Effects of sleep fragmentation in healthy men on energy expenditure, substrate oxidation, physical activity, and exhaustion measured over 48 h in a respiratory chamber\(^1\-\^3\)

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

ABSTRACT

Background: Epidemiologic studies show an inverse or U-shaped relation between sleep duration and BMI. Decreases in total energy expenditure (TEE) and physical activity have been suggested to be contributing factors.

Objective: The objective was to assess the effect of sleep fragmentation on energy metabolism and energy balance in healthy men.

Design: Fifteen healthy male subjects [mean ± SD BMI (in kg/m\(^2\)): 24.1 ± 1.9; age: 23.7 ± 3.5 y] were included in a randomized crossover study in which energy expenditure, substrate oxidation, and physical activity (by radar) were measured twice for 48 h in a respiration chamber while subjects were monitored by electroencephalography to determine slow-wave sleep (SWS), rapid eye movement (REM) sleep, and total sleeping time (TST). During 2 nights, sleep (2330–0730 h) was either fragmented or nonfragmented.

Results: Fragmented sleep led to reductions in TST, SWS, and REM sleep (\(P < 0.001\)). TEE did not differ (9.96 ± 0.17 compared with 9.83 ± 0.13 MJ/d, NS) between the sleep groups, nor did the components of energy expenditure, with the exception of activity-induced energy expenditure (AEE; 1.63 ± 0.15 compared with 1.42 ± 0.13 MJ/d for fragmented and nonfragmented sleep, respectively; \(P < 0.05\)). Physical activity, exhaustion, sleepiness, respiratory quotient (RQ), and carbohydrate oxidation were elevated in comparison with nonfragmented sleep [physical activity counts: 2371 ± 118 compared with 2204 ± 124 counts/d, \(P < 0.02\); exhaustion: 40.1 ± 3.8 compared with 21.8 ± 2.4 mm (by using a visual analog scale; VAS), \(P < 0.001\); sleepiness: 47.4 ± 4.2 compared with 33.9 ± 4.6 mm (VAS), \(P < 0.001\); RQ: 0.94 ± 0.04 compared with 0.91 ± 0.03, \(P < 0.05\); and carbohydrate oxidation: 346.3 ± 23.8 compared with 323.7 ± 22.5 g/d, \(P < 0.05\)], whereas fat oxidation was reduced (29.1 ± 9.1 compared with 61.0 ± 6.6 g/d, \(P < 0.01\)).

Conclusions: Fragmented compared with nonfragmented sleep induced reductions in the most important sleep phases, which coincided with elevated AEE, physical activity, exhaustion, and sleepiness. RQ and carbohydrate oxidation increased and fat oxidation decreased, which may predispose to overweight. This trial is registered at www.who.int/trialregistry and www.trialregister.nl as NTR1919. Am J Clin Nutr 2011;94:804–8.

INTRODUCTION

According to epidemiologic data and several reviews that summarized the present knowledge concerning sleep and obesity, the current increase in the prevalence of obesity is accompanied by a decrease in sleep duration (1–5). This has resulted in research on the effects of reductions in the different sleep stages—namely, non-REM\(^4\) sleep (which consists of stages 1–4), SWS (which is a part of non-REM sleep, namely stages 3–4), REM sleep, and TST—on energy balance and metabolic syndrome characteristics.

Experimental research focused initially on endocrine functions such as insulin sensitivity and glucose homeostasis. For instance, Stamatakis et al (6) found a decrease in insulin sensitivity after 2 nights of sleep fragmentation. Others (7–15) also described alterations in endocrine function after sleep restriction or SWS suppression without affecting TST, which may increase the risk of developing insulin sensitivity and type 2 diabetes. The designs of these studies used sleep restriction of \(\leq 4\) h/night and compared this with sleep recovery gained by “catching up” on sleep hours. Coinciding with these alterations in endocrine function, food intake appeared to increase, as shown by increased feelings of hunger and appetite (10, 11, 16–18), thus affecting energy balance. On the basis of observations made by Stamatakis et al (6), who showed that mild sleep deprivation might induce a positive energy balance, we decided to use mild sleep deprivation in the present study, which reflects a more realistic approach that resembles daily life.

The abovementioned studies point at insulin resistance and increased appetite, which would be present after mild fragmentation of sleep, as an explanation for the positive energy balance. Energy balance is maintained when energy intake equals energy expenditure. In addition to an increased food intake and alterations in glucose metabolism, energy expenditure and physical activity have been suggested to decrease after sleep restriction (11), thus contributing to a positive energy balance, which eventually will lead to weight gain. However, more research is needed to obtain

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\(^4\) Abbreviations used: AEE, activity-induced energy expenditure; EEG, electroencephalography; REM, rapid eye movement; RMR, resting metabolic rate; RQ, respiratory quotient; SMR, sleeping metabolic rate; SWS, slow-wave sleep; TEE, total energy expenditure; TST, total sleeping time; VAS, visual analog scale; \(\text{VO}_2\), maximal oxygen uptake.

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TABLE 1
Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>23.7 ± 3.5</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>80.0 ± 6.8</td>
<td>65.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.82 ± 0.06</td>
<td>1.75</td>
<td>1.90</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 1.9</td>
<td>22.1</td>
<td>27.6</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>63.0 ± 6.5</td>
<td>50.8</td>
<td>74.9</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>17.2 ± 4.1</td>
<td>9.2</td>
<td>24.2</td>
</tr>
<tr>
<td>BF (%)</td>
<td>21.4 ± 4.7</td>
<td>12.1</td>
<td>28.8</td>
</tr>
</tbody>
</table>

BF, body fat; FFM, fat-free mass; FM, fat mass.
sleepiness, and how satisfying the sleep was. Opposing extremes of each feeling were described at either end of a 100-mm horizontal line, and subjects marked the line to indicate how they felt at that moment.

**Statistical analysis**

Data from energy expenditure, physical activity, RQ, and substrate balances are presented as means ± SEs unless otherwise indicated. Data were analyzed by comparing the condition of fragmented sleep with the condition of nonfragmented sleep. This analysis was applied to SWS, REM, TST, TEE and its components, physical activity, sleeping questionnaire variables, and substrate oxidation. A 2-factor repeated-measures ANOVA was carried out for determination of possible differences between the conditions. The level for establishing significant differences was taken at $P < 0.05$. Data were analyzed by using SPSS version 11 (SPSS Inc.).

**RESULTS**

The duration of the sleep phases, namely the non-REM sleep stages 1–4, SWS and REM sleep, and TST were reduced during the nights with sleep fragmentation ($P < 0.001$) (Table 2). Between the 2 conditions, TEE and RMR did not differ significantly, whereas AEE significantly ($P < 0.05$) increased with fragmented sleep compared with nonfragmented sleep. In addition, physical activity increased as well with fragmented sleep ($P < 0.02$). SMR, as part of RMR, was not significantly affected by sleep fragmentation (Table 3).

After analyzing the data for measured energy expenditure and energy intake, subjects appeared to be slightly in positive energy balance. Energy balance did not differ significantly between both conditions, which implies that it did not affect the outcomes differently. Fragmented sleep also coincided with an increase in RQ ($P < 0.05$), increased carbohydrate oxidation ($P < 0.05$), and reduced fat oxidation ($P < 0.01$).

Scores on the sleeping questionnaire differed significantly for exhaustion and sleepiness. Coinciding with fragmented sleep, subjects were more exhausted and sleepier ($P < 0.001$) (Table 3).

**DISCUSSION**

During fragmented compared with nonfragmented sleep, AEE, RQ, carbohydrate oxidation, physical activity counts, exhaustion, and sleepiness were elevated, whereas fat oxidation was reduced. TEE and its components RMR and SMR did not differ significantly between the 2 conditions. Subjects woke up 7–7 times during the fragmented night, and consequently reductions in TST, SWS, and REM sleep were observed.

Our findings with respect to energy expenditure correspond to those reported by Nedeltcheva et al (28). Other studies (29–31) also found an increase in metabolic rate initiated after an (acute) disturbance of sleep. A study by Brebbia et al (32) reported that VO$_2$ was related to sleep stages, with the highest VO$_2$ during REM sleep and the lowest VO$_2$ during SWS. Fontvieille et al (33) concluded that sleep stages were associated with small differences in metabolic rate. Bonnet et al (29) have shown that even arousals during sleep, without waking up the subjects, caused elevations in VO$_2$ for another 3–9 min. The small differences in metabolic rate they measured over relatively short periods of time in partly controlled conditions may be transient in nature. Our study was fully controlled and corresponds with the results of Nedeltcheva et al (28) in which no effect on TEE was found. In addition, our results showed an increase in RQ and carbohydrate oxidation, whereas fat oxidation was reduced.

Nedeltcheva et al (28) reported no differences in TEE after measuring 10 subjects, who spent either 5.5 or 8.5 h time in bed, with doubly labeled water for 14 d during caloric restriction. They found decreased RMR after only 5.5 h in bed compared with 8.5 h, which may be an effect of a decrease in SMR because of fewer sleeping hours. In addition, they reported that subjects who spent 5.5 h in bed lost less fat mass and more fat-free mass than did subjects spending 8.5 h in bed. Comparable to our results, they also reported that RQ increased in the short sleepers, which implies less fat oxidation and more carbohydrate oxidation (28). These results were explained as the increased need for glucose by the brain in the wake state and other glucose-dependent tissues, thereby converting body protein into glucose (34). Despite our similar outcomes, we think that our results were primarily caused by mild sleep fragmentation and less because of a reduction in TST. TST was reduced

### Table 2: Sleep recordings

<table>
<thead>
<tr>
<th></th>
<th>Nonfragmented sleep</th>
<th>Fragmented sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 (min)</td>
<td>10.5 ± 0.9</td>
<td>4.0 ± 0.4*</td>
</tr>
<tr>
<td>S2 (min)</td>
<td>247.3 ± 7.7</td>
<td>214.0 ± 7.0*</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>106.8 ± 7.3</td>
<td>88.3 ± 5.8*</td>
</tr>
<tr>
<td>REM (min)</td>
<td>111.9 ± 5.4</td>
<td>88.9 ± 4.4*</td>
</tr>
<tr>
<td>TST (min)</td>
<td>476.5 ± 5.9</td>
<td>395.3 ± 10.3*</td>
</tr>
<tr>
<td>Wake (min)</td>
<td>3.5 ± 8.3</td>
<td>84.7 ± 9.2*</td>
</tr>
</tbody>
</table>

* All values are means ± SEs. REM, rapid eye movement sleep; S1, sleep stage 1; S2, sleep stage 2; SWS, slow-wave sleep; TST, total sleeping time; wake, time awake. ANOVA repeated-measures was performed ($n = 15$). *Significantly different from nonfragmented nights, $P < 0.001$.

### Table 3: Outcome variables: energy expenditure, substrate oxidation, physical activity, and sleeping questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Nonfragmented sleep</th>
<th>Fragmented sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE (MJ/d)</td>
<td>9.83 ± 0.13</td>
<td>9.96 ± 0.17</td>
</tr>
<tr>
<td>RMR (MJ/d)</td>
<td>8.41 ± 0.05</td>
<td>8.33 ± 0.08</td>
</tr>
<tr>
<td>SMR (MJ/d)</td>
<td>7.49 ± 0.10</td>
<td>7.35 ± 0.10</td>
</tr>
<tr>
<td>AEE (MJ/d)</td>
<td>1.42 ± 0.13</td>
<td>1.63 ± 0.15*</td>
</tr>
<tr>
<td>CHOox (g/d)</td>
<td>323.7 ± 22.5</td>
<td>346.3 ± 23.8*</td>
</tr>
<tr>
<td>FATox (g/d)</td>
<td>61.0 ± 6.6</td>
<td>29.1 ± 9.1**</td>
</tr>
<tr>
<td>RQ</td>
<td>0.91 ± 0.03</td>
<td>0.94 ± 0.04*</td>
</tr>
<tr>
<td>VB (MJ/d)</td>
<td>0.42 ± 0.13</td>
<td>0.41 ± 0.14</td>
</tr>
<tr>
<td>PA (radar counts)</td>
<td>2204 ± 124</td>
<td>2371 ± 118*</td>
</tr>
<tr>
<td>VAS (mm)</td>
<td>21.8 ± 2.4</td>
<td>40.1 ± 3.8*</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>33.9 ± 4.6</td>
<td>47.4 ± 4.2*</td>
</tr>
</tbody>
</table>

* All values are means ± SEs. AEE, activity-induced energy expenditure; CHOox, carbohydrate oxidation; EB, energy balance; FATox, fat oxidation; PA, physical activity; RMR, resting metabolic rate; RQ, respiratory quotient; SMR, sleeping metabolic rate as part of RMR; TST, total energy expenditure; VAS, visual analog scale. ANOVA repeated-measures was performed ($n = 15$). **Significantly different from nonfragmented nights: $*P < 0.05$, $**P < 0.01$, $*P < 0.001$. 

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by 1.0–1.5 h in our study, which is a minor reduction compared with the 3–4-h reduction in previous studies (14, 28). Despite the smaller reduction of TST, the mild sleep fragmentation caused a larger reduction in REM and SWS compared with the sleep restriction studies in which SWS often is preserved (14, 28). Mild sleep fragmentation mainly appears to affect REM sleep and SWS in comparison with reduced TST, which mostly affects REM.

Fontvieille et al (33) reported a reduced RQ during the REM stage and an inverse correlation between REM-sleep duration and fat mass. Therefore, it is suggested that during REM-sleep fat oxidation takes place. Accordingly, when REM sleep was reduced, we observed reduced fat oxidation and increased carbohydrate oxidation. This may underscore diminished insulin sensitivity, which we observed in the same subjects during a 24-h test in which insulin concentrations appeared to be elevated without affecting glucose concentrations after a disturbed night (HKJ Gonnissen, R Hursel, F Rutters, EAP Martens, MS Westerterp-Plantenga, unpublished observations, 2010). Our findings again confirmed earlier observations (6, 7, 10, 14, 35). This shift in substrate oxidation, which implied increased carbohydrate oxidation, may also underscore previously reported increases in food intake by snack consumption (16, 18). Bosy-Westphal et al (36) also showed an increase in carbohydrate oxidation, though they did not find a reduction in insulin sensitivity nor did they observe an effect of 4 nights of consecutive increasing sleep curtailment on TEE. Contrary to our observations, however, Katayose et al (37) observed that REM sleep was associated with increased energy expenditure, RQ, and carbohydrate oxidation and decreased fat oxidation. In a different study, with total sleep deprivation compared with normal sleep duration, Benedict et al (38) examined the effects on RMR and postprandial energy expenditure during the following day, with a ventilated hood system. They reported that fasting and postprandial energy expenditure decreased by 5% and 20%, respectively, after total sleep deprivation. The main difference in our study was that our study was conducted in a respiratory chamber in which subjects could move more freely and Benedict et al (38) performed measurements with a ventilated hood system in which subjects had to lie calmly on a bed. It appears that different outcomes were observed depending on the design of the study and on the accuracy of the measurement methods. In our study, we aimed to approach daily life circumstances under controlled conditions. In daily life, sleep fragmentation often occurs, and this may have a small but cumulative effect on energy balance. We showed that after 2 fragmented nights, metabolic targets for a positive energy balance were affected.

Physical inactivity also may play a role in the etiology of obesity. Speculations about a decrease in physical activity after fragmented sleep were confirmed by Schmid et al (39) who reported that short-term sleep loss decreased physical activity under free-living conditions. Because of our study design, we showed an initial increase in physical activity and AEE as an effect of sleep fragmentation, mainly because the subjects had to turn off their alarm clock 7 times during the night. However, the resulting increased exhaustion and sleepiness during the subsequent day might eventually counterbalance physical activity and AEE. Furthermore, the increased activity that we showed corresponds with the increased carbohydrate oxidation, thus depleting glycogen storage.

A possible limitation of the present study was the mild sleep disturbance, in comparison with the studies that used 4-h sleep deprivation. At the same time, our study shows that even after mild sleep disturbance, which often occurs naturally in today’s society with our modern lifestyle, there was a shift in substrate oxidation. Further limitations might be that the acute effects from this study cannot be extrapolated to chronic effects because adaptations might occur. Therefore, more research over the long term is necessary to establish the initial observations. In that respect, our observations correspond very well to those made over the long term by Nedeltcheva et al (28). Also, the effect of sleep fragmentation needs to be studied in women because the present study was conducted in men only. Finally, our results may only partly resemble real life, because the space for physical activity in the respiration chamber is limited, and because we did not allow our subjects to sleep during the day.

In conclusion, sleep fragmentation while staying in a respiration chamber for 48 h induced reductions in the most important sleep phases, coinciding with elevated AEE, physical activity, exhaustion, sleepiness, RQ, and carbohydrate oxidation and reduced fat oxidation, which may predispose to overweight.

The authors’ responsibilities were as follows—RH, FR, HKJG and MSW-P: designed the study; RH, FR, HKJG, and EAPM: collected and analyzed the data; RH: wrote the manuscript; and MS-W-P: contributed to the interpretation of the data and reviewed the manuscript. The study was executed under the supervision of MSW-P. None of the authors had a personal or financial conflict of interest.

REFERENCES


35. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. J Clin Endocrinol Metab 2009;94:3242–50.


