ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2017 August 15; 8(8): 390-421

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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Monthly Volume 8 Number 8 August 15, 2017

ORIGINAL ARTICLE

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NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Diabetes
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLICATION DATE
August 15, 2017

World Journal of Diabetes

Submit a Manuscript: http://www.f6publishing.com

World J Diabetes 2017 August 15; 8(8): 397-406

DOI: 10.4239/wjd.v8.i8.397

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Observational Study

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.

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
Article in press: March 17, 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 $\geqslant$ 5.7% and/or diabetic pharmacotherapy) or diabetes (HbA1c $\geqslant$ 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

than 40 years (n = 32929), HbA1c levels were inversely and linearly correlated with sleep duration in both sexes. However, in subjects aged 40 years or older (n = 42543), HbA1c levels showed a non-linear relationship against sleep duration with a nadir at 7 h. Multivariate logistic regression analysis showed that in younger subjects, short durations of sleep (≤ 5 h and 6 h) were positively associated with prediabetes (both P < 0.001), but a long duration of sleep (≥ 8 h) was inversely associated with prediabetes (P < 0.001). These associations remained significant after adjustment for relevant confounders, including age, sex, and work duration per day (ORs = 1.20, 95%CI: 1.05-1.37, P < 0.001; ORs = 1.12, 95%CI: 1.02-1.24, P < 0.05; and ORs = 0.84, 95%CI: 0.72-0.99, P < 0.05, respectively). In contrast, in older subjects, besides an association of prediabetes with a short duration of sleep (≤ 5 h) (ORs = 1.12, 95%CI: 1.03-1.21, P < 0.01), diabetes was significantly associated with a long duration of sleep (≥ 8 h) (ORs = 1.11, 95%CI: 1.02-1.25, P < 0.05).

CONCLUSION

A short sleep duration may be associated with prediabetes throughout life. However, the association between a long sleep duration and glucose metabolism can change with aging.

Key words: Sleep; Prediabetes; Diabetes; HbA1c; Aging

Core tip: Short and long durations of sleep have been putatively associated with type 2 diabetes. However, whether age affects these associations is unknown, although sleep duration and glucose homeostasis can change with advancing age. Our study demonstrated that a short sleep duration may be associated with prediabetes throughout the lifespan, whereas a long duration of sleep may be inversely associated with prediabetes in younger subjects. Additionally, a long sleep duration was associated with diabetes in older subjects. Therefore, aging may substantially affect the association between a long sleep duration and glucose homeostasis.

Nakajima K, Suwa K, Toyama K. Age-dependent changes in the association between sleep duration and impaired glucose metabolism. *World J Diabetes* 2017; 8(8): 397-406 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i8/397.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i8.397

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[3,5,8,13,15]. 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 (No. 10-22). 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 (m^2). 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 χ^2 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,

Table 1 Characteristics of younger subjects classified by sleep duration

Sleep duration	⩽ 5 h	6 h	7 h	⩾ 8 h	*P* values
n (%)	4110 (12.5)	16265 (49.4)	9377 (28.5)	3177 (9.6)	
Male, *n* (%)	2865 (69.7)	11121 (68.4)	6349 (67.7)	2026 (63.8)	< 0.0001
Age (yr)	30.5 ± 5.5	30.4 ± 5.3	30.7 ± 5.3	31.1 ± 5.3	< 0.0001
BMI (kg/m^2)	23.4 ± 3.9	23.1 ± 3.7	22.8 ± 3.6	23.0 ± 3.8	< 0.0001
Systolic blood pressure (mmHg)	118 ± 14.3	118 ± 14.5	118 ± 14.6	119 ± 14.8	0.58
White blood cell count (× 10^9/L)	6.67 ± 1.8	6.48 ± 1.7	6.46 ± 1.7	6.48 ± 1.9	< 0.0001
Serum triglycerides (mmol/L)	0.9 (0.6-1.5)	0.9 (0.6-1.4)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.46
Serum HDL-cholesterol (mmol/L)	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	0.04
HbA1c (NGSP, %)	5.35 ± 0.5	5.32 ± 0.5	5.30 ± 0.4	5.29 ± 0.5	< 0.0001
Work duration (h/d)	9.4 ± 1.5	9.0 ± 1.4	8.6 ± 1.3	8.1 ± 1.4	< 0.0001
Pharmacotherapy for					
Hypertension, *n* (%)	25 (0.6)	73 (0.4)	38 (0.4)	19 (0.6)	0.29
Diabetes, *n* (%)	13 (0.3)	39 (0.2)	22 (0.2)	11 (0.3)	0.83
Dyslipidemia, *n* (%)	11 (0.3)	46 (0.3)	24 (0.3)	22 (0.7)	0.0001
Current smokers, *n* (%)	1791 (43.6)	5980 (36.8)	3221 (34.4)	964 (30.3)	< 0.0001
Everyday alcohol consumers, *n* (%)	353 (8.6)	1386 (8.5)	1022 (10.9)	370 (11.6)	< 0.0001
Regular exercisers, *n* (%)[1]	553 (14.4)	3154 (17.2)	2740 (19.4)	1367 (21.8)	< 0.0001
Past history of					
CVD, *n* (%)	46 (1.1)	129 (0.8)	102 (1.1)	46 (1.4)	0.002

Data are presented as mean ± SD, median (interquartile range), or *n* (%). *P* values were determined by ANOVA and χ^2 tests were used for continuous and categorical variables. Serum triglyceride concentrations were log transformed before parametric analysis. [1]Regular exercise was defined as ⩾ 30 min exercise per session at least twice a week. Values of white blood cell count are only available in 32713 subjects (*n* = 4073, 16171, 9313, and 3156, for ⩽ 5 h, 6 h, 7 h, and ⩾ 8 h sleep duration, respectively). BMI: Body mass index; HDL: High-density lipoprotein; NGSP: National Glycohemoglobin Standardization Program; CVD: Cardiovascular disease.

Table 2 Characteristics of older subjects classified by sleep duration

Sleep duration	⩽ 5 h	6 h	7 h	⩾ 8 h
n (%)	3838 (9.0)	18319 (43.1)	14115 (33.2)	6271 (14.7)
Male, *n* (%)	2197 (57.2)	11630 (63.5)	10399 (73.7)	5108 (81.5)
Age (yr)	49.4 ± 6.9	50.4 ± 6.8	51.8 ± 7.2	54.3 ± 8.4
BMI (kg/m²)	23.9 ± 3.7	23.8 ± 3.5	23.7 ± 3.3	23.7 ± 3.2
Systolic blood pressure (mmHg)	125 ± 18.2	126 ± 18.2	128 ± 18.4	131 ± 19.0
White blood cell count (× 10^9/L)	6.6 ± 1.8	6.5 ± 1.7	6.5 ± 1.7	6.6 ± 1.8
Serum triglycerides (mmol/L)	1.1 (0.7-1.8)	1.2 (0.8-1.8)	1.3 (0.8-1.9)	1.3 (0.9-2.0)
Serum HDL-cholesterol (mmol/L)	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4
HbA1c (NGSP, %)	5.69 ± 0.8	5.69 ± 0.8	5.70 ± 0.8	5.77 ± 0.9
Work duration (h/d)	8.9 ± 1.7	8.5 ± 1.5	8.3 ± 1.3	8.1 ± 1.3
Pharmacotherapy for				
Hypertension, *n* (%)	355 (9.3)	1970 (10.8)	1843 (13.1)	1091 (17.4)
Diabetes, *n* (%)	138 (3.6)	633 (3.5)	559 (4.0)	343 (5.5)
Dyslipidemia, *n* (%)	109 (2.8)	621 (3.4)	536 (3.8)	278 (4.4)
Current smokers, *n* (%)	1239 (32.3)	5981 (32.6)	4982 (35.3)	2580 (41.1)
Everyday alcohol consumers, *n* (%)	651 (17.0)	3378 (18.4)	3493 (24.7)	2009 (32.0)
Regular exercisers, *n* (%)[1]	611 (14.9)	2938 (18.1)	1913 (20.4)	617 (19.4)
Past history of				
CVD, *n* (%)	125 (3.3)	620 (3.4)	568 (4.0)	323 (5.2)

Data are presented as mean ± SD, median (interquartile range), or *n* (%). *P* values determined by ANOVA and χ^2 tests for all continuous and categorical variables listed above were < 0.0001 (data not shown). Serum triglyceride concentrations were log transformed before parametric analysis. [1]Regular exercise was defined as ⩾ 30 min exercise per session at least twice a week. Values of white blood cell count are only available in 42124 subjects (*n* = 3809, 18172, 13973, and 6170, for ⩽ 5 h, 6 h, 7 h, and ⩾ 8 h sleep duration, respectively). BMI: Body mass index; HDL: High-density lipoprotein; NGSP: National Glycohemoglobin Standardization Program; CVD: Cardiovascular disease.

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.

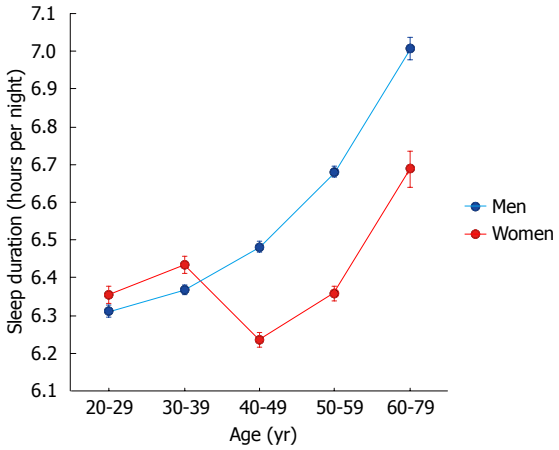

Figure 1 Sleep duration according to age groups and sex. Each point and vertical bar represent the mean ± 1.96 SE. Sleep duration in men and women increased with increasing age (both $P < 0.0001$, ANOVA). Significant differences were observed in sleep duration between men and women in all age groups (all $P < 0.0001$, except for $P = 0.003$ in the 20s, *t*-test). The corresponding number of subjects is shown in the side of the bar.

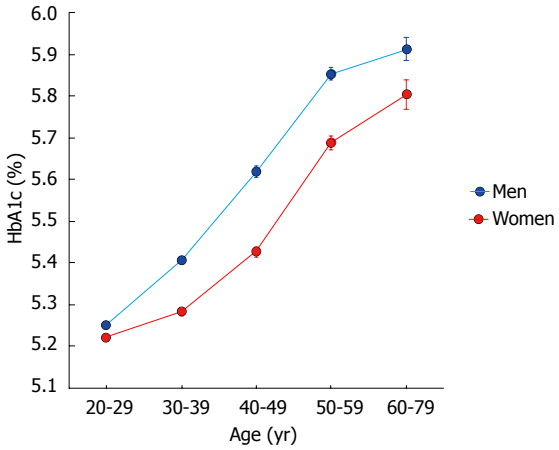

Figure 2 HbA1c levels according to age groups divided by decades. Each point and vertical bar represent the mean ± 1.96 SE. HbA1c levels in men and women increased with increasing age (both $P < 0.0001$, ANOVA). Significant differences were observed in HbA1c levels between men and women in all age groups (all $P < 0.0001$, *t*-test). The corresponding number of subjects is the same as that in Figure 1.

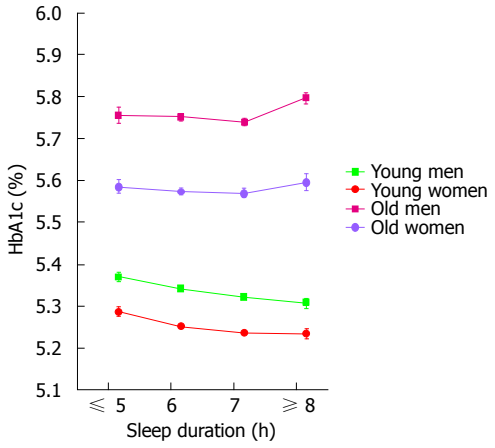

Figure 3 Relationship between HbA1c levels and sleep duration according to age and sex. Each point and vertical bar represent the mean ± SE. *P* values for ANOVA were < 0.0001, 0.0001, 0.002, and 0.56 for young men, young women, older men, and older women, respectively. The corresponding number of subjects is shown in the side of the bar.

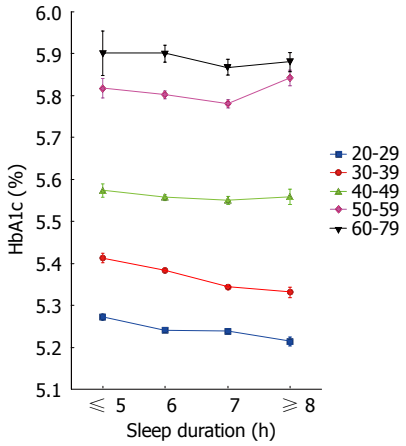

Figure 4 Relationship between HbA1c levels and sleep duration according to age groups divided by decades. Each point and vertical bar represent the mean ± SE. Correlation coefficients and *P* values of Pearson's correlation were $r = -0.03$, $P < 0.0001$ for the 20s, $r = -0.05$, $P < 0.0001$ for the 30s, $r = -0.01$, $P = 0.41$ for the 40s, $r = 0.01$, $P = 0.52$ for the 50s, and $r = -0.01$, $P = 0.32$ for the 60-70s, respectively. The corresponding number of subjects is shown in the side of the bar.

A significant association between a short sleep duration and prediabetes is consistent with many previous studies[1,3,5,6-13,15,16]. 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[29]. 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.

Table 3 Odds ratios (95%CIs) of sleep duration for prediabetes and diabetes in younger subjects *n* (%)

Sleep durations	⩽ 5 h	6 h	7 h	⩾ 8 h	*P* value
Prediabetes					
Cases	418 (10.2)	1463 (9.0)	743 (7.9)	229 (7.2)	
Model 1	1.32 (1.16-1.49)[d]	1.15 (1.05-1.26)[b]	1 (reference)	0.90 (0.77-1.05)	0.88 (0.84-0.92)[d]
Model 2	1.32 (1.16-1.50)[d]	1.18 (1.07-1.29)[b]	1 (reference)	0.89 (0.76-1.04)	0.87 (0.83-0.91)[d]
Model 3	1.20 (1.05-1.37)[b]	1.12 (1.02-1.24)[a]	1 (reference)	0.84 (0.72-0.99)[a]	0.90 (0.86-0.95)[d]
Diabetes					
Cases	58 (1.4)	150 (0.9)	77 (0.8)	27 (0.9)	
Model 1	1.73 (1.23-2.44)[b]	1.12 (0.85-1.42)	1 (reference)	1.04 (0.67-1.61)	0.83 (0.72-0.96)[a]
Model 2	1.72 (1.22-2.43)[b]	1.16 (0.88-1.52)	1 (reference)	1.01 (0.65-1.58)	0.83 (0.72-0.95)[b]
Model 3	1.35 (0.93-1.97)	1.02 (0.76-1.37)	1 (reference)	0.92 (0.58-1.46)	0.90 (0.78-1.04)

Model 1: Unadjusted; Model 2: Adjusted for age and sex; Model 3: Model 2 plus adjustment for current smoking (*vs* non-smoking), daily alcohol consumption (*vs* infrequent/no alcohol consumption), regular exercise (*vs* no regular exercise), pharmacotherapy (hypertension, diabetes, and dyslipidemia), BMI, WBC count, systolic blood pressure, triglycerides, HDL-cholesterol, duration of work (as continuous variables), and past history of CVD (*vs* no history). Triglyceride concentrations were log transformed before analysis. Regular exercise was defined as ⩾ 30 min exercise per session at least twice a week. [a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$. BMI: Body mass index; HDL: High-density lipoprotein; CVD: Cardiovascular disease; WBC: White blood cell.

Table 4 Odds ratios (95%CIs) of sleep duration for prediabetes and diabetes in older subjects *n* (%)

Sleep duration	⩽ 5 h	6 h	7 h	⩾ 8 h	*P* value
Prediabetes					
Cases	1259 (32.8)	6006 (32.8)	4788 (33.9)	2343 (37.4)	
Model 1	0.95 (0.88-1.03)	0.95 (0.91-0.995)[a]	1 (reference)	1.16 (1.09-1.24)[d]	1.07 (1.05-1.10)[d]
Model 2	1.17 (1.09-1.27)[d]	1.08 (1.03-1.14)[b]	1 (reference)	0.97 (0.91-1.03)	0.94 (0.91-0.96)[d]
Model 3	1.12 (1.03-1.21)[b]	1.04 (0.99-1.11)	1 (reference)	0.97 (0.91-1.04)	0.96 (0.94-0.99)[b]
Diabetes					
Cases	271 (7.1)	1379 (7.5)	1181 (8.4)	702 (11.2)	
Model 1	0.83 (0.73-0.95)[b]	0.89 (0.82-0.97)[b]	1 (reference)	1.38 (1.25-1.52)[d]	1.19 (1.15-1.24)[d]
Model 2	1.10 (0.95-1.26)	1.06 (0.98-1.15)	1 (reference)	1.11 (1.00-1.22)	1.00 (0.96-1.04)
Model 3	1.02 (0.88-1.18)	1.01 (0.93-1.11)	1 (reference)	1.11 (1.02-1.25)[a]	1.03 (0.99-1.08)

Model 1: Unadjusted; Model 2: Adjusted for age and sex; Model 3: Model 2 plus adjustment for current smoking (*vs* non-smoking), daily alcohol consumption (*vs* infrequent/no alcohol consumption), regular exercise (*vs* no regular exercise), pharmacotherapy (hypertension, diabetes and dyslipidemia), BMI, WBC count, systolic blood pressure, triglycerides, HDL-cholesterol, duration of work (as continuous variables), and past history of CVD (*vs* no history). Triglyceride concentrations were log transformed before analysis. Regular exercise was defined as ⩾ 30 min exercise per session at least twice a week. [a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$. BMI: Body mass index; HDL: High-density lipoprotein; CVD: Cardiovascular disease; WBC: White blood cell.

This occurred because subjects were apparently healthy people who underwent a health screening checkup. Therefore, patients with poor glucose control were unlikely to be enrolled in this study. Before full adjustment for relevant confounding factors, a significant association between a short sleep duration and diabetes was observed with adjustment for age and sex in young subjects (Table 3). However, statistical significance of this association disappeared after full adjustment. This suggests that factors other than age and sex might contribute to the association between poor glucose metabolism and a short sleep duration. Indeed, patients with type 1 diabetes were not excluded in our study. However, most of the subjects who were determined as having diabetes were likely to have type 2 diabetes because of its higher prevalence in the general population (90%-95%)[26].

The reason for the discrepancy in the association between a long sleep duration and glucose metabolism among younger and older generations is unknown. Several studies have shown that a long duration of sleep may reflect underlying inflammatory etiologies in older people[4,35,36]. Pérez de Heredia *et al*[37] 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[4,12,20]. 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

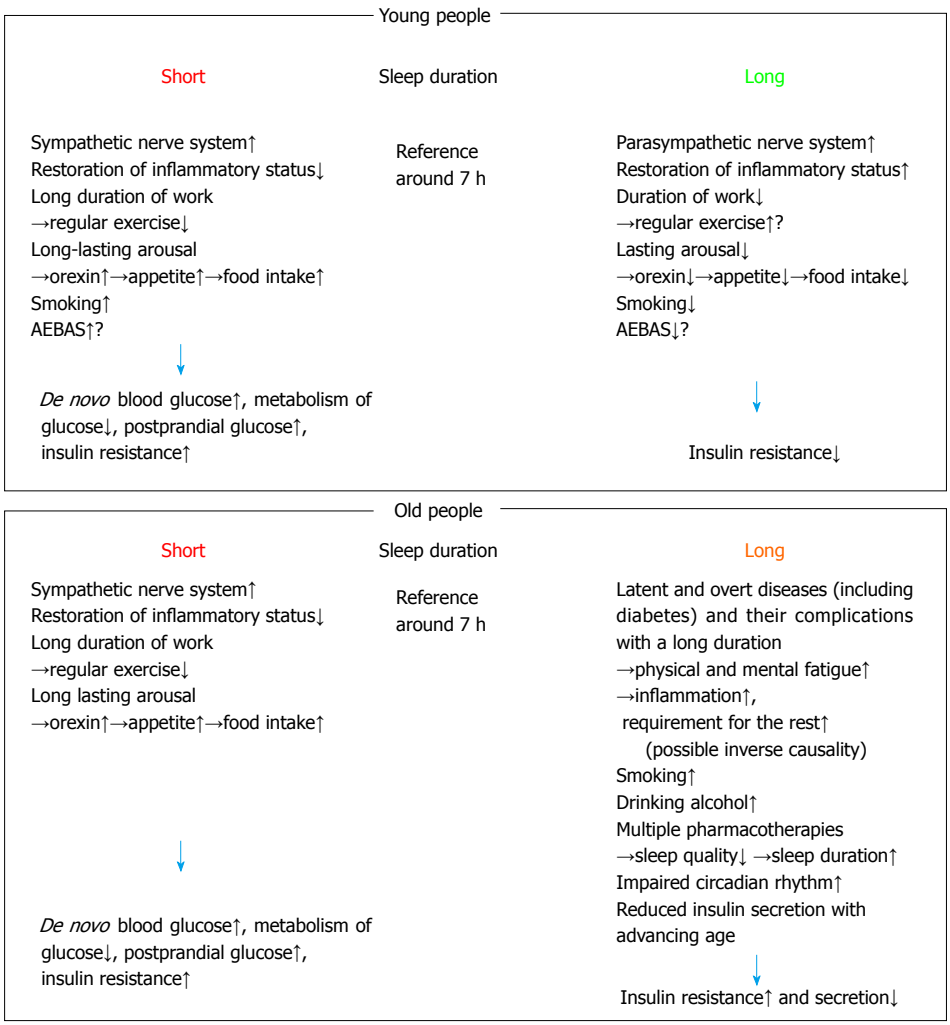

Figure 5 Relationship between sleep duration and impaired glucose metabolism, and plausible underlying mechanisms. AEBAS: Abnormal eating behavior around sleep.

impaired glucose homeostasis may occur approximately in the 40s. Mizukami *et al*[38] 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*[39] 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[40]. 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[20] 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

studies are required to determine this issue. Finally, our study consisted of apparently healthy subjects who underwent an ordinary checkup. As people get older, they usually have more complications and chronic diseases, including cognitive impairment and mental disorders, such as depression. These etiologies often require some pharmacotherapies that predispose to disturbing homeostasis of sleep[41-43]. Prescription for insomnia increases as age advances, which also alters the sleep circadian rhythm[44,45]. Additionally, chronic use of hypnotic might aggravate glucose metabolism, although a conflicting result has been reported[46]. Unfortunately, such pharmacotherapy and sleep medication were not investigated in this study. Therefore, the current findings may not be applicable to other populations who have a different longevity and higher proportions of diabetes and comorbidities.

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).

COMMENTS

Background

Many clinical studies have shown that shorter and longer durations of sleep are associated with cardiometabolic diseases including type 2 diabetes and metabolic syndrome. However, there are conflicting results, especially concerning a long sleep duration, albeit a short sleep duration may be robustly associated with impaired glucose homeostasis.

Research frontiers

Although it has been shown that sleep duration generally decreases with age, individual's sleep duration can become longer in the elderly. Therefore, comparison between young and old populations using the same methods and criteria may be important for the research investigating the association between sleep duration and metabolic disease.

Innovations and breakthroughs

The authors investigated the association between sleep duration and impaired glucose metabolism (prediabetes and diabetes) in a large epidemiological study consisting of 75472 apparently healthy subjects with a wide range of age (20-79 years old), which was subdivided into two age groups (young subjects less than 40 years and old subjects aged 40 years or older). In most of previous studies, subjects were limited to patients with type 2 diabetes, middle-aged, or the elderly. By contrast, the authors compared the results of analysis in two age groups, which include not only healthy subjects but also those with diabetes.

Applications

The cause-effect relationship between long sleep duration and impaired glucose metabolism can vary between young and old populations. In brief, long sleep duration may be a cause for the prevention of diabetes in young people, whereas it may be a result that originated from cardiometabolic diseases and their complications. Therefore, when one encounters a patient with diabetes concomitant with long sleep duration, the causality, backgrounds, and confounding factors should be carefully taken into consideration.

Terminology

In this article, the authors use the term, "abnormal eating behavior around sleep (AEBAS)", which the authors made first time based on the current and previous their studies. AEBAS may include overeating at dinner, late-night-dinner eating, eating snack after dinner, skipping breakfast, and their combinations. Such AEBAS can affect the duration of sleep and deteriorate the quality. On the contrary, abnormal durations of sleep likely deteriorate eating behaviors around sleep. The definition of "prediabetes" includes diabetes in this study, which may complicate the relationship between prediabetes and diabetes. It may be appropriate to use the term such as "hyperglycemia" instead of "prediabetes". However, in comparison with diabetes, the authors dared to use the term "prediabetes". Considering these, the current results should be interpreted with care.

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 **S- Editor**: Song XX
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