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Original Article

# Sleep duration and the risk of future lipid profile abnormalities in middle-aged men: the Kansai Healthcare Study

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ABSTRACT

*Background:* Although short sleep duration has been reported to be associated with future cardiometabolic diseases, it is not fully understood whether sleep duration is prospectively associated with the risk of each lipid profile abnormality.
*Methods:* Subjects were nondiabetic Japanese, 40–55 years of age, who were not taking oral lipid-lowering medications: for the incidence of low high-density lipoprotein cholesterol (HDL-C), 7627 men with an HDL-C level ≥40 mg/dL; for high triglycerides, 6973 men with a triglyceride level <200 mg/dL; for high low-density lipoprotein cholesterol (LDL-C), 7273 men with an LDL-C level <160 mg/dL; for high non-HDL-C, 7415 men with a non-HDL-C level <190 mg/dL; and for high total cholesterol (TC), 7196 men with a TC level <240 mg/dL. Lipid profile abnormalities were defined according to the Adult Treatment Panel III guidelines of the National Cholesterol Education Program.
*Results:* During the 6-year observation period, there were 1022 cases of low HDL-C. Multiple-adjusted hazard ratios for low HDL-C were 0.79 (95% confidence interval, 0.64–0.97) for sleep durations of 5 to <7 h and 0.62 (0.46–0.83) for ≥7 h compared with <5 h. There were 1473 cases of high triglycerides. Multiple-adjusted hazard ratios for high triglycerides were 0.81 (0.68–0.98) for sleep durations of 5 to <7 h and 0.90 (0.72–1.13) for ≥7 h compared with <5 h. However, no association between sleep duration and the risk of future high LDL-C, non-HDL-C, or TC was observed.
*Conclusions:* Moderate and/or long sleep durations decreased the risk of future low HDL-C and high triglycerides.



## 1. Introduction

In many countries, sleep duration among adults has declined. Japan shows the largest decrease in sleep duration overall, with people sleeping 2.8 h less per week in the 2000s than in the 1960s [1]. Sleep duration in Japan is shorter than in any other country [2]. Short sleep duration has been reported to be associated with the risk of mortality [3], cardiovascular events [4], obesity [5–7], diabetes mellitus [8], and hypertension [9]. However, it is not known whether sleep duration is prospectively associated with the risk of future lipid profile abnormalities.

With few exceptions, epidemiologic studies of sleep duration and dyslipidemia have been cross-sectional rather than prospective. The results in previous cross-sectional studies have been inconclusive [10–13]. For high-density lipoprotein (HDL) cholesterol, Hall et al. [10] reported a U-shaped association between sleep duration and low HDL cholesterol in 1214 subjects aged 30–55 years, although the association between shorter sleep duration and low HDL cholesterol was not statistically significant. However, Arora et al. [11] reported that, in elderly subjects aged 50–96 years, shorter self-reported sleep duration was related to a lower odds of low HDL cholesterol. Kaneita et al. [12], in the National Health and Nutrition Survey in Japan, reported no significant association between sleep duration and low HDL cholesterol. As for triglycerides, Hall et al. [10] and Kaneita et al. [12] reported that short sleep duration was associated with an increased odds of high triglycerides, but Arora et al. [11] reported that longer sleep duration was associated with an increased odds of high triglycerides. Differences in the age distribution of study subjects, incomplete control for confounding factors, or not using fasting samples to measure lipid profile levels may explain the inconclusive associations thus far. Only two prospective studies have reported the association between sleep duration and each lipid profile abnormality [14] or hypercholesterolemia [15]. These results have been conclusive. Ruiter Petrov et al. [14] reported in the Coronary Artery Risk Development in Young

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Adults Study that longer sleep duration was associated with increased future total cholesterol levels and triglyceride levels, but not with HDL cholesterol. Gangwisch et al. [15] reported in the National Longitudinal Study of Adolescent Health that longer sleep duration was associated with a decreased risk of hypercholesterolemia, but they did not examine the association between sleep duration and other lipid profiles. In prospective cohort studies, it has not been fully examined whether sleep duration is associated with the risk of each lipid profile abnormality. Therefore, the present study examined the relationship between sleep duration and the risk of each lipid profile abnormality in a 6-year prospective observational study among apparently healthy middle-aged Japanese men.

## 2. Methods

### 2.1. Kansai Healthcare Study

The Kansai Healthcare Study is an ongoing cohort investigation designed to clarify the risk factors for chronic diseases [16]. Study subjects were 9027 non-diabetic male employees of a company in the area of Kansai, Japan, aged 40–55 years, who were enrolled between 1 April 2000 and 31 March 2001 and who were not taking oral lipid-lowering medications at baseline. All employees in this company aged ≥40 years underwent detailed annual medical check-ups. The protocol of this study was reviewed and approved by the Human Subjects Review Committee at Osaka City University.

### 2.2. Data collection and measurements

The clinical examination consisted of a medical history; a physical examination; anthropometric measurements; self-administered questionnaires on lifestyle characteristics, such as sleep duration, regular leisure-time physical activity, smoking habits, and daily alcohol consumption; and measurement of fasting plasma glucose, HDL cholesterol, triglyceride, and total cholesterol levels. Trained nurses carried out all measurements. Blood samples were drawn after an overnight 12 h fast. Serum total cholesterol, HDL cholesterol, and triglyceride levels were measured using a Hitachi 7350 automatic chemistry analyzer (Hitachi Co., Ltd, Tokyo, Japan) at baseline. Non-HDL cholesterol levels were calculated as total cholesterol level minus HDL cholesterol level. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula for those whose triglyceride levels were <400 mg/dL [17]. After resting for ~5 min in a quiet room, systolic and diastolic blood pressures were measured in a sitting position with an automatic sphygmomanometer (BP-203RV; Omron Colin, Tokyo, Japan; and Udex-super; ELK Corp., Osaka, Japan) [18]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hemoglobin A1c (HbA1c) levels were measured by high-performance liquid chromatography standardized to the Japan Diabetes Society (JDS) Committee for the Standardization of Glycohemoglobin [19], using an HA-8150 automatic glycohemoglobin analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan) in the same laboratory. The conversion equation from HbA1c (JDS) to HbA1c (NGSP: National Glycohemoglobin Standardization Program) levels has been officially certified as follows: NGSP (%) = 1.02 × JDS (%) + 0.25% [19]. Follow-up examinations were annually conducted at the multicenter in the area of Kansai, Japan. Blood samples were also drawn after an overnight 12 h fast. All results of detailed medical check-ups were gathered at Kansai Health Administration Center.

The questionnaire on sleep duration included the question: "How long do you sleep daily?" The questionnaire had three possible answers: <5 h, 5 to <7 h, and ≥7 h. To validate that this question was interpreted as "sleep duration in general", not as "sleep duration last night", this was investigated in a sub-cohort of 215 subjects. First, subjects were asked "How long do you sleep daily?", followed by "Which sleep duration were you asked about, in general or last night?" Of 215 subjects, 208 (97%) answered "In general". Therefore, the questionnaire used to assess sleep duration measured "sleep duration in general".

Other lifestyle questionnaires assessing regular leisure-time physical activity, smoking habits, and daily alcohol consumption have been described in detail previously [16]. To describe briefly, regarding leisure-time physical activity, subjects were classified into two groups: regular leisure-time physical activity at least once weekly or less than once weekly. Regarding smoking habits, subjects were classified into three groups: non-smokers, past smokers, and current smokers. Questions regarding alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. Daily alcohol intake (in grams of ethanol per day) was calculated. Except for non-drinkers, subjects were classified into tertiles of daily alcohol consumption levels.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or if subjects were taking antihypertensive drugs [20]. Diabetes was defined as fasting plasma glucose level ≥126 mg/dL, HbA1c level ≥6.5%, or if subjects were taking hypoglycemic medications or insulin [21].

### 2.3. Diagnosis of each lipid profile abnormality

Each lipid profile abnormality was defined according to the Adult Treatment Panel III guidelines of the National Cholesterol Education Program [22]. Specifically, low HDL cholesterol was defined as HDL cholesterol level <40 mg/dL, high LDL cholesterol as LDL cholesterol level ≥160 mg/dL, high non-HDL cholesterol as non-HDL cholesterol level ≥190 mg/dL, high triglycerides as triglyceride level ≥200 mg/dL, and high total cholesterol as total cholesterol level ≥240 mg/dL.

### 2.4. Statistical analysis

The Cox proportional hazards model was used to estimate the hazard ratio for the incidence of each lipid profile abnormality in relation to sleep duration and baseline covariates. Follow-up of each subject was continued until the diagnosis of lipid profile abnormalities at the annual follow-up examination, or until the sixth follow-up examination conducted between 1 April 2006 and 31 March 2007, whichever came first. For all models, the adequacy of the Cox proportional hazards model was assessed. Non-linear effects of continuous independent variables were evaluated by plotting the regression coefficients against the variables [23]. Continuous independent variables in all models fulfilled this linearity assumption. The proportional hazards assumption was checked using log minus log plots for categorical independent variables and the plot of Schoenfeld residuals for continuous independent variables [24]. All independent variables in all models met the assumption. To test the presence of effect modification, each first-order interaction term between sleep duration and age, BMI, smoking habits, alcohol consumption, regular leisure-time physical activity, and hypertension was examined. There were no significant interactions between sleep duration and all independent variables in all models. Multicollinearity was assessed using the variance inflation factor [25]. There was no evidence of multicollinearity. Outliers were checked by plotting the likelihood displacement values and by plotting DFBETAs for all independent variables [24]. Outliers were not detected in any model. The 95% confidence interval was calculated for each hazard ratio. Statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA) and Stata MP, version 12.0 (Stata Corp., College Station, TX, USA).

Multiple linear regression analysis was used to model each future lipid profile level as a function of other variables in relation to sleep duration and baseline covariates. Residual analysis was conducted