

# Short Sleep Duration as a Risk Factor for Hypercholesterolemia: Analyses of the National Longitudinal Study of Adolescent Health

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**Study Objectives:** To explore the relationship between sleep duration in adolescence and hypercholesterolemia in young adulthood. Experimental sleep restriction has been shown to significantly increase total cholesterol and LDL cholesterol levels in women. Short sleep duration has been found in cross sectional studies to be associated with higher total cholesterol and lower HDL cholesterol levels. Sleep deprivation could increase the risk for hypercholesterolemia by increasing appetite and dietary consumption of saturated fats, decreasing motivation to engage in regular physical activity, and increasing stress and resultant catecholamine induced lipolysis. No previous published population studies have examined the longitudinal relationship between sleep duration and high cholesterol.

**Design:** Multivariate longitudinal analyses stratified by sex of the ADD Health using logistic regression.

**Setting:** United States nationally representative, school-based, probability-based sample.

**Participants:** Adolescents ( $n = 14,257$ ) in grades 7 to 12 at baseline (1994-95) and ages 18 to 26 at follow-up (2001-02).

**Measurements and Results:** Among females, each additional hour of sleep was associated with a significantly decreased odds of being diagnosed with high cholesterol in young adulthood (OR = 0.85, 95% CI 0.75-0.96) after controlling for covariates. Additional sleep was associated with decreased, yet not statistically significant, odds ratios for hypercholesterolemia in males (OR = 0.91, 95% CI 0.79-1.05).

**Conclusions:** Short sleep durations in adolescent women could be a significant risk factor for high cholesterol. Interventions that lengthen sleep could potentially serve as treatments and as primary preventative measures for hypercholesterolemia.

**Keywords:** Cholesterol, sleep, epidemiology

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ATHEROSCLEROSIS IS A DISEASE PROCESS RECOGNIZED TO BEGIN IN THE FIRST DECADES OF LIFE.<sup>1</sup> IDENTIFICATION AND MANAGEMENT OF RISK factors for atherosclerosis can decrease the morbidity and mortality from the disease. Evidence from both experimental and population-based studies have implicated short sleep duration in the pathogenesis of obesity,<sup>2,3</sup> diabetes,<sup>4,5</sup> and hypertension,<sup>6,7</sup> all of which are potent risk factors for atherosclerosis. There is growing evidence that short sleep duration may also play a role in the etiology of another primary risk factor for atherosclerosis, high cholesterol. Experimental sleep restriction has been shown to significantly increase total cholesterol and LDL cholesterol levels in postmenopausal women treated with hormone replacement therapy.<sup>8</sup> Cross-sectional associations have been found between short sleep durations and lower HDL cholesterol levels in adult American women with type 2 diabetes<sup>9</sup> and in adult Japanese women from the general population.<sup>10</sup> Short sleep durations were found to be associated with the highest

total cholesterol levels among all sleep duration categories in cross-sectional analyses that included both men and women from Norwegian<sup>11</sup> and Korean<sup>12</sup> adult populations.

A number of mechanisms could mediate the relationship between inadequate sleep and hypercholesterolemia. First, sleep restriction has been shown to increase appetite by decreasing leptin and increasing ghrelin levels.<sup>2</sup> Increased appetite could raise body weight and increase dietary intake of cholesterol, trans-fats, and saturated fats. Second, inadequate sleep is associated with daytime fatigue, which could lessen one's resolve to engage in physical activity. Physical activity has been shown to lower LDL and raise HDL levels.<sup>13</sup> Third, inadequate sleep could increase stress. Acute stress has been shown to significantly increase total and LDL cholesterol levels,<sup>14</sup> and acute stress responsivity has been shown to predict clinically elevated cholesterol levels and LDL cholesterol levels 3 years later.<sup>15</sup> Stress has been theorized to increase blood lipids through catecholamine-induced lipolysis and the release of free fatty acids that serve as substrate for triglyceride resynthesis and hepatic VLDL production.<sup>14</sup>

We are not aware of any previous population-based studies on the relationship between sleep duration and high cholesterol that have had longitudinal designs. A longitudinal study has the advantage of observing the temporal relationship between sleep duration and high cholesterol to strengthen the counterfactual argument that if short sleep duration had not occurred, then high cholesterol would not have occurred. Knowledge of the relationship between sleep duration and the incidence of hypo-

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cholesterolemia could lead to the development of interventions to decrease the morbidity and mortality associated with high cholesterol. In this study, we explored whether short sleep durations in adolescence would be associated with increased odds of having been diagnosed with high cholesterol 7 to 8 years later in young adulthood among subjects who participated in the National Longitudinal Study of Adolescent Health (Add Health). We hypothesized that physical activity, emotional distress, and body weight would act as mediators of the relationship. We theorized that the relationship would be stronger in women than in men given results from previous cross-sectional population based and experimental studies.

## METHODS

### Participants

Subjects for this study were participants in Waves I, II, and III of the National Longitudinal Study of Adolescent Health (Add Health).<sup>16</sup> Add Health is a school-based, nationally representative, probability based sample of adolescents in the United States. In-home interviews were conducted for Wave I in 1994-95 with adolescents in grades 7 to 12. Interviews were administered again in 1996 for Wave II and then in 2001-02 for Wave III, when the cohort was between the ages of 18 and 26. A total of 18,922 subjects were assigned a grand sample weight in the Wave I in-home sample.<sup>17</sup> All of the subjects who answered the sleep duration question at Wave I and who answered the question on hypercholesterolemia at Wave III were included in the analyses (75.3%,  $n = 14,257$ ). All Add Health participants signed informed consent forms. We received institutional review board approval to conduct analyses of this data.

### MEASURES

The primary dependent variable for this study was hypercholesterolemia as determined by subjects' yes/no responses to the following question asked at Wave III: "Has a doctor ever told you that you have high cholesterol?" The main independent variable for this study was the subjects' self-reported sleep durations at Waves I and II as measured by their answers to the question: "How many hours of sleep do you usually get?" with responses ranging in whole numbers from 1 to 20. We averaged the Wave I and Wave II sleep durations since the measures were only one year apart. We imputed missing Wave II sleep duration data ( $n = 3,483$ , 24.4%) with Wave I sleep duration data. To test whether the imputation of sleep duration data affected the model, we included a covariate in the multivariate model indicating whether the Wave II sleep duration data was missing (yes, no). This variable was not significant, so we did not include it in the final model. We retained the sleep duration variable as a continuous variable. To test whether our assumption that the relationship between sleep duration in adolescence and high cholesterol in young adulthood was linear, we included a sleep duration squared term into the multivariate model. This term was not significant, supporting our assumption that the relationship was linear. We therefore did not include the sleep duration squared term in the final model.

The variables theorized to act as mediators of the relationship between sleep duration and hypercholesterolemia includ-

ed baseline (Wave I) physical activity/inactivity, emotional distress, and body weight. The physical activity variable was based upon responses to the following 3 questions: (1) During the past week, how many times did you play an active sport, such as baseball, softball, basketball, soccer, swimming, or football? (2) During the past week, how many times did you do exercise, such as jogging, walking, karate, jumping rope, gymnastics, or dancing? (3) During the past week, how many times did you go rollerblading, roller-skating, skate-boarding, or bicycling? Response options for each of these questions included: Not at all, 1 or 2 times, 3 or 4 times, and 5 or more times. We combined the responses to these 3 questions to categorize the physical activity variable (0-2 times/week, 3-4 times/week, and  $\geq 5$  times/week). We created a composite physical inactivity variable based upon responses to 3 questions asking the number of hours per week the respondent watched television, watched videos, and played video or computer games. Physical inactivity categories included 0-10 hours/week, 11-24 hours/week, and  $\geq 25$  hours/week. The measure of emotional distress was based upon a 17-item emotional distress scale first used by Resnick et al.<sup>18,19</sup> The scale has possible scores ranging from 0 to 54 and measures feelings of depression, loneliness, fear, and moodiness in the past week or past year. Standard cutoff scores for the scale have not been established, so we retained the emotional distress score as a continuous variable. We determined body weight categories by the adolescents' percentile for body mass index ( $\text{kg}/\text{m}^2$ ) for age from CDC growth charts.<sup>20</sup> Body weight categories included: underweight ( $< 5$ th percentile), normal weight ( $\geq 5$ th percentile and  $< 85$ th percentile), at risk for overweight ( $\geq 85$ th percentile and  $< 95$ th percentile), and overweight ( $\geq 95$ th percentile).

Other covariates that we included in our multivariate models included baseline (Wave I) age (continuous variable), sex, race/ethnicity (Caucasian, African American, Hispanic, Other), alcohol consumption (0,  $> 0$  and  $< 28$ , or  $\geq 28$  grams per day), and cigarette smoking (0, 1 to 19, or  $\geq 20$  cigarettes per day).

### Statistical Analyses

After performing preliminary univariate and bivariate analyses, we used hierarchical logistic regression analyses to examine the relationship between sleep duration at baseline and report of hypercholesterolemia at follow-up. We did not find sex, age, alcohol consumption, cigarette smoking, physical activity/inactivity, or emotional distress to be significantly associated with hypercholesterolemia in bivariate analyses; however, these variables were included in multivariate analyses because they are strongly associated with sleep duration and are recognized risk factors for hypercholesterolemia. The first multivariate model (Model 1) included age, sex, race/ethnicity, alcohol consumption, and cigarette smoking. The theorized mediating variables of physical activity/inactivity, emotional distress, and body weight were progressively added in subsequent models (Models 2, 3, and 4) to test whether these variables acted as mediators of the relationship between sleep duration and hypercholesterolemia. We conducted analyses stratified by sex to assess whether there would be differences between men and women in the relationship between sleep duration and hypercholesterolemia. To investigate whether sex acted as an effect

modifier in the relationship between sleep duration and hypercholesterolemia, we ran a regression model with an interaction term between sex and sleep duration. To obtain unbiased estimates from the Add Health data, we corrected for complex sampling design effects and unequal probability of selection using the SAS<sup>21</sup> Callable Version of SUDAAN software.<sup>22</sup> We divided the individual weights by the total mean weight to maintain the original sample size. The significance of individual coefficients in the logistic regression models were determined by the 95% confidence limits for odds ratios.

## RESULTS

A total of 618 adolescents, representing 4% of the total sample, reported at Wave III having been told by a doctor that they had high cholesterol. Table 1 shows results from bivariate analyses. Hypercholesterolemia was significantly associated with shorter sleep duration, age in males, emotional distress, Caucasian and Hispanic race/ethnicity, and overweight and at-risk for overweight body weight. Shorter sleep duration was associated with female sex, older age, African American and other race/ethnicity, higher daily alcohol consumption, higher daily cigarette smoking, lower physical activity, lower physical inactivity, and overweight body weight.

Table 2 shows the odds ratios for hypercholesterolemia at Wave III as computed by logistic regression analyses. In the first adjusted model (Model 1) for the total sample of subjects including both males and females, each additional hour of sleep was significantly associated with decreased odds of being diagnosed with hypercholesterolemia at Wave III. These results were not appreciably attenuated with the inclusion of physical activity/inactivity, emotional distress and body weight in subsequent Models 2, 3, and 4, indicating that these variables did not act as mediators of the relationship between sleep duration and hypercholesterolemia. The relationship between sleep duration and hypercholesterolemia was stronger in females than in males. Among females, each additional hour of sleep was associated with a 17% decreased odds of being diagnosed with high cholesterol in young adulthood (OR = 0.83, 95% CI 0.73-0.95). Controlling for the covariates did not attenuate the results for females. Additional sleep was associated with decreased, yet not statistically significant, odds ratios for hypercholesterolemia in males after controlling for covariates (OR = 0.91, 95% CI 0.79-1.05). The interaction term included in regression analyses to explore whether sex acted as an effect modifier in the relationship between sleep duration and hypercholesterolemia was not significant (P = 0.48).

## DISCUSSION

We found associations between short sleep durations in adolescence and significantly increased odds of having been diagnosed with high cholesterol 7 to 8 years later in young adulthood. These associations were significant in females but not in males. The stronger relationship found in females could be partially explained by sex differences in parameters relating to risk factors for high cholesterol. Female children and adolescents ages 4 to 19 have significantly higher average total cholesterol and LDL levels than males.<sup>23</sup> Females of this age range also consistently have higher fasting leptin levels than males, independent of measures of adiposity.<sup>24</sup> Females have higher

HDL levels following puberty than males.<sup>25</sup> Women in young adulthood have lower variation in circulating cortisol over 24 hours than men.<sup>26</sup>

We theorized that physical activity, emotional distress, and body weight would act as mediators in the relationship between short sleep duration and high cholesterol, but our results were not consistent with this hypothesis. We did find a significant positive relationship between sleep duration and physical activity/inactivity in bivariate analyses, yet controlling for these variables in multivariate analyses did not attenuate the associations between short sleep durations and high cholesterol. Our measure for emotional distress was unlikely to have captured the full breadth of stress from adverse life events and psychosocial factors, so stress could still play a significant role in the association between sleep duration and hypercholesterolemia. Although sleep restriction has been shown to increase appetite, with particular cravings for salty and starchy snacks,<sup>2</sup> increased appetite does not necessarily result in increased consumption and weight gain. If consumption does increase, then characteristics of the foods consumed, such as cholesterol, trans-fat, saturated fat, fiber, and caloric contents, can affect cholesterol levels and weight gain. We were not able to control for nutritional consumption in our analyses, so the effects of sleep duration on levels of leptin, ghrelin, and appetite could still have mediated the relationship between sleep duration and high cholesterol.

The associations between short sleep duration and high cholesterol continued to be statistically significant in women after controlling for potential confounders and mediators. Short sleep duration is therefore likely to have direct effects upon the risk for high cholesterol in women. These findings are consistent with experimental results showing sleep restriction to increase total cholesterol and LDL cholesterol levels.<sup>8</sup> Sleep deprivation could increase the risk for high cholesterol by increasing appetite<sup>2</sup> and dietary consumption of saturated fats and by increasing stress and resultant catecholamine induced lipolysis.

Although our results indicate that short sleep duration in adolescence increases the risk for high cholesterol in early adulthood, these findings should be considered in light of the limitations of these analyses. Our determination of hypercholesterolemia was based upon subjects' self-reports of ever being told by a doctor that they had high cholesterol. Validation studies have shown self-reported high cholesterol to be reasonably accurate.<sup>27,28</sup> In a review of medical records of participants in the Nurses' Health Study, self-reported high cholesterol had a sensitivity of 72%, specificity of 93%, positive predictive value of 86%, and negative predictive value of 85%.<sup>27</sup> We expect that any misclassification of hypocholesterolemia in the Add Health study would have been nondifferential to the exposure of sleep duration; and in most situations, nondifferential misclassification of a binary disease outcome such as high cholesterol will produce bias toward the null hypothesis. Another issue regards the determination of the temporal relationship between sleep duration and hypocholesterolemia. Given the young age of subjects at Wave I, we presume that the diagnoses of high cholesterol reported 7 to 8 years later at Wave III were incident cases. However, we were not able to determine this definitively, since respondents were not asked at Wave I if they had ever been diagnosed with high cholesterol, nor were they asked at Wave III to specify when they had been

**Table 1**—Relationships between sleep duration, covariates, and hypercholesterolemia

Baseline Characteristics	Hypercholesterolemia		Average Sleep Duration in Hours		
	Yes	No			
<i>n</i> (%)	618 (4%)	13,639 (96%)			
	<b>Mean (SE)</b>	<b>Mean (SE)</b>	<b>Wald F (P-value)</b>		
<b>Average sleep duration (h)</b>	7.53 (0.08)	7.77 (0.07)	11.55 (P = 0.0009)		
<b>Age-female</b>	15.9 (0.16)	15.8 (0.13)	1.55 (P = 0.2159)		
<b>Age-male</b>	16.3 (0.17)	15.9 (0.14)	5.58 (P = 0.0197)		
<b>Percentile BMI (kg/m<sup>2</sup>) for age, female</b>	63.4 (2.11)	58.4 (2.12)	5.44 (P = 0.0213)		
<b>Percentile BMI (kg/m<sup>2</sup>) for age, male</b>	72.6 (2.35)	60.1 (2.36)	28.16 (P < 0.0001)		
<b>Emotional distress</b>	9.8 (0.39)	8.7 (0.37)	9.30 (P = 0.0028)		
<b>Sex</b>	<i>n</i> (Column %)	<i>n</i> (Column %)	<i>X</i> <sup>2</sup> (P-value)	Mean (SE)	Wald F (P-value)
Female	336 (54%)	6,982 (51%)	1.05 (P = 0.3071)	7.72 (0.04)	2.54 (P = 0.0124)
Male	282 (46%)	6,656 (49%)		7.81 (0.03)	
<b>Age(Wavel)</b>					
11-13	18 (3%)	558 (4%)	8.28 (P = 0.0885)	8.41 (0.12)	97.39 (P < 0.0001)
14-15	162 (26%)	4,427 (32%)		8.14 (0.11)	
16-17	241 (39%)	4,558 (33%)		7.67 (0.10)	
18-19	188 (30%)	3,837 (28%)		7.37 (0.11)	
20-21	9 (1%)	258 (2%)		7.27 (0.11)	
<b>Race/Ethnicity</b>					
Caucasian	436 (71%)	9,102 (67%)	8.30 (P = 0.0444)	7.81 (0.07)	6.55 (P = 0.0004)
African American	62 (10%)	2,042 (15%)		7.59 (0.07)	
Hispanic	35 (6%)	603 (4%)		7.90 (0.11)	
Other	86 (14%)	1,892 (14%)		7.64 (0.07)	
<b>Alcohol Consumption</b>					
0 grams per day	430 (69%)	9,692 (71%)	0.33 (P = 0.8471)	7.87 (0.08)	50.09 (P < 0.0001)
> 0 and < 28 grams per day	152 (25%)	3,226 (24%)		7.53 (0.08)	
> 28 grams per day	37 (6%)	720 (5%)		7.35 (0.08)	
<b>Cigarettes Smoked Per Day</b>					
0	457 (74%)	10,037 (74%)	0.02 (P = 0.9916)	7.84 (0.11)	24.35 (P < 0.0001)
1 to 19	143 (23%)	3,171 (23%)		7.60 (0.11)	
≥ 20	19 (3%)	431 (3%)		7.26 (0.11)	
<b>Physical Activity</b>					
Low – 0 to 2 times/week	222 (36%)	4,363 (32%)	5.20 (P = 0.0783)	7.65 (0.03)	17.83 (P < 0.0001)
Medium – 3 to 4 times/week	210 (34%)	4,498 (33%)		7.77 (0.03)	
High – ≥ 5 times/week	187 (30%)	4,778 (35%)		7.86 (0.04)	
<b>Physical Inactivity</b>					
Low – 0 to 10 h/week	198 (32%)	4,640 (34%)	4.04 (P = 0.1369)	7.64 (0.04)	16.06 (P < 0.0001)
Medium – 11 to 24 h/week	240 (39%)	4,586 (34%)		7.82 (0.03)	
High – ≥ 25 h/week	181 (29%)	4,413 (32%)		7.83 (0.04)	
<b>Body weight</b>					
Underweight	35 (6%)	815 (6%)	31.47 (P < 0.0001)	7.93 (0.08)	3.40 (P = 0.0198)
Normal weight	348 (56%)	9,522 (70%)		7.75 (0.05)	
At-risk for overweight	111 (18%)	1,914 (14%)		7.79 (0.05)	
Overweight	125 (20%)	1,387 (10%)		7.68 (0.05)	



**Table 2**—Odds ratios (95% CI) for hypercholesterolemia

Total Sample (n = 14,257)	Model 1*	Model 2†	Model 3‡	Model 4§
Sleep Duration	0.86 (0.78-0.95)	0.85 (0.77-0.94)	0.87 (0.79-0.96)	0.87 (0.79-0.96)
<b>Women (n = 7,318)</b>				
Sleep Duration	0.83 (0.73-0.95)	0.83 (0.73-0.94)	0.85 (0.74-0.96)	0.85 (0.75-0.96)
<b>Men (n = 6,939)</b>				
Sleep Duration	0.90 (0.77-1.04)	0.89 (0.77-1.03)	0.90 (0.78-1.04)	0.91 (0.79-1.05)

\*Model 1, adjusted for age, sex, race/ethnicity, alcohol consumption, and cigarette smoking; †Model 2, adjusted for variables in Model 1 plus physical activity and physical inactivity; ‡Model 3, adjusted for variables in Model 2 plus emotional distress; §Model 4, adjusted for variables in Model 3 plus body weight.

diagnosed. Some of the subjects could have been diagnosed with high cholesterol at or before Wave I, making the analyses with those subjects cross-sectional rather than longitudinal. The use of self-reported sleep duration rather than measured sleep duration represents another limitation of this study. Some studies have found good agreement between self-reported sleep duration and those measured through actigraphic monitoring,<sup>29,30</sup> while other studies have found self-reported sleep duration to overestimate those measured through actigraphic<sup>31</sup> and polysomnographic<sup>32</sup> monitoring. Misclassification of sleep duration in the Add Health Study that did occur would be expected to have been predominantly between adjacent hours of sleep responses, independent of the true hours of sleep value, and nondifferential to the outcome of high cholesterol, increasing the likelihood that the resulting bias would be toward the null hypothesis. Other limitations include possible bias arising from loss to follow-up and missing data on baseline risk variables.

The results from this study suggest that short sleep duration could play a role in the etiology of hypercholesterolemia in women. If short sleep duration functions to raise total and LDL cholesterol levels, then interventions that increase the amount and improve the quality of sleep could potentially serve as treatments and as primary preventative measures for high cholesterol. Behavioral interventions could include assistance with implementing sleep hygiene practices and with modifying maladaptive sleep habits. Further research is needed to investigate the mechanistic links between short sleep duration and high cholesterol and to explore the efficacy of sleep interventions for the treatment and prevention of hypercholesterolemia.

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