Effects of late-night short-sleep on in-home polysomnography: relation to adult age and sex

TORBJÖRN ÅKERSTEDT 1,2, MATS LEKANDER 1,2, GUSTAV NILSONNE 1,2, SANDRA TAMM 1, PAOLO D’ONOFRIO 1,2, GÖRAN KECKLUND 2, HÅKAN FISCHER 3 and JOHANNA SCHWARZ 1,2
1Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden; 2Stress Research Institute, Stockholm University, Stockholm, Sweden; 3Department of Psychology, Stockholm University, Stockholm, Sweden

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Correspondence
Torbjörn Åkerstedt, Department of Clinical Neuroscience, Karolinska Institute, 17177 Stockholm, Sweden. Tel.: +46855378947; fax: +46855378900; e-mail: torbjorn.akerstedt@ki.se

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SUMMARY
Bedtime is frequently delayed by many factors in life, and a homeostatic response to the delay may compensate partly for increased time awake and shortened sleep. Because sleep becomes shorter with age and women complain of disturbed sleep more often than men, age and sex differences in the homeostatic response to a delayed bedtime may modify the homeostatic response. The purpose of the present study was to investigate the effect of late-night short-sleep (3 h with awakening at about 07:00 hours) on in-home recorded sleep in men and women in two age groups (20–30 and 65–75 years). Results (N = 59) showed that late-night short-sleep was associated with an increase in percentage of N3 sleep and a decrease in percentage of rapid eye movement sleep, as well as decreases in several measures of sleep discontinuity and rapid eye movement density. Men showed a smaller decrease in percentage of rapid eye movement sleep than women in response to late-night short-sleep, as did older individuals of both sexes compared with younger. Older men showed a weaker percentage of N3 sleep in response to late-night short-sleep than younger men. In general, men showed a greater percentage of rapid eye movement sleep and a lower percentage of N3 sleep than women, and older individuals showed a lower percentage of N3 sleep than younger. In particular, older men showed very low levels of percentage of N3 sleep. We conclude that older males show less of a homeostatic response to late-night short-sleep. This may be an indication of impaired capacity for recovery in older men. Future studies should investigate if this pattern can be linked to gender-associated differences in morbidity and mortality.

INTRODUCTION
Sudden demands in life can force us to delay our normal bedtime and to reduce our sleep duration. This will have immediate effects on fatigue/alertness, seen, for example, in increased physiological and self-reported sleepiness (Åkerstedt and Gillberg, 1986; Härmä et al., 1998). A delayed bedtime will also affect the polysomnography (PSG) of late-night sleep. A delayed bedtime (to 03:00 hours or 05:00 hours), with a time of rising about 07:00 hours, also leads to a homeostatic response in terms of increased N3% and reduction of N1% and N2% (Åkerstedt and Gillberg, 1986; Härmä et al., 1998). The percentage of rapid eye movement (REM) sleep does not seem affected, nor does sleep efficiency. Because N3 is linked to daytime alertness and functioning (Dijk et al., 2010), it is likely that the homeostatic N3 response is important for maintaining next-day alertness. REM density (REMs per minute of REM sleep) in full-sleep is suppressed by sleep deprivation (Marzano et al., 2011), but nothing is known about the effect of late-night short-sleep (LSS).

One possible modifier of the response to LSS may be age, because older individuals have shorter total sleep time (TST), less sleep stage N3, less REM, and more stage N1 during full-night sleep than young individuals (Bixler et al., 2009; Moraes et al., 2014; Ohayon et al., 2004). Older individuals
also show a somewhat lower N3 response to total sleep deprivation than younger ones (Cajochen et al., 1999; Lafortune et al., 2012; Rosinvil et al., 2015). Delta power density decreases with age, while REM density is unaffected (Schwarz et al., 2017). None of the variables above has been studied in relation to LSS.

In addition, women usually report more sleep problems than men (Groeger et al., 2004), but also show longer TST, less N2%, more N3%, longer REM latency and a lower apnea–hypopnea index than men (Ohayon et al., 2004). Similar results have been presented by Bixler et al. (2009) for N1% (lower in women) and N3% (higher in women). No differences were observed regarding REM%, however, although women had a longer REM latency across all ages. In addition, women show higher levels of delta power density (0.5–4 Hz; Dijk et al., 1989). Reynolds et al. (1986) showed a larger N3 response in women to ‘total’ sleep deprivation. Likewise, Armitage et al. (2001) showed a stronger increase in slow-wave activity [spectral power in the delta (0.5–4 Hz) band] in response to 40 h of wakefulness in young females. The observations above suggest that older males could show reduced N3 and other homeostatic responses to LSS and perhaps increased sleepiness.

The purpose of the present study was to investigate the effect on 1 night of LSS in two age groups (20–30 and 65–75 years), and both sexes. The duration of LSS sleep was set to 3 h, while full-sleep was expected to last for 7–8 h. The outcome variables of main interest were stages N3 and REM, particularly as a percentage of TST. In addition, also other PSG measures, traditional PSG variables were studied, as well as REM density, and sleepiness. This study was part of The Stockholm Sleepy Brain Study, focusing on the neural and behavioural consequences of sleep restriction. The present study presents results of the sleep manipulation preceding functional magnetic resonance imaging (fMRI) recording. Some of the fMRI results can be found in Nilsonne et al. (2017) and Tamm et al. (in revision), and the data set is described in detail in Nilsonne et al. (2016).

MATERIALS AND METHODS

Design and participants

The study used a randomized, balanced, cross-over, experimental design, in which healthy young and older volunteers with a similar sex distribution underwent sleep recording on two separate occasions, approximately 1 month apart, after either 1 night of normal sleep or 1 night of sleep restriction (to 3 h; Fig. 1). Groups A and B had the two conditions in a different order. MR data were collected in the evening after the sleep manipulation. The protocol was approved by the regional ethical committee of Stockholm (2012/1870-32). The project was preregistered at: clinicaltrials.gov https://clinicaltrials.gov/ct2/show/NCT02000076).

Participants were recruited through the website www.studentkaninen.se, by posters at university campuses, and by a newspaper advertisement, and were invited to fill in an online screening form (Nilsonne et al., 2016). Participants were included if they fulfilled the following criteria: age 20–30 or 65–75 years; right-handed; habitual bedtime between 22:00 hours and 01:00 hours on weekdays; adequate visual acuity (or milder hyperopia/myopia < 5 diopters); fluent in Swedish; and living in the Stockholm area. Participants were excluded if any of the following criteria applied: current or past psychiatric or neurological morbidity; regular use of nicotine; studying or working in medicine, psychology, health care; consumption of ≥4 cups of coffee (or a corresponding amount of caffeine) per day; diabetes, hypertension; use of any psychoactive drugs; or past heart surgery. Because the study also involved sessions with fMRI (not reported here), having magnetic implants, self-reported claustrophobia or being colour-blind were grounds for exclusion. An Insomnia Severity Index score ≥ 15 (Bastien et al., 2001) or Hospital Anxiety and Depression Scale (HADS) score ≥ 8 (Zigmond and Snaith, 1983) were also grounds for exclusion. Participants were excluded if reporting snoring or sleep apnea symptoms more than three times a week, or showing decreased oxygen levels of at least 3% more than 5 times per h. All participants gave written informed consent, and were compensated with 2500 SEK (approximately 300 USD). Eight participants were excluded for not meeting inclusion criteria or because of incidental MRI findings, and 70 individuals were successfully recorded. However, 11 individuals were excluded from the analyses because their full-sleep was <6 h, or their restricted sleep was >3.8 h. This left 59 participants: 14 young females, 15 old females, 15 young males and 15 old males.

With respect to background data (Table S1), there were no differences between age groups or gender in a 2 × 2 ANOVA for body mass index (BMI), Epworth Sleepiness Scale, subjective HADS. The older group had lower sleep complaints than the younger group.

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Procedure
Participants were instructed to fill in sleep diaries from 3 nights before the experiment until the night after, and to avoid coffee and alcohol on the experimental day. For the habituation night and the nights before the MR recordings, participants were visited in their homes by a researcher who applied the PSG equipment and gave instructions. The equipment was retrieved in the morning. After awakening, and until reporting to the MR laboratory, the participants were free to spend their time as they preferred, except for sleeping, strenuous activity, caffeine-containing beverages, medication, and alcohol. Sleepiness ratings were recorded nine times during the session in the scanner, before, and between, the different experiments and during a time span of 70–80 min in the evening between 17:00 hours and 22:00 hours. The present report uses the mean of ratings 2–8.

Participants were informed in the evening before the experiment as to what order they were randomized, and instructed to avoid behavioural compensatory changes (naps, etc.). Participants were instructed to sleep normally in the full-sleep condition and to go to bed 3 h before their usual wake-up time in the LSS condition. Independent of sleep condition, they were asked to wake up at their usual time. Participants were instructed to press an event marker on the recorder at lights out in the evening and at time of rising in the morning.

Measures
For PSG recordings, a solid state, portable sleep recorder (Embla) was used. Standard electrode (silver/silver chloride) montage for electroencephalogram (EEG) sleep recording was used (C3, C4 referenced to the contralateral mastoid). In addition, two submental electrodes were used for electromyography and one electrode at each of the outer canthi of the eyes was used for electrooculography. To adapt to American Academy of Sleep Medicine (AASM) scoring, F4 was interpolated. Sleep staging and respiratory analyses were performed according to the classification criteria of the AASM (Iber et al., 2007) and as implemented in the Siesta group automatic scoring procedure (Anderer et al., 2005, 2010). Shifts from any of the sleep stages to wake were expressed as awakenings per hour. Spectral analysis and analysis of sleep micro-architecture was performed using the procedure of the Siesta Group (Anderer et al., 2005, 2010). Briefly, offline fast Fourier transform spectral analysis was conducted in 0.25-Hz bins. Artefact-free 4-s epochs were averaged across 30 s. Then, 0.25-Hz bins were collapsed (added up) for the delta range (0.5–4 Hz) and divided by the total power (0.5–40 Hz) to obtain relative delta power. Last, average relative delta power was calculated for non-rapid eye movement (NREM) (N1–N3). REM density was defined as time with REMs/time in stage REM (see Supporting Information for further sleep variables).

Participants rated their sleepiness using the Karolinska Sleepiness Scale (KSS; Akerstedt et al., 2014; Åkerstedt and Gillberg, 1990). This scale ranges from 1 (=very alert) to 9 (=very sleepy, fighting sleep, an effort to keep awake), and is sensitive to a variety of manipulations of sleep (Akerstedt et al., 2014).

Statistics
Data were analysed using a three-factor ANOVA with LSS, age and sex as factors, and with adjustment for BMI. The significance level was set to \( P < 0.05 \), and significant results will be summarized in the text.

RESULTS
Results are shown in Tables 1–3 and Fig. 2. Lights out for the LSS sleep showed a delay for both age groups, while lights on was slightly advanced. TST showed a significant decrease from full-sleep to LSS. Older individuals had a significantly earlier timing and a shorter duration of sleep. N3% showed an interaction for condition \( \times \) age, with a weaker response to LSS in the older group. There was also an interaction sex \( \times \) age, that is, older males had a particularly low N3% compared with older females. In addition, there was an increase of N3% in the LSS condition, with stronger increases for females and for the young. Due to the weak response to LSS among the older males, we carried out a separate post hoc analysis for each sex. This showed a strong interaction between condition and age in males \((F = 18.0, P < 0.001, df = 1, 26)\), indicating that older male showed a considerably weaker response in N3% to LSS than younger males. The corresponding analysis for females was not significant \((F = 2.6, P = 0.12, df = 1, 25)\). Means \pm SE plotted in Fig. 1 are also presented in Table S4. The means \pm SE of variables with non-significant interactions are presented in Table 3.

The partial eta-squared values were large, particularly for the effect of condition for many variables. This includes TST, lights out, KSS, N3%, lights on, delta power density and REM density. Also the effect of age had high values for N3%, sleep efficiency and N1%.

Considering the weak response of N3% to LSS in the older group, it is likely that the 75 Hz amplitude criterion of N3 diverted some sub-criterion increase in delta activity to N2. To test this possibility, a separate ANOVA was carried out for relative delta power during N2. The results did not show an effect of condition \((F = 2.0, P = 0.17, df = 1, 25)\), but a condition \( \times \) age interaction \((F = 15.9, P < 0.001)\). The mean values for the old were 61.8 \pm 1.0% versus 64.3 \pm 1.2% (full-sleep versus LSS) and 68.4 \pm 0.9% versus 67.2 \pm 1.2% for the young. Thus, the older group showed an increase and the younger group a decrease of relative delta power density in N2.

The percentage of REM sleep showed a significant interaction between condition and sex, indicating that females had...
a stronger reduction in REM% than males. There was also a
significant reduction in the LSS condition, but less so in males.
N1% showed an interaction condition × sex, that is, a
stronger reduction in LSS in males than females. In addition,
there was a reduction in LSS, and higher levels in the older
group. N2% showed an interaction between condition and
sex, indicating a stronger decrease in females. It also
decreased in LSS, and was higher in the older group.
Sleep latency decreased in the LSS condition as did N3
latency, and the latter was shorter in the young. REM
latency decreased, and was significantly shorter in the
older group. Sleep efficiency increased in the LSS condi-
tion and was lower among the older participants. The
number of awakenings decreased in LSS and was higher
in the older group. Delta power density (% of total
spectrum) in NREM sleep increased, and was lower in
the older group. REM density decreased, was lower in the
older group, and decreased more in the older group.
Sleepiness (KSS) was increased in LSS and higher in the
younger group.

Table 1 Results from three-factor ANOVA of sleep variables

| Condition   | Sex F-ratio | Age F-ratio | CS F-ratio | CA F-ratio | SA F-ratio | SCA F-ratio |
|-------------|-------------|-------------|------------|------------|------------|-------------|
| Lights out  | 567***      | 1.4         | 9.7**      | 0.2        | 1.6        | 0.3         | 0.7         |
| Lights on   | 23.1***     | 0.9         | 6.3*       | 0.8        | 0.2        | 0.0         | 0.3         |
| TST         | 624***      | 0.2         | 6.7*       | 0.2        | 2.0        | 0.4         | 0.4         |
| N1%         | 20.5***     | 2.8         | 23.5***    | 11.5***    | 1.6        | 1.1         | 1.4         |
| N2%         | 13.2**      | 4.6*        | 14.6***    | 2.3        | 4.1*       | 2.2         | 1.5         |
| N3%         | 92.0***     | 4.4*        | 65.9***    | 1.9        | 14.1***    | 10.4**      | 2.9         |
| REM%        | 18.9***     | 10.1**      | 1.4        | 17.4***    | 1.7        | 2.2         | 2.5         |
| Delta pow den% | 21.8***   | 0.1         | 41.6***    | 0.2        | 1.5        | 0.6         | 0.0         |
| REM dens    | 52.0***     | 1.1         | 6.2*       | 1.1        | 6.2*       | 0.2         | 0.2         |
| Awakenings per h | 11.1**     | 0.5         | 16.7***    | 1.0        | 0.1        | 0.1         | 0.0         |
| Sleep efficiency | 5.1*     | 0.2         | 20.3***    | 0.0        | 1.0        | 1.6         | 0.1         |
| Sleep latency | 5.6*      | 2.6         | 1.0        | 2.9        | 0.6        | 0.2         | 1.4         |
| REM latency | 10.8**      | 2.2         | 6.2*       | 1.0        | 0.0        | 1.6         | 1.0         |
| N3 latency  | 5.8*        | 0.6         | 14.4***    | 1.3        | 1.6        | 1.5         | 1.1         |
| KSS (1–9)   | 70.7***     | 0.6         | 15.4***    | 1.1        | 1.4        | 0.2         | 0.0         |

N = 59, df = 1/51. Adjusted for BMI.
CA, interaction condition by age; CS, interaction condition by sex; delta pow dens, delta power density; KSS, Karolinska Sleepiness Scale; REM, rapid eye movement; REM dens, REM density; SA, interaction sex by age; SCA, interaction sex by condition by age; TST, total sleep time.
*P < 0.05; **P < 0.01; ***P < 0.001.

Table 2 Partial eta for variables with significant F-ratios in Table 1

| Condition   | Sex F-ratio | Age F-ratio | CS F-ratio | CA F-ratio | SA F-ratio | SCA F-ratio |
|-------------|-------------|-------------|------------|------------|------------|-------------|
| Lights out  | 0.83        | 0.10        |            |            |            |             |
| Lights on   | 0.39        | 0.07        |            |            |            |             |
| TST         | 0.90        | 0.14        |            |            |            |             |
| N1%         | 0.15        | 0.31        | 0.08       |            |            |             |
| N2%         | 0.15        | 0.05        | 0.16       |            |            | 0.05        |
| N3%         | 0.59        | 0.15        | 0.55       |            |            | 0.17        | 0.20        |
| REM%        | 0.27        | 0.10        |            | 0.12       |            |             |
| Delta pow den% | 0.30        | 0.55        |            |            |            |             |
| REM dens    | 0.30        | 0.07        |            |            |            |             |
| Awakenings per h | 0.11       | 0.24        |            |            |            |             |
| Sleep efficiency | 0.07       | 0.33        |            |            |            |             |
| Sleep latency | 0.06        |            |            |            |            |             |
| REM latency | 0.20        | 0.13        |            |            |            |             |
| N3 latency  | 0.10        | 0.26        |            |            |            |             |
| KSS (1–9)   | 0.62        | 0.17        |            |            |            |             |

CA, interaction condition by age; CS, interaction condition by sex; delta pow dens, delta power density; KSS, Karolinska Sleepiness Scale; REM, rapid eye movement; REM dens, REM density; SA, interaction sex by age; SCA, interaction sex by condition by age; TST, total sleep time.
DISCUSSION

The age by condition finding

The age by condition interaction was a main focus of the study and was significant for N3%. The lower N3% increase in the older group in response to LSS agrees with what could be expected based on previous work on full-sleep after total sleep loss (Cajochen et al., 1999; Lafortune et al., 2012; Rosinivil et al., 2015). In addition, the reduction in N2% was lower in the older group, which seems logical because of the modest increase in N3% in that group; the two sleep stages normally interact because N3 is scored when the EEG amplitude exceeds criterion (75 μV) and N2 when it falls below the criterion. However, there was no interaction between age and condition for N1%. The significant interaction age × condition for relative delta power density in N2 was caused by an increase in the older group and a decrease in the younger group. Thus, there was a homeostatic response in the older group, but apparently not enough to fulfill the criteria for classification into N3. Apparently, some of the homeostatic response in the older group ended up as an increase in N2 instead of N3. It is not clear, however, if this response has any functional implications for recovery from sleep loss. The amplitude criterion for N3 scoring is also a reasonable explanation for the lack of interaction between age and condition, as well as age and sex, for delta power density. It should be emphasized that delta power was expressed as a percentage of total EEG power, while N3 used an absolute criterion of amplitude. It is an interesting question whether N3 or relative delta power best reflects sleep homeostasis.

With regard to REM%, age groups did not show different responses to LSS, nor with regard to REM latency, which is contrary to earlier findings suggesting that circadian promotion of REM sleep is diminished in older adults (Munch et al., 2005).

With respect to the main effect of age, the lower/shorter: TST, sleep continuity, N3%, N3 latency and higher N1%, agrees with other work (Bixler et al., 2009; Moraes et al., 2014; Ohayon et al., 2004), and supports the impression of objectively worse sleep in older individuals. The lower sleepiness in older individuals agrees with previous work (Dijk et al., 2010; Groeger et al., 2004), but constitutes an unexplained paradox. In addition, the lower N3% level in older individuals in the present study is at odds with their lower sleepiness level, but agrees with observations of Dijk et al. (2010). At present, there is no explanation of this paradox, other than a hypothesized reduction in the need for sleep with aging, or as a weakened sleep drive and a disinhibition of the wake drive with higher age (Putilov and Donskaya, 2016). Mander et al. (2017) has suggested that the reduction of the number of adenosine2 receptors with increasing age would reduce the capacity of the hypothalamus to monitor the need for sleep that adenosine2 is thought to reflect. Thus, the need for sleep would go undetected and unreported.

The sex by condition finding

The second main finding was the sex by condition interaction, significant for REM% and N1%, such that REM% was more reduced in LSS among females and N1% was more reduced in males. The stronger reduction in REM% in females during LSS is a new finding. In general, one would expect a decrease in REM% after sleep loss because of an increase in N3%, but this occurred in females only. The weak male REM reduction in LSS suggests a lower drive for N3 after sleep.
loss, as discussed above, but there was no significant interaction between condition and sex for N3%. There is also a possibility that the lower level of overall N3 in males in this and other studies may be part of the explanation (Bixler et al., 2009; Ohayon et al., 2004). Interestingly, the lower N3% in males and the weaker N3% response to LSS was not reflected in higher sleepiness, which could have been expected, considering the increase in sleepiness after N3 reduction seen in other studies (Dijk et al., 2010). A positive aspect of the male response to LSS was the stronger decrease in N1% during LSS. From a rather high level during full-sleep, the level during LSS fell to levels close to that of women.

The lower overall REM% in females was unexpected, but seems to be an effect of the reduced REM during LSS. For normal sleep duration females do not seem to have lower

Figure 2. Means ± SE for key variables during full-sleep and late-night short-sleep (LSS) in males and females.

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The lower REM density in females suggests a lower REM propensity, in line with their lower REM%. The implication of this finding is not clear and there is no prior work to compare with.

The interaction between age and sex

The condition by gender interaction was not significant for N3%, but when males were analysed separately the older group showed a significantly weaker N3% response to LSS. In women, the corresponding response was strong in both age groups. Thus, the data suggest that older males have a weak N3 response to sleep loss. The present study does not permit a conclusion on whether it is caused by a lack of homeostatic drive after sleep loss, or a stronger circadian promotion of REM sleep at the time of the circadian nadir (Czeisler et al., 1980). The lack of REM reduction in males, together with the lack of N3 increase during LSS, is rather striking, and needs further investigation. In addition, the age/sex interaction was significant for N3%, with a lower N3 in the older males. REM% was higher in older males. The expected (Bixler et al., 2009; Ohayon et al., 2004) higher overall N3% in women adds to the impression of a stronger homeostatic drive in females and is also reflected in the shorter N3 latency.

It is an interesting question whether the weaker N3% response to LSS in older males, and the lower overall levels of N3%, should be interpreted as indications that sleep quality is impaired in males, and particularly in older males. There is some evidence that suppression of N3 leads to increased sleepiness as measured by the multiple sleep latency test or KSS ratings (Dijk et al., 2010). However, KSS values did not show any relation to gender.

The findings of an impaired homeostatic drive in older males also raise the question of a link between short-sleep and increased morbidity and mortality in males. This issue does not seem to have been addressed before. Given that sleep length and sleep quality are related to mortality, there is clearly a need for research into the association between sleep recorded with PSG and mortality/morbidity.

The effect of the experimental manipulation

As expected, the delay of sleep time resulted in deeper and more continuous sleep (Cajochen et al., 1999; Lafortune et al., 2012; Rosinvil et al., 2015). The shortened REM latency is in line with the circadian promotion of REM during late night (Czeisler et al., 1980). However, REM% was reduced, which probably indicates that the homeostatic drive for N3 was stronger and interfered with REM sleep. The reduced REM density, which has never been studied before with the delayed sleep design, is a new observation, and probably reflects a prioritization of N3 over REM. With respect to ratings, the amount of increased sleepiness was expected from previous studies of sleep loss (Akerstedt et al., 2014).

Limitations

The present study is limited by the relatively modest N in the sub-groups, and the large variable space. While observed effects were strong in many cases, the relatively low N increases risks of false negative as well as false positive findings. The present study also lacked markers for circadian phase, which makes conclusions on effects of circadian phase difficult. The sample excluded subjects with major disease, drug intake, insomnia and sleep apnea, rendering a ‘healthy participant effect’ likely, which is most relevant for the age comparisons. There is a need for studying samples of older individuals more representative of the general population.

CONCLUSIONS

The present results showed a particularly weak response of N3% to LSS in older males, implying an impaired capacity for recovery. The relevance of the latter for morbidity and mortality should be a topic for future studies.

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AUTHOR CONTRIBUTIONS

T. Á. initiated the study. G. N. and S. T. coordinated the study. P. d’O. carried out the PSG recordings. All authors participated in the design of the study and commented on the manuscript.

CONFLICT OF INTEREST

T. Á. reports being on the scientific advisory board of CurAegis. None of the other authors report any conflict of interests.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article:

**Table S1.** Background data. Results from two-factor ANOVA with age and sex as factors. F-ratios and p-values.

**Table S2.** Results (F-ratios and p-values) from three-factor ANOVA of additional sleep variables.

**Table S3.** Mean ± SD for both experimental conditions, corresponding to ANOVA results in Table S2.

**Table S4.** Means ± SE for age and sex groups, corresponding to ANOVA results in Table 1 and Fig. 2.