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Longitudinal Associations between Objective Sleep and Lipids: The CARDIA Study

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Study Objective: To investigate the longitudinal relationships between actigraph-derived sleep duration, fragmentation, and lipid levels.

Design and Setting: Longitudinal data from the Coronary Artery Risk Development in Young Adults Sleep Study (2003-05), an observational cohort at the Chicago site.

Participants: There were 503 black and white adults, ages 32-51 years, with no prior history of cardiovascular disease.

Interventions: N/A.

Measurement and Results: Sleep duration and fragmentation were measured using 6 days of wrist actigraphy. Sleep quality was measured with the Pittsburgh Sleep Quality Index. The outcome variables, measured at 3 examinations over 10 years (Baseline [2000-01], 5-year [2005-06], and 10-year follow-up [2010-11]), were total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), and TC/HDL ratio. The associations between each sleep parameter and 10-year change in lipids were analyzed with generalized estimating equation models adjusting for relevant confounders. After adjustment, each hour increase in sleep duration was significantly associated with higher TC (5.2 mg/dL, 95%CI: 1.7, 8.6) and LDL (3.4 mg/dL, 95%CI: 0.2, 6.6) in the total sample, a 1.1 mg/dL increase in TG (95%CI: 1.0, 1.1) among men, and a borderline significant greater odds for a TC/HDL ratio ≥ 5 among men (OR: 1.37, 95%CI: 0.99, 1.90). Overall, sleep fragmentation and sleep quality scores were not associated with change in lipids.

Conclusions: Beyond relevant covariates, over a 10-year follow-up, longer objective sleep duration was longitudinally and significantly associated with a poorer lipid profile. Greater objective sleep fragmentation and self-reported poor sleep quality were not related to a poorer lipid profile.

Keywords: Sleep duration; sleep fragmentation, lipids, sleep quality, ethnicity, sex

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INTRODUCTION

Over the last two decades, studies documented an association between insufficient and disrupted sleep with cardiovascular disease (CVD) and cardiovascular-related mortality.[1-14] Because the mechanisms underlying these relationships are unclear, recent studies have investigated links between sleep and risk factors for CVD, particularly lipoproteins[15-27] and triglycerides.[15-21,25,26] These studies yielded inconsistent results and were limited by self-reported, retrospective sleep measures, little assessment beyond sleep duration, cross-sectional designs, and samples lacking ethnic diversity. Two cross-sectional studies examined the relationship between sleep and lipids using objective sleep measures,[16,23] but little is known about the longitudinal relationships.

Our study group, using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, prospectively demonstrated significant associations between shorter objective sleep duration or greater sleep fragmentation and incident coronary artery calcification[28] and five-year change in blood pressure.[29] In the present study we aimed to determine whether objectively measured sleep parameters are longitudinally associated with lipid profiles among persons without a prior history of CVD. We also tested whether these associations vary by sex and race because disrupted sleep and lipid levels vary by these groups.[30,31]

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METHODS

Study Sample and Design

The CARDIA study was initiated across 4 US sites in 1985-86. The study recruited 18- to 30-year-olds balanced by age (18-24, 25-30 years), race (black, white), sex, and education level (< high school, ≥ high school) at each study site. The CARDIA study procedures have been described previously.[32] The present analysis includes participants from the ancillary CARDIA Sleep Study at the Chicago site who were not pregnant during the year 15 (2000-01) clinical examination. Written consent was provided by 670 participants (82%). Three days of wrist actigraphy and self-reported sleep were collected in 2 waves one year apart between 2003 and 2005. Participants reporting a history of one or more of the following conditions at year 15 were excluded from the analyses: high blood pressure; heart problems; peripheral vascular disease; stroke or transient ischemic attack; blood clot in leg, veins, or lungs requiring blood thinning medicine; high systolic (≥ 140 mm Hg) and diastolic blood pressure (≥ 90 mm Hg); hypertension medication use; and lipid-lowering medication use. After exclusions, 503 participants qualified for the present study (75.1%). The term "baseline" in this study refers to data collected at the year

15 clinical examination. Longitudinal analyses investigated change in lipid levels across clinical examination years 15 (baseline), 20 (5-year follow-up), and 25 (10-year follow-up). For each examination, records were omitted from the analyses if participants reported being pregnant or using lipid-lowering medications. This approach maximized the number of participants with eligible records instead of excluding anyone who met exclusion criteria at the 3 time points. The ancillary CARDIA Sleep Study was approved by the institutional review boards at Northwestern University and the University of Chicago.

Outcome Measures

At baseline, 5-year, and 10-year follow-up, participants had blood drawn by certified technicians in the early to mid-morning after 12 h of fasting. Levels of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) were measured at the Northwest Lipids Research Laboratory in Seattle, WA. Cholesterol and TG were analyzed with the Abbott Spectrum diagnostic system using the Trinder-type method and the ultraviolet method, respectively.[33] LDL was computed with the Friedewald equation[34] for only those participants with TG levels below 400 mg/dL. CARDIA uses an extensive quality control program to ensure comparability of lipid values across examination years.[35] The TC/HDL ratio was also evaluated as a dichotomous variable (i.e., < 5.0 vs. ≥ 5.0) because the clinical recommendation by the American Heart Association is to maintain a ratio below 5 to 1.[36] The TC/HDL ratio is a useful value for gauging a patient's CVD risk.

Sleep Measures

The 3 sleep measures were wrist actigraphy-derived average sleep duration and sleep fragmentation, and the global score from the Pittsburgh Sleep Quality Index (PSQI).[37] The wrist actigraphs (Actiwatch-16, Mini-Mitter Inc, Bend, OR) were worn for up to 6 days from 2003 to 2005. The consistency in sleep duration and fragmentation values was high; therefore, the averages for all available days were computed.[38] Wrist activity was measured in 30-sec epochs using highly sensitive omnidirectional accelerometers. Validated manufacturer software was used to calculate average sleep duration and fragmentation. Sleep duration was the time from sleep onset to final awakening minus the amount of time spent awake during the night. Sleep fragmentation was a measure of the restlessness of the sleep period, from sleep onset to sleep termination, by summing the percentage of time the participant was moving and the percentage of time spent immobile for ≤ 1 min to create a sleep fragmentation score. More detailed information on the actigraphy methods used were previously described.[30] The PSQI is a well-validated measure of sleep quality and disturbances over the past month.[37] Scores > 5 indicate poor sleep quality, and higher scores indicate greater severity (Range: 0-21).

Covariates

Sociodemographic covariates were age, sex, race (self-reported; black or white), income (self-reported; 4-level ordinal variable: < $16K; $16-34,999K; $35-74,999K; ≥ $75K), and education (self-reported; 3-level categorical variable: < high school; high school degree; some college or greater). Poor lipid risk factors were smoking status; physical activity; body mass index (BMI); alcohol use; symptoms of depression; C-reactive protein (CRP); history of diabetes, thyroid problems, or kidney problems; and sleep apnea risk.

Smoking status was classified as never smoked, former, or current smoker. Self-reported physical activity was assessed using the CARDIA Physical Activity History Questionnaire, an instrument that has demonstrated good psychometric properties.[39] Intensity scores assigned to 13 measured physical activities were summated into a continuous measure of "exercise units." Alcohol use was a continuous measure of the average mL/day. Symptoms of depression were measured with the Center for Epidemiologic Studies Depression scale (CES-D).[40] CRP levels were determined using an ultrasensitive ELISA assay[41] derived from purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem). History of diabetes, thyroid, or kidney problems was determined by self-report to the question "has a doctor or nurse ever said that you have…" any of these conditions. Apnea risk was determined by the Berlin Questionnaire.[42] The Berlin Questionnaire categorizes individuals by risk for having sleep apnea if they endorse experiencing ≥ 2 of 3 of the following: frequent daytime sleepiness, loud or frequent snoring, and having either high blood pressure or BMI > 30 kg/m^2. Since persons with high blood pressure were excluded from the study and BMI was already controlled for, only daytime sleepiness and snoring were controlled in the models.

Statistical Analyses

Sample characteristics for the whole sample and their relation to each continuous sleep variable were analyzed with one-way ANOVA for categorical variables and Pearson correlation coefficients for continuous variables. Linear regression models were used to investigate the associations between all continuous sleep parameters and lipid levels—including the TC/HDL ratio—at baseline after adjusting for covariates in a sequence of nested models. Model 1 consisted of the unadjusted relationship between each sleep parameter with lipid levels. Model 2 added sociodemographic factors to Model 1. Model 3 added poor lipid profile risk factors to Model 2. Given the time difference between baseline covariate assessment (2000-01) and the sleep assessment (2003-05), we also analyzed the associations using the 5-year follow-up examination as baseline data to determine any differences between the 2 analysis approaches. Sleep duration and fragmentation were not included in the same models because of a significant inverse relationship between them (r = -0.44, P < 0.001). TG, CRP, and physical activity values were log-normalized due to non-normal distributions.

Generalized estimating equation regression models were used to estimate the relation between each sleep parameter and 10-year change in lipids and the TC/HDL ratio, while controlling for the effect of time on lipids and the correlations between the 3 lipid measurements to correct the standard errors of the time-dependent covariates. The correction for the within-subjects correlations used an unstructured covariance structure. The same sequence of nested models described earlier was used in these analyses. To verify the presence of linear relationships, quadratic associations between sleep duration and lipids were also tested. We also assessed if the associations varied by race and race-sex groups by adding interaction terms into

separate fully adjusted models. If significant interactions were discovered, then stratified analyses by race or race-sex groups were conducted while adjusting for all covariates including sex in sleep-race stratified models. Given known differences in lipid levels between men and women and change in lipids over time,[31] sex-stratified models were conducted even in the absence of significant interactions. In the sex-stratified models, additional time-varying covariates were accounted for in the models on women. These covariates were hormone medication use (dichotomous "yes" or "no" variable), menopause status (i.e., postmenopausal or not), and oral contraceptive medication use (dichotomous "yes" or "no" variable). All regression coefficients were tested for significance at the 0.05 α level using 2-sided tests. Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Gary, NC).

RESULTS

Sample Characteristics

In Table 1, sample characteristics for all predictors and their relation to each sleep variable are displayed. Baseline mean age for the sample was 39.9 years (SD 3.7; range: 32-51). Women represented 54.9% of the sample (n = 276), and 40.4% were black (n = 203; black women n = 119; black men n = 84). Most participants reported moderate-to-high incomes and a high-school level of education or higher. At baseline, many of the covariates were significantly related to at least one of the sleep variables, with the exceptions of alcohol consumption in the total sample and reproductive-related factors among women.

Sleep at Baseline and Lipids Changes over 10-year Follow-up

In the sample, 90.5% of the participants (n = 456) provided 6 nights of recorded sleep, and 99.0% (n = 499) provided ≥ 3 nights. The sample slept on average 6.1 h (SD 1.1, range: 1.8-8.8) per night with an average sleep fragmentation score of 19.1% (SD 8.0, range: 4.4-63.9). The sample perceived their sleep quality to be borderline poor (M = 5.6, SD 2.7, range: 0-16). Half of the sample reported poor sleep quality (> 5; n = 249). Table 2 displays changes in lipid levels for each examination year in the total sample and by race-sex groups. In general, all lipid levels increased over the 10-year interval, although the proportion of participants with a TC/HDL ratio ≥ 5.0 decreased. TC, LDL, and HDL increased the most in white women, and TG increased the most in black women. The proportion of participants with a TC/HDL ratio ≥ 5 reduced for all groups, but white males consistently had the highest proportion over time. Men had significantly greater TC and LDL than women at baseline, but this difference became nonsignificant by 10-year follow-up. However, race differences in TC emerged over time, with whites having greater TC than blacks. HDL over 10-year follow-up was consistently greater among women than men, with white females having the greatest levels. White males consistently had the greatest TG levels over time compared to all other race-sex groups.

Linear Associations between Sleep Variables and Lipid Values at Baseline

Results from the analyses between the sleep variables and baseline and 5-year follow-up examination lipid values were similar. Therefore, we present the results of the linear models, using lipid data at baseline (2000-01) with the sleep data. Adjusting for all covariates, there was a significant positive association between sleep duration and baseline TC (3.6 mg/dL per hour, t_{456} = 2.1, P = 0.039). In addition there was a sex-sleep duration interaction on HDL (P = 0.018), and race-sleep fragmentation interactions on TC (P = 0.011) and LDL (P = 0.006). Stratified analyses, however, did not reveal any significant associations by subgroups (data not presented). There were no other significant associations or interactions noted.

10-year Longitudinal Associations

Sleep Duration

The associations between sleep duration and 10-year change in lipids in the total sample and by sex are described in Table 3. In the overall sample, each hour increase in sleep duration was significantly associated with a 5.2 mg/dL increase in TC (P = 0.003) and a 3.3 mg/dL per hour increase in LDL (P = 0.039) over 10 years in fully adjusted models. Longer sleep duration was also associated with a 27% greater odds of incident TC/HDL ratio ≥ 5.0 (95%CI: 0.99, 1.63) and a 1.0 mg/dL increase in TG in fully-adjusted models, but both results were borderline significant. There were no significant associations with HDL after adjustment. However, there was a significant interaction by sex for HDL (P = 0.031).

In sex-stratified analyses with additional adjustment for reproductive-related factors among women, an hour increase in sleep duration among women was associated with a 1.2 mg/dL increase in HDL and a 0.1 mg/dL decrease among men. Neither of these associations reached statistical significance. In sex-stratified analyses for other outcomes, the positive association between sleep duration and TC remained significant for males but not significant for females once the model adjusted for reproductive-related factors (5.0 mg/dL, 95%CI: -0.2, 10.2, P = 0.06). Adjustment for reproductive-related factors among women also attenuated the association between sleep duration and LDL (2.8 mg/dL, 95%CI: -2.0, 7.5, P = 0.25). Among males, there was a borderline significant positive association between sleep duration and odds of TC/HDL ratio ≥ 5.0 (P = 0.054), and a significant positive association between sleep duration and TG (1.1 mg/dL, 95%CI: 1.0, 1.1, P = 0.042). There were no significant interactions by race or race-sex groups, nor were there any significant quadratic associations.

Sleep Fragmentation

Table 4 displays the associations between sleep fragmentation and 10-year change in lipid levels in the total sample and by sex. Sleep fragmentation was not associated with change in lipid levels after full adjustment in the overall sample or by sex group. There were significant interactions by race for TC (P = 0.009) and LDL (P = 0.003). However, in race-stratified analyses, the separate associations between sleep fragmentation, TC, and LDL for whites and blacks were not significant (data not presented).

PSQI

Table 5 displays the associations between PSQI scores and 10-year change in lipid levels in the total sample and by sex.

Table 1—Sample characteristics and their relation with each sleep parameter at baseline[a]

	Whole Sample		Sleep Duration		Sleep Fragmentation		PSQI	
Variable	**N**	**M (SD) or %**	**M (SD) or *r***	**P**	**M (SD) or *r***	**P**	**M (SD) or *r***	**P**
Age, years	503	39.9 (3.7)	0.04	0.38	-0.11	0.01	-0.06	0.18
Sex				< 0.001		< 0.001		0.12
Female	276	54.9	6.4 (0.9)		17.6 (7.3)		5.8 (2.9)	
Male	227	45.1	5.8 (1.2)		21.0 (8.4)		5.4 (2.5)	
Race				< 0.001		< 0.001		< 0.001
White	300	59.6	6.4 (0.9)		17.8 (6.9)		5.2 (2.4)	
Black	203	40.4	5.6 (1.1)		21.1 (9.0)		6.2 (3.0)	
Race by Sex Groups				< 0.001		< 0.001		0.001
White Women	157	31.2	6.7 (0.8)		16.8 (6.2)		5.4 (2.6)	
White Men	143	28.4	6.1 (0.9)		19.4 (7.3)		5.1 (2.2)	
Black Women	119	23.7	5.9 (0.8)		19.4 (8.3)		6.3 (3.1)	
Black Men	84	16.7	5.1 (1.3)		23.6 (9.4)		6.0 (2.8)	
Income				< 0.001		< 0.001		< 0.001
< $16,000	28	5.6	5.3 (1.4)		22.2 (7.5)		7.8 (4.0)	
$16,000-34,999	58	11.7	5.9 (1.2)		22.7 (10.7)		6.8 (2.8)	
$35,000-75,000	168	33.7	6.0 (1.1)		19.7 (8.2)		5.8 (2.7)	
> $75,000	244	49.0	6.3 (0.9)		17.5 (6.5)		5.0 (2.3)	
Education				< 0.001		< 0.001		< 0.001
< High school	98	19.5	5.7 (1.3)		22.6 (9.2)		6.5 (3.0)	
High school degree	272	54.1	6.1 (1.0)		18.8 (7.6)		5.6 (2.7)	
Some college or higher	133	26.4	6.4 (0.8)		17.2 (6.8)		5.0 (2.3)	
BMI	502	27.6 (5.9)	-0.18	< 0.001	0.17	< 0.001	0.21	< 0.001
Current Smoking				< 0.001		< 0.001		0.034
Never	314	62.6	6.1 (1.0)		18.3 (7.7)		5.4 (2.6)	
Former Smoker	88	17.5	6.4 (0.9)		18.4 (6.2)		5.6 (2.6)	
Current Smoker	100	19.9	5.8 (1.3)		22.5 (9.4)		6.2 (3.0)	
Alcohol, mL/day	501	10.5 (19.2)	-0.01	0.87	0.09	0.059	0.02	0.65
CES-D	499	8.4 (7.4)	-0.13	0.005	0.09	0.049	0.41	< 0.001
Log-Physical activity	503	5.5 (1.2)	-0.01	0.79	-0.11	0.02	0.001	0.98
Log-C-reactive protein	488	0.2 (1.2)	-0.04	0.34	0.13	0.004	0.13	0.004
DM, thyroid, or kidney problems				0.94		0.01		0.49
None	444	88.3	6.1 (1.0)		19.4 (8.2)		5.6 (2.7)	
Problems	59	11.7	6.1 (1.2)		17.3 (5.4)		5.8 (2.7)	
BSQ - snoring				0.22		0.04		0.03
Non-Snorer	443	88.1	6.1 (1.0)		18.7 (7.3)		5.5 (2.7)	
Snorer	60	11.9	5.9 (1.2)		21.9 (11.5)		6.4 (2.8)	
BSQ - tiredness				0.30		0.71		< 0.001
Not Tired	354	70.4	6.1 (1.1)		19.0 (7.9)		5.0 (2.4)	
Tired	149	29.6	6.2 (1.1)		19.3 (8.2)		7.1 (2.7)	
Hormone use				0.20		0.25		0.54
No	267	96.7	6.4 (0.9)		18.4 (7.4)		5.8 (2.9)	
Yes	9	3.3	6.0 (0.8)		23.6 (5.1)		6.6 (4.0)	
Oral Contraceptive Use				0.12		0.81		0.57
No	56	20.3	6.2 (0.8)		17.4 (5.7)		6.0 (3.1)	
Yes	220	79.7	6.4 (0.9)		17.7 (7.7)		5.7 (2.8)	
Post-Menopausal				0.85		0.44		0.62
No	249	94.0	6.4 (0.9)		17.7 (7.5)		5.7 (2.9)	
Yes	16	6.0	6.4 (0.9)		16.4 (6.4)		6.1 (2.7)	

[a]Significant tests of the relations between each sleep parameter and each covariate were conducted with Pearson correlation coefficients for continuous data and one-way ANOVAs for categorical data.M, mean; SD, standard deviation; *r*, correlation coefficient; BMI, body mass index; CES-D, Center for Epidemiologic Studies – Depression Scale; CRP, C-reactive protein; Comorbidities, history of diabetes, thyroid problems, or kidney problems; BSQ, Berlin Sleep Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

Table 2—Sleep and lipid level characteristics by examination year in the total sample and by race-sex groups

Variable	Total Sample N	Total Sample M (SD) or Freq (%)	WF N = 157	WM N = 143	BF N = 119	BM N = 84	Race[a] Comparison P	Sex[a] Comparison P	Race-Sex[a] Comparison P
TC, mg/dL									
Baseline	499	185.8 (34.2)	184.1 (31.4)	191.0 (35.7)	181.6 (34.9)	186.1 (35.3)	0.21	0.048	0.14
5-year FU	417	189.7 (34.1)	191.6 (34.6)	193.6 (35.4)	184.3 (32.3)	187.2 (33.0)	0.035	0.43	0.19
10-year FU	350	199.7 (35.9)	207.9 (31.9)	197.0 (30.3)	192.5 (41.8)	196.7 (56.3)	0.031	0.21	0.013
HDL, mg/dL									
Baseline	499	51.7 (14.0)	58.6 (14.2)	43.8 (10.4)	54.7 (13.7)	47.7 (11.1)	0.80	< 0.001	< 0.001
5-year FU	417	56.2 (16.6)	64.3 (17.5)	47.8 (11.9)	59.6 (16.6)	49.6 (12.0)	0.51	< 0.001	< 0.001
10-year FU	350	61.5 (18.5)	71.2 (19.5)	51.6 (13.7)	61.6 (15.7)	56.3 (16.1)	0.11	< 0.001	< 0.001
TC/HDL ratio ≥ 5									
Baseline	499	88 (17.6)	15 (9.6)	44 (30.8)	12 (10.3)	17 (20.5)	0.11	< 0.001	< 0.001
5-year FU	417	50 (12.0)	8 (6.0)	27 (23.3)	2 (2.0)	13 (18.8)	0.27	< 0.001	< 0.001
10-year FU	350	32 (9.1)	6 (4.9)	15 (16.0)	4 (4.9)	7 (13.7)	0.64	< 0.001	0.012
LDL, mg/dL									
Baseline	493	114.9 (31.6)	108.3 (29.1)	122.4 (30.6)	111.8 (31.3)	119.4 (34.9)	0.99	< 0.001	< 0.001
5-year FU	413	112.9 (30.3)	108.1 (29.3)	120.2 (30.4)	108.6 (27.4)	116.5 (33.5)	0.54	< 0.001	0.005
10-year FU	349	119.1 (31.8)	118.3 (29.4)	123.1 (27.0)	114.2 (35.4)	121.6 (38.6)	0.37	0.09	0.28
TG, mg/dL									
Baseline	499	81.4 (1.7)	75.3 (1.6)	103.8 (1.8)	67.0 (1.5)	81.3 (1.6)	< 0.001	< 0.001	< 0.001
5-year FU	417	88.8 (1.7)	83.3 (1.7)	108.7 (1.8)	73.2 (1.5)	94.4 (1.6)	0.003	< 0.001	< 0.001
10-year FU	350	86.8 (1.6)	83.2 (1.5)	102.3 (1.6)	83.6 (1.5)	85.6 (1.5)	0.009	< 0.001	< 0.001

[a]Comparisons between race and sex groups were made with between-groups, independent *t* tests for TC, HDL, LDL, and TG. Comparisons between race-sex groups were made with one-way ANOVAs for TC, HDL, LDL, and TG. Chi square tests were used to analyze differences in the TC/HDL categorical data between sex, race, and race-sex groups. Freq, frequency; WF, white female; WM, white male; BF, black female; BM, black male; M, mean; SD, standard deviation; y, clinical examination year; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; FU, follow-up.

Table 3—Sequentially adjusted association between one hour increments of sleep duration and 10-year change in lipids in the total sample and by sex[a]

	Model 1			Model 2			Model 3			Model 4[c]		
Lipids[b]	Est. or OR	95% CI	P	Est. or OR	95% CI	P	Est. or OR	95% CI	P	Est. or OR	95% CI	P
TC, mg/dL	4.5	1.7, 7.4	0.002	5.0	1.7, 8.4	0.003	5.2	1.7, 8.6	0.003			
Males	4.4	2.2, 11.2	0.003	4.5	0.1, 8.8	0.044	5.8	1.5, 10.2	0.009			
Females	6.7	2.2, 11.2	0.003	6.6	1.5, 11.7	0.011	6.1	1.1, 11.2	0.018	5.0	-0.2, 10.2	0.06
HDL, mg/dL	2.7	1.5, 3.9	< 0.001	1.0	-0.4, 2.4	0.16	0.5	-0.8, 1.7	0.47			
Males	-0.2	-1.5, 1.1	0.75	0.7	-0.8, 2.2	0.37	-0.1	-1.4, 1.1	0.85			
Females	3.0	0.8, 5.3	0.008	2.1	-0.5, 4.6	0.12	1.6	-0.7, 3.9	0.18	1.2	-1.2, 3.5	0.33
TC/HDL[d]	0.98	0.80, 1.19	0.82	1.15	0.92, 1.47	0.22	1.27	0.99, 1.63	0.058			
Males	1.22	0.95, 1.58	0.12	1.15	0.85, 1.54	0.37	1.37	0.99, 1.90	0.054			
Females	1.05	0.74, 1.64	0.79	1.11	0.74, 1.64	0.62	1.10	0.68, 1.77	0.70	1.12	0.7, 1.9	0.66
LDL, mg/dL	1.2	-1.5, 3.9	0.39	3.1	0.002, 6.3	0.049	3.3	0.2, 6.6	0.039			
Males	3.1	-0.8, 7.0	0.12	2.9	-1.3, 7.0	0.17	4.0	-0.3, 8.3	0.07			
Females	2.4	-1.7, 6.4	0.26	3.6	-1.0, 8.2	0.13	3.5	-1.1, 8.1	0.14	2.8	-2.0, 7.5	0.25
TG[e],mg/dL	1.0	-1.0, 1.1	0.71	1.0	-1.0, 1.1	0.30	1.0	-1.0, 1.1	0.062			
Males	1.05	-0.99, 1.11	0.10	1.02	-1.0, 1.1	0.63	1.06	1.0, 1.1	0.042			
Females	1.05	-0.99, 1.10	0.057	1.03	-1.0, 1.1	0.27	1.03	-1.0, 1.1	0.30	1.03	-1.0, 1.1	0.33

[a]Using generalized estimating equation models. [b]Measured in mg/dL. [c]Additionally adjusted for menopause status, hormone use, and birth control pill use. [d]Expressed in odds ratios with estimates greater than 1.0 indicating greater odds of TC/HDL ratio ≥ 5.0. [e]Log-normalized triglycerides was converted back into mg/dL units. Model 1, unadjusted model; Model 2, Model 1 + age, sex, race, income, and education; Model 3, Model 2 + body mass index, alcohol use, smoking status, CES-D score, physical activity level, C-reactive protein level, apnea risk, and presence of diabetes, thyroid problems or kidney problems; Model 4, Model 3 + oral contraceptive use, hormone therapy use, and menopausal status; Est., regression coefficient estimate generated from generalized estimating equations; CI, confidence interval; OR, odds ratio; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

Table 4—Sequentially adjusted association between sleep fragmentation[a] and 10-year change in lipids in the total sample and by sex[b]

	Model 1			Model 2			Model 3			Model 4[c]		
Lipids	Est. or OR	95% CI	P	Est. or OR	95% CI	P	Est. or OR	95% CI	P	Est. or OR	95% CI	P
TC, mg/dL	-0.23	-0.60, 0.14	0.23	-0.17	-0.56, 0.21	0.38	-0.22	-0.61, 0.18	0.28			
Males	-0.3	-0.8, 0.3	0.32	-0.1	-0.7, 0.4	0.65	-0.3	-0.9, 0.4	0.44			
Females	-0.3	-0.8, 0.2	0.30	-0.2	-0.7, 0.3	0.37	-0.2	-0.7, 0.3	0.40	-0.1	-0.7, 0.4	0.59
HDL, mg/dL	-0.28	-0.44, -0.13	< 0.001	-0.12	-0.27, 0.04	0.13	-0.01	-0.16, 0.13	0.85			
Males	-0.1	-0.3, 0.1	0.28	-0.2	-0.4, 0.01	0.07	-0.1	-0.2, 0.1	0.59			
Females	-0.2	-0.4, 0.1	0.13	-0.1	-0.3, 0.2	0.56	0.02	-0.2, 0.3	0.87	0.02	-0.2, 0.3	0.89
TC/HDL[d]	1.02	1.0, 1.05	0.049	1.01	0.97, 1.04	0.33	0.99	0.96, 1.02	0.66			
Males	1.02	0.99, 0.05	0.24	1.03	1.00, 1.07	0.06	1.02	0.98, 1.06	0.34			
Females	0.98	0.94, 1.03	0.48	0.97	0.92, 1.03	0.30	0.96	0.91, 1.01	0.15	0.97	0.92, 1.03	0.29
LDL, mg/dL	-0.03	-0.36, 0.31	0.88	-0.12	-0.47, 0.22	0.48	-0.19	-0.55, 0.16	0.28			
Males	-0.2	-0.7, 0.3	0.51	-0.02	-0.6, 0.5	0.94	-0.1	-0.7, 0.4	0.62			
Females	-0.1	-0.5, 0.3	0.49	-0.2	-0.7, 0.2	0.28	-0.3	-0.7, 0.2	0.24	-0.2	-0.6, 0.3	0.46
TG[e], mg/dL	1.01	1.0, 1.011	0.017	1.01	-1.0, 1.01	0.06	1.0	-1.0, 1.01	0.65			
Males	1.0	-1.0, 1.01	0.67	1.01	-1.0, 1.013	0.16	1.0	-1.0, 1.01	0.81			
Females	1.0	-1.0, 1.01	0.25	1.0	-1.0, 1.01	0.20	1.0	-1.0, 1.01	0.49	1.0	-1.0, 1.01	0.57

[a]Measured in 10% increments. [b]Using generalized estimating equation models. [c]Additionally adjusted for menopause status, hormone use, and birth control pill use in women only. [d]Expressed in odds ratios, with estimates greater than 1.0 indicating greater odds of TC/HDL ratio ≥ 5.0. [e]Log-normalized triglycerides was converted back into mg/dL units. Model 1, unadjusted model; Model 2, Model 1 + age, sex, race, income, and education; Model 3, Model 2 + body mass index, alcohol use, smoking status, CES-D score, physical activity level, C-reactive protein level, apnea risk, and presence of diabetes, thyroid problems or kidney problems; Model 4, Model 3 + oral contraceptive use, hormone therapy use, and menopausal status; Est., regression coefficient estimate generated from generalized estimating equations; CI, confidence interval; OR, odds ratio; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

Table 5—Sequentially adjusted association between PSQI scores and 10-year change in lipids in the total sample and by sex[a]

	Model 1			Model 2			Model 3			Model 4[b]		
Lipids	Est. or OR	95%CI	P	Est. or OR	95%CI	P	Est. or OR	95%CI	P	Est. or OR	95%CI	P
TC (mg/dL)	-1.0	-2.1, 0.01	0.07	-0.81	-1.9, 0.3	0.14	-0.8	-2.0, 0.3	0.16			
Males	-1.4	-3.2, 0.4	0.12	-1.3	-3.2, 0.5	0.15	-1.4	-3.3, 0.5	0.15			
Females	-0.7	-2.0, 0.6	0.32	-0.6	-1.9, 0.7	0.40	-0.3	-1.7, 1.1	0.66	-0.4	-1.7, 1.0	0.59
HDL (mg/dL)	-0.1	-0.5, 0.3	0.66	-0.2	-0.7, 0.2	0.25	0.2	-0.3, 0.7	0.45			
Males	-0.4	-0.9, 0.2	0.16	-0.6	-1.1, -0.03	0.039	-0.2	-0.8, 0.4	0.43			
Females	-0.2	-0.8, 0.3	0.44	0.1	-0.5, 0.6	0.82	0.5	-0.2, 1.1	0.13	0.5	-0.1, 1.1	0.13
TC/HDL[c]	0.96	0.90, 1.04	0.33	0.98	0.90, 1.06	0.59	0.92	0.83, 1.02	0.12			
Males	0.99	0.90, 1.09	0.90	1.01	0.91, 1.13	0.79	0.98	0.85, 1.14	0.80			
Females	0.94	0.81, 1.10	0.44	0.91	0.79, 1.05	0.21	0.85	0.71, 1.01	0.07	0.85	0.69, 1.04	0.12
LDL (mg/dL)	-1.0	-1.9, 0.01	0.053	-0.8	-1.8, 0.2	0.11	-1.0	-2.0, 0.1	0.07			
Males	-1.4	-3.1, 0.3	0.10	-1.3	-3.0, 0.5	0.17	-1.2	-3.1, 0.6	0.19			
Females	-0.5	-1.7, 0.6	0.38	-0.7	-1.9, 0.5	0.26	-0.7	-1.9, 0.5	0.25	-0.7	-2.0, 0.5	0.23
TG (mg/dL)[d]	1.01	-1.01, 1.02	0.22	1.02	1.002, 1.03	0.025	1.0	-1.01, 1.02	0.64			
Males	1.02	-1.0, 1.04	0.15	1.02	1.0, 1.05	0.034	1.01	.-1.0, 1.03	0.37			
Females	1.01	-1.0, 1.02	0.30	1.01	-1.0, 1.02	0.35	1.0	-1.0, 1.02	0.85	1.0	-1.0, 1.02	0.94

[a]Using generalized estimating equation models. [b]Additionally adjusted for menopause status, hormone use, and birth control pill use in women only. [c]Expressed in odds ratios with estimates greater than 1.0 indicating greater odds of TC/HDL ratio ≥ 5.0. [d]Log-normalized triglycerides was converted back into mg/dL units. PSQI, Pittsburgh Sleep Quality Index scores per one point increase (range: 0-21); Model 1, unadjusted model; Model 2, Model 1 + age, sex, race, income, and education; Model 3, Model 2 + body mass index, alcohol use, smoking status, CES-D score, physical activity level, C-reactive protein level, apnea risk, and presence of diabetes, thyroid problems, or kidney problems; Model 4, Model 3 + oral contraceptive use, hormone therapy use, and menopausal status; Est., regression coefficient estimate generated from generalized estimating equations; CI, confidence interval; OR, odds ratio; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

PSQI scores were not significantly associated with change in lipid levels in the total sample. There were no interactions by sex, race, or race-sex groups.

DISCUSSION

In a sample of early middle-aged black and white adults free of CVD and lipid-lowering medications, we demonstrated that over 10 years, longer sleep duration was associated with significant increases in TC and LDL in the overall sample, significant increases in TG among men, and positive but not significant associations with TC/HDL ratio ≥ 5.0 among men. With further adjustment for reproductive-related factors, the positive associations between sleep duration and TC and LDL among women were attenuated. Sleep fragmentation was not related to 10-year increases in lipid levels in the overall sample. Poor self-reported sleep quality, as measured by PSQI scores, was not associated with 10-year changes in lipid levels.

Our study is one of the first to determine longitudinal associations between objectively derived sleep measures and lipid levels. While several significant and borderline significant associations were noted between the objective sleep measures and changes in lipids, none were found for self-reported sleep quality. This result is in concert with one other study that found nonsignificant associations between PSQI scores and HDL and TG in a cross-sectional, community-based study.[22] Previous studies that examined the cross-sectional associations between self-reported sleep variables and lipids produced inconsistent results.[15-27] These inconsistencies may have been due to the biased, retrospective nature of self-report measures. For example, self-reported sleep duration has been found to represent an overestimate of actual measured sleep by approximately one hour.[30] All of these limitations may account for the inconsistent results in the literature, and the lack of significant associations between PSQI scores and changes in lipids compared to the objective measures in the present study. Furthermore, objective sleep may have a mechanistic role in changes in lipids over time, whereas poor sleep quality may reflect poor health in general rather than serve as a predictive risk factor.

Only two previous studies have measured objective measures of sleep in relation to lipids.[16,23] Using polysomnography, Ekstedt and colleagues found among 24 adults aged 24-43 years that greater sleep fragmentation was cross-sectionally related to higher TC and LDL and lower HDL; while total sleep time was positively associated with LDL-to-HDL ratio, a clinical marker of CVD risk.[16] The second study used actigraphic measures in 768 community-dwelling adults and determined greater sleep duration and time in bed were cross-sectionally related to higher TC and TC-to-HDL ratio in adults aged 57-65 years.[23] Our findings were similar to the results for sleep duration found by both of these studies. All three studies used different age groups, suggesting that longer sleep duration is independently associated with higher cholesterol and LDL in young to middle-aged adults. It is important to note that the average sleep durations in these studies, including the present sample, were fairly low, and the maximums reported were not excessive. Thus, even modestly long sleep durations are related to alterations in lipid levels. In contrast, one longitudinal study found short sleep duration increased the odds of incident hypercholesteremia, but this study was among adolescents and hypercholesterolemia was self-reported.[24]

Although there is much evidence on the mechanisms that may explain a relationship between sleep loss and poor lipid profiles,[43] the literature is scant on the biological mechanisms that elucidate the relationship between longer sleep duration and greater cholesterol levels. Sleep disordered breathing was hypothesized to be a confounder in the relationship,[11] but our study controlled for subjective high risk of sleep disordered breathing. Causal pathways cannot be ascertained with the present study; however, we propose the following potential pathways: (a) a mediated relationship by physiological alterations in mechanisms of lipid metabolism; (b) mediated relationship by an unhealthy lifestyle, e.g., excessive time in bed, low physical activity, or high stress that induce longer sleep durations and detrimental lipid levels; or (c) high cholesterol induces sickness that affects sleep duration. In the context of our study, excessive time in bed is an unlikely mediator, given the short length of the mean sleep duration in the sample. Pathway (c) is also improbable because participants were relatively young, and free of CVD and lipid-lowering medications.

In this study, longer sleep duration was associated with significant 10-year increases in TC and LDL, but these associations were attenuated among women once reproductive-related factors were adjusted for in the model. Premenopausal women tend to have lower TC, LDL, and HDL concentrations than men, which have been related to differences in sex hormones and their effects on lipid metabolism; but as we age, these differences diminish.[44,45] In the study sample, 10-year changes in lipid levels between men and women did tend to converge, with women approaching male levels. Longer sleep duration was related to increases in TC and LDL in women, suggesting sleep duration may have a role in this convergence beyond the effects of age and other cardiac risk factors. However, the literature suggests this convergence may be more related to the menopausal transition.[46] Given the attenuation in the associations between sleep duration, TC and LDL when reproductive-related factors were accounted for in the models for women, it can be deduced that the menopausal transition may explain the increases in lipids more so than sleep duration. However, it may be possible that sleep duration modifies sex hormone concentrations during the menopausal transition, which in turn affects lipid metabolism. To date, there have been no experimental studies on the effects of sleep duration on sex hormones and metabolic control among women.

A major strength of our study is it addresses many voids present in the current literature. It also recruited an ethnically diverse sample with no baseline CVD and controlled for the symptoms of sleep disordered breathing; although this was assessed by self-report. The study also examined lipid profiles over a long follow-up time frame and used objective sleep metrics as predictors.

However, there are pertinent limitations to the study. The sample was relatively small and located at one regional site, which may attenuate the generalization of these results. The use of actigraph-assessed sleep was a definite improvement upon previous studies given its strong congruence with gold standard polysomnography.[47] However, polysomnography would have allowed for a more accurate classification of sleep disordered

breathing, and the examination of sleep stages. While self-reported symptoms of sleep disordered breathing with the Berlin Questionnaire improved our model, it is not a true substitute for validated diagnosis. Our study also suggests that objective sleep parameters may be predictive of lipid changes whereas self-reported sleep parameters are not. This result further implies that an objective measure of sleep disordered breathing may be necessary for accurate estimation in future studies. Despite the robust associations found between sleep and lipid levels over time, causality also cannot be substantiated. Sleep was also measured after the original study's defined "baseline." To mitigate this limitation we evaluated cross-sectional associations between sleep and 5-year follow-up lipid values and found the results to be equivalent to the results using baseline lipid values, suggesting similar longitudinal results would have likely been procured using this data (data not presented). Unmeasured and residual confounding factors, such as self-reported stress, may have also imposed changes in the present results.

In conclusion, our study found over a ten-year period that longer sleep duration is related to significant increases in LDL and TC across race-sex groups, and significant increases in TG among men. Future projects should examine the biological mechanisms that may explain the association between objective sleep and lipid profiles across ethnically diverse high risk groups for CVD.

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