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Early View

Original research article

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Obstructive sleep apnoea and long-term risk of incident diabetes in middle-aged and older general population

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Take-Home Message

In this large population-based study, moderate-severe obstructive sleep apnoea was an independent risk factor for incident type-2 diabetes in the middle-aged and older, which may be a potential target for intervention in prevention strategies for diabetes.

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Abstract

Obstructive sleep apnoea (OSA) is associated with increased risk of type-2 diabetes. However, results from large population-based prospective cohort studies are rare. The main aim of the present study was to investigate the relative risk (RR) of 8-year incident type-2 diabetes in relation to OSA severity in a prospective cohort study of middle-aged and older adults.

A total of 2,918 participants (avg. age of 59 years) of the Korean Genome and Epidemiology Study (KoGES), who underwent homebased overnight polysomnography at baseline examination between year 2011 and 2014, were followed up 4-yearly between 2015 – 2018 and 2019 – 2021. A total of 1,697 participants were present in both the follow-ups. After excluding participants who had diabetes at baseline (n=481), a total of 1,216 participants were eligible for the analyses. OSA at baseline were categorized by apnoea–hypopnoea index (AHI) levels as non-OSA (0–4.9 events/h), mild OSA (5.0–14.9 events/h) and moderate-severe OSA (≥15.0 events/h). Incident type-2 diabetes was identified at each follow-ups.

Compared to non-OSA, participants with moderate-severe OSA had 1.5 times higher risk of developing type-2 diabetes at the end of 8-year follow-up after adjusting for potential covariates (RR=1.50, 95% confidence interval=1.02-2.21). In the same analytical models for 4-year RR of incident type-2 diabetes, none of the OSA groups were in significantly higher risk compared to non-OSA group.

Moderate-severe OSA, a modifiable risk factor, poses a higher risk of incident type-2 diabetes compared to non-OSA group over 8-year period in general middle-aged and older adults.

Introduction:

Type-2 diabetes continues to increase in prevalence, incidence, and is a leading cause of morbidity and mortality [1]. The International Diabetes Federation (IDF) has projected that 629 million people will be diagnosed with type-2 diabetes globally by 2045, compared to 425 million in 2017 [2]. The dramatic increase in newly diagnosed cases of type-2 diabetes and its associated morbidity and mortality urgently demands for identifying potentially modifiable risk factors for primary prevention of diabetes in general population. Obstructive sleep apnoea (OSA), the recurrent episodic disruption of normal breathing during sleep, is highly prevalent in the general adult population ranging from 6% to 17% (as high as 49% in the advanced age-groups) [3]. OSA is a disorder that has also been found to be associated with type-2 diabetes. The mechanisms by which OSA may lead to diabetes can be explained by disruptions of sleep pattern, intermittent hypoxia and oxidative stress, as well as obesity and cardiovascular comorbidities [4].

A growing number of studies have shown that OSA is associated with insulin resistance and glucose intolerance independent of other known risk factors [5-7]. Also, there are data suggesting a higher prevalence of diabetes in subjects with OSA independent of age, gender, and obesity [8]. However, few prospective studies have investigated OSA as an independent risk factor for the future development of diabetes in the general population. A causal relationship of OSA and type-2 diabetes incidence have been reported in a clinic population from a historical cohort study [9], however, prospective population based study results remained mixed [8, 10, 11]. The Australian population-based cohort study reported that moderate-severe sleep apnoea was a significant risk factor for incident diabetes, however, the confidence intervals were so wide that studies with greater power was suggested to verify the relationship [10]. However, from a self-reported diabetes data, severe OSA was found to be associated with a greater risk of incident diabetes, independent of adiposity in a community-based sample of participants during a median follow-up of 13 years [11]. The Wisconsin Sleep Cohort measured sleep apnoea by in-laboratory polysomnography and found a non-significant association between moderate-severe sleep apnoea and

incident physician-diagnosed diabetes after 4 years (OR = 1.62, 95% CI 0.67–3.65) [8].

In this 8-year prospective follow-up study, we investigated the cumulative incidence and relative risk (RR) of type-2 diabetes by OSA severity in Korean general middle-aged and older adults. Based on cross-sectional data, we have previously reported that habitual snoring may affect glucose and insulin metabolism, independent of diabetes and hypertension in non-obese Korean middle-aged men [12].

Methods:

Study design and participants

The study participants are from the Korean Genome and Epidemiology Study (KoGES) [13]. The KoGES-Ansan Aging Study is a sub-cohort of KoGES, which is an ongoing prospective investigation (Figure 1) that was designed to undertake overnight in-home polysomnography (PSG). Details of the KoGES-Ansan Aging Study and sampling method have been provided in a previous reports [14, 15].

Briefly, at the baseline examination between 2011 and 2014, a total of 2,918 participants (avg. age of 59 years) completed home unattended PSG and were followed up 4-yearly with a scheduled site visit for similar interviews, comprehensive health examination and collection procedures of bio-specimens. Two follow-ups were performed between the year 2015 – 2018 and 2019 – 2021 (Figure 1). Written informed consent was obtained from all participants and the study protocol was approved by the institutional ethics committee of Korea University Ansan Hospital.

Polysomnography (PSG)

Overnight PSG was performed with the portable device (Embletta® X-100; Embla Systems, Broomfield, CO, USA) at home. A trained technologist connected the device to the patient at bedtime and data were retrieved in the morning after the unattended overnight recording [16]. All PSG results were manually scored using the standard criteria [17]. Further details of PSG are given in the supplementary document.

Definition of incident type-2 diabetes

All study participants underwent a fasting and 2-hour 75-g oral glucose tolerance test (OGTT) at each follow-up visits [18]. Incident type-2 diabetes was defined as a fasting glucose concentration ≥126 mg/dL or a post 2-hour glucose after the 75-g OGTT (2h-PG) ≥200 mg/dL based on the World Health Organization criteria [19, 20]. Regardless of glucose values, participants who reported currently under antidiabetic medications were considered to have type-2 diabetes.

Other variables

Demographic data, alcohol consumption, physical activity, and medical conditions were obtained via questionnaire. Physical activity was assessed using a scale consisting of 5 categories for activity intensity (sedentary, very light, light, moderate and vigorous) as measured by hours spent in a typical day per intensity level. The total metabolic equivalent (MET/week) score was calculated by multiplying the hours spent at a particular activity intensity by the MET value [21, 22]. Alcohol consumption status was determined by asking the participants

whether they had ever consumed alcoholic beverages in their lifetime, whether there was a time in their life when they regularly consumed alcohol, and whether they drank in the past 30 days. Total alcohol consumption (grams/day) were then calculated based on detailed information of pattern, volume, frequency and type of beverages [22]. Self-reported smoking status (never, former, or current smokers) was collected and pack-year of smoking was calculated. Blood pressure, height, body weight, neck and waist circumference of participants were measured using standard methods. Mean arterial pressure was calculated by following formula: (systolic blood pressure × 2/3 + diastolic blood pressure × 1/3). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). We calculated percent change of BMI and WC from baseline over time (4-year and 8-year follow-up) by ratio of the follow-up measurement divided by baseline measurement (e.g. $[BMI_{follow\text{-}up} / BMI_{baseline}] \times 100$). All blood samples were obtained in the morning after a 12-hour overnight fast and were immediately stored at −80°C for subsequent assays. Plasma concentrations of glucose, total cholesterol (TC), triglycerides (TG), and high density lipoprotein (HDL) cholesterol were measured enzymatically using a 747 Chemistry Analyzer (Hitachi, Tokyo,

Japan). Low-density lipoprotein (LDL) cholesterol levels were estimated using the Friedewald formula [23]. Body fat percent was measured by $InBody_{720}$ body composition analyzer (Biospace Co., Korea) that uses the principle of bioelectrical impedance [24]. The body composition was measured at a fasting state and after voiding in the morning. Excessive daytime sleepiness (EDS) was measured by Korean version of Epworth sleepiness scale (KESS) questionnaire which is widely used to measure the general level of daytime sleepiness [25]. We defined EDS when KESS score was ≥11 [26].

Statistical analysis:

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Demographic, life-style, clinical and sleep characteristics of the study participants were expressed as the mean ± SD or numbers and percentages as per the OSA categories defined as non-OSA (AHI 0–4.9 events/h), mild (AHI 5.0–14.9 events/h) and moderate-severe (AHI ≥15.0 events/h). For continuous variables, one-way analysis of variance and for categorical variables

chi-square test was used. We used relative risk (RR) estimation by 'Poisson regression with robust error variance' [27] to estimate RR and 95% confidence interval (CI) of incident type-2 diabetes in OSA groups, holding non-OSA as reference category. The robust error variances was estimated by using the repeated statement and the subject identifier (subject ID) in the PROC GENMOD procedure. To account for within-subject correlation for subjects an unstructured correlation matrix was used. We examined both univariate and multivariable models. In multivariable models, RRs were examined with adjustment for age, sex, occupation and income first. We found that waist circumference had higher correlation with fasting blood glucose levels compared to the other body habitus measures, which is also consistent with a previous report [28]. When including both BMI and waist circumference in models, BMI was no longer significant; therefore, we chose to use waist circumference as our body habitus measure to be adjusted in the further models. However, we conducted sensitivity analyses with BMI included in the models. Finally, other potentially confounding variables measured at baseline (physical activity, drinking alcohol, smoking, mean arterial pressure, total cholesterol, history of cardio-vascular diseases, total sleep time

and napping) were adjusted to determine if those significantly changed the OSA–diabetes relationship. Two-tailed p-values <0.05 were considered to indicate statistical significance.

Results:

A total of 1,697 participants were present in the both the follow-ups. After excluding participants who had diabetes at baseline (n=481), a total of 1,216 participants (age ranges from 49-79 years) were analyzed (Figure 1). The baseline characteristics of study participants in the three OSA groups are shown in Table 1. Mean age (SD) were 56.6 (4.9), 58.6 (5.9) and 59.5 (6.4) years in non-OSA, mild and moderate-severe OSA groups respectively. The proportion of women were 60.7%, 48.9% and 25.9% in non-OSA, mild and moderate-severe OSA groups respectively. Body-habitus measures (BMI and waist circumference) were highest among the moderate-severe OSA group and were significantly different among the groups (Table 1). Although, regular exercise proportions did not differ significantly, median MET per week was lowest in moderate-severe OSA group. Current alcohol drinkers were proportionately higher in the moderate-severe OSA

group, however current alcohol consumption amount was higher in the mild OSA group. TC and LDL were not significantly different among the OSA groups, however, HDL was lower in moderate-severe OSA group. Mean arterial pressure and history of cardiovascular disease were higher among the moderate-severe OSA group.

Sleep characteristics of the study participants by OSA severity are presented in the Table 1. Excessive daytime sleepiness (EDS) was 4.2%, 5.3% and 6.3% in non-OSA, mild and moderate-severe OSA groups respectively but did not differ significantly among the OSA groups. Self-reported sleep time also was not significantly different among the OSA groups. Mean Oxygen Saturation (MOS) was 96.2%, 95.4% and 94.6% in non-OSA, mild and moderate-severe OSA groups respectively and were significantly different among the groups ($p < .001$).

The 4–year and 8–year cumulative incidence rate of type-2 diabetes were 7.9% and 14% respectively (Table 2). Compared to the non-OSA group, 4-year RR of type-2 diabetes in both mild and moderate-severe OSA groups were not

significantly higher in unadjusted model and in models after adjusting for potential covariates (Table 3). The 8-year RR of type-2 diabetes in mild OSA compared to non-OSA group was not significantly higher as well (Table 4). However, moderate-severe OSA compared to non-OSA group had increased risk of developing type-2 diabetes at the end of 8-year follow-up in the unadjusted model (RR=1.89, 95% CI=1.31-2.72). The risk persisted similar in the model adjusted for age, sex, occupation and income (RR=1.99, 95% CI=1.37-2.91). The RR got attenuated but remained significant after further adjustment for waist circumference and percent change of waist circumference (RR=1.53, 95% CI=1.04-2.24) and for other covariates (RR=1.50, 95% CI =1.02-2.21) (Table 4). In sensitivity analyses including BMI and percent change of BMI overtime (for both 4-year and 8-year) in the models, results did not change essentially (Supplementary Table 3 and Supplementary Table 4). Although, the lower CI limit of 8-year RR was barely >1 (RR=1.47, 95% CI=1.003-2.17, p=0.048), the risk remained positive (Supplementary Table 4). Full regression results including coefficient estimates for all other covariates are shown in supplementary document (Supplementary Table 3 and Supplementary Table 4).

Discussion:

In this KoGES-Ansan Aging Study cohort, moderate-severe OSA was an independent risk factor for the 8-year incident type-2 diabetes in general middle-aged and older adults. A short-term follow-up (4-year) did not yield significant association, indicating the effect of moderate-severe OSA on increased risk of incident diabetes takes time. To the best of our knowledge, this is one of the few studies that reported a significant independent risk between moderate-severe OSA and incident diabetes (ascertained clinically) from a large population-based cohort study over a long-term follow-up period. These data are also the first from an Asian population-based cohort that are ethnically distinct from the Caucasian populations from where the data currently exist.

Our findings are consistent with previous longitudinal studies [10, 11]. However, our study was strengthened in several different ways over the previous studies. In our study, incident diabetes was ascertained clinically with standard laboratory methods that may have prevented us from any misclassification due to potential

measurement errors when using self-reported data [11]. Compared to the Australian population-based cohort that also reported moderate-severe OSA as a significant risk factor for incident diabetes, our study was done in a substantially larger population [10]. In contrast to the longitudinal analysis of the Wisconsin Cohort, our study yielded a significant association between sleep apnoea and diabetes after adjustment for age, sex, and waist circumference [8]. The higher average age and the relatively larger sample size of our study population may have given more power to detect a significant relationship.

There are several potential pathophysiologic mechanisms for developing type-2 diabetes due to OSA. Numerous studies reveal a connection between OSA and abnormal glucose metabolism, insulin resistance (IR), onset and progression of type-2 diabetes. Additionally, Bulcun and colleagues [29] observed that progression from snoring and mild OSA to severe OSA led to increased frequency of abnormal glucose metabolism. Our previous study suggested that habitual snorers tend to be more glucose intolerant and insulin resistant compared with non-habitual snorers [12]. One of the proposed molecular mechanisms is based

on the oxygen-sensitive α-subunit of hypoxia-inducible factor 1 (HIF-1α)—a key regulator of oxygen metabolism. HIF-1α is involved in regulation of metabolic processes and mediates development of IR and diabetes mellitus [30]. Previous study has found patients with OSA (resulting in chronic decrease in oxygen saturation of hemoglobin) present with increased HIF-1α serum protein concentration compared to healthy controls [30].

In recent years, clinical trials on whether treatment of OSA with continuous positive airway pressure (CPAP) improves insulin resistance and glycemic control in non-diabetic and diabetic patients with OSA have yielded favorable results. In patients with prediabetes, 8-hour nightly CPAP treatment for 2 weeks improved glucose metabolism compared with placebo [31], but this level of treatment adherence is rarely found in clinical practice. A longer CPAP treatment (6 months) resulted in improved glycemic control and insulin resistance in type-2 diabetes patients compared with a control group [32]. However, negative studies have also been reported. In a sub-study of 888 participants in the Sleep Apnea cardioVascular Endpoints (SAVE) trial in which patients with OSA and stable CVD

were randomized to receive CPAP plus usual care, or usual care alone [33]. In those with preexisting diabetes (n = 274), there was no significant difference between the CPAP and usual care groups in serum glucose, HbA1c, or antidiabetic medications during a median follow-up of 4.3 years. Another randomized, double-blind crossover study (based on sleep clinical referrals), 50 subjects with moderate to severe sleep apnoea (AHI > 15) and impaired glucose tolerance (IGT) were randomized to 8 weeks of CPAP or sham CPAP, followed by the alternate therapy after a one-month washout [34]. The primary outcome was normalization of the mean 2-h OGTT and the study did not show that IGT normalizes after CPAP in subjects with moderate sleep apnoea.

We did not find the risk of incident type-2 diabetes with increasing severity of OSA. One previous study reported a graded inverse relationship between OSA severity and glucose control in patients with type-2 diabetes [35]. Compared with patients without OSA, the adjusted mean HbA1c was increased in patients with mild, moderate and severe OSA gradually. Intuitively, a similar relationship might be expected with OSA and incidence of diabetes. However, in our study, as well

as previous studies have not found a significant risk of incident diabetes in mild OSA group compared to the non-OSA group. Since, diabetes is a multi-factorial disease, it is possible that only moderate to severe OSA contributes to the additional risk and not mild level of OSA. Another possibility could be that the latent period for the development of type-2 diabetes in the mild OSA group could extend beyond the duration of our study period [8]. Additionally, the prevalent type-2 diabetes at baseline were excluded in the current study (Figure 1) who also had significantly higher prevalent OSA (both mild and moderate-severe OSA compared to the included participants, Supplementary Table 2) leaving participants who were possibly more "resistant" against diabetes development. Although, mild OSA was not found to be a significant risk of incident diabetes, the point estimates were higher in all three models (Table 3, Table 4), which is consistent with findings from previous studies as well. Thus, we cannot rule out the potential effect of mild level of OSA on diabetes incidence. Future cohort studies with greater power needs to investigate this observation since mild OSA is more common than moderate-severe OSA and thus might be more important from a public health perspective [36].

Our study has several limitations. First, due to the observational nature of the study, the participants with moderate-severe OSA were not offered any treatment or intervention, although, we informed them fully about their PSG results. Consequently, the present study did not consider any effects that might have occurred due to any treatment sought by the participants during the follow-up time. However, we assume that the participants seeking treatment for OSA would be very low given that less than 3% of the study participants had an AHI ≥ 30 (data not shown) and were mostly asymptomatic (Table 1). On the other hand, though, our data might serve as an important "real-world" data on the natural course of OSA showing what happens if the patients are left untreated or not intervened. Second, we cannot rule out selection bias in the study due to large number of dropouts and exclusion of participants who had diabetes at baseline (Figure 1). Additionally, some of the general characteristics were significantly different between the cohort and non-participants as evident from the Supplementary Table 1. However, this is one of the biggest population based cohorts that we have followed up for a relatively longer duration. Relevant to this

point, however, our study did not consider the exact interdependence between the development of OSA and the time (both prior to and after the index date of inclusion) lived with the diagnosis of OSA. Third, incident diabetes cases were considered to be type-2 diabetes, therefore, a possible misclassification could not be completely ruled out due to late onset type-1 diabetes. However, we assumed that the number would be low especially because of the incidence of adult-onset type-1 diabetes has been found to be lowest predominantly in East-Asian countries [37]. Fourth, we did not have information about visceral obesity which is an important risk factor for the development of diabetes. Although we adjusted for waist circumference which is a better indicator than BMI for visceral obesity, we cannot completely rule out some residual confounding. However, we performed a sensitivity analysis using body fat percentage in the model and the results were essentially same (data not shown). Our results, however, may not hold in populations with greater overt obesity and high BMI. Racial differences in genetic and epigenetic mechanisms may also limit generalization to other populations. Finally, our results may need to be cautiously interpreted because of data lacking of some disease conditions (e.g. non-alcoholic fatty liver disease,

gestational diabetes mellitus, polycystic ovary syndrome, mental health conditions etc.) and medication usage (e.g. lipid-lowering agents -nicotinic acid, epinephrine, glucocorticoids, thiazide diuretics, antipsychotics etc.) that are potential risk factors for type-2 diabetes or could alter the glycemic index.

Conclusion:

In summary, our results provide evidence that moderate-severe OSA is an independent risk factor for incident type-2 diabetes in the middle-aged and older general population over a long-term period. While future studies are warranted to investigate the effects of treatment of moderate-severe OSA on prevention of incident type-2 diabetes, it seems prudent, however, that long-term monitoring and timely intervention or treatment of OSA could be useful in prevention strategies for diabetes.

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Concept and design: A.T.S., S.K., and C.S.

Acquisition, analysis, or interpretation of data: All authors.

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Supervision: C.S.

FIGURE LEGENDS

Figure 1. Flow diagram of participants in KoGES-Ansan study, 2001 – 2021. KoGES, Korean Genome and Epidemiology Study.

Table 1: Baseline general characteristics of the study participants (n=1216) by obstructive sleep apnoea (OSA) severity.

	Total	**OSA categories** [a]			***p*-value** [b]
	n=1216	**Non-OSA**	**Mild OSA**	**Moderate-severe**	
		n= 717	**n= 356**	**OSA**	
				n= 143	
Age, years	57.5 (5.5)	56.6 (4.9)	58.6 (5.9)	59.5 (6.4)	<.001
Women	646 (53.1)	435 (60.7)	174 (48.9)	37 (25.9)	<.001
Occupation, n (%)					0.042
White-collar job	352 (29.0)	199 (27.8)	98 (27.5)	55 (38.5)	
Blue-collar job	390 (32.0)	230 (32.1)	118 (33.2)	42 (29.4)	
House-keeper	474 (39.0)	288 (40.2)	140 (39.3)	46 (32.2)	
Low income, n (%) [c]	84 (6.9)	46 (6.5)	27 (7.6)	11 (7.7)	0.859
Body mass index (BMI), kg/m^2	24.5 (2.9)	23.8 (2.7)	25.1 (2.7)	26.2 (3.1)	<.001
Obesity (BMI-categories)					<.001
Normal weight (BMI <25)	711 (58.5)	488 (68.0)	177 (49.7)	46 (32.2)	
Overweight (BMI 25 - <30)	470 (38.7)	223 (31.1)	164 (46.1)	83 (58.0)	
Obese (BMI ≥30)	35 (2.9)	6 (0.8)	15 (4.2)	14 (9.8)	
Neck circumference, cm	34.8 (3.7)	34.0 (3.3)	35.4 (4.2)	37.1 (3.2)	<.001
Waist circumference, cm	81.3 (8.4)	79.1 (8.0)	83.3 (7.8)	87.3 (8.1)	<.001
Body fat percent	27.7 (7.0)	27.5 (7.0)	28.1 (7.2)	27.7 (6.5)	0.416
Drinking status, n (%)					0.001

Never	586 (48.2)	369 (51.5)	170 (47.8)	47 (32.9)	
Former	59 (4.9)	28 (3.9)	18 (5.1)	13 (9.1)	
Current	571 (47.0)	320 (44.6)	168 (47.2)	83 (58.0)	
Current alcohol consumption (g/wk)[d]	52.7 (16.1-165.3)	44.2 (15.2-145.2)	81.0 (20.3-249.9)	52.7 (13.7-162.0)	0.007
Smoking status, n (%)					<.001
Never	780 (64.1)	489 (68.2)	222 (62.4)	69 (48.3)	
Former	304 (25.0)	156 (21.7)	94 (26.4)	54 (37.8)	
Current	132 (10.9)	72 (10.0)	40 (11.2)	20 (14.0)	
Current smoking (pack-year)	27.6 (19.1)	27.0 (21.3)	26.9 (14.8)	30.8 (18.9)	0.717
Regular exercise, n (%)	411 (33.8)	231 (32.2)	136 (38.2)	44 (30.8)	0.541
Physical activity (MET/wk)[d]	540 (0-1260)	540 (0-1260)	630 (0-1485)	360 (0-1080)	0.024
Fasting blood glucose, mg/dL	90.0 (7.5)	89.4 (7.7)	90.2 (7.0)	92.2 (7.8)	<.001
Post 2-hour OGTT glucose, mg/dL	127.8 (29.6)	124.9 (29.2)	128.4 (29.4)	140.2 (29.0)	<.001
Glycated hemoglobin A1c (%)	5.5 (0.3)	5.5 (0.3)	5.5 (0.3)	5.6 (0.3)	<.001
Fasting blood insulin (IU/L)	8.1 (3.4)	7.7 (3.0)	8.4 (3.6)	9.6 (4.4)	<.001
Post 2-hour OGTT insulin (IU/L)	44.3 (37.0)	41.3 (34.6)	45.8 (38.9)	54.7 (41.7)	<.001
HOMA-IR	1.8 (0.9)	1.7 (0.8)	1.9 (0.9)	2.2 (1.1)	<.001
Systolic blood pressure, mmHg	113.7 (13.8)	112.2 (13.9)	114.7 (13.7)	118.3 (12.7)	<.001
Diastolic blood pressure, mmHg	75.1 (9.5)	74.2 (9.5)	75.6 (9.6)	78.4 (8.9)	<.001

Mean arterial pressure, mmHg	100.8 (11.9)	99.5 (12.0)	101.7 (11.8)	105.0 (10.8)	<.001
History of CVD, n (%)	75 (6.2)	34 (4.7)	25 (7.0)	16 (11.2)	0.003
Total cholesterol, mg/dL	202.1(35.5)	204.1 (35.6)	199.2 (32.9)	199.8 (40.9)	0.074
HDL cholesterol, mg/dL	49.7 (12.7)	51.0 (12.8)	48.9 (12.4)	44.9 (11.6)	<.001
LDL cholesterol, mg/dL	126.6 (31.9)	128.3 (32.6)	123.6 (29.1)	125.7 (34.3)	0.076
Sleep and PSG variables					
EDS, n (%)	58 (4.78)	30 (4.2)	19 (5.3)	9 (6.3)	0.217
Napping, n (%)	457 (37.6)	270 (37.7)	132 (37.1)	55 (38.5)	0.951
Self-reported sleep time, h	6.07 (1.2)	6.1 (1.2)	6.0 (1.2)	6.1 (1.1)	0.809
Mean Oxygen Saturation, %	95.78 (1.3)	96.2 (1.1)	95.4 (1.2)	94.6 (1.2)	<.001
Lowest Oxygen Saturation, %	87.53 (6.2)	90.0 (5.4)	85.3 (4.7)	80.8 (6.4)	<.001
Oxygen desaturation index	6.04 (7.9)	1.7 (1.3)	7.7 (2.9)	23.2 (10.0)	<.001

Abbreviations: MET = Metabolic equivalent, OGTT = Oral glucose tolerance test, HOMA-IR = Homeostasis model assessment of insulin resistance, CVD = Cardiovascular disease, HDL = High density lipoprotein, LDL = Low density lipoprotein, PSG = Polysomnography, EDS = Excessive daytime sleepiness

Values are presented as mean (SD) or median (interquartile range) for continuous variables and n (%) for categorical variables.

[a] Categories are defined by apnoea–hypopnoea index 0–4.9, 5.0–14.9 and ≥15.0 events/h as non-, mild and moderate-severe OSA, respectively.

[b] P-values are based on one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

[c] Average monthly wage <1 million Korean Won, which approximately corresponds to the government-set minimum wage for

a family of 3.

[d] Statistical significance was estimated after logarithmic transformation.

Table 2: Cumulative incidence rate of type-2 diabetes mellitus among the study participants (n=1216) by obstructive sleep apnoea (OSA).

OSA categories	n	4-year Cumulative incidence rate n (%)	8-year Cumulative incidence rate n (%)
Non-OSA (AHI 0–4.9 events/h)	717	43 (6.0%)	85 (11.9%)
Mild OSA (AHI 5.0–14.9 events/h)	356	33 (9.3%)	53 (14.9%)
Moderate-severe OSA (AHI ≥15.0 events/h)	143	20 (14.0%)	32 (22.4%)
All	1216	96 (7.9%)	170 (14.0%)

Abbreviation: AHI = Apnoea–hypopnoea index

Table 3: 4-year relative risk (RR) of type-2 diabetes mellitus of the study participants (N=1216) by obstructive sleep apnoea (OSA) categories.

OSA category	**n**	**RR (95% confidence interval) [a]**			
		Unadjusted model	**Model 1 (adjusted for age, sex, occupation and income)**	**Model 2 (adjusted for Model 1+ WC and WC-change [b])**	**Model 3 (adjusted for Model 2+ exercise (MET/wk), drinking alcohol (g/wk), smoking (pack-year), MAP, TC, CVD history, TST (self-reported) and Napping**
Non-OSA (AHI 0–4.9 events/h)	717	1.0	1.0	1.0	1.0
Mild (AHI 5.0–14.9 events/h)	356	1.25 (0.91-1.72)	1.47 (0.96- 2.27)	1.24 (0.80-1.90)	1.27 (0.82-1.97)
Moderate-severe (AHI ≥15.0 events/h)	143	1.89 (1.31-2.72)	2.13 (1.27 - 3.57)	1.56 (0.93 - 2.60)	1.58 (0.95 - 2.63)

Abbreviations: AHI = Apnoea–hypopnoea index, WC = Waist circumference, MET = Metabolic equivalent, TC = Total cholesterol, MAP = Mean arterial pressure, TST = Total sleep time and CVD = Cardiovascular disease.

[a] Relative risks (RR) are estimated by Poisson regression with robust error variance.

[b] Percent change of WC from baseline to 4-year follow-up.

Table 4: 8-year relative risk (RR) of type-2 diabetes mellitus of the study participants (N=1216) by obstructive sleep apnoea (OSA) categories.

OSA category	**n**	**RR (95% confidence interval) [a]**			
		Unadjusted model	**Model 1 (adjusted for age, sex, occupation and income)**	**Model 2 (adjusted for Model 1+ WC and WC-change [b])**	**Model 3 (adjusted for Model 2+ exercise (MET/wk), drinking alcohol (g/wk), smoking (pack-year), MAP, TC, CVD history, TST (self-reported) and Napping**
Non-OSA (AHI 0–4.9 events/h)	717	1.0	1.0	1.0	1.0
Mild (AHI 5.0–14.9 events/h)	356	1.25 (0.91-1.72)	1.28 (0.93-1.76)	1.10 (0.80-1.51)	1.12 (0.82-1.54)
Moderate-severe (AHI ≥15.0 events/h)	143	1.89 (1.31-2.72)	1.99 (1.37-2.91)	1.53 (1.04-2.24)	1.50 (1.02-2.21)

Abbreviations: AHI = Apnoea–hypopnoea index, WC = Waist circumference, MET = Metabolic equivalent, TC = Total cholesterol, MAP = Mean arterial pressure, TST = Total sleep time and CVD = Cardiovascular disease.

[a] Relative risks (RR) are estimated by Poisson regression with robust error variance.

[b] Percent change of WC from baseline to 8-year follow-up.

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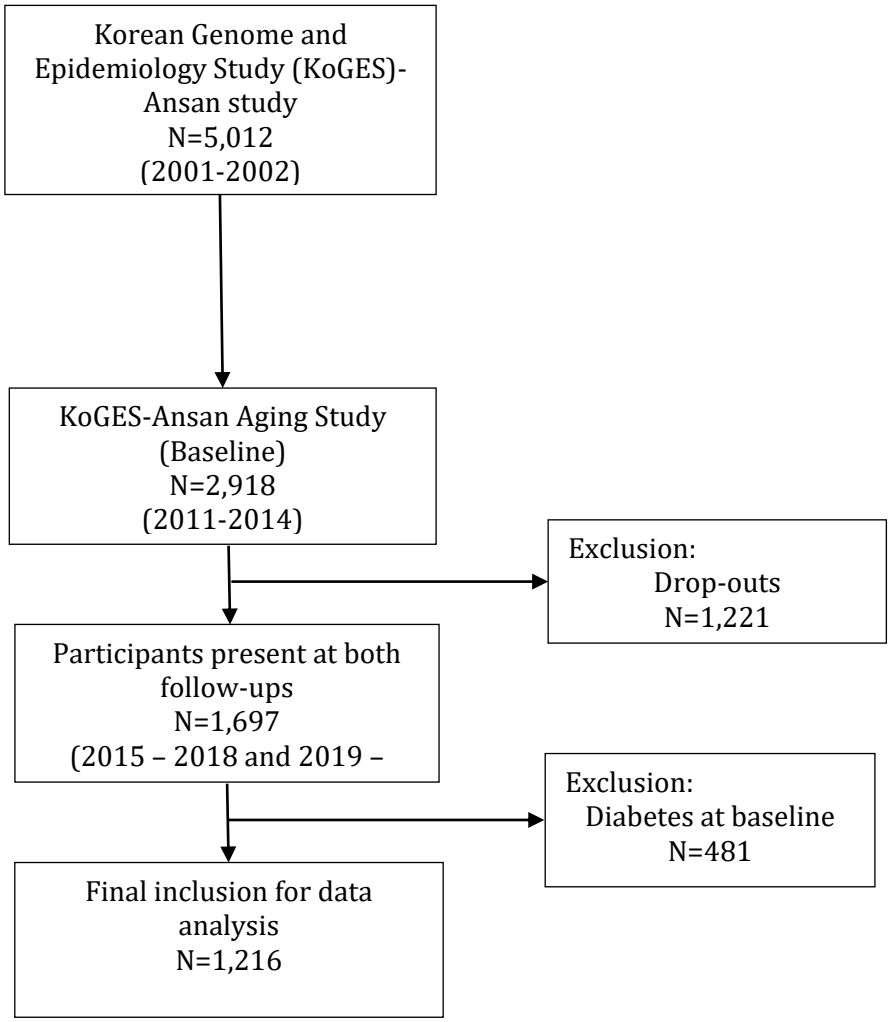
Figure 1.


Korean Genome and Epidemiology Study (KoGES)-Ansan study
N=5,012
(2001-2002)
KoGES-Ansan Aging Study (Baseline)
N=2,918
(2011-2014)
Exclusion:
Drop-outs
N=1,221
Participants present at both follow-ups
N=1,697
(2015 – 2018 and 2019 –
Exclusion:
Diabetes at baseline
N=481
Final inclusion for data analysis
N=1,216

Polysomnography (PSG)

The following signals were documented: single-channel electroencephalogram (EEG) (C4-A1), electrooculogram (EOG), chin electromyogram (EMG), electrocardiography (EKG), airflow at the nose and mouth (using the pressure transducer airflow (PTAF) sensor), the chest and abdominal respiratory movement (respiratory impedance), oxygen saturation (pulse oximetry), and body position. We used the most recent definitions for respiratory events according to the American Academy of Sleep Medicine guidelines. An apnea event was detected if both of the following criteria were met: (1) There was a drop in the peak signal excursion by ≥90% of the pre-event baseline (reference amplitude), (2) The duration of the ≥90% drop in sensor signal was ≥10 seconds. In addition, a hypopnea event was detected if all of the following criteria were met: (1) The peak signal excursions dropped by ≥30% of reference amplitude, (2) The duration of the ≥30% drop in signal excursions was ≥10 seconds, (3) There was ≥3% oxygen desaturation from the reference amplitude or the event was associated with an arousal. The reference amplitude was calculated as the mean value of the peak amplitudes in the period of 100 seconds preceding the event. The apnea-

hypopnea index (AHI) was calculated by averaging the total number of obstructive apnea and hypopnea events per hour of sleep.

Supplementary Table 1. Comparison of baseline general characteristics of the study cohort and non-participants.

	Cohort (n=1,216)	**Non-participants (n=1,702)**	**p-value** [a]
General characteristics			
Age, years	57.5 (5.5)	60.5 (7.5)	<.001
Women	646 (53.1)	830 (48.8)	0.020
Body mass index, kg/m^2	24.5 (2.9)	24.8 (3.0)	0.013
Neck circumference, cm	34.8 (3.7)	35.3 (3.6)	<.001
Waist circumference, cm	81.3 (8.4)	83.0 (8.4)	<.001
Body fat percentage	27.7 (7.0)	27.9 (6.9)	0.323
Current alcohol drinking, yes	571 (47.0)	764 (44.9)	0.518
Regular exercise, yes	411 (33.8)	628 (36.9)	0.084
Systolic blood pressure, mmHg	113.7 (13.8)	117 (14)	<.001
Diastolic blood pressure, mmHg	75.1 (9.5)	75 (9.3)	0.758
Mean arterial pressure, mmHg	100.8 (11.9)	103 (11.5)	<.001
History of CVD	75 (6.2)	159 (9.3)	0.002
Total cholesterol, mg/dL	202.1 (35.5)	193.1 (35.9)	<.001
HDL cholesterol, mg/dL	49.7 (12.7)	46.8 (11.7)	<.001
LDL cholesterol, mg/dL	126.6 (31.9)	118.5 (32.2)	<.001

Sleep and PSG characteristics

Excessive daytime sleepiness	58 (4.77)	94 (5.52)	0.366
Total sleep time, min	379.4 (73.4)	379.3 (81.6)	0.998
Apnoea hypopneoa index [b]	3.5 (1.3- 8.7)	5.2(1.9-11.4)	<.001
Mean Oxygen Saturation, %	95.8 (1.2)	95.5 (1.4)	<.001
Lowest Oxygen Saturation, %	87.5 (6.2)	86.68 (6.0)	<.001
Oxygen desaturation index [b]	3.2 (1-7.9)	4.6 (1.5-10.2)	<.001

Abbreviations: CVD = Cardiovascular disease, PSG = Polysomnography, HDL = High density lipoprotein, LDL = Low density lipoprotein

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables

[a] P-values are based on one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables

[b] Values are presented as median (IQR) and P-values are based on non-parametric test.

Supplementary Table 2: Prevalence of obstructive sleep apnoea (OSA) at baseline by analyzed (n=1216) and excluded prevalent type 2 diabetes (T2D) participants (n=481).

	Analyzed participants (n=1216)	**Excluded prevalent T2D at baseline (n=481)**	**p-value [a]**
OSA categories			<.001
Non-OSA	717 (59.0%)	203 (42.2%)	
Mild OSA	356 (29.3%)	175 (36.4%)	
Moderate-severe OSA	143 (11.7%)	103 (21.4%)	

[a] p-value is based on chi-square test for categorical variable

Supplementary Table3. 4-year relative risk (RR) of type-2 diabetes mellitus of the study participants (N=1216) by obstructive sleep apnoea (OSA) categories. The table shows full regression results including coefficient estimates for all other covariates.

Variables	**Relative risk** [a]	**95% confidence interval**	***p*-value**
Mild OSA vs. non-OSA (ref.)	1.26	0.81-1.96	0.295
Moderate-severe OSA vs. non-OSA (ref.)	1.54	0.90-2.63	0.107
Age (1-year increment)	1.01	0.98-1.05	0.319
Men vs. women	1.10	0.61-1.98	0.734
Occupation (blue-collar vs. white-collar)	1.19	0.72-1.97	0.486
Occupation (house-keeper vs. white-collar)	1.23	0.71-2.11	0.448
Income (~2 million KRW increment)	0.94	0.76-1.15	0.575
Waist circumference (1 cm increment)	1.03	0.99-1.09	0.109
Percent change of waist circumference [b]	1.0	0.96-1.04	0.797
BMI (1 unit increment)	1.03	0.91-1.17	0.606
Percent change of BMI [b]	1.0	0.95-1.05	0.836
Physical activity (1 MET/wk increment)	0.99	0.99-1.0	0.144
Alcohol consumption (1 gram increment)	1.0	0.99-1.01	0.306
Smoking (1 pack-year increment)	1.0	0.99-1.01	0.681
Mean arterial pressure (1 mmHg increment)	1.0	0.98-1.02	0.517
Total cholesterol (1 mg/dL increment)	0.99	0.99-1.0	0.284

Self-reported total sleep time (1 h increment)	0.89	0.76-1.04	0.163
Nap (yes vs. no)	1.08	0.71-1.63	0.706
CVD history (yes vs. no)	1.42	0.62-3.24	0.396

Abbreviation: OSA = Obstructive sleep apnoea, KRW = Korean Won, BMI = Body mass index, MET = Metabolic equivalent, CVD = Cardiovascular disease

[a] Relative risks (RR) are estimated by Poisson regression with robust error variance

[b] Percent change from baseline to 4-year follow-up

Supplementary Table 4. 8-year relative risk (RR) of type-2 diabetes mellitus of the study participants (N=1216) by obstructive sleep apnoea (OSA) categories. The table shows full regression results including coefficient estimates for all other covariates.

Variables	**Relative risk** [a]	**95% confidence interval**	***p*-value**
Mild OSA vs. non-OSA (ref.)	1.10	0.80-1.52	0.525
Moderate-severe OSA vs. non-OSA (ref.)	1.47	1.003-2.17	0.048
Age (1-year increment)	0.98	0.95-1.01	0.362
Men vs. women	1.34	0.87-2.06	0.182
Occupation (blue-collar vs. white-collar)	1.41	0.97-2.05	0.067
Occupation (house-keeper vs. white-collar)	1.36	0.90-2.04	0.140
Income (~2 million KRW increment)	0.91	0.79-1.05	0.230
Waist circumference (1 cm increment)	1.04	1.01-1.08	<.001
Percent change of waist circumference [b]	1.03	1.0-1.06	0.042
BMI (1 unit increment)	0.99	0.90-1.08	0.919
Percent change of BMI [b]	0.95	0.92- 0.99	0.025
Physical activity (1 MET/wk increment)	0.99	0.99-1.0	0.131
Alcohol consumption (1 gram increment)	1.0	0.99-1.0	0.893
Smoking (1 pack-year increment)	0.99	0.99-1.0	0.917
Mean arterial pressure (1 mmHg increment)	1.0	0.99-1.01	0.231
Total cholesterol (1 mg/dL increment)	0.99	0.99-1.0	0.639

Self-reported total sleep time (1 h increment)	0.96	0.86-1.07	0.527
Nap (yes vs. no)	1.12	0.83-1.51	0.431
CVD history (yes vs. no)	0.97	0.56-1.71	0.942

Abbreviation: OSA = Obstructive sleep apnoea, KRW = Korean Won, BMI = Body mass index, MET = Metabolic equivalent, CVD = Cardiovascular disease

[a] Relative risks (RR) are estimated by Poisson regression with robust error variance

[b] Percent change from baseline to 8-year follow-up