Age-dependent changes in the association between sleep duration and impaired glucose metabolism

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Author contributions: Nakajima K designed the overall study and analyzed the data; Suwa K identified eligible subjects from the database at Saitama Health Promotion Corporation and confirmed validation of the measurements and methods; Toyama K prepared the manuscript, including editing and discussion; Nakajima K wrote the manuscript and is the guarantor of the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Kanagawa University of Human Services Institutional Review Board.

Informed consent statement: All subjects provided informed written consent.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: October 20, 2016
Peer-review started: October 31, 2016
First decision: January 14, 2017
Revised: March 3, 2017
Accepted: March 16, 2017
Published online: August 15, 2017

Abstract

AIM
To investigate whether the association between sleep duration and impaired glucose metabolism varies among younger and older populations.

METHODS
We reviewed data of self-reported habitual sleep duration per night, HbA1c levels, and clinically relevant factors in a cross-sectional checkup database of 75472 Japanese from the general population aged 20-79 years (51695 men and 23777 women). Associations of prediabetes (HbA1c ≥ 5.7% and/or diabetic pharmacotherapy) or diabetes (HbA1c ≥ 6.5% and/or diabetic pharmacotherapy) with short and long sleep durations compared with a reference sleep duration (7 h) were investigated by multivariate logistic regression analysis. We controlled for potential relevant confounders, including age, sex, and work duration per day according to younger and older subjects.

RESULTS
As age advanced, sleep duration became longer and this increase in the 40s and 50s was two times greater in men than in women. This finding was accompanied by a deterioration in HbA1c levels. In subjects aged younger...
INTRODUCTION

For the last two decades, many clinical studies have shown that shorter and longer durations of sleep are associated with health hazards, including type 2 diabetes, metabolic syndrome, and increased all-cause mortality[1-16]. Although a short sleep duration may be robustly associated with impaired glucose homeostasis, there are conflicting results, especially concerning a long sleep duration[15,16,21]. Generally, glucose homeostasis is aggravated with aging, probably owing to reduced pancreatic β-cell function and increased insulin resistance[17-19]. In contrast, individual’s sleep duration can become longer and its quality can be aggravated (e.g., more fragmented) as people become older[11,20], although it has been shown that objectively measured sleep duration generally decreases with age[21]. Taken together, these findings suggest that glucose homeostasis and sleep duration likely change with advancing age. However, to date, the effect of aging on the association between sleep duration and impaired glucose metabolism is less clear, regardless of accumulated evidence[1-7,9-15].

Based on the findings mentioned above and the worldwide extension of the life span[22,23], we investigated whether the association between self-reported sleep duration and dysglycemia varies among younger and older generations in the general Japanese population who undergo an annual medical checkup.

MATERIALS AND METHODS

This cross-sectional study consisted of data that were recorded in medical checkups of people living or working in Saitama, a suburb of Tokyo, Japan. The original study has been described in more detail elsewhere[24]. The current study involved two institutions in Kanagawa and Saitama, Japan, including Kanagawa University of Human Services and Saitama Health Promotion Corporation, a public interest corporation.

The protocol was approved by the Ethics Committee of Kanagawa University of Human Services and Saitama Health Promotion Corporation. All procedures that were followed were in accordance with the ethical standards of the responsible committee on human experimentation (Kanagawa University of Human Services, Japan) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Subjects

We reviewed the data for 116817 subjects who underwent a medical health checkup at the Saitama Health Promotion Corporation in 2007. Individuals who required immediate treatment for serious conditions, such as suspected cancer, heart failure, atherosclerotic disease, or infectious pneumonia, were not included from the beginning of the study. All recruited subjects, who were free from disability and hemiplegia, answered a questionnaire about their lifestyle characteristics. After exclusion of subjects with incomplete data (n = 41345), 75472 apparently healthy subjects aged 20-79 years were enrolled, without any special selections. Subjects were primarily divided into younger subjects (<40 years old, n = 32929) and older subjects (≥40 years old, n = 42543).
Anthropometric and laboratory tests, and sleep duration

All anthropometric and laboratory tests were carried out in the morning. Body mass index was calculated as weight (kg) divided by height (m²). Serum parameters were measured using standard methods by the Hitachi autoanalyzer (Tokyo, Japan) at Saitama Health Promotion Corporation. Glycated hemoglobin (HbA1c) was measured in Japan Diabetes Society (JDS) HbA1c units, which were converted to National Glycohemoglobin Standardization Program HbA1c units using the officially certified formula: HbA1c (NGSP) (%) = 1.02 × JDS (%) + 0.25%[25].

Prediabetes (including diabetes) was defined as HbA1c ≥ 5.7% or any pharmacotherapy for diabetes. Diabetes was defined as HbA1c ≥ 6.5% or any pharmacotherapy for diabetes[26]. Accordingly, subjects with prediabetes included those with diabetes. We considered the white blood cell (WBC) count, a surrogate marker for inflammation, as an important confounding factor for the association between sleep duration and dysglycemia. However, available data of the WBC count were limited in this study (n = 74837).

Self-reported sleep duration per night, which was obtained as a response to a simple question about sleep, was divided into five categories of ≤ 5, 6, 7, 8, and ≥ 9 h of sleep duration.

Statistical analysis

Data are expressed as the mean ± SD or median (interquartile range). Differences in continuous variables between men and women were assessed by the t-test. In each age group, subjects were divided into four groups according to sleep duration per night: ≤ 5, 6, 7, and ≥ 8 h. The percentage of subjects with ≥ 9 h sleep duration was small (1.1%). Therefore, subjects with an 8-h sleep duration and subjects with ≥ 9 h of sleep duration were grouped together as subjects with ≥ 8 h of sleep duration. P values for continuous variables were determined using ANOVA and for categorical variables using the χ² test. Linear correlations were examined by Pearson’s correlation coefficients after coding ≤ 5, 6, 7, 8, and ≥ 9 h of sleep duration as continuous values of 5-9, respectively. Multivariate logistic regression models were used to examine the associations between sleep duration and prediabetes or diabetes, compared with a reference sleep duration of 7 h[5,7,8]. These models were used with or without adjustment for relevant confounders, which yielded crude and adjusted odds ratios and 95% CIs. Tests for linear trends (P for trend) were calculated by treating sleep duration as a continuous variable (i.e., 1-4 for a sleep duration of ≤ 5, 6, 7, and ≥ 8 h, respectively), and the same model analysis was conducted. Statistical review of the study was performed by Dr. Eiichiro Kanda, MD, PhD, MPH, Department of Nephrology, Tokyo Kyosai Hospital, Tokyo, Japan. Statistical analyses were performed using SPSS software version 22.0 (SPSS-IBM, Chicago, IL, United States) and Statview version 5.0 (SAS Institute, Cary, NC, United States). Values of P < 0.05 were considered to be statistically significant.

RESULTS

Clinical characteristics of subjects in the younger and older groups are shown in Tables 1 and 2, respectively. Overall, in younger and older subjects, as sleep duration increased, age increased and work duration decreased (both P < 0.0001, ANOVA). In older subjects, as sleep duration became longer, most of the parameters became worse (all P < 0.0001), except for body mass index (BMI) and the prevalence of regular exercise. In short-duration sleepers, the prevalence of current smokers was higher in younger subjects, whereas it was lower in older subjects. Notably, the rates of current smokers and everyday alcohol drinkers were prevalent in older long sleepers (41.1% and 32.0%, respectively) among the overall subjects (Table 2). Duration of sleep was inversely correlated with the WBC count in younger subjects (r = -0.03, P < 0.0001, Pearson’s correlation), but it was positively correlated with the WBC count in older subjects (r = 0.02, P < 0.0001).

Figure 1 shows overall sleep duration according to age groups and sex. Sleep duration became prolonged as age advanced, and this increase was approximately two times greater in men than in women at middle age (40-59 years) owing to a dip in sleep duration in women. HbA1c levels increased with increasing age in both sexes (Figure 2). In younger subjects, sleep duration was inversely and linearly correlated with HbA1c levels (r = -0.04, P < 0.0001), regardless of sex (Figure 3). In older subjects, HbA1c levels showed a non-linear relationship against sleep duration with a nadir 7 h. When subjects were divided by every 10 years, similar results were observed (Figure 4), but the relationship of HbA1c was almost flat against sleep duration in subjects in their 40s (r = -0.006, P = 0.41).

Multivariate logistic regression analysis showed that in younger subjects, short durations of sleep (≤ 5 h, 6 h) were positively associated with prediabetes compared with the reference duration of sleep (7 h). These findings remained significant after adjustment for relevant confounders (Table 3) (P < 0.01 and P < 0.05, respectively). In contrast, a long duration of sleep (≥ 8 h) was inversely associated with prediabetes (P < 0.05). Either short or long duration of sleep were not significantly associated with diabetes after full adjustment for relevant confounding factors. In older subjects, a short duration of sleep (≤ 5 h) was positively associated with prediabetes, which also remained significant after full adjustment (Table 4) (P < 0.01). However, a long duration of sleep (≥ 8 h) was marginally associated with diabetes after full adjustment for relevant confounders (P < 0.05). Overall, prediabetes was inversely associated with sleep duration in younger and older subjects (P < 0.001 and P < 0.01 for linear trend, respectively). However,
a significant association was not observed between diabetes and duration of sleep in both generations.

**DISCUSSION**

This large, epidemiological study of the general Japanese population showed that a short duration of sleep was robustly associated with prediabetes, but not diabetes, in young and old generations. In contrast, a long duration of sleep was inversely associated with prediabetes in the young generation, but it was positively associated with diabetes in the old generation. Therefore, aging may affect the relationship between a long sleep duration and glucose homeostasis.
A significant association between a short sleep duration and prediabetes is consistent with many previous studies\(^1,2,3,5,6,13,15,16\). This association could be explained by physiological mechanisms, such as insulin resistance\(^27,28\), decreased leptin levels, increased ghrelin levels and inflammation, sympathetic nervous system activation, and oxidative stress\(^19\). This association could also be explained by behavioral mechanisms, such as increased food intake, and unfavorable lifestyles, such as smoking and sedentary behavior\(^28\). Long-lasting wakefulness and arousal can increase the level of orexin, a hypothalamic neuropeptide, which is found in the brain and stimulates appetite and food intake\(^30-32\). Additionally, a short sleep duration can be associated with abnormal eating behavior around sleep (AEBAS), such as breakfast skipping and/or late-night-dinner eating. AEBAS is often observed in younger people\(^33\). Sleep duration was shorter in younger subjects in our study. Although data for AEBAS was lacking in our study, previous studies have shown that AEBAS is associated with metabolic syndrome and hyperglycemia\(^33,34\). An elevated WBC and BMI, a higher prevalence of current smokers, and a lower prevalence of regular exercisers in young short-duration sleepers compared with young long-duration sleepers (Table 1) may be compatible with these explanations.

The most plausible explanation for the null association between a short duration of sleep and diabetes, instead of prediabetes, may be partially due to an insufficient number of cases of overt diabetes.
Several studies have shown that a long duration of sleep may reflect underlying inflammatory etiologies in older people. Pérez de Heredia et al. showed that sleep duration was negatively associated with the WBC count in adolescents. Consistent with this previous finding, in our study, the duration of sleep was inversely associated with the WBC count in younger subjects, whereas it was positively associated with the WBC count in older subjects. Taken together, in the young generation, a long sleep duration can provide sufficient rest and lead to improvement of metabolic homeostasis and inflammatory status. However, in older people, a long duration of sleep may reflect required long rest because of latent or overt disease. This situation could simultaneously aggravate glucose homeostasis. Notably, in our study, the relationship between HbA1c levels and the duration of sleep appeared to be flat in subjects in their 40s, and a J-curve relationship gradually occurred after the 40s (Figure 4). This finding indicates that the etiological relation between a long sleep duration and...
Impaired glucose homeostasis may occur approximately in the 40s. Mizukami et al. studied age-related changes of islet structure in Japanese non-diabetic subjects and showed that the mass of pancreatic β-cells was increased during maturation and slowly decreased after the 40s. Additionally, Uehara et al. reported in a large-scale Japanese working population that the prevalence of glucose abnormalities increased with advancing age, especially during the mid-40s and 50s. These findings may partly relate to our results regarding the relationship between long sleep duration, prediabetes, and diabetes. Alternatively, an increase in sleep duration rather than a long sleep duration per se may be a crucial factor that contributes to development of type 2 diabetes. Among the parameters that were investigated in this study, the duration of work, which was longer in younger than in older subjects in this study, may be a pivotal environmental factor that could restrict the duration of sleep. Therefore, in terms of public health, caution should be exercised in people with a long work duration for preventing a short sleep duration, cardiometabolic disease, and other unfavorable lifestyles.

Currently observed relationships between sleep duration and impaired glucose metabolism in young and older people are summarized in Figure 5. Plausible underlying mechanisms are also described in Figure 5.

Several limitations should be mentioned in this study. First, this study was cross-sectional in nature, and did not allow us to determine the causality between abnormal sleep duration and impaired glucose metabolism. However, the age of subjects in the current study widely varied (20-79 years), which could reflect overall trajectories in sleep duration and glucose homeostasis in the general Japanese population. Second, assessment of sleep duration was self-reported and the quality of sleep was not investigated. In particular, in older people, the time spent in bed can be misinterpreted as sleep duration. Additionally, sleep may be fragmented and actual sleep duration may be less than expected. Therefore, more detailed study is required to confirm the association between sleep duration and metabolic abnormalities, including type 2 diabetes. Third, whether prediabetes with a short sleep duration could lead to diabetes after a certain period during the lifetime is unclear. Long-term, prospective
In conclusion, the current study shows that a short sleep duration may be associated with prediabetes throughout the lifetime, whereas a long sleep duration is inversely associated with prediabetes in younger people. This finding indicates that a long sleep duration leads to better glucose homeostasis. In contrast, a long sleep duration may be associated with diabetes in older people, which might reflect an inverse causality owing to chronic diseases and complications of diabetes. Therefore, aging may be a pivotal factor that affects the association between a long sleep duration and impaired glucose homeostasis. Further large studies are required to confirm the current findings and determine the underlying mechanism(s).

Peer-review
The author’s purpose of the investigation is very interesting, also for scientists from related research fields.

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P- Reviewer: Aureliano M, Kumar KVSH
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L- Editor: A
E- Editor: Lu YJ
