Pilot study of sleep and meal timing effects, independent of sleep duration and food intake, on insulin sensitivity in healthy individuals

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A B S T R A C T

This pilot study tested the independent and interactive effects of sleep and meal times, under identical sleep duration and feeding conditions, on insulin sensitivity (Si) in overweight adults. Participants underwent a 4-phase randomized crossover inpatient study differing in sleep times: normal (Nm: 0000-0800 hours) or late (Ls: 0330-1130 hours); and in meal times: normal (Nm: 1, 5, 11, and 12.5 hours after awakening) or late (Lm: 4.5, 8.5, 14.5, and 16 hours after awakening). An insulin-modified frequently sampled intravenous glucose tolerance test, at scheduled breakfast time, and a meal tolerance test, at scheduled lunch time, were performed to assess Si after 3 days in each condition. Six participants were enrolled (4 men, 2 women; mean age 25.1 ± [SD] 3.9 years, body mass index 29.2 ± 2.7 kg/m²); only 1 failed to complete her last study phase. There were no effects of sleep and meal times or sleep × meal time interaction on Si (all P > .35), acute insulin response to intravenous glucose (all P > .20), and disposition index (all P > .60) after adjusting for sex and body mass index. Meal tolerance test glucose and insulin areas under the curve were lower during Nm (glucose P = .11; insulin P = .0088). There were a sleep × meal interaction and an effect of meal times on overnight glucose (P = .0040 and .012, respectively) and insulin (P = .0075 and .067, respectively). Sleep timing, without concomitant sleep restriction, does not adversely affect Si and glucose tolerance, but meal times may be relevant for health. Our results should be confirmed in a larger sample.

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Introduction

Sleep has recently been highlighted as a behavior that is closely associated with health. Indeed, short sleep duration has been shown to be related to an increased risk of obesity, type 2 diabetes, hypertension, and cardiovascular disease. Other sleep disorders are also linked to such adverse metabolic consequences, namely, obstructive sleep apnea and insomnia. More recently, however, studies have noted that not only is sleep duration important in modulating cardiometabolic risk factors but also the timing of the sleep period may have an impact on health. At the population level, epidemiological studies suggest that individuals who work night shift, and thus sleep during the daytime, have an increased risk of obesity, type 2 diabetes, and cardiovascular disease. Less drastic differences in sleep timing are also associated with increased risk of chronic disorders. For example, Facco et al reported an increased risk of gestational diabetes in women with midpoint of sleep later than 0500 hours compared with women with an earlier sleep midpoint, and social jetlag of >2 hours has been associated with a 2-fold increased risk of metabolic syndrome and type 2 diabetes.

Studies have shown that inverting sleep with a 12-hour flip increased 24-hour postprandial glucose and insulin area under the curve (AUC) by 1.6% and 9%, respectively, compared with the usual sleep period during the night (2300-0800 hours). Two-hour postprandial glucose AUC was 12% higher when measured at a test meal in the biological night (2000 hours) compared with morning (0800 hours). However, in that study, total sleep duration was lower when sleep occurred during the day compared with night. To address this limitation, Leproult et al performed a sleep restriction study in
which participants slept either at night (0030-0530 hours) or during the day (0900-1400 hours), introducing an 8.5-hour delay in sleep. An intravenous (IV) glucose tolerance test was performed at 0900 hours after 6 nights of this protocol. Insulin sensitivity (SI) was reduced in both conditions relative to 10-hour baseline sleep, showing a sleep restriction effect on this risk factor. There was no change in the acute insulin response to glucose (AIRg), resulting in a reduction in the disposition index (DI). We are not aware of intervention studies of mild shifts in sleep timing that mimic the real-life situation of the large proportion of Americans suffering from social jetlag or late sleep timing. This is what we aim to achieve in this pilot study.

It is important to note that, in conditions when sleep time is delayed, food intake must also occur later in the day. Mice fed during the light cycle, at a time when they would not be active, have greater body fat than mice fed during the dark cycle and have increased risk of metabolic syndrome. Scher et al noted that glucose and insulin levels vary across the behavioral cycle independent of the circadian cycle. When meals are consumed later in the day, postprandial glucose AUC is increased relative to an earlier eating occasion. However, this may be due to differences in fasting duration prior to the test meal between conditions.

To address the limitations of prior studies, we conducted a randomized, crossover pilot study consisting of 4 phases in which sleep and meal times were fixed and food intake controlled. The main objective of our investigation was to determine the effects of sleep and meal times, independent of sleep duration and energy intake, on SI. We hypothesized that sleeping and eating late in the day would lead to an adverse metabolic profile relative to earlier sleep and meal times.

### Materials and methods

#### Participants

Six men and women, 20-49 years of age with a body mass index between 25 and 34.9 kg/m², were recruited to participate in this study. Recruitment procedures were identical to those previously used in our laboratory and involved 2 weeks of sleep monitoring with actigraphy. Only those with habitual sleep 7-9 hours per night and an intermediate chronotype, based on the Ostberg Morningness-Eveningness questionnaire, were enrolled. Individuals were required to habitually consume a meal within 1 hour of awakening to be eligible. Those with sleep, eating, or other psychological disorders were excluded. The study was approved by the institutional review boards of Columbia University Medical Center and New York University Langone Medical Center and registered on ClinicalTrials.gov (#NCT02347020). All participants provided informed consent prior to enrolling in the study.

#### Experimental design

Once enrolled, participants were randomly assigned 1 of 24 study phase combinations generated from a randomization schedule. The 4 study phases included either normal or late sleep and normal or late meals (Table 1), which were separated by a washout period of 3 weeks to ensure that testing was done in the same phase of the menstrual cycle in women. Sleep and meal times for the normal sleep/normal meals (Ns/Nm) phase were based on data from a convenience sample. Bedtimes for the late sleep (Ls) phases were based on bedtimes for late sleepers from that same study and were delayed by 3.5 hours relative to Ns. However, wake times were later than those of that sample to ensure equal time in bed in each phase. Meal times for the late meal (Lm) phases were delayed by an equal amount of time as the sleep delay (3.5 hours). For each study phase, participants were required to become inpatients in the Columbia University Medical Center Irving Institute for Clinical and Translational Research for 5 nights. During their stay, participants consumed a fixed diet, designed to maintain their body weight, as estimated using the Mifflin-St Jeor equation. Energy intake was distributed as follows: 25% at breakfast, 30% at lunch, 35% at dinner, and 10% at post-dinner snack. When snack was scheduled at bedtime, it was provided 10 minutes prior to scheduled bedtime. Participants were required to consume all foods provided and nothing else during this period.

Inpatient rooms in the Clinical Research Resource were equipped with noise-reducing blackout curtains. Participants were kept in normal indoor room lighting (~200 lux at the level of the eye) during wakefulness and complete darkness during sleep. Sleep was monitored by actigraphy nightly and by polysomnography (PSG) on night 3 only. PSG recordings (Embletta MPR PG/ST+ Proxy, Natus Neurology, Middleton, WI) included frontal, central, and occipital electroencephalogram, electrooculogram, electromyogram (chin and left and right anterior tibia), pulse oximetry, respiratory effort (rib cage and abdominal excursion), nasal airflow (nasal pressure cannula), and electrocardiogram. Recordings were visually scored in 30-second epochs according to standard criteria. All participants had an apnea-hypopnea index <5 events per hour. The first night recording also included electromyography of the left and right anterior tibia for screening of periodic limb movements in sleep, and all participants showed a periodic limb movement index <15 events per hour.

During the night from day 3 to day 4, blood samples were taken from an IV line via a port through the wall. Sampling started at 2200 hours and continued at hourly intervals until 0300 hours and every 2 hours until the start of the insulin-modified frequently sampled IV glucose tolerance test (FISVTGTT). The FISVTGTT was performed at scheduled breakfast time for each phase, and a meal tolerance test (MTT) was done at the scheduled lunch time, per protocol (Table 1). Test times were 0900 hours and 1300 hours for the FISVTGTT and MTT, respectively, during Ns/Nm; 1230 hours and 1630 hours during Ns/Lm and Ls/Nm; and 1600 hours and 2000 hours during Ls/Lm. For the FISVTGTT, 4 basal blood samples were obtained prior to IV dextrose administration over 1 minute (0.03 mg 25% dextrose/kg body weight). Insulin (0.025 U/kg body weight) was injected IV 20 minutes later, and blood samples were collected until 180 minutes from glucose infusion, as previously described. The MINMOD Millenium 2003 program (v. 5.16, Bergman, USC) was used to determine SI, AIRg, and DI (product of SI and AIRg, which reflects β-cell ability to compensate for peripheral insulin resistance; low DI predicts type 2 diabetes in epidemiological studies). For the MTT, a premeal blood sample was obtained, followed by consumption of a liquid meal (Boost, Nestle Nutritional, Fremont, CA) providing 30% of the participant’s estimated energy requirements. Blood samples were obtained at 15, 30, 45, 60, 90, 120, and 180 minutes postprandially. The Matsuda index derived from the MTT parameters was used as a second measure of SI.

Glucose, insulin, and cortisol concentrations were analyzed by oxidase methods and radioimmunoassays (EMD Millipore, Billerica, MA) using standard protocols. Plasma melatonin obtained during the overnight sampling period was analyzed using ELISA.
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