Disadvantageous shift in energy balance is primarily expressed in high-quality sleepers after a decline in quality sleep because of disturbance

Rick Hursel, Hanne KJ Gonnissen, Femke Rutters, Eveline AP Martens, and Margriet S Westerterp-Plantenga

ABSTRACT

Background: Epidemiologic studies have shown an inverse or U-shaped relation between sleep duration and body mass index (BMI; in kg/m²). Moreover, associations between energy balance (EB) and characteristics of quality sleep (QS) have recently been reported.

Objective: We assessed the relation between total energy expenditure (TEE) as well as substrate oxidation and QS after disturbed compared with nondisturbed sleep in EB.

Design: Fifteen healthy men (mean ± SD BMI: 24.1 ± 1.9; age: 23.7 ± 3.5 y) were included in a randomized crossover study. TEE and substrate oxidation were measured twice for 48 h in a respiration chamber, whereas slow-wave sleep (SWS), rapid eye movement (REM)–sleep, total sleeping time (TST), sleep stage 2 (S2), and QS [(SWS + REM) / TST × 100%] were determined by using electroencephalography. During 2 nights, sleep (2330–0730) was either disturbed or nondisturbed (control).

Results: Positive correlations were shown for TEE, activity-induced energy expenditure corrected for body mass (AEE/BM), respiratory quotient (RQ), and carbohydrate oxidation with QS and SWS during nondisturbed sleep. Fat oxidation was inversely correlated with QS and SWS. RQ and carbohydrate oxidation were inversely related to REM sleep. During the disturbed condition SWS, REM, TST, and S2 were reduced, and positive correlations were shown between TEE and AEE/BM with QS. The reduction in QS was stronger in high-quality sleepers; QS reduction was positively associated with increases in energy intake, TEE, and EB.

Conclusion: A disadvantageous shift in energy balance is primarily expressed in high-quality sleepers after a decline in QS because of disturbance, implying that good sleepers are most liable to a positive energy balance because of sleep disturbance. This trial was registered at ISRCTN as NTR1919.

INTRODUCTION

With its increasing prevalence, the cause of obesity has been studied more extensively, thereby creating a basis for new fields of research such as the effect of sleep on body weight regulation. For several years, it has been evident that the increase in body weight within a large amount of the global population has been accompanied by a decrease in sleep duration (1). This association was shown previously and was substantiated by a large number of observational studies. The increasing urbanization and, thus, growing disruption of sleep do not only reduce sleep, but might also decrease quality sleep (QS). However, it is not clear whether QS may still be preserved despite a reduction of sleep hours and whether QS is of higher significance than merely sleep duration. Disadvantageous metabolic effects of poor sleep quality have been reported before (2). Studies that investigated the role of sleep architecture with respect to metabolic variables indicate that not all sleep stages are of equal importance. Slow-wave sleep (SWS) has been regarded as the most restorative stage of sleep, and its suppression might have a negative effect on several metabolic variables including a decrease in insulin sensitivity in humans (3). Rapid eye movement (REM) sleep may be of similar interest as SWS because a reduction in REM sleep during a single night of sleep disturbance led toward decreased fullness and reduced glucagon-like peptide-1 concentrations (4). Therefore, together, SWS and REM sleep seem to be the most important determinants of QS (5). Rutters et al (6) stressed that energy-balance (EB) variables are primarily related to SWS and REM sleep instead of the total sleep duration. Several studies have studied the relation between SWS and REM sleep and energy expenditure as well as substrate oxidation (7, 8). A decrease in total energy expenditure (TEE) because of sleep fragmentation has been suggested as one of the possible causes for weight gain (9). However, we previously observed no difference between nonfragmented and fragmented sleep with respect to the TEE, resting metabolic rate (RMR), sleeping metabolic rate (SMR), activity-induced energy expenditure corrected for body mass (AEE/BM), and EB. However, the activity-induced energy expenditure (AEE), respiratory quotient (RQ), carbohydrate oxidation (CHOox), fat oxidation (FATox), physical activity by radar counts (PA), SWS, REM, total sleeping
time (TST), sleep stage 1, sleep stage 2 (S2), and wake changed significantly during the fragmented compared with nonfragmented sleep (13) (see Online Supplemental Tables S1 and S2 under “Supplemental data” in the online issue). Other studies showed similar results for energy expenditure (10–12). However, very little evidence exists that decreased TEE may be an explanatory factor for weight gain after short sleep duration.

On the basis of previous results, we hypothesized that QS may be of higher significance than the duration of sleep and, therefore, may have a larger effect on TEE and substrate use.

Therefore, the aim of the current study was to examine the relation between energy expenditure and substrate oxidation measured in a respiratory chamber and QS assessed by using electroencephalography after disturbed compared with non-disturbed sleep.

SUBJECTS AND METHODS
Because the within-subjects comparison of the intervention has been published before (13), the Subjects and Methods section is largely similar to that in a previous publication. In the current article, we focus on the between-subjects effects, because differences between subjects appeared to be much larger than differences induced by interventions.

Subjects
Fifteen healthy men [mean ± SD BMI (in kg/m²); 24.1 ± 1.9; age: 23.7 ± 3.5 y] were recruited by advertisements on notice boards at the university. All volunteers participated in an initial screening that involved measurements of body weight and height and included the completion of questionnaires related to eating behavior [ie, the Three-Factor Eating Questionnaire (14)], health, use of medication, physical activity, alcohol consumption, food allergies, smoking behavior, and sleeping behavior. Selected subjects were in good health, had BMI between 20 and 30, were nonsmokers, were not using medication, were, at most, moderate alcohol consumers, were unrestrained eaters (assessed by factor 1 of the Three-Factor Eating Questionnaire; cutoff: ≥9) (14), and slept 7–8 h a night. Baseline characteristics of subjects are presented in Table 1. Subject recruitment started in June 2009, and the study was conducted between September 2009 and May 2010. The study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving human subjects were approved by the Medical Ethical Committee of Maastricht University Medical Centre. Written informed consent was obtained from all subjects. The study was registered at ISRCTN as NTR1919.

Experimental design
The study had a randomized, single-blind, crossover design. Subjects came to the university twice with ≥2 wk in between sessions. Two days before their stay in respiratory chambers, subjects were asked to abstain from strenuous exercise and sleep 8 h during nights. During each visit, subjects stayed for 48 h in a respiration chamber where energy expenditure, PA, and substrate oxidation were measured during a condition with disturbed sleep and a condition of nondisturbed sleep. Subjects had fixed bedtimes, which were indicated by lights that switched off automatically at 2330 and switched on at 0730, which resulted in 8 h time in bed a night. During the daytime, participants were not allowed to sleep. To ensure this, researchers addressed subjects on a regular basis, and polygraphic recordings were made continuously by using an electroencephalograph (BrainRT Digital EEG System; OSG bvba). The artificial light intensity in the respiration chamber was always >400 lx (Energy Saver Tornado E27 900 lm; Philips Lighting). The disturbance of sleep was accomplished with approximately hourly wake-up calls that varied in frequency between 500–2000 Hz and intensity between 40–110 dB; confirmation of waking up was expressed by subjects because they had to put off the alarm after 2 min. Subjects were individually fed in EB 2 d before their stay in the respiration chamber. This diet had the same macronutrient composition (12%, 55%, and 33% of energy from protein, carbohydrate, and fat, respectively) as the diet they received during the subsequent stay in the respiration chamber and consisted of normal everyday food products. Subjects were fed in EB during the first 46 h, and the last dinner before subjects left the chamber was ad libitum. For the calculation of EB, the ad libitum meal was included.

Sleep recordings
Before subjects entered the respiration chamber at 2000, electrodes for electroencephalography, electrocardiogram, electromyogram, and electrooculogram recordings were placed according to appropriate standardized criteria (15). Polygraphic recordings were obtained throughout the entire 48 h (electroencephalography, BrainRT Digital EEG System; OSG bvba). All records were visually scored in 30-s epochs according to the standardized criteria by a skilled researcher for whom the conditions were blinded (15). QS was calculated by using the following formula (electroencephalography: BrainRT Digital EEG System; OSG bvba):

\[(SWS + REM) \div TST \times 100\%\] 

Energy intake
Calculations for both the diet at home and in the respiration chamber were based on individual average daily energy...
requirements. The daily energy requirement for the diet at home was estimated as 1.75 times the RMR (16). The RMR was calculated by using the formula of Harris and Benedict (17). The energy requirement in the respiration chamber was calculated as 1.35 times the measured SMR of the first night. Daily energy intake (EI) was divided over 3 meals as follows: breakfast, 20%; lunch, 40%; and dinner, 40%. Breakfast was given at 0830, lunch was given at 1330, and dinner was given at 1830.

Energy expenditure, physical activity, and substrate oxidation

Subjects stayed in the respiration chambers for 48 h from 2000 h in the evening on day 1 to 2000 h in the evening of day 3. Energy expenditure, PA, and substrate oxidation were measured and calculated according to the similar protocol used in previous studies conducted at the Department of Human Biology, Maastricht University (18–20). Body composition was determined in between both sessions by using the deuterium-dilution (D2O) technique (21, 22).

Statistical analysis

Linear regression analyses were performed to analyze the relation between dependent and independent variables. Multiple regression analyses were conducted to test the mediation model proposed with the most fitting predictors of EB. Data are presented as means ± SEMs unless otherwise indicated, and the level for establishing significant differences was taken at P < 0.05. Data were analyzed with PASW Statistics 18 software (SPSS Inc).

RESULTS

Values for the outcome variables energy expenditure, substrate oxidation, physical activity, and sleep have been published before in Hursel et al (13). In the current article, we report the QS calculated as shown in Equation 1. QS did not differ between the nondisturbed condition (45.9 ± 1.9%) and disturbed condition (44.8 ± 1.5%). Subsequently, the outcome variables TEE, AEE, AEE/BM, RQ, CHOox, FATox, and PA have been correlated with QS as well as SWS, REM, TST, and S2 for each condition. r and P values are reported in Table 2.

During the nondisturbed condition, positive correlations were shown for TEE, AEE, AEE/BM, RQ, and CHOox with QS and SWS. AEE was also inversely related to S2. FATox was inversely related to QS and SWS and positively related to S2. RQ and CHOox were inversely related to REM and S2. PA was positively related to QS. TST and S2 were inversely related to AEE/BM and PA (see Online Supplemental Figures S1–S3 under “Supplemental data” in the online issue).

Although disturbed sleep led to reductions in TST, S2, SWS, and REM sleep (13) (P < 0.001), QS was preserved. During the disturbed condition, positive correlations were observed between TEE, AEE, and AEE/BM and QS. No significant correlations were observed between SMR, RMR, and sleep variables (ie, QS, SWS, REM, TST, and S2) in the nondisturbed and disturbed conditions (data not shown).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Regression analyses between sleep and metabolic variables in nondisturbed and disturbed conditions.</th>
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</thead>
<tbody>
<tr>
<td>QS</td>
<td>TEE (MJ/d)</td>
</tr>
<tr>
<td></td>
<td>AEE (MJ/d)</td>
</tr>
<tr>
<td></td>
<td>AEE/BM (MJ/d kg⁻¹)</td>
</tr>
<tr>
<td></td>
<td>CHOox (g/d)</td>
</tr>
<tr>
<td></td>
<td>FATox (g/d)</td>
</tr>
<tr>
<td></td>
<td>RQ</td>
</tr>
<tr>
<td></td>
<td>PA (radar counts)</td>
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</tbody>
</table>

*Linear regression analyses (n = 15). No significant relations were observed between the sleep variables and resting metabolic rate as well as sleeping metabolic rate and have, therefore, been left out of the table. AEE, activity-induced energy expenditure; AEE/BM, activity-induced energy expenditure corrected for body mass; CHOox, carbohydrate oxidation; FATox, fat oxidation; PA, physical activity; QS, quality of sleep; REM, rapid eye movement; RQ, respiratory quotient; SWS, slow-wave sleep; S2, sleep stage 2; TST, total energy expenditure; TST, total sleeping time.
At closer inspection of the data, it appeared that, in subjects with the highest percentage of QS, QS was affected most as a result of the disturbance. The change in QS

\[
\Delta QS = \text{nondisturbed condition QS} - \text{disturbed condition QS}
\]

was positively associated with QS in the nondisturbed condition and negatively associated with the QS in the disturbed condition (Figure 1). Within subjects, the change in QS led to changes in EI and energy expenditure. The change in EI was negatively correlated with the change in QS, which suggested that EI increased the most in subjects in whom QS declined because of the disturbed condition (Figure 2A). Also, the change in TEE was negatively correlated with the change in QS, which indicated that TEE increased the most in subjects in whom QS declined because of the disturbed condition (Figure 2B). These changes in EI and TEE led to a trend for differences in EB because of changes in QS (Figure 2C). No significant correlations were shown between changes in SWS, REM, TST, and S2 and changes in EI, TEE, and EB. \( r \) and \( P \) values are reported in Table 3.

**DISCUSSION**

In the nondisturbed condition, positive relations were shown between TEE, AEE, and AEE/BM and QS and SWS. Subjects with more QS and SWS during the night showed a larger TEE and AEE over 24 h, which even remained apparent for AEE after correction for body mass. Positive correlations were also showed for substrate oxidation, namely 24-h RQ and 24-h CHOox with the duration of QS and SWS. Contrarily, 24-h FATox was inversely related to the duration of QS and SWS. RQ and CHOox were inversely related to the duration of REM sleep; this result was due to the duration of REM sleep being
FIGURE 2. Inverse relation between the change in quality sleep and change in energy intake ($r = -0.56, P < 0.05$) (A), change in total energy expenditure ($r = -0.57, P < 0.03$) (B), and change in energy balance ($r = -0.51, P = 0.05$). Linear regression analyses ($n = 15$).
Table 3: Regression analyses between the change in sleep variables and change in energy-balance variables

<table>
<thead>
<tr>
<th>ΔQS</th>
<th>ΔTEE (MJ/d)</th>
<th>ΔEI (MJ/d)</th>
<th>ΔEB (MJ/d)</th>
<th>ΔSWS</th>
<th>ΔREM</th>
<th>ΔTST</th>
<th>ΔS2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>ΔQS</td>
<td>-0.57 0.03</td>
<td>-0.46 NS</td>
<td>-0.50 NS</td>
<td>-0.08 NS</td>
<td>0.33 NS</td>
<td>-0.50 0.03</td>
<td>-0.38 NS</td>
</tr>
<tr>
<td>ΔREM</td>
<td>-0.51 0.05</td>
<td>-0.31 NS</td>
<td>-0.33 NS</td>
<td>0.21 NS</td>
<td>0.46 NS</td>
<td>-0.51 0.05</td>
<td>-0.31 NS</td>
</tr>
<tr>
<td>ΔTST</td>
<td>0.57 0.03</td>
<td>-0.51 NS</td>
<td>-0.46 NS</td>
<td>-0.50 NS</td>
<td>-0.33 NS</td>
<td>0.57 0.03</td>
<td>-0.51 NS</td>
</tr>
<tr>
<td>ΔS2</td>
<td>-0.66 0.01</td>
<td>-0.51 NS</td>
<td>-0.46 NS</td>
<td>-0.50 NS</td>
<td>-0.33 NS</td>
<td>-0.66 0.01</td>
<td>-0.51 NS</td>
</tr>
</tbody>
</table>

1 Linear regression analyses (n = 15). EB, energy balance; EI, energy intake; QS, quality sleep; REM, rapid eye movement; SWS, slow wave sleep; S2, sleep stage 2; TEE, total energy expenditure; TST, total sleeping time; Δ, difference between nondisturbed and disturbed condition.

complementary to the duration of SWS. Another important variable that is thought to be affected by sleep, namely PA, was positively correlated with QS (ie, subjects who showed larger QS were more active, or QS increased more in active subjects). The positive correlation between PA and QS also corresponded with the correlation between QS and AEE/BM. PA and AEE/BM as well as RQ were inversely correlated with TST, which indicated that subjects with a shorter TST had increased PA, AEE, and RQ and vice versa. Finally, S2 partly corresponded with TST because AEE, AEE/BM, RQ, CHOox, and activity were all inversely related to S2, whereas FATox was positively related to S2.

A comparison of disturbed with nondisturbed conditions resulted in reductions in sleep variables SWS, REM sleep, TST, and S2. As reported previously, metabolic variables AEE, RQ, CHOox, FATox, and physical activity also changed compared with the nondisturbed condition (13). With respect to the associations between sleep and metabolic variables, shifts were observed that indicated that sleep disturbance may have an unfavorable effect on SWS, REM, TST, and S2, which may affect energy metabolism. However, as our results suggested, the preservation of QS may prevent these disadvantageous effects of sleep disturbance on TEE and AEE/BM. Furthermore, changes that were a result of the sleep disturbance also pointed out that SWS and REM may be important for the regulation of substrate oxidation.

After the sleep disturbance, a reduced range in QS was observed, which could mainly be attributed to subjects with the highest percentage of QS because their QS was affected most. The difference in QS between both conditions was positively associated with QS in the nondisturbed condition and negatively associated with QS in the disturbed condition. The shift in QS within subjects led to changes in EI and energy expenditure. The change in both EI and TEE was negatively correlated with the change in QS, which suggested that EI and TEE increased the most in subjects in whom QS declined the most because of sleep disturbance. The change in TEE after the disturbed condition was most likely attributed to being more awake and increased EI. Furthermore, changes in EI and TEE also led to a trend for differences in EB that was a result of changes in QS. This result implied that the EB became more positive in subjects with the largest reduction in QS as a result of the disturbed condition.

Our findings showed that QS was positively related to TEE in both conditions, which indicated that individuals with more QS show a larger TEE, or individuals with a larger TEE have more QS. QS as well as TEE were preserved in our subjects despite the sleep disturbance, which emphasized the importance of QS for TEE. This finding might explain why hardly any study has shown the unfavorable effect of sleep on TEE (10). Most studies restricted sleep to 4 h while the quality of sleep may still have been preserved. Our results showed that merely decreasing the sleep duration seemed to have no effect, as indicated by the absence of a relation between TEE and TST in both conditions. Also, between TEE and S2, which is the predominant sleep stage that is a derivative of TST (45–55%) and followed by SWS and REM in the sleep cycle, no significant correlation was observed. It would be interesting to investigate whether a change in QS would affect TEE.

In contrast, the relation between SWS and TEE was no longer present when the amount of SWS decreased in our subjects, which indicated that SWS had no effect on TEE or vice versa. Nevertheless, SWS may still have played an important role in energy metabolism through its effect on substrate oxidation (ie, RQ and CHOox). The positive relations between SWS and RQ as well as CHOox that we observed in our subjects were no longer present when SWS was decreased and RQ and CHOox were increased. With QS unchanged, this result may suggest a regulatory role of SWS on CHOox. A role of SWS for glucose and insulin metabolism has been shown before (2–4, 23–25). Contrarily, de Jonge et al (26) reported a higher RQ with decreasing QS, which suggested that QS does play a role in substrate oxidation. Unfortunately, in the study of de Jonge et al (26), RQ was only measured for 30 min, and QS was determined by using questionnaires. Corresponding with the study of de Jonge et al (26), RQ was inversely related to REM, TST, and S2, whereas CHOox was only inversely related to REM and S2. However, these associations disappeared with sleep disturbance. FATox was inversely related to QS and SWS and positively related to S2 during the nondisturbed condition but not related to REM. Still, these results may support the existence of a modulating effect of the sleep architecture on metabolic flexibility. Because no relations between sleep variables and substrate oxidation remained after sleep disturbance, metabolic flexibility may have been disrupted (27).

Physical inactivity may also follow after sleep disturbance as suggested by Schmid et al (28) who reported that a short-term sleep loss decreased physical activity under free-living conditions. A positive relation between PA counts and QS was shown, which indicated that subjects were less sedentary when their QS was preserved. Also, inverse relations between TST as well as S2 and physical activity counts as well as AEE/BM were observed, which confirmed the increase in AEE was a result of an increase in physical activity after sleep disturbance.

The importance of QS was most pronounced in subjects who had the highest percentage of QS. QS dropped substantially in these subjects, and the inverse relation between EI and QS being larger than the inverse relation between TEE and QS eventually led to a trend for a positive EB when QS decreased. Effects on EI and EB because of changes in sleep architecture have been shown previously (6, 29) and suggested that a decrease in QS may lead to a positive EB. This possibility corresponds with the results of subjective studies that have reported that a decrease in QS was related to an increase in BMI (30) and, in contrast, a decrease in body weight led to an improvement in QS (31). For TEE,
a relation between subjective QS and resting energy expenditure has been published, in which poor QS was associated with increased energy expenditure at rest (26).

In summary, the positive relation between TEE as well as AEE/\( \text{BM} \) and QS in both conditions implies that QS plays an important role in the maintenance of TEE and vice versa. Therefore, a possible effect of sleep on energy expenditure may be assessed as the effect of QS on TEE and AEE/\( \text{BM} \). Furthermore, the positive relation between RQ and QS as well as SWS and the inverse relation between RQ and REM sleep implied a balance between \( \text{CHO} \text{o}x \) and \( \text{FATox} \) related to both components of QS that pointed toward a role of sleep architecture in metabolic flexibility. Also, despite the correlations between metabolic variables and sleep variables, changes in energy metabolism were only associated with changes in QS because of sleep disturbance but not with changes in other sleep variables, which underlined the importance of QS in EB. Finally, subjects with the highest percentage of QS suffered most from the sleep disturbance, which resulted in increased EI and a possible positive EB.

In conclusion, sleep disturbance did not affect the usual relations between QS and TEE and with AEE/\( \text{BM} \) because of preserved QS. However, relations between SWS as well as REM and substrate oxidation were unfavorably affected. For subjects with the highest percentage of QS, QS was affected most because of the fragmentation that led to unfavorable shifts in EI, TEE, and EB.

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