolic syndrome for short sleep duration [28]. Our observation was in the same direction, but non-significant which might be due to the small amount of participants that slept less than 7 or more than 9 hours in our cohort as well as the correction for multiple confounders. Additionally, we distinguished sleep duration from week and weekend days, while others only measured average sleep duration of the weekdays; this could have resulted in longer sleep duration in our cohort and obscuring the short sleep duration effect. In contrast to previous findings, we also did not observe an association between insomnia and (parameters of) metabolic syndrome [8,10]. These dissimilarities might be explained by the fact that the percentage of participants suffering from insomnia in our cohort was very low, namely only 5.2%. In addition, the difference might also be caused by differences in definition of insomnia, which to date has not been harmonized.

Part of our results were however in accordance with the literature [11,12]. For example the observed association between day-time napping and the metabolic syndrome, which was confirmed in women, but not for men [11,12], showed a similar effect size. We were the first to show an association between sleep medication use and the association with metabolic syndrome, supporting the suggestion of negative metabolic effects of using such medication. This should be confirmed in longitudinal observational or experimental studies. Additionally, we were the first to show the dose-response association between sleep-related characteristics and the metabolic syndrome, with having two or more sleep-related characteristics being associated with an increased risk of having the metabolic syndrome than having none or one sleep-related characteristic. This observation stresses the importance of assessing not only one but several sleep-related characteristics in research but also the clinic. Future research, preferably randomized controlled trials, should

therefore assess if addressing sleep-related characteristics could reduce the risk of the metabolic syndrome can also be focussed on sleep-related characteristics.

Several possible mechanisms could mediate the association between sleep-related characteristics and the metabolic syndrome. First, the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic activation have been suggested to play a role in the development of metabolic syndrome [27]. Hyperactivation of the HPA axis or sympathetic activation leads to an increase in cortisol levels which contribute to insulin resistance, dyslipidemia and abdominal obesity [8,11]. This pathway is line with our results, showing that fasting glucose concentrations, triglycerides and waist circumference were mainly responsible for the association between day-time napping, sleep medication use and an increased risk of the metabolic syndrome, while blood pressure and other blood lipids were not. Second, the association between long sleep duration and metabolic syndrome is mediated by depression [28], as confirmed by our (non-significant) results. Finally, the hunger regulating hormones leptin and ghrelin are associated with sleep parameters. For example, sleep restriction causes an increase in ghrelin levels and a decrease in leptin levels, which regulate satiety and hunger, respectively. This leads to higher intake of food and subsequently weight gain and higher prevalence of metabolic syndrome [7]. Thereby, shorter sleep duration is associated with more sedentary time in contrast to a normal sleep duration [29]. Except for the affected metabolic parameters, our current study does not enable us to assess these other possible pathways and therefore additional studies are needed.

This study has some limitations that need to be mentioned. First, all the sleep data was self-reported, however to date no golden standard is present to measure sleep. Second, we had no information about snoring or sleep apnea, which also could influence the quality of sleep and is strongly associated with the metabolic syndrome. Thirdly, these data were cross-sectional, making it hard to distinguish cause and effect. Fourthly, we had no information on insulin, so no information on insulin resistance and insulin sensitivity if available. Finally, it is not certain if the different sleep-related characteristics are really different from each other or if they all reflect the same issue, namely poor sleeping quality. We believe they reflect different characteristics as the correlations between the variables was minimal ($P<0.3$ for all). The main strengths of this study were the use of data from a relatively large, middle-aged population-based cohort with detailed phenotyping to allow appropriate adjustment for confounding and we were the first to compare different sleep-related characteristics with each other, instead of looking at a single sleep measure at a time and looking at the effect of the characteristics conjointly.

Overall, from our current study we conclude that sleep-related characteristics are associated with a higher prevalence of the metabolic syndrome in the general population. Interventions targeted at these sleep-related characteristics could provide new ways to reduce the prevalence of metabolic syndrome in the general population.

Supplementary Table 1. Unstandardized Betas and 95% confidence intervals per sleep disturbances and per parameter of the metabolic syndrome.

	Systolic blood pressure (mmHg)	**Fasting plasma glucose (mmol/L)**	**High-density lipoprotein (mmol/L)**	**Log triglycerides (mmol/L)**	**Abdominal circumference (cm)**
Sleep duration model 1					
<7 hours	1.09 (-1.9; 4.0)	0.06 (-0.1; 0.2)	-0.02 (-0.1; 0.0)	0.06 (0.0; 0.1)	0.90 (-1.7; 3.5)
>=7 to <8 hours	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
>=8 to <9 hours	0.45 (-1.7; 2.5)	-0.05 (-0.2; 0.0)	-0.04 (-0.1; 0.0)	0.03 (0.0; 0.1)	**-1.86 (-3.7; 0.0)**
>=9 hours	**3.55 (0.7; 6.4)**	0.04 (-0.1; 0.2)	-0.06 (-0.1; 0.0)	0.06 (0.0; 0.1)	-1.03 (-3.5; 1.4)
Sleep duration model 2					
<7 hours	0.95 (-1.9; 3.8)	0.04 (-0.1; 0.2)	-0.02 (-0.1; 0.0)	0.05 (0.0; 0.1)	0.15 (-2.3; 2.6)
>=7 to <8 hours	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
>=8 to <9 hours	-1.32 (-3.4; 0.7)	-0.06 (-0.2; 0.0)	-0.04 (-0.1; 0.0)	0.03 (0.0; 0.1)	-1.57 (-3.4; 0.2)
>=9 hours	1.48 (-1.3; 4.3)	0.04 (-0.1; 0.2)	-0.07 (-0.1; 0.0)	0.07 (0.0; 0.1)	-0.62 (-3.1; 1.8)
Sleep duration model 3					
<7 hours	1.34 (-1.6; 4.3)	-0.02 (-0.2; 0.1)	-0.02 (-0.1; 0.1)	0.02 (-0.1; 0.1)	0.15 (-2.5; 2.8)
>=7 to <8 hours	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
>=8 to <9 hours	-1.21 (-3.3; 0.9)	-0.07 (-0.2; 0.0)	-0.03 (-0.1; 0.0)	0.03 (0.0; 0.1)	-1.47 (-3.4; 0.4)
>=9 hours	1.84 (-1.1; 4.8)	0.05 (-0.1; 0.2)	-0.06 (-0.1; 0.0)	0.06 (0.0; 0.1)	-0.56 (-3.2; 2.1)
Sleep duration model 4					
<7 hours	0.54 (-2.3; 3.3)	-0.01 (-0.1; 0.1)	-0.02 (-0.1; 0.0)	0.03 (0.0; 0.1)	-0.89 (-2.9; 1.1)
>=7 to <8 hours	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
>=8 to <9 hours	-1.12 (-3.2; 0.9)	-0.04 (-0.1; 0.1)	-0.04 (-0.1; 0.0)	0.04 (0.0; 0.1)	-0.82 (-2.3; 0.7)
>=9 hours	1.41 (-1.4; 4.2)	0.03 (-0.1; 0.2)	-0.07 (-0.1; 0.0)	0.06 (0.0; 0.1)	-0.91 (-2.9; 1.1)
Insomnia					
Model 1	-2.33 (-6.6; 1.9)	-0.02 (-0.2; 0.2)	0.07 (0.0; 0.2)	0.02 (-0.1; 0.1)	-1.27 (-5.1; 2.5)
Model 2	-1.56 (-5.7; 2.6)	0.04 (-0.2; 0.2)	0.07 (0.0; 0.2)	0.04 (-0.1; 0.1)	0.49 (-3.2; 4.2)
Model 3	-1.25 (-5.5; 3.0)	0.01 (-0.2; 0.2)	0.07 (0.0; 0.2)	-0.01 (-0.1; 0.1)	-0.03 (-4.0; 3.9)
Model 4	-2.09 (-6.2; 2.0)	-0.01 (-0.2; 0.2)	0.07 (0.0; 0.2)	0.01 (-0.1; 0.1)	-1.03 (-4.1; 2.0)

Napping model 1					
No napping	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
<=30 min napping	-0.13 (-2.1; 1.9)	**0.19 (0.1; 0.3)**	0.01 (0.0; 0.1)	**0.07 (0.0; 0.1)**	**2.68 (0.9; 4.4)**
>30 min napping	-1.17 (-4.1; 1.7)	**0.41 (0.3; 0.5)**	-0.04 (-0.1; 0.0)	**0.13 (0.1; 0.2)**	**4.65 (2.1; 7.2)**
Napping model 2					
No napping	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
<=30 min napping	-0.83 (-2.8; 1.1)	**0.15 (0.1; 0.2)**	0.01 (0.0; 0.1)	**0.05 (0.0; 0.1)**	1.44 (-0.3; 3.1)
>30 min napping	-1.01 (-3.8-1.8)	**0.39 (0.3; 0.5)**	-0.04 (-0.1; 0.0)	**0.12 (0.0; 0.2)**	**3.80 (1.3; 6.3)**
Napping model 3					
No napping	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
<=30 min napping	-0.94 (-2.9; 1.1)	**0.15 (0.1; 0.3)**	0.01 (0.0; 0.1)	0.04 (0.0; 0.1)	1.50 (-0.3; 3.3)
>30 min napping	-0.65 (-3.7; 2.4)	**0.34 (0.2; 0.5)**	-0.04 (-0.1; 0.0)	0.13 (0.1; 0.2)	**3.29 (0.6; 6.0)**
Napping model 4					
No napping	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
<=30 min napping	-1.35 (-3.3; 0.6)	**0.10 (0.0; 0.2)**	0.01 (0.0; 0.1)	0.03 (0.0; 0.1)	0.01 (-1.4; 1.4)
>30 min napping	-2.12 (-4.9; 0.7)	**0.28 (0.1; 0.4)**	-0.04 (-0.1; 0.0)	0.06 (0.0; 0.1)	0.34 (-1.7; 2.4)
Sleep medication					
Model 1	-4.17 (-8.5; 0.2)	**0.28 (0.1; 0.5)**	0.03 (-0.1; 0.1)	**0.18 (0.1; 0.3)**	0.59 (-3.2; 4.3)
Model 2	-3.65 (-7.8; 0.5)	**0.34 (0.1; 0.6)**	0.02 (-0.1; 0.1)	**0.21 (0.1; 0.3)**	2.36 (-1.3; 6.0)
Model 3	-3.48 (-8.0; 1.0)	**0.40 (0.2; 0.6)**	0.01 (-0.1; 0.1)	**0.14 (0.0; 0.3)**	1.81 (-2.2; 5.8)
Model 4	**-4.14 (-8.3; 0.0)**	**0.29 (0.1; 0.5)**	0.02 (-0.1; 0.1)	**0.18 (0.1; 0.3)**	0.22 (-2.7; 3.2)

Model 1: unadjusted
Model 2: adjusted for age, sex, education, job status
Model 3: as model 2 plus smoking, physical activity, and depression
Model 4: as model 2 plus BMI
p<0.05 in bold

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