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Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children

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Abstract

Background—Insomnia symptoms are the most common parent-reported sleep complaints in children; however, little is known about the pathophysiology of childhood insomnia symptoms, including their association with hypothalamic-pituitary-adrenal (HPA) axis activation. The objective of this study is to examine the association between parent-reported insomnia symptoms, objective short sleep duration and cortisol levels in a population-based sample of school-aged children.

Design—A sample of 327 children from the Penn State Child Cohort (5–12 years old) underwent 9-h overnight polysomnography and provided evening and morning saliva samples to assay for cortisol. Objective short sleep duration was defined based on the median total sleep time (i.e., < 7·7 h). Parent-reported insomnia symptoms of difficulty initiating and/or maintaining sleep were ascertained with the Pediatric Behavior Scale.

Results—Children with parent-reported insomnia symptoms and objective short sleep duration showed significantly increased evening (0·33 ± 0·03 μg/dL) and morning (1·38 ± 0·08 μg/dL) cortisol levels. In contrast, children with parent-reported insomnia symptoms and 'normal' sleep duration showed similar evening and morning cortisol levels (0·23 ± 0·03 μg/dL and 1·13 ± 0·08 μg/dL) compared with controls with 'normal' (0·28 ± 0·02 μg/dL and 1·10 ± 0·04 μg/dL) or short (0·28 ± 0·02 μg/dL and 1·13 ± 0·04 μg/dL) sleep duration.

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Conflict of interests
The authors declare no competing financial conflict of interests.

Conclusions—Our findings suggest that insomnia symptoms with short sleep duration in children may be related to 24-h basal or responsive physiological hyperarousal. Future studies should explore the association of insomnia symptoms with short sleep duration with physical and mental health morbidity.

Keywords

Children; cortisol; insomnia symptoms; objective sleep duration

Introduction

Insomnia symptoms are the most common parent-reported sleep complaints in children, with approximately 20–30% of parents describing problems with sleep initiation or maintenance in their child [1-7]. Whereas many studies report objective sleep data on adults with insomnia complaints, few studies have objectively explored them in children [8]. Our understanding of childhood insomnia symptoms, therefore, is primarily based on clinical observations and subjective parent reports.

In adults, insomnia has been associated with activation of both limbs of the stress system. Several studies have shown increased activity of the hypothalamic-pituitary-adrenal (HPA) and sympathetic-and sympatho-adreno-medullary axes in adults with chronic insomnia [9-25]. For example, 24-h urinary free cortisol, norepinephrine and catecholamine metabolite levels have been shown to be positively correlated with objective measures of sleep disturbance in adult insomniacs [9]. Moreover, among adult insomniacs, those with objective short sleep duration secrete significantly more cortisol than those with ‘normal’ sleep duration [10,14,15,26]. In contrast, few studies have examined the association between sleep duration or ‘poor sleep’ with impaired activity of the stress system in school-aged children [27-29] and none have examined the synergistic effect between insomnia symptoms and objective sleep duration observed in adults. Thus, although the relation between insomnia and the stress system has been well-described in adults, the extent to which this association exists in children with insomnia symptoms has not been established.

The aim of this study was to examine the association between parent-reported insomnia symptoms, objective sleep duration and salivary cortisol levels in children. We hypothesized that children with parent-reported insomnia symptoms and short sleep duration will show increased activity of the HPA axis, while controls with short sleep duration and those with parent-reported insomnia symptoms and ‘normal’ sleep duration will not. This is the first study to explore the synergistic effect of insomnia symptoms and objective sleep duration on HPA axis activity in children from the general population.

Materials and methods

Participants

Subjects for this study were participants in the Penn State Child Cohort (PSCC), a random general population sample of children aged 5–12 years. Detailed descriptions of the study design and data collection have been previously reported [6,7,30,31]. In brief, the PSCC was

designed as a 2-phase study with the first phase designed for collecting general information from the parents about their child's sleep and behavioural patterns (N = 5740). In the second phase, we collected more detailed data in our General Clinical Research Centre on a randomly selected stratified sample from the first phase (N = 700). As shown in Fig. 1, a total of 391 children in the second phase had complete data on sleep-related questions, polysomnography, and salivary cortisol. For the purpose of the present study, we excluded 61 children with a history of severe chronic medical conditions, genetic syndromes and/or use of medications known to affect the HPA axis as well as three children whose evening cortisol levels were inexplicably high (> 8 SDs above the mean). The final sample included in the present study consisted of 327 children that, as shown in Fig. 1, did not differ significantly from the original phase 2 sample of 700 subjects in terms of gender and race distribution (53·7% females and 21% minority), age (110 ± 21 months), or BMI percentile (61 ± 31). These data provide further support for the external validity of the sample. This study was approved by the Institutional Review Board at the Pennsylvania State University College of Medicine. Informed consent from parents of all participants and assent from all children were obtained prior to participation.

Saliva cortisol sampling technique and cortisol analysis

During the participants' visit to the sleep laboratory in phase 2, an evening saliva sample (1800–1900) before dinner and a morning saliva sample (0600–0700) before breakfast were obtained for the assessment of cortisol. All samples were collected in salivary tubes and stored in a −20 °C freezer until assayed. Cortisol concentrations were assessed using commercially-available enzyme immunoassays (EIA; ALPCO Diagnostics, Salem, NH, USA).

Parent-reported insomnia symptoms

A parent completed the Pediatric Behavior Scale (PBS), a 165-item rating scale developed to evaluate behavioural problems in children, including sleep problems [32]. Each item is scored on a 0–3-point scale with 0 indicating no problems and 3 indicating that a behaviour is 'very much' or 'very often' a problem. Children were classified as having insomnia symptoms when the parent reported 'often' or 'very often' for either 'has trouble falling asleep' or 'wakes up often in the night'. The prevalence of parent-reported insomnia symptoms in the sample included in the present study (19·5%) was similar to that previously reported in the 700 subjects and reported in Fig. 1 [6,7].

In-laboratory polysomnography

All children underwent a single overnight 9-h polysomnography (PSG) with a parent present in a sound-attenuated, light- and temperature-controlled room in the General Clinical Research Center at the Pennsylvania State University College of Medicine (Hershey, PA, USA). Each child's bedtime and waketime approximated their typically sleep times (2100–2200 to 0600–0700). Children were monitored with an infrared video and computerized system (24-analogue channel and 10-dc channel TS amplifier using GAMMA software; Grass Telefactor, Inc., Warwick, RI, USA) including four channels of electroencephalogram (EEG), two-channel bilateral electrooculogram (EOG), a single-channel electrocardiogram (ECG), and chin and anterior tibialis electromyogram (EMG). Respiration was assessed

throughout the night by use of a thermocouple at nose and mouth (model TCT R; Grass Telefactor, Inc.), nasal pressure (MP 45–871 ± 2 cm H_2O; Validyne Engineering Corp., Northridge, CA, USA), and Piezo thoracic and abdominal respiratory effort electric belts (model 1312; Sleepmate Technologies, Glen Burnie, MD, USA). We obtained an objective estimate of snoring during the PSG by monitoring breathing sounds with a microphone attached to the throat (model 1250; Sleepmate Technologies), as well as a separate room microphone. All night haemoglobin oxygen saturation (SpO_2) was obtained by pulse oximetry (model 8800; Nonin Medical, Inc., Plymouth, MN, USA). A hypopnoeic event was defined as a reduction of airflow of approximately 50% with an associated decrease in SpO_2 of at least 3% or an associated breathing-related arousal. All PSG records were double-scored for breathing-related events in accordance with the American Thoracic Society standards for cardiopulmonary sleep studies in children [33] and an apnea/hypopnea index (AHI) was calculated ([apnea + hypopnea]/hours of sleep).

Results from the overnight PSG evaluation were used to classify the children's total sleep time (TST) as short or 'normal' sleep duration. Short sleep duration was defined by a TST below the median of the overall sample (< 7·7 h), while 'normal' sleep duration was defined as a TST above the sample's median (≥ 7·7–9·0 h).

Other key measures

As part of the initial questionnaire, parents also reported on children's age and race. Furthermore, parents reported on children's anxiety and depression in the PBS [32]. During the evening before the PSG, all children completed a physical examination, including height, weight and waist measurement. Height was measured in centimetres using a stadiometer (model 242, SECA Corp., Hanover, MD, USA) and weight was assessed in kilograms (model 758c, Cardinal Scale Manufacturing Co., Louisville, KY, USA). Age- and gender-adjusted body mass index (BMI) percentile was calculated based on CDC criteria. In the standing position, the waist circumference was measured in centimetres at the top of the iliac crest [34].

Statistical analyses

Means and proportions of the main variables were calculated for the entire study population, as well as stratified according to parent-reported insomnia status and objective sleep duration. We accounted for the sampling probability from Phase 1 to Phase 2 enrolments in all of the analyses to generate population level estimates and to make inference back to the population from which the Phase 2 study participants were selected [6,7,30,31]. ANOVA was used to assess mean differences among groups on quantitative measures of descriptive data, while Chi-square tests were employed to assess gender and race differences. In order to control for experiment-wise error rate, a full factorial multivariate analysis of covariance (MANCOVA) was used to examine the effects of parent-reported insomnia symptoms, objective sleep duration, and their interaction on morning and evening cortisol levels; we controlled for key potential confounders expected to affect cortisol levels as well as those variables significantly associated with parent-reported insomnia symptoms or objective sleep duration (i.e., gender, age, race, waist circumference, AHI and anxiety and depression). For posthoc analyses, all children were separated based on parent-reported insomnia symptoms status

and objective sleep duration (short vs. 'normal'), yielding four groups as depicted in Fig. 1: controls with 'normal' sleep duration (n = 137), controls with short sleep duration (n = 110), parent-reported insomnia symptoms with 'normal' sleep duration (n = 38), and parent-reported insomnia symptoms with short sleep duration (n = 42). To assess our *a priori* hypotheses that the joint effect of parent-reported insomnia symptoms and objective short sleep duration on cortisol levels is stronger than short sleep duration or parent-reported insomnia symptoms alone, least square difference planned tests, controlling for gender, age, race, waist circumference, AHI, and anxiety and depression, contrasted (i) insomnia symptoms with short duration versus. insomnia symptoms with 'normal' sleep duration, (ii) insomnia symptoms with short sleep duration versus. controls with short sleep duration, (iii) insomnia symptoms with 'normal' sleep duration versus. controls with 'normal' sleep duration, and (iv) controls with short sleep duration versus. controls with 'normal' sleep duration. The critical statistical confidence level for all analyses was $P < 0{\cdot}05$ and two-tailed. All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Table 1 presents the characteristics of the overall sample as well as stratified by parent-reported insomnia symptoms and objective sleep duration. Parent-reported insomnia symptoms were significantly associated with female gender (P = 0·02) and higher anxiety and depression (P = 0·0001), while objective short sleep duration was associated with older age (P = 0·004), increased BMI percentile (P = 0·09) and waist circumference (P = 0·02), and, of course, shorter TST (P = 0·0001). No other comparisons between groups on any of the variables in Table 1 were marginally or fully statistically significant. Table 2 presents the characteristics of the study subgroups based on parent-reported insomnia symptoms and objective sleep duration.

Evening and morning cortisol levels by parent-reported insomnia symptoms and objective sleep duration adjusted for potential confounders are presented in Fig. 2. Factorial analyses showed nonsignificant and significant main effects of parent-reported insomnia symptoms on evening and morning cortisol levels (P = 0·97 and P = 0·04, respectively) as well as marginally significant and significant main effects of objective short sleep duration on evening and morning cortisol levels (P = 0·10 and P = 0·03, respectively). Importantly, these analyses showed marginally significant interaction effects between parent-reported insomnia symptoms and objective short sleep duration on evening and morning cortisol levels (P = 0·06 and P = 0·08, respectively). Specifically, children with parent-reported insomnia symptoms and short sleep duration had significantly higher evening cortisol levels (0·33 ± 0·03 μg/dL) compared with parent-reported insomnia symptoms with 'normal' sleep duration (0·23 ± 0·03 μg/dL, P = 0·048). Furthermore, children with parent-reported insomnia symptoms and short sleep duration had significantly higher morning cortisol levels (1·38 ± 0·08 μg/dL) than controls with short sleep duration (1·13 ± 0·04 μg/dL, P = 0·007), controls with 'normal' sleep duration (1·10 ± 0·04 μg/dL, P = 0·002), or parent-reported insomnia symptoms with 'normal' sleep duration (1·13 ± 0·08 μg/dL, P = 0·030). In contrast, evening and morning cortisol levels did not significantly differ between parent-reported insomnia symptoms and controls with 'normal' sleep duration (P = 0·200 and P = 0·781,

respectively), nor did those between the two control subgroups ($P = 0{\cdot}825$ and $P = 0{\cdot}614$, respectively). Please see Table 3 for mean values for all study subgroups.

Discussion

This is the first study to assess the synergistic association between insomnia symptoms and objective short sleep duration on HPA axis activity in a population-based sample of young children. Our findings suggest that parent-reported insomnia symptoms with objective short sleep duration are associated with higher cortisol levels in the evening and morning, whereas insomnia symptoms with 'normal' sleep duration is not associated with significant activation of the HPA axis. Our novel findings on the synergistic effect of insomnia symptoms and objectively-measured sleep duration on cortisol levels, independent of sociodemographics, body weight, sleep-disordered breathing, anxiety and depression, may offer new insights into the pathophysiology of childhood insomnia symptoms.

In children, insomnia symptoms are typically conceptualized as behavioural problems of initiating or maintaining sleep resulting primarily from bedtime resistance and learned sleep-onset associations [8]. Our results add to the growing body of literature showing an association between disturbed sleep and activity of the HPA axis in school-aged children [27-29] and toddlers [35-38] and parallel those of previous findings in adults which characterize insomnia as a disorder of physiological hyperarousal [39,40]. Adult insomniacs with objective short sleep duration show 24-h elevations in cortisol levels as well as overall sympathetic activation, including enhanced catecholamine secretion, increased 24-h metabolic and heart rate and impaired heart rate variability [9-25], while those with 'normal' sleep duration do not [9,10,14,15,24,26,41-45]. In our study, elevations in both evening and morning cortisol levels suggest that insomnia symptoms with objective short sleep duration in children may be also a result of 24-h hyperarousal. Our study design, which included only one night in the laboratory without adaptation to the novel environment, cannot rule out the possibility that the elevated cortisol levels may reflect an increased response of the stress system to a stressful-unfamiliar environment [46]. In any event, it appears that children with insomnia symptoms and short sleep duration experience HPA axis alterations either in the form of basal hyperactivation or exaggerated response to novel, stressful stimuli. Future studies using multiple measures across different environments should examine these hypotheses.

In children and adolescents, several studies have shown an association between objective sleep and cortisol with behavioural or mental health problems [35-38,47] but not with physical health morbidity. In adults, recent studies have reported that insomnia with objective short sleep duration, in addition to its association with cortisol and mental health, is associated with increased risk of cardiometabolic morbidity – including hypertension and type 2 diabetes [48-50] – as well as neurocognitive impairment [51], depression [52,53], and increased mortality risk [54]. Future studies using objective and subjective measures of sleep should examine these associations in children.

Importantly, our findings should not lead to the conclusion that childhood insomnia is analogous to adult insomnia from a behavioural or pathophysiological stand point. For

example, PSG differences in adult insomniacs compared with controls are significant and consistent across studies, whereas these differences in children are very subtle or not significant (e.g., TST in the present study), which may reflect stronger homeostatic sleep mechanisms in children than in adults. In adults, subjectively-defined insomnia has been associated with normal [9,10,14-16] or decreased morning awakening cortisol levels [55]. However, adult insomniacs with objective short sleep duration have increased plasma cortisol levels in the evening, during the sleep period, and upon awakening, that is, 6:30–8:00 AM [10]. In the present and previous studies in children, objective sleep disturbances were associated with both increased evening and morning cortisol levels [27,28,35-37]. Together, these data suggest the possibility that childhood insomnia symptoms associated with HPA axis alterations (i.e., short sleep duration) may be in a continuum with adult insomnia, while childhood insomnia symptoms without HPA axis alterations (i.e., normal sleep duration) may include different behavioural phenotypes (e.g., bedtime resistance, sleep-onset associations) that are not in a continuum with adult insomnia [52]. Moreover, the question remains open whether pubertal maturity may play a role in the association of insomnia symptoms with activation of the HPA axis and its progression into adulthood. More data from other domains, for example, behavioural profiles, medical morbidity or treatment response, will help us clarify the nature of childhood insomnia symptoms and their natural course.

Some limitations should be taken into account when interpreting our results. First, the study is cross-sectional and does not allow causal conclusions; the possibility exists that HPA axis activation leads to insomnia and *vice versa*. Second, the objective sleep duration in this study was based on one night of fixed-time PSG, which may not be representative of the subjects' *ad libitum* habitual sleep duration and may be affected by rebound and/or first-night effects. Nevertheless, our definitions of short (i.e., < 7·7 h) and 'normal' (i.e., 7·8–9·0 h) sleep duration are consistent with those of a previous study using week-long, at-home actigraphy, which may better represent children's habitual sleep pattern of school-aged children [28]. Our cut-off for short sleep duration was based on a statistical approach (i.e., median sleep duration of the sample); future studies should explore the optimum cut-off of sleep duration based on clinical criteria. Third, we relied on parent-reported insomnia symptoms rather than self-reported data. Although self-reported sleep data may better reflect the child's experience of insomnia symptoms, the use of parent-reports was deemed necessary given the young age of most children in this sample, which allowed comparison across children of all ages. Fourth, we did not assess daytime impairments or chronicity associated with insomnia symptoms, which would have delineated a more homogeneous phenotype of children (i.e., those with chronic insomnia). Future studies should examine the association of insomnia disorder, as defined by current diagnostic criteria, and HPA axis in children. Fifth, we only measured salivary cortisol levels at two time points. Future studies should examine the association of insomnia symptoms, objective sleep duration and activity of the HPA axis using 24-h blood or multiple time-points salivary sampling. Finally, the interactions between insomnia symptoms and objective sleep duration on cortisol levels were marginally significant, which may indicate lack of statistical power. However, given the data distribution across groups and the strength of the *posthoc* comparisons (Fig. 2), we expect

future studies with a larger number of children with insomnia symptoms to replicate these observed interactions with sufficient statistical power.

In conclusion, young children with insomnia symptoms and objective short sleep duration have high evening and morning cortisol levels, while children with insomnia symptoms and 'normal' sleep duration do not show significant HPA axis activation. These findings were independent of sociodemographic factors, body weight, sleep-disordered breathing, anxiety and depression. These findings suggest that the pathophysiology of sleep disturbances may be related to basal or responsive hyperactivity of the stress system in a subgroup of children with insomnia symptoms. Future studies should examine the behavioural profiles, medical morbidity and subtypes of children with insomnia symptoms based on objective sleep measures.

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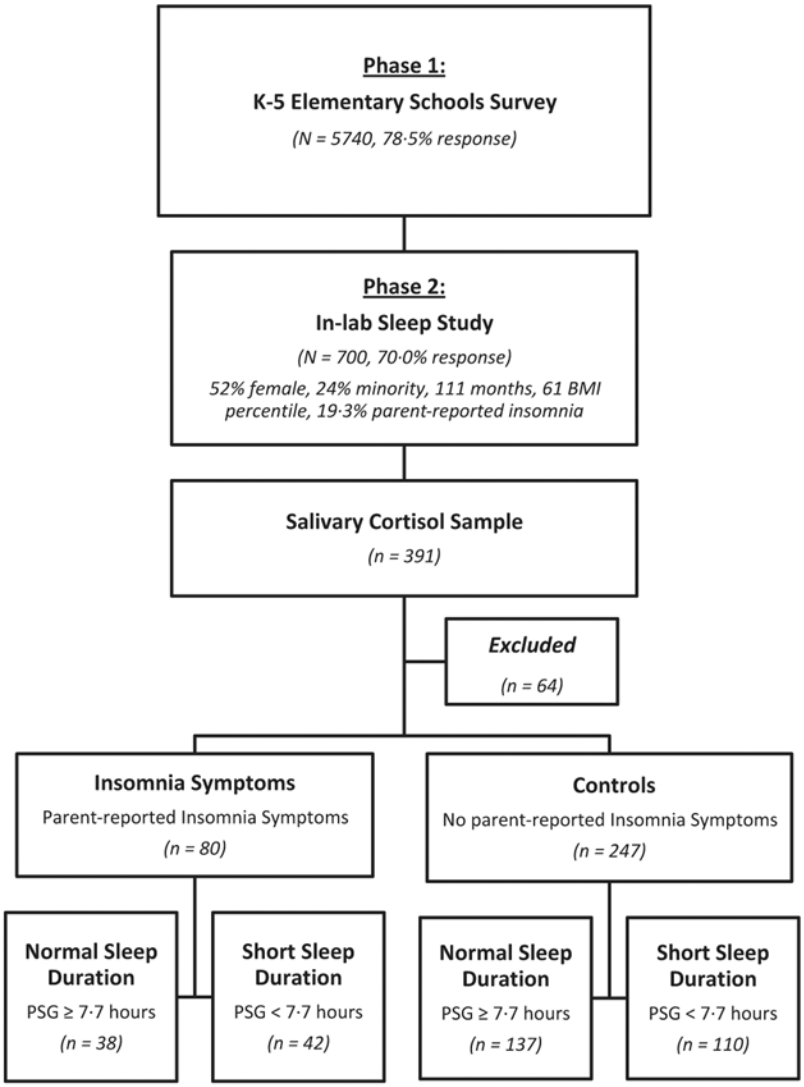

Figure 1.
Penn State Child Cohort two-phase design and participants' flow in the present study.

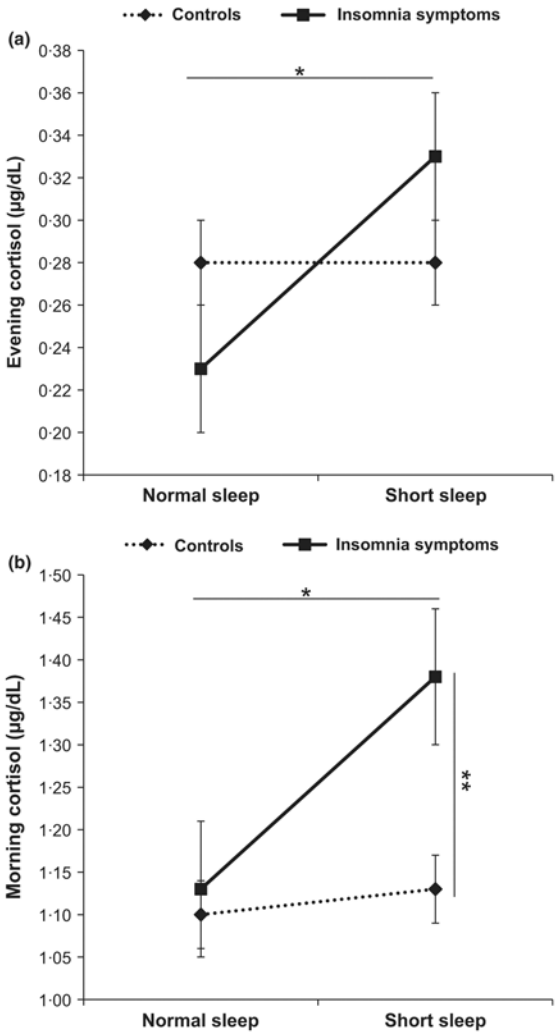

Figure 2.

Salivary cortisol levels by insomnia symptoms and objective sleep duration. Error bars represent standard error of the mean (SEM). Data are adjusted for gender, age, race, waist circumference, AHI, anxiety and depression, and sampling weight. *$P < 0{\cdot}05$ between insomnia symptoms with short sleep duration and insomnia symptoms with normal sleep duration (a, b); **$P < 0{\cdot}01$ between insomnia symptoms with short sleep duration and controls with normal or short sleep duration (b).

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Table 1

Characteristics of the overall sample and stratified by parent-reported insomnia symptoms and objective sleep duration

	All	Controls	Insomnia symptoms	Normal sleep duration	Short sleep duration
n	327	247	80	175	152
Males (%)	46·3	49·0	34·0 *	47·0	45·0
Age (months)	110·0 ± 21·0	110·3 ± 20·0	107·9 ± 23·0	106·6 ± 21·4	113·0 ± 19·0 ***
Minority (%)	21·0	22·0	18·0	22·0	20·0
BMI (%)	61·0 ± 31·0	60·5 ± 30·1	60·7 ± 33·2	58·1 ± 29·8	63·8 ± 31·4 †
Waist (cm)	65·0 ± 10·0	64·5 ± 9·6	65·8 ± 11·9	63·5 ± 9·0	66·1 ± 11·2 ***
TST (min)	460·3 ± 46·6	460·7 ± 48·6	458·4 ± 37·1	492·8 ± 18·2	422·6 ± 40·6 ***
AHI	0·6 ± 0·9	0·6 ± 0·9	0·7 ± 1·2	0·6 ± 0·8	0·7 ± 1·1
Anx/Dep (T)	52·0 ± 12·9	50·3 ± 11·9	58·1 ± 14·7 *	52·6 ± 13·1	51·2 ± 13·0

Values are mean ± SD unless otherwise stated.

TST, total sleep time; AHI, apnea hypopnea index; Anx/Dep, anxiety and depression cluster T score.

* $P < 0{\cdot}05$ insomnia symptoms vs. controls.

*** $P < 0{\cdot}05$ short vs. ‘normal’ sleep duration.

† $P < 0{\cdot}10$ short .vs. ‘normal’ sleep duration.

Table 2

Characteristics of the subgroups based on parent-reported insomnia symptoms and objective sleep duration

	Controls with normal sleep duration	Controls with short sleep duration	Insomnia symptoms with normal sleep duration	Insomnia symptoms with short sleep duration
n	137	110	38	42
Males (%)	50·0	48·0	34·0 *	33·0 *
Age (months)	107·3 ± 20·8	113·8 ± 18·3 **	103·5 ± 24·1	111·9 ± 21·3 **
Minority (%)	23·0	21·0	20·0	16·0
BMI (%)	56·7 ± 29·7	65·1 ± 30·1 ***	63·3 ± 31·2	58·3 ± 35·2
Waist (cm)	63·3 ± 8·8	66·0 ± 10·4 ***	64·7 ± 9·9	66·9 ± 13·5 †
TST (min)	493·3 ± 18·3	419·8 ± 43·9	490·4 ± 18·7	426·6 ± 33·4
AHI	0·6 ± 0·9	0·6 ± 0·8	0·5 ± 0·6	1·1 ± 1·5 ‡
Anx/Dep (T)	50·8 ± 11·9	49·9 ± 11·9	58·5 ± 14·0 *	58·7 ± 15·1 *

Values are mean ± SD unless otherwise stated.

TST, total sleep time; AHI, apnea hypopnea index; Anx/Dep, anxiety and depression cluster T score.

* $P < 0{\cdot}05$ between insomnia symptoms with normal or short sleep duration and controls with normal or short sleep duration.

** $P < 0{\cdot}05$ between insomnia symptoms or controls with short sleep duration and insomnia symptoms or controls with normal sleep duration.

*** $P < 0{\cdot}05$ between controls with normal sleep duration and controls with short sleep duration.

† $P < 0{\cdot}05$ between insomnia symptoms with short sleep duration and controls with normal sleep duration.

‡ $P < 0{\cdot}05$ between insomnia symptoms with short sleep duration and insomnia symptoms with normal sleep duration and controls.

Table 3

Salivary cortisol levels across subgroups based on parent-reported insomnia symptoms and objective sleep duration

	Controls with normal sleep duration	Controls with short sleep duration	Insomnia symptoms with normal sleep duration	Insomnia symptoms with short sleep duration
n	137	110	38	42
Evening, μg/dL	0·28 ± 0·02	0·28 ± 0·02	0·23 ± 0·03	0·33 ± 0·03 *
Morning, μg/dL	1·10 ± 0·04	1·13 ± 0·04	1·13 ± 0·08	1·38 ± 0·08 *, **

Values are mean ± standard error of the mean (SEM) adjusted for gender, age, race, waist circumference.

AHI, anxiety and depression, and sampling weight.

* $P < 0·05$ between insomnia symptoms with short sleep duration and insomnia symptoms with normal sleep duration.

** $P < 0·01$ between insomnia symptoms with short sleep duration and controls with normal or short sleep duration.

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