Characterizing the Effects of Sleep Deprivation on Blood Glucose and Carbohydrate Cravings in Non-Diabetics using N-of-1 Randomized Trials

Katarzyna Wac, PhD
Marily Oppezzo, PhD
Eric J. Daza, DrPH

Our primary goals were twofold: To generate individual-specific hypotheses of the effect of sleep deprivation on blood glucose levels and carbohydrate cravings in non-diabetic individuals. To assess the utility and feasibility of our n-of-1 studies for achieving the aforementioned goal.

INTRODUCTION

METHODS

Study Design

This study consists of two n-of-1 randomized trials (N1RTs). An N1RT is defined as a randomized controlled crossover trial with one participant. Two of the authors were the study participants. We had the following two primary goals.

1. *Generate individual-specific hypotheses*. A priori hypotheses are required to design a N1RT (i.e., define outcomes, treatments, treatment periods, randomization schemes, etc.). However, there are few studies of individual-level effects of sleep deprivation on blood sugar control or carbohydrate craving. We therefore posited basic a priori hypotheses (which are detailed below) to begin structuring the N1RT.

   Each N1RT would be a small-sample study comprised of only accommodate eight treatment periods (with four on each level of a binary treatment). We would therefore not have enough statistical power to be able to strongly infer treatment effects. Hence, we made exploratory hypothesis generation (i.e., not confirmatory hypothesis testing) our primary goal: We would analyze the collected study data with the goal of refining the original a priori hypotheses by assessing post hoc analysis results.

   Randomization would serve to eliminate confounding of the treatment effect for a given treatment period (hereafter, “period”). This would allow us to better assess four other factors that could affect an N1RT outcome: autocorrelation with past outcomes, a time trend in the outcomes (e.g., due to unobserved causes), carryover of treatment effects from past periods, and the trajectory of treatment effects during a period.

2. *Assess study utility and feasibility*. We would report our experiences in designing and implementing this study, to help guide future study designs. This might include recommendations on how to recruit participants, better tailor each N1RT study design to each

participant, and ensure treatment compliance. We might also suggest which statistical methods to use to address the particular hypotheses or interests of each participant, or of the study investigators.

We were interested in the following three a priori study hypotheses regarding non-diabetics (i.e., non-diabetic individuals). Hypothesis 1 was that sleep deprivation (sleep-dep) renders blood sugar control less effective. Hypothesis 2 was that sleep-dep physiologically induces higher craving for quick carbohydrates because of the stress response. Hypothesis 3 was that sleep-dep worsens mood. Specifically, we expected the following average outcomes to occur during the days following sleep-dep compared with days not following sleep-dep: elevated glucose levels for longer intervals of time, more cravings for quick-energy foods, and more reports of negative mood.

The three primary outcomes were defined as follows. Blood glucose (BG) level, a continuous variable, was measured using a continuous glucose monitoring (CGM) device. Presence or absence of carbohydrate craving (carb-craving; i.e., a binary variable) was self-reported. Participant mood was assessed using 20 survey questions, with each self-reported response chosen from a five-point Likert scale (i.e., a five-level ordinal variable). BG level was recorded at least every 15 minutes. Both carb-craving and mood were recorded at the start, middle, and end of each 24-hour study day.

The five secondary outcomes were defined as follows. Craving fulfillment (i.e., eating or not eating the craved food, a binary variable) and craved foods (i.e., a free-text variable) were self-reported. Sleep quality the previous night and current-day diet healthfulness rating were self-reported using five-point Likert scales. Physical activity (PA) was assessed using an actigraphy metric (i.e., a continuous variable) measured using a smartwatch. Craving fulfillment and craved foods were recorded at the start, middle, and end of each 24-hour study day. Sleep quality was recorded at the start of each 24-hour study day. Diet healthfulness was recorded at the end of each 24-hour study day. PA was recorded fairly regularly throughout the study period (i.e., a participant's set of contiguous periods).

Treatments and periods were defined as follows. Each period consisted of three consecutive days. Sleep-dep was defined as getting at most four hours of sleep in a night. Active treatment was defined as sleep-dep on night 1 (i.e., the night of day 1) of a period, followed by recovery over the next two nights. Recovery was defined as getting at least 14 hours of sleep per night on two consecutive nights, with at least six hours per night on one of the nights, in order to fully recover (i.e., for outcomes to return to baseline levels on average). Baseline treatment was defined as getting at least six hours of sleep per night on all three nights of a period. Active-treatment periods were designated as treatment level "A", while baseline-treatment periods were designated as "B".

An exposure was defined as a measured phenomenon occurring before an outcome, that might thereby be associated with that outcome. Specifically, during a given period, an exposure was defined as a variable measured before an outcome that was not the treatment itself. For example, both a lagged outcome and a lagged treatment were considered exposures.

The self-reported outcomes were recorded using Qualtrics (version ??), a web-based survey instrument. CGM data were recorded using a Freestyle Libre device. PA actigraphy data were recorded using a combination of Samsung Gear Fit2 and Fitbit smartwatches.

Randomization Plan

We implemented the following non-blinded, randomized-block design. Each treatment block (hereafter, "block") consisted of two consecutive periods. On the first study day, the participant was randomized (i.e., randomly assigned) either to block AB (i.e., treatment A followed by B) or block BA. The next block was randomized on the last night of the current block, or during the first day of the next block. This procedure was repeated to produce four total consecutive blocks comprising eight periods over a 24-day study period.

This treatment allocation scheme was chosen because we did not suspect a time trend in the outcomes (i.e., we assumed that neither BG nor carb-craving systematically increases or decreases over time). If there was no such time trend, then this scheme would enhance the generalizability (i.e., ecological validity) of our findings. For example, the participant would only able to anticipate within-block treatments, thereby discouraging her from changing her sleep behavior in anticipation of an upcoming treatment assignment (e.g., trying to "stock up" on sleep during a B period in anticipation of an A period in the next block). Hence, her observed sleep behavior may be more representative of her natural habits outside of the study in cases wherein a sleep-dep episode cannot be anticipated over a week in advance. However, if there was an outcome time trend, unobserved time-varying causes may have confounded the treatment effect for some randomized sequences (e.g., AB-AB-AB-AB or BA-BA-BA-BA). We would assess the veracity of this assumption in post hoc analyses that account for a time trend (e.g., include time-dependent covariates).

To try to minimize (and hopefully eliminate) the effect of unassigned sleep-dep carrying over into a subsequent period (i.e., different from a carryover effect, which we only define for randomized treatments), it was important to enforce at least six hours of sleep per night. For example, suppose the participant becomes sleep deprived on night 3 of a B period for reasons not under the control of the study. Because we assumed each participant requires at least 14 hours of sleep over the next two nights to recover from sleep-dep, this unassigned sleep-dep episode may affect outcomes over the following two days, which are part of the next period. Hence, the effect of the next assigned treatment may be interfered with by the carryover effect of unassigned sleep-dep from the previous period.

Statistical Analysis Plan

In a small-sample, exploratory study such as ours, we anticipated relying on descriptive statistics, data visualizations, and exploratory predictive modeling to generate more refined hypotheses of treatment effects. For a given outcome, refining a treatment-effect hypotheses would involve discovering exposures that were highly associated with an outcome ("associated exposures"), and hence might be possible confounders. We planned to discover exposures as follows.

1. Descriptive statistics and data visualizations. For a given period, each exposure can be considered a baseline covariate. Hence, we would first identify possible associated exposures by examining various plots comparing two or more variables at a time. We would then report descriptive statistical summaries for each identified associated exposure.
2. We would flexibly model the dependence of each outcome on sets of predictors using a random forest approach applied within an N1RT framework (Daza 2018). We would then select models with the best predictive power, defined as the lowest test mean squared error (MSE) or highest area under the curve (AUC) for continuous and binary outcomes, respectively. Average period treatment effect (APTE) trajectories would be predicted and assessed using the CAPTEur

package (Daza 20??). The CAPTEur package also aids visual assessment of CAPTEs by producing pancit plots, which are spaghetti plots created by overlaying outcome trajectories created by partitioning an N1RT time series by period.

We anticipated conducting further data exploration as ideas were generated in executing the processes above. This could involve checking if and how exposures are associated with each other, or investigating other relationships between any of the measured variables.

All analyses would be conducted in R (version 3.5.0).

RESULTS

Post Hoc Hypotheses

Dear Eric,

I am catching some deadlines for tomorrow 5pm hence so far i will send you only ONE hypothesis i derived based on my observation (and not looking into the data)

namely:

- the first and the second short nights were relatively easy on me and the next next days were also quite active and energetic and easy too. Not much craving the days after

- the 3rd and 4th nights were difficult to stay up and day after i was more tired

- The third night i already have had a craving in the evening when i needed to stay up (i was tired)

- the third and fourth short nights resulted in craving day afterwards but i do not think i gave in (i don't remember)

I stop here and let you to ask me details for the above ideas such that we agree what we should be looking for in a dataset.

Feedback is welcome!

take care

best wishes for your lovely trip and family visit!

Kate

DISCUSSION

REFERENCES

1. Daza, EJ. Introducing the CAPTEur package for assessing putative single-subject treatment effects. *Journal of Statistical Software*. (manuscript in progress).
2. Daza, EJ. Causal analysis of self-tracked time series data using a counterfactual framework for n-of-1 trials. *Methods of Information in Medicine*. 2018 Feb, vol. 57(01): e10-21.

APPENDIX: Randomizations

Your first treatment block is BA. Hence, please do the following:

“B" (inactive/baseline treatment)

— The nights of 1, 2, and 3 August: Get at least 6hrs of sleep every night.

“A" (active treatment)

— The night of 4 August: Get at most 4hrs of sleep.

— The nights of 5 and 6 August: Get at least 14hrs of sleep total, with at least 6hrs of sleep every night on one of these days (e.g. 6hrs night of 5 Aug + at least 8hrs night of 6 Aug, or 7hrs on 5 Aug + at least 7hrs on 6 Aug, etc.).

Your **second** treatment block is AB. Hence, please do the following:

“A" (active treatment)
— The night of 7 August: Get at most 4hrs of sleep.
— The nights of 8 and 9 August: Get at least 14hrs of sleep total, with at least 6hrs of sleep every night on one of these days (e.g. 6hrs night of 8 Aug + at least 8hrs night of 9 Aug, or 7hrs on 8 Aug + at least 7hrs on 9 Aug, etc.).

“B" (inactive/baseline treatment)
— The nights of 10, 11, and 12 August: Get at least 6hrs of sleep every night.

I will assign your next treatment on the morning of 13 August (Sunday).

Your third treatment block is AB. Hence, please do the following:

“A" (active treatment)

— The night of 13 August: Get at most 4hrs of sleep.
— The nights of 14 and 15 August: Get at least 14hrs of sleep total, with at least 6hrs of sleep every night.

“B" (inactive/baseline treatment)
— The nights of 16, 17, and 18 August: Get at least 6hrs of sleep every night.

I will assign your last treatment on the morning of 19 August (Saturday).

Your last treatment block is AB. Hence, please do the following:

“A" (active treatment)
— The night of 19 August: Get at most 4hrs of sleep.
— The nights of 20 and 21 August: Get at least 14hrs of sleep total, with at least 6hrs of sleep every night.

“B" (inactive/baseline treatment)
— The nights of 22, 23, and 24 August: Get at least 6hrs of sleep every night.