SLEEP STRUCTURE AND CARDIOVASCULAR RISK FACTORS IN THE GENERAL POPULATION

Objective Sleep Structure and Cardiovascular Risk Factors in the General Population: The HypnoLaus Study

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Study Objectives: To evaluate the association between objective sleep measures and metabolic syndrome (MS), hypertension, diabetes, and obesity.
Design: Cross-sectional study.
Setting: General population sample.
Participants: There were 2,162 patients (51.2% women, mean age 58.4 ± 11.1).
Interventions: Patients were evaluated for hypertension, diabetes, overweight/obesity, and MS, and underwent a full polysomnography (PSG).
Measurements and Results: PSG measured variables included: total sleep time (TST), percentage and time spent in slow wave sleep (SWS) and in rapid eye movement (REM) sleep, sleep efficiency and arousal index (ArI). In univariate analyses, MS was associated with decreased TST, SWS, REM sleep, and sleep efficiency, and increased ArI. After adjustment for age, sex, smoking, alcohol, physical activity, drugs that affect sleep and depression, the ArI remained significantly higher, but the difference disappeared in patients without significant sleep disordered breathing (SDB). Differences in sleep structure were also found according to the presence or absence of hypertension, diabetes, and overweight/obesity in univariate analysis. However, these differences were attenuated after multivariate adjustment and after excluding subjects with significant SDB.
Conclusions: In this population-based sample we found significant associations between sleep structure and metabolic syndrome (MS), hypertension, diabetes, and obesity. However, these associations were cancelled after multivariate adjustment. We conclude that normal variations in sleep contribute little if any to MS and associated disorders.
Keywords: diabetes, hypertension, metabolic syndrome, obesity, polysomnography
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INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death worldwide, and is expected to increase in the forthcoming years.[1] Lifestyle factors such as tobacco use, high-fat diet, and physical inactivity strongly increase risk factors for CVD, but they may not fully account for their development.[2] It is therefore important to identify new underlying determinants of CVD.

Recent research identified relationships between sleep quantity and CVD risk factors. Numerous population studies, summarized in recent meta-analyses, suggested that sleep duration may be associated with obesity,[3] hypertension,[4] type 2 diabetes,[5] the metabolic syndrome (MS),[6] cardiovascular outcomes (including coronary heart disease, stroke, and total CVD),[7] and overall mortality.[8] In particular, for most of these outcomes there seems to be a U-shaped relationship with sleep duration.

Some of the aforementioned studies evaluating the association between sleep duration and cardiovascular and metabolic

outcomes yielded conflicting results that can be explained by methodological heterogeneity. Caution has been expressed, from different perspectives, about the interpretation of these findings in critical reviews.[9,10] One important limitation of prior epidemiological studies is that the definition of ''short'' and ''long'' sleep varies across studies. More importantly, almost all previous studies are based on subjective assessments of the duration of sleep, generally based on responses to a single question or by questionnaires that have not been validated against objective sleep measures.

Finally, it was suggested that the effect of sleep on CVD risk may be mediated by poor sleep quality. For example, difficulties in initiating or maintaining sleep were associated with a greater risk of type 2 diabetes.[5] Again, these conclusions are based on subjective assessments and do not allow the identification of sleep variables directly linked with CVD risk outcomes. Laboratory studies in young healthy adults indicated that selective suppression of slow wave sleep (SWS) without any change in total sleep time (TST) affects glucose homeostasis, potentially increasing the risk of type 2 diabetes,[11] and can produce a significant reduction in blood pressure (BP) dipping.[12] Even if these findings demonstrate that sleep structure, independently of sleep duration, can play a role in metabolic disorders, they have not been replicated in large general population studies.

Thus, the aim of this study was to explore the association between sleep structure, objectively measured by

polysomnography (PSG) and several CVD risk factors, specifically MS, hypertension, diabetes, and obesity in a large unselected middle-aged general population sample. We analyzed these associations in the entire sample and after excluding subjects with a significant oxygen desaturation index (ODI > 15/h), as intermittent hypoxia related to respiratory disturbances (apneas/hypopneas) plays an independent role in the pathophysiology of CVD.[13]

METHODS

Population Sampling

The HypnoLaus Sleep Cohort study is based on the first follow-up of the epidemiologic CoLaus/PsyCoLaus study. Details of the CoLaus/PsyCoLaus study were previously described.[14,15] Briefly, the CoLaus/PsyCoLaus study included a random sample of 6,733 subjects (range age: 35–75 y) selected from the residents of Lausanne city (Switzerland) between 2003 and 2006. HypnoLaus evaluated the subjective and objective sleep characteristics of the study population. During the first follow-up of the cohort, 5 y after the initial phase, all subjects who responded underwent a new physical (n = 5,064) and psychiatric (n = 4,000) examination and were given questionnaires by trained interviewers, which included questions on demographic, medical, and treatment history as well as smoking and alcohol consumption. Sleep related complaints and habits were investigated using the Pittsburgh Sleep Quality Index (PSQI),[16] the Epworth Sleepiness Scale (ESS),[17] and the Berlin questionnaire for sleep disordered breathing (SDB).[18]

CoLaus/PsyCoLaus and HypnoLaus were approved by the Ethics Committee of the University of Lausanne and a written informed consent was obtained from all participants at the baseline and the follow-up assessments.

Polysomnography

Three thousand fifty-one consecutive subjects were invited to undergo a full night in-home PSG recording. No selection of the subjects was made based on the questionnaires and the investigators were blinded to the questionnaires' results. During a visit at the Center for Investigation and Research in Sleep (Lausanne University Hospital, Switzerland), trained technicians equipped the subjects with the PSG recorder (Titanium, Embla Flaga, Reykjavik, Iceland) between 17:00 and 20:00. All sleep recordings took place in the subjects' home environment and included a total of 18 channels: six electroencephalography, two electrooculography, three surface electromyography (one submental, two for right and left anterior tibialis muscles), one for electrocardiogram, nasal pressure, thoracic and abdominal belts, body position, oxygen saturation, and pulse rate.

All PSG recordings were visually scored by two trained sleep technicians (DA and NT) using Somnologica software (Version 5.1.1, by Embla Flaga, Reykjavik, Iceland) and reviewed by a trained sleep physician (JHR). Random quality checks were performed by a second physician (RH). Quality control for concordance rate between the two PSG scorers was implemented periodically to ensure that both scorers achieved at least a 90% level of agreement for sleep stages and respiratory events and an 85% level of agreement for arousals.[19] Sleep stages, leg movements, and arousals were scored according

to the 2007 American Academy of Sleep Medicine (AASM) criteria.[20] The ODI represents the number ≥ 3% oxygen saturation drops per hour of sleep. Apneas/hypopneas were scored according to the AASM 2013 rules.[21] The average number of apneas/hypopneas per hour of sleep (apnea-hypopnea index [AHI]) was calculated.

CVD Risk Factors

BP was measured in triplicate on the left arm and values averaged between the last two readings. Arterial hypertension was defined as a systolic BP (SBP) ≥ 140 mmHg and/or a diastolic BP (DBP) ≥ 90 mmHg or current use of antihypertensive medication. A fasting blood sample was collected for various analyses (including glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides). Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/L (126 mg/dL) or current use of antidiabetic medication. The body mass index (BMI) was calculated and subjects were classified as overweight if BMI was between 25 and 30 kg/m² and obese if BMI ≥ 30 kg/m². The MS was defined according to the Adult Treatment Panel III report (ATP-III)[22] in the presence of three of the following five factors: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), elevated triglycerides (≥ 1.7 mmol/L, > 150 mg/dL), reduced HDL cholesterol (< 1.03 mmol/L (40 mg/dL) in men and < 1.20 mmol/L (50 mg/dL) in women), elevated BP (≥ 130/≥ 85 mmHg) (or hypertension), or elevated fasting glucose (≥ 5.6 mmol/L) (or type 2 diabetes mellitus).

Other Variables

Smoking habit was self-reported and was dichotomized as current smoker/ex-smoker or never smoker. Alcohol drinking was dichotomized as currently drinking or no alcohol consumption. Regular exercise was defined as reports of exercising three or more times a week. Medication use, recorded at the time of sleep studies, was coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System (http://www.whocc.no/atcddd). Diagnosis of lifetime major depressive disorder was assigned according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria with information collected using the French translation[23] of the semistructured Diagnostic Interview for Genetic Studies (DIGS).[24] PSGs were recorded between Mondays and Fridays. Because Saturday is generally considered to be a day off, the day of week (Friday versus other weekdays) was considered as a covariate.

Statistical Analysis

All statistical tests were performed using Stata 11 (StataCorp, College Station, TX, USA). For descriptive statistics, continuous variables were summarized as mean ± standard deviation, whereas categorical variables were summarized as number of subjects and percentages. Descriptive statistics were also used for sleep characteristics of the subjects based on presence or absence of MS, hypertension, diabetes, and obesity. Student *t* test or one-way analysis of variance were used to evaluate univariate differences between PSG variables. These included sleep duration or TST: total minutes of any stage of sleep from sleep onset to morning awakening; percentage of

stage N3/SWS: percentage of TST spent in stage N3/SWS; SWS, min: time in min spent in stage N3/SWS; rapid eye movement (REM) sleep: percentage of TST spent in REM sleep; REM, min: time in min spent in REM sleep; sleep efficiency: ratio between TST and time spent in bed; arousal index (ArI): number of arousals divided by hours of TST. These variables are routinely used in clinical practice to describe both sleep continuity and sleep architecture. The PSG variables were considered as continuous variables. SWS, min; REM, min; and ArI were log-transformed (natural log) for analysis. Although extremes of sleep duration were previously associated with adverse cardiovascular risk outcomes, TST was also evaluated as a continuous variable given the low prevalence of long sleepers (0.3% slept more than 10 h) and short sleepers (8% slept less than 5 h) in the HypnoLaus study. However, we also compared the short sleepers and long sleepers, stratifying the subjects in four groups according to the TST: < 6, 6–6.9, 7–7.9, and ≥ 8 h. These analyses are presented in the supplemental material.

At a second step, two multivariate models were used: the first was adjusted for age, sex, and day of PSG recording; the second model was adjusted for the same variables plus the following additional covariates: smoking, alcohol use, regular exercise, depression, and use of medications that affect sleep (hypnotics, benzodiazepines, antidepressants, neuroleptics and/or antihistamines). BMI was included as a covariate for hypertension and diabetes, but not for the MS because BMI is strongly associated with abdominal obesity and overadjustment might occur. A multivariate analysis with subjects stratified in groups according to the TST (< 6, 6–6.9, 7–7.9, and ≥ 8 h) was also performed, and results are presented in the supplemental material.

When studying the association between sleep and cardiovascular morbidity and mortality, SDB constitutes a key phenotype as it is an independent risk factor for hypertension[25] and insulin resistance,[26] and is associated with the MS.[27] SDB describes a group of disorders characterized by abnormalities of respiratory patterns during sleep. These abnormalities cause sleep disturbances (secondary to arousals to resume normal ventilation) and/or repetitive oxygen desaturations. Intermittent hypoxia in SDB seems to be a critical factor in the pathophysiology of cardiovascular and metabolic consequences.[13] Because the purpose of this study was to determine if sleep structure is associated with cardiovascular risk factors independently of the origin of sleep disruption, we analyzed these associations first in the entire group and then, after excluding subjects with a substantial (> 15/h) ODI. We choose a cutoff value of 15/h as the International Classification of Sleep Disorders (ICSD-3) diagnostic criteria for sleep apnea are based on this metric (AHI ≥ 15/h or ≥ 5/h with symptoms).[28] Of note, ODI was also examined as a continuous variable, with the results yielding similar conclusions. For simplicity, we present only the results using the dichotomous ODI variable.

Multiple testing problems are in a wide variety, ranging from testing multiple doses and endpoints jointly, composite endpoint, noninferiority and superiority, etc.[29] In this study, we chose to adjust for multivariate adjustment within each MS component, thus allowing a better control of the type I error rate while not overtly reducing the chances of finding clinically important (and statistically significant) associations. We estimated that within each MS component approximately

Figure 1—Studied population.
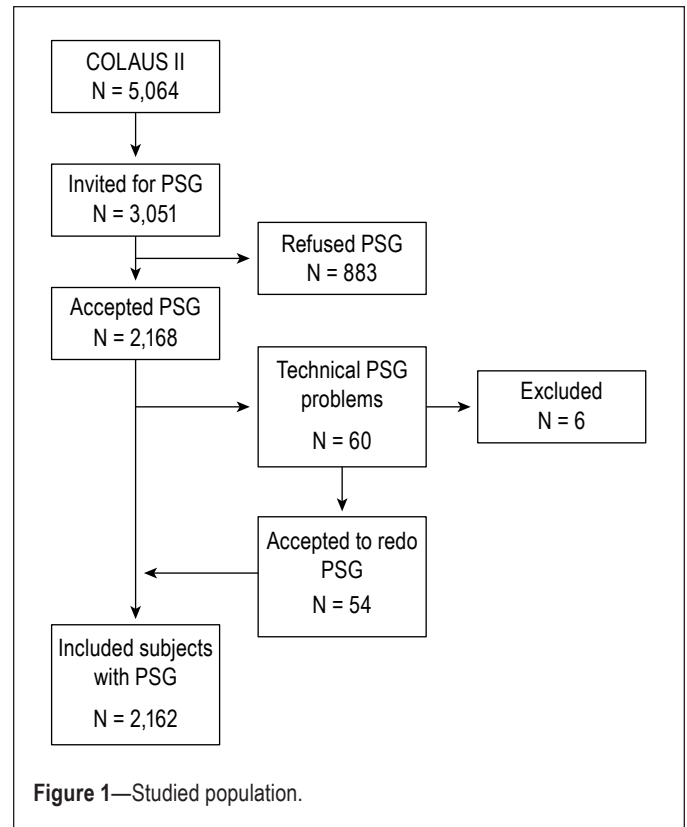
20 associations would be tested, thus leading to an adjusted P value of 0.05/20 = 0.001 (Bonferroni method).

RESULTS

Feasibility and Failures

Of the 3,051 contacted subjects, 2,168 (71.1%) agreed to have a PSG at home. Subjects who agreed to participate were 8.2 y younger and reported less sleepiness than those who declined. BMI (+0.4 kg/m^2) and PSQI scores (+0.3 pts) were slightly higher in those who declined (Cohen d test effect size 0.09 for both). The Berlin score was similar in both groups. Technical problems resulting in insufficient data for PSG scoring were encountered in 60 cases (2.8%), 54 PSG were repeated and 6 subjects declined to repeat the study, resulting in 2,162 participants (51.2% women, mean age 58.4 ± 11.1 y) included in the final analysis (Figure 1).

General Characteristics

Table 1 summarizes the findings for the entire population and in subjects with an ODI ≤ 15/h versus those with an ODI > 15/h. Overall a total of 30.5% individuals had MS, 41.5% hypertension, 9.9% diabetes, 41.1% were overweight (25 ≤ BMI < 30 kg/m^2), and 16.5% were obese (BMI ≥ 30 kg/m^2). The mean TST was 401.2 ± 72.1 min, the time spent in SWS and REM sleep were, respectively, 19.7 ± 8.4% and 21.8 ± 6.1% of the TST, the sleep efficiency was 84.6 ± 10.9%, the ArI was 21.3 ± 11/h of sleep, and the AHI was 15.5 ± 16.3/h.

A total of 751 subjects (34.7% of the sample) had a significant ODI (> 15/h of sleep). Subjects with ODI > 15/h were older, more frequently male, had higher rates of MS, hypertension, diabetes, and overweight/obesity than subjects with

Table 1—Demographic, clinical, and polysomnographic characteristics of the participants.

	All	Subjects with ODI ≤ 15/h	Subjects with ODI > 15/h	P [a]
N	2,162 (100%)	1,411 (65.3%)	751 (34.7%)	
Age, y	58.4 ± 11.1	56.3 ± 10.6	62.8 ± 10.8	< 0.001
Female sex	1,106 (51.2%)	866 (61.4%)	240 (31.9%)	< 0.001
Metabolic syndrome	659 (30.5%)	284 (20.1%)	375 (50.0%)	< 0.001
Hypertension	897 (41.5%)	462 (32.7%)	435 (58.0%)	< 0.001
Diabetes	214 (9.9%)	82 (5.8%)	132 (17.5%)	< 0.001
BMI, kg/m^2	26.2 ± 4.4	25 ± 3.9	28.5 ± 4.4	< 0.001
< 25	909 (42.3%)	764 (54.3%)	145 (19.3%)	< 0.001
25–30	884 (41.1%)	509 (36.2%)	375 (49.9%)	< 0.001
> 30	356 (16.5%)	134 (9.5%)	222 (29.5%)	< 0.001
Smokers/ex-smokers	1,233 (58.2%)	785 (56.7%)	448 (61.2%)	< 0.05
Regular alcool consumption	1,686 (78.0%)	1,078 (76.4%)	608 (80.9%)	< 0.01
Sedentary	1,047 (55.7%)	662 (52.7%)	385 (61.7%)	< 0.001
Taking drugs that influence sleep [b]	400 (18.5%)	250 (17.7%)	150 (20.0%)	< 0.01
Depression (lifetime or current)	284 (14.8%)	184 (14.6%)	100 (15.1%)	< 0.05
TST, min	401.2 ± 72.1	406.5 ± 45.3	391 ± 74.2	< 0.001
SWS, % of TST	19.7 ± 8.4	21.0 ± 8.1	17.2 ± 8.4	< 0.001
SWS, min	78.6 ± 34.8	84.6 ± 33.1	67.1 ± 35.1	< 0.001
REM, % of TST	21.8 ± 6.1	22.7 ± 5.7	20.2 ± 6.6	< 0.001
REM, min	88.6 ± 31.1	93.2 ± 29.8	80.1 ± 31.6	< 0.001
Sleep efficiency, %	84.6 ± 10.9	86.1 ± 9.9	81.7 ± 11.9	< 0.001
Arousal index, n/h	21.3 ± 11.0	17.6 ± 7.9	28.3 ± 12.6	< 0.001
AHI, n/h	15.5 ± 16.3	6.9 ± 14.9	31.8 ± 17.6	< 0.001
ODI n/h	14.7 ± 15.2	6.4 ± 10.6	30.5 ± 16.1	< 0.001

Results are expressed as N (%) or mean ± standard deviation. [a] Comparing ODI ≤ 15/h with ODI > 15/h. [b] Drugs that influence sleep were considered as "present" if participants were using benzodiazepines or derivates (ATC codes: N05BA, N05CD, N03AE), hypnotics (N05CF), antidepressants (N06A), neuroleptics (N05A) or antihistamines (R06A). AHI, apnea-hypopnea index; BMI, body mass index; ODI, oxygen desaturation (≥ 3%) index; REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

an ODI ≤ 15/h. Concerning PSG characteristics, subjects with ODI > 15/h slept less, spent less time in SWS and REM sleep, had lower sleep efficiency, and higher ArI.

Sleep Structure and CVD Risk Factors

The tables show the sleep characteristics of subjects according to the presence or absence of the MS, hypertension, diabetes, and overweight/obesity in the overall sample and in subjects without clinically significant desaturation (ODI ≤ 15/h) either from unadjusted models (Tables S1 and S2, supplemental material) or from models adjusted for age, sex, and day of week of the PSG recording (marked by an asterisk in Tables 2–9), and smoking, alcohol, physical activity, and drugs that affect sleep and depression (marked by a dagger in Tables 2–9).

In bivariate analyses subjects with MS had lower TST, spent less time in SWS and in REM sleep, and had poorer sleep efficiency and higher ArI than those without MS. The differences were attenuated after adjusting for age, sex, and the day on which the recording was performed (Tables 2 and 3). Finally, only the ArI remained significantly different after additional adjustments (adjusted means: 20.2 ± 0.3 versus 22.9 ± 0.5/h; P < 0.001). However, the difference lost statistical significance in subjects with an ODI ≤ 15/h (P = 0.72).

In the whole group, hypertension was associated with lower TST, decreased SWS and REM sleep, lower sleep efficiency, and higher ArI. Sleep efficiency was different in subjects with hypertension when compared with those without hypertension after adjusting for age, sex, and the day of the PSG recording (85.1 ± 0.3 versus 84.2 ± 0.4%; P < 0.05), but no significant differences were found between groups concerning sleep structure after adjusting for additional covariates (BMI, smoking, alcohol, physical activity, drugs that affect sleep and depression) (Tables 4 and 5). In subjects without clinically significant ODI, hypertension was associated with slightly lower sleep efficiency in the multivariable adjusted model (adjusted means: 86.9 ± 0.3% versus 85.4 ± 0.5%; P = 0.02).

Unadjusted analyses showed significant differences in sleep structure between subjects with diabetes when compared with subjects without diabetes: they spent less time in SWS and in REM sleep, and had lower sleep efficiency and higher ArI. In the multivariable adjusted model only TST and sleep efficiency remained slightly different between groups (Tables 6 and 7). In subjects with an ODI ≤ 15/h, after adjusting for potential confounders, the differences showed a marginal trend (P = 0.11 for TST; P = 0.07 for sleep efficiency).

Unadjusted comparisons of sleep structure showed that subjects with a BMI > 25 kg/m^2 had lower TST, spent less time in SWS and in REM sleep, and had poorer sleep efficiency and higher ArI than those with a normal weight. These differences were attenuated in the multivariable adjusted model, but % of

Table 2—Sleep characteristics according to the absence or presence of metabolic syndrome in the entire population.

	Absent*	Present*	P*	Absent[†]	Present[†]	P[†]
Group size	1,503	659		1,503	659	
TST, min	401 ± 2	401 ± 3	0.79	400 ± 2	401 ± 3	0.72
SWS, % of TST	20.0 ± 0.2	19.3 ± 0.3	0.07	20.3 ± 0.2	19.7 ± 0.4	0.18
SWS, min[a]	80 ± 1	77 ± 1	0.12	81 ± 1	78 ± 1	0.42
REM, % of TST	22.2 ± 0.2	21.4 ± 0.2	< 0.01	22.2 ± 0.2	21.7 ± 0.3	0.09
REM, min[a]	90 ± 1	87 ± 1	0.04	90 ± 1	88 ± 1	0.32
Sleep efficiency, %	84.9 ± 0.3	84.3 ± 0.4	0.19	84.8 ± 0.3	85.1 ± 0.4	0.57
Arousal index, n/h[a]	20.3 ± 0.3	23.3 ± 0.4	< 0.001	20.2 ± 0.3	22.9 ± 0.5	< 0.001

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†]Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, drugs that affect sleep and depression. [a]Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table 3—Sleep characteristics according to the absence or presence of metabolic syndrome in subjects without significant oxygen desaturation index (≤ 15/h).

	Absent*	Present*	P*	Absent[†]	Present[†]	P[†]
Group size	1,127	284		1,127	284	
TST, min	406 ± 2	409 ± 4	0.49	405 ± 2	409 ± 5	0.39
SWS, % of TST	21.1 ± 0.2	21.1 ± 0.5	0.99	21.3 ± 0.3	21.4 ± 0.6	0.89
SWS, min[a]	85 ± 1	85 ± 2	0.99	85 ± 1	86 ± 2	0.78
REM, % of TST	22.8 ± 0.2	22.5 ± 0.3	0.45	22.8 ± 0.2	22.9 ± 0.4	0.97
REM, min[a]	93 ± 1	94 ± 2	0.90	93 ± 1	95 ± 2	0.48
Sleep efficiency, %	86.2 ± 0.3	86.4 ± 0.6	0.73	86.2 ± 0.3	87.3 ± 0.6	0.12
Arousal index, n/h[a]	17.4 ± 0.2	17.5 ± 0.5	0.97	17.4 ± 0.2	17.1 ± 0.5	0.72

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†]Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, drugs that affect sleep and depression. [a]Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table 4—Sleep characteristics according to the absence or presence of hypertension in the entire population.

	Absent*	Present*	P*	Absent[†]	Present[†]	P[†]
Group size	1,263	897		1,263	897	
TST, min	402 ± 2	400 ± 3	0.53	402 ± 2	398 ± 3	0.31
SWS, % of TST	19.9 ± 0.2	19.7 ± 0.3	0.57	20.1 ± 0.3	20.1 ± 0.3	0.88
SWS, min[a]	80 ± 1	78 ± 1	0.24	80 ± 1	79 ± 1	0.44
REM, % of TST	22.1 ± 0.2	21.8 ± 0.2	0.33	22.1 ± 0.2	21.9 ± 0.2	0.53
REM, min[a]	90 ± 1	88 ± 1	0.19	90 ± 1	88 ± 1	0.23
Sleep efficiency, %	85.1 ± 0.3	84.2 ± 0.4	< 0.05	85.2 ± 0.3	84.5 ± 0.4	0.16
Arousal index, n/h[a]	20.8 ± 0.3	21.7 ± 0.4	0.24	20.7 ± 0.3	21.2 ± 0.4	0.77

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†]Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, body mass index, and drugs that affect sleep and depression. [a]Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

SWS (20.8 ± 0.3 versus 19.5 ± 0.3%; P = 0.002), time spent in SWS (82 ± 1 versus 78 ± 1 min, P < 0.05) and the ArI (19.6 ± 0.4 versus 22 ± 0.3/h; P < 0.001) remained different (Tables 8 and 9). In subjects with an ODI ≤ 15/h, the percentage and the time spent in REM sleep were higher in overweight/obese subjects (adjusted means: 22.4 ± 0.2% versus 23.4 ± 0.2%, P = 0.002;

91 ± 1 versus 97 ± 1 min, P < 0.005), even though these differences were small.

As previous population studies suggest a U-shaped relationship between subjective sleep duration and cardiovascular outcomes, we performed further analysis stratifying the subjects in four groups according to the TST: < 6, 6–6.9, 7–7.9,

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Table 5—Sleep characteristics according to the absence or presence of hypertension in subjects without significant oxygen desaturation index (≤ 15/h).

	Absent *	Present *	P*	Absent [†]	Present [†]	P [†]
Group size	949	462		949	462	
TST, min	409 ± 2	401 ± 3	< 0.05	408 ± 2	400 ± 4	0.08
SWS, % of TST	21.1 ± 0.3	21.3 ± 0.4	0.74	21.2 ± 0.3	21.6 ± 0.4	0.49
SWS, min [a]	86 ± 1	84 ± 2	0.28	86 ± 1	85 ± 2	0.64
REM, % of TST	22.8 ± 0.2	22.7 ± 0.3	0.90	22.9 ± 0.2	22.8 ± 0.3	0.79
REM, min [a]	94 ± 1	92 ± 1	0.23	94 ± 1	92 ± 2	0.26
Sleep efficiency, %	86.8 ± 0.3	85.1 ± 0.5	< 0.005	86.9 ± 0.3	85.4 ± 0.5	0.02
Arousal index, n/h [a]	17.7 ± 0.3	16.9 ± 0.4	0.17	17.7 ± 0.3	16.6 ± 0.4	0.09

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†] Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, body mass index, and drugs that affect sleep and depression. [a] Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table 6—Sleep characteristics according to the absence or presence of diabetes, in the entire population.

	Absent *	Present *	P*	Absent [†]	Present [†]	P [†]
Group size	1,948	214		1,948	214	
TST, min	401 ± 2	407 ± 5	0.20	399 ± 2	413 ± 6	0.02
SWS, % of TST	19.9 ± 0.2	19.3 ± 0.6	0.32	20.1 ± 0.2	20.2 ± 0.7	0.92
SWS, min [a]	79 ± 1	77 ± 2	0.25	80 ± 1	81 ± 3	0.58
REM, % of TST	22.0 ± 0.1	21.2 ± 0.4	0.06	22.1 ± 0.1	21.7 ± 0.5	0.43
REM, min [a]	89 ± 1	87 ± 2	0.86	89 ± 1	90 ± 2	0.25
Sleep efficiency, %	84.7 ± 0.2	85.0 ± 0.7	0.65	84.8 ± 0.2	86.5 ± 0.8	0.04
Arousal index, n/h [a]	20.9 ± 0.2	24.0 ± 0.7	< 0.005	20.9 ± 0.2	21.8 ± 0.8	0.30

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†] Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, body mass index, and drugs that affect sleep and depression. [a] Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table 7—Sleep characteristics according to the absence or presence of diabetes, in subjects without significant oxygen desaturation index (≤ 15/h).

	Absent *	Present *	P*	Absent [†]	Present [†]	P [†]
Group size	1,329	82		1,329	82	
TST, min	406 ± 2	413 ± 8	0.38	405 ± 2	419 ± 8	0.11
SWS, % of TST	21.1 ± 0.2	21.6 ± 0.9	0.64	21.3 ± 0.2	20.9 ± 1.0	0.69
SWS, min [a]	85 ± 1	86 ± 4	0.81	85 ± 1	85 ± 4	0.61
REM, % of TST	22.8 ± 0.2	21.7 ± 0.6	0.08	22.9 ± 0.2	21.8 ± 0.7	0.13
REM, min [a]	94 ± 1	92 ± 3	0.95	94 ± 1	93 ± 4	0.70
Sleep efficiency, %	86.2 ± 0.3	86.9 ± 1.1	0.58	86.3 ± 0.3	88.4 ± 1.1	0.07
Arousal index, n/h [a]	17.4 ± 0.2	17.5 ± 0.9	0.83	17.3 ± 0.2	17.7 ± 1	0.67

Results are expressed as multivariable adjusted mean ± standard error. *Adjusted for sex, age, and day of week (Friday). [†] Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, body mass index, and drugs that affect sleep and depression. [a] Between-group comparisons performed using log-transformed data. Statistical analysis by analysis of variance. α level set at P < 0.001. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

and ≥ 8 h. These data are presented in the supplemental material (Tables S3 to S6). In this analysis the most consistent finding was that the prevalence of hypertension showed an inverse association with sleep duration for the whole group, and a U-shaped association in subjects without significant ODI (Tables S3 and S4). However, in the multivariate logistic regression analysis (Tables S5 and S6) after adjusting for sex, age, smoking, alcohol, physical activity, drugs that affect sleep, BMI, and depression, the odds ratio (95% confidence interval) for hypertension for subjects sleeping less than 6 h was 1.19 (0.87–1.62) for the entire population and 1.45 (0.97–2.16) for those without significant ODI, taking as reference subjects with a sleep duration of 7–8 h. Significant differences between groups were found for the prevalence of the MS in the entire

Table 8—Sleep characteristics according to the absence or presence of overweight/obesity (body mass index ≥ 25 kg/m^2) in the entire population.

	Absent [*]	Present [*]	P[*]	Absent [†]	Present [†]	P[†]
Group size	909	1,240		909	1,240	
TST, min	399 ± 2	402 ± 2	0.27	399 ± 2	401 ± 2	0.46
SWS, % of TST	20.7 ± 0.3	19.2 ± 0.2	< 0.001	20.8 ± 0.3	19.5 ± 0.3	0.002
SWS, min [a]	82 ± 1	77 ± 1	< 0.01	82 ± 1	78 ± 1	< 0.05
REM, % of TST	21.9 ± 0.2	22.0 ± 0.2	0.62	21.8 ± 0.2	22.3 ± 0.2	0.09
REM, min [a]	88 ± 1	90 ± 1	0.34	88 ± 1	90 ± 1	0.09
Sleep efficiency, %	85.0 ± 0.3	84.5 ± 0.3	0.28	85.0 ± 0.4	84.9 ± 0.3	0.80
Arousal index, n/h [a]	19.5 ± 0.3	22.4 ± 0.3	< 0.001	19.6 ± 0.4	22.0 ± 0.3	< 0.001

Results are expressed as multivariable adjusted mean ± standard error. [*]Adjusted for sex, age, and day of week (Friday). [†]Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, drugs that affect sleep and depression. [a]Between-group comparisons performed using log-transformed data. Statistical analysis by Student t test or analysis of variance. α level set at $P < 0.001$. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table 9—Sleep characteristics according to the absence or presence of overweight/obesity (body mass index ≥ 25 kg/m^2), in subjects without significant oxygen desaturation index (≤ 15/h).

	Absent [*]	Present [*]	P[*]	Absent [†]	Present [†]	P[†]
Group size	764	643		764	643	
TST, min	403 ± 2	410 ± 3	0.06	403 ± 3	409 ± 3	0.12
SWS, % of TST	21.6 ± 0.3	20.6 ± 0.3	< 0.05	21.7 ± 0.3	20.8 ± 0.4	0.06
SWS, min [a]	86 ± 1	84 ± 1	0.23	86 ± 1	84 ± 1	0.37
REM, % of TST	22.5 ± 0.2	23.1 ± 0.2	< 0.05	22.4 ± 0.2	23.4 ± 0.2	0.002
REM, min [a]	92 ± 1	96 ± 1	< 0.01	91 ± 1	97 ± 1	< 0.005
Sleep efficiency, %	86.3 ± 0.3	86.2 ± 0.4	0.90	86.3 ± 0.4	86.5 ± 0.4	0.63
Arousal index, n/h [a]	17.0 ± 0.3	17.9 ± 0.3	0.09	17.1 ± 0.3	17.6 ± 0.3	0.47

Results are expressed as multivariable adjusted mean ± standard error. [*]Adjusted for sex, age, and day of week (Friday). [†]Adjusted for sex, age, day of week (Friday), smoking, alcohol, physical activity, drugs that affect sleep and depression. [a]Between-group comparisons performed using log-transformed data. Statistical analysis by Student t test or analysis of variance. α level set at $P < 0.001$. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

group, as subjects with a TST < 6 h had a higher prevalence of MS than the other groups (no U-shaped relationship), but this difference was not found in subjects without significant ODI (≤ 15/h). No significant differences between groups were found in the multivariate logistic regression analysis. No U-shaped association was found between groups concerning the prevalence of diabetes. In the multivariate logistic regression analysis, the OR for diabetes was lower in subjects with a TST less than 6 h compared with the reference group (OR 0.57, CI: 0.35–0.93) in the entire group, but not in the subjects without significant SDB. Finally, a U-shaped association was found for the prevalence of BMI > 25 kg/m^2 in the whole group, but not when considering subjects with ODI ≤ 15/h. However, in the multivariate logistic regression analysis the OR for a BMI > 25 kg/m^2 was significantly higher in subjects with a TST more than 8 h and no significant ODI, when compared with the reference group (1.63 (1.09–2.43)). Overall, these analyses confirm that TST, whether used as a continuous or a categorical variable, does not show consistent associations with CVD risk factors.

DISCUSSION

To the best of our knowledge, this is one of the largest population-based studies assessing the relationship between sleep variables, objectively measured by PSG, and CV risk factors, specifically, MS, hypertension, diabetes, and obesity. In our study, MS was more prevalent in subjects whose sleep was shorter, lighter (as measured by decreased SWS and REM sleep), more fragmented, and with lower sleep efficiency. However, these differences were attenuated when adjusting for potential confounding factors and only the ArI remained significantly higher in subjects with the MS in the multivariate model. This association disappeared in subjects without significant ODI (clinical cutoff of ODI ≤ 15/h), suggesting that the increased ArI in subjects with MS could be related to the presence of respiratory disturbances. Another possible explanation is that restricting the analysis to subjects with ODI ≤ 15 leads to a reduction in the sample size, and decreased the statistical power to detect differences between groups.

Crude unadjusted analyses also showed significant differences in sleep duration and structure between subjects according to the presence or absence of hypertension, diabetes, and overweight/obesity. But, as for MS, these differences disappeared in subjects without significant ODI after controlling for confounders. In a conservative approach to avoid the possibility of finding significant differences due to chance we preferred a value of $P < 0.001$ for statistical significance. Choosing a less rigorous value of $P < 0.05$ leads to a

statistically significant association between hypertension and sleep efficiency, in subjects without significant ODI and after adjusting for possible confounding factors; yet, these differences are very small (86.9 ± 0.3% versus 85.4 ± 05%, P = 0.02). In the same way, overweight subjects without significant ODI spent more time in REM sleep, but again these differences were small (22.4 ± 0.2% versus 23.4 ± 0.2%, P = 0.002; 91 ± 1 versus 97 ± 1 min, P < 0.005). As indicated by others,[10] such small differences in epidemiological studies, even if statistically significant, are of questionable clinical value because this association must be the result of long-term sleeping habits, and can be easily modified by other behavioral factors, as short exercise exposures or dietary changes. These findings suggest that normal variation in sleep duration and structure does not seem to be associated with MS, hypertension, diabetes, and obesity.

Indirect evidence suggests that sleep deprivation may trigger biological changes contributing to MS. Laboratory studies demonstrated that reduced sleep amount produces short-term adverse effects, such as changes in circulating levels of leptin and ghrelin, impaired glucose tolerance, increased cortisol secretion, altered growth hormone metabolism, and changes in BP and sympathetic activity.[30,31] Also, changes in sleep structure, suppression of SWS in particular, without any change in TST, resulted in decreased insulin sensitivity and reduced glucose tolerance.[11] In the same way, Sayk et al.[12] showed that selective deprivation of SWS for 1 night by acoustic stimulation in healthy subjects produces a significant reduction in BP dipping, but no significant changes in morning BP, urine catecholamine excretion, or HR variability. It should be noted that in laboratory studies, the carefully controlled experimental conditions allow changes in sleep patterns (as major shortening of the sleep duration that cannot be tolerated beyond a few days or the complete absence of SWS) that are not experienced in everyday life in the general population. Additionally, in most of these studies subjects are selected on the basis of the absence of sleep disorders and other comorbidities that can have a significant effect on the development of CVD risk factors.

Our observations differ from those of previous epidemiological surveys that have identified several associations between sleep and adverse cardiovascular risk factors. Almost all epidemiologic studies examining these associations used subjective sleep assessments, such as self-reported sleep duration, which may lead to major methodological issues considering that there is no validated evidence for direct relationships between subjective and objective measures of sleep. The correlation between self-reported and objectively measured sleep was shown to be, at best, moderate, and biased by systematic overreporting.[32] Comparing self-reports of sleep duration with those obtained by wrist actigraphy shows that people subjectively overestimated their sleep by up to 1 h, with R^2 values between these two indices being only 0.22. People estimating their sleep at 5 h usually only slept about 4 h, and those estimating 7 h only slept about 6.6 h.[32] Self-perceived sleep duration is likely to be influenced by factors such as sleep disorders, sociodemographic profile, social demands, or measures time in bed instead of actual sleep duration.

As pointed out by Kurina et al.,[33] in a recent critical review of the studies looking at the association between sleep duration

and mortality, another major issue is that different definitions are used for long and short sleep. Short sleep duration in different studies varied from 4 h or fewer, to fewer than 7 h per night, and long sleep from more than 8 h to 12 h or longer. The reference "normal" category varied from 7 to 9 h. From some previous studies causal inference is also difficult to draw because of the lack of control for major confounders.

Only a limited number of studies analyzed the relationship between objectively measured sleep patterns by PSG and morbidity-mortality. In a prospective study of 184 older adults, Dew et al.[34] showed that short sleepers (< 6 h) did not have significantly higher mortality than the rest of the sample. However, increased mortality was associated with sleep latency > 30 min, sleep efficiency < 80%, and SWS < 1%. The percentage of SWS was not associated with mortality after controlling for age, sex, and baseline medical burden and the potential role of other possible confounders, as the presence of SDB, was not analyzed. In addition, in older adults a prospective analysis of 784 subjects participating in the Outcomes of Sleep Disorders in Older Men Study revealed that the amount of time spent in SWS was inversely related to the development of incident hypertension independently of sleep duration and SDB, and after adjusting for age, race and body mass index.[35] From the same cohort, PSG data from 2,745 older men also showed a significant inverse association between quartiles of SWS and BMI but the association was attenuated in men with a respiratory disturbance index ≥ 15/h.[36] These studies suggest a possible relationship between SWS and hypertension and obesity in selected populations (older men), but they cannot be generalized to the overall population.

Data from the Penn State cohort showed that individuals with insomnia who slept < 6 h had a significantly increased risk of type 2 diabetes,[37] hypertension,[38] and mortality[39] compared to the "normal sleep duration, no insomnia" group, after adjusting for confounders. Insomnia with objectively measured short sleep duration but not normal variation in sleep seems to constitute a vulnerability sleep associated phenotype. In a recently published prospective study on this cohort, self-reported short sleep duration, but not objective sleep duration, was associated with a significant increased risk of incident obesity.[40] Again, perception of one's sleep, as a surrogate marker of emotional stress and subjective sleep disturbances rather than objective sleep duration, seems to be the underlying factor beyond the association.

Two previous studies specifically analyzed the association between sleep and MS using PSG. Nock et al.[41] analyzed PSG data from 533 adults participating in the Cleveland Family Sleep Study. The subjects were selected from families with siblings having extreme high or low values for AHI. The authors found that sleep disturbance was a significant component of MS. They defined a sleep disturbance factor that included four measures: the AHI, the ArI, the percentage of sleep time when oxygen saturation was less than 90%, and the SWS%. Again, disturbances in sleep but not normal sleep were identified as the risk factors. More recently, Hall et al.[42] analyzed the association between sleep and MS in a group of 368 multiethnic middle-aged women (mean age, 51 y) participating in the SWAN Sleep Study. They analyzed various sleep parameters derived from PSG including EEG power spectral

analysis. In bivariate analyses, MS was associated with decreased sleep duration and efficiency and increased beta power in NREM sleep and AHI. When entered simultaneously in a multivariable adjusted model to evaluate their independent contributions, only sleep efficiency and AHI appeared to be independent correlates of MS. Respiratory disturbances seem to be clearly associated with MS, as evidenced in our study and in previous studies,[27,43] but the sleep efficiency is unrelated to MS in our study after adjusting for confounders. Nevertheless, we did find a non- statistically significant association between hypertension and sleep efficiency, which was lower in subjects with hypertension. One main explanation for this discrepancy is that we included men and women in our study, whereas Hall et al.[42] only included women. In addition, our subjects were older and had a higher AHI.

Strengths and Limitations

The major strengths of our study is its population-based design, the large sample size, the availability of detailed information on a number of potential confounders, and the use of PSG to obtain objective measures of sleep structure and sleep comorbidities as SDB. Nevertheless, we acknowledge potential limitations. First, our results are based on a single PSG, and even if the PSG is considered the gold standard for sleep studies, a single recorded night may not fully capture the complexity of a phenomenon such as sleep. Night-to-night variability in sleep is observed in subjects who undergo PSG related to the so called "first night effect", which can be caused by discomfort caused by electrodes, limitation of movements, and the unfamiliar environment of the sleep laboratory.[44] Thus, in order to limit the effect of the first night effect, we performed the PSG at home under "habitual" sleeping environment, and subjects were instructed to maintain their usual sleeping habits. Further, we repeated the PSG in a randomly selected sample of 20 HypnoLaus participants to determine the short-term variability of 2 nights of home PSG. Only the percentage of TST spent in REM sleep was marginally different between nights (21.4 ± 6.7 versus 24 ± 5%, P = 0.04, Table S7, supplemental material). Repeated home PSG in the Sleep Heart Health Study cohort revealed similar results, with no evidence of a major "first-night effect".[45] Second, the HypnoLaus study is a monocentric study allowing uniform collection, processing, and analysis of the data, but it is limited to middle-aged and elderly Lausanne residents; thus, the results may not be easily extrapolated to other populations. Finally, this is a cross-sectional study and future prospective studies are needed to build on the current findings.

In conclusion, in this population-based study, we found significant associations between sleep duration and quality and MS, hypertension, diabetes, and obesity. However, these associations are not independent of other known CVD risk factors, as age, sex, sedentary life style, obesity, ODI, depression, smoking, alcohol, or use of medications that affect sleep. We conclude that normal variations in sleep in adults seem to contribute little, if at all, to MS, hypertension, diabetes, and obesity.

ABBREVIATIONS

AHI, apnea-hypopnea index
ArI, arousal index
ATP-III, Adult Treatment Panel III report
BMI, body-mass index
CVD, cardiovascular disease
DBP, diastolic blood pressure
DIGS, Diagnostic Interview for Genetic Studies
ESS, Epworth Sleepiness Scale
HDL, high-density lipoprotein
MS, metabolic syndrome
ODI, oxygen desaturation index
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
REM, rapid eye movement
SBP, systolic blood pressure
SDB, sleep disordered breathing.

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Table S1—Sleep characteristics according to the absence or presence of cardiovascular disease risk factors in the entire population.

	Metabolic Syndrome			Hypertension			Diabetes			Overweight/Obesity		
	Absent	Present	P	Absent	Present	P	Absent	Present	P	Absent	Present	P
Group size	1,503	659		1,263	897		1,948	214		909	1,240	
TST, min	405 ± 70	393 ± 77	< 0.001	408 ± 71	391 ± 73	< 0.001	402 ± 72	393 ± 74	0.1	405 ± 68	398 ± 75	< 0.05
SWS, % of TST	20.4 ± 8.3	18.1 ± 8.7	< 0.001	20.8 ± 8.1	18.3 ± 8.8	< 0.001	20.0 ± 8.4	17.2 ± 8.8	< 0.001	21.2 ± 8.6	18.7 ± 8.2	< 0.001
SWS, min[a]	82 ± 34	71 ± 35	< 0.001	84 ± 34	71 ± 35	< 0.001	80 ± 35	67 ± 34	< 0.001	85 ± 35	74 ± 34	< 0.001
REM, % of TST	22.4 ± 5.9	20.6 ± 6.7	< 0.001	22.7 ± 5.7	20.7 ± 6.7	< 0.001	22.1 ± 6.0	19.7 ± 7.4	< 0.001	22.2 ± 5.9	21.6 ± 6.4	< 0.05
REM, min[a]	91 ± 30	82 ± 33	< 0.001	93 ± 30	82 ± 32	< 0.001	90 ± 31	79 ± 33	< 0.001	90.7 ± 30.3	87.1 ± 31.6	< 0.05
Sleep efficiency, %	85.7 ± 10.3	82.2 ± 11.8	< 0.001	86.8 ± 9.9	81.6 ± 11.5	< 0.001	85 ± 10.8	81.6 ± 11.2	< 0.001	85.9 ± 10.0	83.6 ± 11.5	< 0.001
Arousal index, n/h[a]	19.7 ± 9.5	25.0 ± 13.3	< 0.001	19.5 ± 9.4	23.9 ± 12.6	< 0.001	20.7 ± 10.4	27.1 ± 14.8	< 0.001	18.7 ± 8.8	23.2 ± 12.1	< 0.001

Unadjusted values. Results are expressed as mean ± standard deviation. [a] Between-group comparisons performed using log-transformed data. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table S2—Sleep characteristics according to the absence or presence of cardiovascular disease risk factors in subjects without significant oxygen desaturation index (≤ 15/h).

	Metabolic Syndrome			Hypertension			Diabetes			Overweight/Obesity		
	Absent	Present	P	Absent	Present	P	Absent	Present	P	Absent	Present	P
Group size	1,127	284		949	462		1,329	82		764	643	
TST, min	408 ± 69	403 ± 75	0.28	413 ± 68	394 ± 74	< 0.001	407 ± 70	401 ± 81	0.43	406 ± 68	407 ± 73	0.79
SWS, % of TST	21.3 ± 8.1	20.2 ± 8.5	< 0.05	21.5 ± 8.0	20.2 ± 8.5	< 0.005	21.1 ± 8.1	19.9 ± 9.1	0.18	21.7 ± 8.4	20.3 ± 7.8	< 0.05
SWS, min[a]	86 ± 33	80 ± 33	< 0.005	88 ± 33	78 ± 33	< 0.001	85 ± 33	77 ± 33	< 0.01	87 ± 34	82 ± 33	< 0.01
REM, % of TST	22.9 ± 5.5	21.8 ± 6.6	< 0.005	23.1 ± 5.5	21.8 ± 6.3	< 0.001	22.8 ± 5.6	20.4 ± 7.8	< 0.001	22.5 ± 5.7	22.9 ± 5.9	0.26
REM, min[a]	94 ± 29	89 ± 33	< 0.05	96 ± 29	87 ± 31	< 0.001	94 ± 29	84 ± 36	< 0.05	92 ± 29	94 ± 30	0.2
Sleep efficiency, %	86.6 ± 9.8	84.5 ± 10.5	< 0.005	87.7 ± 9.0	83.0 ± 11.0	< 0.001	86.3 ± 9.9	83.8 ± 10.3	< 0.05	86.6 ± 9.6	85.7 ± 10.4	0.08
Arousal index, n/h[a]	17.3 ± 7.6	18.6 ± 8.8	< 0.05	17.3 ± 7.9	18.3 ± 7.9	< 0.05	17.5 ± 7.7	19.8 ± 10.0	< 0.05	17.0 ± 7.4	18.2 ± 8.4	< 0.01

Unadjusted values. Results are expressed as mean ± standard deviation. [a] Between-group comparisons performed using log-transformed data. REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.

Table S3—Bivariate association between cardiovascular risk factors and total sleep time in the entire population.

	< 6 h	6–6.9 h	7–7.9 h	≥ 8 h	P
Metabolic syndrome					
No	352 (62.6)	535 (71.7)	421 (72.3)	195 (71.7)	0.001
Yes	210 (37.4)	211 (28.3)	161 (27.7)	77 (28.3)	
Hypertension					
No	274 (48.8)	444 (59.5)	366 (63.0)	179 (65.8)	< 0.001
Yes	287 (51.2)	302 (40.5)	215 (37.0)	93 (34.2)	
Diabetes					
No	492 (87.5)	681 (91.3)	523 (89.9)	252 (92.7)	0.06
Yes	70 (12.5)	65 (8.7)	59 (10.1)	20 (7.4)	
BMI > 25 kg/m^2					
No	217 (38.7)	307 (41.5)	275 (47.4)	110 (40.9)	0.02
Yes	344 (61.3)	432 (58.5)	305 (52.6)	159 (59.1)	

Results are expressed as number of participants and (column percentage). Statistical analysis by chi-square. BMI, body mass index.

Table 4—Bivariate association between cardiovascular risk factors and total sleep time in subjects without significant oxygen desaturation index (≤ 15/h).

	< 6 h	6–6.9 h	7–7.9 h	≥ 8 h	P
Metabolic syndrome					
No	249 (77.1)	394 (80.4)	328 (81.4)	156 (80.0)	0.53
Yes	74 (22.9)	96 (19.6)	75 (18.6)	39 (20.0)	
Hypertension					
No	181 (56)	332 (67.8)	295 (73.2)	141 (72.3)	< 0.001
Yes	142 (44)	158 (32.2)	108 (26.8)	54 (27.7)	
Diabetes					
No	299 (92.6)	467 (95.3)	380 (94.3)	183 (93.9)	0.44
Yes	24 (7.4)	23 (4.7)	23 (5.7)	12 (6.2)	
BMI > 25 kg/m^2					
No	178 (55.1)	256 (52.5)	238 (59.2)	92 (47.4)	0.04
Yes	145 (44.9)	232 (47.5)	164 (40.8)	102 (52.6)	

Results are expressed as number of participants and (column percentage). Statistical analysis by chi-square. BMI, body mass index.

Table S5—Multivariate association between cardiovascular risk factors and total sleep time in the entire population.

	< 6 h	6–6.9 h	7–7.9 h	≥ 8 h
Metabolic syndrome	0.95 (0.70–1.29)	0.90 (0.67–1.19)	1 (ref.)	1.00 (0.67–1.49)
Hypertension	1.19 (0.87–1.62)	1.02 (0.77–1.36)	1 (ref.)	0.94 (0.63–1.41)
Diabetes	**0.57 (0.35–0.93)**	0.69 (0.43–1.08)	1 (ref.)	0.92 (0.48–1.77)
BMI > 25 kg/m^2	1.01 (0.76–1.34)	1.11 (0.87–1.43)	1 (ref.)	1.39 (0.98–1.98)

Results are expressed as odds ratio and (95% confidence interval). Statistical analysis by logistic regression adjusting for sex, age, smoking, alcohol, physical activity, drugs that affect sleep and depression. For hypertension and diabetes, a further adjustment on BMI was performed. Significant values are indicated in bold. BMI, body mass index.

Table S6—Multivariate association between cardiovascular risk factors and total sleep time in subjects without significant oxygen desaturation index (≤ 15/h).

	6 h	6–6.9 h	7–7.9 h	≥ 8 h
Metabolic syndrome	0.87 (0.56–1.36)	1.00 (0.67–1.48)	1 (ref.)	1.09 (0.65–1.82)
Hypertension	1.45 (0.97–2.16)	1.04 (0.72–1.49)	1 (ref.)	1.05 (0.65–1.69)
Diabetes	0.67 (0.31–1.44)	0.54 (0.26–1.12)	1 (ref.)	1.48 (0.64–3.39)
BMI > 25 kg/m^2	0.90 (0.64–1.27)	1.17 (0.86–1.57)	1 (ref.)	**1.63 (1.09–2.43)**

Results are expressed as odds ratio and (95% confidence interval). Statistical analysis by logistic regression adjusting for sex, age, smoking, alcohol, physical activity, drugs that affect sleep and depression. For hypertension and diabetes, a further adjustment on BMI was performed. Significant values are indicated in bold. BMI, body mass index.

Table S7—Night-to-night variability in polysomnographic parameters in a random selection of 20 subjects participating in the HypnoLaus study (mean age: 63.5 ± 11 y).

	First Night	Second Night	P
TST, min	413.5 ± 79.1	402.4 ± 73.8	0.5
SWS, % of TST	17.6 ± 7.5	16.4 ± 7.9	0.17
SWS, min	74 ± 35.7	67.4 ± 36.5	0.12
REM, % of TST	21.4 ± 6.7	24 ± 5	0.04
REM, min	90.6 ± 31.9	98.2 ± 31.6	0.24
Sleep efficiency, %	80.2 ± 9.2	79.3 ± 11.4	0.65
Arousal index, n/h	21.2 ± 8.5	20.1 ± 6.4	0.36
AHI, n/h	22.5 ± 14.7	24.7 ± 17.5	0.32
ODI, n/h	19.5 ± 10.9	21 ± 14.9	0.47

Results are expressed as mean ± standard deviation. AHI, apnea-hypopnea index; ODI, oxygen desaturation (≥ 3%) index; REM, rapid eye movement sleep; sleep efficiency = TST / time spent in bed × 100; SWS, slow wave sleep/stage N3; TST, total sleep time/sleep duration.