NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3080

Short Duration of Sleep Is Associated with Hyperleptinemia in Taiwanese Adults

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SCIENTIFIC INVESTIGATIONS

Background: Higher plasma levels of leptin have been associated with increased cardiometabolic risk. The aim of this study was to investigate the association between short duration of sleep and hyperleptinemia in Taiwanese adults.

Methods: We examined the association between duration of sleep and hyperleptinemia in 254 men and women recruited from the physical examination center at a regional hospital in southern Taiwan. Hyperleptinemia was defined as a plasma leptin level of 8.13 ng/mL and above. Short sleep duration was defined as < 6.5 h/day. Multiple logistic regression analysis was used to assess the association between short duration of sleep and hyperleptinemia.

Results: In females, short duration of sleep (< 6.5 h/day; OR = 2.15, 95% CI = 0.99-4.78), greater hip circumference (OR = 3.00, CI = 1.13-8.78), higher percent body fat (OR = 1.75, CI = 1.07-2.95), and higher white blood cell counts (OR = 1.67, CI = 1.26-2.28) were associated with an increased risk of hyperleptinemia. In males, greater body weight was significantly associated with an increased risk of hyperleptinemia (OR = 3.55, 95% CI = 1.46-10.23). There was also a trend of association (p = 0.096) between short duration of sleep and an increased risk of hyperleptinemia (OR = 4.98, 95% CI = 0.80-42.40).

Conclusions: In this study of healthy Taiwanese adults, short duration of sleep was significantly associated with hyperleptinemia in women, and the association was independent of adiposity.

Keywords: Sleep duration, leptin, leptin resistance, adiposity, gender

Citation: Koo M; Lai NS; Chiang JK. Short duration of sleep is associated with hyperleptinemia in Taiwanese adults. *J Clin Sleep Med* 2013;9(10):1049-1055.

Leptin, first discovered in 1994, is a cytokine secreted by adipocytes that primarily regulates energy balance but also modulates inflammatory processes and other endocrine functions.[1] Elevated plasma leptin levels (i.e., hyperleptinemia) have been demonstrated to correlate with a number of adverse conditions including insulin resistance, metabolic syndrome,[2] type 2 diabetes,[3] hypertension,[4] myocardial infarction,[5] stroke,[6] depression,[7] and Alzheimer disease.[8]

In humans, circulating leptin concentrations exhibit a strong circadian pattern and are influenced by acute changes in energy balance.[9] Levels of leptin are also positively correlated with obesity and alcohol intake but negatively with cigarette smoking.[10,11] In addition, despite a considerable variation exists among individuals, leptin concentrations are twofold to threefold higher in adult premenopausal females than in males.[12] Leptin concentrations in umbilical cord blood are also significantly higher in female neonates compared with male counterparts, suggesting the presence of primary genetic effects, prenatal effects of sex steroids, or both.[13] In adults, it was postulated that a suppressive effect of circulating androgens on leptin concentrations was responsible for sexual dimorphism.[14]

One area that has received much attention recently is the role of sleep duration and leptin levels. Sleep deprivation can affect the neuroendocrine regulation of appetite and food intake.[15] However, the association between duration of sleep and leptin levels is still unclear. Results from laboratory studies have indicated reduced,[16,17] no association,[18,19] or increased[20-23] leptin levels with short-term sleep restriction. The inconsistent findings among these studies can be explained, in part, by variations in the study samples, methods of sleep assessment, and whether caloric intake was controlled.

Regarding the effects of habitual sleep duration, an epidemiologic study of 721 adults showed lower leptin levels were associated with shorter self-reported habitual sleep duration. The association remained significant after adjusting for body mass index, sex, age, and other possible confounding factors.[24] In view of the role of leptin in various cardiometabolic disorders, understanding the effects of habitual sleep duration on leptin is of clinical relevance. Therefore, the aim of this study was to explore the association of sleep duration and hyperleptinemia in healthy Taiwanese adults.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Higher plasma levels of leptin could increase cardiometabolic risk, but the association between duration of sleep and hyperleptinemia is not clear. The aim of the current study was to investigate the association between short duration of sleep and hyperleptinemia in Taiwanese adults.

Study Impact: The study demonstrated that short duration of sleep was significantly associated with hyperleptinemia in females, independent of adiposity.

METHODS

Study subjects were individuals recruited from the physical examination center at a regional hospital in southern Taiwan between July 2010 and June 2012. The study was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital (No. B09901018). Written informed consent was obtained from all participants after full explanation of the study procedure.

Demographic information of the subjects including age, sex, body weight, height, waist circumference, hip circumference, and duration of sleep was assessed using a questionnaire administered face-to-face by a trained research assistant. Mean duration of sleep per day was calculated as [(5/7 × duration of sleep per day during weekday) + (2/7 × duration of sleep per day during weekend)].[25] Clinical characteristics were recorded, including white blood cell count, creatinine, fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and leptin. The methods used were described in previous study.[26,27] Leptin was measured by radioimmunoassay using commercially available kits (Millipore, Missouri, USA). A plasma leptin level above the upper quartile of the observed data was considered as hyperleptinemia in this study.[28]

Statistical Analysis

Statistical analysis was performed using R (Version 2.15.1). Two-sided p-value ≤ 0.05 was considered statistically significant. Since sexual dimorphism in leptin concentrations has been well documented in human adults,[29,30] the data were analyzed separately for males and females.

Categorical variables were analyzed using χ^2 test, and continuous variables were compared using *t*-test or Wilcoxon rank-sum test, as appropriate. Univariate logistic regression analysis was used to evaluate the association between hyperleptinemia and the independent variables. Multiple logistic regression analysis with stepwise procedure was conducted to examine the significant independent variables of hyperleptinemia. To ensure the quality of analysis, basic model-fitting techniques for variable selection, goodness-of-fit assessment, and regression diagnostics were applied. Specifically, the independent variables in the univariate logistic regression analysis were first evaluated using stepwise variable selection procedure with significance levels for entry (SLE) and stay (SLS) set to 0.15. Then, with the aid of substantive knowledge, the best candidate final regression model was identified manually by dropping the covariates with p value > 0.05 one at a time until all regression coefficients were significantly different from 0. In addition, Nagelkerke R^2 and the Hosmer-Lemeshow test were used to examine goodness-of-fit of the models. Residual analysis and detection of influential cases and multicollinearity were also applied for diagnosis of model or data problems.

The optimal cutoff point of mean sleep duration was determined using nonparametric smoothing from generalized additive model after adjusting of significant covariates by an iterative approach. A receiver-operating characteristic (ROC) curves analysis was conducted. Sensitivity, specificity, and positive and negative predictive values were estimated. The optimal cutoff was calculated as the minimum value of the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$, using the pROC coords function in R with the "closest.topleft" option selected. Plots of the sensitivity (true positive) versus 1 − specificity (false positive) were made and the overall diagnostic accuracy was quantified using areas under the curves (AUCs).

RESULTS

Basic characteristics of the 254 study subjects were listed in **Table 1**. The mean leptin level was 6.1 ng/mL. The median was 4.46 ng/mL, and the lower and upper quartiles were 2.53 ng/mL and 8.13 ng/mL, respectively. The upper quartile value was considered as the cutoff point for hyperleptinemia in this study.

Results of the univariate analysis for hyperleptinemia separately for males and females are shown in **Table 2**. In both males and females, greater body weight, body mass index, waist circumference, hip circumference, and percent body fat were significantly associated with an increased risk of hyperleptinemia. In addition, higher levels of triglycerides were significantly associated with an increased risk of hyperleptinemia in males, while a higher white blood cell count was significantly associated with an increased risk of hyperleptinemia in females.

Table 3 presents the findings from the multiple logistic regression analysis for males and females. An optimal cutoff point for sleep duration was found to be 6.5 h/day, based on nonparametric smoothing from generalized additive model of our study sample (**Figure 1**).

In females, short duration of sleep (< 6.5 h/day; OR = 2.15, 95% CI = 0.99-4.78), was associated with an increased risk of hyperleptinemia. A similar but weaker trend of association (p = 0.096) was observed in males (OR = 4.98, 95% CI = 0.80-42.40). Of the several anthropometric measurements, only a greater body weight was significantly associated with an increased risk of hyperleptinemia in males (OR = 3.55 per 10-kg increment, 95% CI = 1.46-10.23), while a greater hip circumference (OR = 3.00 per 10-cm increment, 95% CI = 1.13-8.78) and greater percent body fat (OR = 1.75 per 5% increment, 95% CI = 1.07-2.95) were associated with an increased risk of hyperleptinemia in females. Furthermore, a higher white blood cell count was significantly associated with an increased risk of hyperleptinemia in females (OR = 1.67, 95% CI = 1.26-2.28).

ROC curve analyses revealed that a cutoff value of 6.5 h/day for mean duration of sleep yielded a sensitivity of 83% (95% CI = 36% to 96%), a specificity of 77% (95% CI = 67% to 86%), a positive predictive value (PPV) of 20% (95% CI = 7% to 41%), a negative predictive value (NPV) of 99% (95% CI = 92% to 100%), and an AUC of 0.88 (95% CI = 0.77-0.99) for the prediction of hyperleptinemia in males (**Figure 2**). In females, the sensitivity, specificity, PPV, NPV, and AUC were 67% (95% CI = 54% to 79%), 78% (95% CI = 68% to 85%), 63% (95% CI = 50% to 75%), 81% (95% CI = 71% to 88%), and 0.80 (95% CI = 0.73-0.87), respectively.

DISCUSSION

In this cross-sectional study of generally healthy Taiwanese adults, we found that short duration of sleep was associated with hyperleptinemia, particularly in females. The risk of

Table 1—Demographic and clinical characteristics of the study subjects (n = 254)

	Mean ± standard deviation or frequency (%)			
Variable	Total 254 (100)	Male 94 (37)	Female 160 (63)	p-value
Age (years)	54.1 ± 10.0	54.7 ± 10.7	53.7 ± 9.7	0.420
Systolic blood pressure (mm Hg)	127 ± 21	132.6 ± 19.7	124.3 ± 20.6	0.001
Body weight (kg)	60.3 ± 10.2	68.5 ± 9.1	55.7 ± 7.5	< 0.001
Body height (cm)	159.8 ± 8.3	167.4 ± 6.0	155.4 ± 6.0	< 0.001
Body mass index (kg/m^2)	23.5 ± 2.8	24.4 ± 2.7	23.1 ± 2.8	< 0.001
Waist circumference (cm)	75.8 ± 8.7	82.7 ± 7.2	72.0 ± 6.9	< 0.001
Hip circumference (cm)	91.2 ± 5.5	92.0 ± 4.9	90.8 ± 5.8	0.022
Body fat (%)	26.6 ± 6.2	22.3 ± 5.1	29.0 ± 5.4	< 0.001
White blood cell count (×10^3/μL)	6.2 ± 1.5	6.5 ± 1.4	6.0 ± 1.4	0.004
Creatinine (mg/dL)	0.7 ± 0.2	0.9 ± 0.2	0.6 ± 0.1	< 0.001
eGFR (mL/min/1.73m^2)	119.0 ± 34.4	106.9 ± 26.0	125.6 ± 37.2	< 0.001
Fasting glucose (mg/dL)	90.3 ± 18.2	93.0 ± 16.6	87.9 ± 15.4	< 0.001
Total cholesterol (mg/dL)	186.4 ± 34.4	185.4 ± 36.0	187.6 ± 33.7	0.627
HDL-C (mg/dL)	55.5 ± 13.4	49.4 ± 13.2	58.6 ± 12.0	< 0.001
LDL-C (mg/dL)	121.6 ± 30.9	123.8 ± 32.4	121.0 ± 30.1	0.491
Triglyceride (mg/dL)	108.2 ± 62.5	129.8 ± 76.2	96.9 ± 50.0	< 0.001
Leptin (ng/mL)	6.1 ± 5.7	3.3 ± 2.6	7.9 ± 6.4	< 0.001
Mean sleep duration (hours)	6.7 ± 1.2	6.8 ± 1.3	6.6 ± 1.2	0.120
Energy expenditure (×10^3 kcal/day)	2.7 ± 1.1	3.2 ± 1.3	2.5 ± 0.8	< 0.001
Alcohol use	21 (8.3)	19 (20.2)	2 (1.3)	< 0.001
Smoking	9 (3.5)	9 (9.6)	0	< 0.001

eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2—Univariate logistic regression analysis of hyperleptinemia for males and females

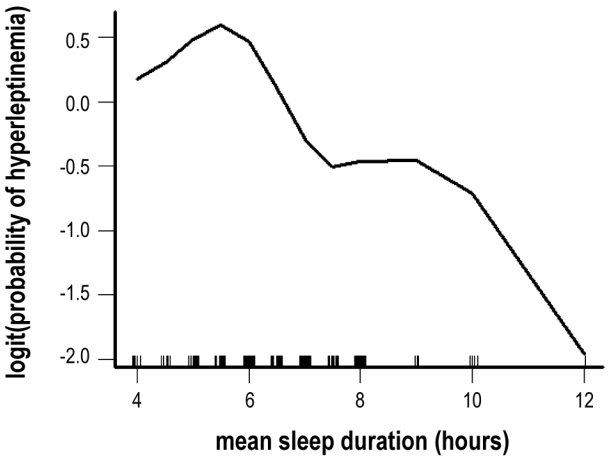
	Male		Female	
Variable	Odds ratios (95% CI)	p-value	Odds ratios (95% CI)	p-value
Age (per 5 years)	0.99 (0.68-1.49)	0.490	1.08 (0.92-1.29)	0.346
Systolic blood pressure (per 10 mm Hg)	1.09 (0.71-1.64)	0.688	1.13 (0.97-1.33)	0.120
Body weight (per 10 kg)	3.63 (1.47-10.4)	0.008	2.01 (1.28-3.27)	0.003
Body height (per 10 cm)	3.26 (0.80-15.7)	0.112	0.78 (0.45-1.34)	0.376
Body mass index (kg/m^2)	1.53 (1.08-2.37)	0.030	1.30 (1.14-1.49)	< 0.001
Waist circumference (per 10 cm)	6.13 (1.71-2.94)	0.010	1.08 (1.03-1.14)	0.003
Hip circumference (per 10 cm)	5.78 (1.05-39.8)	0.053	4.30 (2.13-9.62)	< 0.001
Body fat (per 5%)	2.14 (1.02-5.01)	0.048	2.34 (1.63-3.52)	< 0.001
White blood cell count (×10^3/μL)	1.12 (0.62-1.94)	0.682	1.52 (1.20-1.96)	0.001
Creatinine (mg/dL)	1.71 (0.03-20.2)	0.721	0.90 (0.06-11.4)	0.938
eGFR (per 10 mL/min/1.73m^2)	0.99 (0.96-1.02)	0.429	1.00 (0.99-1.01)	0.673
Fasting glucose (per 10 mg/dL)	0.99 (0.91-1.03)	0.838	1.00 (0.97-1.02)	0.687
Total cholesterol (per 10 mg/dL)	1.15 (0.92-1.48)	0.230	1.05 (0.95-1.15)	0.364
HDL-C (per 10 mg/dL)	0.53 (0.19-1.15)	0.173	0.90 (0.68-1.18)	0.435
LDL-C (per 10 mg/dL)	1.16 (0.90-1.49)	0.244	1.04 (0.93-1.16)	0.477
Triglyceride (per 10 mg/dL)	1.10 (1.01-1.21)	0.026	1.06 (0.99-1.13)	0.082
Energy expenditure (×10^3 kcal/day)	1.13 (0.56-1.90)	0.687	1.06 (0.69-1.60)	0.783
Mean sleep duration (hours)	0.86 (0.45-1.64)	0.654	0.87 (0.65-1.15)	0.325

eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

hyperleptinemia was 2.2 times greater in females with sleep duration of less than 6.5 hours a day than those with a longer duration. Since the association was adjusted for adiposity, the independent effect of short duration of sleep on leptin levels suggested that the elevation in leptin levels might have been a primary increase in response to reduced duration of sleep rather

than a secondary increase in an attempt to overcome end-organ leptin resistance.

Figure 1—Plot of covariate-adjusted nonparametric smoothing from generalized additive model of sleep duration and probability of hyperleptinemia



The mean leptin levels in females were more than twice of that in males, similar to the findings in other studies.[12,19,31] This sexual dimorphism in leptin levels among adults has been suggested to mediate, in part, by effects of sex steriods.[32] In addition, the observations that leptin levels were approximately twofold higher in female neonates compared with male counterparts suggested that primary genetic determinants and prenatal effects of endogenous androgen concentrations might play a role in sexual dimorphism.[33]

A finding in this study that deserves additional consideration was the different independent factors associated with short duration of sleep between males and females. The risk of hyperleptinemia in females was 2.2 times higher in those with duration of sleep of less than 6.5 hours (p = 0.055). In males, although the association did not reach statistical significance (p = 0.096), the magnitude of the odds ratio was larger than that of the association in females. The wide confidence interval, as a result of fewer males in our sample and fewer males being classified with hyperleptinemia, precluded a definite conclusion among males (OR = 4.98, 95% CI = 0.80-42.40).

In contrast to our study, previous reports that involved both male and female subjects either did not report the sex results separately or found no differences between the sexes in the

Figure 2—Receiver-operating characteristic curves for short duration of sleep (< 6.5 h/day) in predicting hyperleptinemia in males and females

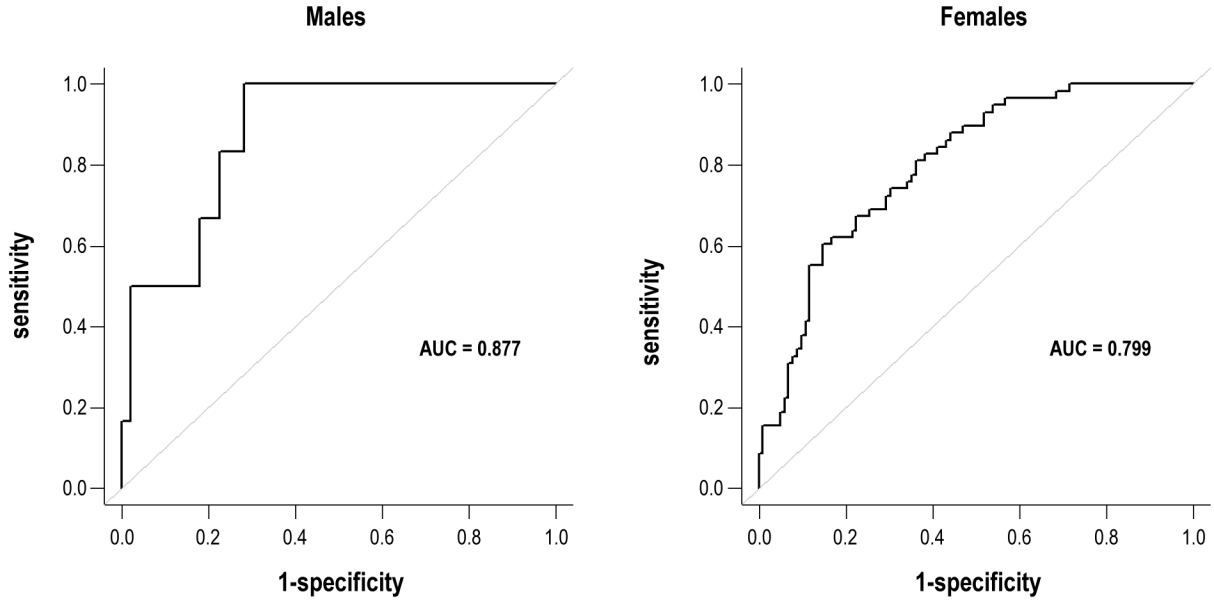


Table 3—Multiple logistic regression analysis of hyperleptinemia for males and females

	Male		Female	
Variable	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Sleep duration < 6.5 hours/day	4.98 (0.80-42.40)	0.096	2.15 (0.99-4.78)	0.055
Body weight (per 10 kg)	3.55 (1.46-10.23)	0.009		
Hip circumference (per 10 cm)			3.00 (1.13-8.78)	0.034
Body fat (per 5%)			1.75 (1.07-2.95)	0.029
White blood cell count (×10^3/μL)			1.67 (1.26-2.28)	0.001

Hosmer-Lemeshow test, p = 0.59 for males and 0.43 for females, indicating good model fit. Nagelkerke R^2 = 0.29 for males and 0.33 for females.

association between sleep and leptin among obese subjects.[19,20,23] In three short-term laboratory studies that reported a lack of association[18] and decreased[16,17] serum leptin levels with sleep curtailment, the participants consisted of only males. In addition, energy intake was restricted in these studies, which might have led to an increased leptin response to the restricted calories.[34] On the other hand, in two short-term sleep deprivation studies conducted on female participants, sleep restriction was associated with increased morning plasma leptin concentrations.[21,22] Clearly, additional studies are deserved to delineate the differences between males and females in the association between leptin levels and habitual short sleep duration and, in particular, whether the observed sex differences were related to biological factors such as the interactions of leptin with gonadal steroids or the results of modification of dietary behavior in response to habitual sleep deprivation.[35]

Results of multiple logistic regression analysis also indicated, as expected, an independent association between greater adiposity, as reflected by hip circumference and percent body fat in females and body weight in males. In a cross-sectional study of 1,393 adult patients, a strong direct relationship between increased leptin levels and increased percent body fat was observed. Percent body fat was measured by duel-energy x-ray absorptiometry (DXA) in the study.[36] In another population-based study of 1,234 Chinese adults, correlation analysis revealed that serum leptin concentrations were significantly associated with a number of adiposity measures. Of those measures, body mass index and triceps skinfold showed the strongest association in men and women, respectively.[37]

Higher white blood cell counts were significantly associated with hyperleptinemia among females in our study. A cross-sectional study of 1,480 type 2 diabetic patients also reported that plasma leptin levels were significantly associated with total white blood cell counts.[38] In vitro studies indicated that leptin at the concentration at 50 to 100 ng/mL could significantly stimulate the appearance of granulocyte-macrophage colonies.[39] Based on the variables obtained from our multiple logistic regression modeling, the probability of hyperleptinemia in males and females could be estimated according to the formula provided in the appendix.

Several limitations of our study deserve mention. First, leptin levels were measured with only a single blood draw during routine physical examinations, which occurred between 14:00 and 16:00. This methodology might not have adequately reflected the diurnal variations of leptin in response to sleep restriction. Second, duration of habitual sleep was ascertained by self-report and might be subject to recall error. Nevertheless, self-report duration of sleep can readily be obtained from patients in a single visit, thus making our prediction tool more practical for clinical use. Third, though the analyses were adjusted for several potential confounding variables, the presence of unrecognized ones is always possible.

In conclusion, a significant association was observed between short duration of sleep and hyperleptinemia in healthy Taiwanese adults and the association was independent of adiposity. Since sleep curtailment is highly prevalent in modern societies, its associations with hyperleptinemia, and in turn, the potential adverse impact on metabolic and endocrine processes, can have important clinical implications. Future studies will be needed to clarify the role of sleep duration as a modifiable risk factor on the effects of leptin on metabolic health.

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ACKNOWLEDGMENTS

Dr. Chiang received research grants from Buddhist Dalin Tzu Chi Hospital (DTCRD 99(2)-E-05).

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2013
Submitted in final revised form May, 2013
Accepted for publication May, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. Work was performed at Buddhist Dalin Tzu Chi Hospital.

APPENDIX

Programming code in OpenOffice Calc, Microsoft Excel, and R environment for calculating the probability of hyperleptinemia (leptin > 8.13 ng/mL) based on our multiple logistic regression model.

In OpenOffice Calc or Microsoft Excel

< for male >

Key in the values for body weight (in kg) in the A1 cell, sleep duration (< 6.5 hours/day = 1, ≥ 6.5 hours/day = 0) in the A2 cell.

Key in the following formula in any empty cell on the spreadsheet to obtain the probability of hyperleptinemia (leptin > 8.13 ng/mL).

= 1/EXP(-(-12.6846 + (0.1267)*A1 + 1.6053*A2)+1)

< for female >

Key in the values for percent body fat (in %) in the A1 cell, hip circumference (in cm) in the A2 cell, white blood cell counts ($\times 10^3/\mu L$) in the A3 cell, sleep duration (< 6.5 hours/day = 1, ≥ 6.5 hours/day = 0) in the A4 cell.

Key in the following formula in any empty cell on the spreadsheet to obtain the probability of hyperleptinemia (leptin > 8.13 ng/mL).

= 1/EXP(-(-17.33179 + (0.1119)*A1 + 0.10981*A2 + 0.51163*A3 + 0.76492*A4)+1)

In R environment

< for male >

To calculate the probability of hyperleptinemia, substitute the values for the variables X1 to X2 in the following regression equation and execute in the R console.

```
yhat < - (-12.6846          #constant
+ 0.1267*X1                #X1 = body weight (in kg)
+ 1.6053*X2                #X2 = sleep duration (< 6.5 hours/day = 1, ≥ 6.5 hours/day = 0)
)

phat < - 1/(exp(-(yhat))+1)
phat
```

< for female >

To calculate the probability of hyperleptinemia, substitute the values for the variables X1 to X4 in the following regression equation and execute in the R console.

```
yhat < - (-17.33179         #constant
+ 0.1119*X1                #X1 = percent body fat (in %)
+ 0.10981*X2               #X2 = hip circumference (in cm)
+ 0.51163*X3               #X3 = white blood cell counts (×10^3/μL)
+0.76492*X4                #X4 = sleep duration (< 6.5 hours/day = 1, ≥ 6.5 hours/day = 0)
)

phat < - 1/(exp(-(yhat))+1)
phat
```