

Evening Chronotype Is Associated With Metabolic Disorders and Body Composition in Middle-Aged Adults

Ji Hee Yu,* Chang-Ho Yun,* Jae Hee Ahn, Sooyeon Suh, Hyun Joo Cho, Seung Ku Lee, Hye Jin Yoo, Ji A Seo, Sin Gon Kim, Kyung Mook Choi, Sei Hyun Baik, Dong Seop Choi, Chol Shin,# and Nan Hee Kim#

Division of Endocrinology and Metabolism (J.H.Y., J.H.A., H.J.C., S.K.L., H.J.Y., J.A.S., S.G.K., K.M.C., S.H.B., D.S.C., N.H.K.), Department of Internal Medicine, Korea University College of Medicine, Ansan 425-707, Korea; Department of Neurology (C.-H.Y.), Bundang Clinical Neuroscience Center, Seoul National University Bundang Hospital, Seongnam 463-707, Korea; Department of Psychology (S.S.), Sungshin Women's University, Seoul 136-742, Korea; and the Institute of Human Genomic Study (C.S.), Korea University Ansan Hospital, Korea University College of Medicine, Ansan 425-707, Korea

Context: Chronotype is a trait determining individual circadian preference in behavioral and biological rhythm relative to external light-dark cycle. However, little is known about the relationship between chronotype and metabolic disorders.

Objective: The aim of this study was to examine whether late chronotype is related to metabolic abnormalities and body composition in middle-aged adults, independent of sleep duration and lifestyle.

Design and Participants: A total of 1620 participants aged 47–59 years were recruited from the Korean Genome and Epidemiology Study.

Main Outcome Measures: Chronotype was assessed by the Morningness-Eveningness Questionnaire. Associations of chronotype with diabetes, metabolic syndrome, sarcopenia, and visceral obesity were analyzed. All participants underwent the oral glucose tolerance test, and body composition was measured with dual energy x-ray absorptiometry. Visceral obesity was designated as visceral fat area, measured by abdominal computed tomography, of $>100 \text{ cm}^2$.

Results: Chronotype was classified as morning in 29.6% of subjects, evening in 5.9%, neither morning nor evening in 64.5%. Evening type, when compared with morning type, was significantly associated with diabetes (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.01–2.95), metabolic syndrome (OR, 1.74; 95% CI, 1.05–2.87), and sarcopenia (OR, 3.16; 95% CI, 1.36–7.33) after adjusting for confounding factors. Gender differences in the associations were evident. In men, evening type was associated with diabetes (OR, 2.98; 95% CI, 1.39–6.39) and sarcopenia (OR, 3.89; 95% CI, 1.33–11.33). Only metabolic syndrome was associated with evening type in women (OR, 2.22; 95% CI, 1.11–4.43).

Conclusions: At the population level, evening chronotype was independently associated with diabetes, metabolic syndrome, and sarcopenia. These results support the importance of circadian rhythms in metabolic regulation. (*J Clin Endocrinol Metab* 100: 1494–1502, 2015)

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* Authors J.H.Y. and C.-H.Y. contributed equally to this work.

Authors C.S. and N.H.K. contributed equally to this work.

Abbreviations: ASM, appendicular skeletal muscle mass; BMI, body mass index; CI, confidence interval; CT, computed tomography; DBP, diastolic blood pressure; DEXA, dual-energy x-ray absorptiometry; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment for insulin resistance; hsCRP, high-sensitivity C-reactive protein; MEQ, morningness-eveningness questionnaire; MetS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; SFA, subcutaneous fat area; VFA, visceral fat area.

The endogenous circadian system modulates the timing of behavioral rhythms and physiological processes, including the sleep-wake cycle and energy metabolism (1). Normal alignment of behavioral rhythms such as activity and feeding with the environmental light-dark cycle is critical for the maintenance of energy metabolism (1, 2). Although human circadian rhythms are entrained to an external light-dark cycle with a period of approximately 24 hours, there are interindividual differences in the timing of circadian rhythms (3). Chronotype is a biological characteristic that constitutes interindividual differences in the circadian phase relative to light-dark cycle and requires a specific timing of behavior (3, 4).

Chronotypes are divided by the terms “morningness” and “eveningness” to distinguish people who endorse extreme diurnal preferences (5–7). Morning and evening types at their extreme may be shifted by about 2–3 hours in circadian oscillations of many bodily functions, including body temperature, melatonin, cortisol, and other hormone secretions (7). In these extremes, the period of biological night (or day) regulated by endogenous circadian system is significantly different from environmental night (or day) determined by external light-dark cycle (3, 8). The biological night is characterized by behavioral inactivity, decrease in energy expenditure and temperature, and elevated secretion of melatonin. Although it usually matches with the environmental dark period in humans, in the extreme chronotypes, biological night (or day) is misaligned with the environmental dark (or bright) period. For example, sleep-wake cycle, as one of most important biological rhythms governed by circadian system, is advanced in the morning types and delayed in the evening types.

However, chronotype represents more than just the time difference in the circadian phase. In general, evening types have been reported to have more health and behavioral problems than morning types. Natale et al (9) found that evening types were twice as likely to experience eating disorders compared to the control group. In addition, evening persons are more likely to suffer from chronic sleep curtailment because they initiate sleep later in the night but need to wake up earlier than their biological morning due to social demands (10). There is abundant evidence that short sleep duration and insomnia are significant risk factors for obesity and diabetes (11, 12). Furthermore, late chronotype is associated with poor glycemic control in patients with type 2 diabetes independent of sleep disturbance (13). Although these data suggest that evening chronotype might be related to metabolic abnormalities and obesity, most studies have been conducted in clinic-based (13) or experimental settings (14). To the best of our knowledge, only one study revealed that evening types had a higher risk of type 2 diabetes and hypertension in the

general population (15), but whether metabolic abnormalities of late chronotype are independent from their unhealthy lifestyles or disrupted sleep has not been established. In addition, there has been no population-based study of chronotype using detailed measurements of metabolism such as insulin resistance, visceral fat, and muscle mass.

The aim of this study was to examine whether late chronotype was associated with metabolic abnormalities and body composition in middle-aged Korean men and women independent of sleep profile and lifestyle factors.

Subjects and Methods

Subjects

All study subjects were derived from the Ansan cohort of the Korean Genome Epidemiology Study (KoGES), an ongoing population-based cohort study that began in 2001. The original cohort consisted of 5020 adults (2523 males) aged 40 to 69 years from Ansan, South Korea. Participants in the KoGES have been biennially evaluated for demographics, lifestyle, sleep-related factors, anthropometric and biochemical variables, and health status, including medical illness and medications. All information was collected by trained interviewers. Among 3372 subjects who participated in the 2010–2011 evaluation, we recruited 1674 who underwent morningness-eveningness evaluation, dual-energy x-ray absorptiometry (DEXA), and abdominal computed tomography (CT). We excluded 54 subjects with the following conditions: 1) history of major cardiovascular diseases ($n = 40$); 2) malignant diseases ($n = 2$); and 3) shift workers ($n = 12$). Finally 1620 subjects were enrolled in the study. Each participant signed an informed consent form. This study was performed according to the principles of the Declaration of Helsinki of the World Medical Association and was approved by the Institutional Review Board of Korea University Ansan Hospital.

Assessments

Demographic, anthropometric, and laboratory measurements

All participants responded to an interviewer-administered questionnaire and underwent a comprehensive physical examination. Lifestyle characteristics, such as smoking status and alcohol consumption, were categorized as never, former, and current. Level of exercise was categorized as never, lightly (1–3 times/wk, ≥ 30 min/session), or regularly (≥ 3 times/wk, ≥ 30 min/session) during the previous month. Hypertension was diagnosed when systolic blood pressure (SBP) or diastolic blood pressure (DBP) was ≥ 140 or 90 mm Hg, respectively, or when participants took antihypertensive medications. Height was measured to the nearest 0.1 cm using a fixed-wall-scale measuring device. Weight was measured to the nearest 0.1 kg using an electronic scale that was calibrated before each measurement. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest 0.5 cm in a horizontal plane at the level of the umbilicus at the end of a normal expiration.

Blood was drawn for biochemical analysis after an overnight fast. Plasma glucose, serum triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol levels were measured with an autoanalyzer (ADVIA 1650; Siemens). High-sensitivity C-reactive protein (hsCRP) levels were measured by an immunoassay (ADVIA1800; Siemens). Insulin was measured with an immunoradiometric assay (IRMA) kit (INS-IRMA Kit; BioSource) using a Packard gamma-counter system. Individual participants also underwent a 75-g oral glucose tolerance test.

Measurements of morningness-eveningness and sleep profile

Subject morningness-eveningness was measured with the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) (5). The MEQ consisted of 19 questions about preferred sleep time and daily performance, such as “What time would you like to get up?” “What time do you feel tired?” and “What would be the best time to perform hard physical work?” The scores ranged from 16 to 86. Based on their scores, individuals were categorized as being a morning (59–86), neither (42–58), or evening (16–41) type.

Participant response to the question “How many hours did you usually sleep per day during the last month?” was designated as self-reported sleep duration. Overall sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) (16). Poor sleep quality was defined as a PSQI score >5 . Subjective daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) (17), and the presence of excessive daytime sleepiness was defined when ESS was 11 or above. Habitual snoring was defined as the presence of snoring at least four nights a week. The presence of insomnia was established when participants had any of the four insomnia symptoms (difficulties in initiation or maintenance of sleep, early morning awakening, or nonrefreshing sleep) for at least 3 days a week during the past month (18).

Measurement of body composition

Whole body composition was determined using DEXA. Total body fat mass (g) and total and regional lean mass (g) were measured using a Lunar DPX-MD + densitometer (GE Medical Systems). Appendicular skeletal muscle mass (ASM; kg) was defined as the sum of the lean soft tissue mass of the arms and legs (19), and height-corrected ASM (kg/m^2) was also calculated (20).

Abdominal adipose tissue area was quantified using single-slice CT scanning (Brilliance 64; Philips) with 120-kV exposure. A single slice of 5-mm thickness was acquired at the level of the L4–L5 vertebral interspace, and total abdominal fat areas were determined by setting the attenuation level between -190 and -30 Hounsfield units. Visceral fat area (VFA; cm^2) was defined by manually tracing adipose tissue within the muscle wall. Subcutaneous fat area (SFA, cm^2) was determined by subtracting VFA from total abdominal fat area.

Definition of diabetes mellitus, metabolic syndrome (MetS), sarcopenia, and visceral obesity

Diabetes mellitus was diagnosed when fasting plasma glucose (FPG) was ≥ 7.0 mmol/L, or 2-hour plasma glucose was ≥ 11.1 mmol/L after a 75-g oral glucose tolerance test, or when participants took antidiabetic medication (21). Insulin resistance was estimated with the homeostasis model of assessment for insulin

resistance (HOMA-IR) and calculated as fasting glucose (mmol/L) \times fasting insulin ($\mu\text{U}/\text{mL}$)/22.5 (22). According to the National Cholesterol Education Program Adult Treatment Panel III (23), MetS was defined by the presence of three or more of the following five conditions: 1) abdominal obesity (waist circumference ≥ 90 cm for men and ≥ 85 cm for women); 2) hypertriglyceridemia (fasting plasma triglycerides ≥ 150 mg/dL); 3) low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women); 4) hypertension (SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, or taking antihypertensive medications); and 5) hyperglycemia (FPG ≥ 100 mg/dL or taking antidiabetic medications).

Sarcopenia was defined as a height-corrected ASM value below the sex-specific mean of a young reference group by more than 1 SD. Thresholds for sarcopenia were 6.75 kg/m^2 in men and 4.96 kg/m^2 in women, calculated from the values of corrected ASM in 100 healthy young adults (50 males, age 25.6 ± 3.1 y; 50 females, age 26.1 ± 4.2 y). Visceral obesity was defined as VFA ≥ 100 cm^2 , which is the proposed cutoff point for Asians according to the Japan Society for the Study of Obesity (24).

Statistical analysis

Baseline characteristics were compared among chronotype groups using one-way ANOVA with Bonferroni post hoc test for numeric variables. The χ^2 test was used to compare categorical variables. Non-normally distributed variables such as triglyceride levels and HOMA-IR were presented as the median and interquartile range for each group, and differences were tested after logarithmic transformation. We also compared clinical characteristics between groups with different chronotypes in each gender by analysis of covariance after adjusting for age, BMI, smoking, alcohol, exercise, occupation, and sleep duration. Multivariate logistic regression analyses were conducted to evaluate associations between chronotype and the presence of diabetes, MetS, sarcopenia, and visceral obesity. Age, sex, BMI, smoking, alcohol, exercise, occupation, sleep duration, and medications for hypertension, diabetes, and dyslipidemia were included as covariates. BMI was not adjusted for in the analysis of body composition data such as VFA, SFA, total body lean mass and fat mass, and ASM/height². A P value $<.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 18.0 (SPSS Inc).

Results

Subject characteristics

Clinical characteristics of the study subjects are listed in Table 1. Of the 1620 subjects, 480 (29.6%) were classified as morning type, 95 (5.8%) as evening type, and 1045 (64.5%) as neither. Participants with late chronotype were younger and were more likely to be female and current smokers than those with morning chronotype. They did less regular exercise, but there were no differences in BMI or the percentage who held a white-collar job. Although participants with late chronotype were younger, they had significantly higher triglyceride and hsCRP levels and sc and total body fat mass, but lower lean mass and SBP. Sarcopenia was more prevalent in subjects with late

Table 1. Characteristics of Study Subjects (MEQ, n = 1620)

	Morning Type	Neither Type	Evening Type	P
n	480	1045	95	
Age, y	53.7 ± 3.0	52.7 ± 3.0 ^a	52.2 ± 2.7 ^a	<.001
Sex, male	262 (54.6)	501 (47.9) ^a	37 (38.9) ^a	.006
SBP, mm Hg	114.5 ± 14.4	113.0 ± 14.4	110.9 ± 14.2	.044
DBP, mm Hg	76.8 ± 9.7	76.4 ± 10.0	80.2 ± 9.4	.288
FPG, mmol/L	5.4 ± 0.9	5.4 ± 1.0	5.5 ± 1.2	.549
HbA1c, %*	5.5 (5.3–5.8)	5.6 (5.3–5.8)	5.6 (5.3–5.9)	.528
HbA1c, mmol/mol*	37 (34–40)	38 (34–40)	38 (34–41)	.528
HOMA-IR*	1.7 (1.3–2.3)	1.8 (1.4–2.4)	1.9 (1.4–2.7)	.125
Total cholesterol, mmol/L	5.1 ± 0.8	5.2 ± 0.9	5.3 ± 0.9	.045
HDL cholesterol, mmol/L	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	.136
Triglyceride, mmol/L*	1.2 (0.9–1.8)	1.4 (1.0–2.0)	1.5 (1.1–2.0) ^a	.008
hsCRP, nmol/L*	5.7 (2.9–10.5)	5.7 (2.9–12.4) ^a	7.6 (3.8–12.4) ^a	.006
BMI, kg/m ²	24.6 ± 2.7	24.6 ± 2.9	24.8 ± 3.5	.726
Waist circumference, cm	79.6 ± 8.1	79.6 ± 8.1	80.2 ± 9.4	.739
VFA, cm ²	74.7 ± 35.3	75.7 ± 34.4	77.4 ± 32.6	.752
SFA, cm ²	184.8 ± 68.0	192.9 ± 71.1	208.0 ± 102.6 ^a	.009
Total body fat mass, g	17 222.7 ± 5692.3	18 193.9 ± 5871.0 ^a	19 034.2 ± 7040.4 ^a	.002
Total body lean mass, g	43 829.9 ± 8956.8	42 579.1 ± 8818.5 ^a	41 265.8 ± 7650.9 ^a	.007
ASM/Ht ² , kg/m ²	6.8 ± 1.1	6.6 ± 1.1 ^a	6.4 ± 1.0 ^a	<.001
Sarcopenia	18 (3.8)	78 (7.5) ^a	10 (10.5) ^a	.007
Visceral obesity	100 (20.9)	204 (19.7)	24 (25.3)	.405
Alcohol, current	245 (51.0)	514 (49.2)	41 (43.2)	.694
Smoking, current	48 (10)	166 (15.9) ^a	18 (18.9) ^a	.001
Regular exercise	157 (32.7)	305 (29.2) ^a	25 (26.3) ^a	.001
Occupation, white-collar	166 (34.6)	381 (36.5)	37 (38.9)	.496
MetS	111 (23.1)	279 (26.7)	29 (30.5)	.172
HTN	148 (30.8)	278 (26.6)	22 (23.2)	.138
DM	97 (20.5)	237 (22.9)	27 (28.7)	.190
MEQ score, total	62.8 ± 3.3	51.3 ± 4.5 ^a	37.3 ± 3.5 ^{a,b}	<.001

Abbreviations: ASM/Ht², ASM divided by height squared; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HTN, hypertension. Data are presented as number (percentage), mean ± SD, or geometric mean (95% CI).

* Statistical significance was estimated after logarithmic transformation.

^a *P* < .05 vs morning type.

^b *P* < .05 vs neither type.

chronotype, but there was no significant difference between groups in the prevalence of visceral obesity, MetS, hypertension, or diabetes.

Chronotype and sleep parameters

We evaluated the association between chronotype and sleep parameters (Table 2). The gap in sleep timing between morning and evening types was about 2 hours. There were no differences between groups in reported sleep duration and the prevalence of excessive daytime sleepiness and habitual snoring. However, sleep quality was worse in the late chronotype group, and insomnia symptoms were more prevalent in the evening types.

Metabolic characteristics according to chronotype

Because of gender difference in anthropometric measures, we analyzed the association between metabolic profile and chronotype by gender (Table 3). In men, evening type was significantly associated with lower SBP, total body lean mass, and height-corrected ASM and with

higher FPG levels after adjustment for several confounding factors. Women with eveningness had a higher waist circumference, triglyceride and hsCRP levels, and total body fat mass, including visceral and sc fat, compared with other chronotypes.

Association of chronotype with diabetes, MetS, sarcopenia, and visceral obesity

In all participants, the odds ratio (OR) for diabetes, MetS, and sarcopenia for evening type was 1.73 (95% confidence interval [CI], 1.01–2.95), 1.74 (95% CI, 1.05–2.87), and 3.16 (95% CI, 1.36–7.33), respectively, compared with morning type after controlling for confounding factors (Figure 1). Visceral obesity was not significantly associated with chronotype (OR, 1.68; 95% CI, 0.97–2.89).

Gender differences were documented in associations between chronotype and metabolic disorders (Figure 1). In men, the ORs for diabetes and sarcopenia were 2.98 (95%

Table 2. Sleep Profiles According to Chronotype (MEQ, n = 1620)

	Morning Type	Neither Type	Evening Type	P
n	480	1045	95	
Sleep duration, h	6.8 ± 1.1	6.8 ± 1.1	6.7 ± 1.4	.355
Bedtime*	22:50 ± 0:59	23:38 ± 1:04 ^a	00:53 ± 1:13 ^{a,b}	<.001
Wake time*	5:38 ± 0:56	6:28 ± 1:05 ^a	7:32 ± 1:23 ^{a,b}	<.001
PSQI score	4.1 ± 2.7	4.6 ± 2.9 ^a	5.0 ± 3.2 ^a	.002
Poor sleep quality	110 (23.2)	311 (30.3) ^a	33 (35.9) ^a	.005
Insomnia	96 (20.0)	263 (25.2)	42 (44.2) ^{a,b}	<.001
ESS score	5.6 ± 3.2	6.0 ± 3.4	5.6 ± 3.2	.148
EDS	34 (7.1)	104 (10.0)	7 (7.4)	.115
Habitual snoring	102 (21.3)	190 (18.2)	16 (16.8)	.583

Abbreviations: EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index. Data are presented as mean ± SD or number (percentage).

* Time is presented in 24-hour clock format.

^a P < .05 vs morning type.

^b P < .05 vs neither type.

CI, 1.39–6.39) and 3.89 (95% CI, 1.33–11.33), respectively, for evening type compared with morning type. However, evening type was not related to MetS in men. In contrast, women with evening type had a significantly higher chance of having MetS (OR, 2.22; 95% CI, 1.11–4.43). In women, neither diabetes nor sarcopenia was associated with evening chronotype.

Discussion

Evening chronotype was present in 5.8% of the middle-aged general population and was associated with a higher prevalence of diabetes, MetS, and sarcopenia, independent of sleep duration and lifestyle. Evening chronotype was associated with lower lean mass in men and higher fat mass in women. To the best of our knowledge, this is the first study to reveal an association between chronotype and sarcopenia or metabolic disorders at the population level, based on systemic measures of metabolic profiles and body composition with DEXA and abdominal CT.

Evening type is likely associated with a worse metabolic profile than other chronotypes for several reasons. One possible explanation is a greater chance of chronic sleep loss in evening type because lack of sleep exerts deleterious effects on metabolic pathways (25). Individuals with evening chronotype are more likely to suffer from sleep curtailment because of the discrepancy between intrinsic sleep-wake rhythm and actual bedtime, the former determined by biological clock and the latter influenced by social requirement (11, 12, 26). Although average sleep duration was not different between evening and other types in our study, evening persons are known to accumulate sleep debt on weekdays and then have extended catch-up sleep on the weekend (27). Therefore, we cannot exclude the possibility that sleep loss repetitively occurring at least

during weekdays contributes to poor metabolic profiles in evening types. In addition to sleep debt, poor sleep quality in evening types may have adverse effects on metabolic profiles. Evening types complained of insomnia symptoms and poor sleep quality more frequently (Table 2), as reported in previous studies (10, 28). However, the main result was not changed even after adjusting for sleep duration and PSQI in the regression model (data not shown). These findings suggest that there may be other causes of impaired metabolic regulation in the evening type beyond short sleep duration or poor sleep quality.

Chronic circadian misalignment could be another reason explaining metabolic derangements in evening types. Late chronotype is typically associated with a greater degree of misalignment between social rhythms and the circadian clock than other chronotypes (26). Disruption of the circadian system may affect sleep, appetite, energy expenditure, and many possible determinants of obesity (29). The discrepancy between biological and social timing measured with differences in bedtime on weekdays and weekends is related to obesity independent of sleep duration (30). In an experimental human study, short-term circadian misalignment (~12-h shift) resulted in systematic increases in postprandial glucose and insulin levels, as well as decreased leptin levels and the complete inversion of the cortisol profile across the behavioral cycle (31). In addition, decreased insulin sensitivity and increased inflammation develop during circadian misalignment (14). In animal models, mutations of circadian clock genes can lead to signs of MetS (32). These findings support the potential negative consequences of circadian disruptions in individuals with evening chronotype. However, the one caveat is that the misaligned time was only a few hours in the present study. Thus, the metabolic adverse effects

Table 3. Metabolic Characteristics According to MEQ Chronotype in Both Genders

Variables	Morning Type	Neither Type	Evening Type	Adjusted P*	P Trend
Men (n = 800)					
n	262	501	37		
Waist circumference, cm	82.6 ± 0.3	82.8 ± 0.2	82.8 ± 0.6	.620	.769
SBP, mm Hg	117.7 ± 0.9	115.8 ± 0.7	111.3 ± 2.2 ^a	.016	.007
FPG, mg/dL	99.1 ± 1.3	102.6 ± 1.0	105 ± 3.2	.040	.089
HbA1c, %†	5.6 (5.5–5.7)	5.7 (5.6–5.7)	5.8 (5.5–6.0)	.197	.151
HbA1c, mmol/mol†	38 (37–39)	39 (38–39)	40 (37–42)	.197	.151
HOMA-IR†	1.8 (1.7–1.9)	1.9 (1.8–2.0)	2 (1.7–2.2)	.296	.305
Total cholesterol, mmol/L	5.1 ± 0.1	5.1 ± 0.04	5.3 ± 0.1	.376	.175
HDL cholesterol, mmol/L	1.3 ± 0.02	1.2 ± 0.02	1.2 ± 0.1	.169	.160
Triglyceride, mmol/L†	1.5 (1.4–1.6)	1.6 (1.5–1.7)	1.8 (1.5–2.1)	.084	.044
hsCRP, nmol/L†	6.7 (5.7–7.6)	7.6 (6.7–8.6)	8.6 (5.7–11.4)	.214	.214
VFA, cm ²	79.7 ± 2.6	84.1 ± 1.9	82.4 ± 6.1	.316	.674
SFA, cm ²	150.2 ± 3.6	154.7 ± 2.6	145.1 ± 8.5	.344	.581
Total body fat mass, g	15 349.7 ± 386.3	16 110.8 ± 278.3	14 645.3 ± 920.9	.090	.477
Total body lean mass, g	51 332.8 ± 341.1	50 751.5 ± 245.8	49 107.8 ± 813.3 ^a	.030	.011
ASM/Ht ² , kg/m ²	7.7 ± 0.05	7.6 ± 0.03	7.3 ± 0.11 ^{a,b}	.005	.001
Women (n = 820)					
n	218	544	58		
Waist circumference, cm	75.8 ± 0.7	76.1 ± 0.6	77.6 ± 0.8 ^{a,b}	.015	.004
SBP, mm Hg	110 ± 2.3	110.5 ± 2.1	111 ± 2.7	.850	.639
FPG, mg/dL	96.1 ± 2.5	94.4 ± 2.3	96.1 ± 3.0	.311	.995
HbA1c, %†	5.7 (5.5–5.9)	5.7 (5.5–5.8)	5.7 (5.5–5.9)	.579	.781
HbA1c, mmol/mol†	39 (37–41)	39 (37–40)	39 (37–41)	.579	.781
HOMA-IR†	1.6 (1.4–1.8)	1.6 (1.4–1.9)	1.7 (1.5–2)	.307	.134
Total cholesterol, mmol/L	5.2 ± 0.2	5.4 ± 0.1	5.4 ± 0.2	.080	.213
HDL cholesterol, mmol/L	1.4 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	.129	.080
Triglyceride, mmol/L†	1.2 (1.0–1.4)	1.3 (1.1–1.5)	1.4 (1.2–1.7) ^a	.013	.007
hsCRP, nmol/L†	4.8 (3.8–6.7)	6.7 (4.8–8.6) ^a	7.6 (4.8–10.5)	.018	.024
VFA, cm ²	72.5 ± 4.9	74.9 ± 4.5	82.2 ± 5.7	.093	.030
SFA, cm ²	194.2 ± 11.6	200.2 ± 10.7	221.8 ± 13.6 ^a	.033	.009
Total body fat mass, g	18 658.4 ± 900.6	19 423.9 ± 835.6	21 118.6 ± 1058.9 ^a	.010	.003
Total body lean mass, g	35 653.3 ± 568.8	35 472.8 ± 527.8	36 460.5 ± 668.8	.114	.121
ASM/Ht ² , kg/m ²	5.8 ± 0.09	5.8 ± 0.09	5.8 ± 0.11	.102	.656

Abbreviations: ASM/Ht², ASM divided by height squared; HbA1c, hemoglobin A1c. Data are presented as number (percentage), adjusted mean ± SE, or geometric mean (95% CI).

* Adjusted for age, BMI, smoking, alcohol, exercise, occupation, and sleep duration. BMI was not adjusted for the analysis of body composition data such as VFA, SFA, total body lean mass, fat mass and ASM/Ht².

† Statistical significance was estimated after logarithmic transformation.

^a P < .05 vs morning type.

^b P < .05 vs neither type.

would appear weaker in this study than that in the experimental study.

From a behavior standpoint, less exercise and more smoking were associated with late chronotype in this study, in agreement with previous results (26, 33). Evening type is associated with lower dietary restraint, less healthful dietary habits, and a tendency for a higher BMI (34, 35). Taken together, these unhealthy behavior patterns might lead to the metabolic dysregulation in evening types. However, in the present study, the association between chronotype and metabolic disorders was significant, even after adjusting for these lifestyle factors. Evening chronotype is also related to later meal time (36). Later sleepers consume more calories after 8 PM, which is related to higher BMI independent of sleep timing and duration (37).

Moreover, weight-loss treatment is less effective in late eaters, although energy expenditure, calorie intake, and sleep duration are comparable to early eaters (38). Eating late not only decreases resting-energy expenditure and glucose tolerance, but also blunts the daily cortisol rhythm and thermal effect of food (39). These metabolic alterations possibly contribute to the development of obesity and insulin resistance in late chronotype.

Another possible mechanism underlying the association between evening type and metabolic disorders is increased exposure to artificial light at night. In experimental studies, light exposure during biological night leads to increased body weight, decreased insulin sensitivity, and exaggerated inflammatory responses (40, 41). Low levels of light at night, interestingly, altered timing of food intake

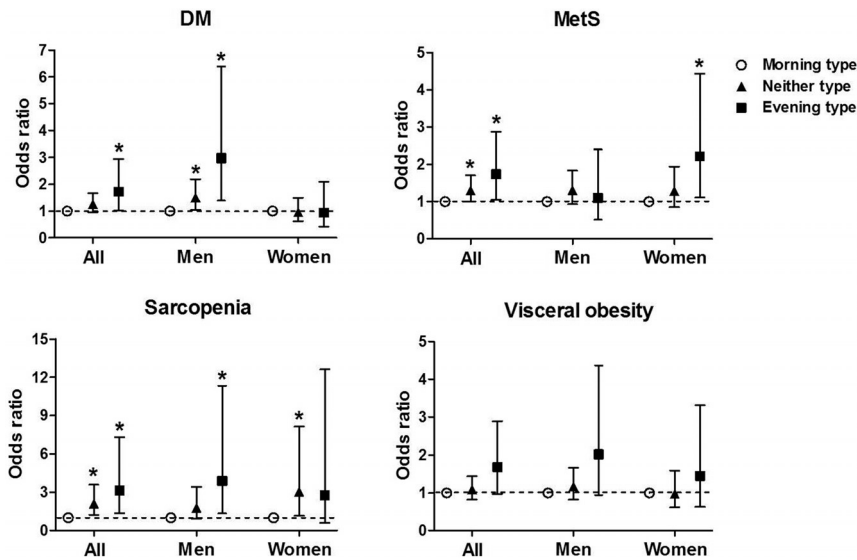


Figure 1. ORs for diabetes, MetS, sarcopenia, and visceral obesity according to MEQ chronotype. Data were adjusted for age, gender, BMI, smoking, alcohol, exercise, occupation, sleep duration, and use of antihypertensive, antidiabetic, or antilipid drugs for the analysis of all participants. Antidiabetic drugs were not adjusted for in the analysis for diabetes. BMI was not adjusted for in the analysis for sarcopenia and visceral obesity. Medications for hypertension, diabetes, and dyslipidemia as well as BMI were not adjusted for in the analysis for MetS. DM, diabetes mellitus. *, 95% CI for the OR does not include 1.

despite having no effect on total caloric intake in both studies (40, 41). Rhythmic feeding appears to be the major synchronizer for peripheral oscillators (42). Therefore, unusual feeding time may produce a disruption of the circadian system, leading to unhealthy metabolic consequences in evening persons.

It is noteworthy that the risk of metabolic disorders according to chronotype differed by gender in this study. It could be explained by sex differences in the relationship between body composition and chronotype. Evening chronotype was associated with high waist circumference, triglyceride levels, and visceral fat in women, but not in men. These findings might explain the increased risk of MetS in women with evening type. In contrast, a higher probability of diabetes was only associated with evening-oriented men. Men with evening type were associated with low lean mass rather than fat mass. Muscle tissue is an important organ for protein storage, glucose regulation, and myokine production, which can modify insulin resistance and oppose the harmful effects of the proinflammatory adipokines (43). Furthermore, sarcopenia can aggravate obesity due to the limited physical activity. Therefore, there is growing evidence that the reduced muscle mass and function are closely associated with insulin resistance and adverse glucose metabolism (44). In the present study, less muscle mass in men may be a linking mechanism between late chronotype and diabetes. However, one caveat for this explanation is that the prevalence of sarcopenia was relatively lower in women (2.3, 6.1, and 5.2% in morning, neither, and evening types, respectively) than in

men. Larger sample sizes may be needed to confirm the relationship between sarcopenia and evening type in women. Additional studies are warranted to elucidate gender differences in the relationship of chronotype with body composition and metabolism.

We observed a higher SBP among morning types, a finding in agreement with a previous study (15). Blood pressure differences could be explained by diurnal rhythm of systemic blood pressure, dipping at night (behavioral sleep period) and surging at the time of waking in the morning (45). In KoGES, blood pressure is typically measured between 8 AM and noon. Morning types could thereby have earlier morning surges of systolic pressures than evening types (46). Even so, the prevalence of hypertension was not significantly

different across the chronotypes in our study. Similar to blood pressure, glucose or insulin levels are under the influence of circadian or sleep-wake rhythm, but their levels are mainly influenced by the fed/fasting state (47). Therefore the effect of circadian or diurnal rhythm on other metabolic parameters might be very minor if present.

Some limitations should be noted in the current study. This study cannot clarify the causal relationship between circadian and metabolic derangements. It is possible that bad metabolic profiles due to unhealthy behavioral habits could influence circadian rhythms, or inversely, that chronic circadian derangement could lead to metabolic dysregulation in evening chronotypes. Further research will be needed to establish the relationship between circadian and metabolic disturbances.

In summary, evening chronotype was associated with an increased risk of diabetes and sarcopenia in men and with MetS in women, independent of sleep duration and behavioral health problems in middle-aged Korean adults. These results support the importance of circadian rhythm in metabolic regulation.

Acknowledgments

Address all correspondence and requests for reprints to: Nan Hee Kim, MD, PhD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 425-707, Korea. E-mail: nhkendo@gmail.com. Or, Chol

Shin, MD, PhD, Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 425-707, Korea. E-mail: chol-shin@hanmail.net.

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References

- Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. *J Clin Invest*. 2011;121:2133–2141.
- Maury E, Ramsey KM, Bass J. Circadian rhythms and metabolic syndrome: from experimental genetics to human disease. *Circ Res*. 2010;106:447–462.
- Baehr EK, Revelle W, Eastman CI. Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness-eveningness. *J Sleep Res*. 2000;9:117–127.
- Roenneberg T, Kuehne T, Juda M, et al. Epidemiology of the human circadian clock. *Sleep Med Rev*. 2007;11:429–438.
- Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*. 1976;4:97–110.
- Paine SJ, Gander PH, Travier N. The epidemiology of morningness/eveningness: influence of age, gender, ethnicity, and socioeconomic factors in adults (30–49 years). *J Biol Rhythms*. 2006;21:68–76.
- Lack L, Bailey M, Lovato N, Wright H. Chronotype differences in circadian rhythms of temperature, melatonin, and sleepiness as measured in a modified constant routine protocol. *Nat Sci Sleep*. 2009;1:1–8.
- Morris CJ, Aeschbach D, Scheer FA. Circadian system, sleep and endocrinology. *Mol Cell Endocrinol*. 2012;349:91–104.
- Natale V, Ballardini D, Schumann R, Mencarelli C, Magelli V. Morningness–eveningness preference and eating disorders. *Pers Individ Dif*. 2008;45:549–553.
- Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. Relation of chronotype to sleep complaints in the general Finnish population. *Chronobiol Int*. 2012;29:311–317.
- Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. 2008;31:619–626.
- Kita T, Yoshioka E, Satoh H, et al. Short sleep duration and poor sleep quality increase the risk of diabetes in Japanese workers with no family history of diabetes. *Diabetes Care*. 2012;35:313–318.
- Reutrakul S, Hood MM, Crowley SJ, et al. Chronotype is independently associated with glycemic control in type 2 diabetes. *Diabetes Care*. 2013;36:2523–2529.
- Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*. 2014;63:1860–1869.
- Merikanto I, Lahti T, Puulijoki H, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiol Int*. 2013;30:470–477.
- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540–545.
- Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007;3:S7–S10.
- Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990;52:214–218.
- Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998;147:755–763.
- Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003;26:3160–3167.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
- Examination Committee of Criteria for ‘Obesity Disease’ in Japan; Japan Society for the Study of Obesity. New criteria for ‘obesity disease’ in Japan. *Circ J*. 2002;66:987–992.
- Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol*. 2009;5:253–261.
- Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int*. 2006;23:497–509.
- Roepke SE, Duffy JF. Differential impact of chronotype on weekday and weekend sleep timing and duration. *Nat Sci Sleep*. 2010;2010:213–220.
- Mongrain V, Carrier J, Dumont M. Chronotype and sex effects on sleep architecture and quantitative sleep EEG in healthy young adults. *Sleep*. 2005;28:819–827.
- Gonnissen HK, Rutters F, Mazuy C, Martens EA, Adam TC, Westerterp-Plantenga MS. Effect of a phase advance and phase delay of the 24-h cycle on energy metabolism, appetite, and related hormones. *Am J Clin Nutr*. 2012;96:689–697.
- Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol*. 2012;22:939–943.
- Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA*. 2009;106:4453–4458.
- Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science*. 2005;308:1043–1045.
- Broms U, Kaprio J, Hublin C, Partinen M, Madden PA, Koskenvuo M. Evening types are more often current smokers and nicotine-dependent—a study of Finnish adult twins. *Addiction*. 2011;106:170–177.
- Sato-Mito N, Shibata S, Sasaki S, Sato K. Dietary intake is associated with human chronotype as assessed by both morningness-eveningness score and preferred midpoint of sleep in young Japanese women. *Int J Food Sci Nutr*. 2011;62:525–532.
- Kanerva N, Kronholm E, Partonen T, et al. Tendency toward eveningness is associated with unhealthy dietary habits. *Chronobiol Int*. 2012;29:920–927.
- Lucassen EA, Zhao X, Rother KI, et al. Evening chronotype is associated with changes in eating behavior, more sleep apnea, and increased stress hormones in short sleeping obese individuals. *PLoS One*. 2013;8:e56519.
- Baron KG, Reid KJ, Kern AS, Zee PC. Role of sleep timing in caloric intake and BMI. *Obesity (Silver Spring)*. 2011;19:1374–1381.
- Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovas JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. *Int J Obes (Lond)*. 2013;37:604–611.
- Bandin C, Scheer FA, Luque AJ, et al. Meal timing affects glucose

- tolerance, substrate oxidation and circadian-related variables: a randomized, crossover trial [published online October 14, 2014]. *Int J Obes (Lond)*. doi: 10.1038/ijo.2014.182.
40. **Fonken LK, Lieberman RA, Weil ZM, Nelson RJ.** Dim light at night exaggerates weight gain and inflammation associated with a high-fat diet in male mice. *Endocrinology*. 2013;154:3817–3825.
 41. **Fonken LK, Workman JL, Walton JC, et al.** Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci USA*. 2010;107:18664–18669.
 42. **Tahara Y, Shibata S.** Chronobiology and nutrition. *Neuroscience*. 2013;253:78–88.
 43. **Kim TN, Choi KM.** Sarcopenia: definition, epidemiology, and pathophysiology. *J Bone Metab*. 2013;20:1–10.
 44. **Srikanthan P, Hevener AL, Karlamangla AS.** Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PLoS One*. 2010;5:e10805.
 45. **Kawano Y.** Diurnal blood pressure variation and related behavioral factors. *Hypertens Res*. 2011;34:281–285.
 46. **Willis TA, O'Connor DB, Smith L.** The influence of morningness-eveningness on anxiety and cardiovascular responses to stress. *Physiol Behav*. 2005;85:125–133.
 47. **Polonsky KS, Given BD, Van Cauter E.** Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest*. 1988;81:442–448.