7-22-2022

Is a blunted cortisol response to stress a premorbid risk for insomnia?

Anthony N. Reffi
Henry Ford Health, areffi1@hfhs.org

Philip Cheng
Henry Ford Health, PCHENG1@hfhs.org

David A. Kalmbach
Henry Ford Health, DKalmba1@hfhs.org

Tanja Jovanovic

Seth D. Norrholm

See next page for additional authors

Recommended Citation

Reffi AN, Cheng P, Kalmbach DA, Jovanovic T, Norrholm SD, Roth T, and Drake CL. Is a blunted cortisol response to stress a premorbid risk for insomnia? Psychoneuroendocrinology 2022; 144:105873.

Authors

Anthony N. Reffi, Philip Cheng, David A. Kalmbach, Tanja Jovanovic, Seth D. Norrholm, Thomas Roth, and Christopher L. Drake

Psychoneuroendocrinology 144 (2022) 105873

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Is a blunted cortisol response to stress a premorbid risk for insomnia?

Anthony N. Reffi [a], Philip Cheng [a], David A. Kalmbach [a], Tanja Jovanovic [b], Seth D. Norrholm [b], Thomas Roth [a], Christopher L. Drake [a,*]

[a] Sleep Disorders and Research Center, Henry Ford Health System, Detroit, MI, USA
[b] Neuroscience Center for Anxiety, Stress, and Trauma (NeuroCAST), Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, USA

ARTICLE INFO

Keywords:
Sleep reactivity
Insomnia
Sleep
Cortisol
Hypothalamic-pituitary-adrenal axis
Blunted stress response
Stress

ABSTRACT

Study objectives: Vulnerability to stress-related sleep disturbances (sleep reactivity) is an established heritable risk factor for insomnia disorder with unclear biological underpinnings. Preliminary research points to a blunted cortisol response to stress as a biological predisposition to familial risk for insomnia, but the role of cortisol response in sleep reactivity is unknown. Therefore, the current studies examined whether sleep reactivity is associated with a blunted cortisol response to two laboratory stressors among participants without insomnia.
Methods: Two community samples of adults with no lifetime history of insomnia completed the Trier Social Stress Test ($N = 35$) or the Cold Pressor Task ($N = 34$). Participants were grouped by insomnia-risk using sleep reactivity scores from the Ford Insomnia Response to Stress Test (FIRST). Physiological responses were measured via markers of the hypothalamic-pituitary-adrenal (HPA) axis (salivary cortisol) and autonomic nervous system (ANS; heart rate, mean arterial pressure, and salivary alpha amylase).
Results: Participants with high insomnia-risk (FIRST score $\geq$ 18) exhibited blunted cortisol responses to both stressors. There were no group differences in ANS responses across stressors.
Conclusions: Insomnia-risk as indicated by sleep reactivity is associated with blunted cortisol responses to psychosocial and physical laboratory stressors among premorbid adults without insomnia disorder. This study replicates previous research and supports a blunted cortisol response to stress as a biomarker for insomnia vulnerability that may be detected using the FIRST. Prospective research is needed to elucidate whether a blunted cortisol response to stress is one mechanism by which sleep reactive individuals may be at risk of developing insomnia.

1. Introduction

The diathesis-stress model is a central feature of our current understanding of the etiology of disturbed sleep and insomnia. As part of the well-established 3 P model of insomnia (Spielman et al., 1987), insomnia arises when latent predispositional vulnerabilities are activated by environmental stressors (Perlis et al., 2014; Spielman et al., 1987). These predispositional vulnerabilities have been characterized along multiple dimensions, including personality (LeBlanc et al., 2009), social context (Gellis et al., 2005), and familial/genetic risk (Bastien and Morin, 2000; Drake et al., 2008; Harvey et al., 2014). Delineating the biological underpinnings of such vulnerabilities may enable investigators to further elucidate the etiology of insomnia disorder, thereby informing efforts to treat and prevent insomnia and its myriad sequelae. To that end, the biological markers of sleep reactivity remain a critical area of inquiry (Kalmbach et al., 2018).

Sleep reactivity is a heritable tendency to exhibit pronounced sleep disruption following environmental perturbations, including stress exposure (Drake et al., 2004, 2011; Fernandez-Mendoza et al., 2014). Individuals reporting high sleep reactivity exhibit sleep disturbance in response to a variety of stimuli, including environmental factors such as sleeping in a foreign environment (i.e., "first night effect"), pharmacological challenges such as caffeine administration (Drake et al., 2006), circadian challenges (Bonnet and Arand, 2003), and psychological stress (Petersen et al., 2012). Sleep reactivity shows within-person stability (Drake et al., 2014; Jarrin et al., 2016; MacNeil et al., 2017), potentiates the effects of stress exposure (Drake et al., 2017), and has strong predictive value for incident insomnia (Kalmbach et al., 2016). Thus, sleep

* Correspondence to: Sleep Disorders & Research Center, Department of Sleep Medicine, Henry Ford Health System, 39450 West Twelve Mile Road, Novi, MI 48377, USA.
E-mail address: cdrake1@hfhs.org (C.L. Drake).

https://doi.org/10.1016/j.psyneuen.2022.105873
Received 31 March 2022; Received in revised form 8 July 2022; Accepted 19 July 2022
Available online 22 July 2022

reactivity is a reliable and valid trait-like marker for insomnia vulnerability. Although the behavioral correlates of sleep reactivity have been well-established, its biological underpinnings have yet to be adequately characterized.

Given sleep reactivity reflects the sleep response to stress, it might be associated with abnormalities in the stress regulation system. In our previous work, we found evidence a blunted cortisol response to stress is an inherited vulnerability that contributes to the development of insomnia (Drake et al., 2017). Specifically, healthy sleepers with familial risk for insomnia demonstrated a blunted cortisol response to the Trier Social Stress Test (TSST), a potent psychosocial stress challenge (Kirschbaum et al., 1993). Notably, this blunted stress response appears specific to cortisol, as studies have found comparable sympathetic activation between groups with high versus low insomnia-risk (Chen et al., 2017; Drake et al., 2017). Considering evidence that sleep reactivity and blunted cortisol responsiveness are both heritable risk factors (Drake et al., 2011; Fernandez-Mendoza et al., 2014; Schuckit et al., 1988, 1987), blunted cortisol responsiveness may be a marker for sleep reactivity as well.

Although preliminary evidence points to blunted cortisol reactivity as a biological predisposition to insomnia, more research is needed on its associations with known risk factors for insomnia. The current study characterized differences in the stress regulatory systems (hypothalamus pituitary adrenal (HPA) axis and autonomic nervous system (ANS)) between adults with high and low sleep reactivity using two different samples via two different daytime laboratory stressors. The first study utilized an archival sample of adults without insomnia with high and low sleep reactivity who completed the TSST (Drake et al., 2017). The second study sought to support the first study's results in a separate sample of premorbid adults with high and low sleep reactivity who completed the Cold Pressor Test (CPT), a physical stress challenge that reliably increases HPA and ANS activity (al'Absi et al., 2002; McRae et al., 2006).

2. Study 1: trier social stress test

2.1. Methods

2.1.1. Participants

Analyses for the first study were completed using archival data that examined the association between familial risk for insomnia and stress reactivity to the TSST (Drake et al., 2017). Participants were recruited through newspaper advertisements and from participation in previous studies. Interested individuals completed a telephone screening, and those who reported psychiatric, medical, or sleep disorders were excluded from study participation to minimize heterogeneity. Women using oral contraceptives were excluded. A history of social use of alcohol was allowed but not while in the study, and smokers were excluded. A total of 42 individuals met initial eligibility based on an initial telephone screening and were invited to complete an in-person interview. An additional seven were excluded due to insomnia assessed via the Insomnia Severity Index and clinical interview using the International Classification of Sleep Disorder (2nd edition) criteria. A final sample of 35 individuals were enrolled in the study (51% female, $M_{age} = 46.5$, $SD = 10.5$, range = 23–64), and were categorized into high ($N = 16$) and low ($N = 19$) sleep reactive groups based on the Ford Insomnia Response to Stress Test (FIRST) using a cut-off of 18 (Kalmbach et al., 2016). High and low sleep reactive groups did not differ by age, sex, or BMI (all $ps > 0.05$).

2.2. Procedures

Prior to participation, volunteers were asked to refrain from naps and maintain a consistent sleep schedule for one week, determined based on habitual sleep times. Sleep diaries were used to verify sleep schedule adherence. Participants were also asked to refrain from use of alcohol, caffeine, tobacco, and other illicit substances for 24 h prior to testing. Urine drug screens ensured abstinence from illicit substances.

2.2.1. Physiological stress response

The autonomic stress response was measured using heart rate (HR), mean arterial pressure (MAP), and salivary alpha amylase. HR was monitored using Masimo SET pulse oximeter, and blood pressure was monitored using a portable HealthSmart blood pressure machine. MAP was calculated by adding one-third of the pulse pressure (subtracting the diastolic pressure from the systolic pressure) to the diastolic pressure (Zheng et al., 2008). Alpha amylase was assayed in salivary samples to index ANS activation (Nater and Rohleder, 2009). Alpha amylase was analyzed in singlet using the Kinetic Enzymatic kit with a sensitivity of 0.4 U/mL (Salimetrics, State College, PA). Mean intra- and inter-assay coefficients of variation were 5.5% and 4.7%, respectively. HPA axis response was measured using cortisol, which was also assayed in salivary samples. Cortisol was analyzed in duplicate using an ELISA kit with a sensitivity of 0.007 μg/dL (Salimetrics, State College, PA). Mean intra- and inter-assay coefficients of variation were 4.6% and 6%, respectively. All saliva samples were obtained using an oral swab and frozen at −20 °C immediately following collection (Salimetrics, State College, PA). Saliva samples for the last five samples were lost for one participant due to technical difficulties.

2.2.2. Trier social stress test protocol

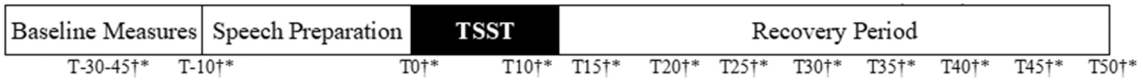
The experimental procedure included three components: (1) collection of baseline measures, (2) speech preparation and stress tasks, and (3) a 40-minute recovery period post-TSST. Physiological measures of stress were collected throughout the experimental protocol, including the baseline pre-speech period, and every five minutes starting 10 min post-TSST (i.e., the recovery period: T10, T15, T20, T25, T30, T35, T40, T45, T50) (see Fig. 1).

2.2.2.1. Baseline. The TSST (Kirschbaum et al., 1993) experimental sessions were run between the hours of 1100–1600. Upon arrival, subjects remained seated for approximately 30–45 min while baseline measurements were recorded. Baseline HR and blood pressure were indexed by an average of three samples during this period, and alpha amylase and cortisol were assayed using one saliva sample.

2.2.2.2. Speech preparation. Following baseline, participants were taken to the speech room, where three hospital staff members (both males and females) were sitting at a rectangular table with a video camera installed and pointed toward the head of the table. Participants were instructed to stand in front of the three staff members while the research assistant instructed the participant to assume the role of a job applicant invited for a personal interview with a company's staff managers. Participants were informed that following a preparation period, they were to present a 5-minute speech persuading the hospital staff that they were the perfect applicant for the vacant position. Participants were also informed the staff were specially trained to monitor nonverbal behavior, and the audio and visual recording would be subjected to both video and voice frequency analyses (Kirschbaum et al., 1993).

Following these instructions, the participants returned to the previous room and were given 10 min for speech preparation. Each participant was provided with paper and pencils for outlining their speech, although written material was not allowed during the speech. Communication with the research assistant was limited during the speech preparation phase. Physiological stress measurements were collected following speech preparation.

2.2.2.3. Stress tests. Following speech preparation, participants were returned to the speech room by wheelchair to control for postural variance in blood pressure and seated at the head of the table in front of the three hospital staff. The lead manager welcomed the participant as a



Note. T = Timepoints (in minutes) before, during, and after the TSST (including the mental arithmetic task) (e.g., T-10 = 10 minutes before).
† Heart rate and blood pressure assessed
* Salivary cortisol and alpha amylase collected

Fig. 1. Timeline of data collection before, during, and after the Trier Social Stress Test (TSST).

job applicant and asked him/her to deliver the speech for the next five minutes. If the speech ended in less than five minutes, the manager would state, "You still have some time left. Please continue." Once the five minutes was complete, the stress measurements were promptly taken.

An oral mental arithmetic challenge immediately followed the speech task. Participants were instructed to serially subtract 13 from 1022 with speed and accuracy for five minutes. Participants restarted at 1022 following each error as instructed by the research assistant. Following the arithmetic portion, stress measurements were taken again and continued throughout the recovery period (Kirschbaum et al., 1993).

2.2.2.4. Recovery period. Participants were allowed 40 min for recovery following the stress tests, during which they remained in the speech room (only research assistant present) with pre-selected National Geographic magazines. Saliva samples (cortisol and alpha amylase) and cardiovascular measures were repeated every five minutes until the end of the recovery period. At the end of the study, participants were debriefed about its goal and informed neither voice frequency nor video analyses would be performed.

2.2.3. Analytical approach

We evaluated cortisol data for normality with skewness and kurtosis, with a threshold of − 2/+ 2 for skewness (Field, 2018; George and Mallery, 2019; Gravetter and Wallnau, 2011; Trochim and Donnelly, 2008) and − 7/+ 7 for kurtosis (Byrne, 2016; Hair, 2010). Changes in physiological stress responses across the experiment were modeled using a mixed-effects approach because it is more robust in handling unequal sample sizes and missing data than the traditional repeated-measures analysis of variance (Gueorguieva and Krystal, 2004). Group differences were modeled using high and low FIRST groups as a categorical factor, entered as both a main effect and as an interaction with Time. Differences in stress responses following the TSST were assessed via the interaction of Time × FIRST. Sex was entered as a covariate in all analyses given that females are generally more likely to report high FIRST (Kalmbach et al., 2018). Age was tested as a covariate in model building, but was removed from final models due to non-significance. The intercept was included as a random effect to account for individual differences in baseline stress levels.

We considered two different models of time because specific components of the stress response system have varying response patterns over time (e.g., ANS versus HPA axis response). Each outcome variable was tested using a spline linear regression ($Time_{lin}$) and a quadratic model ($Time_{quad}$), and the fit of each model was assessed using the McFadden's R^2. Whereas a segmented linear model best captures swift linear changes across time (e.g., a sharp inflection point representing a peak followed by a fast linear recovery), quadratic models can represent non-linear changes across time that better represent physiological responses that have a delayed peak followed by a non-linear recovery (e.g., cortisol response). The final models were selected based on the highest McFadden's R^2 value.

A statistically significant main effect of Time would indicate elicitation of a stress response across groups, and a statistically significant main effect of FIRST would indicate differences in average stress values between high and low FIRST groups. A significant interaction effect of $Time_{quadratic}$ × FIRST would indicate stress responses to the TSST differed by high and low FIRST groups. Finally, area under the curve (AUC) was also calculated for both cortisol and alpha-amylase values using the trapezoid formula correcting for baseline values. AUC was also tested using a mixed-effects model with FIRST groups as the fixed effect and subject as the random effect to examine global HPA axis and ANS responses to the TSST.

3. Results

3.1. HPA axis response

A significant quadratic effect was detected in cortisol, indicating significant responses to the TSST, main effect of $Time_{quadratic}$: $b = -0.21$, $SE = 0.04$, $p < .001$.[1] Furthermore, results also indicated cortisol responses differed by FIRST groups, $Time_{quadratic}$ × FIRST ($b = -0.19$, $SE = 0.07$, $p < .01$). Specifically, the high FIRST group demonstrated a blunted curvature in cortisol, marginal effect of $Time_{quadratic}$ ($b = -0.10$, $SE = 0.05$, $p = .06$), compared to the low FIRST group, marginal effect of $Time_{quadratic}$ ($b = -0.30$, $SE = 0.05$, $p < .0001$; see Fig. 2). Planned contrasts of cortisol values between insomnia-risk groups at each time point (tested using the marginal effects of FIRST in the model) indicated the high FIRST group had lower cortisol values at all the time points

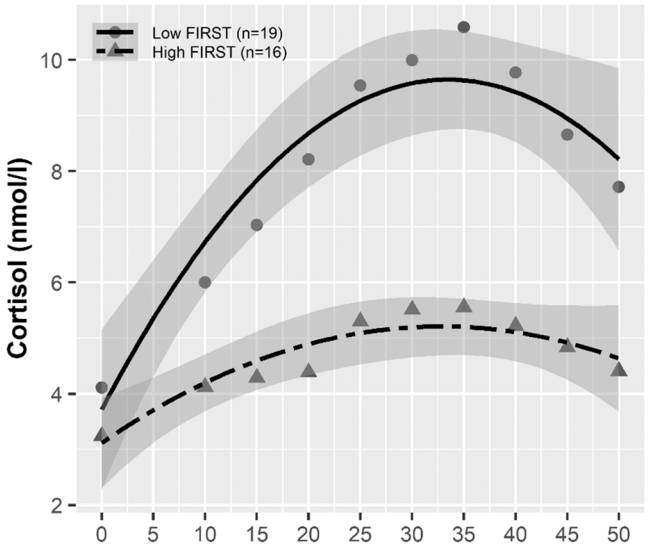


Fig. 2. Cortisol response to the Trier Social Stress Test (TSST) across time (min) compared by insomnia-risk groups. High FIRST = sum ≥ 18, low FIRST = sum < 18. 0 = pre-speech preparation; 5–50 = post-TSST recovery. Shaded areas represent standard error of the parameter estimate for $Time_{quadratic}$.

[1] Cortisol normality values (skewness and kurtosis) were acceptable and thus data were not transformed.

except at baseline. Planned contrasts of the differences in slope between insomnia-risk groups at each time point (tested using the marginal effects of $Time_{linear} \times$ FIRST in the model) showed a lower slope for the high FIRST group at baseline, T10, T15, T20, T25, and T30. Finally, an independent sample t-test of the AUC for cortisol also indicated high FIRST individuals exhibited lower cortisol values ($M = 260.34$, $SE = 29.46$) compared to the low FIRST individuals ($M = 465.13$, $SE = 52.47$), $t(34) = -10.32$, $p < .0001$.

3.2. ANS response

The spline linear regression indicated a significant increase in HR associated with the TSST across risk groups, $Time_{TSST}$: $b = 2.6 \pm 0.8$ SE, $p < .001$, followed by a significant reduction in HR through the recovery period, $Time_{recovery}$: $b = -4.2 \pm 1.0$ SE, $p < .001$. Results did not reveal differences between FIRST groups.

Analyses using MAP also indicated an increase across risk groups associated with the TSST though the results were only approaching statistical significance, $Time_{TSST}$: $b = 1.0 \pm 0.6$ SE, $p = .07$. However, results did show a significant reduction in MAP through the recovery period, $Time_{recovery}$: $b = -2.4 \pm 0.7$ SE, $p < .001$. Results did not reveal differences between FIRST groups.[2]

Analyses using alpha amylase revealed similar results, with an increase across risk groups associated with the TSST, $Time_{TSST}$: $b = 5.0 \pm 1.3$ SE, $p < .001$, and a significant reduction during the recovery period, $Time_{recovery}$: $b = -9.3 \pm 1.7$ SE, $p < .001$. Results did not reveal differences between FIRST groups.

4. Study 2: cold pressor task

4.1. Methods

4.1.1. Participants

Participants ($N = 34$, 50% female, $M_{age} = 28.29$, $SD = 8.79$, range = 19–48) were recruited through newspaper advertisements and from participation in previous studies. To minimize heterogeneity, those with psychiatric, medical, or sleep disorders were excluded based on clinical evaluation by a board-certified sleep specialist and an overnight polysomnography (PSG). Women using oral contraceptives were excluded. Exclusion criteria also included use of > 10 cigarettes per day or any habitual use of cigarettes immediately before bedtime, use of psychotropic medications, or habitual daily consumption of > 250 mg of caffeine (2–4 cups of coffee). A history of social use of alcohol was allowed but not while in the study. Urine drug screens ensured abstinence from illicit substances. Participants were categorized into high ($N = 15$) and low ($N = 19$) sleep reactive groups based on FIRST cut off of 18 (Kalmbach et al., 2016). High and low sleep reactive groups did not differ by age, sex, or BMI (all $ps > 0.05$).

4.1.2. Procedures

The first laboratory visit comprised an overnight PSG scheduled from 23:00 to 7:00 for all subjects. The 8-hour screening PSG included nasal/oral flow measurement and anterior tibialis electromyography to assess for respiratory events and periodic limb movements, respectively (Zucconi et al., 2006). Six electroencephalogram electrodes were used with standard placements: two central (C3 and C4), one occipital (O1), one frontal (F4), and two reference (M1 and M2). Standard electrooculogram and chin electromyogram placements were also used. Sampling rate was set at 200 Hz and impedance was kept below 10 kOhms. No subjects had an apnea-hypopnea index > 5/hr or periodic limb movements > 5/hr. All studies were conducted and scored using previously published criteria (R&K) (Wolpert, 1969).

4.1.3. Physiological stress response

The autonomic stress response was measured using HR and MAP (but not salivary alpha amylase, unlike Study 1). HR and blood pressure were monitored using a standard portable blood pressure monitor (Welch Allyn, Skaneateles Falls, NY). MAP was calculated using the same approach as Study 1. HPA axis response was indexed via salivary cortisol obtained using an oral swab, centrifuged and frozen at − 20 °C following collection (Salimetrics, State College, PA). Cortisol was analyzed in duplicate using an ELISA kit with a sensitivity of 0.007 μg/dL (Salimetrics, State College, PA). Mean intra- and inter-assay coefficients of variation were below 10%.

4.1.3.1. Cold pressor task protocol. The CPT was used as a standard challenge to the HPA axis (McRae et al., 2006; Wolff, 1951). This challenge task required participants to immerse their hand in cold water (4°C) up to just above the wrist for a sustained period to elicit an HPA response identified by increased salivary cortisol. The validity and reliability of this task for eliciting sympathetic and HPA activation have been demonstrated previously (Durel et al., 2007; Kelly and Cooper, 1998; McRae et al., 2006; Micieli et al., 1994; Mizushima et al., 2003, 1998; Schwabe et al., 2008; Yamamoto et al., 1992).

Participants were instructed to keep their hands in the water as long as possible, up to a maximum of three minutes (Min = 13.7 s, Max = 180 s (3 min), Mean = 110.1 s, SD = 67.4 s). Consistent with previous studies using the CPT as an HPA challenge, subjects were observed by a research associate during the CPT to maximize the cortisol response and collect subjective and physiological responses (Schwabe et al., 2008). The task was performed between 1530 and 1630 h and was repeated following a recovery day. Measures of HR and blood pressure were assessed five minutes prior to CPT (T-5), immediately prior to CPT (T0), immediately upon hand removal (T1), and two minutes following hand removal (T2). Salivary cortisol samples were collected immediately prior to the CPT (T0), and at 10, 20, 30, 40 and 50 (T10 to T50) minutes post-CPT on each of two CPT days (see Fig. 3).

4.1.4. Analytical approach

We evaluated cortisol data for normality with skewness and kurtosis, with a threshold of − 2/+ 2 for skewness (Field, 2018; George and Mallery, 2019; Gravetter and Wallnau, 2011; Trochim and Donnelly, 2008) and − 7/+ 7 for kurtosis (Byrne, 2016; Hair, 2010). We then examined consistency of results between the two repetitions of the CPT by comparing outcome variables (HR, MAP, and cortisol) in a mixed-effects model. The models included both intercept and slope as random effects to account for individual differences in baseline stress levels and change in stress response over time. Time (corresponding to respective measurement periods) was examined in the models as both linear ($Time_{linear}$) and quadratic ($Time_{quadratic}$) terms to model any non-linear changes in stress response (e.g., an initial increase of cortisol followed by a subsequent decline throughout the recovery period). A negative coefficient for the $Time_{quadratic}$ term indicated an inverted-U shaped parabola, with higher negative values indicating steeper curvature. Differences in stress response between trials were assessed using interaction terms depending on the growth pattern of dependent variables – a linear change across time was modeled using the $Time_{linear} \times$ Trial interaction term, and a non-linear change across time was modeled using both the $Time_{linear} \times$ Trial and $Time_{quadratic} \times$ Trial interaction terms.

Sleep reactivity was also examined as a moderator of stress response to the CPT. Specifically, the models were conducted with Time × FIRST interaction ($Time_{linear}$ for HR, $Time_{quadratic}$ for MAP), along with all lower order terms. A significant interaction effect of Time × FIRST groups would indicate stress responses to the CPT differed by FIRST groups, and the lower-order terms (i.e., marginal effects) were only examined to aid the interpretation of any observed Time × FIRST group interaction. In cases where FIRST was not a significant moderator, the

[2] Analyses using systolic blood pressure and diastolic blood pressure separately produced the same results.

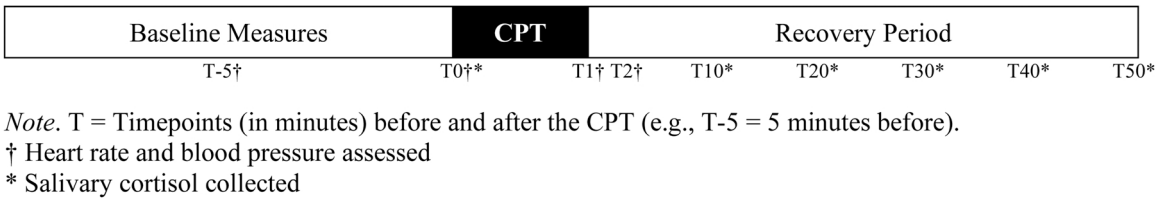


Fig. 3. Timeline of data collection before and after the Cold Pressor Test (CPT).

final models were reduced to a main effects model including Time and FIRST groups as fixed effects. In the main effects model, a statistically significant effect of Time indicated elicitation of a stress response across groups, and a statistically significant effect of FIRST groups indicated a difference in average responses between high and low FIRST groups.

4.2. Results

4.2.1. Inter-trial consistency

Analyses comparing HR, MAP, and cortisol indicated no differences between trials (i.e., the two days of CPT administration).[3] Across both trials, HR demonstrated a linear decrease with time, main effect of $Time_{linear}$ ($b = -0.27$, $SE = 0.12$, $p < .05$). MAP across trials showed a non-linear inverted-U pattern, main effect of $Time_{quadratic}$ ($b = -0.15$, $SE = 0.05$, $p < .01$), indicating an initial increase of MAP followed by a subsequent decrease. Finally, cortisol across trials also showed a significant non-linear inverted-U pattern, main effect of $Time_{quadratic}$ ($b = -0.22$, $SE = 0.04$, $p < .001$). Given that consistency was found across both trials, HR, MAP, and cortisol values were averaged across the two trials, and these averages were used for subsequent analyses for parsimony and to preserve power.

4.3. Sleep reactivity and stress

4.3.1. HPA axis response

Similar to the cortisol results from the TSST study, a significant quadratic effect was detected in cortisol for the CPT, indicating a significant HPA axis response, main effect of $Time_{quadratic}$: $b = -0.22 \pm 0.03$ SE, $p < .001$. Furthermore, results also indicated that FIRST groups moderated the cortisol response, $Time_{quadratic} \times$ FIRST: $b = 0.13 \pm 0.06$ SE, $p < .05$). Specifically, the high FIRST group demonstrated a blunted curvature in cortisol, marginal effect of $Time_{quadratic}$: $b = -0.16 \pm 0.04$ SE, $p < .001$), compared to the low FIRST group, marginal effect of $Time_{quadratic}$ ($b = -0.29 \pm 0.05$ SE, $p < .0001$) (see Fig. 4).

Planned contrasts of the differences in slope between groups at each time point showed a lower slope for the high FIRST group at all time points between the first (pre-CPT) and last (T50) samples collected. Finally, a comparison of the AUC for cortisol also indicated high insomnia-risk individuals ($M = 17.33$, $SE = 2.41$) exhibited significantly lower total cortisol production (by 35.6%) across the task relative to low insomnia-risk individuals ($M = 26.90$, $SE = 2.13$), $t(23.19) = -2.90$, $p < .01$.

4.3.2. ANS response

ANS responses to the CPT were similar to the TSST. FIRST was not a significant moderator of the HR response to the CPT, $Time_{linear} \times$ FIRST: $b = 0.03 \pm 0.64$ SE, $p = .97$. As such, FIRST was replaced as a covariate in the final model. Results in the model did show a significant effect of $Time_{linear}$: $b = -0.74 \pm 0.31$ SE, $p < .05$, and no significant effect of FIRST: $b = 1.58 \pm 3.44$ SE, $p = .65$, suggesting both high and low FIRST groups showed the same pattern of decreased heart rate across the task.

Results for MAP also showed FIRST was not a significant moderator of MAP response to the CPT, $Time_{quadratic} \times$ FIRST: $b = 0.60 \pm 0.73$ SE, $p = .41$. As such, FIRST was replaced as a covariate in the final model. A significant main effect of $Time_{quadratic}$: $b = 1.11 \pm 0.35$ SE, $p = .41$, along with a non-significant effect of FIRST: $b = 1.45 \pm 2.89$ SE, $p = .62$, suggested both high and low FIRST groups experienced a similar MAP response to the CPT.

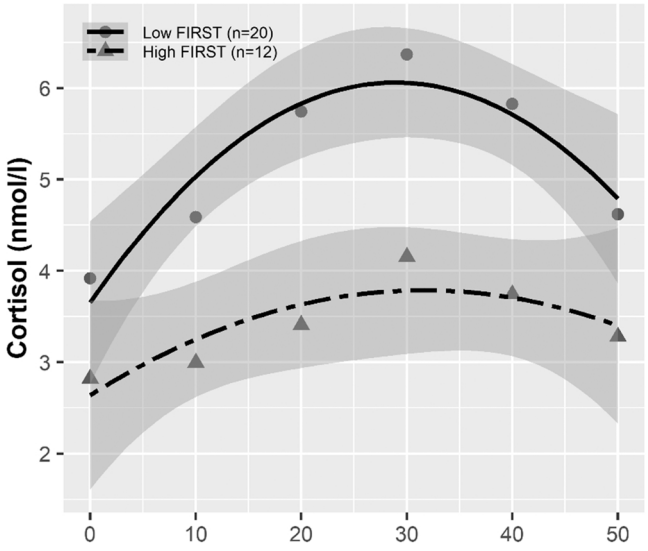


Fig. 4. Cortisol response to the Cold Pressor Task (CPT) across time (min) compared by insomnia-risk groups. High FIRST = sum $\geq$ 18, low FIRST = sum < 18. 0 = immediately prior to CPT; 10–50 = post-CPT recovery. Values are averaged across two days of repeated CPT administration. Shaded areas represent standard error of the parameter estimate for $Time_{quadratic}$.

5. Discussion

These studies examined whether differences in physiological stress regulation were associated with a heritable predisposition for insomnia as indicated by high and low sleep reactivity. Individuals with high sleep reactivity exhibited a dampened HPA axis response to laboratory stressors, whereas their ANS response was no different from individuals with low sleep reactivity. Specifically, individuals with high sleep reactivity exhibited a blunted cortisol response to both the TSST and CPT. These results replicate and extend prior findings on familial risk for insomnia (Drake et al., 2017) and highlight a blunted cortisol response to stress as a shared biomarker of heritable, biological predispositions for insomnia, namely sleep reactivity.

The reasons for our findings are likely varied. One possibility is a blunted cortisol response to stress may indicate reactive sleepers have restricted access to adaptive skills for coping with or regulating emotions following stress (Carroll et al., 2017; Lovallo, 2011). This is consistent with our previous finding that a blunted cortisol response was associated with more avoidance of stressful events.(Drake et al., 2017) When faced with acute stress, cortisol secretion mobilizes energy resources to facilitate an adaptive response and eventual return to homeostasis. Conversely, a blunted cortisol response may impede the

[3] Cortisol normality values (skewness and kurtosis) were acceptable and thus data were not transformed.

ability to respond adaptively to a stressor, ultimately increasing allostatic load and vulnerability to illnesses (Bower et al., 2005; Hébert and Lupien, 2007). Indeed, blunted cortisol responsiveness is associated with deficits in psychological coping (Drake et al., 2017), worse long-term adaptation to stress (Galatzer-Levy et al., 2014), and mental health outcomes marked by regulatory difficulties (i.e., depression, anxiety, PTSD, substance and non-substance addiction, and disordered eating) (Carroll et al., 2017; Schmalbach et al., 2020; Turner et al., 2020). Alternatively, a blunted cortisol response may reflect an HPA system exerting a more robust negative feedback response among reactive sleepers, thus producing greater down-regulation of cortisol. It is also conceivable that the adrenal or pituitary glands of reactive sleepers were less sensitive to stress exposure, resulting in less secretion of hormonal precursors to cortisol (e.g., corticotropin-releasing, or adrenocorticotropic hormones). More research is needed to elucidate the mechanisms driving this blunted stress response and how it might affect risk for future insomnia.

Although these results comport with our previous work on biological correlates of familial risk for insomnia, they only partially replicate another study examining stress responses to the TSST in sleep reactivity. That is, our results converge with Chen and colleagues' finding that autonomic responses to stress did not vary by sleep reactivity, suggesting individuals are comparable in their immediate responses to stress, regardless of insomnia-risk (Chen et al., 2017; Drake et al., 2017). This may be explained by evidence of a dissociation between HPA axis and autonomic responsiveness to stress (Frankenhaeuser et al., 1980; Schommer et al., 2003). Nevertheless, unlike our studies, Chen et al. (2017) did not find differences in cortisol responses between low and high reactive sleepers. This suggests dysregulated HPA axis responsiveness is not implicated in sleep reactivity, a notion difficult to reconcile with the putative links between sleep reactivity, stress reactivity, and HPA functioning (Kalmbach et al., 2018; Lo Martire et al., 2020). Said differently, if sleep reactivity is the expression of stress reactivity in the sleep system, then differences in HPA axis responsiveness would be expected among those with elevated sleep reactivity. One possible explanation for these divergent findings may be time-of-day effects. Whereas we administered our stressors between the late morning and afternoon hours (TSST: 1100–1600, CPT: 1530–1630), Chen et al. (2017) administered the TSST approximately one hour before participants' bedtime. Yet, the circadian rhythm of cortisol secretion follows a gradual decline throughout the day before leveling off around midnight (Buckley and Schatzberg, 2005; Gunnar and Vazquez, 2001), and the timing and strength of a cortisol response is affected by when the stressor occurs (Rankin et al., 2012; Vargas et al., 2018). Thus, it is possible the indiscernible cortisol response between high and low reactive sleepers in their study was due in part by the timing of the stressor or collection of cortisol or both.

Our findings might help clarify the mixed evidence on the role of HPA axis functioning in the developmental trajectory of insomnia. For example, two recent studies found individuals with insomnia showed a greater cortisol response than healthy sleepers following the TSST (Chen et al., 2017) and CPT (Devine et al., 2019), whereas another found no differences following threat of electric shock (Gehrman et al., 2016). Aside from important differences between laboratory stressors, these discrepancies may reflect a methodological artifact owing to these samples selecting for the expression of an insomnia disorder rather than its diatheses. This sampling approach likely produces inconsistent results because some individuals with insomnia will have particular biological risk factors (e.g., family history, trait sleep reactivity) while others will not. Similarly, there may be neurobiological differences between insomnia phenotypes, as emerging evidence implicates blunted cortisol responsiveness in sleep-onset insomnia (Hansen et al., 2021). Put simply, if a blunted cortisol response is specific to a biological predisposition (or phenotype), it may be obscured in a heterogenous sample. Our studies contribute to this literature by utilizing two samples of participants with diathesis for insomnia in the form of sleep reactivity. Taken with evidence that both sleep reactivity and a blunted cortisol response are heritable risk factors (Drake et al., 2011; Fernandez-Mendoza et al., 2014; Schuckit et al., 1988, 1987), perhaps a blunted cortisol response to stress may be an inherited vulnerability that contributes to the development of insomnia. More research is needed to test this hypothesis, however, because our studies cannot speak to causation.

These findings must be contextualized within our studies' limitations. Most notably, we are unable to address the mechanism(s) driving the blunted cortisol responses observed in our sample of reactive sleepers. Although we offer dysregulated HPA functioning and concomitant difficulties in coping as a tentative explanation, this is only one of several possibilities. Future studies that assess more basic hormonal processes could investigate potential pathways to build on our findings. Further, we utilized relatively small samples. As a result, although we discuss a blunted cortisol response to stress as a biological underpinning for insomnia predisposition, prospective research in larger samples is needed to replicate this effect and examine its presumptive downstream consequences. Additionally, recent evidence suggests a blunted cortisol response to stress may be associated with sleep-onset insomnia (Hansen et al., 2021). Considering that reactive sleepers are more likely to develop sleep-onset insomnia (Kalmbach et al., 2018), future investigators are encouraged to test whether a blunted cortisol response to stress is a risk factor for sleep-onset insomnia specifically. Finally, although conducting our studies during daytime hours mitigates some concern about measuring cortisol during its diurnal decline, it is still possible that participants' who completed the TSST earlier (1100–1400 h) may have produced less reliable cortisol responses than those who completed the TSST later (1400–1600 h) (Goodman et al., 2017). More research is needed to understand these potential time-of-day effects. Relatedly, stress reactivity varies across the menstrual cycle, yet we did not collect data on female participants' menstrual cycle phase.

6. Conclusions

Though further research is required to better characterize the role of blunted cortisol in the etiology of insomnia, our results replicate prior work and demonstrate a blunted cortisol response to stress is a reproducible biomarker for premorbid insomnia, regardless of the risk factors measured (familial risk or sleep reactivity) or laboratory stressors used (TSST or CPT). Moreover, this study identifies the FIRST as an instrument that differentiates between those with and without blunted HPA axis functioning in individuals at risk for insomnia. Although familial risk is another robust predictor of insomnia (with the same biological correlate), it relies on second-hand retrospective information that is difficult to validate. In contrast, the FIRST is a brief instrument with stronger predictive validity for incident insomnia than familial risk (Kalmbach et al., 2016). Therefore, the FIRST may expedite efforts to target HPA dysregulation, thereby aiding in the prevention of insomnia, its comorbidities, and other health consequences associated with this nascent biological substrate.

Acknowledgments

This study was supported by National Institute of Mental Health grants (MH-068372; MH-082785) to C.L.D. The authors would like to thank the technical staff of Henry Ford Hospital Sleep Center for their invaluable assistance in the completion of the present study.

Financial disclosures

None.

Non-financial disclosures

None.

Declarations of interest

None.

References

al'Absi, M., Petersen, K.L., Wittmers, L.E., 2002. Adrenocortical and hemodynamic predictors of pain perception in men and women. Pain 96, 197–204. https://doi.org/10.1016/S0304-3959(01)00447-X.

Bastien, C.H., Morin, C.M., 2000. Familial incidence of insomnia. J. Sleep Res. 9, 49–54. https://doi.org/10.1046/j.1365-2869.2000.00182.x.

Bonnet, M.H., Arand, D.L., 2003. Situational insomnia: consistency, predictors, and outcomes. Sleep 26, 1029–1036.

Bower, J.E., Ganz, P.A., Aziz, N., 2005. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom. Med. 67, 277–280.

Buckley, T.M., Schatzberg, A.F., 2005. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. J. Clin. Endocrinol. Metab. 90, 3106–3114. https://doi.org/10.1210/jc.2004-1056.

Byrne, B.M., 2016. Structural Equation Modeling with Amos: Basic Concepts, Applications, and Programming, third ed.. Multivariate Applications Series. Routledge, Taylor & Francis Group, New York.

Carroll, D., Ginty, A.T., Whittaker, A.C., Lovallo, W.R., de Rooij, S.R., 2017. The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. Neurosci. Biobehav. Rev. 77, 74–86. https://doi.org/10.1016/j.neubiorev.2017.02.025.

Chen, I.Y., Jarrin, D.C., Ivers, H., Morin, C.M., 2017. Investigating psychological and physiological responses to the trier social stress test in young adults with insomnia. Sleep Med. 40, 11–22. https://doi.org/10.1016/j.sleep.2017.09.011.

Devine, J.K., Bertisch, S.M., Yang, H., Scott-Sutherland, J., Wilkins, A., Molina, V., Henrikson, K., Haack, M., 2019. Glucocorticoid and inflammatory reactivity to a repeated physiological stressor in insomnia disorder. Neurobiol. Sleep Circadian Rhythms 6, 77–84. https://doi.org/10.1016/j.nbscr.2018.06.001.

Drake, C., Richardson, G., Roehrs, T., Scofield, H., Roth, T., 2004. Vulnerability to stress-related sleep disturbance and hyperarousal. Sleep 27, 285–291. https://doi.org/10.1093/sleep/27.2.285.

Drake, C.L., Jefferson, C., Roehrs, T., Roth, T., 2006. Stress-related sleep disturbance and polysomnographic response to caffeine. Sleep Med. 7, 567–572. https://doi.org/10.1016/j.sleep.2006.03.019.

Drake, C.L., Scofield, H., Roth, T., 2008. Vulnerability to insomnia: the role of familial aggregation. Sleep Med. 9, 297–302. https://doi.org/10.1016/j.sleep.2007.04.012.

Drake, C.L., Friedman, N.P., Wright, K.P., Roth, T., 2011. Sleep reactivity and insomnia: genetic and environmental influences. Sleep 34, 1179–1188. https://doi.org/10.5665/SLEEP.1234.

Drake, C.L., Pillai, V., Roth, T., 2014. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. Sleep 37, 1295–1304. https://doi.org/10.5665/sleep.3916.

Drake, C.L., Cheng, P., Almeida, D.M., Roth, T., 2017. Familial risk for insomnia is associated with abnormal cortisol response to stress. Sleep 40, zsx143. https://doi.org/10.1093/sleep/zsx143.

Durel, L.A., Kus, L.A., Anderson, N.B., McNeilly, M., Llabre, M.M., Spitzer, S., Saab, P.G., Efland, J., Williams, R., Schneiderman, N., 2007. Patterns and stability of cardiovascular responses to variations of the cold pressor test. Psychophysiology 30, 39–46. https://doi.org/10.1111/j.1469-8986.1993.tb03203.x.

Fernandez-Mendoza, J., Shaffer, M.L., Olavarrieta-Bernardino, S., Vgontzas, A.N., Calhoun, S.L., Bixler, E.O., Vela-Bueno, A., 2014. Cognitive–emotional hyperarousal in the offspring of parents vulnerable to insomnia: a nuclear family study. J. Sleep Res. 23, 489–498. https://doi.org/10.1111/jsr.12168.

Field, A.P., 2018. Discovering Statistics Using IBM SPSS Statistics, North American edition, fifth ed. Sage Publications Inc, Thousand Oaks, California.

Frankenhaeuser, M., Lundberg, U., Forsman, L., 1980. Dissociation between sympathetic-adrenal and pituitary-adrenal responses to an achievement situation characterized by high controllability: comparison between type A and type B males and females. Biol. Psychol. 10, 79–91. https://doi.org/10.1016/0301-0511(80)90029-0.

Galatzer-Levy, I.R., Steenkamp, M.M., Brown, A.D., Qian, M., Inslicht, S., Henn-Haase, C., Otte, C., Yehuda, R., Neylan, T.C., Marmar, C.R., 2014. Cortisol response to an experimental stress paradigm prospectively predicts long-term distress and resilience trajectories in response to active police service. J. Psychiatr. Res. 56, 36–42. https://doi.org/10.1016/j.jpsychires.2014.04.020.

Gehrman, P.R., Hall, M., Barilla, H., Buysse, D., Perlis, M., Gooneratne, N., Ross, R.J., 2016. Stress reactivity in insomnia. Behav. Sleep Med. 14, 23–33. https://doi.org/10.1080/15402002.2014.940112.

Gellis, L.A., Lichstein, K.L., Scarinci, I.C., Durrence, H.H., Taylor, D.J., Bush, A.J., Riedel, B.W., 2005. Socioeconomic status and insomnia. J. Abnorm. Psychol. 114, 111.

George, D., Mallery, P., 2019. IBM SPSS Statistics 26 Step by Step: A Simple Guide and Reference, sixth ed. Routledge. https://doi.org/10.4324/9780429056765.

Goodman, W.K., Janson, J., Wolf, J.M., 2017. Meta-analytical assessment of the effects of protocol variations on cortisol responses to the trier social stress test. Psychoneuroendocrinology 80, 26–35. https://doi.org/10.1016/j.psyneuen.2017.02.030.

Gravetter, F.J., Wallnau, L.B., 2011. Essentials of Statistics for the Behavioral Sciences, seventh ed. Wadsworth/Cengage Learning, Belmont, CA, Australia.

Gueorguieva, R., Krystal, J.H., 2004. Move over anova: progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. Arch. Gen. Psychiatry 61, 310–317.

Gunnar, M.R., Vazquez, D.M., 2001. Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in humandevelopment. Dev. Psychopathol. 13, 515–538. https://doi.org/10.1017/S0954579401003066.

Hair, J.F. (Ed.), 2010. Multivariate Data Analysis, seventh ed. Prentice Hall, Upper Saddle River, NJ.

Hansen, D.A., Satterfield, B.C., Layton, M.E., Van Dongen, H.P.A., 2021. Sleep deprivation and sleep-onset insomnia are associated with blunted physiological reactivity to stressors. Mil. Med 186, 246–252. https://doi.org/10.1093/milmed/usaa464.

Harvey, C.-J., Gehrman, P., Espie, C.A., 2014. Who is predisposed to insomnia: a review of familial aggregation, stress-reactivity, personality and coping style. Sleep Med. Rev. 18, 237–247. https://doi.org/10.1016/j.smrv.2013.11.004.

Hébert, S., Lupien, S.J., 2007. The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers. Neurosci. Lett. 411, 138–142. https://doi.org/10.1016/j.neulet.2006.10.028.

Jarrin, D.C., Chen, I.Y., Ivers, H., Drake, C.L., Morin, C.M., 2016. Temporal stability of the ford insomnia response to stress test (FIRST). J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.

Kalmbach, D.A., Pillai, V., Arnedt, J.T., Drake, C.L., 2016. Identifying at-risk individuals for insomnia using the ford insomnia response to stress test. Sleep 39, 449–456. https://doi.org/10.5665/sleep.5462.

Kalmbach, D.A., Anderson, J.R., Drake, C.L., 2018. The impact of stress on sleep: pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. J. Sleep Res. 27, e12710 https://doi.org/10.1111/jsr.12710.

Kelly, C.B., Cooper, S.J., 1998. Plasma norepinephrine response to a cold pressor test in subtypes of depressive illness. Psychiatry Res. 81, 39–50. https://doi.org/10.1016/S0165-1781(98)00086-9.

Kirschbaum, C., Pirke, K.-M., Hellhammer, D.H., 1993. The 'trier social stress test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81.

LeBlanc, M., Mérette, C., Savard, J., Ivers, H., Baillargeon, L., Morin, C.M., 2009. Incidence and risk factors of insomnia in a population-based sample. Sleep 32, 1027.

Lo Martire, V., Caruso, D., Palagini, L., Zoccoli, G., Bastianini, S., 2020. Stress & sleep: a relationship lasting a lifetime. Neurosci. Biobehav. Rev. 117, 65–77. https://doi.org/10.1016/j.neubiorev.2019.08.024.

Lovallo, W.R., 2011. Do low levels of stress reactivity signal poor states of health. Biol. Psychol. 86, 121–128. https://doi.org/10.1016/j.biopsycho.2010.01.006.

MacNeil, S., Deschênes, S.S., Caldwell, W., Brouillard, M., Dang-Vu, T.-T., Gouin, J.-P., 2017. High-frequency heart rate variability reactivity and trait worry interact to predict the development of sleep disturbances in response to a naturalistic stressor. Ann. Behav. Med. 51, 912–924. https://doi.org/10.1007/s12160-017-9915-z.

McRae, A.L., Saladin, M.E., Brady, K.T., Upadhyaya, H., Back, S.E., Timmerman, M.A., 2006. Stress reactivity: biological and subjective responses to the cold pressor and trier social stressors. Hum. Psychopharmacol. Clin. Exp. 21, 377–385. https://doi.org/10.1002/hup.778.

Micieli, G., Tassorelli, C., Bosone, D., Cavallini, A., Viotti, E., Nappi, G., 1994. Intracerebral vascular changes induced by cold pressor test: a model of sympathetic activation. Neurol. Res. 16, 163–167. https://doi.org/10.1080/01616412.1994.11740219.

Mizushima, T., Tajima, F., Nakamura, T., Yamamoto, M., Lee, K.-H., Ogata, H., 1998. Muscle sympathetic nerve activity during cold pressor test in patients with cerebrovascular accidents. Stroke 29, 607–612. https://doi.org/10.1161/01.STR.29.3.607.

Mizushima, T., Tajima, F., Okawa, H., Umezu, Y., Furusawa, K., Ogata, H., 2003. Cardiovascular and endocrine responses during the cold pressor test in subjects with cervical spinal cord injuries. Arch. Phys. Med. Rehabil. 84, 112–118. https://doi.org/10.1053/apmr.2003.50072.

Nater, U.M., Rohleder, N., 2009. Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. Psychoneuroendocrinology 34, 486–496.

Perlis, M.L., Corbitt, C.B., Kloss, J.D., 2014. Insomnia research: 3Ps and beyond. Sleep Med. Rev. 18, 191–193. https://doi.org/10.1016/j.smrv.2014.01.003.

Petersen, H., Kecklund, G., D'onofrio, P., Nilsson, J., Åkerstedt, T., 2012. Stress vulnerability and the effects of moderate daily stress on sleep polysomnography and subjective sleepiness. J. Sleep Res. 22, 50–57. https://doi.org/10.1111/j.1365-2869.2012.01034.x.

Rankin, J., Walker, J.J., Windle, R., Lightman, S.L., Terry, J.R., 2012. Characterizing dynamic interactions between ultradian glucocorticoid rhythmicity and acute stress using the phase response curve. PLoS ONE 7, e30978. https://doi.org/10.1371/journal.pone.0030978.

Schmalbach, I., Herhaus, B., Pässler, S., Runst, S., Berth, H., Wolff-Stephan, S., Petrowski, K., 2020. Cortisol reactivity in patients with anorexia nervosa after stress induction. Transl. Psychiatry 10, 1–15. https://doi.org/10.1038/s41398-020-00955-7.

Schommer, N.C., Hellhammer, D.H., Kirschbaum, C., 2003. Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. Psychosom. Med. 65, 450–460. https://doi.org/10.1097/01.PSY.0000035721.12441.17.

Schuckit, M.A., Gold, E., Risch, C., 1987. Plasma cortisol levels following ethanol in sons of alcoholics and controls. Arch. Gen. Psychiatry 44, 942–945.
Schuckit, M.A., Risch, S.C., Gold, E.O., 1988. Alcohol consumption, ACTH level, and family history of alcoholism. Am. J. Psychiatry 145, 1391–1395.
Schwabe, L., Haddad, L., Schachinger, H., 2008. HPA axis activation by a socially evaluated cold-pressor test. Psychoneuroendocrinology 33, 890–895. https://doi.org/10.1016/j.psyneuen.2008.03.001.
Spielman, A.J., Caruso, L.S., Glovinsky, P.B., 1987. A behavioral perspective on insomnia treatment. Psychiatr. Clin. N. Am. 10, 541–553.
Trochim, W.M.K., Donnelly, J.P., 2008. Research Methods Knowledge Base, third ed. Cengage Learning, Mason, Ohio.
Turner, A.I., Smyth, N., Hall, S.J., Torres, S.J., Hussein, M., Jayasinghe, S.U., Ball, K., Clow, A.J., 2020. Psychological stress reactivity and future health and disease outcomes: a systematic review of prospective evidence. Psychoneuroendocrinology 114, 104599. https://doi.org/10.1016/j.psyneuen.2020.104599.
Vargas, I., Vgontzas, A.N., Abelson, J.L., Faghih, R.T., Morales, K.H., Perlis, M.L., 2018. Altered ultradian cortisol rhythmicity as a potential neurobiologic substrate for chronic insomnia. Sleep Med. Rev. 41, 234–243. https://doi.org/10.1016/j.smrv.2018.03.003.
Wolff, H.H., 1951. The mechanism and significance of the cold pressor response. Q. J. Med. 20, 261–273.
Wolpert, E.A., 1969. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Arch. Gen. Psychiatry 20, 246. https://doi.org/10.1001/archpsyc.1969.01740140118016.
Yamamoto, K., Iwase, S., Mano, T., 1992. Responses of muscle sympathetic nerve activity and cardiac output to the cold pressor test. Jpn. J. Physiol. 42, 239–252. https://doi.org/10.2170/jjphysiol.42.239.
Zheng, L., Sun, Z., Li, Jue, Zhang, R., Zhang, X., Liu, S., Li, Jiajin, Xu, C., Hu, D., Sun, Y., 2008. Pulse pressure and mean arterial pressure in relation to ischemic stroke among patients with uncontrolled hypertension in rural areas of China. Stroke J. Cereb. Circ. 39, 1932–1937. https://doi.org/10.1161/STROKEAHA.107.510677.
Zucconi, M., Ferri, R., Allen, R., Baier, P., Bruni, O., Chokroverty, S., Ferinistrambi, L., Fulda, S., Garciaborreguero, D., Hening, W., 2006. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med. 7, 175–183. https://doi.org/10.1016/j.sleep.2006.01.001.