Gender Differences in the Association between Sleep Duration and Cardiometabolic Risk: A Cross-sectional Study

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Abstract

Background: Inappropriate sleep duration (shorter/longer than optimal sleep duration) has come to be identified as a potential cardiometabolic risk factor, and thereby, as a risk factor for atherosclerotic cardiovascular disease (ASCVD). Few data exist regarding the gender differences in the relationship between sleep duration and cardiometabolic risk.

Methods: This cross-sectional study was conducted in a study population of 9262 apparently healthy (5004 male, 4258 female) subjects at the Health Planning Center of Nihon University Hospital between September, 2015, and October 2016.

Results: In the male subjects, as compared to a sleep duration of 6 to 7 hours, a sleep duration of ³8 hours was associated with an odds ratio (OR) for abdominal obesity (defined according to the Japanese criteria for metabolic syndrome as a waist circumference of ³85 cm) of 1.31 (95% confidence interval [CI], 1.004-1.71) and for a non-high-density lipoprotein cholesterol level of ³150 mg/dL (defined as “Borderline hyper” by the Japan Atherosclerosis Society Guidelines for Prevention of ASCVD 2017) of 1.33 (1.05-1.68), and a sleep duration of <5 hours was associated with an OR (95% CI) for a fasting blood glucose of ³100 mg/dL (defined as “high” by a specialized lifestyle checkup program for the detection of symptoms of metabolic syndrome in Japan) of 1.74 (1.25-2.42). On the other hand, in the female subjects, as compared to a sleep duration of 6 to 7 hours, a sleep duration of <5 hours was associated with an OR (95% CI) for abdominal obesity (waist circumference ³90 cm) of 1.98 (1.11-3.55) and for a hemoglobin A1c (HbA1c) level of ³5.6 % of 1.52 (1.10-2.10), whereas a sleep duration of ³8 hours was not associated with worsening of any of the examined cardiometabolic risk factors.

Conclusions: There may be gender differences in the relationship between sleep duration and cardiometabolic risk. To further reduce the risk of ASCVD, it may be of particular importance to emphasize adequate sleep duration.

Clinical Trial Registration: UMIN (http://www.umin.ac.jp/) Study ID: UMIN000037643 retrospectively registered on 9 August 2019

1. Background

Many epidemiological studies have reported the existence of associations between inappropriate sleep duration (shorter or longer than optimal sleep duration) and worsened cardiometabolic risk factors, such as visceral obesity [1, 2], hypertension [3, 4], dyslipidemia [5, 6] and/or diabetes mellitus [5, 7–10], worsened risk of development of atherosclerotic cardiovascular disease (ASCVD), and worsened risk of all-cause mortality [11–16]. Therefore, in order to avoid the risk of development of ASCVD throughout life, it is essential to ensure an appropriate sleep duration in daily life to prevent exacerbation of the overall cardiometabolic risk. However, although there have been reports on the relationship between sleep duration and individual cardiometabolic risk factors, few studies have investigated the relationship between sleep duration and the overall cardiometabolic risk and therefore, the risk of ASCVD.

The average age of onset of ASCVD, a prototype of which is coronary artery disease, is approximately 10 years later in females than in males. This appears to be related to the decrease in the secretion of estrogen, which has antiatherogenic effects, beginning around menopause, resulting in a rapid increase in visceral obesity and abnormal lipid/glucose metabolism, causing rapid progression of atherosclerosis in middle-aged and older women [17]. However, gender differences in the relationship between sleep duration and cardiometabolic risk have not yet been fully elucidated.

We hypothesized that “inappropriate sleep duration, i.e., shorter/longer than optimal sleep duration, exacerbates the overall cardiometabolic status, including factors such as abdominal obesity, high blood pressure, impaired lipid metabolism and glucose metabolism, and that there are gender differences in the relationship between sleep duration and the overall cardiometabolic risk.”

The purpose of this study was to examine the relationship between shorter/longer than optimal sleep duration and the overall cardiometabolic risk, and furthermore, to examine gender differences in this relationship using a cross-sectional study design.

2. Methods

2-1. *Study Design and Subjects*

This study used a cross-sectional design to investigate the relationship between inappropriate sleep duration and cardiometabolic risk (abdominal obesity, hypertension, abnormal lipid metabolism and abnormal glucose metabolism) in apparently healthy Japanese individuals who underwent health checkups. Of 12 065 individuals who visited the Health Planning Center of Nihon University Hospital between September 1, 2015, and September 30, 2016, for health checkups, those who met any of the following exclusion criteria were excluded and the data of the remaining 9262 (5004 male and 4258 female) subjects were included in the analysis. The exclusion criteria were: <20 years of age, non-availability of records of the sleep duration, past medical history of ASCVD, receiving oral medication(s) for hypertension/diabetes mellitus/dyslipidemia/hyperuricemia or serum triglyceride ³400 mg/dL. The flow diagram of the study participants is shown in Figure 1.

The study endpoints were the relationships between the sleep duration categories (less than 5 hours; 5 hours or more, but less than 6 hours; 6 hours or more, but less than 7 hours; 7 hours or more, but less than 8 hours; and 8 hours or more) and cardiometabolic risk factors (waist circumference [WC], systolic/diastolic blood pressure [BP], serum low-density lipoprotein cholesterol [LDL-C], serum high-density lipoprotein cholesterol [HDL-C], serum triglyceride, serum non-HDL-C, fasting blood glucose [FBG], and hemoglobin A1c [HbA1c]); furthermore, the odds ratio (OR) for each cardiometabolic risk factor ³reference value (values in the sleep duration category of ³6 hours, but <7 hours, which accounted for the largest number of subjects were used as the reference values) in each sleep duration category using multivariate logistic regression analysis.

This study was conducted with the approval of the Institutional Review Board of Nihon University Hospital (approval number: 20180105), in accordance with the ethical principles laid down in by the Declaration of Helsinki. Written consent was obtained from every participant. Information about the study was published on the website of the institute, and potential subjects were assured that they had full freedom to refuse consent for participation in the study.

2-2. *Questionnaire to Determine the Health Behaviors*

Health behavior surveys at our institute are conducted by face-to-face interviews of the subjects by trained interviewers. The surveys consist of comprehensive questions designed to assess the demographic and socioeconomic characteristics of the subjects: age, occupation, previous and current medical history, medication history, family history, and lifestyle behaviors.

The subjects undergoing health checkups are given the following lifestyle questionnaire.

1) Sleep habit: How many hours a day, on average, do you sleep? Do you feel sufficiently satisfied with your sleep (presence/absence of a sense of satisfaction with sleep)?

2) Cigarette smoking habit: Are you a habitual smoker?: No/Yes/I have quit smoking/I quit smoking ( ) years ago.

3) Alcohol drinking habit: Please indicate the frequency at which you drink: Every day/sometimes/I used to drink previously, but have stopped drinking/I stopped drinking ( ) years ago/I drink rarely/I cannot drink; How much do you drink per day when you drink? (ethanol equivalent [g/day]): 0g/0 to <20 g/20 to <40 g/40 to <60 g/³60 g; How many days of the week do you drink?

4) Aerobic exercise habit: Have you engaged in habitual exercise that makes you sweat slightly for ³30 minutes a day, at least twice a week, for ³1 year?

5) Menopause: How old were you at menopause?

6) Weight gain ³10 kg from the age of 20 years: Has your weight increased by 10 kg or more as compared to your weight at the age of 20?: Yes/No. Weight gain has been reported to be associated with the deterioration of physical function and is an indicator of daily physical activity [18-20].

The questionnaire was a modified version of the Questionnaire on Specific Health Examination, which is used for specific health guidance after health checkups under the jurisdiction of the Ministry of Health, Labour and Welfare, Japan [21] (Additional file 1).

2-3. *Health Examinations and Blood Samples*

Anthropometric variables (height, weight and WC) were measured with the subjects in the standing position. Height and weight data were obtained using standardized techniques and equipment. Body mass index was calculated as the (body weight measured in kilograms divided by the height measured in meters) squared (kg/m^2). WC was measured at the level of the umbilicus with a non-stretchable tape measure during the late exhalation phase with the subject in the standing position [22]. BP was measured twice, with a 3-minute interval between the two measurements, using a standard mercury sphygmomanometer, after the patients had rested for a 5-minute rest period; the average of the 1st and 2nd measurements was used for the analysis in this study. Fasting blood samples were collected in the early morning after the subjects had fasted for 8 hours. The serum total cholesterol (TC) and serum triglyceride levels were measured using enzymatic methods at the central clinical laboratory of our institute. The serum HDL-C level was also measured using an enzymatic method following heparin and calcium precipitation. The Friedewald formula was used to calculate the serum LDL-C level [23]. Then, the serum *non-HDL-C* level was calculated as TC minus HDL-C. The HbA1c value was measured using high-performance liquid chromatography.

2-4. *Reference Values for Cardiometabolic Risk*

The following reference values for cardiometabolic risk were used for the analyses: (1) WC: ³85 cm (male), ³90 cm (female) [24], (2) systolic BP ³130 mmHg [24], (3) diastolic BP ³85 mmHg [24], (4) serum LDL-C level ³120 mg/dL [25], (5) serum HDL-C level <40 mg/dL [24], (6) serum triglyceride level ³150 mg/dL [24], (7) serum non-HDL-C level ³150 mg/dL [25], (8) FBG level ³100 mg/dL [24], (9) HbA1c level ³5.6% [24]. The reference values for the serum LDL-C and non-HDL-C levels were set at the values corresponding to borderline hyper-LDL-cholesterolemia and borderline hyper-non-HDL-cholesterolemia, respectively.

2-5. *Statistical Analysis*

Data are expressed as the means ± standard deviation for continuous variables and as percentages for discrete variables. For variables with a significantly skewed distribution, the data are expressed in terms of the interquartile ranges. We performed a subset analysis by one-way analysis of variance using the average sleep duration classified into 5 categorical variables (<5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day), followed by Turkey-kramer's adjustment for covariates if differences were detected in the patient characteristics or cardiometabolic risk factors. Next, the OR and 95% confidence interval (CI) for each cardiometabolic risk factor ³reference value (the values in the sleep duration category of ³6 hours, but <7 hours, which accounted for the largest number of subjects, were used as the reference values) in each sleep duration category were calculated using multivariate logistic regression analysis. In analysis model 1, no adjustments were made, in analysis model 2, adjustments were made for age (in females, ³the mean age at menopause/<the mean age at menopause), exercise habits, smoking habits, alcohol intake, and

presence/absence of a sense of satisfaction with sleep, and in analysis model 3, adjustments were made for the presence/absence of weight gain of ³10 kg from the age of 20 years, in addition to the independent variables entered into analysis model 2. A p-value of <0.05 was regarded as denoting statistical significance. All statistical analyses were performed using SPSS V. 23 statistical package (SPSS, Chicago, Illinois, USA).

3. Results

3-1. *Background Factors*

The characteristics of the subjects are shown in Table 1. The values of all cardiometabolic risk factors, except the serum HDL-C level, were significantly higher in the male than the female subjects. The mean age at menopause in the female subjects was 50.1 ± 4.1 years.

3-2. *Relationship between Sleep Duration and Cardiometabolic Risk*

Waist circumference

In the men with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the WC values were 83.8 ± 9.64 cm, 83.5 ± 8.36 cm, 83.2 ± 8.37 cm, 82.8 ± 8.30 cm, and 84.1 ± 8.39 cm. In the women with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, 76.9 ± 11.5 cm, 75.9 ± 9.20 cm, 75.3 ± 8.53 cm, 75.2 ± 7.99 cm, and 75.1 ± 7.18 cm, respectively.

There tended to be a U-curve relationship between the WC and the sleep duration categories in the men (p = 0.079). In the women, the WC tended to increase as the sleep duration decreased (p = 0.072) (Figure 2).

Blood pressure

In the men with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the systolic BP values were 118 ± 13.3 mmHg, 119 ± 14.3 mmHg, 119 ± 15.1 mmHg, 120 ± 15.3 mmHg, and 122 ± 14.3 mmHg, and the diastolic BP values were 72.6 ± 11.0 mmHg, 72.9 ± 12.0 mmHg, 73.0 ± 12.2 mmHg, 73.8 ± 12.1 mmHg, and 74.4 ± 10.8 mmHg, respectively. In the women with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the systolic BP values were 108 ± 14.0 mmHg, 110 ± 14.3 mmHg, 109 ± 13.8 mmHg, 108 ± 14.4 mmHg, and 108 ± 12.7

mmHg, and the diastolic BP values were 64.7 ± 10.3 mmHg, 65.4 ± 10.7 mmHg, 65.3 ± 10.3 mmHg, 65.0 ± 10.5 mmHg, and 64.3 ± 9.6 mmHg, respectively.

In the men, the systolic BP increased significantly as the sleep duration increased ($p < 0.0001$). Similarly, the diastolic BP also tended to increase as the sleep duration increased ($p = 0.093$). In the women, on the other hand, no association was observed between the sleep duration and the systolic/diastolic BP (Figure 2).

Lipid metabolism markers

In the men with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the serum LDL-C levels were 124.8 ± 29.8 mg/dL, 121.5 ± 29.4 mg/dL, 119.9 ± 28.9 mg/dL, 120.7 ± 29.3 mg/dL, and 124.0 ± 30.7 mg/dL, the serum HDL-C levels were 55.9 ± 13.3 mg/dL, 56.1 ± 14.1 mg/dL, 56.7 ± 13.4 mg/dL, 57.1 ± 13.8 mg/dL, and 56.2 ± 13.2 mg/dL, the serum triglyceride levels were 89 (69/125) mg/dL, 90 (65/130) mg/dL, 94 (63/137) mg/dL, 91 (65/132) mg/dL, and 92 (67/134) mg/dL, and the serum non-HDL-C levels were 147.9 ± 32.9 mg/dL, 145.2 ± 32.6 mg/dL, 144.7 ± 32.8 mg/dL, 145.5 ± 33.2 mg/dL, and 148.6 ± 34.0 mg/dL, respectively. In the women with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the serum LDL-C levels were 110.8 ± 30.5 mg/dL, 112.2 ± 30.3 mg/dL, 110.3 ± 29.5 mg/dL, 109.8 ± 30.7 mg/dL, and 105.2 ± 30.4 mg/dL, the serum HDL-C levels were 69.5 ± 15.9 mg/dL, 69.6 ± 13.9 mg/dL, 69.1 ± 14.2 mg/dL, 68.3 ± 14.0 mg/dL, and 66.7 ± 14.9 mg/dL, the serum triglyceride levels were 60 (45/83) mg/dL, 61 (46/84) mg/dL, 61 (46/84) mg/dL, 62 (46/87) mg/dL, and 64 (49/91) mg/dL, and the serum non-HDL-C levels were 131.5 ± 34.4 mg/dL, 132.3 ± 33.2 mg/dL, 130.8 ± 32.9 mg/dL, 130.7 ± 34.2 mg/dL, and 125.5 ± 33.2 mg/dL, respectively.

In the men, a U-curve relationship was observed between the serum LDL-C level and sleep duration and also between the serum non-HDL-C level and sleep duration, with a significant association between the sleep duration and the serum LDL-C level ($p = 0.031$). An inverted U-curve relationship was observed between the serum HDL-C level and sleep duration, but the association between the two variables was not significant. No significant association was found between the serum triglyceride level and sleep duration either. On the other hand, in the women, there was a significant inverted U-curve relationship between the serum LDL-C level and sleep duration ($p = 0.011$) and between the serum non-HDL-C level and sleep duration ($p = 0.036$). A significant inverted U-curve relationship was observed between the serum HDL-C levels and sleep duration ($p = 0.016$). However, no significant association was found between the serum triglyceride level and the sleep duration (Figure 2).

Glucose metabolism markers

In the men with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the FBG levels were 98.0 ± 15.8 mg/dL, 96.6 ± 15.6 mg/dL, 96.5 ± 12.9 mg/dL, 96.2 ± 12.9 mg/dL, and 95.9 ± 10.9 mg/dL, and the HbA1c values were 5.70 ± 0.67 %, 5.65 ± 0.55 %, 5.62 ± 0.47 %, 5.61 ± 0.45 %, and 5.58 ± 0.39 %, respectively. In the women with a sleep duration of <5 hours, ³5 hours, but less than 6 hours, ³6 hours, but less than 7 hours, ≥7 hours, but less than 8 hours, and ³8 hours per day, the FBG levels were 91.6 ± 11.5 mg/dL, 90.4 ± 8.15 mg/dL, 89.9 ± 8.25 mg/dL, 89.0 ± 8.50 mg/dL, and 89.2 ± 7.36 mg/dL, and the HbA1c values were 5.63 ± 0.51 %, 5.60 ± 0.31 %, 5.56 ± 0.34 %, 5.53 ± 0.33 %, and 5.51 ± 0.31 %, respectively.

In the men, there was no significant association between the sleep duration and FBG. In the women, a significant U-curve relationship was found between the sleep duration and FBG (p <0.0001). In addition, the HbA1c increased significantly as the sleep duration decreased, in both the men and women (p = 0.016 in men, p <0.0001 in women) (Figure 2).

3-3. *ORs and 95% CIs for Worsened Cardiometabolic Risk Factors by the Sleep Duration*

As shown in Table 2, in the men, the values of the OR associated with a sleep duration of ³8 hours for WC ³reference value were 1.21 (95% CI, 0.96-1.51) and 1.16 (0.92-1.46) according to the analyses conducted using models 1 and 2, respectively, with no significant difference between the two values; however, the analysis conducted using model 3 yielded a significantly higher OR of (1.31 [1.004-1.71]) associated with a sleep duration of ³8 hours for WC ³reference value. The OR associated with a sleep duration of ³8 hours for systolic BP ³reference was significantly high in the analysis performed using model 1 (1.34 [1.03-1.74]); however, the statistically significant difference was no longer seen in the analysis performed using models 2 and 3. No significant association was found between the sleep duration and the diastolic BP. The values of OR associated with a sleep duration of <5 hours for serum LDL-C ³120 mg/dL were 1.43 (1.07-1.91) and 1.39 (1.02-1.89) according to the analysis performed using models 1 and 2, respectively, but the significant difference was no longer seen in the analysis using model 3. On the other hand, the OR associated with a sleep duration of ³8 h for LDL-C ³120 mg/dL was significantly high (1.27 [1.01-1.61]) in the analysis by model 3. The values of OR associated with a sleep duration ³8 h for serum non-HDL-C ³150 mg/dL were significantly high in the analysis by model 1 (1.30 [1.04-1.62]), model 2 (1.29 [1.02-1.62]), as well as model 3 (1.33 [1.05-1.68]). Furthermore, a significant OR for non-HDL-C ³150 mg/dL in association with a sleep duration of <5 h was found only in the analysis by model 2 (1.37 [1.01-1.85]). The OR for triglyceride ³150 mg/dL associated with a sleep duration of ³5, but <6 h was significantly low according to the analyses using all 3 models (model 1: 0.82 [0.68-0.996]; model 2: 0.79 [0.64-0.97]; model 3: 0.76 [0.61-0.94]). The OR for FBG of ³100 mg/dL associated with a sleep duration of <5 h was also significantly high as per the analyses conducted using all 3 models (model 1: 1.58 [1.18-2.14]; model 2: 1.77 [1.28-2.45]; model 3: 1.74 [1.25-2.42]).

On the other hand, in the women, as shown in Table 3, the OR for WC ³reference value associated with a sleep duration of <5 hours was significantly high as per analyses by all 3 models (model 1: 1.98 [1.25-3.14]; model 2: 2.26 [1.37-3.71]; model 3: 1.98 [1.11-3.55]). No significant association was noted between the sleep duration and BP. The OR for HDL-C <40 mg/dL associated with a sleep duration of ³5, but <6 hours was significantly low according to the analysis using model 1 (0.34 [0.12-0.98]), although no analyses using models 2 and 3 yielded no significant association. The OR for FBG ³100 mg/dL associated with a sleep duration of ³7, but <8 hours was significantly low as per analyses using all 3 models (model 1: 0.66 [0.49-0.89]; model 2: 0.69 [0.50-0.94]; model 3: 0.70 [0.51-0.95]). Significantly high OR values for HbA1c ³5.6% associated with a sleep duration of <5 hours were obtained in all 3 models (model 1: 1.52 [1.14-2.02]; model 2: 1.59 [1.16-2.19]; model 3: 1.52 [1.10-2.10]). While model 1 yielded a significantly high OR for HbA1c ³5.6% associated with a sleep duration of ³5, but <6 hours (1.20 [1.03-1.40]), no significant associations were yielded by the analyses using model 2 or 3.

3-4. *Proportion of Participants with a Weight Gain of ³10 kg from the age of 20 years in Each Sleep Duration Category in the Men and Women*

As shown in Figure 3, there was a significant U-curve relationship between the sleep duration and the proportion of men showing a weight gain of ³10 kg from the age of 20 years ($p = 0.009$), and the proportion of women showing a weight gain of ³10 kg from the age of 20 years increased significantly as the sleep duration decreased ($p = 0.002$). In addition, the proportion of men showing a weight gain of ³10 kg from the age of 20 years was significantly higher than the proportion of women showing a weight gain of ³10 kg from the age of 20 years across all sleep duration categories ($p <0.0001$).

4. Discussion

We obtained the following findings in this study. In the men, shorter than optimal/longer than optimal sleep duration (<5 h/³8 h) was associated with abdominal obesity and abnormal lipid/glucose metabolism. In the women, shorter than optimal sleep duration (<5 h) was associated with abdominal obesity and abnormal glucose metabolism, but not with abnormal lipid metabolism. Furthermore, in the women, longer than optimal sleep duration (³8 h) was not associated with exacerbation of any of the cardiometabolic risk factors. In addition, sleep duration was not associated with the BP in either the men or the women. Therefore, this study showed that there are gender differences in the relationship between sleep duration and cardiometabolic risk, suggesting that the influence of sleep duration on the cardiometabolic risk differs between men and women.

A new feature of the logistic regression analysis performed to determine the relationship between the sleep duration and cardiometabolic risk in this study was the inclusion of weight gain (+/-) of ³10 kg from the age of 20 years, which is an indicator of insufficient daily physical activity, as an independent variable in model 3. By comparing the results obtained using models 2 and 3, we investigated whether weight gain

(+/-) ³10 kg from the age of 20 years was a confounding factor or not, i.e., whether insufficient daily physical activity affected the relationship between the sleep duration and cardiometabolic risk.

In model 2, the ORs for increased serum LDL-C and increased FBG as compared to the reference values associated with a shorter than optimal sleep duration, and the OR for increased serum non-HDL-C associated with both shorter and longer than optimal sleep durations, were significantly high in the men, whereas in the women, the OR for increased WC and increased HbA1c levels were significantly high only in association with a shorter than optimal sleep duration. This phenomenon is reflected in the results shown in Figure 3 for both men and women. Namely, the proportion of men with weight gain (+) was higher in associated with both shorter than optimal and longer than optimal sleep durations, while the proportion of women with weight gain (+) was higher only in association with a shorter than optimal sleep duration.

However, in the men, the ORs for increased serum LDL-C levels and increased serum non-HDL-C levels were also significantly higher in association with a shorter than optimal sleep duration as compared to the reference in model 2, while in model 3 the ORs for increased serum LDL-C and increased serum non-HDL-C tended to be higher in association with a shorter than optimal sleep duration, but the associations were not statistically significant. The results suggest that it is necessary to take into consideration the influence of decreased physical activity due to inadequate sleep duration on the relationship between the sleep duration and cardiometabolic risk. On the other hand, like in model 2, in model 3, in which adjustment was made for weight gain (+/-) of ³10 kg from the age of 20 years, the OR for increased FBG associated with a shorter than optimal sleep duration and that for increased serum non-HDL-C associated with a longer than optimal sleep duration were significantly high in the men, and the ORs for increased WC and increased HbA1c associated with a shorter than optimal sleep duration were significantly high in women. Furthermore, the ORs for increased serum LDL-C and increased WC were significantly higher in association with a longer sleep duration in the men. These relationships between the sleep duration and cardiometabolic risks may be affected by factors other than daily physical activity.

It has been previously reported that insufficient physical activity may be involved in the exacerbation of cardiometabolic risk due to a shorter than optimal sleep duration. It has been reported that when sleep is limited to 4 hours, the amount and level of physical activity decreased as compared to that associated with a sleep duration of 8 hours in 15 healthy males [26]. As shown in the present study, insufficient physical activity may be associated with the deterioration of the serum LDL-C and non-HDL-C levels associated with a shorter than optimal sleep duration in men.

On the other hand, sleep fragmentation, fatigue, depression, association with sleep apnea syndrome, etc., are considered to be involved in the mechanism by which a longer than optimal sleep duration exacerbates cardiometabolic risk [27]. In addition, bad eating habits associated with a longer than optimal sleep duration may be involved in the exacerbation of the cardiometabolic risk. Longer than optimal sleep duration can be divided into some types, and some individuals have an early bedtime and others have a late bedtime. Ogilvie RP et al. reported that individuals who go to bed at 12:30 am or later

tended to skip breakfast as compared with those who go to bed at 10:30 pm or earlier [28]. In addition, breakfast skipping has been reported to be associated with elevated serum LDL-C levels and increased body weight and body fat mass [29, 30]. In the present study, the men who slept for ³8 h may have had late bedtimes, and bad eating habits could have been involved in the deterioration of the serum LDL-C and non-HDL-C levels and exacerbation of abdominal obesity in these men. In women who slept for ³8 h, the long duration of sleep did not tend to exacerbate any of the cardiometabolic risk factors, and this could be because they had early bedtime and better lifestyle habits. A significantly lower proportion of women who slept for ³8 h showed weight gain (+) of ³10 kg from the age of 20 years, suggesting that the women who slept for ³8 h may have been engaged in sufficient physical activity and furthermore, had good eating habits.

Women with a shorter than optimal sleep duration (<5 h) may have had bad eating habits, which could have been involved in the abnormal glucose metabolism and abdominal obesity observed in them. Women with a shorter than optimal sleep duration were previously reported to have a tendency to eat excessively between meals [31], suggesting that women who sleep for shorter than optimal duration may have poor eating habits. Furthermore, abnormal glucose metabolism occurring in women with a shorter than optimal sleep duration may be represented by postprandial hyperglycemia, which is known to be closely involved in abdominal obesity [32]. Repeated postprandial hyperglycemia may increase the HbA1c [33]. On the other hand, shorter than optimal sleep duration was suggested to deteriorate the FBG levels in the men. This phenomenon may be related to the fact that individuals with a shorter than optimal sleep duration tend to be aware of stress [34] and that stress activates the sympathetic nervous system to increase the blood glucose levels [35].

Another feature of the relationship between the sleep duration and cardiometabolic risk in women is that no relationship was seen between the sleep duration and the lipid profile. This could be related to the abnormal lipid metabolism that begins to be seen from around 50 years of age in women. Estrogen deficiency due to menopause has been reported to have a significant impact on lipid metabolism in females [36, 37]. In the present study, as shown in Figure 4, serum LDL-C and non-HDL-C levels and triglyceride increased rapidly and serum HDL-C levels tended to decrease, though gradually, from around 50 years of age in females. This study found no association between sleep duration and abnormal lipid metabolism in females, and this may be because abnormal lipid metabolism, which occurs from around 50 years of age, has a significant impact. In addition, it is necessary to take into consideration other factors affecting lipid metabolism. A higher prevalence of hyperthyrotropinemia and more adverse effects of hyperthyrotropinemia on lipid metabolism in females than in males were reported [38]. Furthermore, serum thyroid-stimulating hormone (TSH) levels were reported to be significantly higher in night-shift workers than in day-shift workers, suggesting an association between serum TSH levels and work style [39]. The relationship between sleep duration and abnormal lipid metabolism in females needs to be further investigated.

In addition, the results of this study showed a lower risk of hypertriglyceridemia in male subjects who slept ³5, but <6 hours, which is inconsistent with previous reports. Hall MH et al. reported that the risk of

triglyceride elevation to ³150 mg/dL was 1.51 times higher in individuals who slept for ³6, but <7 hours as compared to those who slept for ≥7, but <8 hours [5]. In a cross-sectional study in Japanese diabetic patients conducted by Ohkuma T et al., a U-curve relationship was observed between the sleep duration and the risk of hypertriglyceridemia (a sleep duration of 6.5-7.4 h was used as reference) [40]. Although the reason for the discrepant result of the present study is unknown, it could arise from the separate analysis in male and female subjects performed in this study, unlike in previous studies, and the differences in the characteristics between this study and previous studies.

In a cross-sectional study involving ³700 000 individuals reported by Gradner M et al., shorter than optimal/longer than optimal sleep duration was associated with hypertension in various ethnic groups [3]. In the present study, the mean systolic BP increased as the sleep duration increased in males, and logistic regression analysis without adjustments showed that the OR for systolic BP values ³the reference value was significantly higher in male subjects who slept for ³8 h (1.34 [1.03-1.74]) as compared to those who slept for ³6, but <7 hours; however, the significant difference in the OR disappeared after adjustments for various factors, including age. The sleep duration increased as the mean age of the subjects increased, and a strong association is known to exist between age and BP.

To date, there are only a few published reports of comprehensive analysis of the relationship between sleep duration and cardiometabolic risk factors, while most published reports on this subject have focused on the relationship between sleep duration and only one cardiometabolic risk factor each (obesity, impaired glucose tolerance or dyslipidemia). It was pointed out recently that for the purpose of preventing ASCVD, it is essential to manage all the cardiometabolic risk factors in a comprehensive manner (including measures for improving the lifestyle) [41]. According to a recently published meta-analysis, both shorter than optimal and longer than optimal sleep durations are closely associated with an increased risk of death from any cause and increased risk of onset of cardiovascular events [11-16, 42]. It is therefore desirable to bear in mind that inappropriate sleep duration can exacerbate the overall cardiometabolic risk and thereby increase the risk of onset of ASCVD.

5. Study Limitations And Clinical Implications

Firstly, this was a cross-sectional study, and therefore, cause-effect relationships could not be established. Second, many of the subjects of this study were university teachers/other staff members and employees of major enterprises, that is, a group of individuals that tended to be exposed to much mental/physical stress at work. Therefore, the results of this study may not be directly extrapolatable to the population in general. Third, at the time of enrollment of the subjects in this study, the presence of undiagnosed sleep apnea syndrome (which is well-known to exacerbate cardiometabolic risk [43]) was not completely ruled out. Fourth, the group with a sleep duration of ³8 hours was composed of a small number of subjects and was therefore not further subdivided into male and female groups. That is, there may be a difference in the influence on the cardiometabolic risk between 8 hours and 10 hours of sleep. Finally, this study was focused only on the sleep duration, whereas the duration of sleep that is perceived as satisfactory deep sleep varies among individuals, and the indicators of this type of sleep (e.g.,

satisfaction with the night's sleep upon waking in the morning and absence of excessive daytime sleepiness) cannot be analyzed numerically. To evaluate the influence of sleep on the cardiometabolic risk, it may be necessary to evaluate the relationship of the duration as well as quality of sleep from many angles (i.e., The Pittsburgh Sleep Quality Index as a screening tool for sleep dysfunction). In the near future, we propose to design a prospective cohort study to analyze the relationship between sleep duration and the cardiometabolic risk/risk of onset of ASCVD.

6. Conclusions

A shorter than optimal sleep duration may exacerbate cardiometabolic risk and the risk of ASCVD in both men and women. A longer than optimal sleep duration tended to exacerbate the cardiometabolic risk in men, but not in women. Decreased physical activity associated with excessive weight gain, differences in lifestyle, mainly in the dietary habits, abnormal lipid metabolism in females that begins to be seen from around 50 years of age, and other factors might underlie the difference in the relationship between sleep duration and cardiometabolic risk between men and women.

Abbreviations

ASCVD: atherosclerotic cardiovascular disease; BMI: Body mass index; BP: blood pressure; 95% CI: 95% confidence interval; FBG: fasting blood glucose; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein; OR: odds ratio; TC: total cholesterol; WC: waist circumference

Declarations

Ethics approval and consent to participate

This study was conducted with the approval of the Institutional Review Board of Nihon University Hospital (approval number: 20180105), in accordance with the ethical principles laid down in by the Declaration of Helsinki. Written consent was obtained from every participant. Information about the study was published on the website of the institute, and potential subjects were assured that they had full freedom to refuse consent for participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors' contributions

RM has designed this study in whole and drafted this manuscript. RM and ST have contributed to collect data. RM has contributed to the statistical analysis in this study. NM and YO have contributed to provide advice on interpretation of the results. All authors approved the final version of the manuscript.

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Tables

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Figures

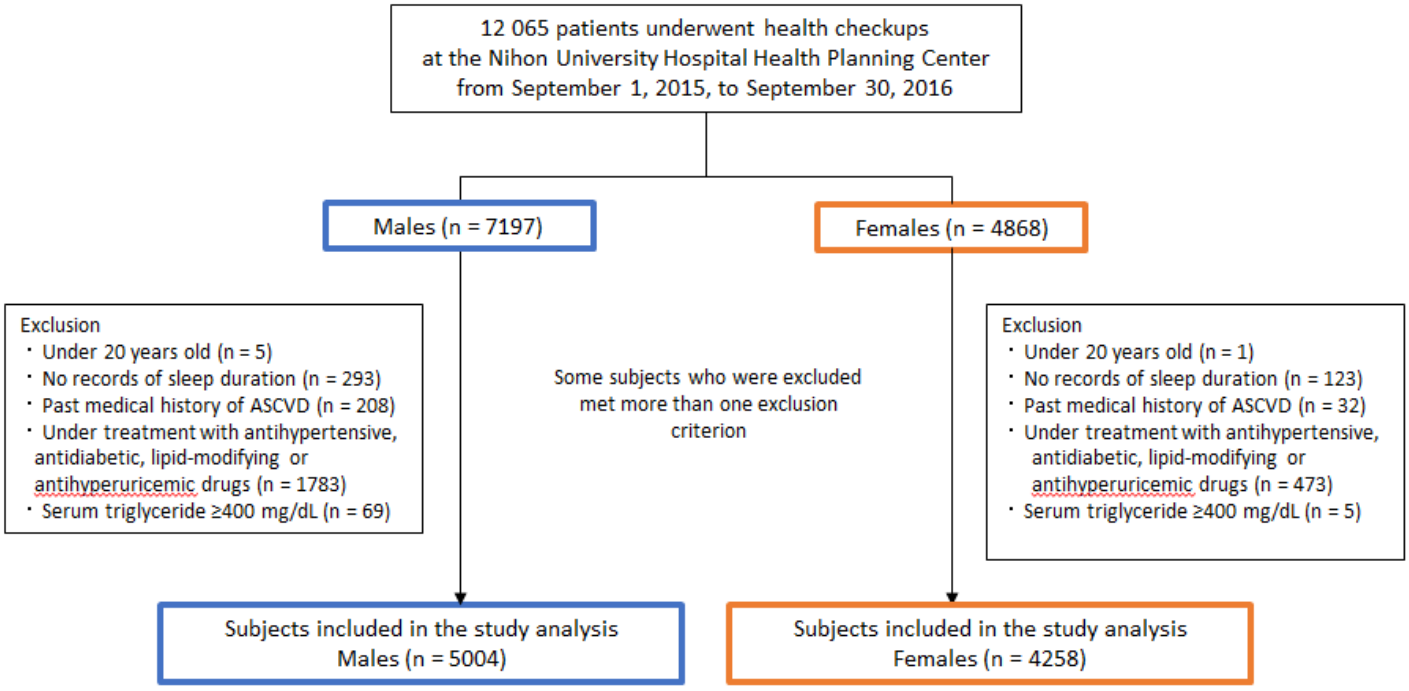

Figure 1

Flow diagram of subject selection Caption: ASCVD = atherosclerotic cardiovascular disease

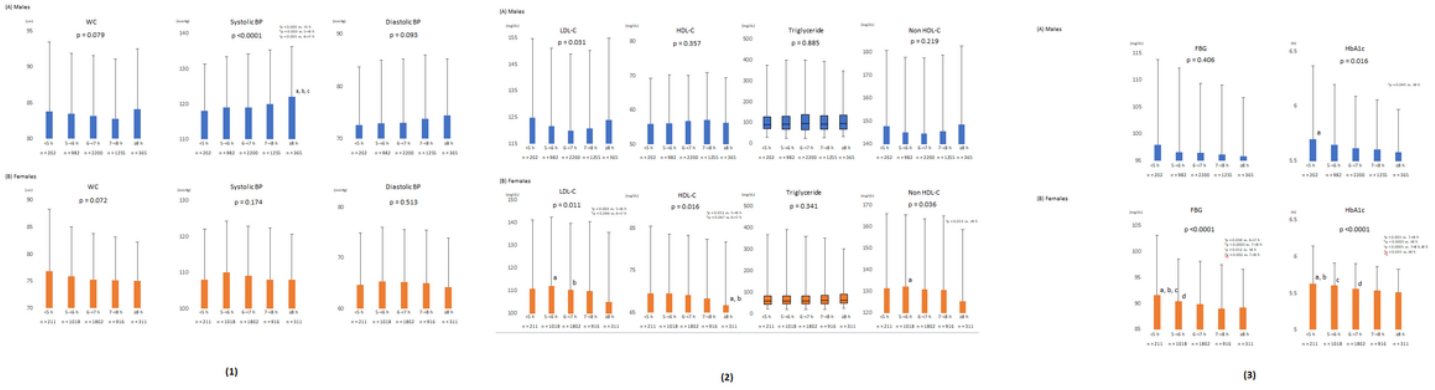

Figure 2

Relationship between Cardiometabolic Risk and Sleep Duration in Males and Females 1)Caption: WC = waist circumference; BP = blood pressure 2)Caption: LDL-C = low-density lipoprotein cholesterol; HDL = high-density lipoprotein 3) Caption: FBG = fasting blood glucose; HbA1c = hemoglobin A1c

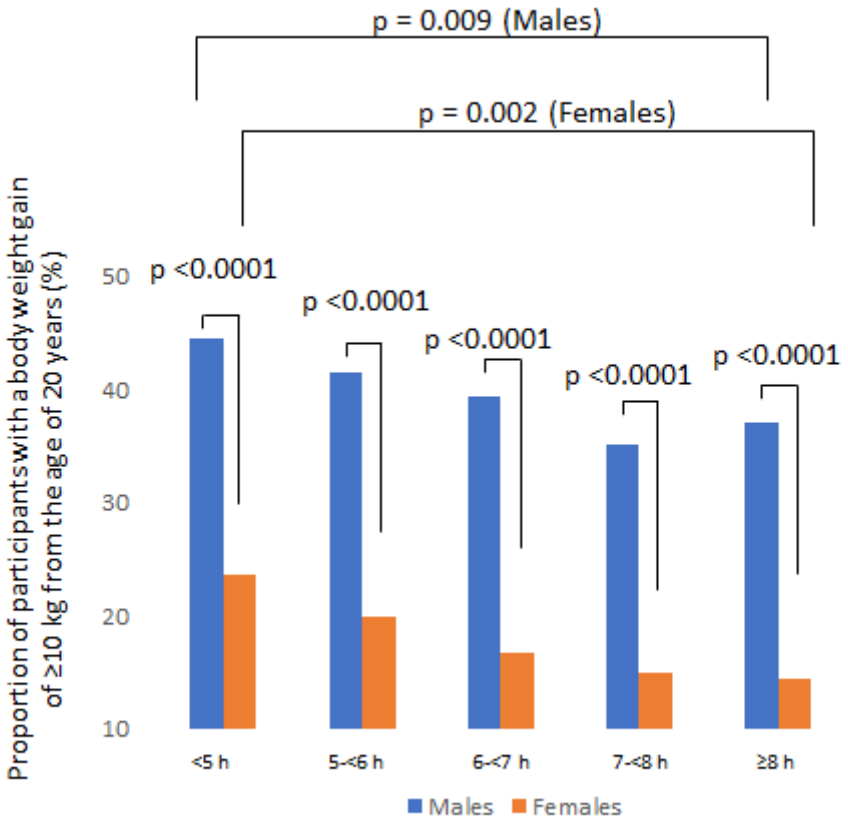

Figure 3

Relationship between Body Weight Gain and Sleep Duration in Males and Females

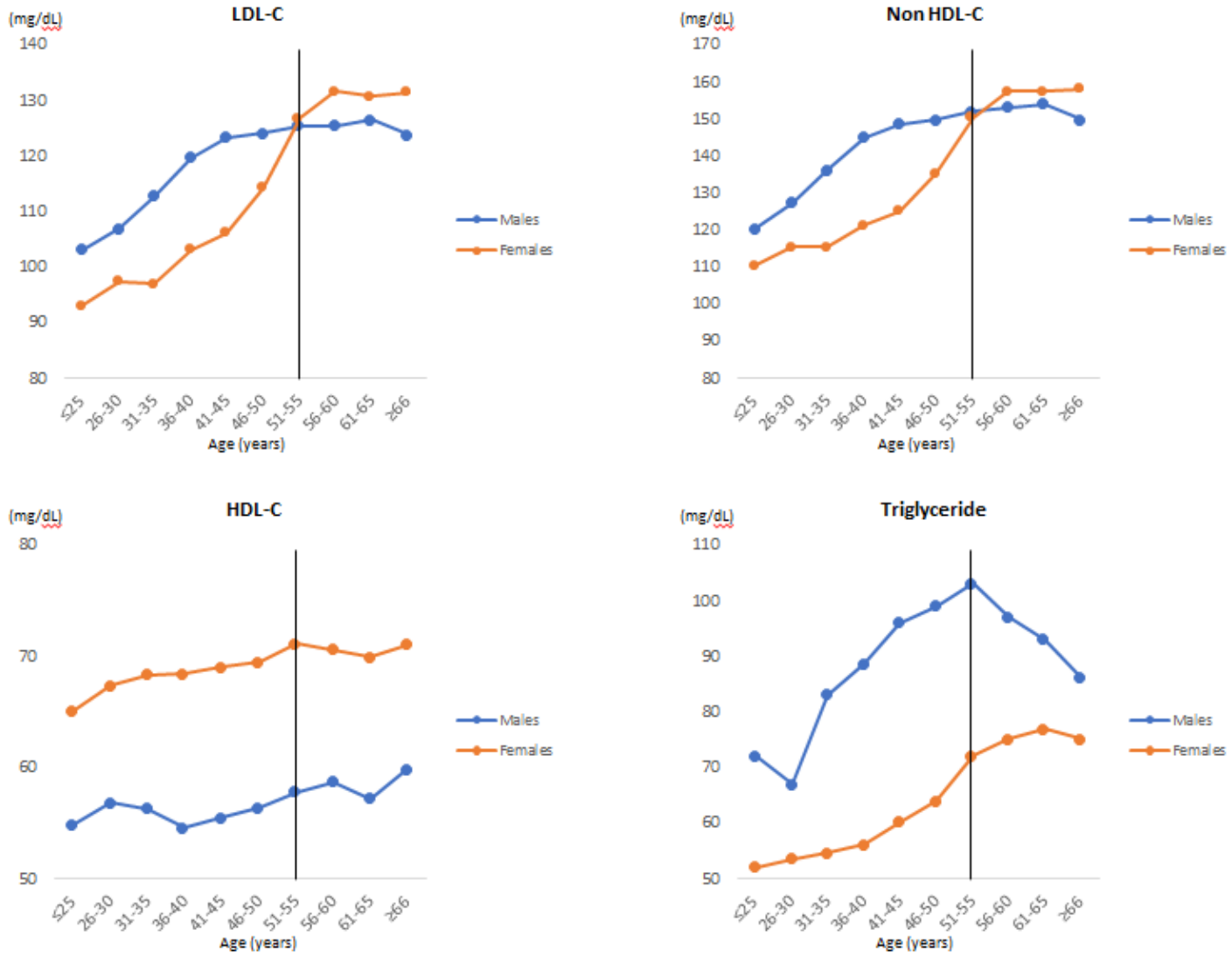

Figure 4

Relationship between Age and the Serum Lipid Profile in Males and Females Caption: LDL-C = low-density lipoprotein cholesterol; HDL = high-density lipoprotein

Supplementary Files

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