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# Metabolic and hormonal effects of 'catch-up' sleep in men with chronic, repetitive, lifestyle-driven sleep restriction

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## Summary

**Objective—**Acutely restricting sleep worsens insulin sensitivity in healthy individuals whose usual sleep is normal in duration and pattern. The effect of recovery or weekend 'catch-up' sleep on insulin sensitivity and metabolically active hormones in individuals with chronic sleep restriction who regularly 'catch-up' on sleep at weekends is as yet unstudied.

**Design—**19 men (mean ± SEM age 28.6±2.0years, BMI 26.0±0.8kg/m$^2$) with at least 6 months' history (5.1±0.9years) of lifestyle driven, restricted sleep during the working week (373±6.6 min/night) with regular weekend 'catch up' sleep (weekend sleep extension 37.4±2.3%) completed an in-laboratory, randomised, cross-over study comprising 2 of 3 conditions, stratified by age. Conditions were 3 weekend nights of 10 hours, 6 hours or 10 hours time-in-bed with slow wave sleep suppression using targeted acoustic stimuli.

**Measurements—**Insulin sensitivity was measured in the morning following the 3$^{rd}$ intervention night by minimal modelling of 19 samples collected during a 2 hour oral glucose tolerance test. Glucose, insulin, c-peptide, leptin, peptide YY, ghrelin, cortisol, testosterone and luteinising hormone (LH) were measured from daily fasting blood samples; HOMA-IR, HOMA-β and QUICKI were calculated.

**Results—**Insulin sensitivity was higher following 3 nights of sleep extension compared to sustained sleep restriction. Fasting insulin, c-peptide, HOMA-IR, HOMA-β, leptin and PYY decreased with 'catch-up' sleep, QUICKI and testosterone increased, while morning cortisol and LH did not change. Targeted acoustic stimuli reduced SWS by 23%, but did not alter insulin sensitivity.

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**Conclusions—**Three nights of ‘catch-up’ sleep improved insulin sensitivity in men with chronic, repetitive sleep restriction. Methods to improve metabolic health by optimising sleep are plausible.

### Keywords

chronic sleep restriction; insulin sensitivity; ‘catch-up’ sleep; recovery sleep

## Introduction

Chronic, lifestyle-driven sleep restriction is common in many modern ‘24/7’ societies, with about 40% of individuals relying on discretional time on weekends to ‘catch-up’ on sleep curtailment during the working week[1, 2]. The prevalence of obesity and type 2 diabetes mellitus is increasing to epidemic proportions, particularly in developing nations, in line with increasing globalisation, changes in nutrition and sedentary lifestyles[3]. Epidemiological, interventional and molecular experiments provide a strong rationale linking sleep restriction with these metabolic disorders. Recent large epidemiological studies have associated sleep loss to the development of both obesity[4] and diabetes mellitus[1], and short sleep duration to increased subcutaneous fat[5]. Experimentally restricting or perturbing sleep for 1 to 14 nights in duration worsens insulin sensitivity in healthy individuals whose usual sleep is normal in duration and pattern[1]. Molecular experiments show that adipocytes from sleep restricted individuals are resistant to insulin’s effects on phosphorylated Akt, a mediator in the insulin-signalling pathway[6]. Together, these data indicate that acute sleep restriction is metabolically harmful.

Although 40% of individuals ‘catch-up’ on sleep over the weekend, the metabolic effects of catch-up sleep is relatively understudied with no interventional studies to date. Cross-sectional epidemiological studies in children show that weekend ‘catch-up’ sleep is associated with a decreased risk of being overweight compared to perpetual short sleepers[7–9]. In adults, an hour of weekend ‘catchup’ sleep was associated with a 39% decreased risk of hypertension[10]. Given these epidemiological data, we therefore examined whether three nights of a saturating amount of ‘catch-up’ sleep following regular weekday sleep curtailment would improve insulin sensitivity in those with a history of such sleep patterns, compared to sustained sleep restriction. We also tried to unravel mechanisms. An exploratory aim was to examine the effect of targeted acoustic perturbation of slow-wave sleep (SWS) on insulin sensitivity since SWS has been implicated mechanistically in glucose homeostasis[11]. Finally, we also explored the effect of both sleep restriction and experimental perturbation of SWS on other hormones known to modify insulin sensitivity and food intake.

## Methods

### Study protocol

The study complied with Good Clinical Practice guidelines, applicable regulatory requirements and the Declaration of Helsinki. All participants provided written informed consent to participate in the study, which was approved by the Sydney South West Area

Health Service Human Research and Ethics Committee (Concord Zone). The study is registered with the Australia New Zealand Clinical Trials Network, www.anzctr.org.au, number ACTRN12609000123246.

## Screening and participants

Healthy male subjects aged between 18 and 50 years were recruited through local advertising. Inclusion criteria included regular sleep-wake patterns as per the description below and being agreeable to spend two weekends at the research institute. Exclusions included shift-workers, habitual napping (more than once per month from history), diabetes mellitus, a history of, or symptoms suggesting, a co-existing sleep disorder, including insomnia, obstructive sleep apnoea, parasomnias or restless legs syndrome. Those with uncontrolled medical conditions or a history of psychiatric disorders or drug abuse, including use of any sedative or neuroactive medications, or indeed any medication that might affect sleep, were also excluded. Subjects could not have crossed time-zones within one month of the study visits.

Screening included a full medical history, physical examination and detailed explanation of the study protocol. No subject had type 2 diabetes mellitus from history, confirmed by oral glucose tolerance test. Habitual sleep-wake patterns were objectively assessed over 2 weeks with at-home actigraphy incorporating sleep diary verification of sleep onset and wake up times (Actiwatch™, Philips/Respironics, PA, USA), analysed by two investigators. Subjects were included if mean weekday nightly sleep period over 2 weeks, between Monday and Thursday nights inclusive, was less than 6.5 hours(h)/night and mean nightly weekend sleep period, Friday and Saturday nights, was greater than 25% of the weekday mean. Sleep disordered breathing was excluded by three nights assessment with a portable single channel nasal flow recording device (Flow Wizard™, DiagnoseIT, Sydney, Australia)[12].

## Randomisation

All participants underwent 2 out of 2 or 3 potential study conditions, in a randomised order, two period crossover design. The three potential study conditions were 3 weekend nights (Friday night to Monday morning) of: (A) 10h time in bed (TIB) each night, (B) 6h TIB each night or (C) 10h TIB with SWS suppression by acoustic stimuli (10h↓SWS) each night-Figure 1. Those aged ≤35 years (group 1) could be randomised to any 2 of the 3 conditions. Those >35 years (group 2) could only be randomised to Condition A (6h TIB) or Condition B (10h TIB). Men >35 years were not randomised to Condition C (10h↓SWS) because SWS is already reduced in this age group. Two separate randomisation lists for young and older men were computer-generated in blocks of 4. There was a minimum of 3 weeks wash-out between each study visit.

## Study visits

**General—**For 2 weeks prior to a study weekend visit, subjects were asked to maintain their regular ‘catch-up’ sleep-wake schedules at home and this was verified by inspection of actigraphy and sleep diaries, with any deviation resulting in a study weekend being rescheduled. Subjects were asked to restrict caffeine and alcohol to two or less drinks or units per day at home. The study was conducted within the chronobiology laboratory in the

research institute. Subjects were encouraged to be sedentary, not to sleep outside of scheduled times, and had their own bedroom with ensuite with access to a shared living area. Ambient lighting was kept at less than 50 lux for the duration of the study visit to minimise any phase shift. Subjects were not permitted to exercise or leave the chronobiology laboratory. Study staff ensured subjects did not nap, through continuous camera or direct visual surveillance.

**Sleep scheduling—**Time of lights out was calculated by the subject's screening actigraphy. The weekday (Monday to Thursday nights inclusive) mean sleep centre-point for each subject was calculated and lights-on and lights-off times were individually centred on that time for each condition. Subjects were only told of their lights-off time immediately prior to bed on the first evening. They were instructed that if they woke prior to lights on, they should remain in bed attempting further sleep until the lights were switched on. Loudspeakers were present in all bedrooms, irrespective of whether used or not.

**Study schedule—**Figure 1 shows the study visit schedule. Subjects arrived fasted on Friday morning for blood sampling (glucose, insulin, c-peptide, leptin, peptide YY (PYY), total ghrelin, cortisol, total testosterone and luteinising hormone (LH)), verification of their sleep compliance with actigraphy data and to answer the Epworth Sleepiness Score (ESS)[13] and Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)[14]. Height and weight were measured by standard methods. Subjects were asked to refrain from caffeine completely from that time. They returned to the facility on Friday from 5pm and then did not leave the facility until after tests were completed on Monday morning. Following each night of the study condition, fasting blood samples were taken immediately after wake-up (for glucose, insulin, c-peptide, leptin, PYY, total ghrelin, cortisol, testosterone and LH). On Monday morning within 30–60 minutes of wake-up, subjects underwent a frequently sampled (19 samples), two hour, oral glucose tolerance test to determine insulin sensitivity. After baseline fasting hormone levels were taken through an intravenous cannula, 75g of glucose was administered orally, then samples were taken after 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110 and 120 minutes for insulin, c-peptide and glucose measurements. Samples were centrifuged immediately and frozen to minus 80 degrees Celsius until assayed. Detailed hormonal assay methodology can be found in Supplementary table S1. Insulin sensitivity was determined by minimal model analysis[15, 16]. Area-under-the-curve (AUC) for glucose and insulin was calculated using the trapezoid rule. HOMA-IR, HOMA-β[17] and QUICKI[18] indices of insulin sensitivity were calculated.

**Polysomnography and slow wave sleep suppression—**Polysomnography was recorded each night using standard electrode placement (Sandman Elite V.9.2, Tyco Healthcare, Denver, Colorado, USA). Leads were referenced to the contralateral mastoid position. Sleep stages were scored using standardised criteria [19] by one scorer, with strict attention to delta wave voltage criteria. SWS was suppressed using acoustic stimuli on all three weekend nights of Condition C. Delta waves were recognised visually in real-time on the central leads of the electroencephalogram (EEG) by the researchers. When two or more consecutive delta waves were seen, a mixed frequency ramped tone was played through bilateral loudspeakers next to the subject's bed, ramping from 40dB to 95dB (measured at

the approximate location of the subject's head), until delta activity was suppressed. If the maximum volume tone did not control delta activity, the researchers would go into the bedroom, gently disturb the subject and say their name.

**Power Spectral Analysis—**Power spectral analysis was performed on a central lead of the EEG to determine non-rapid eye movement (NREM) mean delta power, NREM relative delta power density (% delta power/total power across all frequency bands) and total NREM delta power (mean delta power x number of 30 second epochs x2) after removal of EEG artefact using an automated method with visual verification[20]. If noise artefact was present in over 25% of the channel, it was discarded from analysis (10/114 studies). Lead C3-M2 was utilised unless the signal quality was suboptimal, whereby C4-M1 was substituted for all 6 nights for that subject (n=4). Fast Fourier transformation was performed on five second epochs over the entire frequency bands, with the delta range (0.75–4.5Hz) the primary focus for analysis[20].

**Food intake and exercise—**Meals were chosen from a menu which included healthy balanced frozen meals for breakfast, lunch and dinner, with snacks available. Quantity of food was not restricted over the 1st weekend visit. During the 2nd weekend study visit, each subject was served exactly the same meals and snacks they had consumed during the first weekend, to ensure dietary intake was standardised over both weekends. Food intake for each individual was summed from the available nutritional information. No caffeine, alcohol or chocolate was available. Breakfast was served 30 minutes after the subject's wake-up time, lunch at 12.30pm and dinner at 6.30pm. All subjects obliged with the dietary instructions and minimal deviation occurred, except occasionally for food availability, when a similar meal was provided. Diet was not monitored in between study visits.

## Statistical analysis

Our primary aim was to determine if 'catch-up' sleep would improve insulin sensitivity, and our exploratory aim was to unravel potential mechanisms by which this might occur, such as through changes in SWS and/or hormones known to be metabolically active. The primary outcome was the difference in insulin sensitivity, determined by minimal modelling, after three nights of each sleep condition. Secondary outcomes were disposition index and hormones (leptin, PYY, ghrelin, cortisol, testosterone, LH). Tertiary outcomes were insulin sensitivity measured by HOMA and QUICKI, fasting and/or AUC glucose, insulin and c-peptide. The polysomnographic findings are not outcomes – these variables were analysed to verify that the intervention (i.e. catch-up sleep, slow wave sleep suppression) altered sleep duration and architecture as expected. Data were analysed using SAS version 9.2 (SAS Institute) using paired t tests and mixed model analysis for repeated measures where appropriate incorporating 'condition', 'day' and interaction terms, with two-tailed p values $<0.05$ considered significant. Normality of data or of residuals was assessed, as appropriate. Data transformation was not required. Period and crossover effects were excluded from available baseline data of each weekend[21]. Results were assessed separately for group 1 compared to overall, and a 'group*condition' term was utilised to assess for any age interaction of the older group on the overall results. Data are described as means and standard errors, or differences and 95% confidence intervals as appropriate.

# Results

## Demographics

315 people responded to advertising; 49 attended full screening, of which 21 men were randomised: 18 in group 1 (≤ 35 years) and 3 in group 2 (>35 years), with 19 subjects completing both weekend visits. The main reasons for screen failures were not exhibiting sufficient sleep restriction during the working week (n=9 of 28; 32%), or not reaching the criteria set of 25% catch-up sleep on weekends (n=6 of 28; 22%). In group 1; one subject was randomised who did not undergo either weekend visit and another subject withdrew following one weekend due to needle phobia. Due to within-person study design, neither individual could be analysed. The following participants completed each of the 3 possible condition pairings:

10h TIB/6h TIB: n=8

10h TIB/10h↓SWS: n=6

6h TIB/10h↓SWS TIB: n=5

Screening characteristics are shown in Table 1; demonstrating subjects were sleep restricted during the working work (6h 12min/night±7min). All men showed a significant increase in weekend sleep compared to weekday sleep (mean weekend sleep extension 37.3%±2.4)-Supplementary Figure S1. Hence, a 6h sleep opportunity was almost identical to the average time spent asleep during weekdays, whereas a 10h sleep opportunity exceeded the time each slept during weekends-Supplementary Figure S1. All subjects had habituated to these sleep patterns regularly at home for at least six months and on average 5.1years±0.9. The most common reason for these sleep patterns was working long hours, alongside studying and time commuting to and from work and/or study. MEQ excluded preference for morning or evening (mean 47.3± 1.5; 'neither type' category range 42–58[14]). Other than age and BMI being higher, descriptively the older group did not alter the overall mean demographics. ESS was within the normal range, excluding subjective sleepiness. No significant differences in BMI or sleep parameters by actigraphy for the 2 weeks leading up to study visits were found between the two weekends-Supplementary Table S2.

## Sleep parameters- the intervention

PSG sleep parameters and power spectral analysis results are shown in Figure 2 and Supplementary Figures S2. Across the pairs of conditions, expected significant differences were seen in total sleep time (TST)-Figure 2A, sleep efficiency (percentage time asleep during time in bed)-Figure 2B and sleep latency-Supplementary Figure 2A. Notably sleep efficiency exceeded 90% for all conditions, and the 10h↓SWS condition compared to 10h did not significantly reduce TST nor sleep efficiency, despite the acoustic stimuli-Figure 2A, B. The 6h condition had a significantly reduced arousal index compared to 10h ($p<0.001$) or 10h↓SWS ($p<0.001$), consistent with maintaining a more consolidated sleep with sustained sleep restriction-Figure 2C. Arousal index in the 10h↓SWS condition compared to 10h although higher, did not reach significance ($p=0.09$). The 10h↓SWS condition reduced SWS quantity by 23% (− 12.6min, −23.4 to −1.8, $p=0.02$) compared to 10h and by 62% compared to 6h (−43.6min, −55.0 to −32.3, $p<0.001$), as expected by the experimental protocol-

Supplementary Figure S2B. The 6h condition had the highest SWS proportion (%TST) across all pairs of conditions (compared to 10h, p<0.001; compared to 10h↓SWS, p<0.001)-Figure 2D.

In examining the delta power of the EEG, 10h↓SWS reduced mean NREM delta power by 10% (−41.7 $\mu V^2$, −69.3 to −13.9, p=0.005) and relative delta power compared to 10h (p=0.0002), as anticipated by the acoustic stimuli protocol-Supplementary Figure S2E, F. The 6h condition had significantly higher mean NREM delta power and relative delta power compared to either 10h (p<0.001) or 10h↓SWS (p<0.001), as expected with sustained sleep restriction-Supplementary Figure S2E, F.

### Metabolic outcomes-insulin sensitivity

Results for the main metabolic parameters are shown in Figures 3 & 4. Period and carryover effects were excluded by analysing Friday baseline values where available. Insulin sensitivity (ISx) was significantly increased following 3 nights of 'catch-up' sleep (10h) compared to continuing sleep restriction (6h) ($8.57\times10^{-4}$ $min^{-1}$ $(\mu U/ml)^{-1}$, 1.1 to $16.1\times10^{-4}$, p=0.03)-Figure 3A. There were no significant differences between 10h↓SWS and either 10h (p=0.17) or 6h (p=0.6). Changes of similar magnitude and direction were seen for disposition index (DI), but these were not statistically significant-Figure 3B. Glucose AUC was significantly lower in 10h compared to 6h in the younger men (−69.2 $mmol.min.L^{-1}$ CI −119.7, −18.6), p=0.02), but not in the young and old men together (p=0.14)-Figure 3C. Insulin AUC differences were not significant-Figure 3D. Daily fasting morning hormone levels showed significant reductions in fasting insulin, c-peptide, HOMA-IR, HOMA-β and an increase in QUICKI following 10h compared to 6h-Figure 4- all consistent with improvements. Only 1% of insulin, c-peptide and glucose values were missing. Certain results showed an age effect, with the older subjects having higher C-peptide, glucose and leptin levels, however this did not alter the overall significances of differences when an age factor was applied to the model.

### Metabolic outcomes-appetite hormones, cortisol, testosterone

Leptin was significantly reduced following 10h 'catch-up' sleep compared to 6h (−1.69ng/mL (−0.6, −2.8); p=0.003), along with a corresponding reduction in PYY (−12.7pg/mL (−2.1, −23.3); p=0.02), but no change was seen in total ghrelin (p=0.59)-Figure 5A–C. There was no significant change in fasting morning cortisol levels between any of the condition pairings-Figure 5D.

The amount of food consumed between weekend visits was not significantly different for each individual ($1^{st}$ weekend=6230kcal, $2^{nd}$ weekend= 6291kcal; p=n/s). Nor was there any significant difference between the amount of energy intake between sleep conditions, when specifically looking at only the first weekend chronologically when food choices were made, independent of condition pairing (10h = 6394kcal, 6h=5845kcal, 10h↓SWS = 6426kcal; p=n/s). Only food choices from the first weekend were analysed because subjects were not allowed to rechoose on the second weekend. Furthermore when exploring only those in the 10h/6h condition pairing, no significant difference was seen between food choice as determined by energy intake on the first weekend (10h = 6250kcal, 6h= 5844kcal; p=n/s).

Fasting morning testosterone levels were significantly higher following 10h compared to 6h (2.2nM (0.2, 4.2); p=0.03) in both the group as a whole (n=8) and in the younger group alone (n=5)-Figure 5E. The older men (n=3) had lower levels compared to the younger men, as expected with ageing (p=0.01). LH was not significantly different between any of the condition pairings-Figure 5F.

## Discussion

'Catch-up' sleep is highly prevalent with >40% of working aged adults sleeping more on weekends compared to weekdays[2]. Understanding the metabolic implications of these lifestyle choices is therefore highly relevant. We show that men who regularly adopt lifestyle-driven, chronic, repetitive sleep restriction with weekend 'catch-up' sleep, significantly improved insulin sensitivity by 45% following three nights of a saturating sleep compared to ongoing sleep restriction, as measured by minimal model after an oral glucose challenge. HOMA-IR decreased and QUICKI increased. Accordingly, 3 separate measures of ISx all showed improved insulin sensitivity with 'catch-up' sleep. These data are novel and together attest to the veracity of this finding. Previous studies have shown that sleep restriction of 1 night to 2 weeks has a negative impact on markers of glucose homeostasis[22–25], but have examined subjects with regular sleep patterns, unlike those in our study. Our finding of a 45% improvement in ISx with 'catch-up' sleep is complementary and consistent with previous studies showing a 20–25% worsening of ISx with sleep restriction[1].

'Catch-up' sleep decreased fasting insulin, c-peptide and HOMA-β, likely reflecting the concomitant improvement in ISx. 'Catch-up' sleep increased morning testosterone and did not change morning cortisol. These findings are consistent with other studies of sleep restriction[26, 27]. Randomised controlled trials directly show that testosterone treatment improves ISx in men who are obese[28], as well as in men with disrupted and reduced sleep from obstructive sleep apnoea[29]. Testosterone improves glycaemic control in men with type 2 diabetes mellitus[30] and reduces obesity and metabolic syndrome[31]. Meta-analyses show significant reductions in fasting plasma glucose, fat mass and triglycerides with testosterone therapy in men with type 2 diabetes mellitus[30]. Previous studies have shown that sleep restriction can increase evening, but not morning, cortisol[22, 24–26], with no change in mean cortisol across 24 hours[1]. Interventional studies conclusively show that increased afternoon/evening cortisol worsens insulin resistance in humans[32] and rodents[33]. These findings occur because maintaining cortisol concentrations during the 4–6 hours of the circadian nadir (early evening) is important to avoid effects of glucocorticoid excess on peripheral tissues[33]. Whether or not sleep impacts insulin sensitivity through these hormonal changes is plausible, but remains to be determined.

We examined satiety and hunger hormones released by adipose tissue (leptin-satiety signal), small intestine (PYY-satiety) and stomach (ghrelin-hunger) as secondary outcomes. 'Catch-up' sleep decreased leptin and PYY compared with continued sleep restriction, but did not alter ghrelin or food choice determined by energy intake. Studies have shown conflicting changes in appetite hormones with sleep restriction due to differing food intake, energy balance at time of assessment, gender differences and possible changes in circadian rhythm[1, 26, 34]. However, our subjects ate the same meals across both weekends, albeit ad

libitum during the first weekend. Energy expenditure was not measured, however exercise was not allowed. Circadian shift was minimised, as sleep opportunity was centred individually to home sleep patterns and lighting was <50 lux. Although decreased leptin and PYY should decrease satiety, we did not observe a change in energy intake. Although surprising, these data are consistent with recent data showing sleep restriction increased leptin and PYY, and decreased ghrelin in a carefully conducted study utilising 24h assessment of these hormones[34]. We found no change in ghrelin with 'catch-up' sleep, although decreasing SWS increased ghrelin. This novel finding requires replication in other studies since we did not adjust for multiple testing for this or any of the other secondary outcomes.

SWS is a metabolically active sleep stage and others have shown that disrupting SWS can worsen ISx [11]. In our hands, targeted acoustic stimuli significantly disrupted SWS and reduced delta power, but the absolute effect, although significant, was small in magnitude. ISx was not altered, in contrast with previous studies[11, 35]. This discrepancy could be explained if a minimal reduction in SWS required to worsen ISx was not achieved in our chronically sleep restricted subjects, or if other factors such as sleep fragmentation and/or arousals per se are ultimately responsible[35]. On the other hand, our study was likely underpowered to show an effect of SWS suppression on ISx, in part because both baseline SWS and ability to suppress SWS were highly variable in our study population and also because it proved to be much more difficult to suppress SWS in a population that is chronically sleep deprived than we had originally anticipated.

These experimental findings exploring chronic repetitive sleep restriction are highly relevant because such sleep patterns are common in modern society and it has been suggested that chronic sleep restriction leads to the development of obesity and diabetes mellitus[36], in addition to other cardiometabolic consequences[37]. Over a prolonged period of time (years or decades) this improvement in insulin sensitivity could be highly relevant in delaying or even preventing prediabetes or type 2 diabetes mellitus in a relatively healthy young individual. In a population of millions of individuals, this change in insulin sensitivity would translate to decreased prediabetes and diabetes mellitus in the community. Furthermore, interventional studies now show that sleep restriction increases weight[38] and decreases fat proportion lost in those trying to lose weight through planned negative energy balance[1]. Studies attempting to manipulate sleep in the home setting have not been adequately powered to show changes in ISx given the increased variability that can occur in an uncontrolled non-laboratory environment. Nevertheless, larger community based sleep extension trials are required, but need to be sufficiently large to account for variable adherence to the sleep intervention, the introduction of confounders outside of the laboratory and possibly for a between-group study design.

Indeed, this wide variability in ISx is one potential limitation for our investigation. This variability was readily observed by examining the inter-individual differences in response to 10h of sleep repletion (Figure 3A), and could be related to age, lifetime duration of chronic sleep deprivation, degree of at-home sleep restriction or many other variables. In fact, these factors may contribute to the wide variability observed in ISx in the general population. Our sample size was too small for us to determine these factors, but the goal of the study was to

determine effects of recovery ‘catch-up’ sleep on ISx and here, the crossover study design allowed a paired statistical analysis to examine the effect of sleep repletion within the same person, using 57 measurements (19 measurements each for insulin, C-peptide and glucose) to precisely measure ISx, thereby negating the impact of inter-individual differences in ISx among individuals. Indeed, paired student t-tests, as we implemented, remain valid without an increase in type 1 error over 0.05 even with these sample sizes[39] and Student’s original paper utilised a sample size of 4[40]. Another possible limitation is that 3, not 2, nights of ‘catch-up’ sleep was tested, whereas the latter might be more consistent with a weekday/weekend pattern. However, our proof-of-concept study of 3 nights ‘catch-up’ sleep is still feasible in the community, wherein additional sleep on the 3rd (Sunday) night could be achieved with an earlier bedtime. Nevertheless further studies of 1 and 2 nights of sleep repletion are needed to explore the chronology of metabolic recovery. Our population was specifically in individuals with ‘catch-up’ sleep patterns, and may not be generalisable to the other populations including those with other sleep disorders such as obstructive sleep apnea.

Our study examines, for the first time, a population regularly using ‘catch-up’ sleep. We show that ‘catch-up’ sleep improved ISx over continued sleep restriction, thereby confirming that extending sleep is potentially beneficial at least in non-diabetic men with long-standing chronic, repetitive sleep restriction. Critically, our intervention of 10h sleep opportunity translated to actual sleep since sleep efficiencies >90% and exceeded the usual amount of sleep extension of every participant, raising the possibility that their habitual attempts at ‘catch-up’ sleep were suboptimal. These data suggest that many in our society should sleep more, but further studies will be required to determine how much more sleep is needed in which specific individuals and whether planning to consistently sleep more every night is, in the long-run, ultimately superior to the occasional 1, 2 or 3 nights of ‘catch-up’ sleep.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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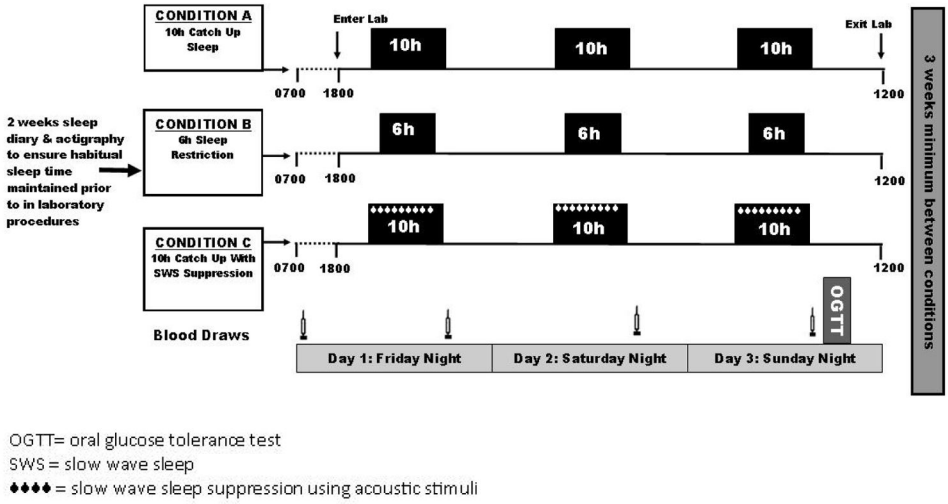


OGTT= oral glucose tolerance test
SWS = slow wave sleep
♦♦♦♦ = slow wave sleep suppression using acoustic stimuli

**Figure 1.**

Study design. Subjects were randomised to undergo 2 of 3 (young men) or 2 (older men) conditions in random order: i.e. AB, BA, AC, CA, BC or CB in young men; or, AB or BA in older men. There was 3 weeks washout between conditions.

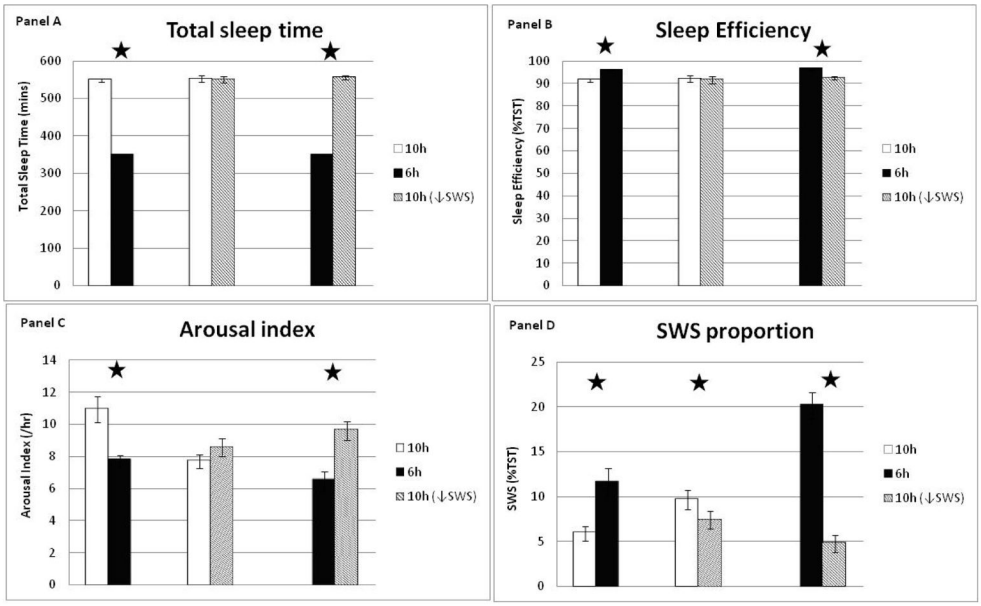


**Figure 2.**

Polysomnographic sleep parameters between pairs of conditions averaged over 3 experimental nights.

Panels: A- TST (mins), B- sleep efficiency (%TST), C-arousal index (events/hr), D- SWS proportion (%TST)

10h/6h n=8, 10h/10h↓SWS n=6, 6h/10h↓SWS n=5. Error bars are SEM.

* represents significance $p<0.05$

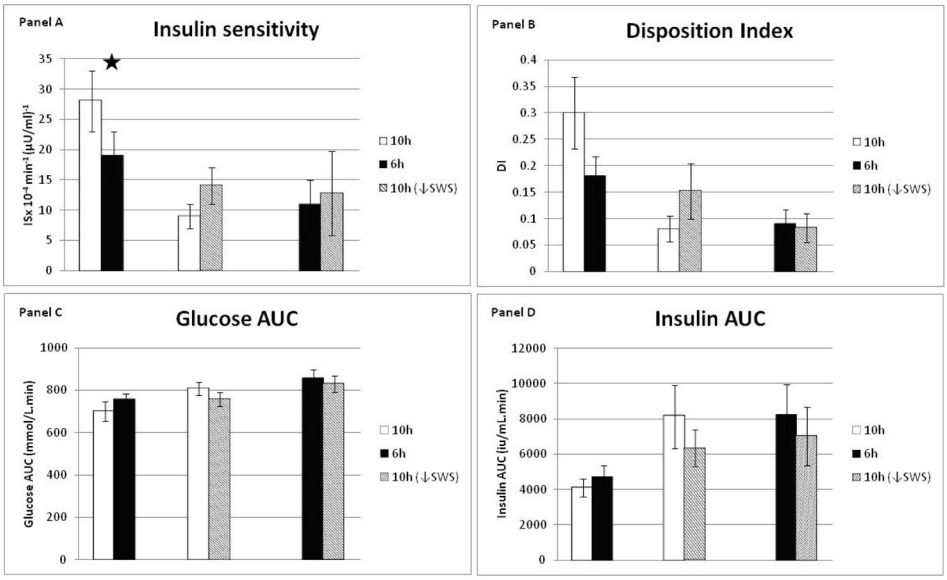


**Figure 3.**

Metabolic outcomes between pairs of conditions from minimal model of an oral glucose tolerance test performed on Monday after 3 nights of each condition.

Panels: A-insulin sensitivity ($min^{-1}$ $(\mu U/mL)^{-1}$), B-disposition index, C-glucose area-under-the-curve (AUC- mmol/L.min), D-insulin AUC (iu/mL.min).

10h/6h n=8, 10h/10h↓SWS n=6, 6h/10h↓SWS n=5. Error bars are SEM.

* represents significance $p<0.05$

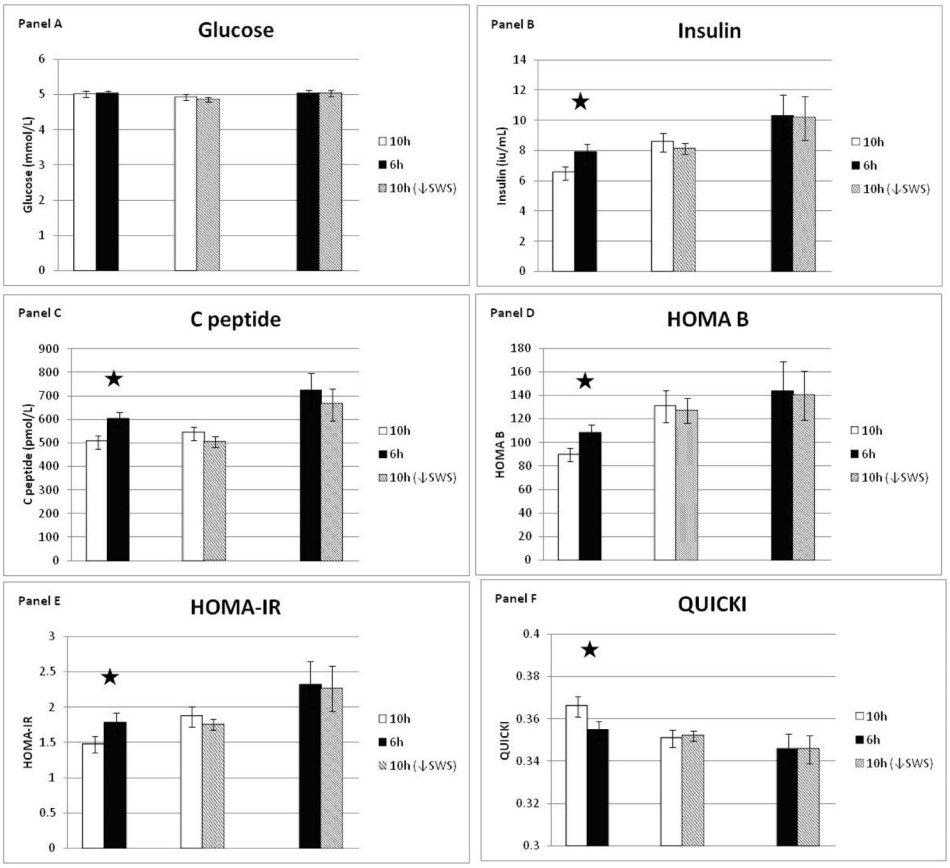


**Figure 4.**

Metabolic outcomes between pairs of conditions from daily fasting blood samples showing mean values across Sat/Sun/Mon.

Panels: A-glucose (mmol/L), B-insulin (iu/ml), C- c peptide (pmol/L), D-HOMA-β, E-HOMA-IR, F- QUICKI.

10h/6h n=8, 10h/10h↓SWS n=6, 6h/10h↓SWS n=5. Error bars are SEM.

* represents significance $p<0.05$

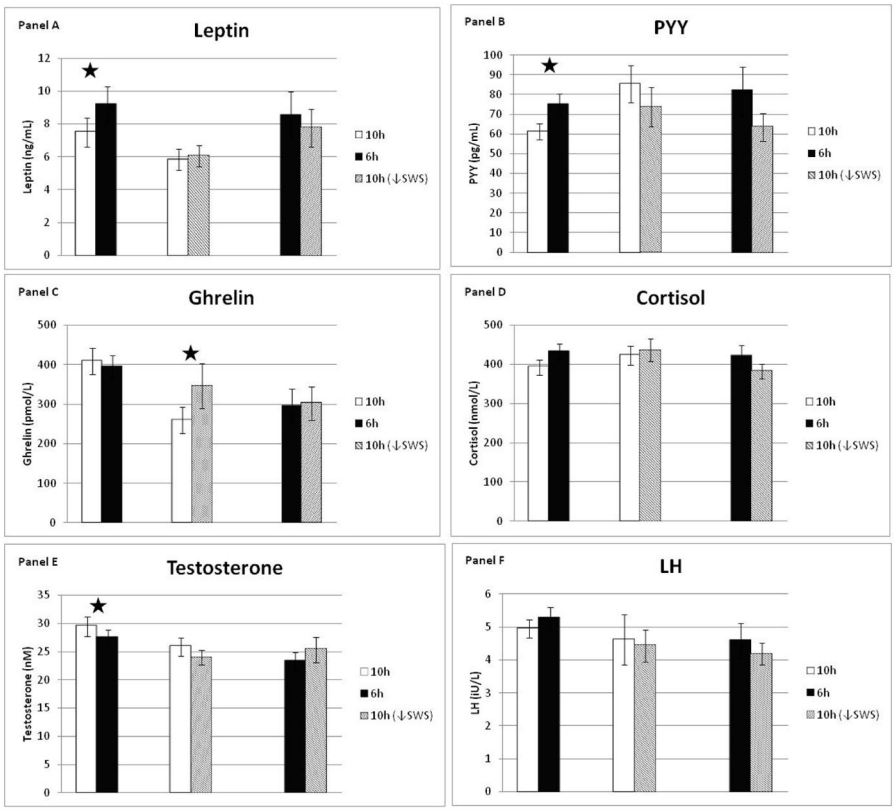


**Figure 5.**

Metabolic outcomes between pairs of conditions from daily fasting blood samples showing mean values across Sat/Sun/Mon.

Panels: A-leptin (ng/ml), B- PYY (pg/mL), C-ghrelin (pmol/L), D-cortisol (nmol/L), E-testosterone (nM), F-lutenising hormone (LH-iU/L).

10h/6h n=8, 10h/10h↓SWS n=6, 6h/10h↓SWS n=5. Error bars are SEM.

* represents significance $p<0.05$

**Table 1**

Screening characteristics (means ± SEM)

| n=19 | Mean ± SEM | Range |
|---|---|---|
| Age (yrs) | 28.6±2.0 | 19–49 |
| Midweek sleep[1] | 6h 12m±7m | 5h 18m–6h 54m |
| Weekend sleep[2] | 8h 30m±9m | 6h 59m–9h 39m |
| Weekend sleep extension[3] (%) | 37.3±2.4 | 19–56 |
| Duration of catch-up sleep patterns (yrs) | 5.1±0.9 | 0.5–15 |
| MEQ score[4] | 47.1±1.5 | 34–58 |

[1]Defined as average rest period Monday to Thursday inclusive over 2 weeks screening by actigraphy and diaries

[2]Defined as average rest period Friday and Saturday over 2 weeks screening

[3]Defined as % more weekend sleep compared to midweek sleep over 2 weeks screening

[4]MEQ- Horne-Ostberg Morningness-Eveningness Questionnaire (definite evening type 16–30; moderate evening type 31–41; neither type 42–58; moderate morning type 59–69; definite morning type 70–86)