Depression-mediated effects of socioeconomic status on sleep quality and time-varying effects of sleep quality on hypertriglyceridemia

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Depression-mediated effects of socioeconomic status on sleep quality and time-varying effects of sleep quality on hypertriglyceridemia

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ABSTRACT

Depression-mediated effects of socioeconomic status on sleep quality and time-varying effects of sleep quality on hypertriglyceridemia

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Introduction

Sleep quality may deteriorate as a return of continuously being exposed to unfavorable environments such as depressive symptoms or impoverished social resources. Deteriorated sleep quality may eventually influence triglycerides related to increased insulin resistance or inflammation markers. However, previous studies did not observe the further changes in sleep quality according to the preceding factors (e.g., SES and depressive symptoms). Furthermore, although sleep quality changes over time, a single appraisal measurement was utilized to examine its impact on triglyceride.

Therefore, this study aimed to investigate the associations regarding sleep quality separately in two main parts. First, the current study aimed to examine how SES affects the changes in sleep quality, and further examine the mediation effect of depressive symptoms. Second, the study aimed to investigate whether time-dependent sleep quality affects hypertriglyceridemia onset.

PART I: Association between socioeconomic status and longitudinal sleep quality patterns mediated by depressive symptoms

We utilized data on 3,347 participants in the Korean Genome and Epidemiology Study aged 40–69 years who were followed up for 16 years from a baseline. A group-based modeling approach was used to identify sleep quality trajectories utilizing the Pittsburgh Sleep Quality Index, which was five times repeatedly measured over time. Educational attainment (college graduated or less), monthly household income (≥$2,500 or less) at baseline (year 0) were used for analyses. Depressive symptoms were assessed using Beck's Depression Inventory at year 4. Associations between SES and sleep quality patterns were examined using a multinomial logistic regression model, and PROC CAUSALMED was used to examine the mediation effect of depressive symptoms. Five distinct sleep quality trajectories were identified: "normal-stable" (n=1,697), "moderate-stable" (n=1,157), "poor-persistent" (n=320), "developing to poor" (n=84), and "severely poor-persistent" (n=89). Overall, associations between SES levels and longitudinal sleep patterns were not apparent after full adjustments for socio-demographic and lifestyle factors. Depressive symptoms, however, tended to fully mediate associations between SES levels and sleep quality patterns (odds ratio range for indirect effects of depressive symptoms: for education, 1.05–1.17; for income, 1.05–1.15). A significant mediating role for depressive symptoms between SES levels and longitudinal sleep

quality patterns warrants consideration among mental health care professionals.

PART II: Association between time-dependent sleep quality and hypertriglyceridemia onset

We utilized data on 1,773 participants (mean age: 49.8) with at least three times of repeated sleep quality data and without baseline dyslipidemia in the Korean Genome and Epidemiology Study. Poor sleep was determined as Pittsburgh Sleep Quality Index (PSQI) >7 according to the cut-offs for discriminating insomnia patients reported from the Korean validation study. Hypertriglyceridemia onset was defined as triglyceride ≥200 mg/dL during the study period. Survival curves according to the baseline sleep quality status were represented using the Kaplan-Meier curves. Extended Cox models using time-dependent sleep quality were conducted separately by sex to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) adjusting for demographics, biological, and lifestyle factors. During a median follow-up of 11.8 years, 233 male participants and 192 female participants developed hypertriglyceridemia. In women, those with the time-dependent poor sleep showed significantly higher hazards of hypertriglyceridemia onset compared to those with normal sleep quality (HR=1.53, 95% CI=1.07-2.17) after full adjustments. However, a significant association between time-dependent poor sleep and hypertriglyceridemia onset was not observed in men (HR=1.03, 95% CI=0.68-1.55). Adequate sleep quality needs to be considered for cardio-metabolic health in middle-aged women who maintain their lipid levels in normal range.

Conclusion

In primary care, maintaining adequate sleep quality may be suggested to middle-aged women with relatively healthy lipid levels, which may finally give benefit to their cardio-metabolic health. Furthermore, as a way to achieve this goal at the community level, it may be helpful to reconsider mental health care to preserve adequate sleep quality among middle-aged women especially those with low SES levels.

[Key words] longitudinal study, socioeconomic status, depressive symptoms, mediation analysis, insufficient sleep, hypertriglyceridemia, extended Cox model

I. INTODUCTION

1. *Background*

While the need for appropriate sleep quality has been recognized as a public health issue, plenty of the population still report sleep complaints [1,2]. From 2006 to 2013, the prevalence of insomnia increased from 3.9% to 6.2% according to a previous study using US Medicare data [1]. Meanwhile, in another study using a two-stage sampling method, 17% of a South Korean sample reported insomnia symptoms at least three nights per week (e.g., difficulty in waking up or maintaining sleep, etc.) [2].

Sleep quality has a feature of fluctuating nature over time [3], and previous studies reported physiological and psychological factors contributing to changes in sleep quality (Figure 1) [4-8]. Especially, it has been frequently mentioned that depressive symptoms are closely related to sleep quality [5]. In addition, beyond individual levels, socio-economic status (SES) is another important factor that may influence sleep quality [6,9]. People with low SES levels are more likely to experience stressful life events due to fewer economic or social resources, which may lead to depression or anxiety disorder [10]. Meanwhile, insomnia is a common comorbid or predictable condition of depressive symptoms [11,12]. As shown in previous studies, SES levels, depressive symptoms, and sleep quality are closely related to each other [9-13]. However, few studies considered their temporal trends; most of the previous studies investigated cross-sectional associations between SES levels, depressive symptoms, and sleep quality [6,9,12,14] which may limit the causal interpretation of study results. Moreover, the further development of sleep quality according to SES levels and depressive symptoms had not been known in previous studies.

As a return of continuously being exposed to unfavorable environments (e.g., depressive symptoms or impoverished social resources), sleep quality would deteriorate, and this may influence lipid levels (Figure 1) which could finally link to cardiovascular risk [15]. More specifically, triglyceride (TG) is likely to be influenced by sleep disturbance considering previous study results that reported the impact of poor sleep on insulin resistance or inflammation[16,17]. Overall poor sleep quality including longer sleep onset latency or frequent problems falling asleep had been reported to be associated with higher fasting insulin and inflammatory biomarkers[17], which are commonly accompanying by hypertriglyceridemia[18]. However, there still exist inconsistent results between sleep quality and TG levels [19-21]. A longitudinal study with 503 US participants aged 32-51 years from the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study reported that poor sleep quality (Pittsburgh Sleep Quality Index, PSQI > 5) at baseline was not associated with changes in lipid profiles [20]. On the other hand, there are several previous studies reported the deleterious impact of poor sleep quality on TG levels [21-23]. In a cross-sectional study with 1,956 post-menopausal women from the Women's Health Initiative (WHI) in the United States, self-reported habitual sleep quality (e.g., difficulty in initiating sleep, difficulty in maintaining sleep) was associated with lipid metabolites, which was linked to the elevated TG levels [21].

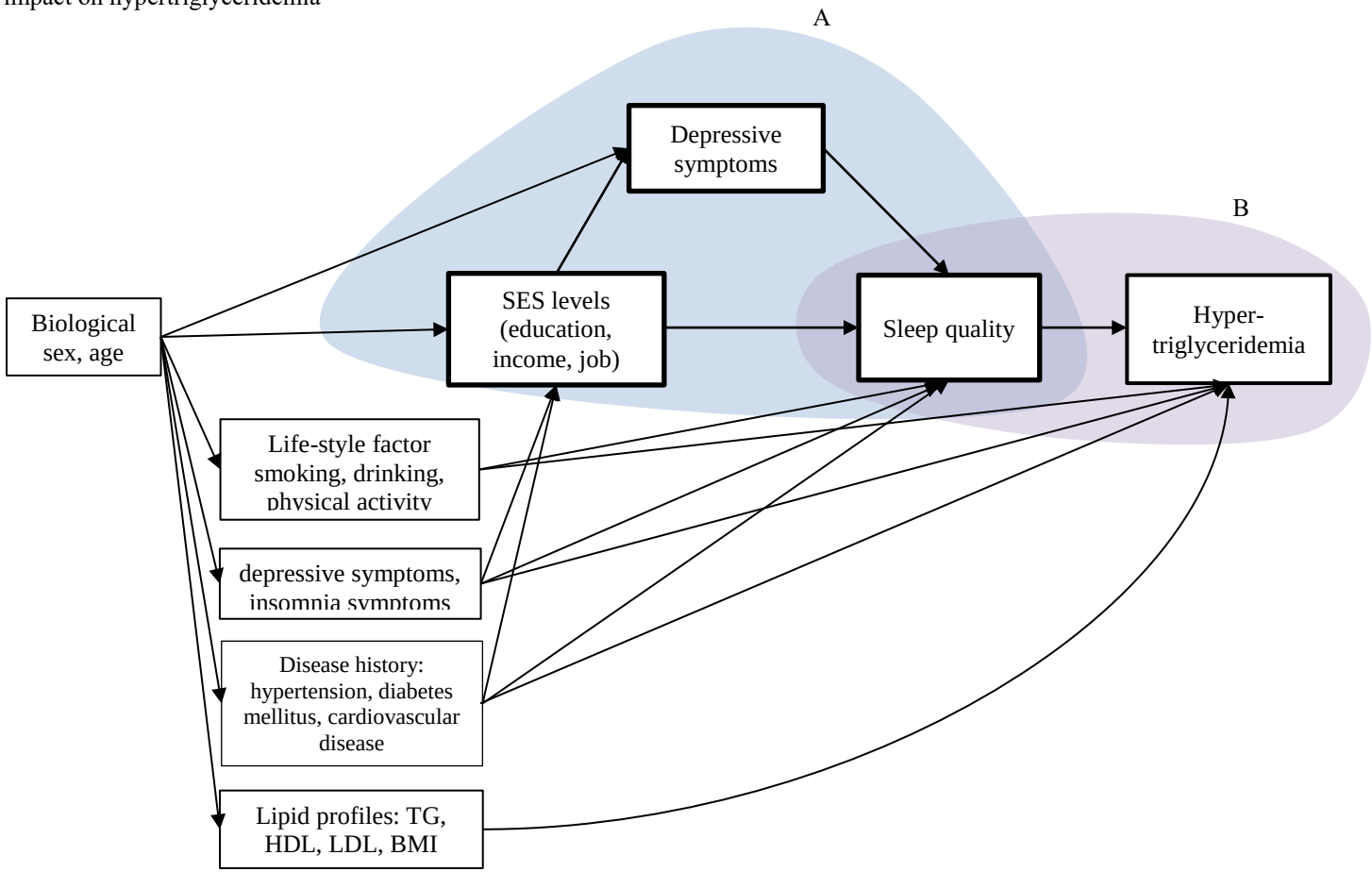
In common, previous studies investigating the impact of sleep quality on TG levels had several limitations. Limited sleep quality measurements (i.e., a single appraisal approach at baseline) were used [19,20,22] although sleep quality has a time-varying nature [3]. Additionally, even in a longitudinal study setting, sleep quality was evaluated in limited years (i.e., one year) [21]. These limitations may prevent the results from representing the full sustained effect of sleep quality. Moreover, although a meta-analysis using 13 prospectively investigated studies with the general population reported null results for the negative impact of sleep disturbance on lipid levels [24], a small number of studies (i.e.,

only four of the previous studies utilized sleep quality for representing sleep disturbance) and their heterogeneity (i.e., different tools to measure sleep quality) limit the interpretation. Given inconsistent results, more studies with sleep quality reflecting its time-dependent characteristics are required to yield more definitive answers.

2. *Objective of the study*

Therefore, our research questions deal with two main parts regarding sleep quality; the development of sleep quality over time according to SES levels and depressive symptoms (Figure 1-A) and the impact of sleep quality on hypertriglyceridemia (Figure 1-B). More specifically, in the first part, the current study aimed to identify the association between SES and longitudinal sleep quality patterns, and further examine the mediation effect of depressive symptoms between the association. In the latter part, regarding the impact of sleep quality on TG levels, the current study aimed to investigate the association between sleep quality and the hypertriglyceridemia onset considering its time-varying nature as revealed in previous studies.

Figure 1. A hypothetical diagram depicting socioeconomic status and depressive symptoms that affect sleep quality, and its consecutive impact on hypertriglyceridemia



PART I. Association between socioeconomic status and longitudinal sleep quality patterns mediated by depressive symptoms

II. MATERIALS AND METHODS

1. *Data and study participants*

In the current study, data from Ansan-KoGES were utilized. Detailed information of the data has been previously reported [25]. In total, 5,012 participants aged 40–69 years with residence in the Ansan region, an industrialized community, were recruited between 2001 and 2003. All participants underwent baseline examinations and were followed up biennially up to the 7th follow-up survey. In the present study, we used the participants' baseline examination data and data from five repeated surveys of sleep quality information, which were conducted at years 2, 6, 8, 10, and 12 (Figure 2). The attrition rates were 80.3% (n=4,023), 64.9% (n=3,255), 65.1% (n=3,262), 60.9% (n=3,052), and 59.9% (n=3,000) at years 2, 6, 8, 10, and 12, respectively. We excluded participants who were only included in the baseline study (n=680), those without sleep quality data (n=51), or those included in less than three surveys on sleep quality (n=932). Lastly, participants who had missing data on educational attainment and monthly household income (n=2) were also excluded. Hence, only 3,347 participants (1,701 men and 1,646 women) were included in the final analyses. Details on the exclusion criteria are provided in Figure 3. The final study samples completed three (n=464, 13.9%), four (n=773, 23.1%), or five (n=2,110, 63.0%) of the sleep quality surveys.

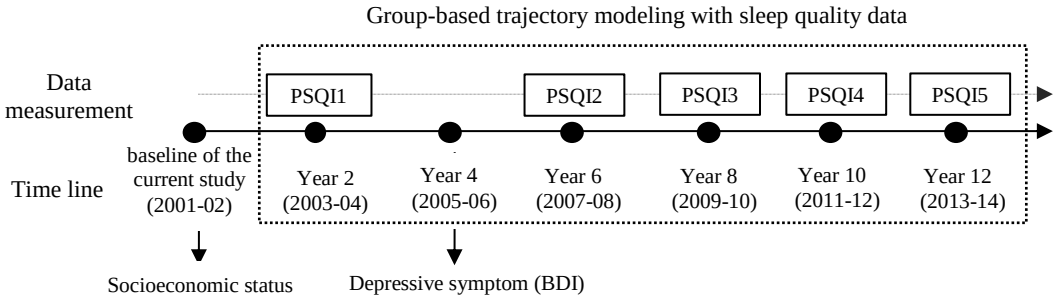


Figure 2. Timeline of the current study using KoGES data (Part I).

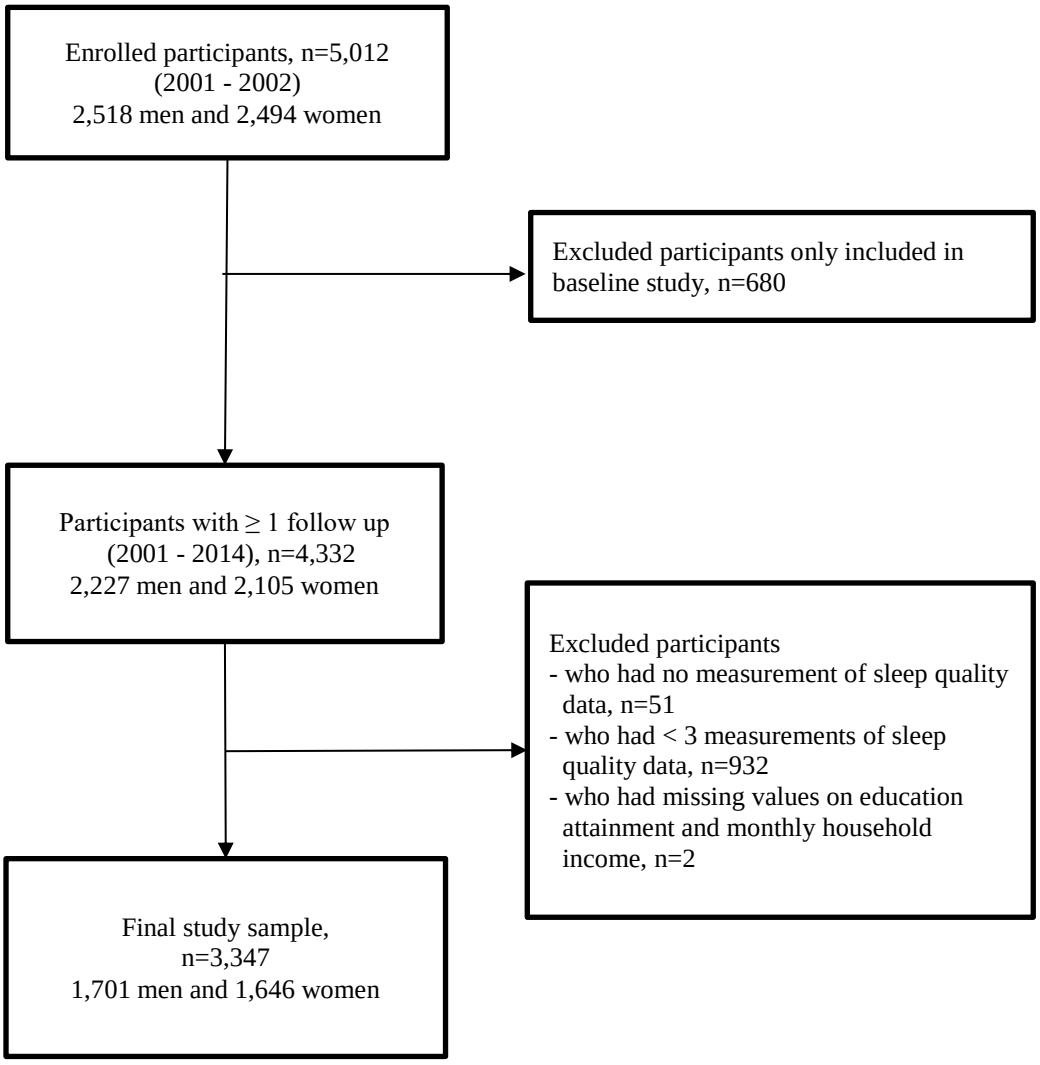


Figure 3. Flow chart of the selection of study participants in the Korean Genome and Epidemiology Study, Ansan (Part I).

2. *Measurements*

Assessment of exposure variables: socioeconomic status

Participants were asked to answer questions about their educational attainment and monthly household income. Educational attainment was initially queried as "elementary or less," "middle school," "high school," "college," "university," or "graduate school or above." Monthly household income was initially queried as follows: "<$400," "$400 to <800," "$800 to <$1,250," "$1,250 to <$1,650," "$1,650 to <$2,500," "$2,500 to <$3,300," "$3,300 to <$5,000," or "≥ $5,000," which were converted from Korean won to United States (US) dollar. For feasible interpretation, first, educational attainment was divided into two groups (lower attainment: high school or less; higher attainment, reference: college or above) considering the high enrollment rates (passed 90% since 1994) for high schools in Korea [26]. Second, monthly household income was also divided into two groups (lower income: <$2,500; higher income, reference: ≥$2,500). We utilized $2,500 (3,000,000, KRW) as a proxy for the highest tertile of household income, consistent with previous studies [27,28]. Lastly, occupation was classified into "unemployed," "manual labor," and "professional labor" [29]. Homemakers, etc. were classified as "unemployed"; office workers and expertise were classified as "professional laborers"; others were classified as "manual laborers." (Appendix Table 1).

Assessment of outcome variable : sleep quality trajectory

The overall sleep quality was assessed using global PSQI scores, which have been validated in the Korean population (Cronbach's alpha coefficient of 0.84, the sensitivity of 0.94, and specificity of 0.84, with a cut-off value of 8.5)[30]. The PSQI is an 18-item measure of self-reported sleep quality

and duration that evaluates sleep over the previous 4 weeks. Global PSQI scores (range, 0–21) consist of seven subdomain component scores, including those for sleep quality perception, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction, with the scores of each item ranging from 0 to 3. Higher PSQI scores indicate worse sleep quality and duration. Normally, a PSQI total score ≤ 5 is considered the threshold for "good" sleep quality, whereas a PSQI total score > 5 indicates "poor" sleep quality [31].

Assessment of potential mediators: depressive symptoms

We assumed depressive symptoms at year 4 as a potential proxy mediator between SES and longitudinal sleep quality patterns. Depressive symptoms were assessed using the Beck Depression Inventory (BDI), which has been validated in the South Korean population [32] (Cronbach's alpha coefficient of ≥0.87, the sensitivity of 0.78, and specificity of 0.77, with a cutoff value of 13). The BDI consists of 21 items, and each item is rated on a 3-point Likert scale, with a total score of 63. This tool is used to assess depressive symptoms over the most recent 2 weeks. Higher scores indicate severe depressive symptoms.

Assessment of covariates

In the KoGES, all participants provided their demographic information, personal health history, and lifestyle factors. Marital status was categorized into "never married," "currently married," and "separated, divorced, or widowed." The number of family members was reported. More than 15.0 metabolic equivalent (MET) hours/week were categorized as "moderate exercise." [33]. Disease

diagnosis included hypertension, diabetes mellitus, cardiovascular (cerebrovascular disease, chronic heart failure, coronary artery disease), and cancer. Disease-specific self-reported diagnosis by a physician or taking disease-specific medication was considered as baseline disease diagnosis. In terms of drinking and smoking status, participants were classified as current, former, or none. Baseline insomnia symptoms were determined by positive responses to the question, “Do you have insomnia?” And baseline depressive symptoms were determined by positive responses to the question, “Are you feeling depressed?” Physical examinations, including measurements of body size, composition, and blood pressure, were conducted by trained research personnel. Biochemical analyses of blood samples obtained after 8-hour fasting were performed.

3. *Statistical analyses*

Group-based trajectory analysis modeling

Sleep quality trajectories were modeled among all 3,347 KoGES study participants, with the PSQI measured in at least three examinations [34]. We used latent class growth modeling, a group-based modeling approach (SAS Proc Traj), to identify subgroups that share a similar underlying trajectory in sleep quality [35]. The model assumes that the population consists of multiple trajectory groups, rather than simply fitting the overall population mean [36]. We used a censored normal model with PSQI scores, and the time scale was age during the survey examination [35]. A group-based trajectory method is a statistical method for analyzing the evolution of an outcome over age or time [37]. As aging is one of the prominent factors affecting sleep quality [38], we chose age as a time scale for investigating sleep quality patterns: for example, 10-year sleep quality changes in individuals aged 40 to 50 years cannot be treated equally as changes in individuals aged 60 to 70 years. Bayesian information criteria were used to determine the optimal number and shapes of the trajectory groups: a smaller value indicated a better model fit [36]. We calculated the posterior predicted probability for each participant of the five trajectory groups and assigned them to the trajectory group with the greatest posterior probability of membership [39]. The average posterior probabilities of ≥ of 0.70 for each trajectory group indicate high internal reliability within each trajectory and sufficient discrimination of individuals with different sleep quality patterns between trajectories [40].

Descriptive Analyses and Multinomial Logistic Regression Model

We used the analysis of variance for normally distributed continuous variables, the Kruskal–Wallis test for skewed distributed variables, and the chi-square test for categorical variables to compare the baseline characteristics of participants in the five sleep quality trajectory groups. We used a multinomial logistic regression model to estimate the associations between baseline SES and trajectory groups of sleep quality. The model evaluated whether SES affects the sleep quality trajectory groups, and odds ratios (OR) with 95% confidence intervals (CIs) were calculated. The associations between baseline SES indices (education, income, and occupation) and sleep quality trajectory groups were analyzed. Potential common confounding factors were chosen based on the literature review: biological sex [41,42], age [41,42], life-style factors [43] (drinking, smoking, moderate exercise), marital status[44], number of family members, and disease diagnosis[45,46]. All adjusted covariates were obtained from baseline survey data. Additionally, baseline insomnia/depressive symptoms were adjusted considering their time-varying nature [47]. Lastly, educational attainment and occupation were further adjusted when monthly household income was used as the exposure variable and vice versa.

Mediation analysis

We used mediation models (SAS PROC CAUSALMED) to assess the potential mediation effect of depressive symptoms on the association between baseline SES and longitudinal sleep quality patterns [48]. The outcome variable, sleep quality pattern, was dichotomized (normal-stable vs. moderate-stable, normal-stable vs. poor-persistent, normal-stable vs. developing to poor, and

normal-stable vs. severely poor-persistent) because of its limitation in the statistical procedure [48]. PROC CAUSALMED estimates causal mediation effects and confidence intervals for the effects based on the maximum likelihood estimates. Alternatively, we utilized 1,000 bootstrap resampling to compute confidence intervals for causal mediation effects considering our small sample sizes (e.g., developing to poor trajectory categories) [49]. The factors adjusted in the mediation analyses were the same as those in the main analyses. Lastly, percentages of the total effect that are attributed to mediation and interaction, and the percentage of the total effect eliminated by controlling the mediator level were also calculated [48].

Sensitivity analyses

We conducted sensitivity analyses with BDI scores calculated without sleep-related items to confirm the robustness of our findings. First, the corresponding scores for the following responses were deleted: “I don't sleep as well as I used to,” “I wake up 1-2 hours earlier than usual and find it hard to get back to sleep,” or “I wake up several hours earlier than I used to and cannot get back to sleep.” Additionally, whether changes in household income [e.g., “persistently low (n=1,797),” “low to high (n=422),” “high to low (n=288),” “persistently high (n=684, reference)”] affects the depressive symptoms and sleep quality patterns, we evaluated the association between the changes in household income and longitudinal sleep quality patterns and whether the depressive symptoms still mediate the association. Owing to small sizes of sleep quality pattern groups, we re-classified participants into “normal-stable (n=1,619)”, “moderate-stable (n=1,107)”, “persistently or developing to poor (n=465).”

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-sided P-value of <0.05 was considered significant.

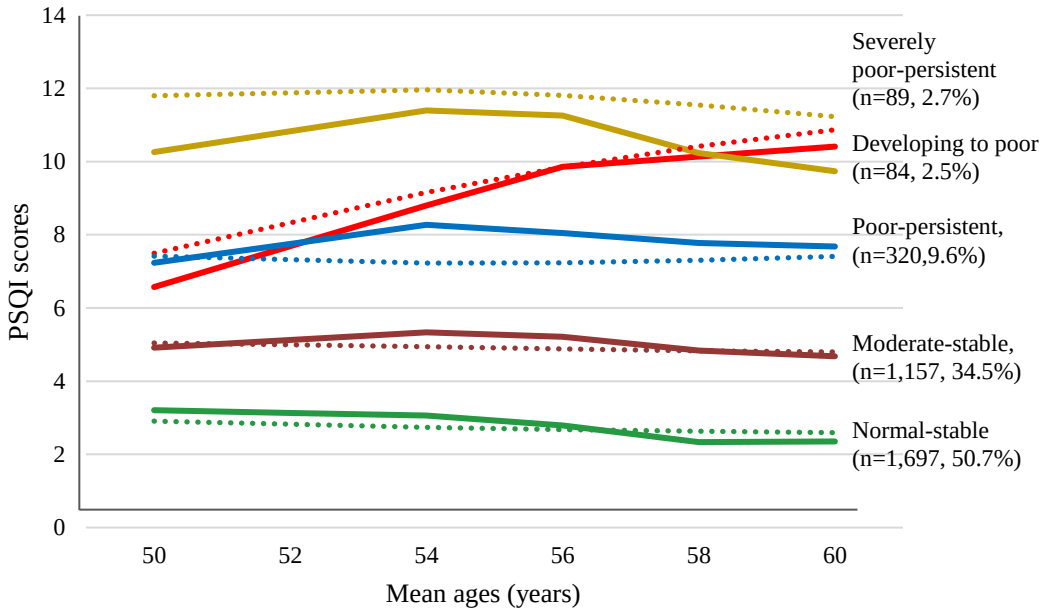
Ethics

Data in this study were from the Korean Genome and Epidemiology Study (KoGES; 4851-302), National Research Institute of Health, Centers for Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. This study was approved by the institutional review board of Severance Hospital at Yonsei University College of Medicine (Y-2020-0218).

III. RESULTS

1. *Longitudinal sleep quality patterns among middle-aged Korean population*

We identified five distinct sleep quality trajectories in the middle-aged South Korean participants (Figure 4). Of the 3,347 participants, 1,697 (normal-stable, 50.7%) had low PSQI scores, 1,157 (moderate-stable, 34.5%) had moderate PSQI scores, 320 (poor-persistent, 9.6%) had poor PSQI scores, 84 (developing to poor, 2.5%) had increasingly poorer PSQI scores, and 89 still had severely high PSQI scores (severely poor- persistent, 2.7%). The average posterior probabilities for all trajectory groups were ≥0.70 (normal-stable: 0.88, moderate-stable: 0.78, poor-stable: 0.77, developing to poor: 0.77, and severely poor-stable: 0.82).



*Observed means are presented as solid lines and expected means are presented as dashed lines.

Figure 4. Trajectory groups of sleep quality over 12 years.

2. *Baseline characteristics of the study participants according to sleep quality patterns*

Table 1 presents the descriptive characteristics of study participants stratified according to the sleep quality trajectory. The participants in the poor-persistent, developing to poor, and severely poor-persistent groups were more likely to be women, older, have lower education and lower household income than those in the normal-stable group. They were also more likely to be depressed at year 4 and to have shorter sleep durations and higher means of PSQI scores than those in the normal-stable group. No statistical differences were observed in the disease diagnosis, body mass index, and biologic markers at baseline among the sleep quality groups.

Table 1. Baseline characteristic of participants according to trajectories of sleep quality

Baseline Characteristics	Sleep quality patterns determined by PSQI scores					p-value
	Normal-stable (n=1,697)	Moderate-persistent (n=1,157)	Poor-persistent (n=320)	Developing to poor (n=84)	Severely poor-persistent (n=89)	
Men, %	984 (58.0)	555 (48.0)	111 (34.7)	21 (25.0)	30 (33.7)	<.001
Age,years	47.94±7.11	49.09±7.38	50.04±7.77	49.64±7.24	49.44±8.05	<.001
Mean of PSQI scores (0-21)[1]	2.67±1.61	5.2±0.85	8.11±1.05	9.56±2.2	10.82±1.85	<.001
Beck's Depression Inventory[2]	5 [2-9]	7 [4-12]	9.5 [6-15]	10 [7-16]	14 [7-20]	<.001
Education, %						
Lower: high school or less	1,295 (76.4)	891 (77.0)	275 (85.9)	77 (91.7)	79 (89.8)	<.001
Higher: college or above	400 (23.6)	266 (23.0)	45 (14.1)	7 (8.3)	9 (10.2)	
Monthly household income, %						
< $2,500	1,144 (67.8)	799 (69.6)	238 (75.1)	67 (79.8)	71 (79.8)	0.004
≥ $2,500	544 (32.2)	349 (30.4)	79 (24.9)	17 (20.2)	18 (20.2)	
Occupation, %						
Unemployment (homemaker or etc.)	840 (49.6)	659 (57.1)	227 (71.4)	57 (67.9)	58 (65.2)	<.001
Manual labor	590 (34.8)	343 (29.7)	64 (20.1)	22 (26.2)	25 (28.1)	
Professional labor	265 (15.6)	152 (13.2)	27 (8.5)	5 (6.0)	6 (6.7)	
Sleep drug intake[3], %	42 (2.5)	63 (5.5)	44 (13.8)	15 (18.3)	31 (34.8)	<.001
Sleep duration, hour	6.9±1.12	6.52±1.22	6.14±1.28	6.22±1.63	6.18±1.55	<.001
Currently Married, %	1,622 (95.6)	1,082 (93.5)	289 (90.3)	81 (96.4)	83 (93.3)	0.011
Currently Smoking, %	419 (24.8)	222 (19.1)	65 (20.4)	11 (13.3)	17 (19.1)	<.001
Currently Drinking, %	910 (53.7)	604 (52.2)	148 (46.3)	36 (42.9)	38 (42.7)	0.013
Moderate exercise, %	648 (38.6)	448 (39.4)	134 (42.1)	26 (32.5)	38 (43.2)	0.481

Disease diagnosis[4], %	326 (19.2)	253 (21.8)	75 (23.1)	21 (25.0)	20 (22.5)	0.234
BMI,kg/m²	24.67±2.83	24.81±2.89	24.65±2.97	24.48±2.92	24.69±2.69	0.676
Total cholesterol,mg/dL	196.12±35.3	196.69±35.7	195.74±33.56	193.74±32.7	192.78±34.89	0.821
HDL cholesterol,mg/dL	44.36±9.52	44.84±10.01	45.28±9.59	45.61±9.98	46.15±9.48	0.187
LDL cholesterol,mg/dL	121.27±31.43	121.28±30.82	120.21±30.96	117.04±29.15	120.51±32.49	0.777
SBP,mmHg	116.34±16.12	116.63±16.85	116.47±17.73	117.39±17.62	114.01±16.48	0.665
DBP,mmHg	78.27±11.19	77.91±11.05	77.12±11.64	77.86±12.26	76.45±11.65	0.320
Triglyceride,mg/dL	132 [97-186]	134 [97-186]	140 [97-187]	138 [100-189]	121 [89-158]	0.173
HbA1c,%	5.5 [5.3-5.8]	5.6 [5.3-5.8]	5.5 [5.3-5.8]	5.5 [5.3-5.8]	5.5 [5.3-5.9]	0.631
Fasting insulin,uIU/mL	6.8 [5.0-9.1]	6.9 [5.1-9.2]	6.6 [4.7-9.0]	7.1 [5.0-9.6]	6.5 [5.0-8.8]	0.437
Fasting glucose,mg/dL	83 [78-91]	83 [78-92]	82 [77-88]	83.5 [77-90]	82 [76-90]	0.226
High-sensitivity C-reactive protein	0.14 [0.07-0.23]	0.13 [0.06-0.23]	0.14 [0.06-0.25]	0.15 [0.06-0.23]	0.09 [0.04-0.18]	0.099

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c.
1.mean of repeatedly-measured PSQI scores during study follow-up.
2.assessed at years 4.
3.including past and current users.
4.including cardiovascular disease (coronary artery, myocardial infarction, and cerebrovascular diseases), hypertension, diabetes, dyslipidemia, and cancer.

3. *Association between baseline SES levels and sleep quality patterns*

Table 2 shows the associations between baseline education/monthly household income and sleep quality trajectory groups. Overall, SES level indicators did not show apparent associations with longitudinal sleep quality patterns in both education level (moderate-stable: odds ratio [OR]=0.83, 95% confidence interval [95% CI]=0.68–1.01; poor-persistent: OR=1.08, 95% CI=0.74–1.58; developing to poor: OR=2.04, 95% CI=0.84–4.95; and severely poor-persistent: OR=1.41, 95% CI=0.66–2.99) and household income level (moderate-stable: OR=0.98, 95% CI=0.82–1.17; poor-persistent: OR=1.06, 95% CI=0.78–1.43; developing to poor: OR=1.33, 95% CI=0.74–2.40; and severely poor-persistent: OR=1.50, 95% CI=0.84–2.67). In addition, the overall association between occupation and longitudinal sleep quality was not observed (Appendix Table 2)

Table 2. Association between socioeconomic status (education attainment/monthly household income) and sleep quality patterns

Socioeconomic status	Trajectory groups of sleep quality											
	Moderate-stable (n=1,157) vs Normal-stable (n=1,697, ref)			Poor-persistent (n=320) vs Normal-stable (n=1,697, ref)			Developing to Poor (n=84) vs Normal-stable (n=1,697, ref)			Severely poor--persistent (n=89) vs Normal-stable (n=1,697, ref)		
	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)
Education attainment*												
Lower attainment[1] (n=2,617)	891	0.83	(0.68 - 1.01)	275	1.08	(0.74 - 1.58)	77	2.04	(0.84 - 4.95)	79	1.41	(0.66 - 2.99)
Higher attainment[2] (n=727)	266	1.00	reference	45	1.00	reference	7	1.00	reference	9	1.00	reference
Monthly household income†												
Lower income[3] (n=2,319)	799	0.98	(0.82 - 1.17)	238	1.06	(0.78 - 1.43)	67	1.33	(0.74 - 2.40)	71	1.50	(0.84 - 2.67)
Higher income[4] (n=1,007)	349	1.00	reference	79	1.00	reference	17	1.00	reference	18	1.00	reference

1. High school or less
2. College or above
3. < $2,500
4. ≥ $2,500

*Adjustments for sex, age, job, monthly household income, drinking, smoking, moderate exercise, marital status, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

†Adjustments for sex, age, job, education attainment, drinking, smoking, moderate exercise, marital status, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

4. *Mediation effect of depressive symptom between SES and sleep quality patterns*

The mediation effects of depressive symptoms between SES (education/monthly household income) and longitudinal sleep quality patterns are presented in Table 3. There were no direct or total effects of educational attainment on longitudinal sleep quality. However, there were indirect effects of lower educational attainment on longitudinal sleep quality through depressive symptoms (moderate-stable: OR=1.05, 95% CI=1.01–1.09; poor-persistent: OR=1.10, 95% CI=1.03–1.19; developing to poor: OR=1.13, 95% CI=1.05–1.26; and severely poor-persistent: OR=1.17, 95% CI=1.05–1.31). Similarly, lower household income was indirectly associated with worse sleep quality through the depressive symptoms (moderate-stable: OR=1.05, 95% CI=1.02–1.09; poor-persistent: OR=1.09, 95% CI=1.03–1.16; developing to poor: OR=1.09, 95% CI=1.03–1.18; and severely poor-persistent: OR=1.15, 95% CI=1.05–1.26).

However, no significant mediating role of depressive symptoms was found for the associations between occupation and longitudinal sleep quality (Appendix Table 3). Percentage mediated, due to interaction, and eliminated are provided in Appendix Table 4. If the mediated effect has a different sign than other direct effects in a model, the absolute values of the direct and indirect effects should be considered before calculating the proportion mediated [35] (e.g., lower income; OR for the direct effect of SES:0.98, OR for the indirect effect of SES through depressive symptom:1.05).

Sensitivity analyses with BDI scores eliminating the sleep-related items were similar to the main results (Appendix Table 5). Another sensitivity results with changes in income showed similar results with main analyses; participants with “persistently low income” or “high to low income”

were indirectly associated with “persistently or developing to poor” sleep quality through depressive symptoms (Appendix Table 6, 7).

Table 3. Association between socioeconomic status and sleep quality patterns mediated by depressive symptom at years 4

Socioeconomic status	Trajectory groups of sleep quality									
	Normal-stable (reference, n=1,697)		Moderate-persistent (n=1,157)		Poor-persistent (n=320)		Developing to Poor (n=84)		Severely poor-persistent (n=89)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Education attainment*										
Lower attainment[1] (n=2,617) vs Higher attainment[2] (ref, n=727)										
Total effect	1.00	reference	0.80	(0.64 - 1.00)	1.15	(0.73 - 1.85)	1.59	(0.62 - 5.59)	2.82	(0.98 - 8.58)
Natural direct effect	1.00	reference	0.76	(0.62 - 0.96)	1.04	(0.68 - 1.69)	1.41	(0.57 - 4.75)	2.41	(0.91 - 7.30)
Natural indirect effect	1.00	reference	1.05	(1.01 - 1.09)	1.10	(1.03 - 1.19)	1.13	(1.05 - 1.26)	1.17	(1.05 - 1.31)
Monthly household income†										
Lower income[3] (n=2,319) vs Higher income[4] (ref, n=1,007)										
Total effect	1.00	reference	0.98	(0.82 - 1.20)	0.99	(0.71 - 1.39)	1.02	(0.51 - 2.34)	1.24	(0.58 - 3.00)
Natural direct effect	1.00	reference	0.93	(0.78 - 1.15)	0.90	(0.65 - 1.28)	0.93	(0.48 - 2.18)	1.07	(0.51 - 2.60)
Natural indirect effect	1.00	reference	1.05	(1.02 - 1.09)	1.09	(1.03 - 1.16)	1.09	(1.03 - 1.18)	1.15	(1.05 - 1.26)

Notes: 395 data were deleted due to no measurements of BDI scores at years 4
1. High school or less
2. College or above
3. < $2,500
4. ≥ $2,500
*Adjustments for sex, age, job, monthly household income, drinking, smoking, moderate exercise, marital status, disease diagnosis, insomnia symptom, and depressive mood at baseline
†Adjustments for sex, age, job, education attainment, drinking, smoking,, moderate exercise, marital status, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

IV. DISCUSSION

1. *Summary of findings*

We attempted to examine the preceding factors affecting sleep quality and the impact of sleep quality on cardio-metabolic health, especially focusing on longitudinal sleep quality. First, regarding factors affecting sleep quality, we identified five distinct trajectories of sleep quality over 12 years in a middle-aged Korean adult population: normal-stable, moderate-stable, poor-persistent, developing to poor, and severely poor-persistent patterns. Although there were no significant overall or direct associations between SES levels and longitudinal sleep quality patterns, depressive symptoms fully mediated the association between SES (education attainment and monthly household income) and longitudinal sleep quality patterns.

2. *Comparisons with previous studies*

Changes in sleep quality overtimes

The prevalence of insomnia symptoms in the present study was similar to that reported in a previous South Korean population study [2]. In the current study, 15% of the participants experienced deleterious changes in their sleep quality or maintained poor sleep quality. Consistent with our results, 20% of 5,000 South Korean individuals aged 20–69 years, who were included in a study using a stratified, multistage random sampling method based on the geographical region, residence, sex, age, occupation, and income, reported insomnia symptoms (i.e., difficulty in waking up or getting back to sleep at night) [2]. Changes in sleep quality (developing to poor) among people with

insomnia symptoms were also in line with the findings of a previous study [3]. Among 250 Canadian individuals, changes in sleep quality in people with insomnia were investigated during 3 years; one-half of the sample with insomnia at baseline experienced good sleep quality at least once, while some of them eventually developed insomnia during subsequent assessments [3]. In addition, participants in the developing to poor and severely poor-persistent groups in this study were more likely to be women and older than those in other sleep pattern groups. In support thereof, research has shown that aging is a prominent factor that affects sleep quality and that women have a higher prevalence of insomnia than men in general [38].

SES levels and longitudinal sleep quality patterns

In current analyses, the overall association between SES level and longitudinal sleep quality patterns over 12 years was not apparent, which did not align with previous studies [6,50]. In a cross-sectional study of 301 women aged ≥55 years, higher education attainment was associated with reduced sleep latency based on PSQI scores [50]. Additionally, researchers have shown that highly educated people have higher chances of access to obtaining greater knowledge about sleep hygiene practices and strategies that can improve their sleep environment, as well as better recognition of the importance of sleep for health [14,51]. Therefore, highly educated people may proactively seek help for their sleep problems [51]. In addition, among 160,000 participants aged ≥18 years from 36 states/regions across the US, people with lower SES frequently reported sleep complaints, such as trouble falling asleep or staying asleep, in a cross-sectional manner [6]. Notwithstanding, these previous studies only presented the cross-sectional associations between the level of SES and sleep quality [6,14,50], whereas we investigated the further impact of SES levels on sleep quality changes.

Depressive symptoms mediating the SES and sleep quality

In this study, depressive symptoms significantly mediated the association between SES level (education/household income) and longitudinal sleep quality. These findings suggest that low SES can decrease sleep quality over time through depressive symptoms, even in a population wherein a link between SES and sleep quality is not observable. Several previous studies have reported that people with lower education or income are more likely to be depressed [10] and that lower education or income may affect sleep quality [5]. According to a community-based longitudinal study of 7,000 populations from California, SES measured by education or income presented dose-response relationships with prevalent and incident depression status [52]. This could be due to economic stress or disadvantages across the life course that people with lower SES may experience [53]. Approximately 14%–21% of people with insomnia were reported to experience major depression in two community-based epidemiological studies, compared to those without sleep complaints [54]. This could be supported by the findings of our study in that participants with worse sleep quality patterns had higher BDI scores at year 4, which indicate more severe depressive symptoms. Based on the cross-sectional understanding of SES or mood status effects on sleep quality, we further reported the impact of lower SES levels and depressive symptoms related to longitudinal poor sleep quality.

3. Confounding assumptions in causal mediation analyses

There are confounding assumptions that should be considered when using causal mediation analyses [55]. First, control must be made for exposure-outcome. Second, control must be made for

exposure-mediator. According to the literature review, sex, age, marital status, disease diagnosis (e.g., hypertension, diabetes mellitus, cardiovascular diseases, and cancer) would act as confounders on SES and sleep quality or on SES and depressive symptoms. Women [41], old age [42], and chronic diseases[45,46] have been closely related to worse sleep quality or depressed mood, and married status has a protective impact on those factors overall [6,44]. Third, no mediator-outcome confounder that is itself affected by the exposure should be warranted. Lifestyle habits[43] (e.g., drinking, smoking, and moderate exercise), which may act as confounders in this link, were additionally controlled. People with lower SES are more likely to be under circumstances to have unhealthy lifestyle due to experiencing of frequent stressful events[53], and this may affect depressive symptoms and sleep quality[4]. Although lifestyle habits were controlled, there is a possibility of residual confounding of measurement errors in self-reported lifestyle habits. Additionally, neighborhood environments also might act as confounders in the association between SES, depressive symptoms, and sleep quality [56].

4. Strengths and limitations

The strengths of this study are the prospective nature of the study and the repeated assessments of validated sleep quality data over 12 years. Furthermore, we investigated the longitudinal changes of sleep quality; since previous studies utilized limited assessments of sleep quality [14,57] and limited observation time [3], it was difficult to report longitudinal sleep quality changes. In addition, we presented the mediation effect of depressive symptoms in the association between baseline SES and longitudinal sleep quality patterns. However, several limitations need to be considered. First, the observational study design may limit causal inference of the association between SES and sleep

quality patterns mediated by depressive symptoms. However, since we assumed that depressive symptoms at year 4 would be a potential mediator, the temporality of the association may give benefits to the causality of the association [58]. Second, we could not find a significant association between occupation, depressive symptoms, and longitudinal sleep quality. However, the cultural context of Korea may explain the null results for occupation: women are primarily in charge of housework in Korea, and this may lead to differing distributions in occupation [59]. This could be supported by our data in that almost 68% of women were included as "homemakers," whereas around 67% of men were categorized as manual labor or professional labor (Appendix Table 1). However, we could not conduct analyses stratified by sex due to small sample sizes. Therefore, utilizing an occupational classification as a socioeconomic indicator may not adequately capture disparities in working conditions across sex [60]. Furthermore, people who are not currently employed (i.e., homemakers) are not easily assigned to occupation classification [60]; for example, homemakers and retired persons cannot be simply placed together with the "unemployed." Considering the sex-specific nature of the occupation, we may not have completely reflected all aspects thereof as a proxy for SES level in our data. Third, the study results should be interpreted with caution with regard to generalizability. The participants of our study are representative of Ansan city, an industrialized community in South Korea; therefore, it would be difficult to generalize the study results to all middle-aged Korean adults. The study participants tended to be of higher socioeconomic status and have healthier lifestyle habits, compared to the national representative sample for Korea [61] (Appendix Table 8). Fourth, residual confounding may still exist, even though we have adjusted sex considering its different proportion in each sleep pattern. There might be a chance to conceal the influence of lifestyle behavior which is highly correlated to sex (e.g., current smoking or alcohol drinking) on sleep and mood, and that may partially affect the generalizability of the findings. Additionally, the mediator-outcome confounder that is itself affected by the exposure

[55] may not be fully satisfied due to residual confounding (i.e., measurements errors of self-reported lifestyle habit). Moreover, neighborhood environments according to SES levels, which had been reported to be associated with depressive symptoms or sleep quality[56], could not be controlled. Fifth, although we used longitudinal data within the 12 years, sleep quality patterns were derived using a limited number of sleep quality measurements. However, sleep quality changes, especially those in people with insomnia [3], were reflected in our findings on sleep quality patterns. In addition, trajectory groups in our study showed posterior probabilities ≥ of 0.7, which indicates sufficient discrimination of the participants in each trajectory group. Finally, not all participants had available PSQI information at all examination periods. However, missing PSQI data (i.e., three or four measurements of sleep quality) are unlikely to have altered our findings, as the mean number of PSQI measurements was 4.3 to 4.6 according to sleep quality trajectory groups.

PART II: Association between time-dependent sleep quality and hypertriglyceridemia onset

II. MATERIALS AND METHODS

1. *Data and study participants*

The participants of the present study were part of the Korean Genome and Epidemiology Study (KoGES), which is an ongoing, population-based cohort study. Detailed information on the study design and aims of the KoGES have been previously reported [25]. In total, 5,012 participants aged 40–69 years with residence in the Ansan region, an industrialized community, were recruited between 2001 and 2003. Registered residents in Ansan were randomly selected and contacted via mail, telephone, or home visits for selecting representative samples [25]. All participants underwent examinations between 2001 and 2002 and were followed up biennially up to the 7th follow-up (2015-2016) survey. In the present study, since we utilized a sub-cohort of Ansan-KoGES due to the availability of sleep quality data, the baseline of the current study corresponded to 1st follow-up (Figure 5).

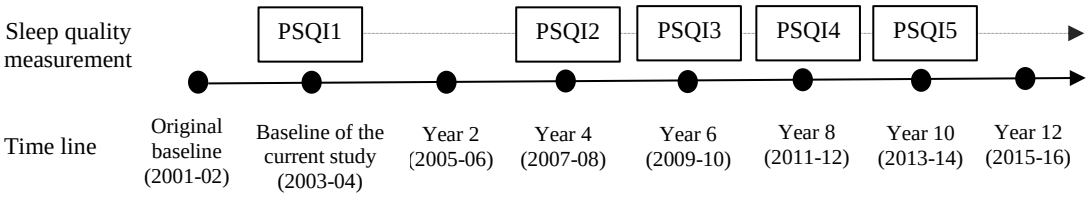


Figure 5. Timeline of the current study using Ansan-KoGES data (Part II).

First, a total of 3,696 participants (men: 1,982, women: 1,714) with sleep quality data assessed by the PSQI scores at baseline were utilized in a cross-sectional study after excluding those without sleep quality data at baseline (n=41), lipid profiles (n=48), and menopausal status in women (n=163). Second, for testing the impact of time-dependent sleep quality, we further excluded participants < 3 measurements of sleep quality (n=592). Lastly, participants with dyslipidemia at baseline (TG≥200 mg/dL, HDL<40 mg/dL, or LDL≥160 mg/dL) were excluded (n=1,331) since dyslipidemia patients are more likely to receive pharmacologic or non-pharmacologic intervention (i.e., lifestyle changes) during study period. As a result, final analyses were conducted with 1,773 participants. Details of the exclusion criteria are provided in Figure 6.

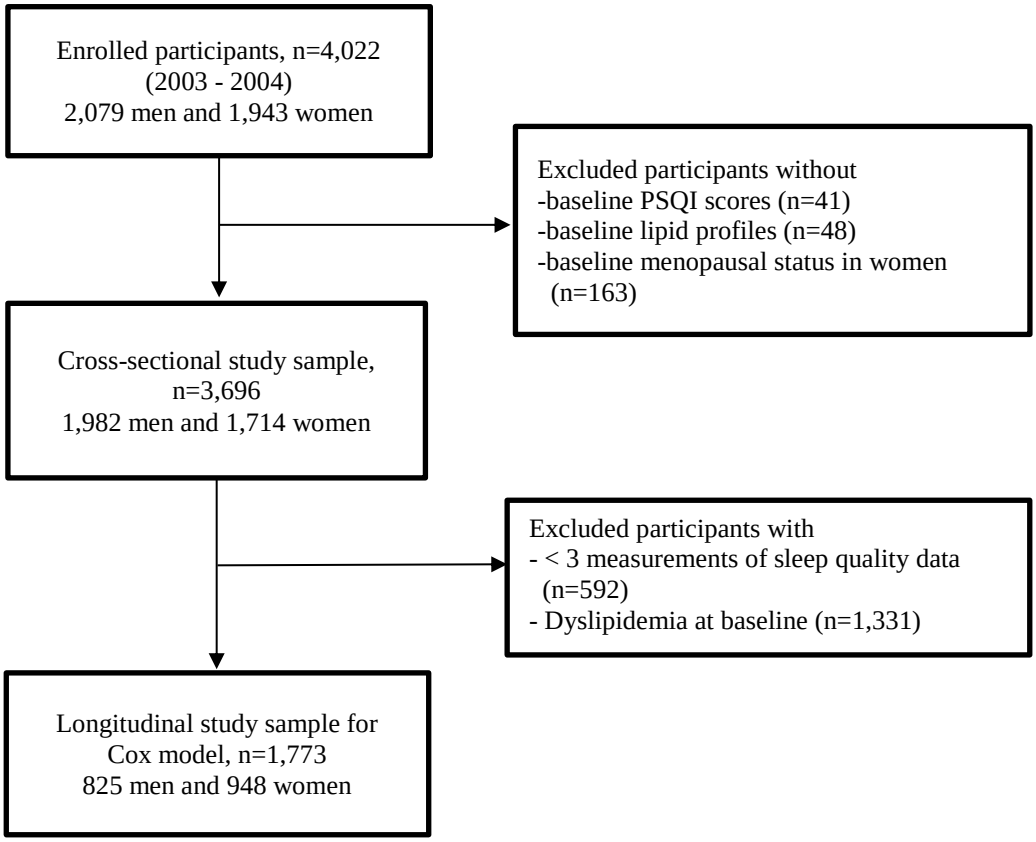


Figure 6. Flow chart of the selection of study participants in the Korean Genome and Epidemiology Study, Ansan (Part II)

2. *Measurements*

Assessment of sleep quality and hypertriglyceridemia

The overall sleep quality was assessed using PSQI. Detailed information or validity of PSQI has been described [30,31]. Higher PSQI scores (0-21) indicate worse sleep quality and duration. Poor sleep was operationally defined utilizing a PSQI total score > 7 according to results from a validation study in Korea; the best cutoff point to distinguish poor and good sleepers was 8.5 of PSQI scores in Korean (sensitivity: 0.943. specificity: 0.844) [30]. Hypertriglyceridemia, the main outcome in the current study, was determined by TG ≥ 200mg/dL.

Assessment of covariates

In the KoGES, all participants underwent an interview and physical examination during the baseline and follow-up phases. The participants were questioned by trained interviewers regarding their demographic information, personal disease history, and lifestyle factors. Since we analyzed the sub-cohort of Ansan KoGES (1st follow-up data of the original cohort study), absent demographic data (e.g., education attainment, household income, job, and marriage status) and self-reported insomnia symptoms were drawn from the original baseline survey (2001-2002). Self-reported insomnia symptom was also considered, which was queried as “Do you have insomnia?” Educational attainment was divided into two groups (lower attainment: high school or less; higher attainment: college or above). Monthly household income was also divided into two groups (lower-income: <$2,500; higher-income: ≥$2,500). The occupation was classified into “unemployed,” “manual labor,” and “professional labor.” Homemakers, etc. were classified as “unemployed”; office

workers and expertise were classified as “professional laborers”; others were classified as “manual laborers” (Appendix Table 1). Marital status was classified into “married” or “the others (unmarried, separated, divorced, and widowed)”.

The other covariates were obtained from the current study baseline study. Information on disease diagnosis was identified by combining the lifetime history of diseases and newly diagnosed diseases during the last interval. Disease history included hypertension, diabetes mellitus, and cardiovascular diseases (CVD; myocardial infarction, coronary artery disease, cerebrovascular disease, or congestive heart failure). Hypertension was identified by self-reporting of a physician’s diagnosis, taking anti-hypertensive medication. Diabetes mellitus was identified by self-reporting of a physician’s diagnosis, taking the oral diabetes medication, or insulin injection. CVD was determined by self-reported diagnosis by a physician. The frequency of experiencing depressive symptoms was queried as “How frequently do you experience depressed- or anxiety feeling in last two weeks?” with a 5-point Likert scale (1: never, 2: rarely, 3: sometimes, 4: frequently, 5: always). In terms of drinking and smoking status, participants were classified as current, former, or none. The frequency of late-night snack was queried as “Do you frequently have snacks after dinner or before bed?” with a 4-point Likert scale (1: almost every day, 6-7 times/week, 2: frequently, 4-5 times/week, 3: sometimes, 2-3 times/week, 4: rarely, 0-1 time/week). For women, menopausal status was categorized into pre-menopausal, menopausal-transition, and post-menopausal status. Since menopausal status was not asked at baseline survey, it was retrospectively collected using reproductive history information including the current menopausal status (“Do you have your period in last three months?”) and age at menopause (“If not still having periods, what was your age when you had your last period?”), which was queried during the follow-ups. Participants who responded as no period during more than consecutive 12 months were classified into “post-menopausal,” those

who experienced occasionally in the past 12 months but no period during the last three months were into “peri-menopausal,” and the others were into “in the period.”

Anthropometric and clinical measurements were utilized in the data from the survey at the baseline of the current study. Body mass index (BMI, kg/m^2) was calculated as the bodyweight divided by the standing height squared. After 8-hours of fasting, blood samples were drawn from the participants. The biochemical analysis included TG and HDL-cholesterol. Since LDL-cholesterol was not directly measured, it was calculated using Friedewald equation (LDL-cholesterol (mg/dL) = TC (mg/dL) − HDL-cholesterol (mg/dL) − TG (mg/dL)/5) among those with < 400mg/dL of TG [62]. Insulin resistance was calculated by homeostasis assessment model (HOMA-IR) and calculated from fasting insulin and glucose concentration according to the formula: insulin (μIU/mL) x glucose (mg/dL)/405 [63]. Due to a percentage of missing values in fasting insulin at baseline was more than 50%, we drew the value of HOMA-IR from the original baseline.

3. *Statistical analyses*

Descriptive analyses

Correlations were assessed by Pearson's correlation regarding 1) between PSQI scores and TG through the whole follow-ups, 2) between five repeatedly measured PSQI scores, and 3) seven sleep components of baseline PSQI scores and baseline lipid markers. In addition, median values of TG by baseline sleep status (poor or not) through the follow-ups were graphically presented. We used the independent t-test for normally distributed continuous variables, the Mann-Whitney U test for skewed distributed variables, and the chi-square test for categorical variables to compare the baseline characteristics of participants according to sleep quality status (poor or normal) by sex. Mean (SD) or median (interquartile range [IQR]) was used to describe data distribution. Additionally, the internal consistency of global PSQI scores at each time point was also examined in the current study. Cronbach's alpha coefficient describes the extent to which the observed items measure the same concept [64]. A higher alpha value at least 0.7 is consumed as an acceptable value for internal consistency.

Cross-sectional analyses

For cross-sectional associations between baseline poor sleep and prevalent hypertriglyceridemia, a multivariate logistic regression model was conducted. Since there is a notable difference in lipid markers by sex [65], all analyses were conducted separately by sex. The model evaluated whether sleep quality status is associated with prevalent hypertriglyceridemia, and odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Sleep quality status at baseline was put into the model.

First, the demographic factors adjusted model included age, SES (education attainment, household income, and job), disease diagnosis (hypertension, diabetes mellitus, and CVD), and self-reported depressive symptoms. Second, biological factors including BMI, HDL-C, LDL-C, and menopausal status (for women). Lastly, lifestyle factors including smoking, drinking, physical activity, and frequency of late-night snacks were additionally adjusted. In addition, generalized linear models at each time point were conducted to examine continuous PSQI scores and log-transformed TG. Adjustments were the same as those in the logistic models.

Proportional hazard assumption testing in Cox model

For longitudinal associations between baseline sleep quality status and hypertriglyceridemia onset, all participants were followed up starting in 2003-2004 and ending at hypertriglyceridemia, end of the study, or loss to follow-up whichever came first. Incidence rates of hypertriglyceridemia per 1,000 person-years were calculated by baseline sleep quality status. Proportional hazard assumption was tested before applying the Cox proportional hazard model. Assumptions were graphically tested by plotting the Kaplan-Meier survival curve and statistical comparison of survival curves between baseline sleep quality groups (poor vs normal) was provided by the log-rank test. The extended Cox model was applied due to a violated proportional hazard assumption in the current study [66].

Time-dependent Cox proportional hazard model

Multivariate Cox models were used to estimate the association between time-dependent sleep quality status and hypertriglyceridemia onset. The model evaluated whether time-dependent sleep

quality is associated with hypertriglyceridemia onset, and hazard ratios (HR) with 95% confidence intervals (CIs) were calculated. Given that sleep quality varies over time, we assessed the associations between time-dependent sleep quality and hypertriglyceridemia onset by using the counting process approach [67]. The counting process method has multiple records for each individual, with each record corresponding to an interval of time during which all covariates remain constant. If the interval does not end in an event, it is treated as censored [67]. For example, if a participant has normal sleep at baseline, and it is changed to poor sleep at year 6, the participant will have two records as follows: (1) from baseline to < year 6 participants were treated as having normal sleep quality and (2) from year 6 and at the censoring time as having poor sleep quality. Under each respective risk set, the hazard of hypertriglyceridemia according to sleep quality status is evaluated. For women, menopausal status was also considered time-dependent given that lipid changes before and after menopause [65]. The associations between time-dependent sleep quality status (poor vs not) and hypertriglyceridemia onset were analyzed. First, demographic factors adjusted model included age, SES (education attainment, household income, and job), hypertension diagnosis, diabetes mellitus diagnosis, and CVD diagnosis, self-reported insomnia symptom, and self-reported depressive symptoms. Second, biological factors including BMI, HDL-C, LDL-C, HOMA-IR, and menopausal status (for women). Lastly, lifestyle factors including smoking, drinking, physical activity, and frequency of late-night snacks were additionally adjusted.

Missing data

Since complete-case analysis with no missing information may provide biased results [68], we utilized data from participants with at least 3 repeated sleep quality data. The proportion of missing

sleep quality data was 11%, 9%, 12%, and 14% at year 4, 6, 8, and 10, respectively. All covariates had < 1% of missing information except for the frequency of late-night snacks. (Appendix Table 9). Since its non-response rate (44%) was evenly distributed according to sleep quality status (45% of normal sleep and 44% of poor sleep), the missing value was coded as "non-response." For missing values, multiple imputations separately by sex using fully conditional specification (FCS), also known as chained equations, were applied to consider the dichotomous and continuous form of missing covariates [69] (number of imputation=30).

Sensitivity analyses

Several sensitivity analyses were conducted to present the robustness of our findings. First, to find out whether the history of dyslipidemia diagnosis or current use of lipid-lowering drugs affects TG levels at baseline, we additionally excluded participants who had a lifetime history of dyslipidemia diagnosis by a physician (n=31), newly diagnosed dyslipidemia including physician diagnosis and current use of lipid-lowering drugs before the baseline of the current study (n=4). Second, associations between time-dependent sleep quality and hypertriglyceridemia onset were evaluated utilizing those ≥ 4 or 5 times of PSQI data. Third, to find out whether our results are confounded by hormonal changes in women, the associations were evaluated after stratifying menopausal status. Fourth, associations were examined after stratifying the frequency of late-night snacks at baseline (less frequently: < 4 times/week vs frequently: ≥ 4 times/week) to determine whether the findings differed by the frequencies. Fifth, poor sleep was differently determined as PSQI > 5. Lastly, to check whether the lifestyle factors (e.g., smoking, drinking, or physical activity) and BMI are time-varying, the trajectories were additionally investigated using data from baseline to final survey of

the study. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-sided p-value of <0.05 was considered significant.

Ethics

Data in this study were from the Korean Genome and Epidemiology Study (KoGES; 4851-302), National Research Institute of Health, Centers for Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. This study was approved by the institutional review board of Severance Hospital at Yonsei University College of Medicine (Y-2020-0218).

III. RESULTS

1. *Validity of the global Pittsburgh Sleep Quality Index scores*

In the current study, all internal consistencies of PSQI scores were satisfied with ≥ 0.7: at baseline (0.73), year 4 (0.79), year 6 (0.80), year 8 (0.81), and year 10 (0.79). It can conclude that PSQI scores surveyed at each time point are well-representing the concept of overall sleep quality.

2. *Changes in TG levels by baseline sleep quality status*

Descriptive changes of median TG levels over time according to baseline sleep quality status are presented in Figure 7. Women with poor sleep at baseline were more likely to have higher TG levels during follow-ups compared to the normal sleep quality female group. Men with poor sleep had higher TG levels compared to the normal quality group during study follow-up except for the last four years of the study end.

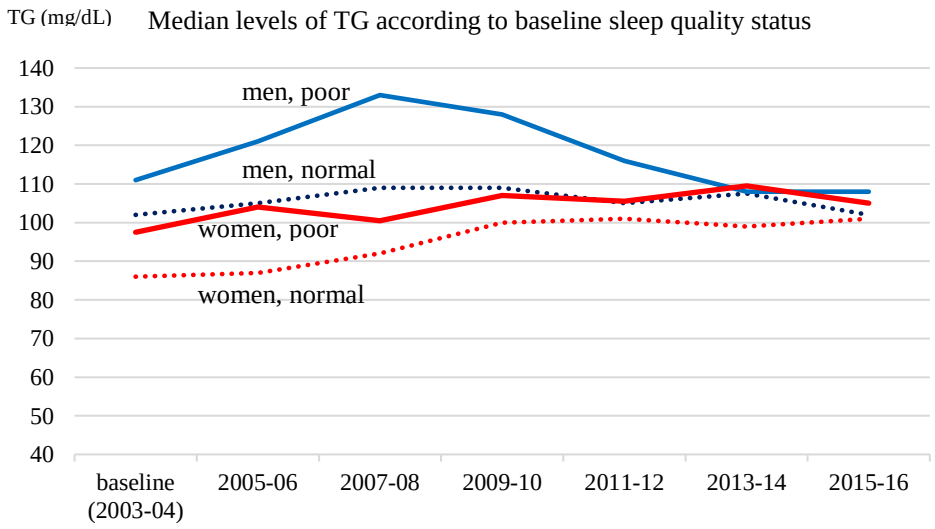


Figure 7. Changes in triglyceride levels overtime according to the baseline sleep quality

3. *Correlations between main variables at each time point*

PSQI scores and triglyceride level

Table 4 presents correlations between global PSQI scores and TG at each time point by sex. In men, the correlations between PSQI scores and TG at year 8 and 10 were positively correlated. In women, PSQI scores were positively correlated with TG levels overall. Especially, correlations between PSQI scores and TG at respective time points were significant or marginally significant (at baseline: r=0.067, p-value=0.039; at year 4: r=0.063, p-value=0.066; at year 6: r=0.073, p-value=0.033; at year 8: r=0.082, p-value=0.018; at year10: r=0.064, p-value=0.066).

Between PSQI scores at each time point

Table 5 shows correlations between repeated measured PSQI scores at each time point. In common, the strongest correlations (r= 0.73 to 0.515, p-value: <0.001) between PSQI scores when they were adjacent in times. The correlations between PSQI scores at baseline and those at year 10 had relatively weak correlations in both men (r:0.370, p-value: <0.001) and women (r:0.383, p-value: <0.001) compared to those with year 4.

Table 4. Correlations between global PSQI scores and triglyceride levels at each time point by sex

Men (n=825)

TG / PSQI		baseline (2003-04)	At year 2 (2005-06)	At year 4 (2007-08)	At year 6 (2009-10)	At year 8 (2011-12)	At year 10 (2013-14)	At year 12 (2015-16)
baseline (2003-04)	correlation	0.027	-0.004	0.045	0.056	0.091	0.068	0.076
	p-value	0.436	0.915	0.221	0.122	0.015	0.073	0.045
	n	818	774	752	768	718	702	702
At year 2 (2005-06)	correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-value							
	n							
At year 4 (2007-08)	correlation	-0.034	-0.004	0.001	0.010	0.097	0.091	0.053
	p-value	0.363	0.921	0.977	0.787	0.015	0.023	0.188
	n	731	706	734	692	636	625	626
At year 6 (2009-10)	correlation	0.019	0.026	0.040	0.060	0.092	0.106	0.027
	p-value	0.593	0.485	0.283	0.099	0.017	0.007	0.497
	n	756	723	706	762	667	646	650
At year 8 (2011-12)	correlation	-0.032	0.058	0.026	0.036	0.095	0.085	0.029
	p-value	0.398	0.136	0.511	0.354	0.011	0.032	0.466
	n	710	671	649	668	714	639	646
At year 10 (2013-14)	correlation	-0.033	0.009	0.021	0.015	0.024	0.071	0.013
	p-value	0.390	0.819	0.594	0.709	0.545	0.062	0.743
	n	696	661	640	651	641	701	647
At year 12 (2015-16)	correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-value							
	n							

Women (n=948)

TG / PSQI		baseline (2003-04)	At year 2 (2005-06)	At year 4 (2007-08)	At year 6 (2009-10)	At year 8 (2011-12)	At year 10 (2013-14)	At year 12 (2015-16)
baseline (2003-04)	correlation	0.067	0.119	0.087	0.102	0.082	0.037	0.015
	p-value	0.039	0.000	0.010	0.003	0.017	0.289	0.673
	n	940	874	873	878	846	829	817
At year 2 (2005-06)	correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-value							
	n							
At year 4 (2007-08)	correlation	0.141	0.105	0.063	0.110	0.153	0.070	0.031
	p-value	<.0001	0.003	0.066	0.002	<.0001	0.057	0.398
	n	841	795	847	785	757	737	739
At year 6 (2009-10)	correlation	0.079	0.041	0.053	0.073	0.105	0.061	0.024
	p-value	0.022	0.246	0.139	0.033	0.004	0.094	0.523
	n	844	786	784	852	766	750	742
At year 8 (2011-12)	correlation	0.095	0.052	0.026	0.068	0.082	0.013	0.004
	p-value	0.006	0.144	0.463	0.056	0.018	0.729	0.912
	n	836	781	777	789	842	764	756
At year 10 (2013-14)	correlation	0.092	0.055	0.006	0.074	0.117	0.064	0.034
	p-value	0.009	0.131	0.865	0.041	0.001	0.066	0.342
	n	820	767	758	770	765	826	774
At year 12 (2015-16)	correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-value							
	n							

Table 5. Correlations between 5-time of repeated global PSQI scores at each time point by sex.

Men (n=825)

PSQI scores		baseline (2003-04)	At year 4 (2007-08)	At year 6 (2009-10)	At year 8 (2011-12)	At year 10 (2013-14)
baseline (2003-04)	correlation p-value n	1 825	0.515 <.0001 734	0.456 <.0001 762	0.435 <.0001 714	0.370 <.0001 701
At year 4 (2007-08)		correlation p-value n	1 734	0.560 <.0001 689	0.489 <.0001 633	0.455 <.0001 624
At year 6 (2009-10)			correlation p-value n	1 762	0.524 <.0001 663	0.446 <.0001 645
At year 8 (2011-12)				correlation p-value n	1 714	0.536 <.0001 638
At year 10 (2013-14)					correlation p-value n	1 701

Women (n=948)

PSQI scores		baseline (2003-04)	At year 4 (2007-08)	At year 6 (2009-10)	At year 8 (2011-12)	At year 10 (2013-14)
baseline (2003-04)	correlation p-value n	1 948	0.473 <.0001 847	0.433 <.0001 852	0.435 <.0001 842	0.383 <.0001 826
At year 4 (2007-08)		correlation p-value n	1 847	0.570 <.0001 761	0.483 <.0001 754	0.505 <.0001 734
At year 6 (2009-10)			correlation p-value n	1 848	0.560 <.0001 763	0.538 <.0001 747
At year 8 (2011-12)				correlation p-value n	1 832	0.573 <.0001 761
At year 10 (2013-14)					correlation p-value n	1 821

Baseline characteristics of the study participants

Table 6 shows baseline characteristics according to sleep quality status at baseline, separately by sex. In common, the poor sleep group was older and they had a shorter sleep duration and experienced more frequent depressive symptoms compared to the normal sleep group. In men, favorable lipid markers (e.g., LDL-C and HDL-C) of the poor sleep group were shown compared to the normal sleep quality group. However, the other demographics and lifestyle factors were not different according to the sleep quality status in men. In women, the poor sleep quality group had higher median TG values and total cholesterol means compared to the normal sleep quality group. Additionally, female participants with poor sleep tended to have a higher percentage of frequent late-night snacks. The other demographics and lifestyle habits were not significantly different by sleep quality status.

Table 6. Baseline characteristic of the participants according to the sleep quality status by sex

Baseline characteristic	Men (n=825)		p-value	Women (n=948)		p-value
	Normal sleep quality[1] (n=736)	Poor sleep quality[1] (n=89)		Normal sleep quality[1] (n=819)	Poor sleep quality[1] (n=129)	
Age,years	50.08 ± 7.22	52.25 ± 8.57	0.024	49.1 ± 6.86	51.93 ± 7.82	<.001
40 to <50	430 (58.4)	45 (50.6)	0.055	538 (65.7)	66 (51.2)	0.001
50 to <60	203 (27.6)	23 (25.8)		191 (23.3)	36 (27.9)	
≥ 60	103 (14.0)	21 (23.6)		90 (11.0)	27 (20.9)	
mean of PSQI scores (0-21)	3.64 ± 1.71	7.44 ± 2.49	<.001	4.33 ± 2.01	8.16 ± 2.62	<.001
BMI,kg/m²	23.91 ± 2.71	23.52 ± 2.47	0.187	24.09 ± 2.97	23.82 ± 2.68	0.346
Sleep duration, hours/day	6.85 ± 1.06	6.22 ± 1.22	<.001	6.52 ± 1.21	5.99 ± 1.4	<.001
Prevalent insomnia symptom[2], n (%)	58 (7.9)	21 (23.9)	<.001	94 (11.5)	58 (45.0)	<.001
Menopause status, n (%)						
pre-menopause				404 (49.3)	42 (32.6)	<.001
peri-menopause		N/A		95 (11.6)	15 (11.6)	
post-menopause				320 (39.1)	72 (55.8)	
Frequent depressive symptoms[3], n (%)	25 (3.4)	10 (11.2)	0.002	57 (7.0)	23 (17.8)	<.001
Frequent late-night snack[4], n (%)	106 (21.3)	15 (25.4)	0.471	74 (20.3)	19 (29.7)	0.092
Physical activity, n (%)	445 (60.5)	49 (55.1)	0.326	473 (57.8)	65 (50.4)	0.117
Currently Smoking, n (%)	246 (33.4)	36 (40.5)	0.201	17 (2.1)	1 (0.8)	0.124
Currently Drinking, n (%)	566 (76.9)	76 (85.4)	0.166	299 (36.5)	56 (43.4)	0.261
Total cholesterol,mg/dL	192.3 ± 24.2	190.9 ± 21.0	0.588	193.0 ± 24.9	199.4 ± 24.1	0.008
LDL cholesterol,mg/dL	121.4 ± 22.2	117.0 ± 20.3	0.076	122.9 ± 21.2	127.5 ± 21.3	0.025
HDL cholesterol,mg/dL	49.4 ± 8.5	50.9 ± 9.1	0.118	51.2 ± 8.6	51.6 ± 10.1	0.634
Triglyceride,mg/dL	102 [75-138]	111 [84-146]	0.077	86 [65-116]	97.5 [71-125]	0.027
Fasting glucose,mg/dL	86 [80-93]	85 [80-95]	0.869	80 [76-85]	81 [76-85]	0.927
Fasting insulin,μIU/㎖	6.2 [4.8-8.1]	6.5 [4.8-8.4]	0.446	7.0 [5.3-9.4]	6.5 [4.5-9.0]	0.032
HOMA-IR	1.47 ± 0.80	1.55 ± 0.94	0.458	1.49 ± 0.74	1.35 ± 0.71	0.025
SBP,mm/Hg	114.7 ± 14.4	116.2 ± 15.4	0.368	108.8 ± 15.0	110.4 ± 15.0	0.270
DBP,mm/Hg	77.5 ± 10.5	78.2 ± 9.6	0.571	71.8 ± 10.3	72.3 ± 10.4	0.591

Education[2], n (%)									
High school or less	481	(65.4)	66	(74.2)	0.097	716	(87.4)	116	(89.9)	0.421
College or above	255	(34.7)	23	(25.8)		103	(12.6)	13	(10.1)	
Monthly household income, n (%)										
< $2,500	471	(64.0)	62	(69.7)	0.291	590	(72.6)	103	(79.8)	0.082
≥ $2,500	265	(36.0)	27	(30.3)		223	(27.4)	26	(20.2)	
Job, n (%)										
Unemployed (homemaker etc.)	184	(29.2)	69	(35.6)	0.172	493	(74.7)	233	(81.2)	0.034
Manual labor	284	(45.0)	85	(43.8)		130	(19.7)	47	(16.4)	
Professional labor	162	(25.7)	40	(20.6)		37	(5.6)	7	(2.4)	
Disease history[5], n (%)										
Diabetes mellitus diagnosis	62	(8.4)	14	(15.7)	0.024	47	(5.7)	13	(10.1)	0.060
Hypertension diagnosis	133	(18.1)	22	(24.7)	0.129	109	(13.3)	22	(17.1)	0.252
Cardiovascular disease diagnosis[6]	15	(2.0)	0	(0.0)	0.392	4	(0.5)	2	(1.5)	0.191

Abbreviations: PSQI, Pittsburgh sleep quality index; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein
1. Poor sleep quality: PSQI > 7, and normal sleep quality: PSQI ≤ 7
2. Obtained from 2 years ahead of the baseline (=original baseline of KoGES data, year 2001-20002)
3. "Frequently" or "always" experience in depressed feeling during last 2 weeks
4. More than 4 to 5 times per week. Drawn from part of the participants (n=788) owing to missing information.
5. Self-reported diagnosis by physician or taking disease-specific medication
6. Myocardial infarction, coronary artery disease, congestive heart failure, and cerebrovascular disease.

4. *Cross-sectional associations between sleep quality and prevalent hypertriglyceridemia*

Table 7 presents the cross-sectional associations between sleep quality status and prevalent hypertriglyceridemia at baseline stratified by sex. Overall, women had a higher proportion of poor sleep compared to men (men: 10% vs women: 15%). A percentage of prevalent hypertriglyceridemia in poor sleep group was 17% in men and 13% in women. In men, poor sleep status was not significantly associated with hypertriglyceridemia (OR=0.75, 95% CI=0.49-1.15). On the other hand, female participants with poor sleep showed significantly higher odds of hypertriglyceridemia compared to those with normal sleep quality (OR=1.61, 95% CI=1.01-2.57).

Appendix Table 10 shows the association between PSQI scores and TG. In men, the level of TG was not associated with PSQI scores in most of the time points. In women, as 1 point of PSQI score increases, elevated TG levels were found at years 6 (β=0.009, SE=0.003, p-value=0.008) and 8 (β=0.009, SE=0.003, p-value=0.004).

Table 7. Cross-sectional associations between sleep quality status and prevalent hypertriglyceridemia at baseline (n=3,696)

Sex	Sleep quality status	total n	case n (%)	Demographic factors adjusted model[1]		Biological factors adjusted model[2]		Life-style factors adjusted model[3]	
				OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Men (n=1,982)	Normal sleep (PSQI ≤ 7)	1,782	330 (18.5)	1.00	reference	1.00	reference	1.00	reference
	Poor sleep (PSQI > 7)	200	34 (17.0)	0.88	(0.58 - 1.33)	0.79	(0.51 - 1.21)	0.75	(0.49 - 1.15)
Women (n=1,714)	Normal sleep (PSQI ≤ 7)	1,454	123 (8.5)	1.00	reference	1.00	reference	1.00	reference
	Poor sleep (PSQI > 7)	260	34 (13.1)	1.42	(0.90 - 2.22)	1.61	(1.01 - 2.56)	1.61	(1.01 - 2.57)

Abbreviations: PSQI, Pittsburgh sleep quality index; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein

1.Adjusted for age, household income, job, education attainment, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported insomnia symptom, and self-reported depressive symptoms

2. Additionally adjusted for BMI, LDL-cholesterol, HDL-cholesterol, and menopausal status (only for women)

3. Additionally adjusted for current smoking, current drinking, current physical activity, and frequency of late-night snack

5. *Kaplan-Meier survival curves of hypertriglyceridemia onset by baseline sleep quality status*

Figure 10 presents the Kaplan-Meier survival curves of hypertriglyceridemia onset according to the baseline poor sleep status (PSQI >7), separately by sex. In both men and women, the survival curves between sleep quality groups were not parallel, which implies that the proportional hazard ratio assumptions were not satisfied. Therefore, extended Cox models using the time-dependent sleep quality status were utilized instead of standard Cox proportional models using baseline poor sleep quality status.

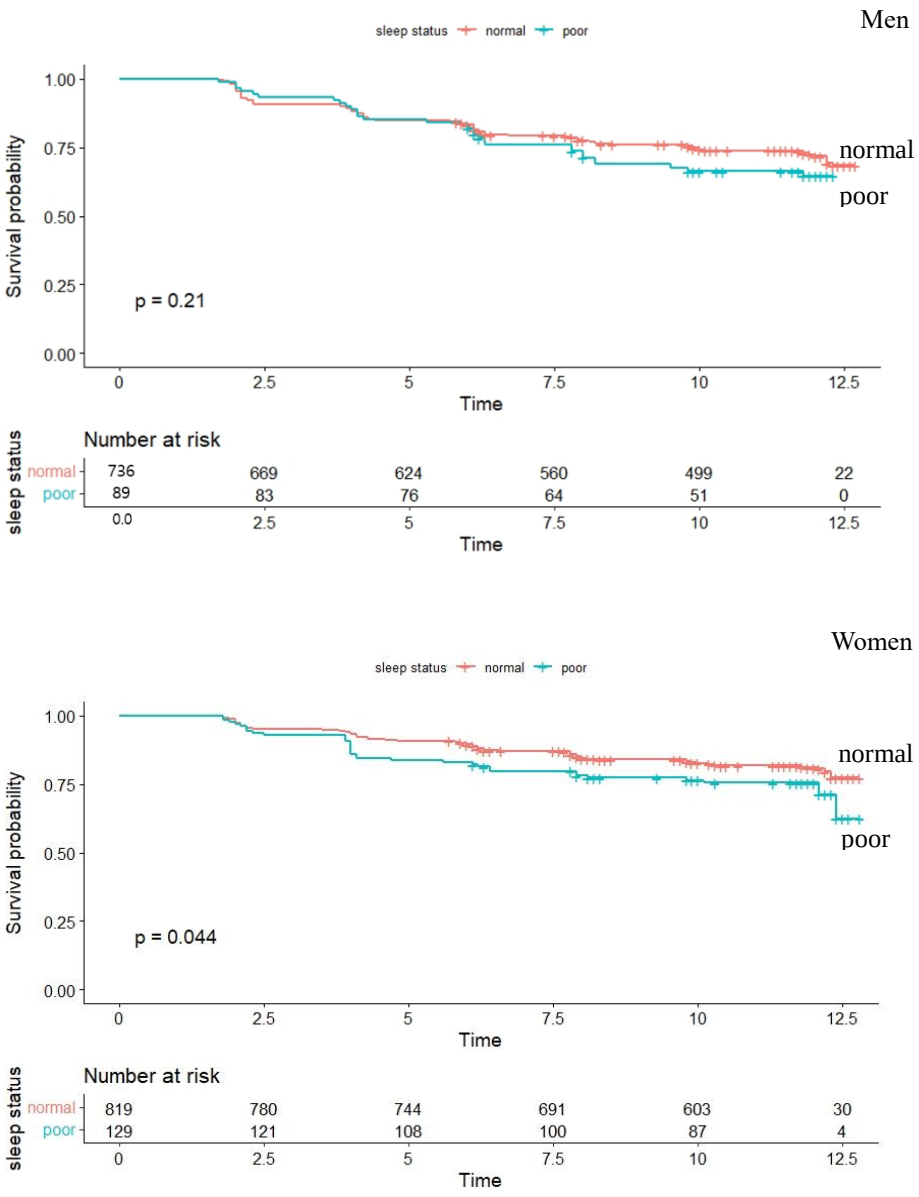


Figure 10. Kaplan-Meier survival curves of hypertriglyceridemia according to the baseline poor sleep quality status (PSQI > 7) by sex

6. *Associations between time-dependent sleep quality and hypertriglyceridemia onset*

Table 8 presents the association between time-dependent sleep quality status and dyslipidemia diagnosis. In men, with a median follow-up of 11.8 years, 28.3 of hypertriglyceridemia incident cases were occurred by 1,000 person-years in the baseline normal sleep group (PSQI ≤ 7) and 36.4 cases occurred in the baseline poor sleep group (PSQI > 7). After full adjustments for demographic, biological, and lifestyle factors time-dependent poor sleep quality was not associated with hypertriglyceridemia onset in men (HR=1.03, 95%CI=0.68-1.55, p-value=0.90).

In women, with a median follow-up of 11.8 years, the baseline poor sleep quality group (PSQI > 7) had a higher incidence rate per 1,000 person-years compared to the baseline normal sleep quality group (normal: 18.5 per 1,000 person-years vs poor: 26.8 per 1,000 person-years). A significantly elevated hazards of hypertriglyceridemia in female participants with poor sleep group was observed after full adjustments (HR=1.53, 95%CI=1.07-2.17, p-value=0.02).

Results of sensitivity analyses after excluding participants with a lifetime diagnosis of dyslipidemia by a physician or current use of lipid-lowering drugs at baseline (Appendix Table 11) were similar to the main results. Similarly, sensitivity results with those who had ≥ 4 or 5 times of PSQI data (Appendix Table 12-13) were consistent with main ones and so were the results after stratification with a frequency of late-night snack at baseline or menopausal status at baseline (Appendix Figure 1). Additionally, differently determined poor sleep as PSQI > 5 did not change the directions of the associations (Appendix Table 14). Lastly, regarding the time-dependent changes of current smoking (yes/no), drinking (yes/no), exercise (yes/no), and BMI (continuously) in female participants, there were no time-dependent changes in BMI (Appendix Figure 2-D). In current smoking, although there

was a decreasing trend, it was not treated as time-dependent due to its extremely small size in corresponding group (n=18). Since a decreasing trend in current drinking group and an increasing trend in without current exercise group were found, those were treated as time-dependent variables respectively. The results were similar with the main results in time-dependent current drinking (HR=1.53, 95%CI=1.07-2.17, p-value=0.02) and in time-dependent current exercise (HR=1.56, 95%CI=1.09-2.21, p-value=0.01). Respective trajectories of lifestyle factors and BMI are provided in Appendix Figure 2-A to 2-D.

Table 8. Associations between time-dependent poor sleep status and hypertriglyceridemia (n=1,773)

Sleep quality status by sex	Person-years	Incident cases	Incidence rate (per 1,000 pys)	Demographic factors adjusted[1]			Biological factors adjusted[2]			Life-style factors adjusted[3]		
				HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Men (n=825)												
Normal sleep (PSQI ≤ 7, n=736)	7167.6	203	28.3	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=89)	825.3	30	36.4	1.11	(0.74 - 1.67)	0.61	1.05	(0.70 - 1.57)	0.82	1.03	(0.68 - 1.55)	0.90
Women (n=948)												
Normal sleep (PSQI ≤ 7, n=819)	8524.0	158	18.5	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=129)	1266.5	34	26.8	1.65	(1.16 - 2.33)	0.00	1.55	(1.10 - 2.19)	0.01	1.53	(1.07 - 2.17)	0.02

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein

1. adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, and self-reported insomnia symptom
2. additionally adjusted for BMI, LDL, TG, HDL, HOMA-IR, and menopausal status for women
3. additionally adjusted for smoking, drinking, physical activity, and frequency of late-night snack

IV. DISCUSSION

1. *Summary of findings*

We found both cross-sectional and longitudinal associations between poor sleep quality and hypertriglyceridemia in women. Female participants with poor sleep had significantly higher odds of prevalent hypertriglyceridemia. The same trends were observed in longitudinal associations using repeatedly measured sleep quality data. In female participants with normal lipid levels at the baseline, poor sleep quality which was treated as time-dependent variables was significantly associated with hypertriglyceridemia onset; 53% increased hazards of hypertriglyceridemia onset compared to the normal sleep quality group were observed.

2. *Validity of the Pittsburgh Sleep Quality Index*

In current studies, global PSQI scores were utilized to represent the participants' overall sleep quality. PSQI consisted of seven components including sleep quality perception, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction [31]. PSQI is a globally validated measurement tool for evaluating sleep quality [70-72]. PSQI was also validated in the Korean population [30]. In a validation study, convenience samples (age ≥ 18) were selected from a sleep center. Poor sleepers were 261 included those who had primary insomnia (n=211) according to DSM-IV or narcolepsy (n=50) which was determined by the International Classification of Sleep Disorder-2 criteria. Healthy controls (n=133) with good sleep quality (i.e., no sleep complaints, no previous history of other medical diseases) were selected from the health screening center. Test-retest correlation for the global PSQI scores was acceptable ($r=0.65$, $p<0.001$)

among 53 randomly selected participants. In addition, all seven component scores, except for daytime dysfunction, of insomnia patients were significantly higher than those of healthy controls. Internal consistency of PSQI was tested through Cronbach's α coefficient (0.84), which means high reliability.

In the validation study on the Korean population, sleep efficiency and sleep latency measured by polysomnography (PSG), which was considered as a gold standard for objective measurement of sleep quality [73], were significantly associated with PSQI scores, but small in magnitude. In the German population, global PSQI scores showed lower correlations with polysomnography data [70]. These relatively weak associations should be considered with the first night effect of PSG, which refers that laboratory sleep may contain a more changeable sleep pattern [74], and subjects' daily sleep fluctuation.

3. Comparisons with previous studies

Sex difference in lipid development

There exists a significant difference between sex regarding lipid metabolism [75]. Especially, the difference between men and women in lipid changes is prominent during mid-life, as women experience a decline of endogenous estrogens with menopause [76]. According to descriptive analyses using data from the Korea National Health and Nutrition Examination Survey (KNHANES 2010 - 2016) [65], the trend of TG level was reversed during the age of '50s; men had a higher value compared to women until the late '50s, but since after that elevated TG above the male level were observed in women. These trends were also observed in our data using participants (mean age at baseline: 49.8)

in the KoGES-Ansan study (Figure 7). Women showed an overall increasing trend of TG levels, while a decreasing trend of TG levels was found in men during the study period.

Sleep quality and hypertriglyceridemia

The cross-sectional findings of baseline sleep quality and prevalent hypertriglyceridemia were aligned to a previous study. A cross-sectional study used 301 Korean, aged over 20 years old, without clinical issues (e.g., cardiovascular diseases) recruited from the primary care clinic. Poor sleep group defined as PSQI>5 had higher odds for metabolic syndrome after full adjustments and had a higher prevalence of hypertriglyceridemia compared to the normal sleep group [77]. However, another previous study using around 4,600 ~ 9,800 individual data (age ≥ 20 years) from 2005–2008 National Health and Nutrition Examination Surveys in the United States reported the null impact of poor sleep [19]. Insomnia symptoms (i.e., the frequency of difficulty falling asleep, prolonged nocturnal awakening, and undesired early morning awakening) were not associated with the elevated level of TG.

Regarding the longitudinal results of sleep quality, there exist inconsistent results in previous studies. Results from a study using 503 black and white adults (aged 32-51 years), who were free of CVD and lipid-lowering medications, from the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study in the United States were not aligned to our findings [20]; PSQI scores at baseline were not associated with 10-year changes in lipid levels, measured 3 times at baseline, 5-year follow-up, and 10-year follow-up. However, the cross-sectional and longitudinal study results using Women's Health Initiative (WHI) data in the United States were supportive of our findings in the deleterious impact of poor sleep on hypertriglyceridemia. In the study, associations between

sleep quality and lipids-related metabolites in post-menopausal women (n=1,956) were found [21]. Also, the result was maintained in a replication study with 209 participants from an independent sample in the Nurses' Health Study II (NHS II). Sleep quality was assessed from the baseline 10-item sleep questionnaire in the WHI and the PSQI in the NHS II study. For feasible comparison, a sleep-quality score (SQS) was newly constructed using four major areas related to insomnia symptoms (i.e., subjective sleep quality, sleep latency, sleep disturbance, and sleep medication use) from both cohorts. After adjusting for age, race, BMI, and smoking, 69 metabolites that were associated with sleep quality were found. In the replication study, 16 metabolites were replicated, and 15 metabolites were classified as lipids including 6 triglycerides and 1 was a non-lipid metabolite. For replicated plasma metabolites, to prevent reversal causation, the longitudinal association between baseline SQS and changes in metabolite levels among 889 WHI women who had a second metabolomics measurement at 1-year follow-up. As a result, TG was consistently elevated among women with poorer sleep quality.

In previous longitudinal studies, there still exists a common limitation of sleep quality data which may not fully represent its time-varying nature during a long period. Although there is a study that tested the reproducibility of sleep quality at baseline (0.68 of the intra-class correlation coefficient) to confirm its long-term effect, the interval was 1 year which was a relatively short period to confirm the long-term effect [21]. In addition, the other previous studies utilized only a one-time measurement of sleep quality at baseline [20,22,78], hence it may hard to observe the impact of the sustained sleep quality. The current study utilized repeated measured sleep quality data over 12 years so that it could reflect its sustained effect on triglyceride.

Sex-specific association between poor sleep and hypertriglyceridemia

In the current study, the deleterious impact of poor sleep on hypertriglyceridemia was prominent in women. Female participants had a significantly worse sleep quality compared to men in all measured global PSQI scores, and this may contribute to the magnitude of the sleep quality impact on TG. Moreover, female participants were more likely to have worse status in specific PSQI components (i.e. sleep latency, sleep disturbance, and sleep drug), which was revealed to be associated with the elevated TG levels in the previous study [21] (Appendix Table 15). Among the sleep quality components, sleep latency may play an important role to increase TG levels. Several previous findings reported that women with higher sleep latency had increased insulin resistance or elevated inflammation levels[16,17]. Increased insulin resistance or inflammation biomarkers are frequently accompanying with hypertriglyceridemia[18]. A cross-sectional study using 374 US community-based participants reported abnormal glucose homeostasis among women with higher sleep onset latency, and inflammatory cytokines partially mediated the association between higher sleep onset latency and increased insulin resistance [16]. In another study of 210 healthy US community dwellers, quantities of PSQI scores (e.g., overall poor sleep quality, problems falling sleep, sleep latency) were associated with higher fasting insulin and inflammatory biomarkers only in women[17]. Sex-related differences in dysregulation of the serotonergic system, which is involved in the regulation of sleep maintenance or affective states[79], may explain the sex-specific associations between poor sleep and putative risk factors. Another plausible explanation for the sex difference is testosterone-related increases in the expression of the peroxisome proliferators-activated receptor (PPAR)-α. PPAR-α leads to a decreased expression of nuclear factor-kappa B[80], which are transcription factors implicated in inflammation.

4. *Possible mechanisms*

Several plausible mechanisms may explain the deleterious impact of poor sleep on TG levels. First, increased insulin resistance or inflammation biomarkers resulted from poor sleep quality may affect the TG levels[16,17]. Second, altered cholesterol pathways among poor sleepers have been reported [21,81]. Decreased expression of genes encoding cholesterol transporters and increased expression in pathways involved in inflammatory responses were observed in the context of both experimental and habitual sleep restriction [81]. Third, another physiological mechanism connecting sleep to lipid metabolism is the autonomic nervous system, which consists of the sympathetic and parasympathetic nervous systems [82]. Sleep disturbance has been reported to be associated with increased sympathetic nervous system activity, and it has been related more to the disruption of sleep than to the amount of sleep deprivation [83]. Chronic activation of the sympathetic nervous system has been linked to increased free fatty acids [84], which is often related to lipid levels [85]. Lastly, sleep disturbance is closely related to circadian rhythm abnormalities [86], which may have an impact on impaired lipid homeostasis [87]. The accumulation of triglycerides in white adipose tissue was observed in mice with circadian clock disruption [88].

5. *Causal inference of the findings*

We reviewed our findings by applying the requirements for causal inference. First, a temporal relationship should be warranted. For this, the current study eliminated participants with abnormal lipid levels at the baseline survey. We also utilized poor sleep status that was measured before hypertriglyceridemia onset. Second, the strength of the association should be considered. The stronger the association, the more likely it is that the association is causal. In the current study, 50%

of elevated hazards of hypertriglyceridemia in women were observed. Third, the dose-response association could give benefit to causal interpretation of the findings. As poor sleep was determined with a higher cutoff PSQI score, which indicates the worse status, the hazard ratios for hypertriglyceridemia were increased in the current study. Fourth, the findings need to be replicated in different studies. Although there are inconsistent results between sleep quality and triglyceride levels, it should be considered that most previous studies did not examine the full sustained impact of sleep quality. Additionally, several previous studies reported a deleterious impact of self-reported poor sleep on triglycerides [21,89]. Fifth, biological plausibility for the findings is needed. Increased insulin resistance[17], activated sympathetic nervous system [84], circadian rhythm abnormalities [88], or altered cholesterol pathway [81] may explain the association between poor sleep and elevated TG levels. Sixth, coherence has been viewed as being similar to biological plausibility, in that the cause-and-effect association should make sense with all knowledge [90]. Seventh, there might be an analogous hypothesis that a similar agent may cause a similar outcome. Poor sleep quality may be an indication of a sleep disorder (e.g., obstructive sleep apnea). Previous studies suggested that obstructive sleep apnea had an adverse impact on insulin resistance[91], inflammation[92]. Eighth, it is expected to a decline of disease risk after the cessation of the exposure. There is a report that intervention for improving sleep quality (e.g., cognitive behavioral therapy) among insomnia patients showed significantly lower biological risk score, which included TG, compared to control after one-year follow-up [93]. Lastly, the deleterious impact of poor sleep was specific to TG in lipids (Appendix Table 16), but specificity is the weakest of all the guidelines.

6. *Strengths and limitations*

Strengths of this study include a prospective cohort study design, and the availability of multiple measurements in sleep quality, which could reflect its fluctuating nature of sleep quality. In addition, the wealth of information on potential confounders including demographics, biological, and lifestyle factors that could affect both sleep quality and hypertriglyceridemia onset.

However, several limitations need to be addressed. First, results should be carefully interpreted regarding their causality. The nature of the observational study does not generally allow for causal inference [94]. Additionally, although we controlled plenty of confounders, residual confounding cannot be ignored such as more severe disease conditions (i.e., obstructive sleep apnea). Second, the current study findings cannot be generalized to all Korean middle-aged women. The impact of poor sleep on hypertriglyceridemia was examined using participants with normal lipid levels at the baseline survey considering the possibility of pharmacologic or non-pharmacologic intervention (i.e., lifestyle pattern changes) in dyslipidemia patients. Therefore, it may be hard to apply the study findings to all Korean middle-aged women. Third, longitudinal associations were evaluated using 1,773 participants (825 men and 948 women), which is relatively a small sample size. However, the current study sample size exceeded the minimum sample size that needs to conduct the study at 95% CI and 80% power (a minimum required sample size=664) [95]. A detailed calculation process is provided in Appendix Table 17. Nontheless, further studies with large samples would be needed to yield more definitive answers. Fourth, we could not examine the impact of respective sleep components (i.e., sleep latency, sleep disturbance, etc.). However, significant correlations between several components of baseline PSQI scores (i.e., subjective sleep quality, sleep latency, sleep efficiency), and baseline triglyceride level in women were found (Appendix Table 18), which was

aligned to the previous studies [21]. Further longitudinal studies to investigate the impact of the specific sleep components on lipid levels would be needed. Fifth, the effects of omega-3 fatty acids on triglycerides[96] could not be evaluated due to a lack of nutritional information. Lastly, missing data of repeated sleep quality data may affect the results. Although the results were robust after multiple imputations for missing data, the bias due to a non-ignorable missing data-generating mechanism cannot be ignored [97].

V. CONCLUSION

Sleep quality is highly related to both physical and psychological health. Despite its importance, only a few existing studies have evaluated the sustained effect of sleep quality. In the current study, we found longitudinal changes in sleep quality according to SES and a significant mediating role of depressive symptoms that links the association. Further, we examined a significant association between time-dependent sleep quality and hypertriglyceridemia onset in middle-aged women with normal lipid levels, which may threaten their cardio-metabolic health.

In the first part, we identified five heterogeneous sleep quality trajectories among 3,347 middle-aged Korean individuals during 12 years. Baseline SES levels were indirectly associated with longitudinal sleep quality patterns; a substantial amount of the association was mediated by depressive symptoms. Lower education attainment and household income had an impact on depressive symptoms, which in turn leads to an increase in worse sleep quality (e.g., developing to poor or severely poor-persistent levels). In the second part, we further evaluated the impact of time-dependent sleep quality on hypertriglyceridemia onset since its time-varying nature was revealed in the previous part. Repeatedly measured sleep quality data over 12 years rather than a single appraisal at baseline was utilized to reflect its sustained effect. As a result, among 1,738 participants with a normal range of all lipid levels, time-dependent poor sleep was revealed to be associated with an increased hazard of hypertriglyceridemia onset in women.

Our discovery of a mediation effect of depressive symptoms between SES levels and longitudinal sleep quality patterns holds important clinical significance: the mental health of people with lower SES levels matters to their sleep health. Moreover, poor sleep seemed to have detrimental effects on triglyceride levels in middle-aged women with normal lipid levels. Therefore, in primary care,

maintaining adequate sleep quality may be suggested to middle-aged women who have relatively healthy lipid levels, which may finally give benefit to their cardio-metabolic health. Furthermore, as a way to achieve this goal at the community level, mental health care should be reconsidered to preserve adequate sleep quality among middle-aged women, especially those who are with low SES levels.

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Appendix

Appendix Table 1. Distribution of occupations by sex in KoGES-Ansan data

Occupation classification	Sex	
	Men (n=1,697)	Women (n=1,643)
Homemaker	2 (0.12)	1,111 (67.62)
Office worker	226 (13.32)	27 (1.64)
Farmworker	11 (0.65)	7 (0.43)
Self-employed	562 (33.12)	185 (11.26)
Sales	26 (1.53)	46 (2.80)
Factory worker	154 (9.07)	53 (3.23)
Expertise	165 (9.72)	37 (2.25)
Etc.	551 (32.47)	177 (10.77)

Notes. homemaker and etc. were classified as “unemployed”; office worker and expertise were classified as “professional laborers”; others were classified as “manual laborers.”

Appendix Table 2. Associations between occupation and sleep quality patterns

Occupation	Trajectory groups of sleep quality									
	Normal-stable (n=1,697)		Moderate-stable (n=1,157)		Poor-persistent (n=320)		Developing to Poor (n=84)		Severely poor-persistent (n=89)	
	OR	(95% CI)	n OR	(95% CI)	n OR	(95% CI)	n OR	(95% CI)	n OR	(95% CI)
Manual Labor (n=1,044) vs Unemployed (ref, n=1,841)	1.00	reference	343 0.92	(0.75 - 1.11)	64 0.59	(0.42 - 0.83)	22 0.95	(0.53 - 1.70)	25 0.96	(0.56 - 1.67)
Professional Labor (n=455) vs Unemployed (ref, n=1,841)	1.00	reference	152 0.93	(0.71 - 1.21)	27 0.66	(0.40 - 1.08)	5 0.85	(0.31 - 2.36)	6 0.75	(0.29 - 1.93)

Adjustments for sex, age, education attainment, marital status, monthly household income, education attainment, drinking, smoking, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

Appendix Table 3. Associations between occupation and sleep quality patterns mediated by depressive symptoms at year 4

Occupation	Trajectory groups of sleep quality									
	Normal-stable (n=1,697)		Moderate-stable (n=1,157)		Poor-persistent (n=320)		Developing to Poor (n=84)		Severely poor-persistent (n=89)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Manual Labor (n=1,044) vs Unemployed (ref, n=1,841)										
Total effect	1.00	reference	0.90	(0.71 - 1.10)	0.56	(0.34 - 0.78)	1.08	(0.35 - 1.82)	0.63	(0.14 - 1.11)
Natural direct effect	1.00	reference	0.87	(0.68 - 1.06)	0.56	(0.34 - 0.78)	1.06	(0.34 - 1.78)	0.60	(0.14 - 1.06)
Natural indirect effect	1.00	reference	1.04	(1.00 - 1.07)	0.99	(0.92 - 1.06)	1.02	(0.95 - 1.09)	1.05	(0.94 - 1.15)
Professional Labor (n=455) vs Unemployed (ref, n=1,841)										
Total effect	1.00	reference	1.01	(0.15 - 0.71)	0.52	(0.20 - 0.83)	0.78	(0.00 - 1.84)	0.69	(0.00 - 1.61)
Natural direct effect	1.00	reference	1.01	(0.15 - 0.71)	0.54	(0.21 - 0.86)	0.80	(0.00 - 1.89)	0.71	(0.00 - 1.64)
Natural indirect effect	1.00	reference	1.00	(0.02 - 0.96)	0.96	(0.86 - 1.05)	0.97	(0.86 - 1.08)	0.98	(0.85 - 1.10)

Notes: 395 data was deleted due to no measurements of BDI scores at years 4.
Adjustments for sex, age, job, marital status, monthly household income, education attainment, drinking, smoking, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

Appendix Table 4. Associations between socioeconomic status and sleep quality patterns mediated by depressive symptoms at years 4 with percentage mediated

Socioeconomic status	Trajectory groups of sleep quality									
	Normal-stable (reference, n=1,697)		Moderate-stable (n=1,157)		Poor-persistent (n=320)		Developing to Poor (n=84)		Severely poor-persistent (n=89)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Education attainment*										
Lower attainment[1] (n=2,617)										
vs Higher attainment[2] (ref, n=727)										
Total effect	1.00	reference	0.80	(0.64 - 1.00)	1.15	(0.73 - 1.85)	1.59	(0.62 - 5.59)	2.82	(0.98 - 8.58)
Natural direct effect	1.00	reference	0.76	(0.62 - 0.96)	1.04	(0.68 - 1.69)	1.41	(0.57 - 4.75)	2.41	(0.91 - 7.30)
Natural indirect effect	1.00	reference	1.05	(1.01 - 1.09)	1.10	(1.03 - 1.19)	1.13	(1.05 - 1.26)	1.17	(1.05 - 1.31)
Percentage mediated				-	72.57	(-136.0 - 281.15)	30.37	(-122.0 - 266.6)	22.55	(3.90 - 41.19)
Percentage due to interaction			8.3	(3.1 - 13.6)	4.95	(-32.6 - 42.47)	11.80	(-32.7 - 46.4)	24.73	(12.45 - 37.02)
Percentage eliminated				-	74.67	(-118.0 - 267.30)	33.35	(-113.7 - 260.7)	34.08	(15.32 - 52.84)
Monthly household income†										
Lower income[3] (n=2,319)										
vs Higher income[4] (ref, n=1,007)										
Total effect	1.00	reference	0.98	(0.82 - 1.20)	0.99	(0.71 - 1.39)	1.02	(0.51 - 2.34)	1.24	(0.58 - 3.00)
Natural direct effect	1.00	reference	0.93	(0.78 - 1.15)	0.90	(0.65 - 1.28)	0.93	(0.48 - 2.18)	1.07	(0.51 - 2.60)
Natural indirect effect	1.00	reference	1.05	(1.02 - 1.09)	1.09	(1.03 - 1.16)	1.09	(1.03 - 1.18)	1.15	(1.05 - 1.26)
Percentage mediated				-		-		-	69.34	(-155.0 - 293.7)
Percentage due to interaction			24.9	(14.98 - 257.6)	121.1	(-105.0 - 178.2)		-	9.85	(-61.6 - 81.3)
Percentage eliminated				-		-		-	74.53	(-112.3 - 261.3)

Notes: 395 data was deleted due to no measurements of BDI scores at years 4
1. High school or less
2. College or above
3. < $2,500
4. ≥ $2,500
*Adjustments for sex, age, job, monthly household income, marital status, drinking, smoking, moderate exercise, disease diagnosis, insomnia symptom, and depressive mood at baseline
†Adjustments for sex, age, job, education attainment, marital status, drinking, smoking,, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

Appendix Table 5. Associations between socioeconomic status and sleep quality patterns mediated by depressive symptom at years 4, eliminating sleep related-questionnaires from depressive symptoms

Socioeconomic status	Trajectory groups of sleep quality									
	Normal-stable (n=1,697)		Moderate-stable (n=1,157)		Poor-persistent (n=320)		Developing to Poor (n=84)		Severely poor-persistent (n=89)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Education attainment*										
Lower attainment[1] (n=2,617) vs Higher attainment[2] (ref, n=727)										
Total effect	1.00	reference	0.80	(0.63 - 0.97)	1.15	(0.66 - 1.64)	1.58	(0.09 - 3.07)	2.61	(0.00 - 5.30)
Natural direct effect	1.00	reference	0.77	(0.60 - 0.93)	1.06	(0.61 - 1.50)	1.44	(0.08 - 2.80)	2.27	(0.00 - 4.61)
Natural indirect effect	1.00	reference	1.04	(1.01 - 1.08)	1.09	(1.02 - 1.16)	1.10	(1.02 - 1.18)	1.15	(1.04 - 1.26)
Monthly household income†										
Lower income[3] (n=2,319) vs Higher income[4] (ref, n=1,007)										
Total effect	1.00	reference	0.98	(0.79 - 1.17)	1.01	(0.65 - 1.36)	0.98	(0.33 - 1.64)	1.25	(0.31 - 2.18)
Natural direct effect	1.00	reference	0.93	(0.76 - 1.11)	0.93	(0.60 - 1.25)	0.91	(0.30 - 1.52)	1.09	(0.27 - 1.92)
Natural indirect effect	1.00	reference	1.05	(1.02 - 1.08)	1.09	(1.02 - 1.15)	1.08	(1.01 - 1.15)	1.14	(1.04 - 1.24)

Notes. 395 data were deleted due to no measurements of BDI scores at years 4
1. High school or less
2. College or above
3. < $2,500
4. ≥ $2,500
*Adjustments for sex, age, job, monthly household income, drinking, smoking, moderate exercise, disease diagnosis, insomnia symptom, and depressive mood at baseline
†Adjustments for sex, age, job, education attainment, drinking, smoking,, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline
‡Sleep-related questionnaire was eliminated from scoring of Beck's Depression Inventory

Appendix Table 6. Associations between changes in household income and sleep quality patterns

Changes in household income	Trajectory groups of sleep quality							
	Normal-stable (n=1,619)		Moderate-stable (n=1,107)			Persistently or developing to poor (n=465)		
	OR*	(95% CI)	n	OR*	(95% CI)	n	OR*	(95% CI)
Persistently low[1] (n=1,797) vs Persistently high[2] (reference, n=684)	1.00	reference	628	1.01	(0.82 - 1.25)	299	1.20	(0.86 - 1.66)
Low[1] to high[2] (n=422) vs Persistently high2 (reference, n=684)	1.00	reference	143	1.00	(0.76 - 1.32)	55	1.13	(0.74 - 1.72)
High[2] to low[1] (n=288) vs Persistently high2 (reference, n=684)	1.00	reference	100	1.01	(0.74 - 1.38)	39	1.05	(0.65 - 1.70)

1. < $2,500
2. ≥ $2,500
*Adjustments for sex, age, job, education attainment, marital status, drinking, smoking, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

Appendix Table 7. Associations between household income changes and sleep quality patterns mediated by depressive symptom at years 4

Changes in household income	Trajectory groups of sleep quality							
	Normal-stable (n=1,619)		Moderate-stable (n=1,107)			Persistently or developing to poor (n=465)		
	OR	(95% CI)	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Persistently low[1] (n=1,797) vs Persistently high[2] (reference, n=684)								
Total effect	1.00	reference	1.02	(0.80 - 1.27)	0.895	1.07	(0.71 - 1.60)	0.740
Natural direct effect	1.00	reference	0.95	(0.75 - 1.19)	0.660	0.90	(0.58 - 1.34)	0.578
Natural indirect effect	1.00	reference	1.07	(1.03 - 1.12)	0.003	1.19	(1.10 - 1.30)	0.001
Low[1] to high[2] (n=422) vs Persistently high[2] (reference, n=684)								
Total effect	1.00	reference	1.02	(0.73 - 1.35)	0.918	0.83	(0.44 - 1.50)	0.471
Natural direct effect	1.00	reference	0.98	(0.71 - 1.31)	0.875	0.74	(0.40 - 1.37)	0.227
Natural indirect effect	1.00	reference	1.04	(0.98 - 1.12)	0.198	1.11	(0.99 - 1.28)	0.076
High[2] to low[1] (n=288) vs Persistently high[2] (reference, n=684)								
Total effect	1.00	reference	0.97	(0.70 - 1.41)	0.848	1.11	(0.55 - 2.00)	0.744
Natural direct effect	1.00	reference	0.91	(0.65 - 1.32)	0.588	0.97	(0.50 - 1.76)	0.927
Natural indirect effect	1.00	reference	1.06	(1.00 - 1.15)	0.090	1.14	(1.01 - 1.36)	0.051

1. < $2,500
2. ≥ $2,500

Adjustments for sex, age, job, education attainment, marital status, drinking, smoking, moderate exercise, number of family members, disease diagnosis, insomnia symptom, and depressive mood at baseline

Appendix Table 8. Comparisons in characteristic of participants between KoGES-Ansan baseline data and Korea National Health and Nutrition Examination Survey (KNHANES) 2001 data

Baseline characteristics	Data, aged 40 to 69	
	Ansan KoGES 2001-2002 (n=3,347)	KNHANES 2001 (n=13,003)
Men, %	1,701 (50.8)	5,701 (49.0)
Age,years	48.62 ± 7.33	51.72 ± 8.64
40 to < 50	2,174 (65.0)	6,243 (48.0)
50 to < 60	800 (23.9)	3,728 (28.7)
60 to < 70	373 (11.1)	3,032 (23.3)
BMI,kg/m²	24.72 ± 2.86	24.17 ± 3.05
Education, %		
High school or less	2,617 (78.3)	10,913 (84.1)
College or above	727 (21.7)	2,056 (15.9)
Monthly household income, %		
< $2,500	2,319 (69.7)	10,019 (83.0)
≥ $2,500	1,007 (30.3)	2060 (17.1)
Occupation, %		
Unemployment (homemaker or etc.)	1,841 (55.1)	4,673 (36.1)
Manual labor	1,044 (31.3)	6,773 (52.3)
Professional labor	455 (13.6)	1,500 (11.6)
Currently Married, %	3,130 (93.5)	11,191 (86.1)
Currently Smoking, %	734 (22.0)	1,160 (30.0)
Currently Drinking, %	1,736 (51.9)	2,263 (65.2)

Disease diagnosis*, %	602 (18.0)	1,799 (15.5)
Sleep duration, hour	6.66 ± 1.23	7.21 ± 6.75
SBP,mmHg	116.42 ± 16.58	126.23 ± 19.61
DBP,mmHg	77.98 ± 11.22	79.93 ± 11.52
LDL cholesterol,mg/dL	119.2 [99.2-140.8]	119 [97.4-140.4]
Triglyceride,mg/dL	133 [97-186]	130 [92-191]
HbA1c,%	5.5 [5.3-5.8]	6 [5.0-6.0]
Fasting glucose,mg/dL	83 [78-91]	96 [88-107]

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c.
*including coronary artery, myocardial infarction, hypertension, diabetes, and cancer.

Appendix Table 9. Missing data information in time-dependent cox analyses

Covariates	men (n=825)		women (n=948)	
	missing n	%	missing n	%
PSQI scores at baseline	0	0.0	0	0.0
PSQI scores at year 4	91	11.0	101	10.7
PSQI scores at year 6	63	7.6	96	10.1
PSQI scores at year 8	111	13.5	106	11.2
PSQI scores at year 10	124	15.0	122	12.9
Self-reported insomnia symptom	3	0.4	4	0.4
Self-reported depressive symptom	0	0.0	1	0.1
Education attainment	0	0.0	0	0.0
Household income	0	0.0	6	0.6
Job	0	0.0	0	0.0
Smoking status	0	0.0	0	0.0
Alcohol drinking	0	0.0	0	0.0
Exercise	0	0.0	0	0.0
Age	0	0.0	0	0.0
Body mass index	0	0.0	0	0.0
Triglyceride	7	0.8	8	0.8
Low-lipoprotein lipid cholesterol	7	0.8	8	0.8
High-lipoprotein lipid cholesterol	7	0.8	8	0.8
HOMA-IR	0	0.0	0	0.0
Disease diagnosis	0	0.0	0	0.0
Frequency of late-night snack*	269	32.6	519	54.7
Menopausal status (during whole follow-up)	n/a		0	0.0

*missing variables were not multiple imputed, but coded as 'non-response'

Appendix Table 10. Results from generalized linear model in the association between Pittsburgh Sleep Quality Index scores and log-transformed TG at each time point

Time	Exposure	Men				Women			
		Total n	β[1]	S.E	p-value	Total n	β[1]	S.E	p-value
Baseline[2]	PSQI scores, by 1 score increasing	1,982	0.003	0.004	0.433	1,714	0.005	0.004	0.242
year 4		1,523	0.001	0.004	0.901	1,431	0.003	0.003	0.444
year 6		1,488	0.002	0.004	0.577	1,392	0.009	0.003	0.008
year 8		1,390	0.005	0.004	0.188	1,367	0.009	0.003	0.004
year 10		1,370	0.007	0.004	0.097	1,340	-0.001	0.003	0.731
Baseline[2]	Poor sleep (PSQI > 5), compared to normal sleep	1,982	0.034	0.024	0.161	1,714	0.021	0.023	0.372
year 4		1,523	0.007	0.023	0.747	1,431	0.026	0.022	0.247
year 6		1,488	0.013	0.024	0.584	1,392	0.038	0.022	0.092
year 8		1,390	0.022	0.025	0.375	1,367	0.043	0.022	0.051
year 10		1,370	0.012	0.025	0.623	1,340	0.017	0.022	0.456

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; S.E., standard error; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein

1. Adjusted for education attainment, household income, job, marital status, age, BMI, smoking, drinking, physical activity, self-reported dyslipidemia diagnosis, cardiovascular diseases, hypertension, diabetes mellitus, LDL, TG, HDL (it varies by depending on lipid outcomes) and menopausal status (for women) at corresponding year

2. additionally adjusted frequency of late-night snacks

Appendix Table 11. Associations between time-dependent poor sleep status and hypertriglyceridemia onset after additional excluding of dyslipidemia diagnosis (a physician diagnosis or lipid-lowering drugs) before baseline (n=1,738)

Sleep quality status by sex	Person-years	Incident cases	Incidence rate (per 1,000 pys)	Demographic factors adjusted[1]			Biological factors adjusted[2]			Life-style factors adjusted[3]		
				HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Men (n=806)												
Normal sleep (PSQI ≤ 7, n=718)	7003.8	196	28.0	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=88)	821.4	29	35.3	1.00	(0.65 - 1.54)	1.00	0.92	(0.60 - 1.41)	0.70	0.90	(0.58 - 1.39)	0.64
Women (n=932)												
Normal sleep (PSQI ≤ 7, n=805)	8381.6	155	18.5	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=127)	1252.2	32	25.6	1.65	(1.15 - 2.35)	0.01	1.63	(1.14 - 2.33)	0.01	1.61	(1.12 - 2.31)	0.01

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein
1. adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, and self-reported insomnia symptom
2. additionally adjusted for BMI, LDL, TG, HDL, HOMA-IR, and menopausal status for women
3. additionally adjusted for smoking, drinking, physical activity, and frequency of late-night snack

Appendix table 12. Associations between time-dependent poor sleep status and hypertriglyceridemia onset with participants ≥4 measurements of sleep quality data (n=1,524)

Sleep quality status by sex	Person years	Incident cases	Incidence rate (per 1,000 pys)	Demographic factors adjusted[1]			Biological factors adjusted[2]			Life-style factors adjusted[3]		
				HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Men (n=716)												
Normal sleep (PSQI ≤ 7, n=640)	6344.2	181	28.5	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=76)	723.2	26	36.0	1.21	(0.79 - 1.85)	0.38	1.13	(0.74 - 1.73)	0.58	1.11	(0.72 - 1.70)	0.64
Women (n=841)												
Normal sleep (PSQI ≤ 7, n=734)	7776.1	148	19.0	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=107)	1071.1	26	24.3	1.67	(1.16 - 2.42)	0.01	1.50	(1.04 - 2.18)	0.03	1.52	(1.04 - 2.21)	0.03

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein
1. adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, and self-reported insomnia symptom
2. additionally adjusted for BMI, LDL, TG, HDL, HOMA-IR, and menopausal status for women
3. additionally adjusted for smoking, drinking, physical activity, and frequency of late-night snack

Appendix table 13. Associations between time-dependent poor sleep status and hypertriglyceridemia onset with complete case of sleep quality (n=1,175)

Sleep quality status by sex	Person-years	Incident cases	Incidence rate (per 1,000 pys)	Demographic factors adjusted[1]			Biological factors adjusted[2]			Life-style factors adjusted[3]		
				HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Men (n=545)												
Normal sleep (PSQI ≤ 7, n=493)	4959.1	136	27.4	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=52)	513.2	17	33.1	1.10	(0.66 - 1.81)	0.72	1.07	(0.64 - 1.77)	0.80	0.98	(0.58 - 1.63)	0.92
Women (n=630)												
Normal sleep (PSQI ≤ 7, n=554)	5929.8	118	19.9	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 7, n=76)	748.4	21	28.1	1.90	(1.28 - 2.83)	<0.01	1.81	(1.21 - 2.72)	<0.01	1.85	(1.23 - 2.79)	<0.01

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein
1. adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, and self-reported insomnia symptom
2. additionally adjusted for BMI, LDL, TG, HDL, HOMA-IR, and menopausal status for women
3. additionally adjusted for smoking, drinking, physical activity, and frequency of late-night snack

Appendix Table 14. Associations between time-dependent poor sleep status determined as PSQI > 5 and hypertriglyceridemia (n=1,773)

Sleep quality status by sex	Person-years	Incident cases	Incidence rate (per 1,000 pys)	Demographic factors adjusted[1]			Biological factors adjusted[2]			Life-style factors adjusted[3]		
				HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Men (n=825)												
Normal sleep (PSQI ≤ 5, n=631)	6142.1	174	28.3	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 5, n=194)	1850.8	59	31.9	1.02	(0.74 - 1.40)	0.91	1.03	(0.75 - 1.41)	0.86	1.00	(0.73 - 1.38)	0.99
Women (n=948)												
Normal sleep (PSQI ≤ 5, n=661)	6976.6	124	17.8	1.00	reference		1.00	reference		1.00	reference	
Poor sleep (PSQI > 5, n=287)	2813.9	68	24.2	1.42	(1.04 - 1.93)	0.03	1.29	(0.94 - 1.76)	0.11	1.25	(0.91 - 1.71)	0.18

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein
1. adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, and self-reported insomnia symptom
2. additionally adjusted for BMI, LDL, TG, HDL, HOMA-IR, and menopausal status for women
3. additionally adjusted for smoking, drinking, physical activity, and frequency of late-night snack

Appendix Table 15. The mean values of the components in the global Pittsburgh Sleep Quality Index component scores by sex

PSQI Components		Subjective sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbance	Sleep medication use	Daytime dysfunction
score range		(0-3)	(0-3)	(0-3)	(0-3)	(0-3)	(0-3)	(0-3)
baseline	men	0.97	0.69	1.07*	0.25	0.85*	0.02	0.49*
	women	1.00	0.74	1.34*	0.24	0.91*	0.03	0.39*
year 4	men	0.93	0.73*	0.98*	0.28*	0.83*	0.04*	0.73*
	women	0.96	0.89*	1.30*	0.35*	0.91*	0.10*	0.64*
year 6	men	0.96*	0.62*	1.02*	0.27*	0.40*	0.04*	0.62
	women	1.07*	0.89*	1.38*	0.44*	0.67*	0.10*	0.62
year 8	men	0.94*	0.49*	1.19*	0.37*	0.27*	0.05	0.39
	women	1.03*	0.71*	1.50*	0.56*	0.42*	0.09	0.43
year 10	men	0.91*	0.46*	1.17*	0.38*	0.29*	0.05*	0.47
	women	1.00*	0.68*	1.40*	0.49*	0.44*	0.11*	0.41

Higher scores indicate the worse status
* p-value for difference <0.05

Appendix Table 16. Associations between time-dependent sleep quality and hyper-LDL-cholesterolemia/hypo-HDL-cholesterolemia by sex

Sleep quality status by sex	Hyper-LDL-cholesterolemia			Hypo-HDL-cholesterolemia		
	case n/ total n	HR	95%CI	case n/ total n	HR	95%CI
Men (n=1,295)						
Normal sleep (PSQI ≤ 7)	425/1,159	1.00	reference	740/1,159	1.00	reference
Poor sleep (PSQI > 7)	43/136	0.71	(0.44 - 1.16)	91/136	1.22	(0.89 - 1.67)
Women (n=1,400)						
Normal sleep (PSQI ≤ 7)	625/1,202	1.00	reference	570/1,202	1.00	reference
Poor sleep (PSQI > 7)	114/198	0.98	(0.75 - 1.29)	101/198	1.17	(0.88 - 1.56)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein, TG; triglyceride.
Adjusted for age, education, household income, job, marriage status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, self-reported insomnia symptom, BMI, LDL, TG, HDL, menopausal status, smoking, drinking, and physical activity

Appendix Table 17. Power calculation in cohort studies for evaluating the impact of poor sleep on hypertriglyceridemia onset.

- Sample size estimation for independent cohort studies [95]

n = Total number of desired study subjects (case) to identify true relative risk with two-sided Type-I error
m = Number of subjects (control) per experimental subject
$Z_{1-\beta}$ = It is the desired power (0.84 for 80% power and 1.28 for 90% power)
$Z_{1-\alpha/2}$ = Critical value and a standard value for the corresponding level of confidence.
(at 95% CI it is 1.96 and at 99% CI or 1% type I error it is 2.58)
p_0 = Possibility of event in controls
p_1 = Possibility of event in experimental
$p = P_1 + m * P_0 / m+1$

The estimation formula: $(n)= [Z_{1-\alpha/2} \surd\{(1+ 1/ma)p*(1-p)\} + Z_{1-\beta} \surd\{ p_0 *(1- p_0 /m) p_1 (1- p_1)\}]^2 / (p_0- p_1)^2$

Applying on the current study

$m = 1$, $Z_{1-\beta}=0.84$, $Z_{1-\alpha/2} =1.96$, $p_0*=0.29$, $p_1*=0.35$, $p=0.32$

*possibility of event in control (p_0)/experimental (p_1)was drawn from a previous study [19].

$(n)= [1.96 \surd\{(1+ 1/1\}0.32)*(1-0.32)\} + 0.84 \surd\{0.29*(1- 0.29 /1) 0.35(1- 0.35)\}]^2 / (0.29-0.35)^2$

$= (1.96*0.660+0.84*0.216)^2 /0.0036=604.005$

(n)=604+60 (considering 10% dropout of study participants)

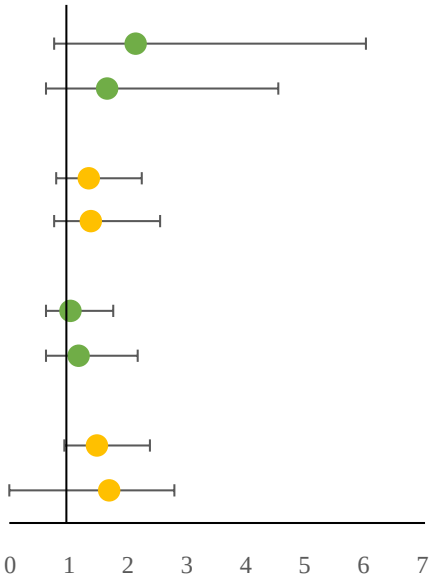
Appendix Table 18. Correlations between sleep components of Pittsburgh Sleep Quality Index and triglyceride at baseline.

sex	correlation value	Sleep quality component (score range: 0~3)						
		Subjective sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbance	Sleep drug	Daytime dysfunction
Men (n=1,982)	r	0.043	0.021	-0.021	-0.005	-0.014	-0.008	0.039
	p-value	0.057	0.343	0.340	0.815	0.520	0.707	0.086
Women (n=1,714)	r	0.056	0.090	0.028	0.052	0.064	0.065	-0.045
	p-value	0.020	<0.001	0.247	0.031	0.008	0.007	0.062

*Higher scores of sleep quality component indicate the worse status

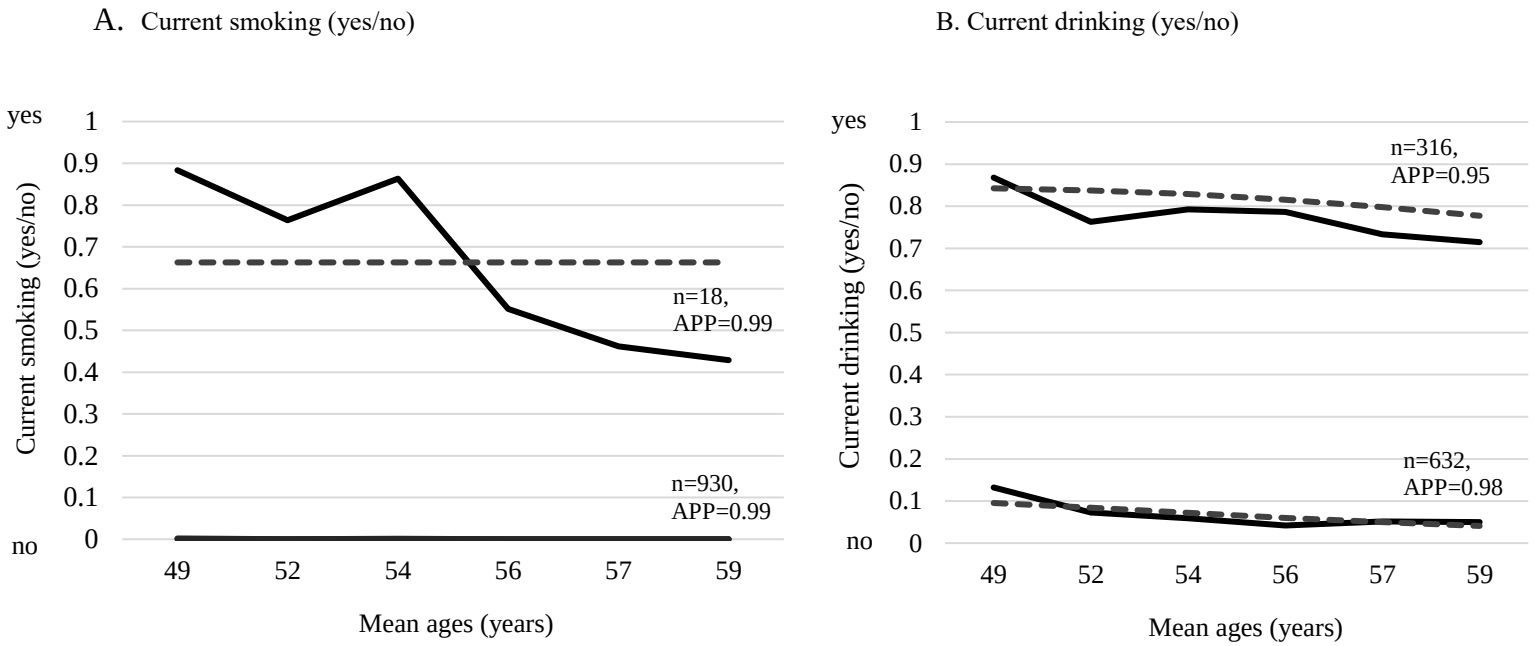
Appendix Figure 1. Forest plots of the associations between time-dependent sleep quality and hypertriglyceridemia onset with stratification by frequent late-night snack and menopausal status at baseline in women.

Stratification	HR	95% CI
Less frequent late-night snack[1,3] (n=336)		
Poor sleep (PSQI > 5, n=98) vs normal sleep (PSQI≤5)	2.14	(0.76 - 6.08)
Poor sleep (PSQI > 7, n=45) vs normal sleep (PSQI≤7)	1.67	(0.61 - 4.58)
Frequent late-night snack[2,3] (n=93)		
Poor sleep (PSQI > 5, n=40) vs normal sleep (PSQI≤5)	1.33	(0.78 - 2.26)
Poor sleep (PSQI > 7, n=19) vs normal sleep (PSQI≤7)	1.38	(0.75 - 2.54)
Pre-menopausal[4] (n=446)		
Poor sleep (PSQI > 5, n=104) vs normal sleep (PSQI≤5)	1.03	(0.61 - 1.75)
Poor sleep (PSQI > 7, n=42) vs normal sleep (PSQI≤7)	1.16	(0.63 - 2.17)
Post-menopausal[4] (n=392)		
Poor sleep (PSQI > 5, n=148) vs normal sleep (PSQI≤5)	1.47	(0.91 - 2.38)
Poor sleep (PSQI > 7, n=72) vs normal sleep (PSQI≤7)	1.68	(1.01 - 2.80)



Abbreviations: HR; hazard ratio, 95% CI; 95% confidence interval, PSQI; Pittsburgh Sleep Quality Index.
1. none to 2-3 times/week
2. more than 4-5 times/week
Adjusted for age, education, household income, job, marital status, hypertension diagnosis, diabetes mellitus diagnosis, cardiovascular disease, self-reported depressive symptoms, self-reported insomnia symptom, BMI, LDL, TG, HDL, HOMA-IR, menopausal status, smoking, drinking, physical activity, (menopausal status or frequent late-night snack)

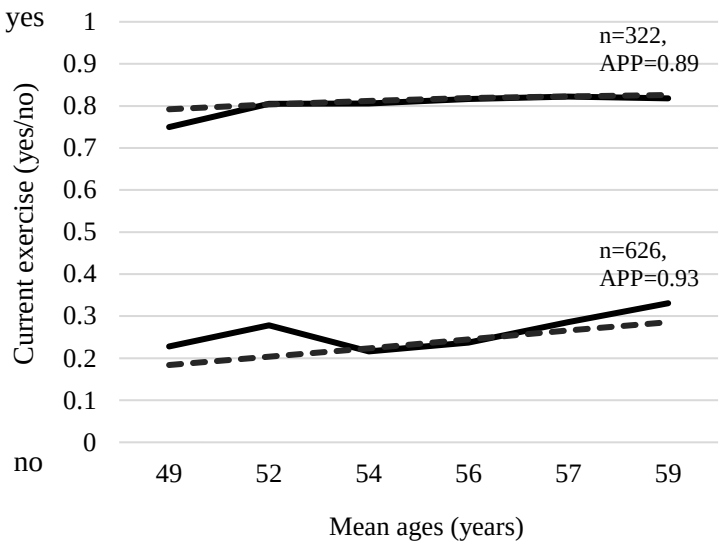
Appendix Figure 2-A to 2-D. Time-dependent changes in life-style factors (e.g., current smoking, drinking, and exercise) and body mass index in women.



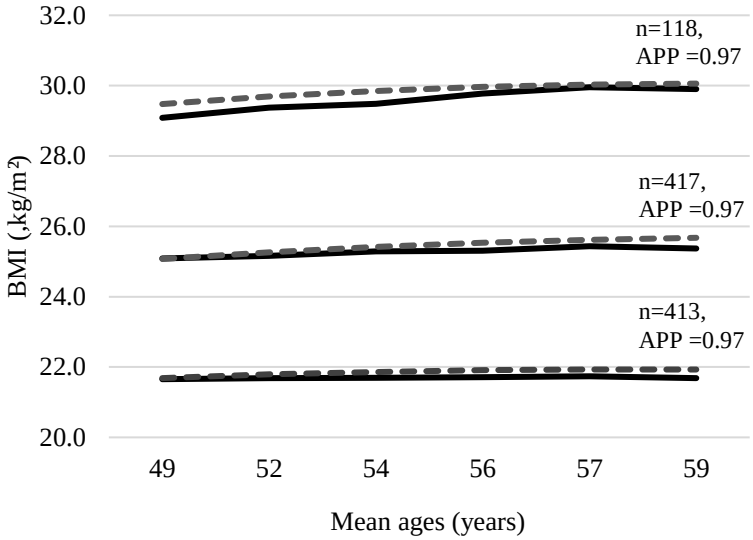
Abbreviations: APP, average posterior probabilities.

* The average posterior probabilities of ≥ 0.70 indicate sufficient discrimination of individuals between trajectories. Observed means are presented as solid lines and expected means are presented as dashed lines.

C. Current exercise (yes/no)



D. Body mass index (continuously)



Abbreviations: APP, average posterior probabilities.

* The average posterior probabilities of ≥ 0.70 indicate sufficient discrimination of individuals between trajectories. Observed means are presented as solid lines and expected means are presented as dashed lines.

수면의 질에 대한 사회경제적 수준의 우울증 매개 효과와 고중성지방혈증에 대한 수면 질의 시간 변화 효과

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[연구 배경 및 목적] 수면의 질은 우울 증상이나 빈곤한 사회자원 등 불리한 환경에 지속해서 노출될 경우 악화될 수 있고, 이렇게 악화된 수면의 질은 중성지방에 영향을 미칠 수 있다. 수면의 질은 시간에 따라 변하는 특성이 있지만, 대부분의 사전 연구들은 한 번 측정된 수면 정보만 활용하였다. 사전연구의 한계점을 고려하여, 본 연구는 두 가지 측면으로 크게 나누어서 수면의 질에 관해 연구하는 것을 목표로 한다. 첫 번째, 사회경제적 수준이 수면의 질 변화에 어떤 영향을 미치는지, 그리고 더 나아가 해당 연관성을 우울 증상이 매개하

는지 살펴보고자 한다. 두 번째로, 시간에 따른 수면의 질 변화가 고중성지방혈증 발생에 어떤 영향을 미치는지 연구하는 것을 목표로 한다.

[파트 1. 사회경제적 수준과 수면의 질 패턴 사이의 연관성과 우울 증상의 매개 효과]

본 연구는 한국인 유전체 역학 조사사업의 일부인 안산 지역 대상자 3,347명의 정보를 사용하였고, 이들은 40-69세의 연령으로 기반조사로부터 16년 동안 2년 주기로 추적되었다. 종단적 수면의 질 패턴을 위해 5번 반복 측정된 피츠버그 수면의 질 지표 정보를 이용하여 궤적모형분석을 시행하였다. 기반조사의 교육수준 (전문대학 졸업 이상/미만), 월 가정 수입 (300만 원 이상/미만)이 분석에 사용되었다. 기반조사 시행 4년 후 측정된 '벡의 우울 증상 지표'로 우울 증상을 평가했다. 다항 로지스틱 회귀분석으로 기반조사의 사회경제적 지표와 수면의 질 패턴 사이의 연관성을 분석했고, 인과적 매개모형으로 우울증상의 매개 효과를 분석했다. 총 다섯 가지의 수면의 질 패턴을 관찰하였는데, "정상 수준 유지"에 1,697명, "적정 수준 유지"에 1,157명, "낮은 수준 지속"에 320명, "수면의 질 악화"에 84명, "매우 낮은 수준 지속"에 89명의 대상자가 속했다. 전반적으로, 사회경제적 수준과 종단적 수면의 질 패턴 사이에는 유의한 직접 연관성이 보이지 않았다. 하지만 우울 증상이 사회경제적 수준과 수면의 질 패턴의 연관성을 유의하게 매개하는 것으로 나타났다. 상대적으로

더 낮은 교육 수준 혹은 가정수입을 보유한 대상자에서 우울증상을 통해 더 좋지 않은 수면 패턴과 유의하게 연관되는 결과를 관찰했다 (매개효과 오즈비 범위: 교육수준=1.05-1.17; 가정수입=1.05-1.15). 사회경제적 지표와 수면의 질 패턴 사이를 우울증상이 유의하게 매개한다는 본 연구의 결과를 바탕으로, 낮은 사회경제적 수준을 가진 인구들의 수면건강을 위해 그들의 정신 건강 관리가 지역사회 수준에서 고려되어야 한다는 점을 제안할 수 있다.

[파트 2. 시간에 따른 수면의 질 변화가 고중성지방혈증 발생에 미치는 영향]

본 연구는 안산 코제스 대상자 중 기반조사 당시 이상지질혈증이 없고 최소 3번 이상의 수면의 질이 측정된 1,773명의 대상자를 활용하였다. 낮은 수면의 질은 피츠버그 수면의 질 지표 〉 7점으로 정의되었고, 고중성지방혈증 발생은 중성지방 200mg/dL이상인 경우로 정의되었다. 시간에 따른 변화를 고려한 수면의 질을 활용하는 확장된 콕스 모형으로 위험비 및 95% 신뢰구간이 계산되었다. 성별을 나누어서 분석했으며, 인구학적, 생물학적, 그리고 생활습관 요인을 보정하였다. 추적 기간의 중앙값은 11.8년이었고, 총 425명의 대상자가 새롭게 고중성지방혈증을 진단받았다. 여성에서, 시간 변화를 고려한 낮은 수면의 질과 고중성지방혈증의 연관성이 발견되었다 (위험비: 1.53, 95% 신뢰구간: 1.07-2.17). 남성에서는 낮은 수면의 질과 고중성지방혈증 사이에 유의한 연관성이 관찰되지 않았다 (위험비:

1.03, 95% 신뢰구간: 0.68-1.55). 정상 지질 수준을 가진 중년 여성의 심장 대사 건강을 위해 그들이 적절한 수면 질을 유지할 수 있도록 권장되어야 한다.

[결론] 비교적 건강한 지질 수준을 유지하고 있는 중년 여성들을 대상으로 그들의 심장 대사 건강을 위해 수면 질을 적절하게 유지하는 것이 일차 진료 현장에서 권장될 수 있다. 앞선 목표를 달성하기 위해서는, 특히 낮은 사회경제적 수준을 가진 중년여성들의 정신건강이 지역사회 수준에서 관리되어야 할 필요가 있다.

핵심이 되는 말: 종단분석, 사회경제적 수준, 우울증상, 매개 분석, 낮은 수면의 질, 고중성지방혈증, 확장된(extended) 콕스 모형