DiVA – Digitala Vetenskapliga Arkivet <http://umu.diva-portal.org>

This is a book chapter published in **The Role of Saliva Cortisol Measurement in Health and Disease**, ed. Margareta Kristenson, Peter Garvin, Ulf Lundberg.

Citation for the published paper:

Anne Helene Garde, Berndt Karlsson, Åse Marie Hansen, Roger Persson, Torbjörn Åkerstedt
Sleep and Salivary Cortisol

The Role of Saliva Cortisol Measurement in Health and Disease, 2012, p. 116-128

URL: <http://dx.doi.org/10.2174/978160805342111201010116>

Sleep and Salivary Cortisol

Anne Helene Garde^{1,*}, Berndt Karlson², Åse Marie Hansen³, Roger Persson⁴ and Torbjörn Åkerstedt⁵

¹Senior researcher at the National Research Centre for the Working Environment, Lersø Parkallé 105, 2100 København Ø, Copenhagen, Denmark; ²Doctor in Occupational and Environmental Medicine, at the Department of Public Health and Clinical Medicine, Umeå University, Sweden; ³Senior researcher at the National Research Centre for the Working Environment, Copenhagen, Denmark; ⁴Senior researcher at the National Research Centre for the Working Environment, Copenhagen, Denmark and ⁵Professor at the Stress Research Institute, Stockholm University, Stockholm, Sweden

Abstract: The aim of the present chapter was to analyze whether measures of cortisol in saliva were associated with measures of sleep and to explore if divergent results were related to underlying differences in theoretic assumptions and methods. Measures of sleep quality included sleep duration, overall sleep quality, difficulty falling asleep, disturbed sleep, and sleep deprivation. Twenty-three papers were found to fulfil the inclusion criteria. Cortisol measures were grouped into single time points at different times during the day, deviations at different time periods during the day, reactivity and recovery after a standardized laboratory test, area under the curve and response to dexamethasone test. A large proportion of the studies included showed nonsignificant findings, which, in several cases, may be a result of low power. The most consistent results were a positive association between sleep duration and single measures of salivary cortisol at awakening, which was observed in 3 studies. In these studies, sleep duration was also associated with low evening cortisol levels, steep diurnal deviation of cortisol and/or high area under the curve. Together these findings suggest that longer sleep duration is related to a more dynamic cortisol secretion. Two of the 6 studies on disturbed or restless sleep showed relations to flat diurnal deviation and low laboratory stress test reactivity. This to some extent corroborates the findings on sleep duration. However, the many nonsignificant findings as well as the theoretical and methodological differences (e.g., heterogeneity in measures) complicate comparisons. Conflicting results may be at least partially due to differences in methods and underlying assumptions.

Keywords: Salivary cortisol, sleep, sleep quality, sleep duration, sleep deprivation, difficulty falling asleep, single time point measures, deviations measures, area under the curve, dexamethasone.

INTRODUCTION

The stress response can be described as an increase in arousal in response to a real or anticipated perturbation of homeostasis [1]. The Hypothalamus-Pituitary-Adrenal Cortex (HPA) axis is one of the main stress systems with cortisol as a main actor [2, 3]. The underlying anatomy of the stress response is closely interconnected with the anatomy that regulates sleep and wakefulness [4, 5]. Emotional and cognitive arousal may therefore provide inputs that override the normal circadian and homeostatic processes that otherwise govern sleep and wakefulness in normally healthy humans [4, 6]. The interconnectedness also makes sleep a potent factor that may modulate most components of the endocrine system [6]. To summarize, there is a possible bidirectionality between stress and sleep.

Cortisol levels have a circadian peak early in the morning, show a decline throughout the day and are near the limits of detection in the late evening [6]. The secretion of cortisol is inhibited at sleep onset, and during the early part of the sleep period, and cortisol concentrations continue to decrease until a few hours before normal waking time when they start to rise again [6-8].

In experimental studies, induced sleep deprivation lead to higher cortisol concentrations the subsequent

*Address correspondence to Anne Helene Garde: Senior researcher at the National Research Centre for the Working Environment, Lersø Parkallé 105, 2100 København Ø, Copenhagen, Denmark; Tel: +45 39 16 52 00; Fax: +45 39 16 52 01; E-mail: ahg@nrcwe.dk

evening [8] and HPA axis hormones such as cortisol-releasing hormone had a negative effect on sleep quality with increased episodes of rapid eye movement sleep and inhibited Slow-Wave Sleep (SWS). In contrast, cortisol has been shown to promote SWS [9].

Although the theoretic and empirical evidence of a close interconnectedness between sleep and HPA axis hormones is strong, there are still several unknowns with regard to understanding the interplay between stress reactions and sleep. As in other areas of stress research, findings have been disparate on these interactions.

AIM

The aim of the present chapter was to analyze whether measures of cortisol in saliva were associated with measures of sleep and to see if possible divergent results were functions of differences in assumptions made and methods used.

METHOD

In a first step, an online search of the NCBI PubMed database (National Library of Medicine, National Institutes of Health, Bethesda, MD, USA-<http://www.ncbi.nlm.nih.gov/PubMed>) was conducted. The search covered the time period up to October 1, 2009. The search terms were “sleep AND (saliva OR salivary) AND cortisol”. One hundred and eight-eight papers were found after limiting the search to papers written in English and studies on humans. Of these, 69 were selected for further scrutiny based on the titles and abstracts. They were supplemented with hand searches. In this step, studies were only included in this review if the study group comprised healthy adults and the study included specific statistical analyses of the association between sleep and cortisol.

Measures of sleep quality included (1) sleep duration, (2) overall sleep quality, (3) difficulty falling asleep, (4) disturbed sleep, (5) premature awakening, and (6) sleep deprivation. Sleep duration is a well-defined measure of the number of hours a person sleeps. It may be assessed from self-reports, actigraphy, or polysomnography (PSG). Reports on sleep quality such as ease of awakening, sleep efficiency, and sufficient sleep by use of questionnaire, logbook or actigraphy were all considered as indicators of overall sleep quality. Sleep quality may be related to sleep problems and divided into categories related to different parts of the sleep: difficulty falling asleep, disturbed sleep (difficulties maintaining sleep), and premature awakening. Difficulty falling asleep covered ease of sleep (inverted), speed of sleep onset (inverted), sleep latency, but not sleep onset, and time of falling asleep. Disturbed sleep covered restless sleep, nocturnal awakenings, time awake after sleep onset, number of microarousals during the night, and number of wake periods after sleep onset. In studies of sleep deprivation participants are actively kept awake.

In the following analyses findings were considered significant if p-values were <0.05 . As most of the studies had small numbers and seemingly low statistical power, we also included marginally significant results ($0.05 < p < 0.10$) denoted by arrows in parentheses in Table 1.

RESULTS

In total 23 papers fulfilled the inclusion criteria. A brief summary of the results (indicated as arrows denoting positive associations, or negative association and zero for a nonsignificant finding) are presented in Table 1. More detailed information on study design, statistical approach, main results, and discussion for each of the 23 papers is presented in Table 2.

Results are presented for each sleep measure. Cortisol measures were grouped as follows. Single time points at: a1, awakening; a2, morning; a3, midday; a4, evening; a5, all day. Deviations during: b1, morning; b2, midday; b3, morning to evening; b4, laboratory test. Area Under the Curve (AUC): c1, morning (increase/ground). Suppression test: d, response to dexamethasone (DST). No studies were found for premature awakening.

Sleep Duration

Thirteen papers were found to test the association between salivary cortisol and sleep duration [10-22]. In the 13 papers there were 37 analyses on relationships between measures of salivary cortisol and sleep

duration. The proportion of significant relationships were 4/16 (25%) for single time points, 6/12 (50%) for deviations, 2/8 (25%) for AUC and 0/1 (0%) for dexamethasone test.

The most consistent results were a positive association between sleep duration and a single measure of salivary cortisol at awakening found in 3 studies [19-21]. In these studies, sleep duration was also associated with low evening cortisol levels [19], steep diurnal deviation of cortisol [19, 20], and with high AUC [21].

In 7 studies the authors failed to find any statistically significant associations between single measures of cortisol and sleep duration [11, 12, 15-17, 22]. The size of these studies was, in general, very small.

The association between sleep duration measures and deviations in cortisol measures was investigated in 7 studies. Morning deviations in cortisol concentrations were found to be positively associated with sleep length in an experimental study of 16 young people (8 morningness and 8 eveningness) using PSG [16]. In 2 ambulatory studies with more than 200 participants [10, 14] and a study of 2761 civil servants using self-reports negative associations to morning deviation in cortisol concentrations [20] were found.

Two studies showed a positive association between self-reported sleep duration and diurnal deviation of cortisol [19, 20]. In 4 other studies, no significant associations were found [11, 12, 15, 22], although tendencies were observed in 1 [22].

Morning AUC was the only AUC investigated in relation to sleep duration [12, 13, 18, 21, 22]. One study, a case study with 50 days of sampling, showed a positive relationship. In contrast, 1 study, which used an insomnia scale and defined sleep duration as “more than six hours sleep”, showed a negative relationship. Two out of 4 studies had only nonsignificant findings.

Overall Sleep Quality

Associations between sleep quality and measures of salivary cortisol were assessed in 8 studies [11, 12, 15, 17, 19, 21, 23, 24]. In the 8 papers there were 28 analyses on relationships between measures of salivary cortisol and overall sleep quality. The proportion of significant relationships was 5/21 (24%) for single time points, 1/5 (20%) for deviations, and 0/2 (0%) for AUC. Sleep quality was measured mainly by use of self-reports, but also PSG [13].

The most consistent pattern, a positive association to a single measure at awakening [11] or in the morning [17, 23], was observed in 3 studies. However, 5 other studies found no associations with a single morning or awakening cortisol measure [12, 15, 19, 21, 24]. In 4 studies, sleep quality was examined in relation to single measures in the afternoon or an evening measure; no associations were found [11, 15, 19, 24]. No significant associations were seen for sleep quality and deviations in cortisol concentrations [12, 19, 24].

One study found a positive relationship between stress reactivity and sleep quality measured as sleep efficiency by actigraphy, but not by self-reports [15]. One study examined associations between sleep quality and morning AUC, and found no significant relationship [21].

Difficulty Falling Asleep

Three studies assessed a total of 10 associations between salivary cortisol and difficulty falling asleep [15, 23, 25]. The proportion of significant relationships was 0/5 (0%) for single time points, 2/3 (67%) for deviations, and 1/2 (50%) for AUC. Difficulty falling asleep was assessed by use of actigraphy and self-reports (ease of sleep (inverted), speed of sleep onset (inverted), sleep latency, and time to fall asleep). The studies all used different types of cortisol measures.

Only 1 of the 3 studies reported significant associations, and the results were mixed [25]. In the same study the association between self-reported difficulty falling asleep in terms of ease of sleep was positively related to slope, whereas speed of sleep onset was negatively related [25]. High self-reported difficulty falling asleep was related to high AUC morning [25]. No other significant associations were observed between self-reported ease of sleep and measures of cortisol [15, 23, 25].

Disturbed Sleep/Restless Sleep

Disturbed or restless sleep was examined in 6 studies [11, 12, 15, 20, 21, 26] analyzing a total of 22 relationships. The proportion of significant relationships was 3/13 (23%) for single time points, 4/7 (57%) for deviations, and 0/2 (0%) for AUC. Disturbed sleep was assessed as the number of microarousals during the night using PSG, forced awakening, actigraphy, and self-reports (restless sleep, nocturnal awakenings, time awake after sleep onset, and number of wake periods after sleep onset).

Four studies included associations with a single cortisol measure at awakening or in the morning: 1 found a positive association with the number of microarousals [12], 1 found a negative association with self-reported frequency of nightly awakenings, but no association with self-reported wake time after sleep onset [11], and 2 found no associations [20, 21]. No associations were observed for single measures of cortisol later in the day [11, 15].

One study investigated the relation between disturbed sleep and diurnal deviation and found a negative association [20]. No significant findings were seen in the 3 studies that investigated the relationship between morning deviations of cortisol and disturbed sleep in terms of nightly microarousals [12], forced awakenings [26], and sleep disturbance [20]. One study investigated the effect of disturbed sleep the night before a laboratory stress test, and found negative associations with reactivity [15].

AUC in the morning was tested in relation to disturbed sleep on a day to day basis in a case study with 50 days of sampling; and no significant associations were found [21].

Sleep Deprivation

Six studies investigated a total of 8 associations between sleep deprivation and measures of salivary cortisol with mixed results [27-32]. The proportion of significant relationships was 2/5 (40%) for single time points, 1/3 (33%) for deviations, and 0/0 (0%) for AUC. The studies used either 1 night of sleep deprivation [28-30, 32] or 5-6 nights of only 4 h sleep [27, 31].

In 1 study sleep restriction was associated with increased concentrations of cortisol in the evening and smaller decline in cortisol during the afternoon [27]. In another study it was found that cortisol concentrations were higher in the afternoon after sleep deprivation [29]. In 4 studies using cortisol concentrations in the morning, evening, and during the day following sleep deprivation, no associations were observed [28, 30-32].

Table 1: Summary of main findings of associations between measures salivary cortisol and studied domains sorted by year of publication

References	Year	Exposure	Awakening time	Design	n	M/W	Single time points (or sum/mean of two or more time points)					Deviation Difference/slope for two or more time points				AUC	Dexamethasone suppression test
							a1	a2	a3	a4	a5	b1	b2	b3	b4	c1	d
Sleep duration																	
Wüst [10]	2000	SR		C-S	509	190/319						↓					
Backhaus [11]	2004	SR		C-C	29	21/8	(↓)	0		0							
Ekstedt [12]	2004	PSG	07:00 h ±1 h	C-S	24	10/14	0	0				0					
Federenko [13]	2004	SR	04:00 h	Exp	49	0/49						0				0	
Schlotz [14]	2004	SR		C-S	219	102/117	0					↓					
Wright [15]	2007	SR/AG			53	0/53			0						00		
Griefahn	2008	PSG		Exp	16	16/0		0				↑ ^b					

[16]																			
Gustafsson [17]	2008	SR		C-S	25	13/12		00											
Liberzon [18] ^a	2008	SR		Pros	31	13/18											0	0	
Hsiao [19]	2009	SR	06.65 h, SD 1.3	C-S	106	35/71	↑			↓				↑					
Kumari [20]	2009	SR	06:13-07:44 h	C-S	275 1	?	↑					↓		↑					
Stalder [21]	2009	SR		C	1	1/0	↑										0	↑	
Vreeburg [22]	2009	SR	07:20, SD 1.1	C-S	491	199/292		0		0		(↓)		(↓)			↓	0	0
Overall sleep quality																			
Bailey [23]	1991	SR		C-S	20	16/4		↑*											
Backhaus [11]	2004	SR		C-C	29	21/8	↑↑	00		00									
Ekstedt [12]	2004	PSG	07:00 h ±1 h	C-S	24	10/14	0	0				0							
Wright [15]	2007	SR			53	0/53				00						↑0			
Gustafsson [17]	2008	SR		C-S	25	13/12		↑↑00											
Dahlgren [24]	2009	SR		Pros	14	8/6	0	0		0		0							
Hsiao [19]	2009	SR	06.65 h, SD 1.29	C-S	106	35/71	0			0				0					
Stalder [21]	2009	SR		C	1	1/0	0										0	0	
Difficulty falling asleep																			
Bailey [23]	1991	SR		C-S	20	16/4		00											
Wright [15]	2007	AG			53	0/53			0							0			
Lasikiewicz [25]	2008	SR		C-S	147	68/79					00			↓↑			↓0		
Disturbed sleep																			
Backhaus [11]	2004	SR		C-C	29	21/8	↓0	00		00									
Ekstedt [12]	2004	PSG	7 AM ± 1 h	C-S	24	10/14	↑	↑				0							
Dettenborn [26]	2007	Forced awake		Exp	13	0/13						0							
Wright [15]	2007	AG			53	0/53				000						↓↓↓			
Kumari [20]	2009	SR	6:13-7:44	C-S	275 1		0					0		↓					
Stalder [21]	2009	SR		C	1	1/0	0										0	0	
Sleep deprivation																			
Spiegel [27]	1999	Sleep restricted		Exp	11	11/0				↑				↓					
Heiser [28]	2000	Forced		Exp	10	10/0								0					
Goh [29]	2001	One night		Exp	14	0/14			↑										
Pagani [30]	2009	One night		Exp	24	12/12		0		0									
Van Leeuwen [31]	2009	Restricted		Exp	19	19/0				0									
Birchler-Pedross [32]	2009	40 h		Exp	32	16/16								0					

Abbreviations: a1, awake; a2, morning; a3, midday; a4, evening; a5, all day; b1, morning; b2, midday; b3, morning to evening; b4, laboratory test reactivity/recovery; c1, morning increase/ground; AG, actigraphy; AUC, Area under the curve (increase vs ground); C, case; C-C, case-control; C-S, cross-sectional; Exp, experimental; M, men; Pros, prospective; PSG, polysomnography; SR, self-reported; W, women. ↑ indicates that the slope is steeper.

^aSleep length >6 h.

^bSignificant finding only in evening types.

Table 2: Descriptives of the articles on salivary cortisol and sleep parameters sorted by domain of sleep parameter and year of publication

References	Outcome	Study design/group characteristics	Sampling	Laboratory method and standardization in sampling	Statistical approach for cortisol measurement in relation to sleep	Statistical analysis, cortisol in relation to outcome	Results on cortisol and sleep
Wüst 2000 [10]	<i>Sleep length:</i> TST <i>Method:</i> Self-report	Design: C-S No.: 509 M/W: 190/319 Age: 37.3 (18-71) years Group: Healthy	Days: 2 Samples per day: 4 Times for sampling: Awakening, +15, 30, and 60 min, Setting: Ambulatory (at home)	RIA	Measurement(s): a1. Cortisol on awakening b1. Mean increase from awakening c1. AUC	Cortisol data: Continuous Statistics: Pearson correlation and ANOVA with repeated measures	Positive correlation between sleep duration and mean cortisol increase from awakening (b1)
Backhaus 2004 [11]	<i>Sleep length:</i> TST <i>Sleep quality:</i> PSQI, feeling of recovery <i>Disturbed sleep:</i> Frequency of nightly awakenings, wake time after sleep onset <i>Method:</i> Questionnaire (PSQI), feeling of recovery	Design: C-C No.: 29 M/W: 21/8 Age: 32-62 years Group: insomniacs (n=14) and healthy controls (n=15)	Days: 7 Samples per day: 3 Times for sampling: Awakening, +15 min and before going to bed Setting: Ambulatory (at home)	RIA Not to use food, alcoholic beverages, caffeine, fruit juice, or brush teeth 1 h before sampling	Measurement(s): All by means of same time point over the 3 consecutive days a1. Cortisol on awakening a2. Cortisol 15 min after awakening a4. Cortisol at bedtime	Cortisol data: Continuous Statistics: Pearson correlation and ANOVAs	Trend for negative correlation between TST and cortisol at awakening (a1) Positive correlation between sleep quality, and feeling of recovery, and cortisol at awakening (a1) Negative correlation between frequency of nightly awakenings and cortisol at awakening (a1). No correlation between wake time after sleep onset and awakening cortisol (a1) No correlation between sleep parameters and cortisol 15 min after awakening (a2) or cortisol at bedtime (a4)
Ekstedt 2004 [12]	<i>Sleep length:</i> TST <i>Sleep quality:</i> Sleep efficiency <i>Disturbed sleep:</i> Number of arousals <i>Method:</i> 2 PSG recordings carried out in the subject's home (before workday/ day off)	Design: C-S No.: 24 M/W: 10/14 Age: 30.5 ± 0.5 years Group: High (n=12) and low (n=12) burnout, recruited from a Swedish IT company	Days: 2 Samples per day: 9 Times for sampling: Awakening, +15, 30, and 60 min, 11:00, 15:00, 19:00, 21:00 h and bedtime Setting: Ambulatory. Saliva collected at day after the PSG	RIA No current smokers, non-sedentary lifestyle and moderate alcohol intake	Measurement(s): a1. Single awakening sample a2. Awakening cortisol as a mean morning value of 4 samples, at awakening, 15, 30, 60 min post awakening b1. Deviation morning value (CAR (difference 0-60 min))	Cortisol data: Log transformed Statistics: Stepwise multiple regression analyses. Pearson correlation coefficient Confounders:	No association between total sleep time and awakening cortisol or mean cortisol within 60 min after awakening No association between sleep efficiency and cortisol More nightly arousals were associated with higher awakening cortisol and mean cortisol within 60 min after awakening No association between any sleep measure and morning deviation
Federenko 2004 [13]	<i>Sleep duration:</i> TST <i>Method:</i> Self-report	Design: Exp No.: 49 M/W: 0/49 Age: nurses: 40.3 years, students: 25 years Group: Nurses working shifts (n=18) and students with regular sleep cycle (n=31)	Days: 2 Samples per day: 4 Times for sampling: Awakening, +30, 45 and 60 min Setting: Nurses: collected 1st and 2nd day of 3 different shifts. Students: after early evening nap on 2 days	RIA Not to smoke, eat and drink just water in the first hour after awakening, not to brush teeth, avoid microinjuries in oral cavity	Measurement(s): b1. Mean increase from awakening c1. AUC _{ground}	Cortisol data: Statistics: Person's correlations Confounders: Oral contraceptives	No correlation between sleep duration and mean increase from awening or AUC _{ground}

Schlotz 2004 [14]	<i>Sleep length:</i> ? <i>Method:</i> ?	Design: C-S No.: 219 M/W: 102/117 Age: 48.6 (24-83) years Group: Healthy	Days: 7 consecutive Samples per day: 4 Times for sampling: Awakening, +15, 30, and 60 min, Setting: Ambulatory (at home)	RIA	Measurement(s): a1. Cortisol on awakening b1. Mean increase from awakening	Cortisol data: Continuous Statistics: ANOVA with repeated measures	No association between sleep duration and cortisol on awakening (a1) Positive association between sleep duration and mean cortisol increase from awakening (b1)
Wright 2007 [15]	<i>Sleep duration:</i> TST (actigraphy and self-reports) <i>Sleep quality:</i> Sleep quality and sleep efficiency <i>Difficulty falling asleep:</i> Sleep latency <i>Disturbed sleep:</i> Wake up %, minutes awake, number of wake periods <i>Method:</i> Actigraph and sleep log (Pittsburgh sleep diary) over 7 days	Design: C-S No.: 53 M/W: 0/53 Age: 37.3 ($\pm$ 9.9) years Group: Healthy	Days: 1 Samples per day: 4 Times for sampling: Base line cortisol before stress test (14:00 h), post test, +30 min and 45 min post test Setting: Laboratory with stress test	Immunoassay After stress test the participants were asked to relax and read general interest magazines	Measurement(s): a3. Single measure at baseline (14:00 h) b4. Reactivity to test	Cortisol data: Logarithmic (base 10) Statistics: Pearson's correlations, univariate analysis and partial correlations adjusting for baseline cortisol	Positive association between sleep efficiency (actigraph) and cortisol reactivity to test Negative association between all 3 disturbed sleep and cortisol reactivity to test No association between TST, sleep latency, self-reports of sleep quality and length and cortisol reactivity to test No association between actigraph measures and baseline cortisol (14:00 h)
Greifahn 2008 [16]	<i>Sleep duration:</i> TST <i>Method:</i> PSG	Design: Exp No.: 16 M/W: 16/0 Age: 19-27 years Group: morningness (n=8), eveningness (n=8)	Days: 6 days (?) Samples per day: 2 Times for sampling: 7:00 h, +30 min. Only those when wakeup is after 06:50 h Setting: Laboratory	LIA (IBL) No smoking, no teeth brushing prior sampling	Measurement(s): a2. Single measures at 07:00 h b1. Deviation morning concentration, at 07:00 h and 30 min later	Cortisol data: Continuous? Statistics: ANCOVA with repeated measures correlation Confounders:	TST had positive association with b1 after night sleep TST not associated with cortisol at awakening (a2)
Gustafsson 2008 [17]	<i>Sleep duration:</i> Sleep length <i>Sleep quality:</i> Sufficient sleep, generally difficulties sleeping because of work <i>Method:</i> Questionnaire	Design: C-S No.: 25 M/W: 13/12 Age: 24-62 years Group: White collar workers	Days: 2 Samples per day: 6 Times for sampling: 15-30 min after awakening and every 2 h until 20:00 h Setting: Ambulatory	RIA All participants were asked to rise and go to bed at the same times during days of measurement	Measurement(s): a2. Two measures, approx. 07:00 h and 09:00 h	Cortisol data: ? Statistics: Linear regression. Repeated measures ANOVA Confounders:	Association between less sufficient sleep (better sleep quality) and higher morning cortisol. (both measures) No association between sleep duration or difficulties sleeping because of work and morning cortisol
Liberzon 2008 [18]	<i>Sleep duration:</i> <i>Method:</i> Not mentioned in methods section	Design: Follow-up No.: 31 M/W: 13/18 Age: 18-38 years Group: Students (n=23) and science staff (n=4) and ships crew member (n=4)	Days: 6 Samples per day: 4 Times for sampling: Awakening, +15, 30, 45 min Setting: Ambulatory	RIA Not to eat, drink, smoke, brush teeth or rinse mouth until after 45 min sample	Measurement(s): c1g. AUC with respect to ground c1i. AUC for increase (awakening response)	Cortisol data: Statistics: Confounders: Perceived stress and control (Likert scale)	No other correlation between total sleep time and cortisol measures in total sample
Hsiao 2009 [19]	<i>Sleep duration:</i> Total time slept <i>Sleep quality:</i> Sleep quality last night <i>Method:</i> Questionnaire	Design: C-S No.: 106 M/W: 35/71 Age: 38.5 years (SD 9.7) Group: 106 healthy subjects (and 126 patients)	Days: Samples per day: 5 Times for sampling: Awakening, + 45 min, 12:00 h, 17:00 h, 21:00 h Setting: Ambulatory	RIA Not to brush teeth, avoid oral blood contamination before sampling. Not to eat 45 min after awakening and 30 min before collecting samples	Measurement(s): single measures at awakening and over a day a1. Awakening cortisol a4. Evening cortisol b3. Deviation (diurnal	Cortisol data: Natural logarithm Statistics: Two-level individual growth curve model. (multiple regression model for nested, repeated data) Confounders: Several	Association between longer sleep and steeper slope (b3), higher awakening cortisol (a1), lower cortisol in the evening (a4) No association between sleep quality and cortisol

		with major depression - not used in present review)			profile)	confounders are adjusted for in two different models	
Kumari 2009 [20]	<i>Sleep duration:</i> TST divided into 1-h categories <i>Disturbed sleep:</i> Sleep disturbance <i>Method:</i> Logbook and questionnaire	Design: C-S No.: 2751 M/W: ? Age: ? Group: Whitehall	Days: Samples per day: 5 Times for sampling: Awakening, +30 min, +2.5, 8, 12 h Setting: Ambulatory	Immunoassay method Provide 6 samples on a normal weekday	Measurement(s): a1. Single time point, awake b1. Deviation morning profile b3. Deviation morning to evening (profile)	Cortisol data: Log cortisol data Statistics: Multilevel, interaction term Confounders: Age, sex, employment grade, awakening time, smoking status, waist circumference	Association between long sleep duration and higher cortisol. at awakening (a1) and steeper diurnal slope (b3). Association between long sleep duration and flatter morning slope (b1) Association between less disturbed sleep and steeper diurnal slope (b3)
Stalder 2009 [21]	<i>Sleep duration:</i> TST <i>Sleep quality:</i> <i>Disturbed sleep:</i> Nocturnal awakenings <i>Method:</i> Sleep log	Design: Case study No.: 1 M/W: 1/0 Age: 27 years	Days: 50 with 3 days interval Samples per day: 4 Times for sampling: Awakening, +15, 30 and 45 min Setting: Ambulatory	ELISA method Sat for 15-30 min when sampling, otherwise moved freely in relation to sampling times	Measurement(s): a1. Awakening concentration c1. AUC _{ground} c1. AUC _{increase}	Cortisol data: Log transform Statistics: Repeated measures ANOVA Confounders: Alcoholic drinks consumed the evening before measurement day	Positive association between sleep duration and awakening cortisol and AUC _{ground} No association between disturbed sleep and sleep quality and cortisol No association between any sleep parameters and AUC _{increase}
Vreeburg 2009 [22]	<i>Sleep duration:</i> Sleep length (more or less than 6 h) <i>Method:</i> Insomnia rating scale	Design: C-S No.: 491 M/W: 199/292 Age: 43.0 years Group: volunteers without psychopathology Excl: Taking antidepressants, pregnant or breastfeeding, on medication with corticosteroids P rate: 78.3%, with at least one usable cortisol measurement	Days: 1 Samples per day: 7 Times for sampling: Awakening, +30, 45, 60 min, 22:00 h, 23:00 h. Samples taken more than 5 min from protocol time were discarded Setting: Ambulatory. Day after dexamethasone 0.5 mg directly after sampling time at 23:00 h	Immunoassay method When sampling no eating, smoking, drinking tea or coffee, or brushing teeth 15 min before	Measurement(s): a2. a4. b1. Deviation morning b3. Deviation 23:00 h, awakening time divided by numbers of hours in between (diurnal slope) c1i. AUC _{increase} morning c1g. AUC _{ground} morning d. Post dexamethasone (DST)	Cortisol data: AUC, evening cortisol and DST were log transformed Statistics: Linear mixed models or linear regression analysis Confounders: Sociodemographic factors, health indicators	Less than 6 h sleep is associated with increase in CAR (AUC _{increase}) Tendency for less than 6 h sleep is associated with steeper morning deviation (b1) and a steeper diurnal slope (b3) No association with morning cortisol (a2), evening cortisol (a4), AUC _{ground} morning, or post dexamethasone
Bailey 1991 [23]	<i>Sleep quality:</i> Sleep quality <i>Difficulty falling asleep:</i> Sleep onset <i>Method:</i> Sleep log	Design: C-S No.: 20 M/W: 16/4 Age: 23-39 years Group: morning types (n=10) and evening types (n=10). Recruited from the general population	Days: 1 Samples per day: 7 Times for sampling: Arising, +20, 40, 60, 80, 100, and 120 min Setting: Ambulatory	RIA	Measurement(s): a2. Single cortisol levels	Cortisol data: Continuous Statistics: <i>t</i> -test, Pearson product-moment correlation coefficients, Spearman rho correlation coefficients	Positive association between sleep quality and total cortisol in evening type group, but not in morning type group No association between sleep onset and total cortisol in evening or morning type group
Dahlgren 2009 [24]	<i>Sleep quality:</i> <i>Method:</i> Karolinska sleep diary for 4 weeks	Design: C-S No.: 14 M/W: 8/6 Age: 44 years Group: Office workers	Days: 28 Samples per day: 3 Times for sampling: Awakening, +15 min, bedtime Setting: Ambulatory	RIA No food, no teeth brushing 30 min before saliva sampling	Measurement(s): Single time points: a1. Awake a2. Morning a4. Evening b1. Deviation morning	Cortisol data: Log data Statistics: Multiple regression analyses by time. ANOVA of repeated measurements Confounders: Work day, work load, awakening time, stress at bedtime, sleep quality, stress, sleepiness exhaustion, self related health	No associations between sleep quality and measures of cortisol

Lasikiewicz 2008 [25]	<i>Difficulty falling asleep:</i> Ease of sleep and speed of sleep onset <i>Method:</i> Questionnaire (Leeds Sleep Evaluation Questionnaire)	Design: C-S No.: 147 M/W: 68/79 Age: mean age 46.2 years (± 7.2) Group: volunteers	Days: 1 ($n=64$) or 3 ($n=83$) Samples per day: 8 Times for sampling: Awakening, +15, 30, 45 min, +3, 6, 9, 12 h Setting: Ambulatory	Immunoassay method Not to consume food or drink other than water in relation to sample collection. Avoid teeth brushing and vascular leakage	Measurement(s): Mean of same time point on consecutive days a5. b4. Deviation evening from 45 min post awakening (slope) c1. AUC not specified	Cortisol data: Log transformed Statistics: Pearson's correlation. Cluster analysis (M)ANOVA Confounders: Age, gender	Association between higher ease of sleep (less difficulty falling asleep) and low AUC Association between high ease of sleep (less difficulty falling asleep) and less steep slope (b3) Association between high speed of sleep onset (less difficulty falling asleep) and more steep slope (b3) No association between ease of sleep, speed of sleep onset and diurnal mean (a5)
Dettenborn 2007 [26]	<i>Disturbed sleep:</i> <i>Method:</i> Three experimentally induced awakenings (phone call). The wake up in the morning was optional or set up by alarm clock. No other sleep registration	Design: Exp No.: 13 M/W: 0/13 Age: 24 years	Days: 3 intervention nights + 3 reference nights Samples per day: 8 on intervention nights and 2 on recovery nights Times for sampling: Awakening and +15 min in the morning Setting: Ambulatory	CLIA	Measurement(s): b1. Repeated measures	Cortisol data: continuous Statistics: ANOVA and ANCOVA Confounders: Oral contraceptives, thyroid hormone	The morning CAR after disturbed nights was not different from CAR on undisturbed nights There was a lack of HPA axis activation by forced nightly awakenings
Spiegel 1999 [27]	<i>Sleep deprivation:</i> Sleep restriction	Design: Exp No.: 11 M/W: 11/0 Age: 18-27 years Group: Young healthy volunteers	Days: 3 Samples per day: 12-20 Times for sampling: Every 30 min between 15.00 and bedtime Setting: Laboratory. 3 nights with 8 h in bed, 6 nights with 4 h in bed, and 7 nights with 12 h in bed	RIA	a4. Single evening concentration b2. Deviation between 16:00 h and 21:00 h	Cortisol data: Continuous Statistics: ANOVA for repeated measures	Higher evening cortisol concentration after sleep restriction Lower rate of decrease in the afternoon after sleep restriction
Heiser 2000 [28]	<i>Sleep deprivation:</i> 3 days covered, after ordinary sleep, 1 night of total sleep deprivation and 1 night of recovery	Design: Exp No.: 10 M/W: 10/0 Age: 27.4 ± 2.8 years Group: healthy volunteers	Days: 3 Samples per day: 3 Times for sampling: 07:00, 13:00, 19:00 h Setting: Laboratory	RIA All intake of pineapples, bananas, almonds, nuts, tomatoes, vanilla, or alcohol forbidden, no smokers	Measurement(s): b3. Diurnal profile with 3 measures per day over 3 days	Cortisol data: ? Statistics: ANOVA with repeated measures	No effect on salivary cortisol rhythm of sleep deprivation
Goh 2001 [29]	<i>Sleep deprivation:</i> 24 h sleep deprivation or 8 h sleep (control)	Design: Exp No.: 14 M/W: 14/0 Age: 20-30 years Group: healthy subjects, military service members	Days: 2 Samples per day: 3-5 Times for sampling: 08:00, 13:30, 18:00, 21:00, 24:00 (day 1), 08:00, 13:30, 18:00 (day 2) Setting: Laboratory	Immunoassay	b3. Deviation, all day	Cortisol data: Continuous Statistics: Two-way ANOVA with repeated measures and interaction terms	Significant interaction between sleep status and time. Cortisol levels at 13:30 h were increased after sleep deprivation
Pagani 2009 [30]	<i>Sleep deprivation:</i> 7 normal nights + 24 h sleep deprivation) or normal living conditions (strict sleep-wake schedule 23:00-07:00 h)	Design: Exp No.: 24 M/W: 12/12 Age: 27-45 years Group: healthy subjects	Days: 8? Samples per day: 2 Times for sampling: 10.30 and 18.00 h Setting: Laboratory	RIA	Measurement(s): a2. a4.	Cortisol data: Continuous Statistics: Mixed model or GLM analysis. Intraclass correlations Confounders:	No effect of sleep deprivation on cortisol

Van Leeuwen 2009 [31]	<i>Sleep deprivation:</i> 2 baseline (8 h sleep), 5 nights of 4 h sleep, and 2 recovery nights of 8 h. Controls (8 h sleep) all nights	Design: Exp No.: 19 M/W:19/0 Age: 19-29 years Group: 13 young healthy men + 6 controls	Days: Samples per day: 10 Times for sampling: Not specified Setting: Laboratory	Competitive CLIA Napping during day time was not allowed, meals standardized (calories and time), controlled illumination and room temperature	Measurement(s): a5. Averaged throughout the day	Cortisol data: Statistics: <i>t</i> -tests and Wilcoxon signed ranks test for not normally distributed differences Confounders:	No change in salivary cortisol after sleep restriction
Birchler-Pedross 2009 [32]	<i>Sleep deprivation:</i> 40 h sleep deprivation or nap protocol	Design: Exp No.: 32 M/W: 16/16 Age: 25.0±3.3 and 65.0±5.5 years Group: Young and older healthy volunteers	Days: 2 Samples per day: 5-6. Times for sampling: every 30 min collapsed into 08:00, 12:00, 16:00, 20:00, 24:00 h (day 1), 04:00, 08:00, 12:00, 16:00, 20:00, 24:00 h (day 2) Setting: Laboratory	RIA	b3. Deviation, all day	Cortisol data: Continuous Statistics: Repeated measures ANOVA with interaction terms	Significant four-way interaction term (time of day, age, gender, sleep pressure) in model for cortisol, most likely driven by time of day None of the other variables were significant
Vreeburg 2009 [22]	<i>Sleep duration:</i> Sleep length (more or less than 6 h) <i>Method:</i> Insomnia rating scale	Design: C-S No.: 491 M/W: 199/292 Age: 43.0 years Group: volunteers without psychopathology Excluded: Taking antidepressants, pregnant or breastfeeding, on medication with corticosteroids P rate: 78.3%, with at least one usable cortisol measurement	Days: 1 Samples per day: 7 Times for sampling: Awakening, +30, 45, 60 min, 22:00, 23:00 h. Samples taken more than 5 minutes from protocol time were discarded Setting: Ambulatory. Day after dexamethasone 0.5 mg directly after sampling time at 23:00 h	Immunoassay method When sampling no eating, smoking, drinking tea or coffee, or brushing teeth 15 min before	Measurement(s): a2. a4. b1. Deviation morning b3. Deviation 23:00 h to awakening time divided by number of hours in between (diurnal slope) c1i. AUC _{increase} morning c1g. AUC _{ground} morning d. Post DST	Cortisol data: AUC, evening cortisol and DST were log transformed Statistics: Linear mixed models or linear regression analysis Confounders: Sociodemographic factors, health indicators	Less than 6 h sleep is associated with increase in CAR (AUC _{increase}) Tendency for less than 6 h sleep is associated with steeper morning deviation (b1) and a steeper diurnal slope (b3) No association with morning cortisol (a2), evening cortisol (a4), AUC _{ground} morning, or post dexamethasone

Abbreviations: AUC, Area under the curve; C-C, case-control; C-S, cross-sectional; CAR, cortisol awakening response; CLIA, chemiluminescence-assay; DST, Dexamethasone test; ELISA, Enzyme Linked Immuno-Sorbant Assay; Exp, experimental; GLM, generalized linear model; LIA, luminescence immunoassay; M, Male; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; P rate, Response rate; RIA, radioimmunoassay; TST, total sleep time, W, women.

DISCUSSION

The aim of the present chapter was to analyze whether measures of cortisol in saliva were associated with measures of sleep to see if divergent results were functions of differences in theoretic assumptions made and methods used. Relatively few papers were first identified ($n=188$), and only 23 papers met the final inclusion criteria.

The most consistent results were a positive association between sleep duration and a single measure of salivary cortisol at awakening, which was observed in 3 studies [19-21]. In these studies, sleep duration was also associated with low evening cortisol levels [19], steep diurnal deviation of cortisol [19, 20], and with high AUC [21]. Together these findings suggest that longer sleep duration is related to a more dynamic cortisol secretion.

However, long sleep duration is also associated with a lower CAR [10, 14, 20]. Since a lower CAR implies a less dynamic response these observations seem to contradict the suggestion that longer sleep duration is related to a more dynamic cortisol secretion. However, a lower CAR needs not to be mutually exclusive with a dynamic cortisol secretion as assessed by the decline in concentrations during the entire day. Indeed, a lower CAR might just reflect the diurnal rhythmicity of cortisol secretion. For example, to the extent that participants, who sleep long wake up later than usual, they are likely to take their first sample at a time when the concentrations of cortisol already have risen due to the normal diurnal rhythm. Hence, there is simply less room to obtain a high CAR as the morning value has been inflated by the underlying diurnal rhythm. However, there might also be several other explanations and this question deserves more attention in future studies.

Two of the 6 studies on disturbed sleep showed that it was associated with less diurnal deviation [20], and lower reactivity to a laboratory stress test [15]. This to some extent corroborates the findings on sleep duration. However, the many nonsignificant findings as well as the theoretic and methodological differences (*e.g.* heterogeneity in measures) complicate comparisons.

As expected, statistically significant associations were more often reported in studies with a large number of participants or a high sampling frequency. Among the papers included, statistically significant findings were generally seen in studies with more than 100 participants [10, 14, 19, 20], or samples (case study) [21]. In the large studies, it was more common to focus on general sleep patterns, whereas the case study registered day to day variations within the same person. The results suggest that a relationship between sleep and salivary cortisol is observable both within and between subjects, but requires many observations due to high variability in both cortisol and sleep measures. The use of small study samples and non-optimal measurement procedures might lead to studies with low power and failure to detect statistically significant results.

Even if the inclusion criteria drastically reduced the number of papers, the papers included covered several different types of measures and indicators for cortisol and sleep. This heterogeneity in measures and methods appears to generate a mixed pattern of results that are also conflicting at times. For example, in the same study a positive relationship was observed between stress reactivity and sleep quality measured as sleep efficiency by actigraphy, but not by self-reports [15]. As differences between objectively measured and self-reports of sleep have been observed previously, this conflict may be partially related to the selected instrument for measurement of sleep quality [33].

There are several methodological problems in studies of sleep and saliva cortisol. Because saliva sampling requires that the person is awake, it is virtually impossible to sample saliva during sleep and to establish the relationship with different sleep stages or other processes that may occur during sleep. It is often not practically feasible in field studies to obtain direct measurements during the sleep period with, for example, PSG or endocrine measures. Even if it is technologically possible to use such measures, the procedures and commitments necessary for successful implementation have often been considered to be cumbersome and too expensive to be considered as a realistic option. Stress researchers often have to rely on less sophisticated and simpler approaches such as motion logging (*e.g.*, actigraphy) and subjective reports of various aspects of sleep (*e.g.*, bedtime, awakening time, and perceived quality of sleep).

Many of the studies were not conducted primarily to evaluate the relationship between sleep and salivary cortisol. Even so, all studies included in the present chapter have used statistical tests to address the overall question about the relationship between sleep and saliva cortisol. Considering that research have been driven by many points of departures, it is not surprising that most of the result do not act in concert.

CONCLUSIONS

In total 23 studies examining sleep quality in relation to salivary cortisol measures were identified. There was a large proportion of nonsignificant findings and many operational definitions of sleep quality and cortisol secretion. Because many of the studies included were small and entailed few measurements, there is reason to believe that the nonsignificant findings partly reflect low statistical power.

The most consistent results were our observation of a positive association between sleep duration and a single measure of salivary cortisol at awakening, which was observed in 3 studies. In these studies, sleep duration was also associated with low evening cortisol levels, steep diurnal deviation of cortisol, and/or with high AUC. Together these findings suggest that longer sleep duration is related to a more dynamic cortisol secretion. Two of the 6 studies on disturbed or restless sleep showed a relationship with flat diurnal deviation and low laboratory stress test reactivity. This to some extent corroborates the findings regarding sleep duration. However, the many nonsignificant findings as well as the theoretic and methodological differences (*e.g.*, heterogeneity in measures) complicate comparisons. Conflicting results may be at least partially due to differences in methods and underlying assumptions.

REFERENCES

- [1] Ursin H, Eriksen HR. The cognitive activation theory of stress. *Psychoneuroendocrinology* 2004; 29: 567-592.
- [2] Mason JW. A historical view of the stress field part 2. *J Human Stress* 1975; 1: 22-36 concl.
- [3] Mason JW. A historical view of the stress field part 1. *J Human Stress* 1975; 1: 6-12 contd.
- [4] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005; 437: 1257-1263.
- [5] Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol* 2009; 5: 374-381.
- [6] Van Cauter E. temp- in sleep chapter. Presented in draft 100621 from Anne Helene. 2005.
- [7] Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal man. *J Clin Endocrinol Metab* 1983; 56: 352-358.
- [8] Steiger A. Sleep and the hypothalamo-pituitary-adrenocortical system. *Sleep Med Rev* 2002; 6: 125-138.
- [9] Steiger A, Antonijevic IA, Bohlhalter S, Frieboes RM, Friess E, Murck H. Effects of hormones on sleep. *Horm Res* 1998; 49: 125-130.
- [10] Wust S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C. The cortisol awakening response - normal values and confounds. *Noise Health* 2000; 2: 79-88.
- [11] Backhaus J, Junghanns K, Hohagen F. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology* 2004; 29: 1184-1191.
- [12] Ekstedt M, Akerstedt T, Soderstrom M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. *Psychosom Med* 2004; 66: 925-931.
- [13] Federenko I, Wust S, Hellhammer DH, Dechoux R, Kumsta R, Kirschbaum C. Free cortisol awakening responses are influenced by awakening time. *Psychoneuroendocrinology* 2004; 29: 174-184.
- [14] Schlotz W, Hellhammer J, Schulz P, Stone AA. Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response. *Psychosom Med* 2004; 66: 207-214.
- [15] Wright CE, Erlich J, Valdimarsdottir HB, Bovbjerg DH. Poor sleep the night before an experimental stressor predicts reduced NK cell mobilization and slowed recovery in healthy women. *Brain Behav Immun* 2007; 21: 358-363.
- [16] Griefahn B, Robens S. The cortisol awakening response: a pilot study on the effects of shift work, morningness and sleep duration. *Psychoneuroendocrinology* 2008; 33: 981-988.
- [17] Gustafsson K, Lindfors P, Aronsson G, Lundberg U. Relationships between self-rating of recovery from work and morning salivary cortisol. *J Occup Health* 2008; 50: 24-30.

- [18] Liberzon J, Abelson JL, King A, Liberzon I. Naturalistic stress and cortisol response to awakening: adaptation to seafaring. *Psychoneuroendocrinology* 2008; 33: 1023-1026.
- [19] Hsiao FH, Yang TT, Ho RT, Jow GM, Ng SM, Chan CL, *et al.* The self-perceived symptom distress and health-related conditions associated with morning to evening diurnal cortisol patterns in outpatients with major depressive disorder. *Psychoneuroendocrinology* 2009; 35: 503-515.
- [20] Kumari M, Badrick E, Ferrie J, Perski A, Marmot M, Chandola T. Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab* 2009; 94: 4801-4809.
- [21] Stalder T, Evans P, Hucklebridge F, Clow A. Associations between psychosocial state variables and the cortisol awakening response in a single case study. *Psychoneuroendocrinology* 2010; 35: 209-214.
- [22] Vreeburg SA, Kruijtzter BP, van Pelt J, van Dyck R, DeRijk RH, Hoogendijk WJ, *et al.* Associations between sociodemographic, sampling and health factors and various salivary cortisol indicators in a large sample without psychopathology. *Psychoneuroendocrinology* 2009; 34: 1109-1120.
- [23] Bailey SL, Heitkemper MM. Morningness-eveningness and early-morning salivary cortisol levels. *Biol Psychol* 1991; 32: 181-192.
- [24] Dahlgren A, Kecklund G, Theorell T, Akerstedt T. Day-to-day variation in saliva cortisol-relation with sleep, stress and self-rated health. *Biol Psychol* 2009; 82: 149-155.
- [25] Lasikiewicz N, Hendrickx H, Talbot D, Dye L. Exploration of basal diurnal salivary cortisol profiles in middle-aged adults: associations with sleep quality and metabolic parameters. *Psychoneuroendocrinology* 2008; 33: 143-151.
- [26] Dettenborn L, Rosenloecher F, Kirschbaum C. No effects of repeated forced wakings during three consecutive nights on morning cortisol awakening responses (CAR): a preliminary study. *Psychoneuroendocrinology* 2007; 32: 915-921.
- [27] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; 354: 1435-1439.
- [28] Heiser P, Dickhaus B, Schreiber W, Clement HW, Hasse C, Hennig J, *et al.* White blood cells and cortisol after sleep deprivation and recovery sleep in humans. *Eur Arch Psychiatry Clin Neurosci* 2000; 250: 16-23.
- [29] Goh VH, Tong TY, Lim CL, Low EC, Lee LK. Effects of one night of sleep deprivation on hormone profiles and performance efficiency. *Mil Med* 2001; 166: 427-431.
- [30] Pagani M, Pizzinelli P, Traon AP, Ferreri C, Beltrami S, Bareille MP, *et al.* Hemodynamic, autonomic and baroreflex changes after one night sleep deprivation in healthy volunteers. *Auton Neurosci* 2009; 145: 76-80.
- [31] van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, *et al.* Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One* 2009; 4: e4589.
- [32] Birchler-Pedross A, Schroder CM, Munch M, Knoblauch V, Blatter K, Schnitzler-Sack C, *et al.* Subjective well-being is modulated by circadian phase, sleep pressure, age, and gender. *J Biol Rhythms* 2009; 24: 232-242.
- [33] Harvey AG, Tang NK, Browning L. Cognitive approaches to insomnia. *Clin Psychol Rev* 2005; 25: 593-611.