

Title

Impact of sleep disordered breathing on glucose metabolism among individuals with a
family history of diabetes: the Nagahama Study

Subtitle

Sleep Apnea and Family History of Diabetes

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Abstract

Study Objectives: It is well known that a family history of diabetes (FHD) is a definitive risk factor for type 2 diabetes. It has not been known whether sleep disordered breathing (SDB) increases the prevalence of diabetes in those with FHD.

Methods: We assessed SDB severity in 7,477 study participants by oximetry corrected by objective sleep duration determined by wrist actigraphy. HbA1c $\geq 6.5\%$ and/or current medication for diabetes indicated the presence of diabetes. In addition to the overall prevalence, the prevalence of recent-onset diabetes during the almost 5 years before the SDB measurements was investigated.

Results: Of the 7,477 participants (mean age 57.9 [range 34.2-80.7, SD 12.1] years, females 67.7%), 1,569 had FHD. The prevalence of diabetes in FHD participants with moderate-to-severe SDB (MS-SDB) was higher than in those without SDB (MS-SDB vs. without SDB: all, 29.3% vs. 3.3%, $P < 0.001$; females, 32.6% vs. 1.9%, $P < 0.001$; males, 26.2% vs. 11.7%, $P = 0.037$). However, multivariate analysis showed that MS-SDB was significantly associated with a higher prevalence of diabetes only in FHD (+) females (OR [95%CI]: females, 7.43 [3.16-17.45]; males, 0.92 [0.37-2.31]). Among the FHD (+) participants, the prevalence of recent-onset diabetes was higher in those with MS-SDB

than those without SDB, but only in females (MS-SDB vs. without SDB: 21.4 % vs. 1.1%, $P < 0.001$).

Conclusions: MS-SDB was associated with diabetes risk in females with FHD, and future studies are needed on whether treatment of SDB in females with FHD would prevent the onset of diabetes.

Keywords

Heritability; gene; environment; obstructive sleep apnea; effect modification

Brief Summary

Current Knowledge/Study Rationale: A family history of diabetes (FHD) is a strong risk factor for type 2 diabetes. Although it is said that sleep disordered breathing (SDB) is also a risk factor for diabetes, whether there is an additional increase in the prevalence of diabetes in individuals with FHD is not known.

Study Impact: In our large community-based study, moderate-to-severe SDB was significantly associated with an increased prevalence of type 2 diabetes and of recent-onset type 2 diabetes during a period of nearly 5 years, especially in females with FHD. Thus, MS-SDB might be associated with an increased prevalence of type 2 diabetes in females with FHD.

Introduction

Sleep disordered breathing (SDB), especially obstructive sleep apnea (OSA), is a common condition characterized by recurrent intermittent hypoxia during sleep and sleep fragmentation. Individuals with SDB have a high prevalence of comorbidities such as cardio-metabolic disorders, particularly with concurrent obesity.^{1,2} Of the comorbidities associated with SDB, abnormal glucose metabolism has been identified in both public health and clinical settings. Indeed, several studies have shown that the prevalence of moderate to severe OSA exceeds 30% in patients with diabetes worldwide.^{3–5} Furthermore, longitudinal observational studies and meta-analyses showed that OSA was an independent risk factor for incident diabetes,^{6–13} and increased insulin resistance.^{14–16}

Previously, we showed that the impact of SDB on the prevalence of diabetes was modified by gender and menopausal status.¹⁷ These findings implied that the effect of SDB might vary according to an individual's genetic characteristics. Of the various factors related to glucose metabolism, a positive family history of diabetes (FHD) is a well-established strong risk factor for development of diabetes,¹⁸ which also exhibits synergistic interactions in the presence of concurrent obesity.^{19,20} Nevertheless, whether SDB modifies the impact of an FHD on glucose metabolism has not been addressed. Recently, much attention has been paid to the role of hypoxia-mediated epigenetic

regulation in several diseases.²¹ Therefore, intermittent hypoxia induced by OSA might contribute to the development of diabetes in individuals with FHD.

In the present study, we hypothesized that SDB would augment the risk for abnormal glucose metabolism in those with an FHD. To test this hypothesis we investigated the associations between SDB and the prevalence of diabetes, the prevalence of recent-onset diabetes determined in the study's most recent 5 years, and insulin resistance among study participants with or without an FHD in the Nagahama Cohort.¹⁷ Preliminary findings have been previously reported in abstract form.²²

Methods

Participants

The Nagahama study is an on-going prospective cohort study in the general population (Figure 1).¹⁷ During this cohort study, the 1st survey was conducted from 2008 to 2010 and the 2nd survey was conducted from 2013 to 2016. We evaluated objective sleep parameters among the participants at the 2nd survey of the Nagahama study (see Detailed Methods in the supplemental material). Figure 1 is a flow chart in the present analyses. We investigated the associations among SDB, FHD, and prevalence of type 2 diabetes

and homeostatic model assessment-insulin resistance (HOMA-IR) in participants who had fasting blood data and who were not being treated for diabetes. In addition, we investigated the prevalence of recent-onset type 2 diabetes during 5 years prior to SDB measurements in the 2nd survey. The ethics committee of Kyoto University and Nagahama City approved the study, and all participants signed a consent form.

Assessment of Objective Sleep Duration and Activity Count

Participants were requested to wear a pulse oximeter (PULSOX-Me300; Konica Minolta, Inc., Tokyo, Japan) for 4 consecutive nights and an actigraph (Actiwatch 2 or the Actiwatch Spectrum Plus; Philips Respironics, Murrysville, PA, USA) for a week on the non-dominant wrist concurrently to assess SDB and objective sleep duration. In our other study, as we measured the mean sleep duration for an entire week, participants were requested to wear the actigraph for a week.¹⁷ Bed-in time and bed-out time were set by well-trained investigators and manually confirmed based on sleep diaries and the light sensor in the actigraph. Total sleep duration (from sleep onset time to wake-up time) and actual sleep duration (sleep duration after exclusion of wake-time after sleep onset from total sleep duration) were determined using the standard factory-default algorithm.¹⁷ Objective sleep duration was categorized into <5 h, 5-7 h, and ≥ 7 h per night averaged

over a period of a week. To assess objective daily physical activity, we used the activity count per minute while awake as recorded by an actigraph.¹⁷

Assessment of SDB

Each oximetry tracing was reviewed by trained staff members. Start and end times of sleep were set according to actigraphy, and actual sleep duration determined from assessments of objective sleep duration was used to calculate the oxygen desaturation index (Acti-ODI3%). A minimum of the average of 2 nights of oximetry data were required for analysis. SDB severity was defined by Acti-ODI3% indices as follows: normal, <5 per hour; mild, 5 to <15 per hour; moderate, 15 to <30 per hour; and severe, ≥ 30 per hour. As shown in the previous study,²³ Acti-ODI3% was more comparable to the apnea-hypopnea index (AHI) derived from attended polysomnography in 32 patients ($r = 0.99$, $P < 0.001$; $AHI = \text{Acti-ODI3\%} \times 1.04 + 1.45$) than simply-measured ODI3% without actigraphy-modification ($r = 0.92$, $P < 0.001$; $AHI = \text{usual ODI3\%} \times 1.27 + 2.06$).

FHD, Diabetes, HOMA-IR, and Recent-Onset Diabetes

FHD was defined as having one or more first degree relatives with diabetes among biological parents, siblings, and children.

Because not all participants had fasting blood test results, we used HbA1c (%) to classify glucose metabolism status as follows: normal, <6.5 ; and diabetes, ≥ 6.5 and/or current medication for diabetes.²⁴ The HOMA-IR was estimated from fasting insulin and glucose levels (Detailed Methods in the supplemental material).

Recent-onset diabetes was defined as diabetes that developed de novo during the interval between the 1st and 2nd surveys prior to SDB measurements.

Other variables

BMI was calculated as body weight (kg) divided by height (m) squared. Waist circumference was measured on the umbilicus level while standing. These variables were measured at the study site with the participant in a fasting state. Smoking habits, alcohol consumption, menopausal status in females, hypertension, and results of the Japanese version of the Epworth Sleepiness Scale²⁵ were obtained from questionnaires. From responses in the questionnaires about luxury grocery items, we obtained weekly consumption of alcohol according to units of Japanese sake. One unit of Japanese sake contains about 22 g ethanol. We calculated daily consumption of ethanol (g/day) as $(22 \times \text{weekly consumption of alcohol by units of Japanese sake})/7$. Moderate alcohol intake may have a preventive effect on the development of diabetes.²⁶ We classified

consumption of ethanol = 0 g/day, 0 g/day < ethanol $\leq$ 25 g/day, and ethanol > 25 g/day as a categorized variable in addition to ethanol (g/day) as a continuous variable. We defined hypertension as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg and/or current use of anti-hypertensive agents.

Data Analysis

Values are expressed as mean (SD), median [IQR], or percentages (%). We used the Student's t-test, analysis of variance, Mann-Whitney test, or the Kruskal-Wallis test to compare continuous values as appropriate and the Chi-square test to compare categorical values. Tukey-Kramer and Dunn-Bonferroni tests were employed as appropriate to perform post hoc pairwise comparisons among groups.

First, we comprehensively investigated the associations between FHD and the prevalence of diabetes in all participants. Next, we evaluated the impact of SDB on the prevalence of diabetes, HOMA-IR, and the prevalence of recent-onset diabetes among participants with or without FHD. Our analyses also included the total participant population and females and males separately.¹⁷ In the analyses of the prevalence of diabetes and HOMA-IR, we showed these values according to SDB severity and BMI categories among those with FHD [FHD (+)] or without FHD [FHD (-)]. BMI was

categorized from 17.5 to 27.5 kg/m² in 2.5 kg/m² increments. The upper category of BMI was ≥ 27.5 kg/m² because of the low number of participants with BMI ≥ 30.0 in the present analysis.

In the analysis of the prevalence of diabetes, we conducted multivariate logistic analyses after adjusting for possible confounders such as age and obesity-related parameters. In the analysis of HOMA-IR, we used natural log-transformed values to approximate Acti-ODI3% and HOMA-IR to a normal distribution to finally perform multivariate regression analysis. We added one to “HOMA-IR” and “Acti-ODI3%”, respectively, before log-transformation to a positive value. In the multivariate regression analysis for log-(HOMA-IR), log-(Acti-ODI3%) was included as a continuous variable in those with or without FHD.

For each analysis, we evaluated the joint contributions of SDB and FHD by using interaction terms as follows: FHD x SDB severity and FHD x log-(Acti-ODI3%) (Detailed Methods in the supplemental material).

P value <0.05 was considered significant in all analyses. Analyses were conducted by using SPSS software, version 25 (SPSS Inc., Chicago, IL, USA).

Results

Number of participants in each analysis

Figure 1 shows the number of participants for each analysis. The 2nd survey of the Nagahama study had 9,850 participants. After excluding 741 individuals who refused a sleep study and 1,632 participants without sufficient objective sleep data, activity count, or medical information and with comorbidities, we evaluated 7,477 participants in the analysis. For the analysis of insulin resistance, we evaluated 5,736 participants after excluding 1,741 participants undergoing diabetic treatment, without fasting blood data, and/or with prominently high or low plasma glucose or insulin values from the above 7,477 participants. Of the 7,477 participants described above, 6,160 participated in the 1st survey. After excluding 243 diabetic participants and 20 pregnant female participants at the 1st survey, we investigated the prevalence of recent-onset diabetes in 5,897 participants.

Associations between FHD and the Prevalence of Diabetes

Of the 7,477 eligible participants (5,061 females and 2,416 males) (Figure 1 and Table 1), 1,569 (21.0%) had an FHD. FHD (+) participants were younger, had a higher body mass index (BMI), greater waist circumference, had a larger proportion of menopausal

females, higher random plasma glucose and/or HbA_{1c}, and greater prevalence of diabetes than FHD (-) participants. There is no difference in the proportions of degrees of SDB severity between FHD (+) and FHD (-) (Table 1). Figure 2 shows the prevalence of diabetes by FHD status and BMI categories. FHD (+) led to a higher prevalence of diabetes than FHD (-) in each BMI category, and the prevalence of diabetes steeply increased in FHD (+) participants according to BMI increases.

Prevalence of Diabetes according to FHD Status and the Severity of SDB

Table 2 shows characteristics of participants according to FHD status and SDB severity. Although the prevalence of diabetes was greater according to the severity of SDB in participants with and without FHD, the degree of the increase was clearly greater in females with FHD (Figure S1 in the supplemental material).

The multivariate logistic regression analyses showed that mild SDB and MS-SDB were significantly associated with the prevalence of diabetes in all participants and females with FHD but not male participants (odds ratio [95%CI]: overall, mild SDB 1.93 [1.15-3.25], MS-SDB 2.75 [1.48-5.11]; females, mild SDB 2.63 [1.29-5.37], MS-SDB 7.43 [3.16-17.45]; males, mild SDB 1.03 [0.47-2.27], MS-SDB 0.92 [0.37-2.31]) (Figure 3). However, in the analysis of FHD (-) female and male participants, mild SDB and MS-

SDB were not significantly associated with the prevalence of diabetes. There was a significant interaction between FHD and SDB severity only in females ($P_{\text{interactions}}$ [FHD x SDB severity] were overall, 0.16; females, 0.033, males, 0.54) (Figure 3).

HOMA-IR according to the Severity of SDB and FHD Status

Figure 4 shows log-(HOMA-IR) according to SDB severity and BMI categories among FHD (+) and FHD (-) participants. Only FHD (+) females with MS-SDB had consistently higher insulin resistance than SDB (-) and mild SDB in each BMI category. Multivariate regression analyses for log-(HOMA-IR) additionally showed that log-(Acti-ODI3%) was positively associated with higher insulin resistance only in FHD (+) females (Table 3). $P_{\text{interaction}}$ (FHD x log-[Acti-ODI3%]) was also significant only in females (overall, 0.051; females, 0.001, males, 0.092).

Prevalence of Recent-Onset Diabetes according to the Severity of SDB and FHD Status

Of the above 5,897 participants, 204 (3.5%) had recent-onset diabetes by the time of the 2nd survey; the mean interval (SD) between the 1st and 2nd surveys was 4.96 (0.36) y. Figure 5 shows the prevalence of recent-onset diabetes according to SDB severity among

FHD (+) or FHD (-) participants. Although the prevalence of recent-onset diabetes increased significantly according to the severity of SDB among the overall population, there were significant differences among the overall FHD (+) participants, FHD (+) females, and FHD (-) participants overall regarding the prevalence of recent-onset diabetes. However, a significant $P_{\text{interaction}}$ (FHD x SDB severity) was seen only in females ($P = 0.033$).

Discussion

In the present study of a large prospective cohort, we first evaluated associations between the prevalence of diabetes and SDB in the context of an FHD. SDB was associated with the prevalence of type 2 diabetes only in females with FHD. Also, there was a significant interaction between SDB and FHD only in females. Furthermore, in females with FHD, SDB was related to an increase in insulin resistance. In addition, although the data were not prospective, females with FHD and MS-SDB had the highest prevalence of recent-onset diabetes during the nearly 5 years before SDB measurements. Taken together, MS-SDB might have an association with the increased prevalence of type 2 diabetes in females with FHD.

Clinical and epidemiological studies have consistently reported independent

associations between OSA and cardiovascular and metabolic dysfunction as well as the modulation of the adverse impact of obesity in this context.^{1,2,27-30} FHD is also a well-established risk factor for the development of diabetes.¹⁸ However, the potential contributions of SDB on the impact of FHD on diabetes risk have not been explored. Here, the presence of such a contribution was detected among the whole cohort, with clear differences across genders, whereby SDB did not appear to influence the effect of FHD in men, but displayed a robust effect among women. We considered two possible explanations for this gender difference. The first is the effect of menopause. Mean age of the participants was almost 58 years (Table 1); thus, many peri-postmenopausal females were in the study cohort. Menopausal females generally have multiple risk factors for developing diabetes (e.g., central adiposity, androgenicity, and mood disorder), making older females vulnerable to diabetes.³¹ Secondly, sex hormone (progesterone and estrogen) levels decrease dramatically following menopause. Female hormones strongly affect hypoxic sensitivity, which is significantly associated with diabetes.³² These 2 factors might account for the gender difference in this study.

In addition, current findings suggest that the impact of the genetic and environmental components of FHD on impaired glucose regulation (probably due to increased insulin resistance) was augmented by SDB. Since diabetes is a polygenic

disease, many single nucleotide polymorphisms have been identified as being related to the pathogenesis of the disease. Nevertheless, single nucleotide polymorphisms could not fully explain the heritability of FHD in isolation,^{33,34} and gene-environmental interactions are considered as critical contributors to diabetes risk along with epigenetic modifications. Indeed, some environmental factors provide not only an additive but also a synergistic effect on specific genetic variants through an epigenetic modification such as DNA methylation.³⁵ There is growing evidence that physiological features of SDB have the potential to evoke such epigenetic modifications. For example, exposures of pregnant rodents to intermittent hypoxia and sleep fragmentation induce epigenetic changes to affect metabolic dysfunction in their offspring that only become manifest in late adulthood.^{36,37} These epigenetic factors are also affected by sex hormones.³⁸ Future research efforts appear warranted to unravel possible mechanistic pathways involving SDB, genetic variants (particularly those associated with insulin resistance), and epigenetic modifications linked to abnormal glucose metabolism.

Clinically, a recent epidemiological study in a similar Japanese cohort showed that SDB was associated with the prevalence of diabetes only in females.¹⁷ Indeed, although several longitudinal studies showed that OSA was associated with incident diabetes,^{7,9,11} treatment of OSA did not necessarily improve glycemic control. Our current

findings suggesting that the impact of SDB on glucose metabolism is stronger in females than in males raise the possibility that gender differences might have influenced the outcomes of such trials that included a vast majority of male participants.^{27,28,39}

The combined impact of FHD and SDB on worsening of glucose metabolism could be of clinical importance. Indeed, while FHD includes both genetic and environmental risk factors inherited and shared among family members, it is estimated that genetic components predominantly account for FHD.^{33,40} FHD is readily accessible clinical information; however, the genetic aspects of FHD are unmodifiable. In contrast, SDB is a treatable disease. In clinical practice, physicians should pay close attention to the potential incidence or the high prevalence of abnormal glucose tolerance status in females with SDB and FHD and recognize that such populations may benefit through glycemic control by SDB treatment, a proposition that will require corroboration by appropriate clinical trials.

We acknowledge several limitations in this study. First, analyses were cross-sectional, and the findings cannot be considered as providing causal inferences. Although data were not prospective, the higher prevalence of recent-onset diabetes in female participants with both an FHD and MS-SDB than with either one of those factors would support the hypothesis that MS-SDB might induce diabetes in female participants with

an FHD. Second, we did not assess objective sleep parameters by polysomnography and could not distinguish the SDB type. However, although the participants with SDB in our cohort could include not only those with OSA but also those with other types of SDB, prevalence of other types of SDB (e.g. central sleep apnea) is exceedingly less common than OSA in the general population.⁴¹ Third, recall-bias of FHD may exist. Participants without diabetes may not have remembered FHD precisely. Fourth, we analyzed a homogeneous ethnic group (only Japanese). As shown in a prior study, racial differences may have existed with regard to the impact of SDB on glucose metabolism.⁴² Frequencies of genetic variants associated with diabetes and lifestyle vary across ethnicities, and therefore expansion of studies like the present one to other racial backgrounds is of importance.

In summary, SDB was significantly associated with a high prevalence of diabetes and a recent incidence of diabetes in females with FHD in this cohort. Therefore, if women with OSA and FHD are identified in clinical settings, careful evaluation of their glucose metabolism would be recommended. Future studies on genetic factors that influence the clinical phenotype and the beneficial effects of SDB treatment on glycemic control in the presence or absence of underlying FHD appear warranted.

Abbreviations

BMI: body mass index

FHD: family history of diabetes

HOMA-IR: homeostatic model assessment-insulin resistance

MS: moderate to severe

OSA: obstructive sleep apnea

SDB: sleep disordered breathing

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Figure Captions

Figure 1. Flow chart of enrollment of participants in the present study

SDB = sleep disordered breathing.

Figure 2. Prevalence of diabetes according to FHD and categories of BMI

FHD (+) participants had a higher prevalence of diabetes than FHD (-) in each BMI category. Prevalence increased sharply with increases in BMI.

Diabetes was considered according to HbA1c $\geq 6.5\%$ and/or current medication for diabetes. FHD (+) was defined as having a first degree relative(s) with diabetes. FHD = family history of diabetes; BMI = body mass index.

Figure 3. Multivariate logistic regression analysis of the prevalence of diabetes among participants with or without FHD.

(A) all participants; (B) female participants; (C) male participants.

Having mild SDB or MS-SDB was significantly associated with the prevalence of diabetes among FHD (+) participants overall, females, and FHD (-) participants overall; however, $P_{\text{interaction}}$ (FHD x SDB severity) was significant only in females.

Analyses were adjusted for age, sex (only A), body mass index, waist circumference,

alcohol consumption (ethanol = 0 g/day, 0 g/day < ethanol $\leq$ 25 g/day, and ethanol >25 g/day), pack-years smoking, sleep duration categories, activity count, hypertension, and menopause (only B).

Diabetes was considered according to HbA1c $\geq$ 6.5% and/or current medication for diabetes. SDB was classified by 3% oxygen desaturation index modified by sleep duration from actigraphy as follows: SDB (-), <5/hour; mild SDB, 5 to <15/hour; MS-SDB, $\geq$ 15/hour. FHD = family history of diabetes; SDB = sleep disordered breathing; MS = moderate to severe.

Figure 4. Insulin resistance by HOMA according to SDB and categories of BMI among participants with or without FHD.

(A) Log-(HOMA-IR) in all participants; (B) Log-(HOMA-IR) in female participants; (C) Log-(HOMA-IR) in male participants.

Among only FHD (+) female participants, those with MS-SDB consistently and clearly showed higher insulin resistance than SDB (-) and mild SDB in each BMI category.

SDB was classified by the 3% oxygen desaturation index modified by sleep duration from actigraphy as follows: SDB (-), <5/hour; mild SDB, 5 to <15/hour; MS-SDB, $\geq$ 15/hour.

HOMA = homeostatic model assessment; SDB = sleep disordered breathing; BMI = body

mass index; FHD = family history of diabetes; MS = moderate to severe.

Figure 5. Prevalence of recent-onset diabetes according to SDB among participants with or without FHD.

(A) all participants; (B) female participants; (C) male participants.

Among FHD (+) participants overall, females, and FHD (-) participants overall, the increase in SDB severity significantly led to a high prevalence of recent-onset diabetes at each degree of SDB severity. However, $P_{\text{interaction}}$ (FHD x SDB severity) was significant only in females.

Recent-onset diabetes was considered according to $\text{HbA1c} \geq 6.5\%$ and/or current use of medication for diabetes at the 2nd survey in participants without diabetes at the 1st survey.

SDB was classified by the 3% oxygen desaturation index modified by sleep duration from actigraphy as follows: SDB (-), $<5/\text{hour}$; mild SDB, 5 to $<15/\text{hour}$; MS-SDB, $\geq 15/\text{hour}$.

FHD = family history of diabetes; SDB = sleep disordered breathing; MS = moderate to severe. The Chi-square test was used to compare the prevalence of recent-onset diabetes between each SDB severity.

Table 1. Characteristics of study participants according to FHD.

	All N = 7,477	FHD (+) N = 1,569	FHD (-) N = 5,908	P value (FHD [+] vs. FHD [-])
Females	5,061 (67.7%)	1,114 (71.0%)	3,947 (66.8%)	0.002
Age (y)	57.9 (12.1)	57.2 (11.7)	58.1 (12.2)	0.007
Body mass index (kg/m ²)	22.3 (3.3)	22.5 (3.4)	22.2 (3.3)	0.001
Waist circumference (cm)	81.9 (9.4)	82.5 (9.3)	81.7 (9.4)	0.003
Pack-years smoking in current/past smoker*	18.8 [8.0-33.0]	16.5 [6.0-32.0]	19.0 [8.0-33.0]	0.096
Alcohol consumption				
Ethanol (g/day)*	0.89 [0.00-12.21]	0.86 [0.00-10.00]	0.89 [0.00-12.50]	0.056
Ethanol = 0 g/day	3,393 (45.4%)	729 (46.5%)	2,664 (45.1%)	
0 g/day < ethanol ≤ 25 g/day	2,917 (39.0%)	630 (40.2%)	2,287 (38.7%)	0.024
Ethanol > 25 g/day	1,167 (15.6%)	210 (13.4%)	957 (16.2%)	
Activity count (/min)	332.5 (99.0)	334.8 (93.6)	331.8 (100.4)	0.29
Menopausal females	3,324 (65.7%)	698 (62.7%)	2,626 (66.5%)	0.016
Hypertension	2,849 (38.1%)	600 (38.2%)	2,249 (38.1%)	0.90
JESS*	6 [3-8]	6 [3-8]	6 [3-8]	0.084
Actigraphy-modified ODI3% (/hour)*	5.91 [3.64-10.09]	5.86 [3.44-9.93]	5.94 [3.69-10.11]	0.27
SDB severity				
SDB (-)	3,074 (41.1%)	662 (42.2%)	2,412 (40.8%)	
Mild SDB	3,496 (46.8%)	709 (45.2%)	2,787 (47.2%)	0.37

MS-SDB	907 (12.1%)	198 (12.6%)	709 (12.0%)	
Objective sleep duration				
<5 (h)	1,048 (14.0%)	214 (13.6%)	834 (14.1%)	
5-7 (h)	5,395 (72.2%)	1,142 (72.8%)	4,253 (72.0%)	0.82
≥7 (h)	1,034 (13.8%)	213 (13.6%)	821 (13.9%)	
Current medication for diabetes				
Anti-hyperglycemic agents	323 (4.3%)	133 (8.5%)	190 (3.2%)	<0.001
Insulin use	23 (0.3%)	14 (0.9%)	9 (0.2%)	<0.001
Random plasma glucose (mg/dl)	87.6 (13.1)	89.7 (15.4)	87.0 (12.3)	<0.001
HbA _{1c} (%)	5.56 (0.48)	5.65 (0.57)	5.53 (0.45)	<0.001
Diabetes (all)	469 (6.3%)	178 (11.3%)	291 (4.9%)	<0.001
Diabetes (females)	211 (4.2%)	88 (7.9%)	123 (3.1%)	<0.001
Diabetes (males)	258 (10.7%)	90 (19.8%)	168 (8.6%)	<0.001

Data are expressed as mean (SD), median [IQR], or number (%).

*Mann-Whitney test was used to compare medians between groups. Student's t-test was used otherwise.

Definition of abbreviations: FHD = family history of diabetes; SDB = sleep disordered breathing; JESS = Japanese version of The Epworth Sleepiness Scale; Acti-ODI3% = 3% oxygen desaturation index modified by sleep duration derived from actigraphy; MS = moderate to severe.

Diabetes was considered according to HbA_{1c} ≥6.5% and/or current medication for diabetes. FHD (+) was defined as having first degree relative(s) with diabetes.

<5 (h)	93 (14.0%)	87 (12.3%)	34 (17.2%)		317 (13.1%)	368 (13.2%)	149 (21.0%)	
5-7 (h)	480 (72.5%)	521 (73.5%)	141 (71.2%)	0.44	1,753 (72.7%)	2,023 (72.6%)	477 (67.3%)	
≥7 (h)	89 (13.4%)	101 (14.2%)	23 (11.6%)		342 (14.2%)	396 (14.2%)	83 (11.7%)	
Current medication for diabetes								
Anti-hyperglycemic agents	17 (2.4%)	78 (11.0%)	39 (19.7%)	<0.001	25 (1.0%)	115 (4.1%)	50 (7.1%)	<0.001
Insulin use	0 (0.0%)	5 (0.7%)	9 (4.5%)	<0.001	1 (0.0%)	8 (0.3%)	0 (0.0%)	0.042
Random plasma glucose (mg/dl)	85.2 (11.4)	91.7 (16.9) [†]	97.9 (16.9) ^{†‡}	<0.001	83.7 (8.4)	88.4 (12.7) [†]	93.1 (17.2) ^{†‡}	<0.001
HbA _{1c} (%)	5.46 (0.44)	5.73 (0.60) [†]	5.95 (0.60) ^{†‡}	<0.001	5.42 (0.35)	5.58 (0.47) [†]	5.73 (0.58) ^{†‡}	<0.001
Diabetes (all)	22 (3.3%)	98 (13.8%)	58 (29.3%)	<0.001	40 (1.7%)	168 (6.0%)	83 (11.7%)	<0.001
Diabetes (females)	11 (1.9%)	46 (10.2%)	31 (32.6%)	<0.001	25 (1.2%)	73 (4.4%)	25 (10.3%)	<0.001
Diabetes (males)	11 (11.7%)	52 (20.2%)	27 (26.2%)	0.037	15 (4.2%)	95 (8.4%)	58 (12.4%)	<0.001

Data are expressed as mean (SD), median [IQR], or number (%).

*Kruskal-Wallis test was used to compare differences among groups. Analysis of variance was used otherwise. [†]P < 0.05 vs. SDB (-), [‡]P < 0.05 vs. Mild SDB.

Definition of abbreviations: FHD = family history of diabetes; SDB = sleep disordered breathing; MS = moderate to severe; JESS = Japanese version of The Epworth Sleepiness Scale; Acti-ODI3% = 3% oxygen desaturation index modified by sleep duration derived from actigraphy.

Diabetes was considered according to HbA_{1c} ≥ 6.5% and/or current medication for diabetes. FHD (+) was defined as having first degree relative(s) with diabetes. SDB was classified by Acti-ODI3% as follows: normal, <5/hour; mild to severe SDB, ≥5/hour

Table 3. Multivariate regression analysis for log-(HOMA-IR) according to FHD.**A. Individuals with FHD**

Variables	All		Females		Males	
	N = 1,150		N = 852		N = 298	
	β	P value	β	P value	β	P value
Age (y)	-0.10	<0.001	-0.10	0.0497	-0.08	0.14
Body mass index (kg/m ²)	0.39	<0.001	0.37	<0.001	0.41	<0.001
Waist circumference (cm)	0.20	<0.001	0.18	<0.001	0.21	0.019
Females	0.06	0.069	-	-	-	-
Pack-years smoking	0.01	0.72	0.02	0.56	0.002	0.96
Ethanol (g/day)	-0.04	0.17	-0.01	0.71	-0.04	0.39
Activity count (/min)	-0.09	<0.001	-0.06	0.032	-0.13	0.008
Menopause	-	-	-0.01	0.81	-	-
Hypertension	0.09	<0.001	0.09	0.002	0.08	0.12
Log-(Acti-ODI3%)	0.06	0.058	0.13	<0.001	-0.10	0.055
R ² (adjusted R ²) (%)	36.2 (36.0)		40.2 (39.6)		40.9 (39.2)	

B. Individuals without FHD

Variables	All		Females		Males	
	N = 4,586		N = 3,112		N = 1,474	
	β	P value	β	P value	β	P value
Age (y)	-0.10	<0.001	-0.11	<0.001	-0.10	<0.001
Body mass index (kg/m ²)	0.40	<0.001	0.41	<0.001	0.34	<0.001
Waist circumference (cm)	0.20	<0.001	0.16	<0.001	0.26	<0.001
Females	0.06	0.001	-	-	-	-
Pack-years smoking	0.01	0.56	-0.03	0.08	0.01	0.60
Ethanol (g/day)	-0.07	<0.001	-0.03	0.02	-0.11	<0.001
Activity count (/min)	-0.07	<0.001	-0.06	<0.001	-0.07	<0.001
Menopause	-	-	0.01	0.59	-	-
Hypertension	0.09	<0.001	0.10	<0.001	0.06	0.011
Log-(Acti-ODI3%)	0.02	0.19	0.01	0.68	0.02	0.31
R ² (adjusted R ²) (%)	36.4 (36.3)		34.7 (34.5)		39.4 (39.1)	

Definition of abbreviations: FHD = family history of diabetes; β = standardized partial regression coefficient; Acti-ODI3% = 3% oxygen desaturation index modified by sleep duration derived from actigraphy. FHD (+) was defined as having first degree relative(s)

with diabetes.

Figure 1.

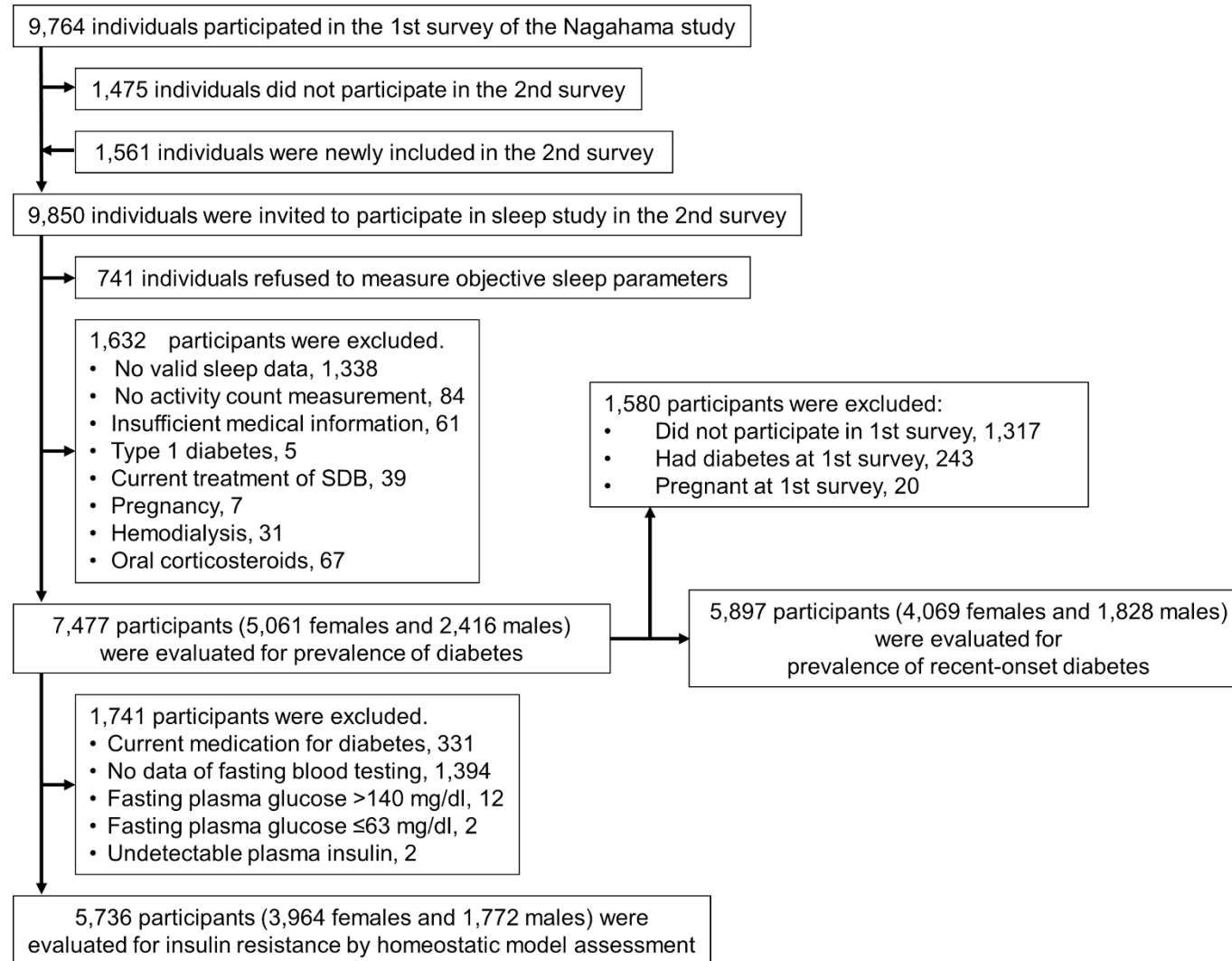
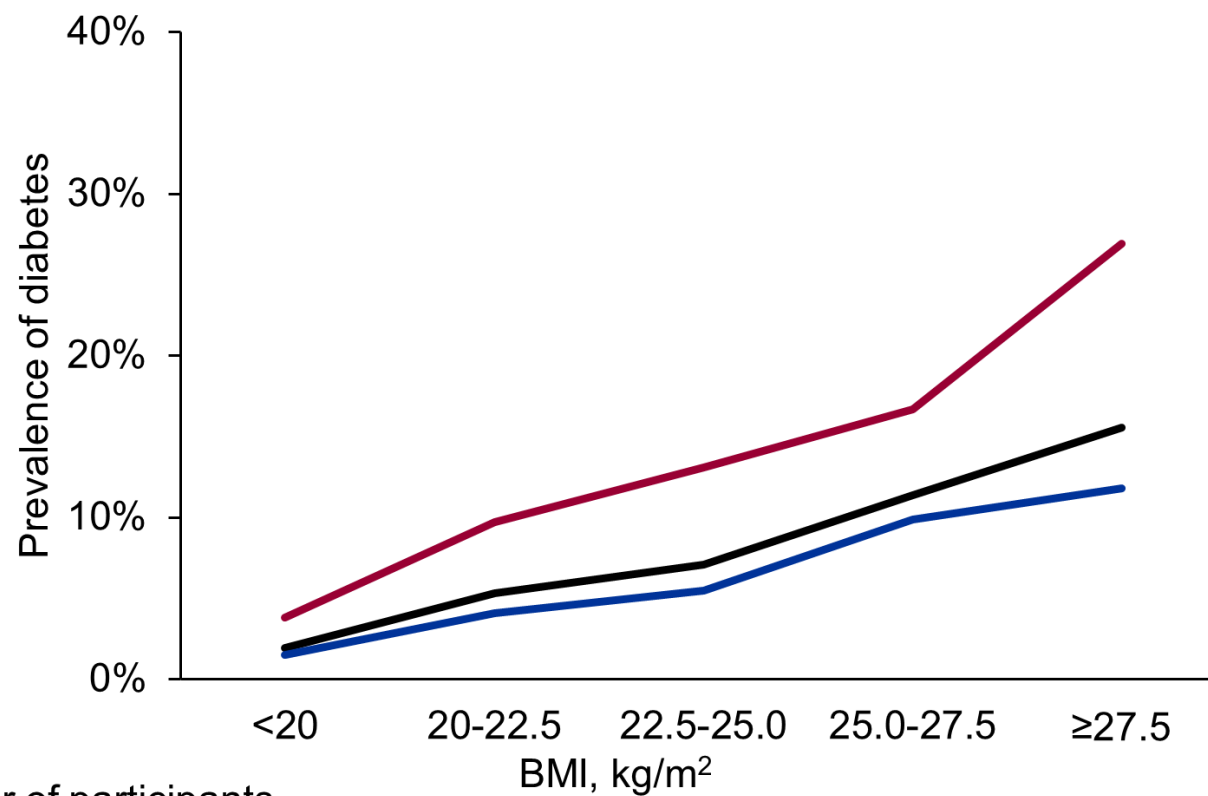


Figure 2.

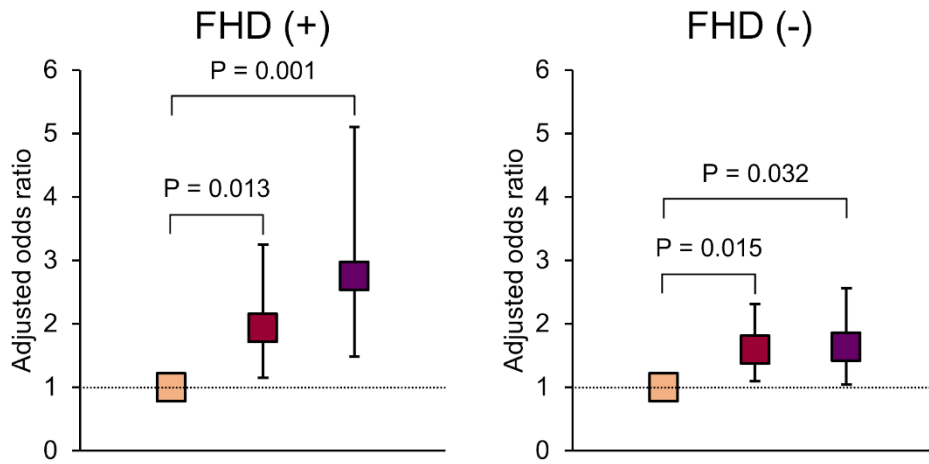


Number of participants

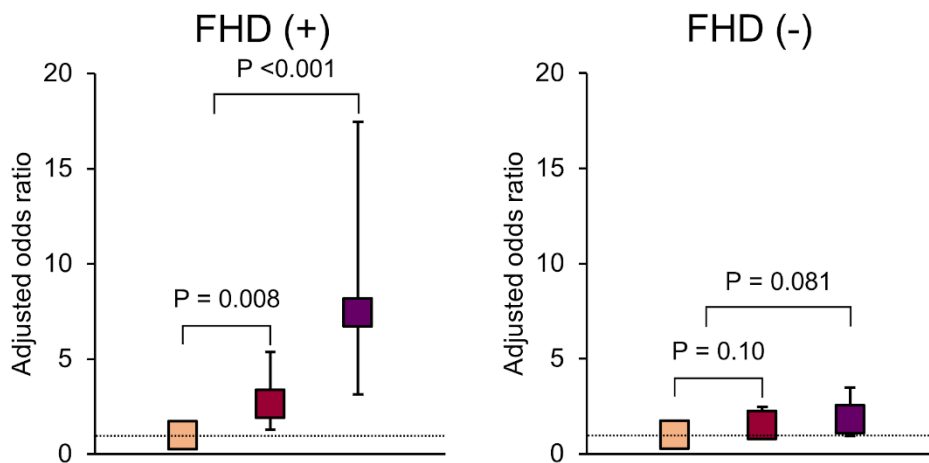
All	1,881	2,360	1,874	886	476
FHD (+)	366	496	396	192	119
FHD (-)	1,515	1,864	1,478	694	357

Figure 3.

A. All: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.16$



B. Females: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.033$



C. Males: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.54$

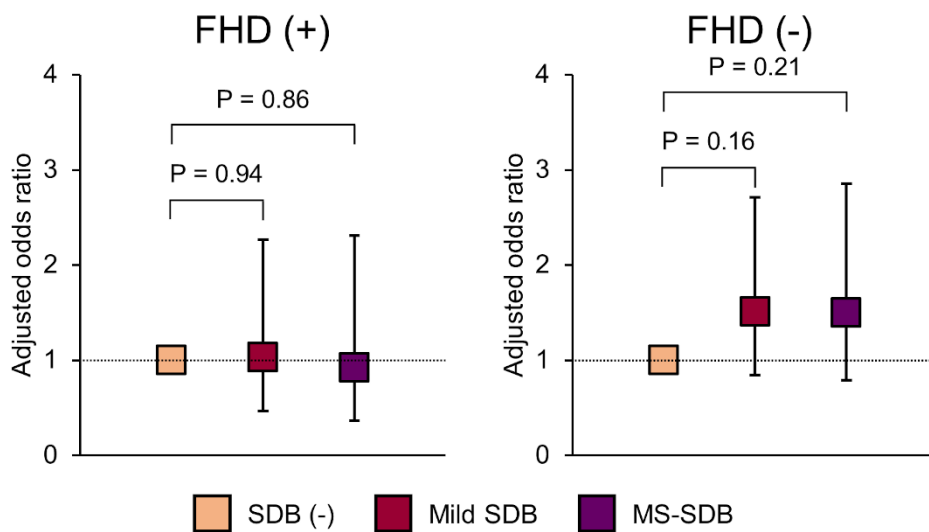
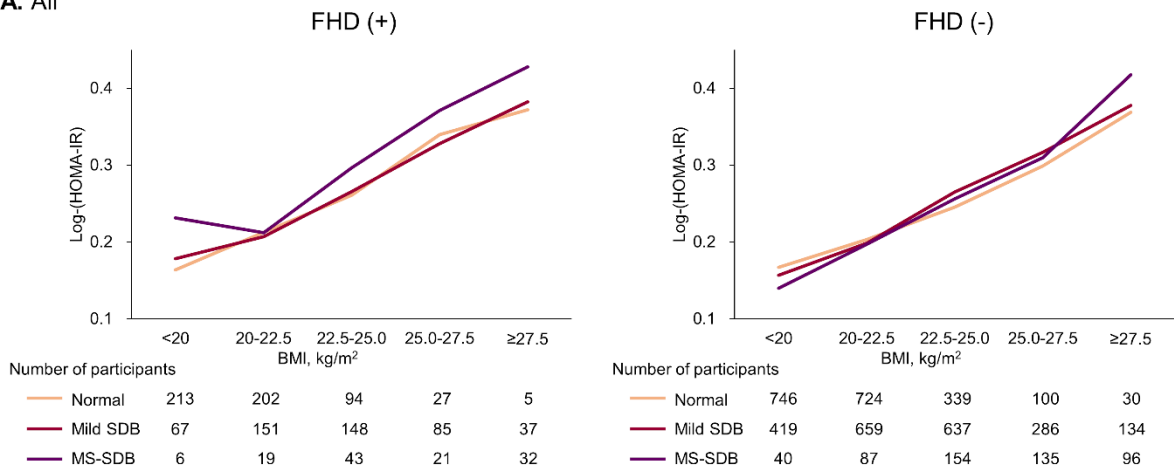
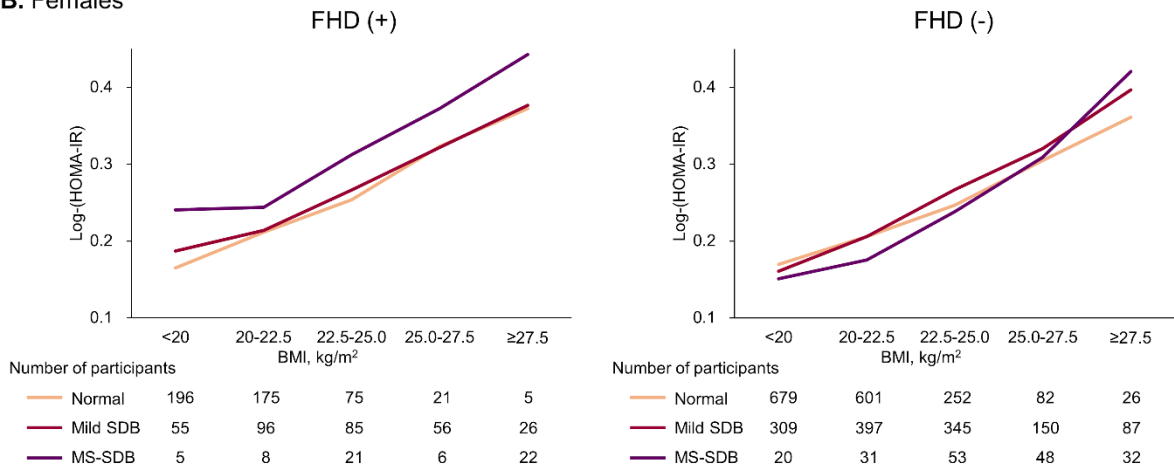


Figure 4.

A. All



B. Females



C. Males

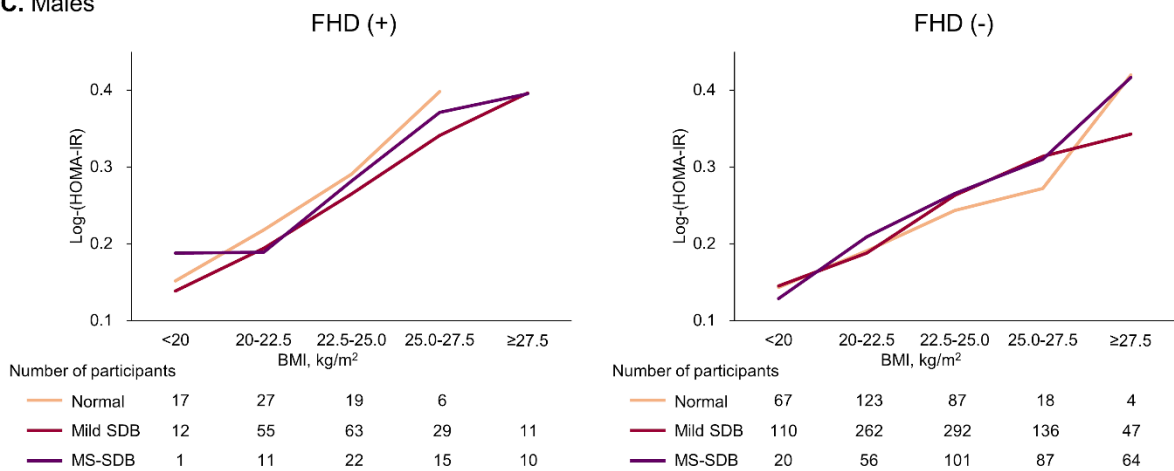
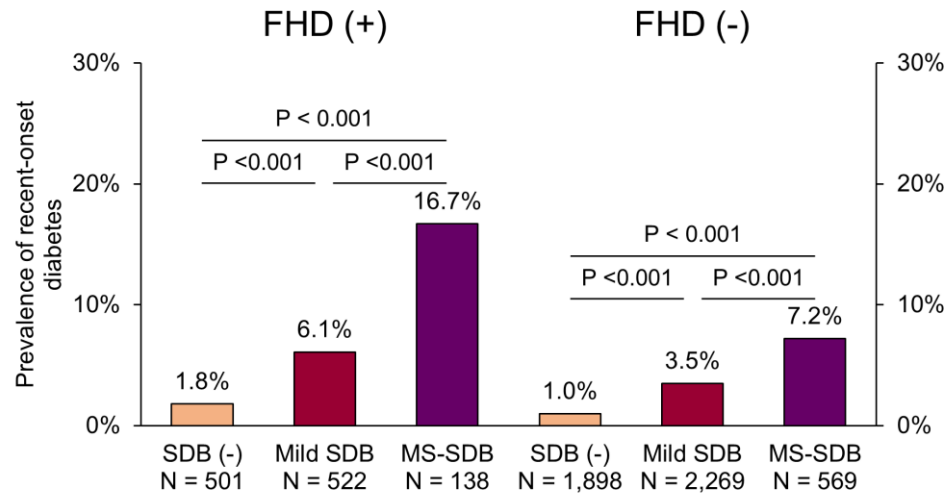
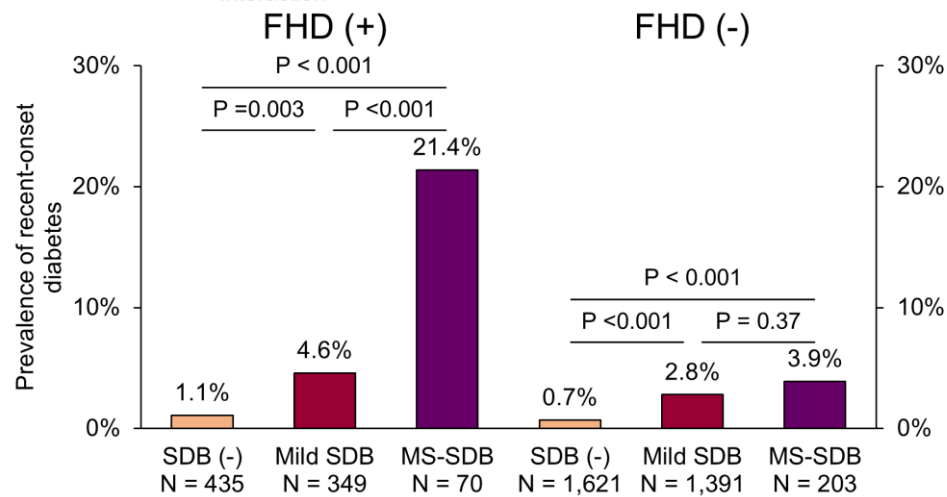


Figure 5.

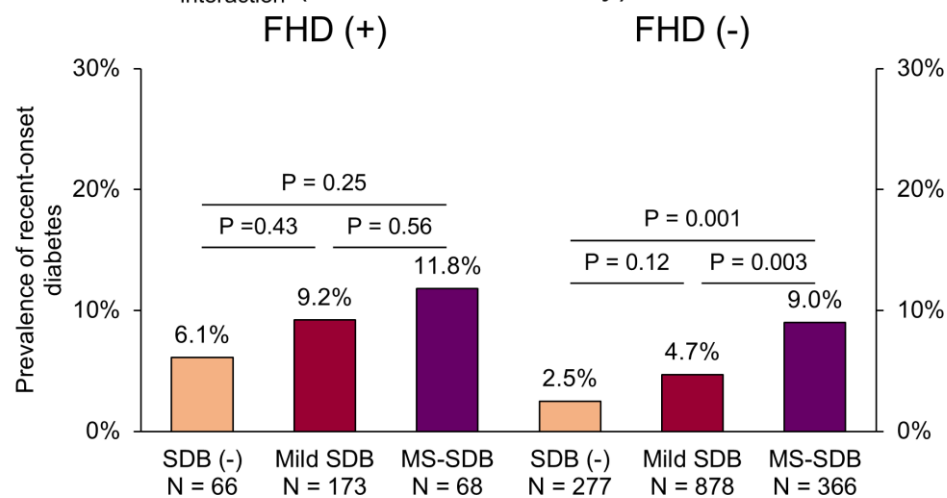
A. All: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.36$



B. Females: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.033$



C. Males: $P_{\text{interaction}} (\text{FHD} \times \text{SDB severity}) = 0.34$



Supplemental Material

Impact of sleep disordered breathing on glucose metabolism among individuals with a family

history of diabetes: the Nagahama Study

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Detailed Methods

The Nagahama Study

The Nagahama study is an on-going prospective cohort study in the general population (Figure 1).¹ Participants are followed up with a survey every 5 years. The first survey was conducted from 2008 to 2010 and the second survey from 2013 to 2016. In the second survey, we evaluated objective sleep parameters among the participants. To maintain the size of the cohort (about 10,000 participants), participants in 2016 were newly enrolled; therefore, no baseline data from the first survey were available for these participants.

Inclusion Criteria for Assessment by Homeostatic Model Assessment-insulin Resistance

For the secondary analyses, we used the homeostatic model assessment (HOMA) to evaluate insulin resistance in eligible participants (Figure 1).

The HOMA insulin resistance was estimated as:

$$\text{HOMA-IR} = (\text{fasting plasma glucose [mg/dl]} \times \text{fasting plasma insulin [\mu U/ml]}) / 405.^2$$

So that the HOMA could be used with accuracy, we excluded participants with fasting blood glucose >140 mg/dl or ≤63 mg/dl.^{3,4}

Blood Testing

We measured HbA1c (Determiner L HbA1c, Kyowa Medex Co., Ltd., Tokyo, Japan), plasma glucose (Quick-auto II GLU-HK[s], Shino-Test Corp., Tokyo, Japan), and plasma insulin (Lumipulse Presto Insulin, Fujirebio Inc., Tokyo, Japan). We defined a fasting blood test as a blood test conducted ≥8 hours from the last meal to the sampling time.⁵

Statistics to Investigate Interactions between SDB and FHD

We evaluated interactions between SDB and FHD by multivariate analyses to evaluate the synergistic impact of SDB and FHD as described below. In multivariate logistic analyses for the prevalence of diabetes, we included SDB severity, FHD, and SDB severity x FHD as an interaction term after adjusting for sex, age, body mass index, waist circumference, pack-years smoking, alcohol consumption (ethanol = 0 g/day, 0 g/day < ethanol ≤25 g/day, and 25 g/day < ethanol g/day), activity count, hypertension, menopause (females only). In multivariate regression analysis for log-(HOMA-IR), we included log-(Acti-ODI3%), FHD, and log-(Acti-ODI3%) x FHD as an interaction term after adjusting for sex, age, body mass index, waist circumference, pack-years smoking, alcohol consumption (continuous variable), activity count, menopause (females only), and hypertension. In the analyses of recent-onset diabetes, because the number of participants with recent-onset diabetes was low (N = 204), we only included FHD, SDB severity, and SDB severity x FHD as an interaction term without confounders. In analyses of the prevalence of recent-onset diabetes, because the number of participants with recent-onset diabetes was small (N = 204), we evaluated the interaction between SDB and FHD

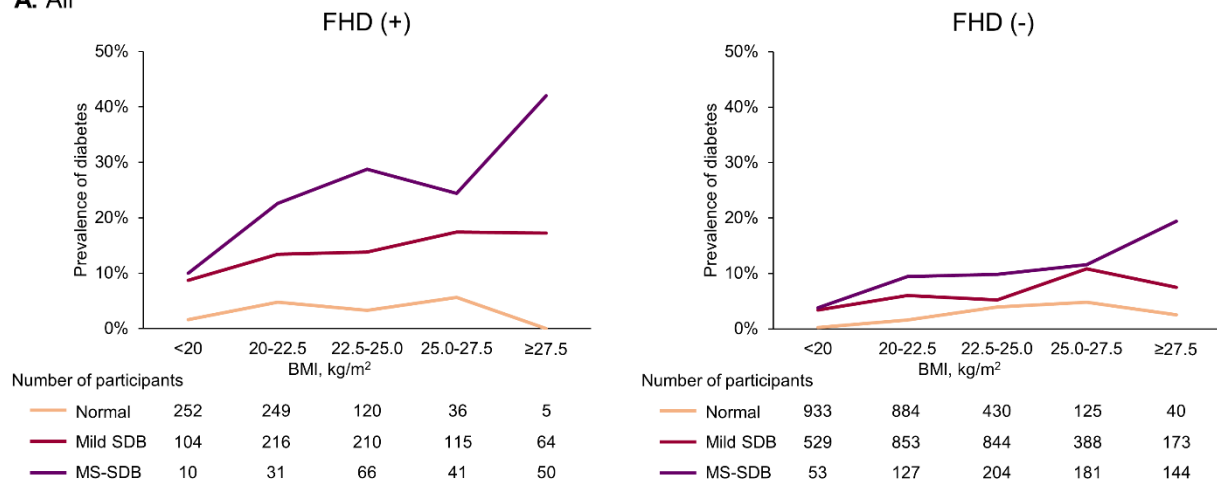
by including SDB severity, FHD, and SDB severity x FHD as an interaction term without confounders in multivariate logistic analyses.

References

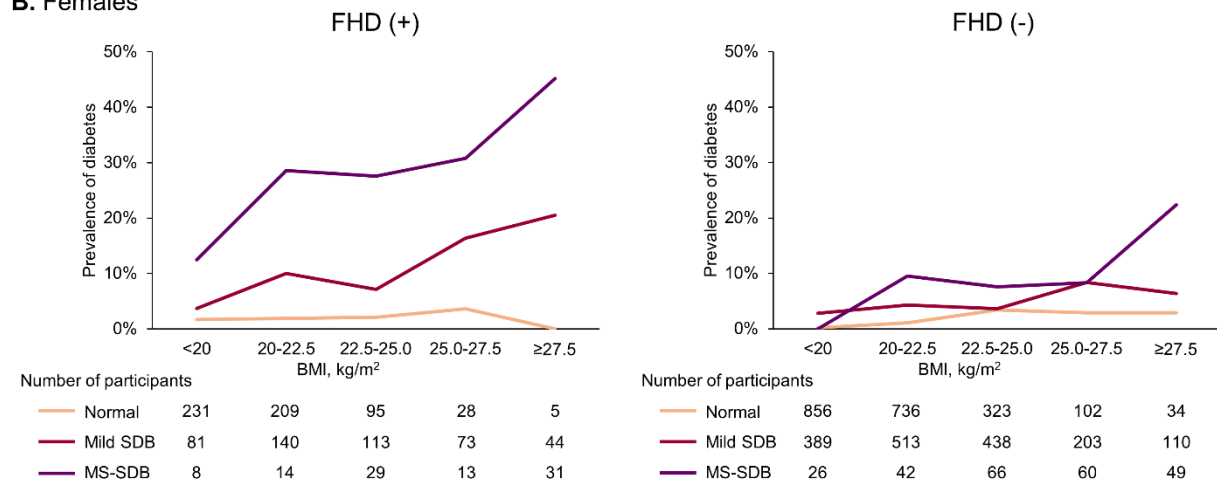
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Figure S1. Prevalence of diabetes according to SDB and categories of BMI among participants with or without FHD

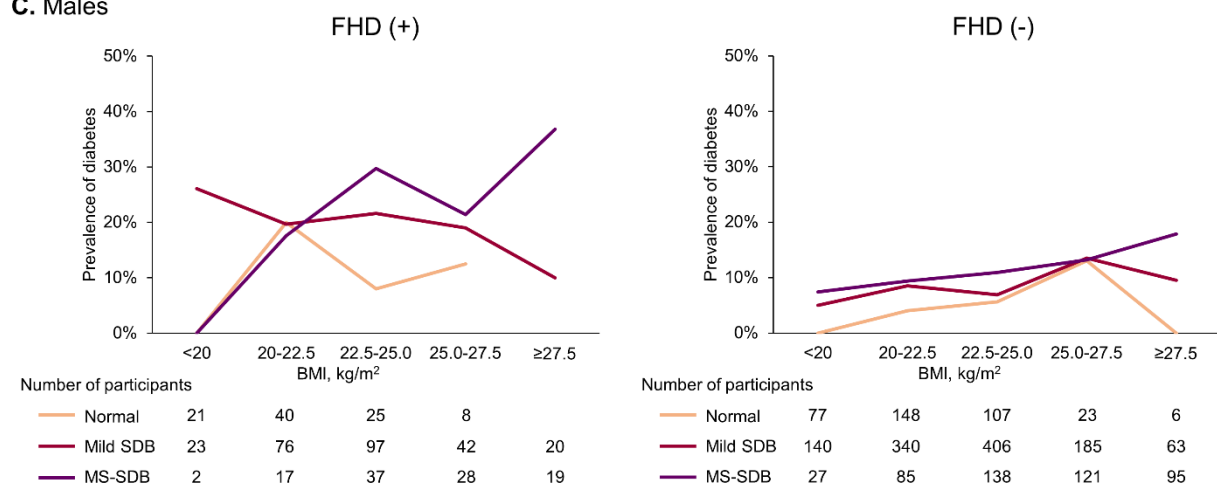
A. All



B. Females



C. Males



(A) all participants; (B) female participants; (C) male participants.

Among FHD (+) overall and female participants, mild SDB and MS-SDB showed consistently higher prevalence of diabetes than SDB (-) in each BMI category, and MS-SDB more strongly contributed to the higher prevalence than mild SDB. However, among the other participants,

mild SDB and MS-SDB did not show a clearly higher prevalence compared with SDB (-).

Diabetes was considered according to HbA1c $\geq 6.5\%$ and/or current medication for diabetes.

SDB was classified by the 3% oxygen desaturation index modified by sleep duration from actigraphy as follows: SDB (-), $<5/\text{hour}$; mild SDB, 5 to $<15/\text{hour}$; MS-SDB, $\geq 15/\text{hour}$. SDB = sleep disordered breathing; BMI = body mass index; FHD = family history of diabetes; MS = moderate to severe.