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**Depner CM, Melanson EL, Eckel RH, Snell-Bergeon JK, Perreault L, Bergman BC, Higgins JA, Guerin MK, Stothard ER, Morton SJ, Wright KP Jr. Ad libitum Weekend Recovery Sleep Fails to Prevent Metabolic Dysregulation during a Repeating Pattern of Insufficient Sleep and Weekend Recovery Sleep. Curr Biol. 2019 Mar 18;29(6):957-967.e4.**

## What We Know, Think We Know, or Are Starting to Know

In a recent Research Lecture, we covered the influence of sleep loss on dietary choices, energy intake and body composition. Of the various environmental exposures that influence dietary habits, sleep loss may rank among those with the strongest effect, negatively impacting objective measures of energy balance regulation, and increasing subjective appetite and compensatory energy intake [1,2].

The question over whether we do in fact sleep less in modern societies remains an open one, and the data is ambiguous [3]. Nevertheless, recent developments in the field of chronobiology have demonstrated that other metrics of sleep behaviour may be associated with increased risk [4,5].

For example, "social jetlag" describes the differences between sleep timing on work days, with enforced wake times, and sleep timing on free days, creating a discordance between internal biological timing and social timing that can lead to a chronic form of jetlag [5]. A characteristic of social jetlag is that sleep is typically curtailed during the working week, and people may seek to compensate on free days [i.e., weekends] by oversleeping [5].

Could there be an increase in metabolic risk from such a behavioural pattern of sleep timing and duration? Eckel *et al.* [6] examined the effects of sleep curtailment for five consecutive nights with 5hr/night sleep durations, preceded and succeeded by five days of 9hr/night sleep durations, respectively, showing impaired glucose tolerance and insulin sensitivity from sleep restriction [6].

Can "recovery sleep" mitigate the effects of sleep restriction? The present study tested this question.

## The Study

The study used an in-patient laboratory design to test the effects of sleep restriction and simulated weekend recovery sleep on sleep measures, energy intake, and insulin sensitivity. Prior to admission to the laboratory, participants were required to adhere to a 7-day baseline run-in maintaining ~9hr/night sleep, according to their habitual sleep-wake timing. Adherence to this pre-lab run-in period was confirmed by actigraphy* [see ***Geek Box** below for further details].

For the final 3-days before admission to the lab, participants were required to omit all caffeine, alcohol, and exercise, and were provided with their diets by study nutritionists, designed to maintain weight and with a macronutrient composition of 30% fat, 55% carbohydrate, and 15% protein. This remained the macronutrient prescription of participant's diets once in the lab. Total energy intake was distributed equally between main meals [30% energy at breakfast, lunch, and dinner, with a 10% energy snack].

The total duration of the in-patient laboratory study was 13 days. Days 1-3 served as an extension of the pre-lab run-in to established baseline sleep and melatonin measures, and to maintain diet. Days 4-13 included sleep manipulation, for which participants were randomised to one of three groups:

- **Control [CON]**: 8 participants who maintained 9hr/night sleep.
- **Sleep Restriction [SR]**: 14 participants on 5hr/night sleep from day 4–13.
- **Weekend Sleep Recovery [WR]**: 14 participants on 5hr/night sleep from day 4–7, followed by a self-selected wake time on day 8 and two nights [days 9/10] of *ad libitum* recovery sleep.

To assess energy intake, diets were presented to participants with the same macronutrient prescription as baseline, however, 33% more energy was presented with each meal; participants were free to consume as much as desired. Snacks were available to participants throughout all waking periods.

The stated outcomes of the study included sleep duration during *ad libitum* recovery sleep; melatonin timing; total daily energy intake, energy intake after dinner, body weight, and insulin sensitivity. The study also explored potential sex differences in the outcomes.

## *Geek Box: Measuring Sleep

*Other than questionnaires for subjective sleepiness, two primary methods are used in research to assess sleep: actigraphy and polysomnography [PSG].*

*Actigraphy devices are worn like wrist watches and provide an indirect assessment of sleep that is calculated through scoring systems which estimate sleep and wake time, and therefore additional parameters, largely from movement. Actigraphy devices estimate sleep as immobility, which may bias the actual results. However, the use of actigraphy has primarily been validated to estimate sleep in free-living, naturalistic environments, and is best deployed for field studies.*

*Conversely, PSG is the current gold standard for objective measures of sleep, but the complex nature of the technology confines the use of PSG to laboratory studies. Several studies directly comparing PSG to actigraphy have found good correlation between sleep efficiency [% of total sleep time spent asleep], sleep latency [time to fall asleep], actual wake and sleep time.*

*However, an issue which may arise in relation to the use of actigraphy is an overestimation of sleep time, and underestimation of wake time. This measurement error may be derived from the fact that actigraphy estimates the onset of sleep as immobility, and because the device is worn on the wrist, depending on an individual's sleep habits it may look like there is less, or more, movement during the night.*

*Actigraphy is an important method, limitations aside, as it allows for field studies to be conducted with useful data on activity levels during the day, night, and can also quantify light exposure. This can be helpful as a condition of entry to a laboratory study, to ensure that participants complied with any recommended sleep-wake timing and light-dark exposures. In a laboratory study, however, if objective measures of sleep quality are desired, then PSG is the current gold standard.*

**Results:** 36 participants [18 female/18 male] with a mean age of 25yrs and BMI of 22.4kg/$m^2$ completed the in-patient laboratory study.

***Sleep Loss and Sleep Duration*:** Sleep duration during baseline (days 1–3) was similar at ~8hr/night in each group. During sleep recovery (days 8–9), participants in the WR group slept 10hrs and 9.2hrs, respectively.

However, on the final day of sleep recovery (day 10) participants self-selected to stay up later [despite knowing wake time on the following day was scheduled for early], leaving a total of 6.1hrs sleep duration.

Thus, simulated weekend sleep recovery did not compensate for the sleep loss induced during the 5hr/night condition.

***Melatonin Timing*:** In the WR group, self-selected waketimes during recovery sleep were 3.9hr and 3.5hr later on each respective day of simulated weekend recovery sleep. In the WR group, melatonin timing was delayed by 1.7hrs after simulated weekend sleep recovery [more under ***Interesting Finding***, below]. In the SR group, melatonin timing was delayed by ~25mins by the end of the 5hr/night sleep condition. As expected, melatonin timing in the CON group was similar across all study days.

***Energy Intake, Hunger, and Bodyweight***: In the SR and WR groups, total daily energy intake compared to baseline was 480–1,130kcal higher, while in the CON group total daily energy intake was ~1,100kcal higher. During simulated weekend recovery sleep, participants in the WR group consumed ~524–667kcal less compared to their periods of sleep restriction. Energy intake at specific meals did not differ between breakfast, lunch, and dinner, between groups.

However, after-dinner energy intake was ~481–507kcal higher in the SR group compared to baseline, and was ~409–641kcal higher in the WR group during sleep restriction compared to both baseline and the simulated weekend sleep recovery.

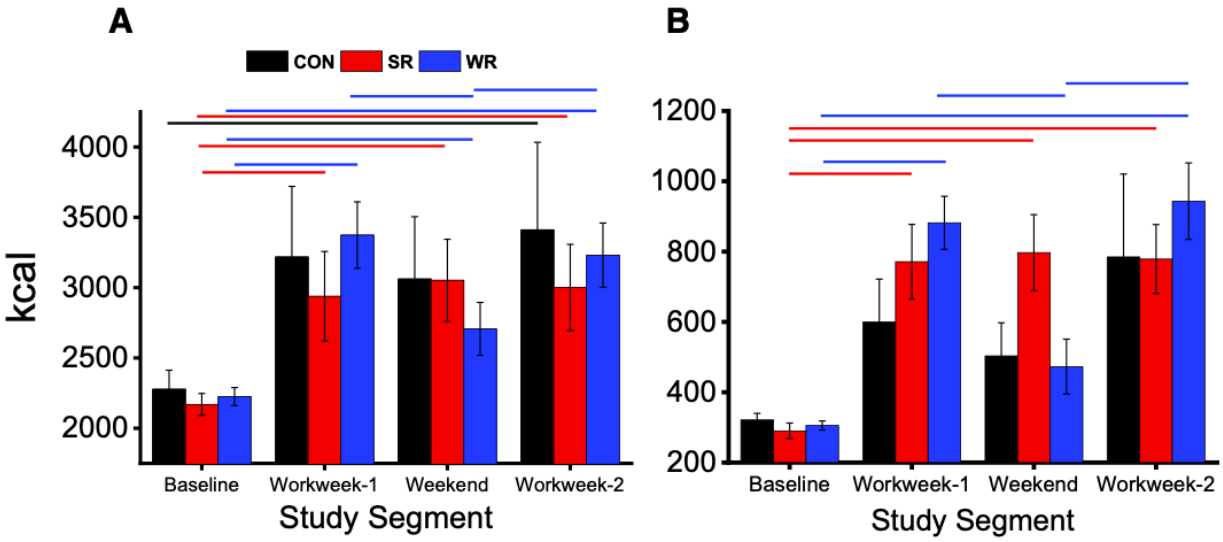



***Figure*** *from the paper illustrating total daily energy intake [**left**] and after-dinner energy intake [**right**] for each group across each distinct period of sleep restriction ["workweek 1 and 2"], and the "weekend". Recall that in the CON group, sleep-wake timing was consistent throughout the study, while the SR group, sleep remained restricted on the weekend.*

Subjective hunger decreased by ~40% in the SR group compared to baseline, and by ~34–44% in the WR group. Thus, the increase in energy intake occurred without concomitant increases in subjective hunger.

In the SR and WR groups, bodyweight increased by 1.4kg and 1.3kg, respectively, by the end of the intervention, while the CON group gained ~1kg during the study.

***Insulin Sensitivity***: Insulin sensitivity was similar in the CON group after the intervention compared to baseline. In the SR and WR groups, insulin sensitivity decreased by ~13% and ~27%, respectively, after the intervention compared to baseline. After adjusting for bodyweight change in the WR group, the effect on insulin sensitivity was no longer significant, indicating that weight gain in part explained the decrease in insulin sensitivity in this group.

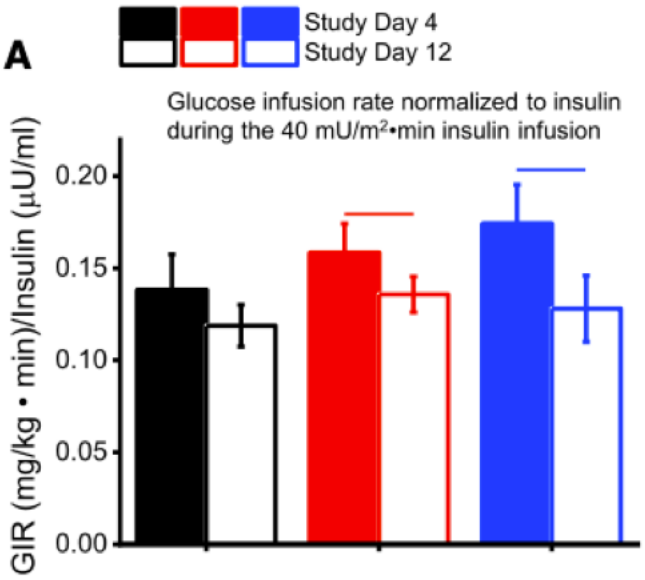



*__Figure__ from the paper illustrating the differences in insulin sensitivity, assessed as glucose infusion matching glucose uptake in tissues during, between baseline [__solid bars__] and end of intervention [__open bars__]. CON = black bars; SR = red bars; WR = blue bars.*

## The Critical Breakdown

**Pros:** The study had a very strong experimental design. The baseline run-in period would be expected to minimise any sleep-wake and circadian variation prior to entry into the laboratory. The in-patient study period allowed for rigorous control of the participant's environment, including light-dark exposure, sleep-wake timing, and dietary intake. The study also included a dedicated control group, which can be rare for in-patient lab studies such as this. Each of the CON, SR, and WR groups were matched for sex, which was equal in each group, and was achieved through a block randomisation process. This is important given evidence of sex differences in consequences of circadian misalignment on metabolism [more under ***Key Characteristic***, below]. Sleep, insulin sensitivity, and melatonin were each measured using their respective "gold standard" techniques; sleep with polysomnography, melatonin with dim-light melatonin onset [DLMO; more under ***Interesting Finding***, below], and insulin sensitivity using the hyperinsulinemic-euglycemic clamp. For an in-patient study of this level of control, and expense, the sample size was respectable.

**Cons:** The method of randomisation was not described, which is odd given the method of achieving balance for sex between groups was stated. The study just broadly listed a range of "outcome variables" with no specificity for primary and secondary outcomes. This always leaves open the possibility for selective emphasis in reporting "statistically significant" findings. Despite having the most robust assessment of circadian phase with DLMO, the study did not conduct any analysis to determine correlations between altered melatonin timing and insulin sensitivity. While the WR group was provided with some leeway to self-select for sleep and wake times, thus providing some external validity to the protocol, it should be noted that in-patient laboratory studies such as this may not necessarily reflect real life, particularly with consecutive 5hr/night sleep opportunities. Bizarrely, the authors do not discuss any strengths, but more importantly potential limitations, to their work.

## Key Characteristic

Arguably the key characteristic of this study is the deliberate approach to balancing the design between sex and conducting exploratory analysis for potential sex differences in the outcomes. We know that women are generally underrepresented in clinical research, which means that potentially important sex differences are not observed [7,8].

For the fields of sleep and chronobiology this is particularly important because sex differences in the metabolic consequences of circadian misalignment have previously been shown [9]. In the WR group in the present study, both total weekend recovery sleep duration and napping were higher in men compared to women when given the *ad libitum* sleep and napping opportunities on the simulated weekend. The study also found that compared to baseline, men had a greater proportional increase in energy intake during sleep restriction compared to women. However, no differences in subjective hunger between men and women were observed.

Previous in-patient laboratory studies have demonstrated impacts on hunger and appetite measures, with men exhibiting increased hedonic appetite while women exhibited lower fullness [9]. However, the finding of greater need for recovery sleep in men adds to previous research indicating sex differences in circadian timing of sleep, with women more likely to report a morning diurnal preference and exhibit an earlier chronotype compared to men [10]. However, women also are more likely to exhibit delayed sleep timing, i.e., behavioural timing, relative to their earlier circadian timing [11].

Given the greater prevalence of sleep disorders and insomnia in women compared to men [11], it is prudent not to treat the greater weekend recovery sleep time in men as evidence that women are less prone to adverse effects of curtailed sleep. Nevertheless, this study serves as a reminder for why more representation for women in research is important.

## Interesting Finding

A particularly interesting finding is that melatonin timing continued to delay in the WR group, despite the fact that the participants were afforded greater sleep time during those study days. In the figure from the paper below, take a look at how the "melatonin onset" symbol continues to move to the right, i.e., delaying to a later relative clock time.

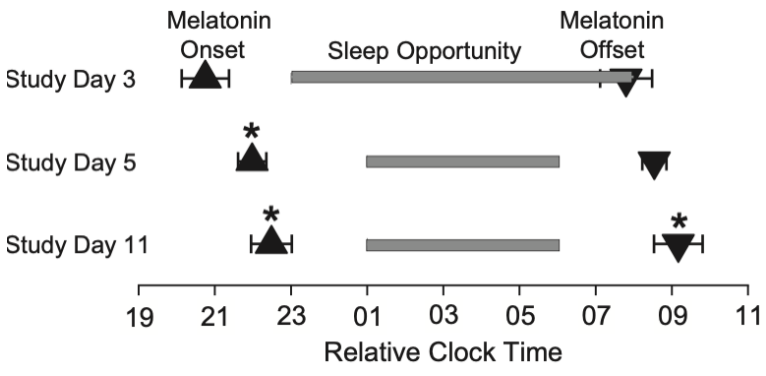
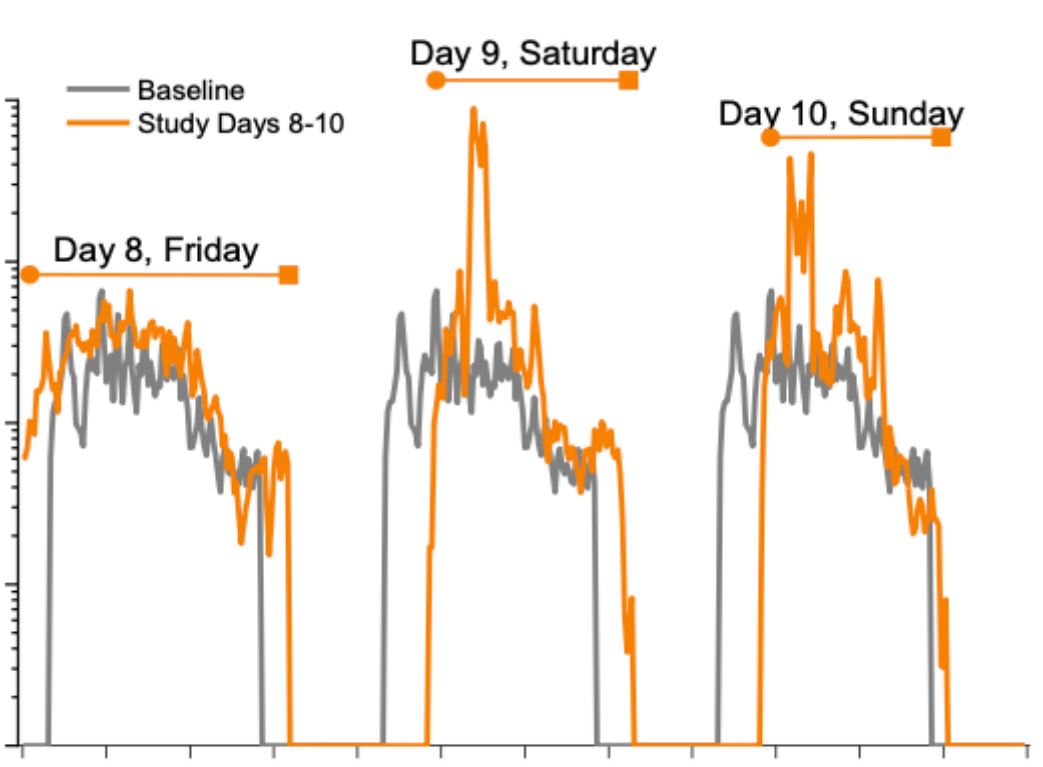



***Figure*** *from the paper illustrating the changes in melatonin timing in the weekend recovery [WR] sleep group. The triangles indicate the clock time at which melatonin onset [**left of grey bars**] and offset [**right of grey bars**] occurred. Onset and offset are defined by rises and falls in melatonin levels above or below, respectively, certain levels in the blood. The grey bars illustrate the sleep opportunity provided to participants.*

What could explain this? The most likely explanation is the additional light exposure which this group experienced on the simulated weekend days, which is evident in the **figure** below; the orange lines show that light exposure was much higher on the simulated weekend days at a later clock time compared to their baseline light exposure [grey lines].




Bear in mind that DLMO is a measure of the "central clock" in the brain, and light is the most potent time-cue for the synchronisation of DLMO with the external clock time [12–15]. "Circadian misalignment" describes a state where the timing of environmental time-cues [e.g., the light dark cycle] and/or behavioural cycles [e.g., sleep/wake cycle] are misaligned with the timing of melatonin rhythms [16,17].

What this study suggests is that weekend recovery sleep is not sufficient to recover circadian alignment when individuals are exposed to artificially changing light-dark environmental time-cues. This meant that participants in the WR group were beginning the second simulated "workweek" in a state of social jetlag, which is associated with risk of metabolic syndrome [18].

## Relevance

The present study was a comprehensive and tightly controlled study that attempted, as best an in-patient laboratory study could, to replicate working weeknight sleep restriction followed by weekend sleep recovery. What is most compelling about the findings is that almost all outcomes, including melatonin timing [i.e., circadian disruption], total daily energy intake and energy intake after dinner, and insulin sensitivity, showed a more adverse impact in the WR group compared to the SR group.

The SR group did show negative impacts on these outcomes that the 5hr/night sleep condition would be expected to produce, based on previous research demonstrating adverse metabolic consequences of this magnitude of sleep restriction [6,19]. The fact that melatonin timing remained broadly similar in the SR group confirms that sleep restriction, independent of additional circadian misalignment, exerts deleterious effects on metabolism and energy balance [1,2].

However, the fact that the WR group had even more deleterious outcomes indicates the additional adverse effects of circadian misalignment on top of sleep restriction. There is also previous research to which these findings add more support. Leproult *et al.* [19] investigated the effects of 5hr/night sleep durations, with the timing of that sleep occurring either during the biological night or delayed by 8.5hr. Irrespective of sleep loss, which was similar in both groups, circadian misalignment resulted in greater impairment of insulin sensitivity and higher C-reactive protein [CRP], a marker of inflammation, compared to sleep curtailed during the biological night.

Other findings are also consistent. Previous research has shown sleep curtailment of 1.5hr/night led to significantly greater energy intake, particularly from snacks, and an altered distribution of energy to later in the evening [>19:00hr] [20]. Thus, this pattern of altered energy distribution, with significantly greater energy intake in the after-dinner period, appears to be a consistent consequence of sleep restriction.

Finally, while there was no effect on subjective hunger in the present study, the weight of literature does suggest that sleep restriction impacts on subjective measures of desire to eat [21].

## Application to Practice

As an environmental exposure with strong impacts on diet, sleep should be a consideration for every health professional. Of course, the extent to which sleep timing may be a modifiable factor may depend on other occupational hazards, such as children.

Nevertheless, the weight of evidence indicates that insufficient sleep alters timing of energy intake and distribution, with greater energy intake occurring during the biological night. This pattern of altered energy intake, concomitant with adverse impacts on metabolic outcomes such as glucose tolerance and insulin sensitivity, may explain the increased risk of metabolic disease associated with sleep restriction and social jetlag [18,22].

While the implications of the impacts of sex differences in circadian timing and sleep restriction remain to be fully determined, one unifying recommendation from this

research area is that irrespective of sex, aligning sleep-wake timing with personal time-of-day preferences as much as possible would be expected to create more harmony between our biological and social clocks. Of course, this also requires some attention to the timing of other time-cues for the system, of which light is the most important.

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