Microarousals During Sleep Are Associated With Increased Levels of Lipids, Cortisol, and Blood Pressure

MIRJAM EKSTEDT, BNSCI, TORBJÖRN ÅKERSTEDT, PHD, AND MARIE SÖDERSTRÖM, MSCI

Objective: Previous work has demonstrated a link between restricted sleep and risk indicators for cardiovascular and metabolic disease, such as levels of cortisol, lipids, and glucose. The present study sought to identify relations between polysomnographic measures of disturbed sleep (frequency of arousals from sleep, total sleep time, and sleep efficiency) and a number of such indicators. A second purpose was to relate the number of arousals to mood, stress, work characteristics, and other possible predictors in daily life. **Methods:** Twenty-four people (10 men, 14 women; mean age 30 years), high vs. low on burnout, were recruited from a Swedish IT company. Polysomnographically recorded sleep was measured at home before a workday. Blood pressure, heart rate, morning blood sample, and saliva samples of cortisol were measured the subsequent working day. They were also recorded for diary ratings of sleep and stress, and a questionnaire with ratings of sleep, stress, work conditions, and mood was completed. **Results:** A stepwise regression analysis using sleep parameters as predictors brought out number of arousals as the best predictor of morning cortisol (serum and saliva), heart rate, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL)-, low-density lipoprotein (LDL)-cholesterol, and LDL/HDL-ratio. Work stress/unclear boundaries between work and leisure time was the best predictor of arousals among the stress variables. **Conclusion:** Consistent with sleep restriction experiments, sleep fragmentation was associated with elevated levels of metabolic and cardiovascular risk indicators of stress-related disorders. Number of arousals also seems to be related to workload/stress. **Key words:** sleep arousals, polysomnography, metabolic, cortisol, stress, burnout.

ABP = ambulatory blood pressure; **DBP** = diastolic blood pressure; **EEG** = electroencephalogram; **EMG** = electromyographic; **EOG** = electro-oculogram; **HAD** = hospital anxiety and depression scale; **PSG** = polysomnography; **SBP** = systolic blood pressure; **SMBQ** = Shirom Melamed burnout questionnaire; **TST** = total sleep time; **WHR** = waist to hip ratio.

INTRODUCTION

Recent epidemiological studies have shown a connection between disturbed sleep and subsequent occurrence of cardiovascular disease (1–3), diabetes type II (4) and overall mortality (2,5–7). To some extent, such links receive support from studies demonstrating insulin resistance, as well as increased levels of lipids and cortisol, after several days of partial sleep deprivation (8). All are established risk factors for cardiovascular disease or diabetes (9–11), and several constitute the so-called metabolic syndrome (12). The same parameters are increased also in clinical groups suffering from insomnia and sleep apnea (13,14). In addition, an increased metabolic rate and elevated heart rate and cortisol levels have been demonstrated in insomniacs (15,16).

The observations above suggest that sleep may affect risk factors for diabetes and cardiovascular disease. As indicated, this notion is mainly based on experimental sleep reduction and on observations in clinical groups. Among the latter, it is conceivable that not only total sleep time (TST) is important, but also sleep fragmentation, because that is a characteristic of both insomnia and sleep apnea (17,18). This possibility is supported by the fact that it is frequently observed that blood pressure, heart rate, and cortisol secretion increase in connection with awakenings from sleep (16,19). However, there does not seem to be any study available on the relation between polysomnographically (PSG) recorded sleep fragmentation and the risk indicators discussed (cortisol, blood pressure, heart rate, lipids, glucose, and insulin).

The present paper reports on an attempt to study the relation between sleep fragmentation and the physiological risk indicators discussed above, using existing data and multiple regression techniques. To optimize the analyses, a study with a high level of variability in sleep fragmentation was selected. This study was initially focused on sleep in high and low burnout subjects (20) and had the advantage of being carried out on rather young subjects without any established pathology. They also had a stable life situation with successful employment (in an IT company), and had rather normal levels of TST so as to avoid confounding with that variable.

Sleep fragmentation was defined as the number of arousals per hour. An arousal is a sudden transient cortical activation during sleep, but does not necessarily result in a behavioral awakening (21). The origin of an arousal is usually “cortical” but it can also be generated in response to sensory perturbations, such as respiratory interruption (apnea or snoring), alteration of heart rate or blood pressure, noise, or movement disorders (22). The criterion for pathology in terms of number of arousals has not yet been determined, but a reasonable cut-off point, used in “normal” sleepers, is approximately 10 to 12 arousals per hour (18,23).

The main PSG predictor of interest was the number of arousals per hour. However, in view of the previous observations of effects of experimentally reduced TST, this latter variable need also be considered, as should sleep efficiency, since this factor relates TST to the time in bed. Those three variables are the traditional key indicators of disturbed sleep (24,25). Other sleep variables may have been used also, but many would be closely related to those selected (ie, stage Wake or stage 1), whereas others are not seen as primary indicators of disturbed sleep (for example, REM sleep or stages 3 and 4). However, since they constitute major descriptors of sleep they were also included.

From the Department of Public Health Science, Karolinska Institutet, Stockholm, Sweden (M.E., T.A., M.S.), and the National Institute for Psychosocial Factors and Health, Stockholm, Sweden (M.E., T.A., M.S.).

Address correspondence and reprint requests to Mirjam Ekstedt, National Institute for Psychosocial Medicine, P.O. Box 230, S-171 77 Stockholm, Sweden. E-mail: mirjam.ekstedt@ipm.ki.se

Received for publication June 4, 2004; revision received July 7, 2004.

DOI: 10.1097/01.psy.0000145821.25453.f7

0033-3174/04/6606-0925

In addition to the main purpose of relating fragmentation of sleep to physiological variables, possible moderating variables were explored. These included stress (17,26), anxiety (27), and depression (28). Also, specific work stress variables were investigated since such variables have been related to subjective reports of disturbed sleep (29). Work stress research is currently dominated by two models: the demand–control–support model (30,31) and the effort–reward model (32).

METHODS

Participants

The study was carried out in a Swedish IT company in which initially 414 employees (out of 676) completed a computerized questionnaires ($n = 676$). This included the SMBQ (33,34) modified from the original range 1 to 7 to a 4-graded scale to better suit the computer administration. This was used to identify subjects with high $\geq$2.75 (4.5 on the 7-graded) and low $\leq$1.5 (2.0 on the 7-graded) burnout scores. Six percent of the total group was classified with high and 14% with low burnout. Twelve subjects in the high burnout group were randomly selected to participate in the study. All of them agreed to participate. Twelve control subjects were thereafter selected from the low burnout group, through matching on gender, age, and duration of employment in the company. If more than one individual in the low burnout group met the matching criteria, selection between these individuals was made randomly.

Twenty-four individuals (14 women and 10 men, mean age 30.5 ± 1 year, range 24–43 years) finally entered the study. Their mean score on the 7-graded SMBQ, completed 2 months after the computerized version, was 4.8 ± 0.4 and 2.4 ± 0.2, ($p < .001$) for the high and low burnout group, respectively. All were working full time, 8 were managers or project leaders, 11 were married/cohabitant, and 6 had children. There were no current smokers among the 24 participants; they all reported a nonsedentary lifestyle and a moderate alcohol intake. The medical screening showed that none of them had been suffering from cardiovascular or lung disease, diabetes, or other metabolic diseases during the last 12 months. No one used anxiolytics, beta-receptor stimulators, angiotensin-converting enzyme inhibitors, or antidepressive drugs. Nine of the women used contraceptives, and 2 participants had temporarily been treated with sleep medication (Propavon-Propiomazine® Sanofi-SynthelaboAB) during the last 12 months. One suffered from allergic symptoms in the springtime and was then treated with aerosol terbutaline sulfate, and 1 had once been treated with omeprazole for gastric symptoms.

After recruitment, the subjects were given verbal information about the procedures, and all subjects gave written informed consent to participate. There was no monetary incentive involved. The study was approved by the ethical committee of the Karolinska Institute (No 00–306).

Procedure

The sleep and work pattern of the subjects was followed during a 2-week period with a sleep diary filled out every day on awakening (not used here) and a daytime diary, completed at bedtime.

During the 2 weeks, two ambulatory PSG recordings were carried out in the subject's home; one night before a workday and one night before a day off in a balanced design. The morning after the workday PSG, a fasting blood sample was collected between 8 and 9 AM. At that time, a recording of ambulatory blood pressure (ABP) was started and data were collected during 24 hours. The data used in the present analysis were the workday PSG (since no blood measures were assessed in conjunction with the weekend PSG), the diary ratings in the evening before the PSG, and the resting ABP values monitored before rising from bed in the morning (at 7 AM ± 1 hour).

During the same day as above (after workday PSG), repeated saliva samples were collected. The morning sampling followed a schedule used in previous studies (35,36): immediately after awakening, and 15, 30, and 60 minutes thereafter. This was followed by five additional samples: at 11.00 hours, 3 PM, 7 PM, 9 PM, and at bedtime. For statistical analysis, the awakening value (at 7 AM ± 1 hour) was used, as well as the mean values of all four morning samples. Also, the difference between the samples at 0 and 60 minutes after awakening was used.

Instruments and Measures

Polysomnography

Sleep was recorded polysomnographically using "Embla" recorders (Flaga HF®/Medcare) with two electroencephalogram (EEG) derivations C3–A2 and C4–A1, one bipolar chin electromyographic (EMG) derivation and two electro-oculogram (EOG) oblique derivations. Ag/AgCl electrodes were used. Sleep stages were scored visually in 30-second epochs according to Rechtschaffen and Kales (37). Arousals were scored using the American Academy of Sleep Medicine Task Force criteria (21). An arousal was defined as an EEG shift to at least alpha activity from stages 2 to 4 or rapid eye movement (REM). During REM sleep, an increase in EMG activity was required. For an arousal to be scored, it had to last for more than 3 seconds and for less than 15 seconds (>15 seconds were scored as an awakening). At least 10 seconds of uninterrupted sleep was required before an arousal.

Blood Samples

From the blood samples, the following seven parameters were obtained: plasma glucose, insulin/glucose ratio, cortisol levels in plasma, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), LDL/HDL ratio, and serum triglycerides. Further physiological measures included were as follows: the waist to hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and free circulating cortisol in saliva.

Serum was separated and frozen within 2 hours. All blood samples from each participant were analyzed in the same assay. This sample was analyzed for levels of serum glucose, total cholesterol, and triglycerides by solid-phase chemistry (Vitros, Johnsson & Johnsson). The average total coefficient of variation was less than 6% for plasma glucose and 4.7% for cholesterol and triglycerides. LDL-C and HDL-C were measured by colorimetry (Hitachi 911, Roche) with a total coefficient of variation of less than 6%. Serum insulin and cortisol were measured by immunofluorescence (Auto Delfia, Wallac), with a limit of sensitivity of 20 pmol/l and a total coefficient of variation of 15% for insulin and 3.5% for cortisol.

Salivary Cortisol and Blood Pressure

Cortisol in saliva samples (using Salivette®, Sarstedt; Rommelsdorf, Germany) was determined through radioimmunoassay (Orion Diagnostica, Finland). The lower limit of sensitivity was 20 nmol/L in plasma and 1 nmol/L in saliva and the average inter- and intra-assay coefficient of variation never exceeded 10%.

For the ABP, an Ultralite™ monitor (90217, Spacelabs medical) was used. The cuff was attached to the nondominant arm, and the recorder was programmed to operate every hour during waking hours and every second hour during nighttime sleep (between 12 PM and 5 AM).

Diary

The daytime diary contained items about health, fatigue, sleepiness, and stress during the day and at bedtime, and is presented in detail in Söderström et al. (20). The variables used in this study were the ratings day before the PSG night "anticipated sleep" (scales ranging from 1 = very poor to 9 = very good sleep), "activation at bedtime" (1 = very relaxed to 9 = very activated) and "thoughts of work during leisure time" (1 = always to 5 = never).

Questionnaire

The questionnaires (filled out by all employees at the IT company, $n = 414$) included questions concerning background, sleep, work, health and mood, characteristics, HAD, and the SMBQ. The items concerning *work* were inspired by the demand–control–support model and effort–reward model and are extensively presented in Söderström et al. (38). Psychosocial work factors included job demands (10 item, Cronbach's $\alpha = 0.85$), control (ie, decision latitude, 3 items, Cronbach's $\alpha = 0.88$), support from managers (4 item; Cronbach's $\alpha = 0.86$), support from colleagues (5 item; Cronbach's $\alpha = 0.83$), "thoughts of work during leisure time" (1 item), "work interferes with leisure time" (3 item, Cronbach's $\alpha = 0.82$), working hours per week and frequency of "bringing work home" (1 item). The response alternatives were as follows: 1 (totally disagree) to 4 (totally agree), except for "bringing work home," the scale of which ranged from 1 (never) to 5 (always/almost every day).

The *health and mood* assessment consisted of 22 items, used in the clinical work at the stress clinic. The checklist is similar to the Symptom Checlist-90, SCL-90: (39) and General Health Questionnaire, GHQ-12, (40) and concern to what extent complaints such as irritability, pain, worry, and so on had occurred during the last 3 months. The response alternatives varied from 1 (never) to 5 (always/almost every day). The 22 items were factor analyzed ($n = 414$, varimax rotation) for purposes of data reduction (unpublished). The orthogonal factor solution yielded five factors with an eigenvalue greater than 1: "cognitive symptoms" (5 item), "ache complaints" (4 item), "tension" (3 item), "passivity" (3 item), and "fatigue" (3 item). The remaining 4 items had a factor loading below 0.4 and were not accepted. Since "tension" appears to be an important predictor of disturbed sleep (41), and nonspecific aches and pains may be associated with insomnia (42), those two factors were used in this paper. The remaining indexes overlap with SMBQ and are not suitable for inclusion in the present analyses. The "tension" index consisted of "irritability," "anger," and "tension/restlessness" (Cronbach's $\alpha = 0.85$), and the "ache complaints" included the items "pain from neck and shoulders," "upper back pain," "lower back pain," and "aching hands and joints" (Cronbach's $\alpha = 0.88$).

In addition, the Hospital Anxiety (HAD-A) and Depression scale, (HAD-D) (43) was used. HAD has been tested and evaluated in different groups as a useful instrument because of its brevity, simplicity, and lack of effect of somatic conditions (43,44). It shows strong correlations with the Beck Depression Inventory and Spielberger's State Trait Anxiety Inventory in a Swedish sample (45).

The SMBQ (33,46), consists of a list of 22 symptom sentences that measure four aspects of energetic exhaustion on a 7-point scale (1 = never; 7 = always). The main subscale consists of the following: emotional exhaustion and physical fatigue (8 items), the tension and listlessness subscales (4 items each), and the cognitive weariness subscale (6 items). A total index with the four subscales was calculated, for each participant, with a reliability coefficient (Cronbach's alpha) of 0.90. This index correlates highly with the emotional exhaustion subscale of Maslachs Burnout Inventory (47) and with Pines Burnout measure (48) in a recent study of burnout women (49).

Statistical Analyses

In order to understand the relation between disturbed sleep and the physiological parameters, stepwise multiple regression analyses were carried out using hemodynamic, metabolic, and endocrine risk indicators as dependent variables and number of arousals, sleep efficiency, and TST as predictors, as well as burnout group and gender. The latter were included as independent variables in the regression analysis since it would be important for several biological measures. However, the gender effects per se are not the focus of the present study. Burnout group was included to control for possible confounding from the selection of extreme groups on this variable (coded 0/1).

In addition, another set of stepwise regression analyses was carried out to identify the relation between frequency of arousals and work conditions, mood, and other possible predictors. Also Pearson correlation coefficients were calculated between the physiological variables, possible stress, and control factors and frequency of arousals.

The internal consistency of the indexes used in the analysis was tested by computing the alpha coefficient (50). Variables with skewness more than ±2.0 were log transformed. All calculations were carried out using Statview software (SAS Institute Inc.©, version 5.0.1). The significance level was set to 0.05.

RESULTS

Associations Between Sleep and Physiological Variables

The stepwise multiple regression analyses yielded (Table 1) number of arousals as the *only* significant predictor for the following: (higher) SBP, DBP, P-cortisol at awakening, total cholesterol, and LDL-C. Number of arousals was also the *main* predictor of (higher) morning salivary cortisol (at awakening and the mean of the four morning measurements), HR, and LDL/HDL ratio. In addition to the numbers of arousals, TST was positively related to the LDL/HDL ratio and negatively to cortisol in saliva. For the latter, burnout group also entered the regression (higher cortisol in burnout subjects). Sleep efficiency was negatively related to HR. Gender was the only predictor of WHR (higher in women) and was accompanied by burnout group and sleep efficiency as significant predictors of higher HDL-C (Table 1).

Triglycerides, P-glucose, and the insulin/glucose ratio were not significantly related to any of the sleep variables, burnout group, or gender. The difference in salivary cortisol 0 to 60 minutes after awakening was also tested but did not correlate significantly with gender, group, or any of the PSG variables. Minutes of REM sleep and slow wave sleep (SWS) were tested as predictors of each of the dependent variables in simple regression analyses but did not yield any significant correlations.

The intercorrelations between the dependent variables were high within the group of lipid variables ($r < 0.6$, $p < 0.01$) and within blood pressure/heart rate measures ($r < 0.8$, $p < 0.001$), but between the clusters of variables there were no significant correlations.

Comparison of High and Low Arousal Groups

Since the correlations with arousals were consistent for most variables, it may be of interest to present mean values for the group dichotomized into high and low groups on arousals. The cut-off point was set to >9 arousals/hour (18,23) for the high group to produce equal-sized groups. This yielded 8 women and 4 men in the high arousal group and 6 women and 6 men in the low arousal group. The mean number of arousals was the only sleep variable in Table 2 (or any other standard sleep parameter) that differed significantly between the groups. Mean sleep length was slightly shorter than average sleep need (51). The mean ± SE time of awakening was 6.34 hours ± 0.15 hours (range 05.25 hours–07.30 hours). The participants with a high frequency of arousals had higher DBP, HR, P-cortisol, cortisol in saliva at awakening, total cholesterol, LDL-C, and LDL/HDL ratio (Table 2).

Relations Between Frequency of Arousals and Possible Stress Factors in Daily Life

To investigate the link between frequency of arousals and possible stress factors, a set of stepwise multiple regressions was carried out in four steps, with number of arousals per hour during the workday PSG as the *dependent* variable, and work conditions, mood/health complaints, snoring, and other background variables as possible predictors.

Firstly, all *work-related* variables were used as independent variables. These included "demands at work" ($r = 0.33$ with number of arousals/h), "decision latitude" ($r = 0.26$), "support from managers" ($r = -0.17$), "support from colleagues" ($r =$

TABLE 1. Stepwise Multiple Regression Analysis Against Metabolic and Cardiovascular Risk Indicators Using Polysomnographic Sleep Disturbances (Arousals During Sleep, Sleep Efficiency, and Total Sleep Time) Burnout Groups and Gender as Predictors

Dependent variable	Predictors	*r*	Beta	R2-change	F-ratio	Dependent variable	Predictors	*r*	Beta	R2-change	F-ratio
WHR	Gender	−.485	−.485	.20	6.8*	Triglycerides (mmol/l)	# Aro	.324			
	# Aro	−.485					TST	.325			
	Sleep eff[a]	.256					Sleep eff[a]	−.019			
	TST	.177					Group	.108			
	Group	−.081					Gender	−.070			
SBP (mm Hg)	# Aro	.505	.505	.20	4,8*	Tot. cholesterol (mmol/l)	# Aro	.528	.528	.25	8.5**
	TST	.232					TST	.335			
	Sleep eff[a]	−.184					Sleep eff[a]	.163			
	Group	.323					Group	.311			
	Gender	.117					Gender	.226			
DBP (mm Hg)	# Aro	.529	.529	.23	5,5*	LDL/HDL ratio	# Aro	.538	.555	.26	8.1**
	TST	.090					TST	.362	.386	.12	
	Sleep eff[a]	−.154					Sleep eff[a]	.117			
	Group	.399					Group	.471			
	Gender	.235					Gender	.265			
HR (beats/min)	# Aro	.576	.556	.30	8,1**	LDL-C (mmol/l)	# Aro	.488	.488	.20	6,9*
	Sleep eff[a]	−.423	−.394	.13			TST	.268			
	TST	−.044					Sleep eff[a]	.074			
	Group	.135					Group	.152			
	Gender	.324					Gender	.148			
Salivary cortisol at awakening (nmol/l)	# Aro	.517	.460	.22	6,1**	HDL-C (mmol/l)	Gender (i)	.583	.544	.31	8,7***
	TST	−.297	−.475	.12			Group (ii)	.341	.431	.10	
	Group	.434	.392	.11			Sleep eff[a]	.287	.338	.09	
	Sleep eff[a]	−.012					# Aro	.169			
	Gender	−.054					TST	.141			
Salivary cortisol mean 60 min after awakening[b] (nmol/l)	# Aro	.458	.458	.17	5.1*	P-glucose (mmol/l)	# Aro	−.060			
	TST	−.108					TST	−.165			
	Sleep eff[a]	.126					Sleep eff[a]	−.042			
	Group	.098					Group	.135			
	Gender	.160					Gender	.004			
P-cortisol (mmol/l)	# Aro	.555	.555	.28	8,1**	Insulin/glucose ratio	# Aro	−.235			
	TST	−.013					TST	.286			
	Sleep eff[a]	−.186					Sleep eff[a]	−.146			
	Group	.161					Group	−.339			
	Gender	.329					Gender	−.022			

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TST, total sleep time.

[a] This variable is skewed and has been log transformed.

[b] Mean value of four assays taken at awakening +15, +30, +60 min thereafter.

TABLE 2. Mean ± Standard Error and *t*-Test From High/Low Arousals and Polysomnography and Physiological Variables

	Arousals	
	Low (≤9/h) n = 12	High (>9/h) n = 12
Sleep efficiency (%)	90 ± 1	87 ± 2
Total sleep time, TST (min)	391 ± 5	388 ± 17
Frequency of arousals (#/h)	6.3 ± .6	14.2 ± 1***
Rapid eye movement sleep, REM (%)	24 ± 2	22 ± 2
Slow wave sleep, SWS, (st 3 + 4, %)	6.3 ± 2	8.6 ± 2
Waist hip ratio, WHR	.83 ± .01	.81 ± .01
Heart rate, HR (bpm)	70 ± 2	82 ± 3*
Systolic blood pressure, SBP (mmHg)	117 ± 5	128 ± 2
Diastolic blood pressure, DBP (mmHg)	73 ± 3	82 ± 1*
Salivary cortisol aw. (nmol/l)	10.0 ± 1	17.1 ± 2**
Mean^a salivary cortisol (nmol/l)	13.5 ± 1	17.1 ± 1.6
P-cortisol (mmol/l)	395 ± 19	573 ± 25**
P-triglycerides (mmol/l)	.99 ± .1	1.3 ± .2
Total cholesterol (mmol/l)	4.5 ± .3	5.5 ± .2*
HDL-C (mmol/l)	1.5 ± .1	1.6 ± .1
LDL-C (mmol/l)	2.6 ± .3	3.3 ± .2*
LDL/HDL-ratio	2.9 ± .3	4.0 ± .3**
P-glucose (mmol/l)	4.0 ± .3	4.0 ± .1
Insulin/glucose ratio	1.9 ± .3	1.4 ± .2

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

[a] Mean value of four assays taken at awakening +15, +30, +60 min thereafter.

* $p < .05$, ** $p < .01$, *** $p < .001$.

0.15), "thoughts of work during leisure time" ($r = 0.08$), "work interferes with leisure time" ($r = -0.34$), "working hours per week" ($r = 0.04$), and frequency of "bringing work home" ($r = 0.53$, $p = 0.016$). The stepwise multiple regression analysis yielded "bringing work home" (Adj $R^2 = 21.5\%$; $F_{1/22} = 6.76$; $\beta = -0.503$; $p < 0.017$) as the only significant predictor of arousals. Removing "bringing work home" did not lead to any other variable entering the model.

Secondly, the relation of *mood,* that is, anxiety, HAD-A ($r = 0.28$), depression, HAD-D ($r = 0.25$) and "tension" (anger/irritability/nervousness) ($r = 0.46$, $p = 0.037$) with arousals was tested in a stepwise multiple regression analysis. "Tension" became the only significant predictor (Adj $R^2 = 17{,}6$; $F_{1/21} = 5{,}47$; $\beta = 0.464$; $p = 0.030$). Removing "tension" did not lead to any other variable entering the model.

Thirdly, *diary ratings* in the evening before the PSG of "activation at bedtime" ($r = 0.15$), "anticipated sleep" ($r = -0.21$) and "thoughts of work during leisure time" ($r = -0.19$) were also tested in a stepwise multiple regression against arousals, but yielded no significant predictor.

In a final step, the *significant variables* in the regression analyses above ("bringing work home" and "tension") were tested in a stepwise multiple regression analysis together with *possible control factors* that might cause arousals such as: "self-reported snoring" ($r = -0.02$), "ache/pain complaints" ($r = 0.39$), "having small children" <7 years ($r = 0.13$), and "burnout group" ($r = 0.40$). The *dependent* variable was again number of arousals per hour during sleep before the workday. "Bringing work home" was the only predictor entering the model (Adj $R^2 = 16.8\%$; $F_{1/19} = 4.84$; $\beta = 0.461$; $p = 0.041$). Removing "bringing work home" made "tension" enter the model (Adj $R^2 = 15.9\%$; $F_{1/19} = 4.59$; $\beta = 0.451$; $p = 0.046$), and removing "tension" made burnout group enter the model (Adj $R^2 = 15.6\%$; $F_{1/19} = 4.5$; $\beta = 0.447$; $p = 0.048$). After also removing the burnout group, no other variable entered the model. The independent variables "bringing work home," "tension," and "burnout" were highly intercorrelated ($r > 0.6$, $p < 0.01$).

DISCUSSION

The present study showed that HR, SBP and DBP, cortisol in saliva and blood, total cholesterol, LDL-C, and LDL/HDL ratio were clearly related to the frequency of arousals from sleep. The same parameters also differed between the arousal groups. The frequency of arousals was also related to "bringing work home" and to "tension." To the best of our knowledge, this kind of relation has not been demonstrated before.

The link between fragmented sleep and the physiological variables receives certain support from other studies. For example, this includes the increased levels of lipids and cortisol seen after experimental sleep reduction or in insomniacs (8,14,15,19,52,53). It also agrees with the increased HR and blood pressure shown in studies of individuals with disturbed sleep (1,16,54). The present observations, that the number of arousals was the strongest predictor among the PSG variables tried, suggest that this variable may be an important factor in itself irrespective of sleep loss. This is in accordance with other studies claiming that fragmentation impairs the restorative function of sleep (16).

TST and sleep efficiency did in some cases (ie, TST; salivary cortisol and LDL/HDL-ratio, sleep efficiency; heart rate and HDL-C) enter the regression together with frequency of arousals but was clearly of less importance than fragmentation. Possibly, the variation of TST or sleep efficiency in the sample may need to be larger in order to dominate a relation with cortisol and other metabolic variables. In the sleep restriction studies discussed previously, TST was reduced to 5 or 4 hours (8,53).

The reason for the link between arousals and metabolic parameters is not clear but, as was discussed in the introduction, cortisol secretion (and catecholamines) is increased in arousals from sleep (8,19) and so are HR and blood pressure (16). Cortisol also stimulates lipolysis (55,56) among other things, which might affect lipid levels. It is an interesting question whether such metabolic and hemodynamic changes can be linked to subsequent pathology as suggested by the prospective links between complaints of disturbed sleep and subsequent cardiovascular disease (5) and diabetes type II (4). In addition, diabetics (57) and patients with cardiovascular disease (3,27) often suffer from disturbed sleep.

In the present study, no relations were found between fragmentation and insulin/glucose or triglycerides, in contrast to the effects seen in partial sleep restriction (8,53). The reason is not clear, but apart from the possibility of sleep fragmentation being too weak a stimulus for effect, it may also be the case that the present study was too small to detect any relations.

Gender was entered mainly as a control variable, and the reduced amount of SWS in men is in accordance with other studies (58,59). The gender difference in WHR was also expected (10). The beneficial effect of estrogen on lipids, especially on HDL-C levels (60), may be one possible interpretation of the relation between gender and HDL-C. Possibly women may also be more aware than men of the effects of a healthy diet (9).

Even though the present results, together with support from other studies, suggest a link between arousals and cortisol, lipids, and blood pressure, it should be emphasized that it is correlative and conclusions on causality must await experimental evidence with a larger and randomly selected sample of subjects. When interpreting the results, one should also bear in mind that the sample was small and that the data represent a secondary analysis carried out on a sample of young individuals scoring high and low on burnout. The variable "burnout group" was tried in all the stepwise multiple regression analyses but did not enter any of them, suggesting that the selection procedure may not have had any confounding effects. Possibly, the large number of analyses carried out in the present study with a small sample size may have inflated the risk of type 1 errors, yielding too many significant regressions.

The correlation between fragmentation and "bringing work home" seems logical. Workload/unclear borders between work and leisure time is a well-established cause of both stress (61) and disturbed sleep (29), and tension/irritability is a common effect of stress (62) as well as predictor of disturbed sleep (17,41). Furthermore, the parameters constituting the metabolic syndrome are also sensitive indicators of stress (63,64), and there is growing evidence that both the endocrine and the sympathetic nervous system (SNS) are regulated from the same central origin (65). As shown in the present study, a high frequency of arousals was accompanied by higher subjective tension, and it could be hypothesized that extended stress or tension may result in a more or less permanent hyperarousal, mediating frequent microdisturbances of sleep. The tension/irritability could also reflect a type-A behavior, which has been associated with frequent waking from sleep (66) and hostility is a well-known risk trait for cardiovascular disease (67,68). This could interfere with the normal anabolic dominance in sleep when the stress hormones from both peripheral limbs of the stress systems, the HPA (hypothalamic–pituitary–adrenal) axis and the SNS system, are downregulated (69). The fact that pain/ache problems, snoring, having small children, anxiety, or depression did not enter any of the stepwise multiple regression analyses strengthens the interpretation somewhat, since these variables otherwise may have represented alternative explanations.

The discussion above is based on correlations between a physiological parameter and subjective ratings of different types. One might argue that subjective ratings may present difficulties, and compliance in diary studies might be low (70). On the other hand, many of the subjective variables have been validated, and in our hands diaries seem to provide reliable data (71), partly due to close and frequent interaction between the experimenter and participant. No data loss occurred other than as exceptions.

In summary, the present study has demonstrated that sleep fragmentation in otherwise normal sleep was related to physiological changes that in the long run may affect health. Also, long-term work stress and tension/ irritability were associated with the sleep fragmentation. Obviously, the present study was cross sectional and no conclusions about causation can be drawn. Also, we do not know whether the selection procedure may have yielded an abnormal representation of arousals. The results do, however, suggest that future studies should investigate whether the suggested chain "work stress–tension–sleep fragmentation–metabolic changes" can be verified in longitudinal/experimental studies on random selections of subjects.

REFERENCES

1. Parish JM, Shepard JW. Cardiovascular effects of sleep disorders. Chest 1990;97:1220–26.
2. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. J Intern Med 2002;251:207–16.
3. Leineweber C, Kecklund G, Janszky I, Åkerstedt T, Orth-Gomér K. Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease. The Stockholm Female Coronary Risk Study. J Psychosom Res 2003;54:121–7.
4. Nilsson P, Rööst M, Engström G, Hedblad B, Janzon L, Berglund G. Incidence of diabetes in middle-aged men is related to resting heart rate and difficulties to fall asleep. (Abstract). 7th International Congress of Behavioural Medicine. Helsinki, Finland, 2002.
5. Nilsson P, Nilsson J-Å, Hedblad B, Berglund G. Sleep disturbances in association with elevated pulse rate for the prediction of mortality—consequences of mental strain? J Intern Med 2001;250:521–9.
6. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131–6.
7. Dew MA, Hoch CC, Buysse DJ, Monk TH, Begley AE, Houck PR, Hall M, Kupfer DJ, Reynolds CF. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. Psychosom Med 2003;65: 63–73.
8. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. The Lancet 1999;354:1435–39.
9. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Cats VM, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2003;10:S1–10.
10. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
11. Reaven GM. Role of insulin in human disease. Diabetes 1988;37: 1595–607.
12. Björntorp P. Visceral obesity: A "civilization syndrome". Obes Res 1993;1:206–22.
13. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin H-M, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151–8.
14. Vgontzas AN, Bixler EO, Lin H-M, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implication. J Clin Endocrinol Metab 2001;86:3787–94.

15. Monroe L. Psychological and physiological differences between good and poor sleepers. J Abn Psychol 1967;72:255–64.
16. Bonnet MH, Arand DL. Insomnia, metabolic rate and sleep restoration. J Intern Med 2003;254:23–31.
17. Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. Psychosom Med 2003;65:259–67.
18. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. Chest 1993;104:781–7.
19. Späth-Schwalbe E, Gofferje M, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psychiatry 1991; 29:575–84.
20. Söderström M, Ekstedt M, Nilsson M, Axelsson J, Åkerstedt T. Sleep and sleepiness in young individuals with high burnout scores. Sleep, in press.
21. ASDA. EEG arousals: scoring rules and examples. Sleep 1992;15:173–84.
22. Guilleminault C, Dave R. Upper airway resistance syndrome, insomnia, and functional somatic syndromes. Chest 2003;123:12–4.
23. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest 2002;121:1531–40.
24. Morin CM. Insomnia—psychological assessment and management. New York: The Guilford Press; 1993.
25. Hauri P. Primary insomnia. In: Kryger MH, Roth T, Dement CW, editors. Principles and practice of sleep medicine. 2000. p. 633–46.
26. Healey ES, Kales A, Monroe LJ, Bixler EO, Chamberlin K, Soldatos CR. Onset of insomnia: role of life-stress events. Psychosom Med 1981;43: 439–51.
27. Edell-Gustaffson UM. Insufficient sleep, cognitive anxiety and health transition in men with coronary artery disease: a self-report and polysomnographic study. J Adv Nurs 2002;37:414–22.
28. Hall M, Buysse DJ, Nowell PD, Nofzinger EA, Houck P, Reynolds CF, Kupfer DJ. Symptoms of stress and depression as correlates of sleep in primary insomnia. Psychosom Med 2000;62:227–30.
29. Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours. A cross-sectional study. J Psychosom Res 2002;53:741–8.
30. Karasek RA. Job demands, job decision latitude and mental strain. Implications for job redesign. Adm Sci Q 1979;24:285–308.
31. Karasek R, Theorell T. Healthy work: stress, productivity, and the reconstruction of working life. New York: Basic Books; 1990.
32. Siegrist J, Peter R. The effort-reward imbalance model. Occup Med 2000;15:83–7.
33. Melamed S, Kushnir T, Shirom A. Burnout and risk factors for cardiovascular diseases. Behav Med 1992;18:53–60.
34. Kushnir T, Melamed S. The Gulf War and its impact on burnout and well-being of working civilians. Psychol Med 1992;22:987–95.
35. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 1994;19:313–33.
36. Pruessner JC, Wolf OT, Helhammar DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kasapers F, Kirschbaum C. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci 1997;61:2539–49.
37. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, MD: US Department of Health, Education and Welfare, Public Health Service, 1968.
38. Söderström M, Ekstedt M, Jeding K, Åkerstedt T. Workload and impaired recovery as prediction of burnout. In preparation.
39. Derogatis LR. Symptom checklist-90 manual. Baltimore, MD: Johns Hopkins University Press; 1977.
40. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med 1979;9:139–45.
41. Rosa RR, Bonnet MH. Reported chronic insomnia is independent of poor sleep as measured by electroencephalography. Psychosom Med 2000;62: 474–82.
42. Kales JD, Kales A, Bixler EO, Soldatos CR, Cadieux RJ, Kashurba GJ, Vela-Bueno A. Biopsychobehavioral correlates of insomnia, V: clinical characteristics and behavioral correlates. Am J Psychiatry 1984;141: 1371–6.
43. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.
44. Hopwood P, Howell A, Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer 1991;64:353–6.
45. Lisspers J, Nygren A, Söderman E. Hospital Anxiety and Depression Scaale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand 1997;96:281–6.
46. Shirom A. Burnout in work organizations. In: Robertson CLCaI, editor. International review of industrial and organizational psychology. New York: John Wiley & Sons Ltd.; 1989. p. 25–48.
47. Maslach C, Jackson SE, Leiter MP. Maslach Burnout Inventory manual. Palo Alto, CA: Consulting Psychologists Press, Inc.; 1996.
48. Pines AM, Aronson E, Kafry D. The research, burnout from tedium to personal growth. New York: The Free Press; 1981. p. 202–5.
49. Grossi G, Perski A, Evengård B, Blomkvist V, Orth-Gomér K. Physiological correlates of burnout among women. J Psychosom Res 2003;55: 309–16.
50. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psykometrika 1951;16:297–333.
51. Bonnet MH, Arand DL. We are chronically sleep deprived. Sleep 1995; 18:908–11.
52. Born J, Schenk U, Späth-Schwalbe E, Fehm HL. Influences of partial REM sleep deprivation and awakenings on nocturnal cortisol release. Biol Psychol 1988;24:801–11.
53. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. Clin Endocrinol 1999;51:205–15.
54. Corcoran DWJ. Changes in heart rate and performance as a result of loss of sleep. Br J Psychol 1964;55:307–14.
55. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994;74:761–811.
56. Brindley DN, McCann BS, Niaura R, Stoney CM, Suarez EC. Stress and lipoprotein metabolism: modulators and mechanisms. Metabolism 1993; 42:3–15.
57. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM. Diabetes and sleep disturbances. Diabetes Care 2003;26:702–9.
58. Webb WB. Sleep in older persons: sleep structures of 50- to 60-year-old men and women. J Ger 1982;37:581–6.
59. Ehlers CL, Kupfer DJ. Slow-wave sleep: do young adult men and women age differently? J Sleep Res 1997;6:211–5.
60. Nanda S, Gupta N, Mehta HC, Sangwan K. Effect of oestrogen replacement therapy on serum lipid profile. Aust N Z J Obstet Gynaecol 2003;43:213–6.
61. Theorell T. How to deal with stress in organizations? A health perspective on theory and practice. Scand J Work Environ Health 1999;25: 616–24.
62. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. JAMA 1992;267:1244–52.
63. McEwen B, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
64. Vrijkotte TGM, van Doornen LJP, de Geus EJC. Work stress and metabolic and hemostatic risk factors. Psychosom Med 1999;61:796–805.
65. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000;157:683–94.
66. van Diest R. Subjective sleep characteristics as coronary risk factors. Their association with type A behaviour and vital exhaustion. J Psychosom Res 1990;34:415–26.
67. Friedman M, Rosenman RH. Type A behavior and your heart. New York: Random House Inc.; 1974.
68. Haynes SG, Feinleib M, Kannel WB. The relationship of psychosocial factors to coronary heart disease in the Framingham study. Am J Epidemiol 1980;111:37–58.
69. Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab 1983; 56:352–8.
70. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002;324:1193–4.
71. Åkerstedt T, Hume K, Minors D, Waterhouse J. Good sleep—its timing and physiological sleep characteristics. J Sleep Res 1997;6:221–9.