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Original Article

ORIGINAL ARTICLE

Association between weekend catch-up sleep and high-sensitivity C-reactive protein levels in adults: a population-based study

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Abstract

Study Objectives: To investigate the association between weekend catch-up sleep (WCS) and the levels of high-sensitivity C-reactive protein (hsCRP)—a serum inflammatory maker—in adults

Methods: Data of 5,506 adults aged 19 years or older were obtained from the nationwide cross-sectional Korea National Health and Nutrition Examination Surveys conducted in 2016. Serum hsCRP level, weekday and weekend sleep durations, and sociodemographic and health-related characteristics were assessed. Participants whose weekend sleep duration was more than 1 h longer than their weekday sleep duration were included in the WCS group. hsCRP level was categorized into quartiles (i.e. highest, middle-high, middle-low, and lowest). Obesity was defined by body mass index ≥ 25.0 kg/m^2.

Results: The WCS group included 1,901 participants (34.5%). In the logistic regression analysis controlling for all variables, adults in the WCS group were significantly less likely to show the highest hsCRP level (versus the lowest level) compared with those without WCS in the complete sample (adjusted odds ratio = 0.795, 95% confidence interval [CI] = 0.662 to 0.955). In a subgroup analysis, this association was significant only for those with weekday sleep duration of 6 h or lower. Longer WCS (≥3 h) was not associated with hsCRP levels. Non-obese people with WCS demonstrated a lower risk for high hsCRP levels, while there was no significant difference in obese people with WCS.

Conclusions: Our findings indicate that WCS may be beneficial for low-grade systemic inflammation in adults, particularly among those with shorter weekday sleep durations. WCS may also interact with obesity.

Statement of Significance

Weekend catch-up sleep (WCS)—inadequate sleep during weekdays and "catch-up" sleep over the weekend to compensate for the sleep debt—is prevalent in contemporary society. This study is the first to investigate the association between WCS and the levels of a peripheral blood-based inflammatory marker—serum high-sensitivity C-reactive protein (hsCRP)—in 5,506 adults aged 19 years or older. We found that adults with WCS (i.e. weekend sleep 1 h or longer than that on weekdays) had reduced hsCRP levels compared with those without WCS. This association was only significant for non-obese adults and for those with short weekday sleep duration (≤6 h). We also found that extremely long WCS (≥3 h) did not have beneficial effects on the hsCRP level.

Key words: weekend catch-up sleep; sleep duration; high-sensitivity C-reactive protein; inflammation; obesity

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Introduction

Sufficient sleep plays a critical role in physical and mental health, and sleep loss is one of the most common sleep-related problems [1]. In contemporary society, habitual sleep restriction during the weekdays and "catch-up" sleeping over the weekend is a prevalent sleep pattern caused by work and academic schedules, social obligations, and competitive sociocultural environments [2, 3]. A growing body of evidence has shown that weekend catch-up sleep (WCS), a coping strategy for weekday sleep deficiency that involves a pattern of weekday sleep deprivation and compensatory sleeping during the weekend, can significantly impact health. Potential associations of WCS with obesity, hypertension, dyslipidemia, glycemic control, and health-related quality of life have been suggested [2–6]. The pathophysiology of these cardiovascular and metabolic risks are especially closely connected with inflammatory processes in the human body [7–9].

An emerging body of evidence has suggested that sleep interacts with the immune system. In particular, experimental human studies manipulating sleep duration have reported that sleep restriction or deprivation are associated with increased levels of inflammatory markers such as interleukin (IL)-6 or C-reactive protein (CRP) [10–12]. A recent meta-analysis of sleep duration and inflammatory markers reported that shorter sleep durations—determined by both subjective and objective measures—were significantly associated with increased CRP levels [13]. Although there is abundant evidence regarding the effects of sleep restriction on increased systemic inflammation, few studies have investigated the impact of recovery sleep after sleep restriction on the levels of inflammatory markers. Several human studies with experimental sleep restriction and recovery sleep or naps have indicated that recovery sleep was associated with normalization of the elevated inflammatory marker levels induced by sleep restriction [14–16]. However, these studies were based on samples with small sizes due to their experimental design, and no previous study has attempted a population-level direct investigation of the association between WCS and inflammatory markers. A pattern of sleep restriction during weekdays and recovery sleep in the weekend is a modifiable lifestyle factor; thus, a population-level assessment of the potential impact of WCS on inflammatory markers, which are deeply involved in cardiovascular and metabolic risks, might provide meaningful data for public health recommendations.

Two recent population-based studies reported that WCS was associated with lower risks of obesity and hypertension in adults [2, 3]. These studies also indicated that the durations of WCS and weekday sleep may be critical moderating factors in the association between WCS and health status [2, 3]. Furthermore, the study by Im et al. suggested that WCS was significantly associated with obesity in the adult population [2]. Considering the accumulated evidence on the close relationship between obesity and low-grade systemic inflammation [17, 18], obesity can be regarded as a potential moderating factor in the relationship between WCS and inflammation.

Therefore, in the present study, we aimed to investigate the association between WCS and the serum level of an inflammatory maker—high-sensitivity CRP (hsCRP)—in adults by using a nationally representative sample of the Korean population. CRP is a significant serum biomarker related to systemic inflammation and is synthesized in the liver under the control of IL-6 [19]. Multiple studies have shown that elevated CRP levels are a significant marker for increased risk of cardiovascular diseases such as ischemic heart disease, atherosclerosis, and stroke and metabolic syndrome [20–22]. Generally, the CRP level is elevated in patients with severe inflammation, and high-sensitivity assays of CRP (i.e. hsCRP) are adequate for quantification of low CRP levels in healthy populations [23]. Therefore, the present study used the serum hsCRP level as a marker for low-grade systemic inflammation. We also examined the potential moderating effect of WCS and weekday sleep durations and the effects of obesity on the association between WCS and serum hsCRP level.

Methods

Study population

Data were obtained from a nationwide cross-sectional survey, the Korea National Health and Nutrition Examination Surveys (KNHANES), conducted in 2016 in South Korea. This survey has been annually conducted by the Korea Centers for Disease Control and Prevention since 2007 and aims to investigate public health and nutritional status and their correlations with socioeconomic, health-related, and environmental factors at a population level [24, 25]. To obtain a systematic and representative sample of a non-institutionalized general population, the survey adopted a stratified multi-stage clustered sampling design and used weighted values after adjusting for non-response, extreme values, and post-stratification [26]. Annually, approximately 10,000 people are sampled from 192 primary sample units (PSUs), which are selected from a sampling frame of all census blocks containing national resident registration addresses [27]. The detailed processes for the stratified multi-stage clustered sampling have been described in previous studies [24, 27, 28]. Each yearly survey included a new, independent sample of individuals aged one year or older in 192 PSUs in South Korea, and field survey teams with well-trained interviewers assessed the socioeconomic and health-related characteristics of respondents by using semi-structured and self-administered questionnaires [26]. In KNHANES 2016, among the 10,806 people in the sample, 8,150 people responded to the survey (response rate = 75.4%). Among 6,381 individuals aged 19 years or older from KNHANES 2016, we enrolled 5,506 individuals and excluded 875 people who had missing values for the following variables (Figure 1): hsCRP level (n = 495), weekday and weekend sleep time (n = 254), education level (n = 581), household income (n = 27), marital status (n = 1), economic activity (n = 576), prevalence of chronic disease (n = 542), alcohol consumption (n = 365), cigarette smoking (n = 381), body mass index (BMI, n = 264), physical activity (n = 581), and scores on the depressive symptoms questionnaire—the Patient Health Questionnaire-9 (PHQ-9) (n = 621). Written informed consent of the participants was not required in the present study because the KNHANES dataset is publicly available (https://knhanes.cdc.go.kr/knhanes/main.do). The protocol of this study was approved by the by the ethics committee of Korea University Ansan Hospital (IRB no. 2019AS0081).

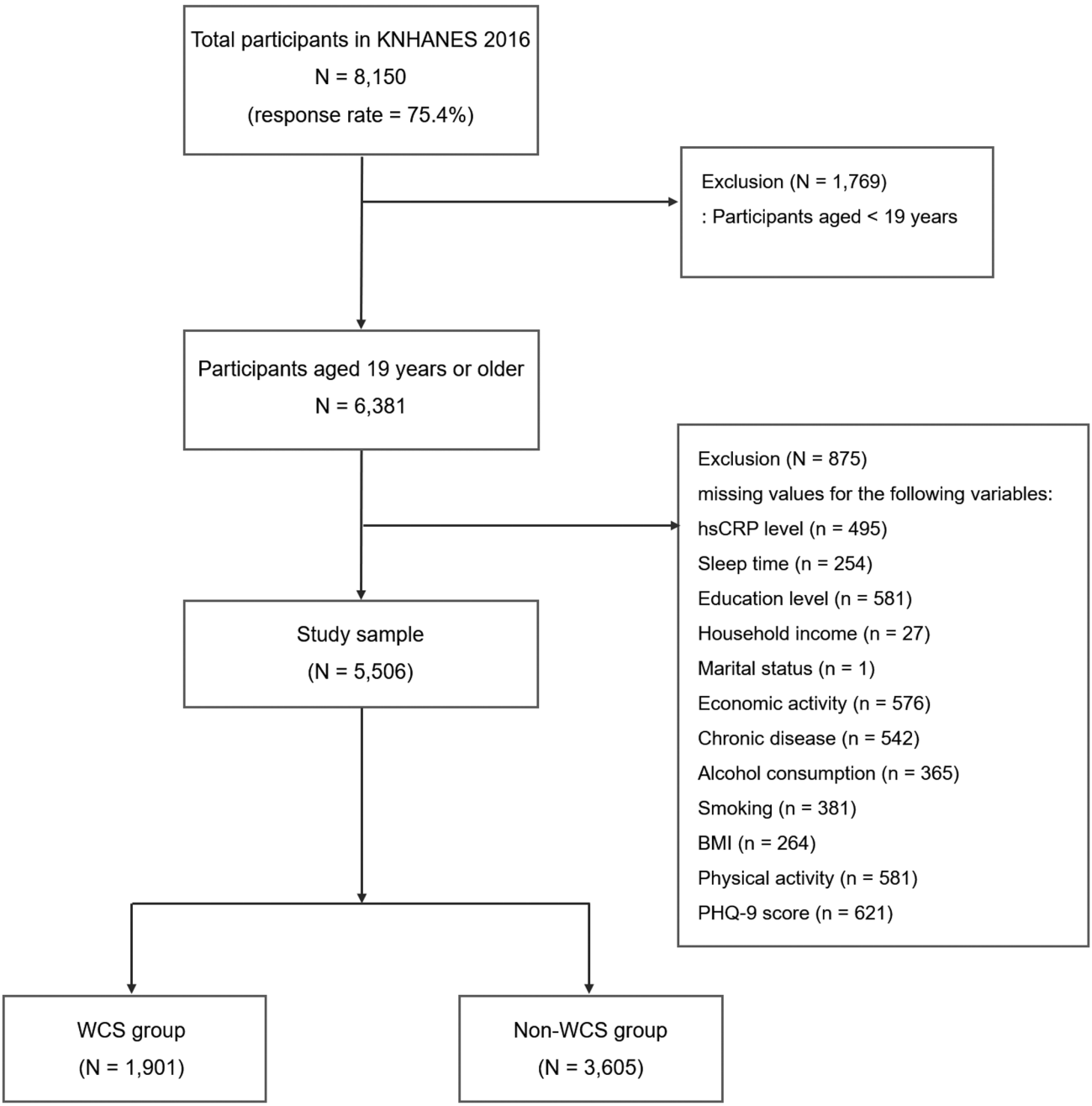

Figure 1. Flow chart for selection of the participants in the analysis.

Measurement of hsCRP level

Peripheral blood samples were obtained from participants (approximately 3 mL), and the serum hsCRP level was measured using immunoturbidimetric methods (Cobas, Roche, Germany) with "Roche Cardiac C-Reactive Protein High Sensitive" (Roche, Germany). Blood sampling was performed on weekdays immediately after completing the questionnaires. All laboratory analyses were performed by the Neodin Medical Institute, which was certified by the Korean Ministry of Health and Welfare, and the measurements were calibrated daily with reference standards between 1.0 and 200.0 mg/L [29]. There is no consensus regarding the cutoff hsCRP level related to sleep duration; therefore, we categorized hsCRP level into quartiles (i.e. highest, middle-high, middle-low, and lowest subgroups) [27, 30, 31].

Assessments of sleep duration and WCS

In the KNHANES 2016 survey, sleep duration was determined on the basis of participants' responses to the following questions separately for weekdays and the weekend: (1) "What time do you usually fall asleep and wake up on a weekday (working day)?" and (2) "What time do you usually fall asleep and wake up in the weekend (day off or the day before the day off)?"

The responses were provided separately for weekdays and the weekend as follows: (1) time when the participant fell asleep: () o'clock () minute AM/PM and (2) waketime: () o'clock () minute AM/PM. Sleep durations on weekdays and the weekend were measured on the basis of the responses, and average sleep duration was calculated using the following weighted mean value: (5 × weekday sleep duration + 2 × weekend sleep duration)/7 [2]. In the present study, WCS was defined when weekend sleep duration was more than 1 h longer than weekday sleep duration (i.e. weekend sleep duration – weekday sleep duration ≥ 1 h), and WCS duration was calculated as weekend sleep duration minus weekday sleep duration.

Covariates

We included the following sociodemographic and health-related characteristics as covariates to control their effects as confounding factors: age, sex, education level, equivalent monthly household income level, economic activity (yes [wage workers, employer, or self-employed]; no [unemployed, students, or housewives]), marital status, residential region, number of chronic diseases (none, 1, 2, or more [i.e. multimorbidity]), alcohol consumption, cigarette smoking, obesity (defined by BMI ≥25.0 kg/m^2), physical activity, and prevalence of depressive symptoms. The equivalent monthly household income was determined by dividing the raw monthly household income by the square root of family size [26]. For assessments of morbidity of chronic disease, diagnoses of 24 chronic diseases by a physician were investigated, and the list of chronic diseases is presented in Table S1. We defined physical activity by engagement in the following activities: (1) medium-intensity aerobic physical activity at least 2.5 h/week or (2) at least 1.25 h/week of high-intensity aerobic physical activity. Depressive symptoms were assessed with a self-administered questionnaire, the PHQ-9. The PHQ-9 consists of nine items rated with a 4-point Likert scale ranging from 0 to 3 according to the depressive symptom frequency (0, not at all; 1, several days; 2, more than half the days; 3, nearly every day) [32]. The prevalence of depressive symptoms was defined by PHQ-9 scores of 10 or above in accordance with previous studies [32, 33]. Detailed information about the category of each covariate is provided in Table 1.

Statistical analyses

The primary aim of the present study was to investigate the association between WCS and hsCRP level. The main analysis was multinomial regression analyses including WCS (yes/no) as an independent variable, hsCRP quartile level (i.e. highest, middle-high, middle-low, and lowest levels) as a dependent variable, and all sociodemographic and health-related variables (i.e. age, sex, education level, household income, marital status, economic activity, residential region, chronic disease, obesity, alcohol consumption, smoking, physical activity, and depressive symptoms) as covariates. The multinomial regression analyses were performed in subgroups based on weekday sleep duration (i.e. duration ≤ 6 h; 6 h < duration ≤ 7 h; 7 h < duration ≤ 8 h; duration > 8 h) and in the complete sample (including weekday sleep duration as an additional covariate). We also performed one-way analysis of covariance to compare hsCRP level (continuous variable) between adults with and without WCS, with the same covariates as in the main analysis. To explore the correlation between WCS duration and hsCRP level, multiple linear regression analysis including the WCS/weekday sleep duration ratio (i.e. WCS duration [minutes] divided by weekday sleep duration [minutes]) and all sociodemographic and health-related variables as independent variables and hsCRP level (continuous variable, mg/L) as a dependent variable was performed. Second, we investigated the association between WCS duration (duration ≥ 3 h; 2 h ≤ duration < 3 h; 1 h ≤ time < 2 h; duration < 1 h [none]) and hsCRP level by using multinomial regression analyses in the complete sample and in subgroups based on the weekday sleep duration (i.e. duration ≤ 6 h; duration > 6 h), with the same covariates as in the main analysis. Third, to explore the potential moderating effect of obesity on the association between WCS and hsCRP levels, we constructed a combined categorical variable of WCS and obesity (i.e. adults with WCS and without obesity; those with WCS and obesity; those without WCS and with obesity; and those without WCS and without obesity) and included this as an independent variable in multinomial regression analyses with the same covariates as in the main analysis (including weekday sleep duration). Multinomial regression analyses were also performed in subgroups based on obesity (i.e. adults with and without obesity). All statistical analyses in the present study were performed by using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corporation, Armonk, NY, USA), and statistical significance was considered at $p = 0.05$.

Results

Sociodemographic and health-related characteristics of the sample

Among 5,506 adults, 1,901 people (34.5%) were included in the WCS group. In a chi-squared test, in comparison with individuals without WCS, those with WCS were less likely to show the highest or middle-high hsCRP levels ($p < 0.001$, Table 1). The WCS group showed significant differences in sociodemographic and health-related variables in comparison with the non-WCS group (Table 1). Adults with WCS showed significantly shorter weekday and longer weekend sleep duration than those without WCS (all, $p < 0.001$), while there was no significant difference related to average sleep duration ($p > 0.1$, Table 1).

Association between WCS and hsCRP level

For the main analysis, we investigated the association between WCS and hsCRP level by using multinomial regression. In this analysis, individuals with WCS were significantly less likely to show the highest hsCRP level (versus the lowest level) compared with those without WCS in the complete sample (adjusted odds ratio [aOR] = 0.795, 95% CI = 0.662 to 0.955, Table 2). Among subgroups based on weekday sleep duration, a significantly lower OR for the highest hsCRP level (versus the lowest level) was observed only in adults with WCS who had weekday sleep durations of 6 h or lower (aOR = 0.639. 95% CI = 0.454 to 0.901). In comparisons between adults with and without WCS in the complete sample, there was no significant difference in the hsCRP level (Figure 2, Table S2). However, in subgroup analysis based on weekday sleep duration, only adults with WCS and a weekday sleep duration of 6 h or lower had a significantly lower hsCRP level than those without WCS ($F = 4.050$, $p = 0.044$, with WCS: 1.026 ± 1.801 mg/L, without WCS: 1.417 ± 2.343 mg/L, Figure 2, Table S2).

Table 1. Characteristics of adults with and without weekend catch-up sleep

Characteristics	WCS (+) (*n* = 1,901)		WCS (–) (*n* = 3,605)		Chi-squared test or *t*-test	
	n	%	*n*	%	χ^2 or t	p
Sex						
Male	776	40.8	1618	44.9	8.35	0.004
Female	1125	59.2	1987	55.1		
Age						
19–29 years	332	17.5	311	8.6	579.87	<0.001
30–39 years	477	25.1	526	14.6		
40–49 years	509	26.8	547	15.2		
50–59 years	332	17.5	683	18.9		
60+ years	251	13.2	1538	42.7		
Mean ± SD	43.25	13.83	54.28	16.62	–26.20	<0.001
Education level						
Elementary school graduation or below	178	9.4	942	26.1	305.61	<0.001
Middle school graduation	134	7.0	436	12.1		
High school graduation	679	35.7	1099	30.5		
College degree or above	910	47.9	1128	31.3		
Marital status						
Widowed	60	3.2	394	10.9	194.27	<0.001
Divorced or separated	75	3.9	183	5.1		
Never married	441	23.2	432	12.0		
Married	1325	69.7	2596	72.0		
Monthly household income (quartile)						
Less than Q1	189	9.9	822	22.8	166.23	<0.001
Q1–Q2	445	23.4	911	25.3		
Q2–Q3	592	31.1	949	26.3		
More than Q3	675	35.5	923	25.6		
Residential region						
Urban	1647	86.6	2808	77.9	61.66	<0.001
Rural	254	13.4	797	22.1		
Economic activity						
Yes	1060	55.8	1247	34.6	229.13	<0.001
No	841	44.2	2358	65.4		
Chronic disease						
No	1010	53.1	1422	39.4	164.66	<0.001
1	566	29.8	1006	27.9		
2+ (multimorbidity)	325	17.1	1177	32.6		
Alcohol consumption frequency						
4 or more times/week	108	5.7	286	7.9	123.35	<0.001
2–3 times/week	320	16.8	512	14.2		
2–4 times/month	515	27.1	718	19.9		
1 time/month	222	11.7	323	9.0		
<1 time/month	370	19.5	631	17.5		
Past or never	366	19.3	1135	31.5		
Smoking						
Current	382	20.1	710	19.7	29.77	<0.001
Former	268	14.1	719	19.9		
Never	1251	65.8	2176	60.4		
Obesity (BMI ≥ 25 kg/m^2)						
Yes	612	32.2	1329	36.9	11.90	0.001
No	1289	67.8	2276	63.1		
Physical activity						
Yes	963	50.7	1525	42.3	35.08	<0.001
No	938	49.3	2080	57.7		
Depression (PHQ-9 score ≥ 10)						
Yes	85	4.5	249	6.9	12.96	<0.001
No	1816	95.5	3356	93.1		
hsCRP level (mg/L)						
Highest (1.1 or above)	382	20.1	997	27.7	65.85	<0.001
Middle-high (0.60–1.09)	460	24.2	980	27.2		
Middle-low (0.39–0.59)	494	26.0	828	23.0		
Lowest (0–0.38)	565	29.7	800	22.2		

Table 1. Continued

Characteristics	WCS (+) (*n* = 1,901)		WCS (–) (*n* = 3,605)		Chi-squared test or *t*-test	
	n	%	*n*	%	χ^2 or t	p
Mean ± SD	1.08	1.97	1.39	2.48	-4.95	<0.001
Weekday sleep duration						
Time ≤ 6 h	709	37.3	803	22.3	269.16	<0.001
6 h < time ≤ 7 h	674	35.5	1077	29.9		
7 h < time ≤ 8 h	377	19.8	1019	28.3		
time > 8 h	141	7.4	706	19.6		
Mean ± SD (min)	397.76	74.51	434.96	84.13	-16.83	<0.001
Weekend sleep duration						
Time ≤ 6 h	65	3.4	933	25.9	1032.00	<0.001
6 h < time ≤ 7 h	251	13.2	1087	30.2		
7 h < time ≤ 8 h	587	30.9	968	26.9		
time > 8 h	998	52.5	617	17.1		
Mean ± SD (min)	512.80	78.36	428.17	84.27	37.12	<0.001
Average sleep duration (mean + SD, min)	430.63	70.11	433.02	82.80	-1.13	0.259
Weekend catch-up sleep						
Time ≥ 3 h	336	17.7				
2 h ≤ time < 3 h	560	29.5				
1 h ≤ time < 2 h	1005	52.9				
Mean ± SD (min)	115.04	62.78				

WCS (+), adults with weekend catch-up sleep; WCS (–), adults without weekend catch-up sleep; SD, standard deviation; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; BMI, body mass index (kg/m^2); PHQ-9, the Patient Health Questionnaire-9; hsCRP, serum high-sensitivity C-reactive protein level.

Table 2. Multinomial regression analyses for association between weekend catch-up sleep and serum high-sensitivity C-reactive protein level in adults

Weekend catch-up sleep (≥1 h)	Highest hsCRP level (vs. lowest)		Middle-high hscrp level (vs. Lowest)		Middle-low hsCRP level (vs. lowest)	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Complete sample						
Yes (*n* = 1901)	0.795†	0.662–0.955	0.903	0.758–1.076	1.017	0.857–1.208
No (*n* = 3605)	1		1		1	
Weekday sleep ≤ 6 h						
Yes (*n* = 709)	0.639‡	0.454–0.901	0.797	0.572–1.110	0.916	0.659–1.273
No (*n* = 803)	1		1		1	
6 h < weekday sleep ≤ 7 h						
Yes (*n* = 674)	0.743	0.541–1.021	0.887	0.655–1.202	0.984	0.735–1.318
No (*n* = 1077)	1		1		1	
7 h < weekday sleep ≤ 8 h						
Yes (*n* = 377)	0.927	0.635–1.351	0.904	0.628–1.300	1.188	0.831–1.698
No (*n* = 1019)	1		1		1	
Weekday sleep > 8 h						
Yes (*n* = 141)	1.005	0.565–1.788	1.384	0.806–2.377	1.262	0.753–2.114
No (*n* = 706)	1		1		1	

Multinomial regression analyses adjusted for age, sex, education level, household income, marital status, economic activity, residential region, chronic disease, obesity, alcohol consumption, smoking, physical activity, depressive symptoms, and weekday sleep time (only for the complete sample) were performed.
hsCRP, high-sensitivity C-reactive protein; aOR, adjusted odds ratio; 95% CI, 95% confidence interval of odds ratio.
†$p = 0.014$.
‡$p = 0.011$.

Association between WCS duration and hsCRP level

To investigate the association between WCS duration and hsCRP level, the categorical variable WCS time was included in the multinomial regression analysis. In this analysis, WCS of 1 h or more and less than 2 h (aOR = 0.762. 95% CI = 0.612 to 0.947) and 2 h or more and less than 3 h (aOR = 0.748. 95% CI = 0.560 to 0.999) were significantly associated with reduced OR for the highest hsCRP level in the complete sample (Table 3). In subgroup analysis based on weekday sleep duration (i.e. duration ≤ 6 h; duration > 6 h), WCS of 1 h or more and less than 2 h was associated with reduced OR for the highest, middle-high, and middle-low hsCRP levels (versus the lowest level) only in participants with weekday sleep durations of 6 h or lower (Table 3). We also performed a secondary multiple linear regression analysis to examine the correlation between the WCS/weekday sleep duration ratio and the hsCRP level (mg/L)

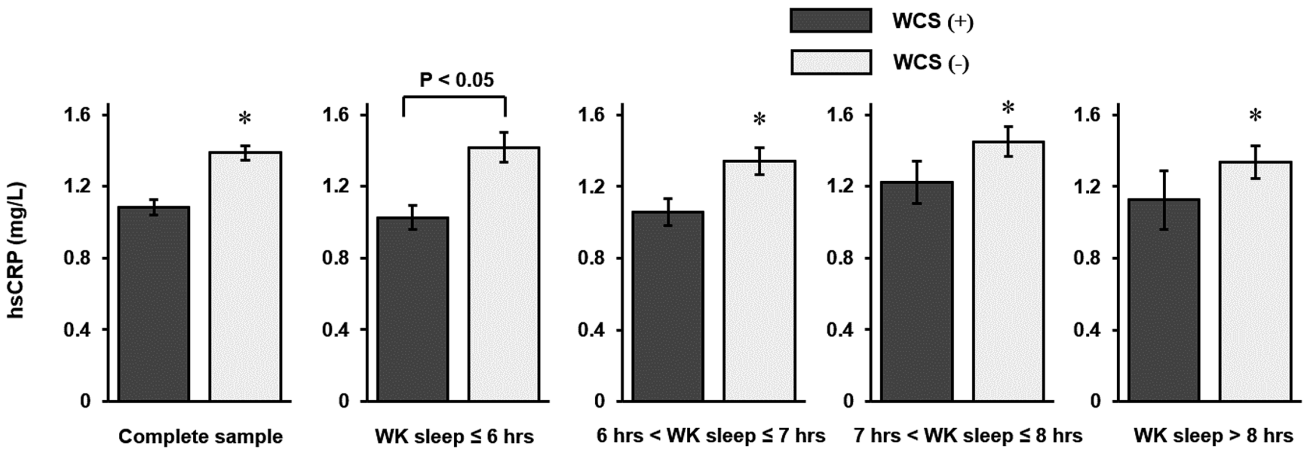

Figure 2. Comparison of high-sensitivity C-reactive protein (hsCRP) levels between adults with and without weekend catch-up sleep according to weekday sleep duration. The error bar represents standard error. *$p > 0.1$

Table 3. Multinomial regression analyses for association between weekend catch-up sleep time and serum high-sensitivity C-reactive protein level in adults

Weekend catch-up sleep time (h)	Highest hsCRP level (vs. lowest)		Middle-high hsCRP level (vs. lowest)		Middle-low hsCRP level (vs. lowest)	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Complete sample						
Time ≥ 3 h (*n* = 336)	1.045	0.729–1.497	1.220	0.868–1.713	1.115	0.793–1.568
2 h ≤ time < 3 h (*n* = 560)	0.748†	0.560–0.999	0.873	0.665–1.146	1.224	0.953–1.571
1 h ≤ time < 2 h (*n* = 1005)	0.762‡	0.612–0.947	0.847	0.688–1.043	0.898	0.732–1.101
None (*n* = 3605)	1					
Weekday sleep ≤ 6 h						
Time ≥ 3 h (*n* = 218)	0.933	0.573–1.521	1.055	0.661–1.685	0.979	0.609–1.575
2 h ≤ time < 3 h (*n* = 222)	0.700	0.424–1.155	0.889	0.554–1.425	1.388	0.894–2.155
1 h ≤ time < 2 h (*n* = 269)	0.466§	0.301–0.720	0.616‖	0.408–0.931	0.633¶	0.418–0.958
None (*n* = 803)	1					
Weekday sleep > 6 h						
Time ≥ 3 h (*n* = 118)	1.128	0.622–2.046	1.556	0.903–2.679	1.460	0.853–2.500
2 h ≤ time < 3 h (*n* = 336)	0.751	0.525–1.074	0.865	0.618–1.211	1.130	0.829–1.539
1 h ≤ time < 2 h (*n* = 736)	0.894	0.694–1.151	0.960	0.754–1.223	1.027	0.811–1.299
None (*n* = 2802)	1					

Multinomial regression analyses adjusted for age, sex, education level, household income, marital status, economic activity, residential region, chronic disease, obesity, alcohol consumption, smoking, physical activity, depressive symptoms, and weekday sleep time (only for the complete sample) were performed.
hsCRP, high-sensitivity C-reactive protein; aOR, adjusted odds ratio; 95% CI, 95% confidence interval of odds ratio.
†$p = 0.049$.
‡$p = 0.014$
§$p = 0.001$.
‖$p = 0.021$.
¶$p = 0.031$.

as a continuous variable. We observed that the WCS/weekday sleep duration ratio showed a significant negative correlation with hsCRP level after adjusting for all sociodemographic and health-related variables (B = –0.339, standard error = 0.156, β = –0.030, $p = 0.030$, Table S3).

Moderating effect of obesity on the association between WCS and hsCRP level

We found that obesity was significantly associated with an increased risk for higher hsCRP levels in the complete sample by using the same statistical method as that used in the main analysis (Table S4). In the obesity-stratified regression analysis, WCS was associated with a reduced risk for the highest hsCRP level only among non-obese adults (aOR = 0.777. 95% CI = 0.617 to 0.979, Table 4), but not in obese adults (Table 4). In an interaction model using the combined variable of WCS and obesity, non-obese people with WCS had a lower risk for showing the highest (aOR = 0.153. 95% CI = 0.117 to 0.200), middle-high (aOR = 0.230. 95% CI = 0.178 to 0.297), and middle-low hsCRP levels (aOR = 0.527. 95% CI = 0.406 to 0.684), while obese people with WCS showed no significant difference in the OR for higher hsCRP levels in comparison with obese people without WCS (Table 4). The absolute values of sleep duration and hsCRP levels stratified by obesity are shown in Table S5.

Table 4. Multinomial regression analyses for association between weekend catch-up sleep and serum high-sensitivity C-reactive protein level in adults with/without obesity

	Highest hsCRP level (vs. lowest)		Middle-high hsCRP level (vs. lowest)		Middle-low hsCRP level (vs. lowest)	
Weekend catch-up sleep (≥ 1 h)	aOR	95% CI	aOR	95% CI	aOR	95% CI
Obesity (–)						
Yes (*n* = 1289)	0.777†	0.617–0.979	0.878	0.711–1.083	0.967	0.798–1.173
No (*n* = 2276)	1		1		1	
Obesity (+)						
Yes (*n* = 612)	0.909	0.628–1.317	1.047	0.723–1.516	1.262	0.848–1.879
No (*n* = 1329)	1		1		1	
Interaction model						
WCS (+) & Obesity (–), *n* = 1289	0.153‡	0.117–0.200	0.230‡	0.178–0.297	0.527‡	0.406–0.684
WCS (+) & Obesity (+), *n* = 612	1.233	0.871–1.747	1.293	0.913–1.831	1.442	0.996–2.089
WCS (–) & Obesity (–), *n* = 2276	0.226‡	0.181–0.283	0.273‡	0.218–0.342	0.551‡	0.434–0.699
WCS (–) & Obesity (+), *n* = 1329	1		1		1	

Multinomial regression analyses adjusted for age, sex, education level, household income, marital status, economic activity, residential region, chronic disease, obesity, alcohol consumption, smoking, physical activity, depressive symptoms, and weekday sleep time were performed.
hsCRP, high-sensitivity C-reactive protein; aOR, adjusted odds ratio; 95% CI, 95% confidence interval of odds ratio; Obesity (+), adults with obesity; Obesity (–), adults without obesity; WCS (+) & Obesity (–), non-obese adults with weekend catch-up sleep; WCS (+) & Obesity (+), obese adults with weekend catch-up sleep; WCS (–) & Obesity (–), non-obese adults without weekend catch-up sleep; WCS (–) & Obesity (+), non-obese adults without weekend catch-up sleep.
†$p = 0.032$.
‡$p < 0.001$.

Discussion

In the present study, we used a nationally representative sample and demonstrated that WCS in adults was significantly associated with a lower risk of high serum hsCRP levels. However, a significant association between WCS and hsCRP level was only observed among adults with short weekday sleep duration (<6 h/night). This finding was supported by the result that the WCS group showed a significantly lower hsCRP level compared with the non-WCS group only among adults with short weekday sleep durations. For the association between WCS time and hsCRP level, we also found that a relatively longer duration of WCS (≥3 h) was not associated with the hsCRP level, while adults with short durations of WCS were less likely to show the highest hsCRP level. In addition, we found a significant moderating effect of obesity on the association between WCS and hsCRP level. Non-obese people with WCS demonstrated a lower risk for being in the higher hsCRP level groups, while there was no significant difference in obese people with WCS.

Our main finding was that WCS was associated with lower hsCRP levels independent of weekday sleep time, sociodemographic and health-related characteristics, and other potential confounding factors, especially in adults with shorter durations of weekday sleep (≤6 h). To the best of our knowledge, this is the first population-level study to investigate the relationship between compensatory extended weekend sleep and an inflammatory marker. There have been few studies on recovery sleep after sleep restriction and inflammation. Pejovic et al. [14] examined whether WCS reverses the effect of mild sleep restriction on 24-h serial IL-6 plasma levels by using an experimental setting of four nights of baseline sleep (8 h), followed by six sleep-restricted nights (6 h) and three recovery nights (10 h) in 30 healthy young men and women. They found that sleep restriction was associated with a significant increase in plasma IL-6 level, while the IL-6 level significantly decreased and returned to baseline levels after WCS. The study by Pejovic et al. supports our main finding by indicating that the impact of mild sleep restriction on low-grade systemic inflammation was reversed by weekend recovery sleep. Recovery napping was also reported to be associated with normalization of elevated inflammatory marker levels after sleep restriction. A previous study by Faraut et al. [15] found that 30-min morning and afternoon naps after one night of sleep restriction (2 h) normalized the increased salivary IL-6 level to baseline levels in 11 healthy young men. Vgontzas et al. [16] also reported similar results, in which a 2-h midafternoon recovery nap following a night of sleep deprivation significantly reduced the plasma IL-6 levels that had increased after sleep loss in 41 young healthy individuals. These findings may support our assumption that WCS is beneficial against increased systemic inflammation in adults with shorter weekday sleep duration (≤ 6 h). Even though, there is no consensus on the critical cutoff point of short duration, a growing body of evidence in population-level samples also have shown that short sleep duration (< 6 h or < 7 h) is associated with increased levels of systemic inflammatory markers including CRP level [34, 35]. Therefore, the present study may be the first population level evidence implicating that increased inflammation caused by short sleep may be recovered by catch-up sleep. Furthermore, the beneficial effect of WCS (≥1 h) for hsCRP levels—only among adults who slept 6 h or fewer in the present study—may support a recent recommendation on optimal sleep duration by the American Academy of Sleep Medicine and Sleep Research Society: "7 h or more sleep per night on a regular basis for optimal health" [36]. Contradictory findings have also been reported. One study investigated the association between actigraphy-assessed sleep duration and serum CRP level in healthy adolescents and found that those with 2 or more hours of WCS were likely to be in the high CRP level group (>3 mg/L) than those without WCS [37]. However, that study did not adjust weekday sleep duration as a covariate in the analysis. This may explain the discrepancy between that study and our findings, because the effect of WCS on the likelihood of showing high CRP levels was not compared in individuals with shorter

weekday sleep durations (e.g. ≤6 h). A significant interaction between the self-reported sleep duration and the frequency of naps in relation to the serum hsCRP level was also reported in a healthy young adult cohort [38]. Furthermore, with regard to other aspects of health status such as metabolic regulation, a recent study reported that WCS did not prevent weight gain or reduced insulin sensitivity and suggested that WCS cannot be an effective strategy for metabolic dysregulation owing to insufficient weekday sleep [39]. In contrast to the present study, the study by Depner et al. used polysomnographic data to assess participants' sleep durations [39]. This may explain the different results between the study by Depner et al. and the present study. Considering the controversy regarding WCS and health outcomes, further studies are required to clarify this issue.

For significant findings regarding the continuous variable of hsCRP level, we observed that the WCS group showed significantly lower hsCRP levels compared with the non-WCS group only among adults with short weekday sleep duration (Table S2), however, the effect size of this difference was small (Cohen's $d = 0.19$). We could not directly compare this finding to previous findings, because this is the first population-based study on WCS and hsCRP levels, however, a recent meta-analysis including 11 studies ($n = 3,490$) reported that the effect size (i.e. Cohen's d) of difference in CRP levels between normal (7–8 h) and shorter (< 7 h) sleep duration was 0.08 (95% CI = 0.01 to 0.16), which was smaller than our finding [13].

We also found that the duration of WCS influences its effects on the hsCRP level. Longer durations of WCS (i.e. ≥3 h) could not reduce the likelihood of the highest hsCRP levels in the complete sample, and particularly among adults with shorter weekday sleep durations, only WCS durations of 1 h or more and less than 2 h were associated with the hsCRP level. In a comparison of ORs for the highest CRP level, the ORs gradually decreased in accordance with a decrease in weekday sleep duration (Table 2). This indicates that excessive weekend sleep extension beyond a "compensatory level" may not have a beneficial effect on systemic inflammation. In the same vein as our findings, a recent population-level study with a cohort of 10,741 young adults reported that excessive sleep duration (>9 h) was associated with higher hsCRP levels in women [34], and a meta-analysis of a total of 72 cohort and experimental studies by Irwin et al. also found that long sleep duration was associated with significantly increased levels of CRP and IL-6 compared with a reference normal of 7–8 h [13]. Interestingly, these findings parallel the results of a previous meta-analysis in which extended sleep (>8 h) increased all-cause mortality risk by 30%, while short sleep (<7 h) increased the risk by 12% in comparison to a reference period of 7–8 h of sleep [40]. However, no study has investigated the association between WCS duration and the levels of inflammatory markers; thus, future studies are required to clarify this complex issue. The survey data used in the present study gathered participants' weekday and weekend sleep duration data using a self-reporting questionnaire. In addition to subjective measurement-related recall bias problems, previous evidence has reported that there was disagreement between subjective and objective measurements (i.e. polysomnography or actigraphy) in sleep research [41, 42]. Therefore, our findings cannot be directly compared with studies performed with objective measures. Future population-based studies with objective sleep measure might be required.

A significant moderating effect of obesity on the association between WCS and hsCRP level was observed in the present study. The likelihood for the highest hsCRP level was lower in non-obese adults with WCS, but not in obese adults with WCS. Our finding may indicate that the beneficial effect of WCS on hsCRP level was neutralized by the harmful effects of obesity in obese adults. In accordance with our findings showing an association between obesity and hsCRP level, accumulated evidence has shown that obesity is significantly associated with increased levels of inflammatory markers [43–45]. Obesity also interacts with sleep duration, which is associated with activation of human inflammation systems [46, 47]. Although no previous study has directly explored the potential moderating effect of obesity on the impact of WCS or recovery sleep on inflammation, there might be indirect evidence for this phenomenon. Obstructive sleep apnea (OSA) is associated with increased levels of proinflammatory cytokines and CRP mediated by sleep disturbances, repetitive and severe nocturnal hypoxemia, and activated vascular inflammatory processes [48]. A recent meta-analysis on OSA and CRP/hsCRP level found that obesity (BMI ≥30) moderated the effect of OSA on the CRP/hsCRP level [19]. In the subgroup analysis, the authors observed that the weighted mean difference between people with and without OSA was higher in obese adults than in non-obese adults (obese adults: serum CRP, 2.10 mmol/L; hsCRP, 2.49 mmol/L vs. non-obese adults: serum CRP, 1.90 mmol/L; hsCRP, 1.31 mmol/L). This may indirectly support our results showing a significant interaction between obesity and WCS in terms of hsCRP. However, in the present study, the prevalence of OSA was not investigated; therefore, we could not clearly elucidate whether OSA could affect the relationships among WCS, obesity, and hsCRP levels in our sample.

A hypothetical explanation for the pathway underlying the effects of WCS on the CRP level in adults with short sleep duration could be as follows: WCS may have a beneficial effect on activated systemic inflammation in adults with sleep deprivation via its modulating effects on the hypothalamus–pituitary–(HPA) axis and sympathetic nervous system (SNS) [13]. Sleep debt may induce an innate stress response system in the human body through the HPA axis and SNS, and this in turn, may shift the basal gene expression profiles involved in the inflammation system toward a proinflammatory status [49]. Actually, β-adrenergic signaling by SNS induces increases in nuclear factor (NF)-κB expression and the expression of proinflammatory immune response genes, including *IL1B*, *IL6*, and *TNF*, and eventual overproduction of proinflammatory cytokines and other inflammatory markers [13, 49]. In another possible pathway, the sleep debt induced by short weekday sleep without WCS may activate the inflammation system via its harmful effects on other aspects of mental health, such as depressive symptoms or anxiety. Actually, sleep debt may mediate the relationship between short sleep duration and depression and anxiety [50], which are associated with increased levels of CRP [51, 52].

Although this study yielded novel findings with a nationally representative sample from a genetically homogenous Korean adult population, it had several limitations. First, determination of the WCS group was based on participants' self-reports on weekday and weekend sleep duration rather than objectively measured sleep duration by actigraphy or polysomnography; thus, this study is not free from a recall bias. Second, the present study had a cross-sectional design; therefore, we could

not elucidate the complex causal relationship between WCS, changes in serum hsCRP levels, and obesity. Third, residual confounding factors not assessed in this survey could not be controlled in the analysis. Actually, seasonal variation, acute medical conditions such as infection, or prescribed medication might also have affected hsCRP levels in the present study [23]. Fourth, our operational definition of WCS—weekend sleep duration more than 1 h longer than weekday sleep duration—may be different with an experimental sleep restriction condition such as 2-h sleep restriction and recovery sleep [14]. Although we investigated the association between WCS and hsCRP levels moderated by weekday sleep duration, the definition of WCS in the present study could not ensure restricted sleep on weekdays and this may affect our results. Finally, there were significant differences in sociodemographic and health-related characteristics between the WCS+ and WCS– groups. We also observed that in the present study, younger females with higher incomes, education levels, and economic activity and without chronic diseases were more likely to be WCSers. Although we included these factors as covariates in all the analyses in our study, we could not exclude the possibility that between-group differences in hsCRP levels may have been derived from differences in sociodemographic and health-related factors. Furthermore, a difference in sex and age distribution between two groups may have affected the results because of their effect on inflammatory markers and BMI. We hope to study the issue further.

In summary, we found that WCS was significantly associated with reduced serum hsCRP levels, which reflects low-grade systemic inflammation, among adults with short weekday sleep durations, and we also observed that relatively longer durations of WCS did not have beneficial effects on the hsCRP level. Obesity had a significant moderating effect on the association between WCS and hsCRP level by neutralizing the beneficial effect of WCS on inflammation in obese adults. These novel findings related to WCS and inflammation may provide additional clinical evidence for the complex relationship between sleep and inflammation. We hope that further studies elucidate the underlying pathophysiological mechanism for the association between WCS and inflammation.

Supplementary material

Supplementary material is available at *SLEEP* online.

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References

1. Knutson KL, *et al*. Trends in the prevalence of short sleepers in the USA: 1975-2006. *Sleep*. 2010;**33**(1):37–45.
2. Im HJ, *et al*. Association between weekend catch-up sleep and lower body mass: population-based study. *Sleep*. 2017;**40**(7). doi:10.1093/sleep/zsx089
3. Hwangbo Y, *et al*. Association between weekend catch-up sleep duration and hypertension in Korean adults. *Sleep Med*. 2013;**14**(6):549–554.
4. Ness KM, *et al*. Two nights of recovery sleep restores the dynamic lipemic response, but not the reduction of insulin sensitivity, induced by five nights of sleep restriction. *Am J Physiol Regul Integr Comp Physiol*. 2019;**316**(6):R697–R703.
5. Kuula L, *et al*. Sleep and lipid profile during transition from childhood to adolescence. *J Pediatr*. 2016;**177**:173–178.e1.
6. Oh YH, *et al*. Association between weekend catch-up sleep and health-related quality of life of Korean adults. *Medicine (Baltimore)*. 2019;**98**(13):e14966.
7. Willerson JT, *et al*. Inflammation as a cardiovascular risk factor. *Circulation*. 2004;**109**(21 Suppl 1):II2–I10.
8. Esser N, *et al*. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*. 2014;**105**(2):141–150.
9. Rodríguez-Hernández H, *et al*. Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. *Int J Endocrinol*. 2013;**2013**:678159.
10. Haack M, *et al*. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007;**30**(9):1145–1152.
11. Irwin MR, *et al*. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med*. 2006;**166**(16):1756–1762.
12. Frey DJ, *et al*. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. *Brain Behav Immun*. 2007;**21**(8):1050–1057.
13. Irwin MR, *et al*. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;**80**(1):40–52.
14. Pejovic S, *et al*. Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. *Am J Physiol Endocrinol Metab*. 2013;**305**(7):E890–E896.
15. Faraut B, *et al*. Napping reverses the salivary interleukin-6 and urinary norepinephrine changes induced by sleep restriction. *J Clin Endocrinol Metab*. 2015;**100**(3):E416–E426.
16. Vgontzas AN, *et al*. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *Am J Physiol Endocrinol Metab*. 2007;**292**(1):E253–E261.
17. Rocha VZ, *et al*. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;**6**(6):399–409.
18. Shoelson SE, *et al*. Obesity, inflammation, and insulin resistance. *Gastroenterology*. 2007;**132**(6):2169–2180.
19. Li K, *et al*. Is C-reactive protein a marker of obstructive sleep apnea?: a meta-analysis. *Medicine (Baltimore)*. 2017;**96**(19):e6850.
20. Genest J. C-reactive protein: risk factor, biomarker and/or therapeutic target? *Can J Cardiol*. 2010; **26**(Suppl A):41a–44a.
21. Yu H, *et al*. High-sensitivity C-reactive protein in stroke patients—The importance in consideration of influence of multiple factors in the predictability for disease severity and death. *J Clin Neurosci*. 2017;**36**:12–19.
22. Kazemi-Bajestani SM, *et al*. The prevalence of metabolic syndrome increases with serum high sensitivity C-reactive protein concentration in individuals without a history of cardiovascular disease: a report from a large Persian cohort. *Ann Clin Biochem*. 2017;**54**(6):644–648.
23. Lee S, *et al*. Sex difference in the association between high-sensitivity c-reactive protein and depression: the 2016 Korea national health and nutrition examination survey. *Sci Rep*. 2019;**9**(1):1918.

24. Kweon S, *et al*. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). *Int J Epidemiol*. 2014;**43**(1):69–77.
25. Kim Y. The Korea National Health and Nutrition Examination Survey (KNHANES): current status and challenges. *Epidemiol Health*. 2014;**36**:e2014002.
26. Han KM, *et al*. Tinnitus, depression, and suicidal ideation in adults: a nationally representative general population sample. *J Psychiatr Res*. 2018;**98**:124–132.
27. Kim BJ, *et al*. Inverse relationship between serum hsCRP concentration and hand grip strength in older adults: a nationwide population-based study. *Aging (Albany, NY)*. 2018;**10**(8):2051–2061.
28. Oh J, *et al*. Serum lipid levels in depression and suicidality: the Korea National Health and Nutrition Examination Survey (KNHANES) 2014. *J Affect Disord*. 2017;**213**:51–58.
29. Park RJ, *et al*. Association between high sensitivity CRP and suicidal ideation in the Korean general population. *Eur Neuropsychopharmacol*. 2017;**27**(9):885–891.
30. Shetty T, *et al*. High-sensitivity C-reactive protein: retrospective study of potential blood biomarker of inflammation in acute mild traumatic brain injury. *J Head Trauma Rehabil*. 2019;**34**(3):E28–E36.
31. Kim J, *et al*. The co-existence of elevated high sensitivity C-reactive protein and homocysteine levels is associated with increased risk of metabolic syndrome: a 6-year follow-up study. *PLoS One*. 2018;**13**(10):e0206157.
32. Kroenke K, *et al*. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;**16**(9):606–613.
33. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr Ann*. 2002;**32**(9):509–515.
34. Bakour C, Schwartz S, O'Rourke K, *et al*. Sleep duration trajectories and systemic inflammation in young adults: results from the National Longitudinal Study of Adolescent to Adult Health (Add Health). *Sleep*. 2017;**40**(11). doi:10.1093/sleep/zsx156
35. Prather AA, *et al*. Sleep duration, insomnia, and markers of systemic inflammation: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Psychiatr Res*. 2015;**60**:95–102.
36. Watson NF, *et al*. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of sleep medicine and sleep research society. *Sleep*. 2015;**38**(6):843–844.
37. Hall MH, *et al*. Sleep duration during the school week is associated with C-reactive protein risk groups in healthy adolescents. *Sleep Med*. 2015;**16**(1):73–78.
38. Mantua J, *et al*. The interactive effects of nocturnal sleep and daytime naps in relation to serum C-reactive protein. *Sleep Med*. 2015;**16**(10):1213–1216.
39. Depner CM, *et al*. Ad libitum weekend recovery sleep fails to prevent metabolic dysregulation during a repeating pattern of insufficient sleep and weekend recovery sleep. *Curr Biol*. 2019;**29**(6):957–967.e4.
40. Cappuccio FP, *et al*. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*. 2010;**33**(5):585–592.
41. Van Den Berg JF, *et al*. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. *J Sleep Res*. 2008;**17**(3):295–302.
42. McCall C, *et al*. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. *J Sleep Res*. 2012;**21**(1):122–127.
43. Choi J, *et al*. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev*. 2013;**14**(3):232–244.
44. Hagger-Johnson G, *et al*. Pathways from childhood intelligence and socioeconomic status to late-life cardiovascular disease risk. *Health Psychol*. 2012;**31**(4):403–412.
45. Sharma SK, *et al*. Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. *Sleep Med*. 2008;**9**(2):149–156.
46. Patel SR, *et al*. Short sleep duration and weight gain: a systematic review. *Obesity (Silver Spring)*. 2008;**16**(3):643–653.
47. Krueger PM, *et al*. Cumulative exposure to short sleep and body mass outcomes: a prospective study. *J Sleep Res*. 2015;**24**(6):629–638.
48. Nadeem R, *et al*. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. *J Clin Sleep Med*. 2013;**9**(10):1003–1012.
49. Irwin MR, *et al*. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol*. 2011;**11**(9):625–632.
50. Dickinson DL, *et al*. Personal sleep debt and daytime sleepiness mediate the relationship between sleep and mental health outcomes in young adults. *Depress Anxiety*. 2018;**35**(8):775–783.
51. Köhler-Forsberg O, *et al*. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. *Brain Behav Immun*. 2017;**62**:344–350.
52. Naudé PJW, *et al*. Anxiety disorders and CRP in a population cohort study with 54,326 participants: the LifeLines study. *World J Biol Psychiatry*. 2018;**19**(6):461–470.