BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022752
Article Type:	Research
Date Submitted by the Author:	04-Mar-2018
Complete List of Authors:	Strausz, Satu; Institute for Molecular Medicine Finland; University of Helsinki and Helsinki University Hospital, Department of Oral and Maxillofacial Diseases, Orthodontics Havulinna, Aki; Institute for Molecular Medicine Finland; National Institute for Welfare and Health Tuomi, Tiinamaija; Institute for Molecular Medicine Finland; University of Helsinki and University Helsinki Hospital, Endocrinology, Abdominal Centre Bachour, Adel; Helsinki University Hospital, Sleep Unit, Heart and Lung Center Groop, Leif ; Lund University, Diabetes Centre; Institute for Molecular Medicine Finland Mäkitie, Antti; University of Helsinki and University Helsinki Hospital, Department of Otorhinolaryngology - Head and Neck Surgery Koskinen, Seppo; National Institute for Welfare and Health Salomaa, Veikko; National Institute for Welfare and Health Palotie, Aarno; Massachusetts General Hospital, Dept. Psychiatry; Institute for Molecular Medicine Finland Ripatti, Samuli; Institute for Molecular Medicine Finland; University of Helsinki, Department of Public Health Palotie, Tuula; University of Helsinki and Helsinki University Hospital, Department of Oral and Maxillofacial Diseases, Orthodontics
Keywords:	Obstructive sleep apnea, Coronary heart disease < CARDIOLOGY, Type 2 diabetes, Diabetic kidney disease, Mortality, Longitudinal

Obstructive sleep apnea and the risk for coronary heart disease, type 2 diabetes and its complications: a longitudinal population-based study

DDS. Satu Strausz[1,2,3], PhD. Aki S. Havulinna[3,4], Assoc. Prof. Tiinamaija Tuomi[3,5], Assoc. Prof. Adel Bachour[6], Prof. Leif Groop[3,7], Prof. Antti Mäkitie[8], Prof. Seppo Koskinen[4], Prof. Veikko Salomaa[4], Prof. Aarno Palotie[3,9,10], Prof. Samuli Ripatti[3,11]*, Assoc. Prof. Tuula Palotie[1,2]*.
*These authors contributed equally to this project.

1) Department of Oral and Maxillofacial Diseases, Helsinki University Hospital (HUH), Finland
2) Orthodontics, Department of Oral and Maxillofacial Diseases, Clinicum, Faculty of Medicine, University of Helsinki, Finland
3) Institute for Molecular Medicine Finland (FIMM/HiLIFE), University of Helsinki, Finland
4) National Institute for Health and Welfare, Helsinki, Finland
5) Endocrinology, Abdominal Centre, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Diabetes and Obesity Research Program, University of Helsinki and Folkhälsan Research Center, Helsinki, Finland.
6) Sleep Unit, Heart and Lung Center, Helsinki University Hospital (HUH), Finland.
7) Lund University Diabetes Centre, Department of Clinical Sciences, Malmö, Lund University, Skåne University Hospital, Malmö, Sweden
8) Department of Otorhinolaryngology - Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
9) Analytic and Translational Genetics Unit (ATGU), Department of Medicine, Department of Neurology and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
10) Broad Institute of MIT and Harvard, Cambridge, MA, USA
11) Department of Public Health, University of Helsinki, Finland

Correspondence to:

Satu Strausz, DDS,
Tel. +358 40 583 8443
Fax. +358 29 412 5737
Institute for Molecular Medicine Finland (FIMM)
PO BOX 20
00041 University of Helsinki,
Finland
satu.strausz@helsinki.fi

2553 words, 5 tables, 1 figure

Keywords: obstructive sleep apnea, coronary heart disease, type 2 diabetes, diabetic kidney disease, mortality, longitudinal

ABSTRACT

Objective: To evaluate if obstructive sleep apnea (OSA) modifies the risk of coronary heart disease (CHD), type 2 diabetes (T2D) and diabetic complications in a gender-specific fashion.

Design and Setting: A longitudinal population-based study with up to 25 years follow-up data on 37352 individuals (> 500,000 person years) from three population-based cohorts: the FINRISK study, the H2000 Study and the Botnia Study.

Main outcome measures: Incident OSA, CHD, diabetic kidney disease (DKD), T2D and all-cause mortality from the Finnish National Hospital Discharge Register and the Finnish National Causes-of-Death Register.

Results: After adjustment for traditional risk factors OSA increased the risk for CHD (HR=1.36, p=0.0014, CI=1.12 to 1.64), particularly in females (HR=2.01, CI=1.31 to 3.07, p=0.0012). T2D clustered with OSA independently of obesity (HR=1.48, CI=1.26 to 1.73, p=9.11×10^{-7}). The risk of diabetic kidney disease increased 1.75-fold in OSA patients (CI=1.13 to 2.71, p=0.013). OSA increased the risk for CHD similarly among T2D patients and in general population (HR=1.36). All-cause-mortality was increased by OSA in the general population and slightly more in diabetic individuals (HR=1.22, CI=1.03 to 1.44, p=0.0184; HR=1.35, CI=1.06 to 1.71, p=0.016, respectively).

Conclusion: OSA is an independent risk factor for CHD, T2D and DKD. A novel finding was that this effect is more pronounced even in women, who until now have received less attention in diagnosis and treatment of OSA than men.

Strengths and limitations of this study

- A large-scale population-based study of 37,352 individuals with up to 25 years of follow-up.
- Follow-up registers have excellent validity and coverage.
- Our study takes a large amount of confounding factors related to OSA into consideration.
- Prospective study design should limit the risk of bias.
- Registry-based ascertainment through hospitalization may miss non-hospitalized cases and treatment information.

INTRODUCTION

Obstructive sleep apnea (OSA) is a more common disorder than currently diagnosed in the clinic. Due to its many comorbidities, including an increased risk to coronary heart disease (CHD) and type 2 diabetes (T2D), it is a serious public health problem.[1, 2] The main known risk factors for OSA are obesity, male gender, high age, increased neck circumference and problems of upper airway or jaw anatomy.[3-6]

Obesity is present in roughly 70% of OSA patients and about 50% of OSA patients are hypertensive.[7, 8] Conversely, about 30% of hypertensive patients have OSA, which is often undiagnosed.[3, 4] Treatment of OSA by continuous positive airway pressure (CPAP) has been shown to reduce both systolic and diastolic blood pressure.[9] It has been estimated that up to 40% of the risk of OSA is genetically predisposed.[10] In addition, many risk factors for OSA, such as BMI, craniofacial and upper airway soft tissue structure, demonstrate familial aggregation.[6]

Longitudinal studies have shown an association of OSA with incident or recurrent cardiovascular events and increased mortality.[2, 11] The risk of developing CHD is particularly increased in middle-aged men with OSA but women have been absent from or underrepresented in these studies.[12, 13] Risk of CHD and mortality is usually increased if T2D is diagnosed before OSA.[14]

There is mounting evidence that OSA is an independent risk factor for the development of T2D but it is not always clear what is cause and consequence.[1, 15, 16] Most of the available studies have been cross-sectional,[5, 15, 16] and not able to account for residual confounding factors.[5, 16] Other studies did not distinguish between T1D and

T2D,[17] nor to generalize the results to the overall population.[5] In some studies this association has been dispersed after adjustments for other risk factors.[18]

Also, studies investigating the synergistic effects of OSA and T2D on the progression of diabetic kidney disease (DKD) are scarce and often limited by a cross-sectional design [19-21] and lack of follow-up data.[22]

To explore the role of OSA for CHD, T2D and increased mortality we conducted a large-scale population-based study of 37,352 individuals with up to 25 years of follow-up. We specifically aimed at evaluating 1) if OSA modifies the risk of CHD and T2D independently of known risk factors like BMI, blood pressure and lipids, 2) the role of OSA for development of diabetic complications including DKD and 3) examine if OSA has similar effects in females and males.

METHODS

Study population

We included 37,352 participants in our study from national FINRISK Studies (FINRISK), Health 2000 Cohort (H2000) and a subset of the Botnia and PPP-Botnia Studies (Botnia) including 1601 (4.3%) OSA patients (ICD 10: G47.3, ICD 9: 327.23). Baseline characteristics of the participants are presented in Table 1.

	FINRISK				H2000				Botnia T2DM		
	Overall	Non-OSA	OSA	p	Overall	Non-OSA	OSA	p	Overall	Non-OSA	OSA
	n = 29250	n = 28008	n = 1242		n = 6697	n = 6457	n = 240		n = 1405	n = 1286	n = 119
Gender (male)	13981 (47.8%)	13079 (46.7%)	902 (72.6%)	2.0×10^{-71}	2990 (44.6%)	2814 (43.6%)	176 (73.3%)	1.6×10^{-19}	735 (52.3%)	651 (50.6%)	84 (70.6
Baseline age	48.03 (13.2)	47.98 (13.3)	49.26 (11.3)	1.1×10^{-4}	53.8 (15.7)	53.9 (15.8)	50.8 (10.52)	2.4×10^{-5}	58.94 (11.5)	59.20 (11.6)	56.1 (9.9
Age at OSA diagnosis			55.31 (10.5)				55.99 (10.1)				61.93 (1
BMI	26.75 (4.7)	26.59 (4.6)	30.32 (5.7)	8.7×10^{-98}	26.7 (4.7)	26.8 (4.58)	30.6 (5.73)	6.6×10^{-21}	29.26 (4.8)	28.99 (4.7)	32.20 (4
Current smoking	7061 (24.2%)	6738 (24.2%)	323 (26.1%)	0.13	1423 (21.4%)	1366 (21.3%)	57 (23.8%)	0.39	193 (13.7%)	165 (12.8%)	28 (23.5
Systolic mmHg	135.7 (20.0)	135.7 (20.1%)	137.0 (17.6)	8.7×10^{-3}	135.1 (21.68)	135.0 (21.8)	136.2 (19.0)	0.36	144.6 (20.4)	144.6 (20.4)	145.0 (2
Diastolic mmHg	80.48 (11.6)	80.34 (11.6)	83.7 (11.2)	6.3×10^{-24}	81.65 (11.31)	81.5 (11.3)	86.4 (10.1)	2.6×10^{-12}	84.4 (10.4)	84.0 (10.3)	87.9 (10
CHOL mmol/l	5.51 (1.1)	5.51 (1.1)	5.56 (1.0)	0.06	5.9 (1.1)	5.9 (1.1)	6.0 (1.1)	0.17	5.5 (1.1)	5.6 (1.1)	5.3 (1.0)
LDL mmol/l	3.349 (0.9)	3.34 (0.9)	3.48 (0.8)	2.3×10^{-3}	3.7 (1.1)	3.7 (1.1)	3.8 (1.0)	0.31	3.2 (1.0)	3.2 (1.0)	3.1 (0.9)
HDL mmol/l	1.435 (0.4)	1.44 (0.4)	1.28 (0.3)	1.8×10^{-54}	1.3 (0.4)	1.3 (0.4)	1.2 (0.35)	6.0×10^{-5}	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Prevalent cases											
CHD	772 (2.6%)	710 (2.5%)	62 (5.0%)	2.1×10^{-7}	253 (3.8%)	248 (3.8%)	5 (2.0%)	0.23	43 (3.1%)	38 (3.0%)	5 (4.2%)
STROKE	341 (1.2%)	325 (1.2%)	16 (1.3%)	0.8	176 (2.6%)	174(2.7%)	2 (0.8%)	0.12	21 (1.5%)	20 (1.6%)	1 (0.8%)
T2DM	1525 (5.3%)	1403 (5.1%)	122 (10.0%)	4.2×10^{-14}	381 (5.8%)	362 (5.7%)	19 (8.1%)	0.16	1018 (72.5%)	938 (72.9%)	80 (67.2
DKD	40 (0.1%)	39 (0.1%)	1 (0.1%)	1	9 (0.1%)	9 (0.1%)	0	1	3 (0.2%)	2 (0.2%)	1 (0.8%)
CHD/T2DM	238 (5.9%)	214 (5.9%)	24 (6.5%)	0.74	63 (7.5%)	62 (8%)	1 (1.6%)	0.08	43 (3.1%)	38 (3.0%)	5 (4.2%)
DKD/T2DM	9 (0.2%)	9 (0.2%)	0	1	2 (0.2%)	2 (0.3%)	0	1	3 (0.2%)	2 (0.2%)	1 (0.8%)
Incident cases											
CHD	2251 (7.7%)	2099 (7.5%)	152 (12.2%)	1.2×10^{-9}	594 (8.9%)	562 (8.7%)	32 (13.3%)	0.02	254 (18.2%)	230 (18.0%)	24 (20.1
STROKE	1359 (4.6%)	1295 (4.6%)	64 (5.2%)	0.42	363 (5.4%)	349 (5.4%)	14 (5.8%)	0.89	179 (12.8%)	162 (12.7%)	17 (14.3
T2DM	2481 (8.8%)	2231 (8.0%)	250 (20.6%)	2.0×10^{-52}	456 (6.9%)	411 (6.5%)	45 (19.1%)	1.3×10^{-13}	387 (27.5%)	348 (27.1%)	39 (32.8
DKD	353 (1.2%)	310 (1.1%)	43 (3.5%)	2.9×10^{-13}	123 (1.8%)	119 (1.8%)	4 (1.7%)	1	91 (6.5%)	77 (6%)	14 (11.8
CHD/T2DM	657 (16.4%)	584 (16.1%)	73 (19.6%)	0.10	154 (18.4%)	141 (18.2%)	13 (20.3%)	0.81	254 (18.2%)	230 (18.0%)	24 (20.1
DKD/T2DM	151 (3.8%)	128 (3.5%)	23 (6.2%)	0.02	43 (5.1%)	42 (5.4%)	1 (1.6%)	0.24	91 (6.5%)	77 (6%)	14 (11.8

Table 1. Baseline characteristics in FINRISK, H2000 and type 2 diabetic patients in the Botnia.

Baseline demographics and clinical characteristics *p*-values were based on χ^2 test. Fisher´s exact-test was used if the sample size was ≤ 5. For continuous variables we used t-test. Data are mean(SD) or number (%). OSA=obstructive sleep apnea. CHOL=total cholesterol. CHD=coronary heart disease. T2DM=type 2 diabetes. DKD=diabetic kidney disease. CHD/T2DM=coronary heart disease among type 2 diabetic patients. DKD/T2DM=diabetic kidney disease among type 2 diabetic patients.

Population-based FINRISK surveys are independent random samples drawn from the population register of six geographic areas of Finland (North Karelia, Kuopio, Lapland, Oulu, Turku/Loimaa and Helsinki/Vantaa) and stratified according to gender, 10-year age group and study area. The survey included a mailed questionnaire and a clinical examination at which a blood sample was drawn.[23] Participants from different survey years (1992, 1997, 2002 or 2007) were pooled together.

The total sample size for all FINRISK surveys was 29257 and participants (n=7) who had missing information on risk factors were excluded from the study. Thus, the total sample size was 29250 where 13981 male and 15269 female participants aged 24–74 years at baseline were included in the analyses. Of these participants, 1242 (4.2%) had OSA.

The H2000 Study is a comprehensive combination of health interview and health examination survey. The study was based on a nationally representative sample of 8028 persons aged ≥ 30 years living in mainland Finland.[24] After excluding participants who had missing information (n=1331), the final dataset consisted of 6697 participants, 2990 males and 3707 females. Out of this cohort 240 (3.6%) participants were diagnosed with OSA.

The Botnia Study was established in 1990 to investigate familial clustering of diabetes in the Ostrobothnia region in western Finland, and the non-diabetic participants have been prospectively followed.[25] The population-based PPP-Botnia Study was conducted in the same geographical area.[26] From the Botnia/PPP Botnia Studies (referred to as Botnia Study) we included 1405 T2D patients, 735 males and 670 females. In this cohort 119 participants (8.5%) had OSA diagnosis.

Prospective follow-up and event definitions

During the follow-up of the study cohorts, data for hospitalizations and causes of death were obtained from the Finnish National Hospital Discharge Register and the Finnish National Causes-of-Death Register. These registers have excellent validity and coverage.[27, 28] Follow-up for FINRISK ended on Dec 31, 2014, for H2000 on Dec 31, 2013, and for Botnia on Dec 31, 2015.

In the FINRISK cohorts the follow-up was up to 22 years (median 12.9 years, IQR 8.5-17.9) and in the H2000 the follow-up was up to 14.5 years (median13.9, IQR 13.6-14.2). In the Botnia the follow-up was up to 25 years (median 14.7 years, IQR 10.2-21.4). Altogether we had 528,476 person years of follow-up.

OSA diagnosis is based on ICD codes which usually are based upon subjective symptoms, clinical examination and sleep registration applying apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) ≥ 5. Incident CHD events were defined as the first occurrence of myocardial infarction, CHD death, or coronary revascularization procedure at any time between the baseline examination and final follow-up date. Incident stroke events (STR), and diabetic kidney disease (DKD; including codes from ICD 10: N18, N19, E102, E112, ICD 9: 585, 2503A, 2503B and ICD8: 58200, 25004) were defined as the first occurrence of such event during this time period in hospital discharges or causes of deaths register. In FINRISK and H2000 cohorts incident T2D was registered as the first occurrence of T2D in hospital discharges, causes of deaths register or entitlement to a reimbursed diabetes medication. Also, diabetes medication purchases were checked. If diabetic medication was the only evidence, at least 3 separate purchases were required. Persons with

gestational or T1D were excluded from the analyses. In the Botnia Study diabetes was defined based on a 75 g oral glucose tolerance test (OGTT), with plasma glucose ≥7.0mmol/l at fasting (FPG) or ≥11.1mmol/l at 2 hours or previous diagnosis and use of anti-diabetic medication.

ICD-codes for each endpoint definition can be found in Supplementary Table 1.

Statistical Methods

We tested associations between OSA and incident CHD events, DKD events and T2D using Cox proportional hazard models. Age at onset of OSA was used as a time-dependent covariate in our analyses and age was used as the time scale. In such Cox model a person contributes in the model only for his/her at-risk period (i.e., for a certain age range). During that period, he/she could become an OSA case, before the T2D diagnosis or cardiovascular event. In this case, using OSA as a time-dependent covariate, he/she contributes to the model as a non-OSA case until the age at OSA diagnosis, and as an OSA case for the remaining of his/her at-risk period [29]. Prevalent cases were excluded from the Cox regression analyses and the assumptions of the models were tested by cox.zph -function.

In our FINRISK raw model for CHD we used age, gender, geographical area and cohort year as covariates. In the adjusted model we used, in addition to aforementioned factors, traditional risk factors as covariates for cardiovascular events: HDL, total cholesterol (CHOL), current cigarette smoking, BMI, hypertension (defined as a

measured blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications), prevalent T2D, and family history of stroke or myocardial infarction.

In the raw analysis, similar to CHD, the association between OSA and T2D was adjusted for age, gender, geographical area and cohort year. In the adjusted model we used also BMI as a covariate. Among T2D patients with the end point of DKD the model was adjusted for BMI and hypertension.

In the H2000 we were not able to adjust the model for family history of stroke or myocardial infarction because that information was not determined in the study. Otherwise the Cox time-dependent hazard model was adjusted for the same risk factors as mentioned before.

We combined the evidence from the FINRISK and H2000 to analyze CHD and T2D. To analyze T2D complications in more detail we used the Botnia as a third cohort. The results were combined using fixed effect meta-analysis.

Differences in baseline demographics and clinical characteristics were tested using Chi-square tests. Fisher's exact -test was used if the expected cell size was ≤ 5. For continuous variables we used t-test (Table 1). We considered $p<0.05$ as statistically significant, and all tests were two-sided.

The R statistical package (version 3.2.5) was used for all analyses (www.r-project.org).[29]

RESULTS

General results

To analyze the comorbidity of OSA and CHD, T2D outcomes and T2D complications we combined longitudinal data from three population-based cohorts including 37,352 participants with 1601 (4.3%) OSA patients. These cohorts included FINRISK (n=29250) with follow-up of up to 22 years (median 12.9 years, IQR 8.5-17.9), H2000 (n=6697) with the median follow-up of 13.9 (IQR 13.6-14.2) and T2D patients from the Botnia Study (n=1405) with the median follow up of 15.3 years (IQR 10.8-21.34). Altogether we had 6248 T2D patients (16.7%).

We used the Finnish nationwide health registry data to construct diagnosis events. To evaluate the performance of the diagnostic events, we compared the main risk factor distributions between OSA cases and the rest of the population. In Figure 1. we show that BMI and systolic blood pressure are on average higher and HDL lower in the OSA group compared to the rest of the population. Table 1. presents a more thorough comparison of the groups.

Cardiovascular outcomes

We first tested if OSA is associated with risk of incident CHD. In a model adjusted for age, sex and geographical region, OSA diagnosis elevates the risk of CHD by 54% (CI=1.28-1.86, p=4.43×10^{-6}; Table 2).

	Number of events / Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	2129/28785	1.43 [1.17-1.75]	7.34×10^{-4}	1.25 [1.01-1.54]	0.037
H2000	565/6438	2.13 [1.40-3.24]	4.08×10^{-4}	1.91 [1.25-2.92]	2.80×10^{-3}
Combined	2694/35223	1.54 [1.28-1.86]	4.43×10^{-6}	1.36 [1.12-1.64]	1.40×10^{-3}
Men					
FINRISK	1480/13653	1.33 [1.06-1.67]	0.015	1.18 [0.94-1.49]	0.157
H2000	306/2867	1.81 [1.13-2.91]	0.014	1.57 [0.97-2.55]	0.069
Combined	1786/16520	1.41 [1.15-1.73]	1.10×10^{-3}	1.25 [1.01-1.54]	0.039
Women					
FINRISK	649/15132	1.99 [1.24-3.19]	4.11×10^{-4}	1.66[1.03-2.68]	0.036
H2000	259/3571	4.12 [1.68-10.18]	2.06×10^{-3}	4.03 [1.62-10.01]	2.64×10^{-3}
Combined	908/18703	2.33 [1.53-3.53]	7.19×10^{-5}	2.01 [1.31-3.07]	1.20×10^{-3}

Table 2. Hazard ratios between individuals with OSA and the population for incident coronary heart disease events. The FINRISK raw model is adjusted for age, cohort year, geographical area and gender. The adjusted model is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension, prevalent type 2 diabetes and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 raw model is adjusted for geographical area and gender. H2000 adjusted model is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension and prevalent type 2 diabetes in addition to covariates of the raw model.

When adjusting for CHD risk factors (age, sex, region, HDL and total cholesterol, current cigarette smoking, BMI, hypertension, T2D baseline, and family history of stroke or myocardial infarction), the estimate attenuated to 36% (CI=1.12-1.64, p=1.40×10^{-3}). The estimates were similar across these cohorts and were slightly higher for females (adjusted HR=2.01, CI=1.31-3.07, p=1.20×10^{-3}) than for males (adjusted HR=1.25, CI=1.01-1.54, p=0.039). OSA did not, however, associate with stroke risk (Supplementary Table 2).

The effect of OSA on T2D and its complications

We next tested if OSA modifies the risk for T2D. Among OSA patients this risk was elevated by 2.52-fold ($p=1.91\times10^{-32}$, CI=2.16-2.93). After further adjustment for BMI, the risk remained at 1.48-fold ($p=9.11\times10^{-7}$, CI=1.26-1.73) showing a similar effect in both cohorts. Again, the effect was more prominent in females (adjusted HR = 1.63, CI=1.20-2.23, $p=2.20\times10^{-3}$) than in males (HR = 1.44, CI=1.27-2.21, $p=9.62\times10^{-5}$), (Table 3).

	Number of DM / Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	2435/27917	2.40 [2.03-2.84]	1.53×10^{-24}	1.38 [1.16-1.64]	2.74×10^{-4}
H2000	455/6336	3.18 [2.20-4.59]	7.03×10^{-10}	2.05 [1.42-2.97]	1.41×10^{-4}
Combined	2890/34253	2.52 [2.16-2.93]	1.91×10^{-32}	1.48 [1.26-1.73]	9.11×10^{-7}
Men					
FINRISK	1372/13424	2.21 [1.81-2.69]	2.55×10^{-15}	1.28 [1.05-1.57]	0.017
H2000	257/2883	3.65 [2.44-5.44]	2.23×10^{-10}	2.27 [1.51-3.41]	8.08×10^{-5}
Combined	1629/16307	2.43 [2.04-2.90]	4.16×10^{-23}	1.44 [1.27-2.21]	9.62×10^{-5}
Women					
FINRISK	1063/14493	3.14 [2.28-4.33]	3.12×10^{-12}	1.65 [1.18-2.29]	2.98×10^{-3}
H2000	198/3453	2.16 [0.80-5.87]	0.13	1.48 [0.55-4.02]	0.44
Combined	1261/17946	3.03 [2.23-4.12]	1.25×10^{-15}	1.63 [1.20-2.23]	2.20×10^{-3}

Table 3. Hazard ratios between individuals with OSA and the population for incident type 2 diabetes. The FINRISK raw model is adjusted for age, cohort year, geographical area and gender. The adjusted model is adjusted for BMI in addition to covariates of the raw model. The H2000 raw model is adjusted for geographical area and gender. The adjusted model is adjusted for BMI in addition to covariates of the raw model.

To analyze T2D complications more in detail we included the Botnia cohort into the meta-analysis. H2000 lacked incident DKD events among OSA patients.

Among T2D patients OSA elevated the risk for DKD 2.16-fold (CI=1.40-3.34, p=5.00×10^{-4}; Table 4).

	Number of events / Subjects at risk	Raw model		Adjusted model	
DKD		HR [95% CI]	p	HR [95% CI]	p
FINRISK	147/4183	2.15 [1.27-3.62]	4.10×10^{-3}	1.72[1.01-2.93]	0.044
Botnia	91/1466	2.19 [1.003-4.79]	0.049	1.80 [0.82-3.96]	0.143
Combined	238/5649	2.16 [1.40-3.34]	5.00×10^{-4}	1.75 [1.13-2.71]	0.013
CHD		HR [95% CI]	p	HR [95% CI]	p
FINRISK	640/3931	1.44 [1.07-1.95]	0.01610	1.40 [1.04-1.90]	0.028
H2000	152/802	1.46 [0.74-2.82]	0.272	1.46 [0.74-2.89]	0.274
Botnia	236/1352	1.18 [0.60-2.31]	0.630	1.07 [0.54-2.11]	0.840
Combined	1028/6085	1.40 [1.10-1.81]	8.50×10^{-3}	1.36 [1.05-1.76]	0.019

Table 4. Hazard ratios for type 2 diabetes complications. The FINRISK raw models are adjusted for age, cohort year, geographical area and gender. The H2000 raw models are adjusted for age, geographical area and gender. The Botnia raw models are adjusted for age and gender. The adjusted models for DKD are adjusted for BMI and hypertension in all cohorts in addition to covariates of the raw model. The FINRISK adjusted model for CHD is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 and Botnia adjusted models for CHD are adjusted for HDL and total cholesterol, current cigarette smoking, BMI and hypertension in addition to covariates of the raw model.

When adjusted for the known risk factors for DKD (BMI and hypertension) the hazard ratio was slightly reduced to 1.75 (CI=1.13-2.71, p=0.013). The effects were similar in both cohorts.

Among T2D patients OSA alone increased the risk for CHD by 1.40 (CI=1.10-1.81, p=8.50×10^{-3}; Table 4). This was almost unaffected by adding the following risk factors: HDL and total cholesterol, current cigarette smoking, BMI, hypertension, and family history of stroke or myocardial infarction (HR=1.36, CI=1.05-1.76, p=0.019).

The effect of OSA to mortality risk

We also examined whether OSA was an independent risk factor for all-cause mortality. OSA increased the risk in the raw model by 21% (CI = 1.02-1.42, p = 0.024) and this risk remained the same after adjustment for other risk factors. Among T2D individuals OSA increased the all-cause mortality risk in the raw model 40% (CI=1.21-1.62, p=2.03×10^{-6},) and after adjustments 35% (CI=1.06-1.71, p=0.016; Table 5).

	Number of events / Subjects at Risk	Raw model		Adjusted model	
General population		HR [95% CI]	p	HR [95% CI]	p
FINRISK	3326/29895	1.14 [0.95-1.37]	0.163	1.06 [0.88-1.28]	0.524
H2000	1318/6769	1.54 [1.06-2.23]	0.022	1.61 [1.11-2.33]	0.012
Combined	4644/36664	1.21 [1.02-1.42]	0.024	1.22 [1.03-1.44]	0.018
T2DM		HR [95% CI]	p	HR [95% CI]	p
FINRISK	719/4197	1.37 [1.01-1.84]	0.041	1.23 [0.91-1.67]	0.179
H2000	284/864	1.35 [0.68-2.71]	0.390	1.48 [0.74-2.98]	0.267
Botnia	348/1384	1.84 [1.14-2.99]	1.44×10^{-4}	1.62 [1.00-2.65]	0.052
Combined	1351/6445	1.40 [1.21-1.62]	2.03×10^{-6}	1.35 [1.06-1.71]	0.016

Table 5. Hazard ratios for all-cause mortality among general population and type 2 diabetes individuals. The FINRISK raw models are adjusted for age, cohort year, geographical area and gender. The H2000 raw models are adjusted for age, geographical area and gender. The Botnia raw models are adjusted for age and gender. The FINRISK adjusted is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 and Botnia adjusted models are adjusted for HDL and total cholesterol, current cigarette smoking, BMI and hypertension in addition to covariates of the raw model. Adjusted models for general population are also adjusted for prevalent type 2 diabetes.

DISCUSSION

Our results from three prospective population-based cohorts show a severe impact of OSA on cardiovascular health, T2D and mortality during a life course. We show that OSA is an independent risk factor for CHD and T2D in general population. Using a combination of population cohorts and a T2D cohort, Botnia, we present evidence for the role of OSA in the risk of T2D complications. To our knowledge this is the largest study of the role of OSA in CHD and T2D diseases, combining sample size of over 37,000 individuals with up to 20+ years of follow-up.

These results allow us to draw several conclusions. First, our results show that nationwide health registry data can successfully be used to identify cases of obstructive sleep apnea. Second, the registry-based obstructive sleep apnea cases show an increased risk for future CHD events and T2D. This risk was surprisingly high in females, even after adjusting for risk factors, sheading new light to the potential sex differences in OSA. This finding may provide tools to identify particularly women in high risk of CHD and T2D. Third, we observed strong evidence showing that T2D accumulated to OSA patients independent of obesity.

OSA seems to increase the risk for CHD to the same extent in diabetic and non-diabetic individuals but the risk of diabetic kidney disease was 75% higher among OSA patients compared to diabetic individuals without OSA diagnosis. All-cause-mortality was increased by OSA in the general population and slightly more among T2D patients. The main cause of mortality was CHD both in diabetics (33.8%) and in the general population (30.8%).

While previous studies mostly lacked the longitudinal dimension, also our study has limitations: 1) Registry-based ascertainment through hospitalization may miss non-hospitalized cases (false negatives) and 2) treatment information, and 3) emphasize more severe OSA cases affecting the hazard estimates. However, in spite of these limitations the study design provides comprehensive estimates of the adverse effects of OSA on CHD and T2D disorders. This is supported by a recent meta-analysis reporting an RR of 1.49 for the association of OSA and T2D,[30] which is well in line with the results from our study.

It is being increasingly recognized that OSA can accelerate loss of kidney function,[31] but OSA usually presents with other risk factors of kidney function like obesity, T2D and hypertension.[32, 33] It has been hypothesized that there is a bidirectional relationship between OSA and kidney disease, where kidney disease promotes OSA and OSA kidney disease.[31] Our study supports the latter hypothesis that in diabetic patients OSA increased the risk for kidney disease by 1.75-fold after adjustment for other risk factors. This is in line with previous, smaller studies.[22, 31]

An important advantage of our large sample size, was that we could investigate gender differences in the CHD and T2D risk associated with OSA. While we did not observe a significantly higher risk in females than in males, our data opposite to previous studies clearly show that the severe outcome of OSA is as severe in females as in men (if not more severe).[2, 34] It is possible explanation for this finding may be delayed diagnosis of OSA in women compared with men.

Taken together, our longitudinal study with up to 528,476 person years of follow-up demonstrates that OSA is an independent risk factor not only for CHD and T2D but also markedly increase risk for DKD. This emphasizes the need to search for signs of OSA in T2D patients with rapid progression of T2D and evaluate whether this progression can be halted by CPAP therapy.

NOTES:

We would like to thank Sari Kivikko, Mervi Kinnunen, and Elina Kilpeläinen for management assistance. The FINRISK data used for the research were obtained from THL Biobank and the Health 2000 data from THL. The skillful assistance of the Botnia Study Group is gratefully acknowledged. We thank all study participants for their generous participation in the FINRISK, the Health 2000 and the Botnia studies.

Contributions: SS, TP, TT, LG, AP and SR wrote the manuscript. All authors analyzed and interpreted the results and critically reviewed the manuscript for important intellectual content. SK acquired H2000 data, VS acquired FINRISK data, TT and LG acquired Botnia data. ASH phenotyped study samples. Statistical analysis was done by SS and ASH. TP, SR and AP supervised the study.

Funding: This work was supported by Finnish Woman Dentists' Association, the Finnish Dental Society Apollonia, the Helsinki University Central Hospital Research Funds (HUS 369/2017), Academy of Finland Center of Excellence in Complex Disease Genetics (312062), Academy of Finland (251217 and 285380), The Finnish Foundation for Cardiovascular Research, the Sigrid Juselius Foundation and HiLIFE Fellows grants 2017-2020. The sources of funding had no role in study design, data collection, analyses, interpretation, and decision to submit the article for publication.

FINRISK surveys have been funded mainly by budgetary funds of the National Institute for Health and Welfare. Additional funding has been obtained as research grants from the Finnish Academy and several domestic foundations. VS was supported by the Finnish Foundation for Cardiovascular Research.

The Health 2000 Study is funded by the National Institute for Health and Welfare (THL), the Finnish Centre for Pensions (ETK), The Social Insurance Institution of Finland (KELA), The Local Government Pensions Institution (KEVA) and other organizations listed on the website of the survey (http://www.terveys2000.fi).

The Botnia and The PPP-Botnia studies have been financially supported by grants from Folkhälsan Research Foundation, the Sigrid Juselius Foundation, Nordic Center of Excellence in Disease Genetics, EU (EXGENESIS, EUFP7-MOSAIC), Signe and Ane Gyllenberg Foundation, Ollqvist Foundation, Swedish Cultural Foundation in Finland, Finnish Diabetes Research Foundation, Foundation for Life and Health in Finland, Finnish Medical Society, Paavo Nurmi Foundation, Helsinki University Central Hospital Research Foundation, Perklén Foundation, Närpes Health Care Foundation and Ahokas Foundation. The study has also been supported by the Ministry of Education in Finland,

Municipal Heath Care Center and Hospital in Jakobstad and Health Care Centers in Vasa, Närpes and Korsholm.

No Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: FINRISK data is stored in the THL Biobank which distributes it to researchers on the basis of written applications. The Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital District has approved the THL Biobank with the decision # 238/13/03/00/2014. H2000 Study protocol is approved by the Ethical Committee of the National Public Health Institute (decision number 8/99). The Botnia/PPP Botnia Study protocols were approved by the Ethics Committee of the Helsinki University Central Hospital, Finland, with the decision #574/E5/03.

Data sharing: Additional information is available from the corresponding author.

REFERENCES:

1 Wang X, Bi Y, Zhang Q, et al. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013;18:140-6 doi:https://dx.doi.org/10.1111/j.1440-1843.2012.02267.x [published Online First: Jan].

2 Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-60 doi:https://dx.doi.org/10.1161/CIRCULATIONAHA.109.901801 [published Online First: Jul 27].

3 Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population, *Lancet* 1984;2:1005-8 doi:S0140-6736(84)91107-3 [pii] [published Online First: Nov 3].

4 Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension, *Am Heart J* 1984;108:373-6 [published Online First: Aug].

5 Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest* 2014;146:982-90 doi:https://dx.doi.org/10.1378/chest.13-2403 [published Online First: Oct].

6 Varvarigou V, Dahabreh IJ, Malhotra A, et al. A review of genetic association studies of obstructive sleep apnea: field synopsis and meta-analysis, *Sleep* 2011;34:1461-8 doi:10.5665/sleep.1376 [doi] [published Online First: Nov 1].

7 Malhotra A, White DP. Obstructive sleep apnoea, *Lancet* 2002;360:237-45 doi:S0140-6736(02)09464-3 [pii] [published Online First: Jul 20].

8 Silverberg DS, Oksenberg A, Iaina A. Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction? *Curr Opin Nephrol Hypertens* 1998;7:353-7 [published Online First: Jul].

9 Fava C, Dorigoni S, Dalle Vedove F, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis, *Chest* 2014;145:762-71 doi:S0012-3692(15)35945-6 [pii] [published Online First: Apr].

10 Kent BD, Ryan S, McNicholas WT. The genetics of obstructive sleep apnoea, *Curr Opin Pulm Med* 2010;16:536-42 doi:10.1097/MCP.0b013e32833ef7fe [doi] [published Online First: Nov].

11 Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;31:1071-8 [published Online First: Aug].

12 Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *American Journal of Respiratory & Critical Care Medicine* 2002;166:159-65 [published Online First: Jul 15].

13 Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study, *The Lancet* 2005;365:1046-53 doi:https://doi-org.libproxy.helsinki.fi/10.1016/S0140-6736(05)71141-7 [published Online First: 3/19–25].

14 Beck MK, Westergaard D, Jensen AB, et al. Temporal Order of Disease Pairs Affects Subsequent Disease Trajectories: the Case of Diabetes and Sleep Apnea, *Pac Symp Biocomput* 2016;22:380-9 doi:9789813207813_0036 [pii].

15 Botros N, Concato J, Mohsenin V, et al. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009;122:1122-7 doi:https://dx.doi.org/10.1016/j.amjmed.2009.04.026 [published Online First: Dec].

16 Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. *Thorax* 2009;64:834-9 doi:https://dx.doi.org/10.1136/thx.2009.115105 [published Online First: Oct].

17 Kendzerska T, Gershon AS, Hawker G, et al. Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med* 2014;190:218-25 doi:https://dx.doi.org/10.1164/rccm.201312-2209OC [published Online First: Jul 15].

18 Reichmuth KJ, Austin D, Skatrud JB, et al. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005;172:1590-5 doi:https://dx.doi.org/10.1164/rccm.200504-637OC [published Online First: Dec 15].

19 Ozol D, Carlioglu A, Karamanli H, et al. Influence of snoring on microalbuminuria in diabetic patients. *Sleep Breath* 2011;15:295-300 doi:https://dx.doi.org/10.1007/s11325-010-0380-1 [published Online First: Sep].

20 Leong WB, Nolen M, Thomas GN, et al. The impact of hypoxemia on nephropathy in extremely obese patients with type 2 diabetes mellitus. *J Clin Sleep Med* 2014;10:773-8 doi:https://dx.doi.org/10.5664/jcsm.3870 [published Online First: Jul 15].

21 Hwu DW, Lin KD, Lin KC, et al. The association of obstructive sleep apnea and renal outcomes-a systematic review and meta-analysis, *BMC Nephrol* 2017;18:313,017-0731-2 doi:10.1186/s12882-017-0731-2 [doi] [published Online First: Oct 16].

22 Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes Care* 2013;36:3718-25 doi:https://dx.doi.org/10.2337/dc13-0450 [published Online First: Nov].

23 Borodulin K, Vartiainen E, Peltonen M, et al. Forty-year trends in cardiovascular risk factors in Finland, *Eur J Public Health* 2015;25:539-46 doi:10.1093/eurpub/cku174 [doi] [published Online First: Jun].

24 Kattainen A, Salomaa V, Harkanen T, et al. Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s, *Eur Heart J* 2006;27:296-301 doi:ehi630 [pii] [published Online First: Feb].

25 Groop L, Forsblom C, Lehtovirta M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects, *Diabetes* 1996;45:1585-93 [published Online First: Nov].

26 Isomaa B, Forsen B, Lahti K, et al. A family history of diabetes is associated with reduced physical fitness in the Prevalence, Prediction and Prevention of Diabetes (PPP)-Botnia study, *Diabetologia* 2010;53:1709-13 doi:10.1007/s00125-010-1776-y [doi] [published Online First: Aug].

27 Tolonen H, Salomaa V, Torppa J, et al. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil* 2007;14:380-5 doi:https://dx.doi.org/10.1097/01.hjr.0000239466.26132.f2 [published Online First: Jun].

28 Pajunen P, Koukkunen H, Ketonen M, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease, *Eur J Cardiovasc Prev Rehabil* 2005;12:132-7 doi:00149831-200504000-00007 [pii] [published Online First: Apr].

29 Anonymous . https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf.

30 Anothaisintawee T, Reutrakul S, Van Cauter E, et al. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis, *Sleep Med Rev* 2016;30:11-24 doi:S1087-0792(15)00146-X [pii] [published Online First: Dec].

31 Abuyassin B, Sharma K, Ayas NT, et al. Obstructive Sleep Apnea and Kidney Disease: A Potential Bidirectional Relationship? *J Clin Sleep Med* 2015;11:915-24 doi:10.5664/jcsm.4946 [doi] [published Online First: Aug 15].

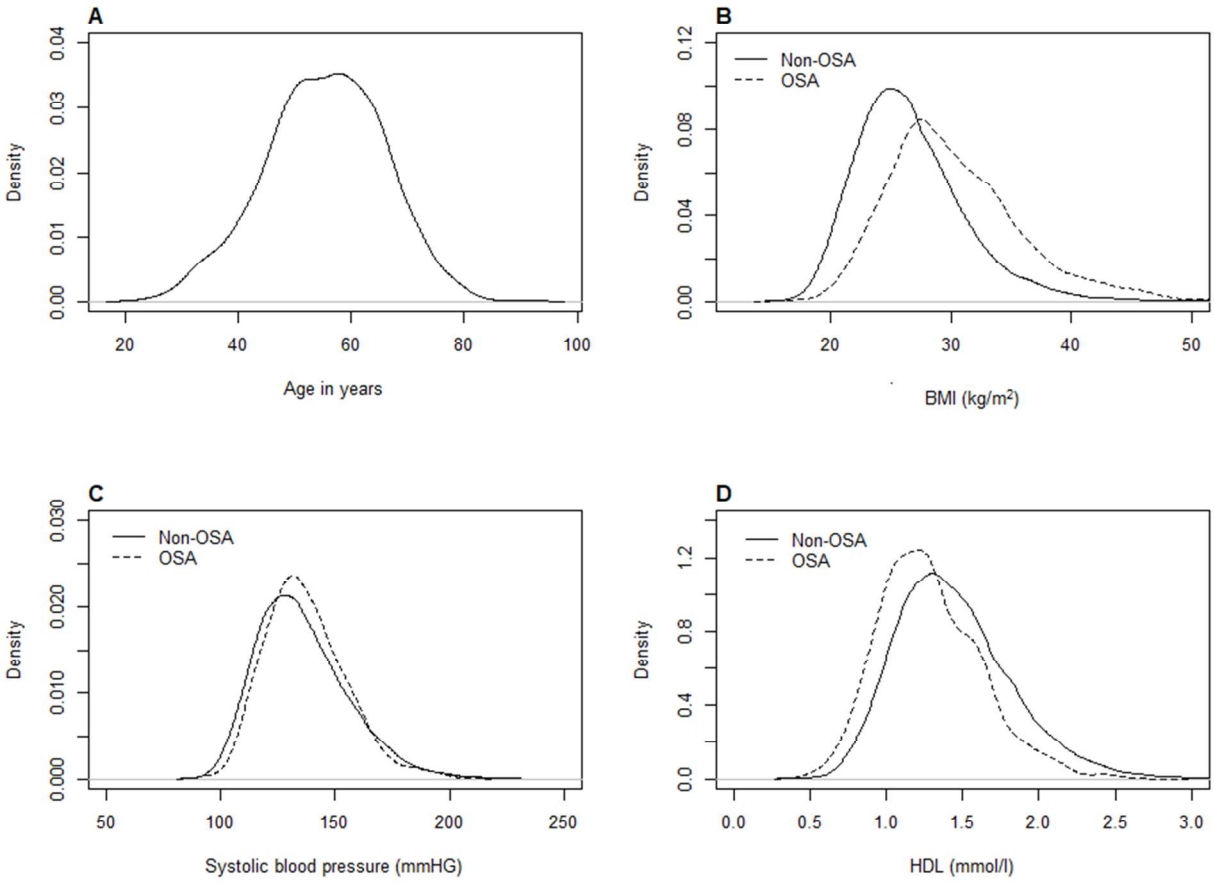
32 Tada T, Kusano KF, Ogawa A, et al. The predictors of central and obstructive sleep apnoea in haemodialysis patients, *Nephrol Dial Transplant* 2007;22:1190-7 doi:gfl748 [pii] [published Online First: Apr].

33 Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences, *Nutr Metab Cardiovasc Dis* 2007;17:233-40 doi:S0939-4753(06)00266-3 [pii] [published Online First: Mar].

34 Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study, *PLoS Med* 2009;6:e1000132 doi:10.1371/journal.pmed.1000132 [doi] [published Online First: Aug].

Figure legend

Figure 1. Distributions of age at OSA diagnosis (mean 55.31 years) (A) and significant differences in BMI ($p = 8.65\times10^{-78}$) (B), systolic blood pressure ($p = 8.72\times10^{-3}$) (C) and HDL ($p = 1.78\times10^{-54}$) (D) among OSA patients and non-OSA individuals in FINRISK.



Supplemental Material

	ICD 8	ICD 9	ICD 10
OSA	-	327.23	G47.3
CHD	410|4110	410|4110	I200|I21|I22
STR	431|433|434|436	431|4330A|4331A|4339A|4340A|4341A|4349A|436	I61|I63|I64
T2DM	250	250	E11|E12|E13|E14
DKD	58200|25004	585|2503A|2503B	N18|N19|E102|E112

Supplementary Table 1. ICD-codes (Finnish national version) for each endpoint definition. OSA=obstructive sleep apnea. CHD=coronary heart disease. STR=stroke. T2DM= type 2 diabetes. DKD=diabetic kidney disease.

	Number of events/ Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	1317/29553	0.99 [0.73-1.36]	0.981	0.92 [0.67-1.26]	0.602
H2000	356/6606	1.34 [0.68-2.62]	0.395	1.36 [0.69-2.67]	0.378
Combined	1673/36159	1.05 [0.79-1.39]	0.736	0.98 [0.74-1.31]	0.951

Supplementary Table 2. Hazard ratios between individuals with OSA and the population for incident stroke events. The FINRISK raw model is adjusted with age, cohort year, geographical area and gender. The adjusted model is adjusted with HDL and total cholesterol, current cigarette smoking, BMI, hypertension, prevalent type 2 diabetes and family history of stroke or myocardial infarction in addition to covariates of the raw model. The H2000 raw model is adjusted with geographical area. The adjusted model is adjusted with HDL and total cholesterol, current cigarette smoking, BMI, hypertension and prevalent type 2 diabetes in addition to covariates of the raw model.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2-5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19-20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Obstructive sleep apnea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022752.R1
Article Type:	Research
Date Submitted by the Author:	05-Jun-2018
Complete List of Authors:	Strausz, Satu; Institute for Molecular Medicine Finland; University of Helsinki and Helsinki University Hospital, Department of Oral and Maxillofacial Diseases, Orthodontics Havulinna, Aki; Institute for Molecular Medicine Finland; National Institute for Welfare and Health Tuomi, Tiinamaija; Institute for Molecular Medicine Finland; University of Helsinki and University Helsinki Hospital, Endocrinology, Abdominal Centre Bachour, Adel; Helsinki University Hospital, Sleep Unit, Heart and Lung Center Groop, Leif ; Lund University, Diabetes Centre; Institute for Molecular Medicine Finland Mäkitie, Antti; University of Helsinki and University Helsinki Hospital, Department of Otorhinolaryngology - Head and Neck Surgery Koskinen, Seppo; National Institute for Welfare and Health Salomaa, Veikko; National Institute for Welfare and Health Palotie, Aarno; Massachusetts General Hospital, Dept. Psychiatry; Institute for Molecular Medicine Finland Ripatti, Samuli; Institute for Molecular Medicine Finland; University of Helsinki, Department of Public Health Palotie, Tuula; University of Helsinki and Helsinki University Hospital, Department of Oral and Maxillofacial Diseases, Orthodontics
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Global health, Public health, Renal medicine, Cardiovascular medicine
Keywords:	Obstructive sleep apnea, Coronary heart disease < CARDIOLOGY, Type 2 diabetes, Diabetic kidney disease, Mortality, Longitudinal

Obstructive sleep apnea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland

DDS. Satu Strausz[1,2,3], PhD. Aki S. Havulinna[3,4], Assoc. Prof. Tiinamaija Tuomi[3,5], Assoc. Prof. Adel Bachour[6], Prof. Leif Groop[3,7], Prof. Antti Mäkitie[8], Prof. Seppo Koskinen[4], Prof. Veikko Salomaa[4], Prof. Aarno Palotie[3,9,10], Prof. Samuli Ripatti[3,11]*, Assoc. Prof. Tuula Palotie[1,2]*.
*These authors contributed equally to this project.

1) Department of Oral and Maxillofacial Diseases, Helsinki University Hospital (HUH), Finland
2) Orthodontics, Department of Oral and Maxillofacial Diseases, Clinicum, Faculty of Medicine, University of Helsinki, Finland
3) Institute for Molecular Medicine Finland (FIMM/HiLIFE), University of Helsinki, Finland
4) National Institute for Health and Welfare, Helsinki, Finland
5) Endocrinology, Abdominal Centre, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Diabetes and Obesity Research Program, University of Helsinki and Folkhälsan Research Center, Helsinki, Finland.
6) Sleep Unit, Heart and Lung Center, Helsinki University Hospital (HUH), Finland.
7) Lund University Diabetes Centre, Department of Clinical Sciences, Malmö, Lund University, Skåne University Hospital, Malmö, Sweden
8) Department of Otorhinolaryngology - Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
9) Analytic and Translational Genetics Unit (ATGU), Department of Medicine, Department of Neurology and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
10) Broad Institute of MIT and Harvard, Cambridge, MA, USA
11) Department of Public Health, University of Helsinki, Finland

Correspondence to:

Satu Strausz, DDS,
Tel. +358 40 583 8443
Fax. +358 29 412 5737
Institute for Molecular Medicine Finland (FIMM)
PO BOX 20
00041 University of Helsinki,
Finland
satu.strausz@helsinki.fi

2554 words, 5 tables, 1 figure, 6 supplementary figures, 2 supplementary tables
Keywords: obstructive sleep apnea, coronary heart disease, type 2 diabetes, diabetic kidney disease, mortality, longitudinal

ABSTRACT

Objective: To evaluate if obstructive sleep apnea (OSA) modifies the risk of coronary heart disease, type 2 diabetes (T2D) and diabetic complications in a gender-specific fashion.

Design and Setting: A longitudinal population-based study with up to 25 years follow-up data on 36,963 individuals (> 500,000 person years) from three population-based cohorts: the FINRISK study, the H2000 Study and the Botnia Study.

Main outcome measures: Incident coronary heart disease, diabetic kidney disease, T2D and all-cause mortality from the Finnish National Hospital Discharge Register and the Finnish National Causes-of-Death Register.

Results: After adjustments for age, sex, region, HDL and total cholesterol, current cigarette smoking, BMI, hypertension, T2D baseline, and family history of stroke or myocardial infarction OSA increased the risk for coronary heart disease (HR=1.36, p=0.0014, CI=1.12 to 1.64), particularly in females (HR=2.01, CI=1.31 to 3.07, p=0.0012). T2D clustered with OSA independently of obesity (HR=1.48, CI=1.26 to 1.73, $p=9.11\times10^{-7}$). The risk of diabetic kidney disease increased 1.75-fold in OSA patients (CI=1.13 to 2.71, p=0.013). OSA increased the risk for coronary heart disease similarly among T2D patients and in general population (HR=1.36). All-cause-mortality was increased by OSA in diabetic individuals (HR=1.35, CI=1.06 to 1.71, p=0.016).

Conclusion: OSA is an independent risk factor for coronary heart disease, T2D and diabetic kidney disease. This effect is more pronounced even in women, who until now have received less attention in diagnosis and treatment of OSA than men.

Strengths and limitations of this study

- A large-scale population-based study of 36,963 individuals with up to 25 years of follow-up.
- Follow-up registers have excellent validity and coverage.
- Our study takes a large amount of confounding factors related to OSA into consideration.
- Prospective study design should limit the risk of bias.
- Registry-based ascertainment through hospitalization may miss non-hospitalized cases and treatment information.

INTRODUCTION

Obstructive sleep apnea (OSA) is a more common disorder than currently diagnosed in the clinic.[1] It is a serious public health problem due to its many comorbidities, including an increased risk to coronary heart disease and T2D.[2, 3] The main known risk factors for OSA are obesity, male gender, high age, increased neck circumference and problems of upper airway or jaw anatomy.[4-7]

Longitudinal studies have shown an association of OSA with incident or recurrent cardiovascular events and increased mortality.[3, 8] The risk of developing CHD is particularly increased in middle-aged men with OSA.[9, 10] Risk of CHD and mortality is usually increased if T2D is diagnosed before OSA.[11]

There is mounting evidence that OSA is an independent risk factor for the development of T2D.[2, 12, 13] Most of the available studies have been cross-sectional,[6, 12, 13] and not able to account for residual confounding factors.[6, 13] Other studies did not distinguish between T1D and T2D,[14] nor to generalize the results to the overall population.[6] In some studies this association has been dispersed after adjustments for other risk factors.[15]

Also, studies investigating the synergistic effects of OSA and T2D on the progression of diabetic kidney disease are scarce and often limited by a cross-sectional design [16-18] or small sample size.[19]

To explore the role of OSA for coronary heart disease, T2D and increased mortality we conducted a large-scale population-based study of 36,963 individuals with up to 25 years of follow-up. We specifically aimed at evaluating 1) if OSA modifies the risk of

coronary heart disease and T2D independently of known risk factors like BMI, blood pressure and lipids, 2) the role of OSA for development of diabetic complications including diabetic kidney disease and 3) examine if OSA has similar effects in females and males.

METHODS

Study population

We included 36,963 participants in our study from national FINRISK Studies (FINRISK), Health 2000 Cohort (H2000) and a subset of the Botnia and PPP-Botnia Studies (Botnia) including 1568 (4.2%) OSA patients (ICD 10: G47.3, ICD 9: 3472A). Baseline characteristics of the participants are presented in Table 1.

	FINRISK				H2000				Botnia T2DM		
	Overall	Non-OSA	OSA	p	Overall	Non-OSA	OSA	p	Overall	Non-OSA	OSA
	n = 28953	n = 27739	n = 1214		n = 6605	n = 6370	n = 235		n = 1405	n = 1286	n = 119
Gender (male)	13792 (47.6%)	12915 (46.6%)	877 (72.2%)	1.26×10^{-68}	2940 (44.6%)	2768 (43.5%)	172 (73.2%)	3.8×10^{-19}	735 (52.3%)	651 (50.6%)	84 (70.6
Baseline age	48.01 (13.2)	47.95 (13.3)	49.27 (11.3)	8.2×10^{-5}	53.8 (15.7)	53.9 (15.8)	50.7 (10.5)	9.7×10^{-6}	58.94 (11.5)	59.20 (11.6)	56.1 (9.9
Age at OSA diagnosis			55.30 (10.4)				55.81 (10.5)				61.93 (1
BMI	26.74 (4.7)	26.58 (4.5)	30.34 (5.7)	3.5×10^{-96}	26.9 (4.7)	26.8 (4.59)	30.6 (5.74)	1.5×10^{-20}	29.26 (4.8)	28.99 (4.7)	32.20 (4
Current smoking	6978 (24.2%)	6666 (24.1%)	312 (25.8%)	0.20	1397 (21.3%)	1340 (21.2%)	57 (24.4%)	0.27	193 (13.7%)	165 (12.8%)	28 (23.5
Systolic mmHg	135.7 (20.0)	135.6 (20.1%)	137.0 (17.5)	7.8×10^{-3}	135.0 (21.70)	135.0 (21.8)	136.1 (19.2)	0.41	144.6 (20.4)	144.6 (20.4)	145.0 (2
Diastolic mmHg	80.48 (11.6)	80.33 (11.6)	83.7 (11.2)	6.4×10^{-25}	81.7 (11.30)	81.5 (11.3)	86.5 (10.2)	2.8×10^{-12}	84.4 (10.4)	84.0 (10.3)	87.9 (10
CHOL mmol/l	5.51 (1.1)	5.51 (1.1)	5.56 (1.0)	0.07	5.9 (1.1)	5.9 (1.1)	6.0 (1.1)	0.12	5.5 (1.1)	5.6 (1.1)	5.3 (1.0)
LDL mmol/l	3.352 (0.9)	3.34 (0.9)	3.50 (0.8)	1.0×10^{-3}	3.7 (1.1)	3.7 (1.1)	3.8 (1.0)	0.29	3.2 (1.0)	3.2 (1.0)	3.1 (0.9)
HDL mmol/l	1.436 (0.4)	1.44 (0.4)	1.28 (0.3)	9.0×10^{-53}	1.3 (0.4)	1.3 (0.4)	1.2 (0.36)	9.7×10^{-5}	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Prevalent cases											
CHD	749 (2.6%)	691 (2.5%)	58 (4.8%)	1.4×10^{-6}	242 (3.7%)	237 (3.7%)	5 (2.1%)	0.27	43 (3.1%)	38 (3.0%)	5 (4.2%)
STROKE	324 (1.1%)	311 (1.1%)	13 (1.1%)	0.98	167 (2.5%)	166(2.6%)	1 (0.4%)	0.06	21 (1.5%)	20 (1.6%)	1 (0.8%)
T2DM	1525 (5.3%)	1403 (5.1%)	122 (10.0%)	4.2×10^{-14}	381 (5.8%)	362 (5.7%)	19 (8.1%)	0.16	1018 (72.5%)	938 (72.9%)	80 (67.2
DKD	20 (0.1%)	20 (0.1%)	0	1	5 (0.1%)	5 (0.1%)	0	1	3 (0.2%)	2 (0.2%)	1 (0.8%)
CHD/T2DM	238 (5.9%)	214 (5.9%)	24 (6.5%)	0.74	63 (7.5%)	62 (8%)	1 (1.6%)	0.08	43 (3.1%)	38 (3.0%)	5 (4.2%)
DKD/T2DM	9 (0.2%)	9 (0.2%)	0	1	2 (0.2%)	2 (0.3%)	0	1	3 (0.2%)	2 (0.2%)	1 (0.8%)
Incident cases											
CHD	2181 (7.5%)	2035 (7.3%)	146 (12.0%)	1.9×10^{-9}	576 (8.7%)	546 (8.6%)	30 (13.3%)	0.03	254 (18.2%)	230 (18.0%)	24 (20.1
STROKE	1325 (4.6%)	1264 (4.6%)	61 (5.0%)	0.49	352 (5.3%)	338 (5.3%)	14 (6.0%)	0.77	179 (12.8%)	162 (12.7%)	17 (14.3
T2DM	2481 (8.8%)	2231 (8.0%)	250 (20.6%)	2.0×10^{-52}	456 (6.9%)	411 (6.5%)	45 (19.1%)	1.3×10^{-13}	387 (27.5%)	348 (27.1%)	39 (32.8
DKD	296 (1.0%)	262 (0.9%)	34 (2.8%)	7.9×10^{-10}	112 (1.7%)	109 (1.7%)	3 (1.3%)	0.80	91 (6.5%)	77 (6%)	14 (11.8
CHD/T2DM	657 (16.4%)	584 (16.1%)	73 (19.6%)	0.10	154 (18.4%)	141 (18.2%)	13 (20.3%)	0.81	254 (18.2%)	230 (18.0%)	24 (20.1
DKD/T2DM	151 (3.8%)	128 (3.5%)	23 (6.2%)	0.02	43 (5.1%)	42 (5.4%)	1 (1.6%)	0.24	*91 (6.5%)*	*77 (6%)*	*14 (11.8*

Table 1. Baseline characteristics in FINRISK, H2000 and type 2 diabetic patients in the Botnia.

Baseline demographics and clinical characteristics p-values were based on χ^2 test. Fisher´s exact-test was used if the sample size was ≤ 5. For continuous variables we used t-test. Data are mean(SD) or number (%). OSA=obstructive sleep apnea. CHOL=total cholesterol. CHD=coronary heart disease. T2DM=type 2 diabetes. DKD=diabetic kidney disease. CHD/T2DM=coronary heart disease among type 2 diabetic patients. DKD/T2DM=diabetic kidney disease among type 2 diabetic patients.

Population-based FINRISK surveys are independent random samples drawn from the population register of six geographic areas of Finland (North Karelia, Kuopio, Lapland, Oulu, Turku/Loimaa and Helsinki/Vantaa) and stratified according to gender, 10-year age group and study area. The survey included a mailed questionnaire and a clinical examination at which a blood sample was drawn.[20] Participants from different survey years (1992, 1997, 2002 or 2007) were pooled together.

The total sample size for all FINRISK surveys was 29257 and participants who had missing information (n=7) or type 1 diabetes (n=297) were excluded from the study. Thus, the total sample size was 28953 where 13792 male and 15161 female participants aged 24–74 years at baseline were included in the analyses. Of these participants, 1214 (4.2%) had OSA.

The H2000 Study is a comprehensive combination of health interview and health examination survey. The study was based on a nationally representative sample of 8028 persons aged ≥ 30 years living in mainland Finland.[21] After excluding participants who had missing information (n=1331) or type 1 diabetes (n=92), the final dataset consisted of 6605 participants, 2940 males and 3707 females. Out of this cohort 235 (3.6%) participants were diagnosed with OSA.

The Botnia Study was established in 1990 to investigate familial clustering of diabetes in the Ostrobothnia region in western Finland, and the non-diabetic participants have been prospectively followed.[22] The population-based PPP-Botnia Study was conducted in the same geographical area.[23] From the Botnia/PPP Botnia Studies (referred to as Botnia Study) we included 1405 T2D patients, 735 males and 670 females. In this cohort 119 participants (8.5%) had OSA diagnosis.

Patient and Public Involvement

Patients and public were not involved in the designing process of this study. The patients will not be informed individually of the study results otherwise than through possible media coverage.

Prospective follow-up and event definitions

During the follow-up of the study cohorts, data for hospitalizations and causes of death were obtained from the Finnish National Hospital Discharge Register and the Finnish National Causes-of-Death Register. These registers have excellent validity and coverage.[24, 25] Follow-up for FINRISK ended on Dec 31, 2014, for H2000 on Dec 31, 2013, and for Botnia on Dec 31, 2015.

In the FINRISK cohorts the follow-up was up to 22 years (median 12.9 years, IQR 8.5-17.9) and in the H2000 the follow-up was up to 14.5 years (median13.9, IQR 13.6-14.2). In the Botnia the follow-up was up to 25 years (median 14.7 years, IQR 10.2-21.4). Altogether we had 523,372 person years of follow-up.

OSA diagnosis is based on ICD codes which usually are based upon subjective symptoms, clinical examination and sleep registration applying apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) ≥ 5.[26] Incident coronary heart disease events were defined as the first occurrence of myocardial infarction, coronary heart disease death, or coronary revascularization procedure at any time between the baseline examination and final follow-up date. Incident stroke events

(STR), and diabetic kidney disease (including codes from ICD 10: N18, N19, E102, E112, ICD 9: 585, 2503A, 2503B and ICD8: 58200, 25004) were defined as the first occurrence of such event during this time period in hospital discharges or causes of deaths register. In FINRISK and H2000 cohorts incident T2D was registered as the first occurrence of T2D in hospital discharges, causes of deaths register or entitlement to a reimbursed diabetes medication. Also, diabetes medication purchases were checked. If diabetic medication was the only evidence, at least 3 separate purchases were required. Persons with gestational or type 1 diabetes were excluded from the analyses. In the Botnia Study diabetes was defined based on a 75 g oral glucose tolerance test (OGTT), with plasma glucose ≥7.0mmol/l at fasting (FPG) or ≥11.1mmol/l at 2 hours or previous diagnosis and use of anti-diabetic medication.

ICD-codes for each endpoint definition can be found in Supplementary Table 1.

Statistical Methods

We tested associations between OSA and incident coronary heart disease events, diabetic kidney disease events and T2D using Cox proportional hazard models. Age at onset of OSA was used as a time-dependent covariate in our analyses and age was used as the time scale. In such Cox model a person contributes in the model only for his/her at-risk period (i.e., for a certain age range). During that period, he/she could become an OSA case, before the T2D diagnosis or cardiovascular event. In this case, using OSA as a time-dependent covariate, he/she contributes to the model as a non-OSA case until the age at OSA diagnosis, and as an OSA case for the remaining of

his/her at-risk period [27]. Prevalent cases were excluded from the Cox regression analyses and the assumptions of the models were tested by cox.zph -function.

In our FINRISK raw model for coronary heart disease we used age, gender, geographical area and cohort year as covariates. In the adjusted model we used, in addition to aforementioned factors, traditional risk factors as covariates for cardiovascular events: HDL, total cholesterol (CHOL), current cigarette smoking, BMI, hypertension (defined as a measured blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications), prevalent T2D, and family history of stroke or myocardial infarction.

In the raw analysis, similar to coronary heart disease, the association between OSA and T2D was adjusted for age, gender, geographical area and cohort year. In the adjusted model we used also BMI as a covariate. Among T2D patients with the end point of diabetic kidney disease the model was adjusted for BMI and hypertension.

In the H2000 we were not able to adjust the model for family history of stroke or myocardial infarction because that information was not determined in the study. Otherwise the Cox time-dependent hazard model was adjusted for the same risk factors as mentioned before.

We combined the evidence from the FINRISK and H2000 to analyze coronary heart disease and T2D. To analyze T2D complications in more detail we used the Botnia as a third cohort. The results were combined using fixed effect meta-analysis.

Differences in baseline demographics and clinical characteristics were tested using Chi-square tests. Fisher's exact -test was used if the expected cell size was ≤ 5. For

continuous variables we used t-test (Table 1). We considered $p<0.05$ as statistically significant, and all tests were two-sided.

The R statistical package (version 3.2.5) was used for all analyses (www.r-project.org).[27]

RESULTS

General results

To analyze the comorbidity of OSA and coronary heart disease, T2D outcomes and T2D complications we combined longitudinal data from three population-based cohorts including 36,963 participants with 1568 (4.2%) OSA patients. These cohorts included FINRISK (n=28953) with follow-up of up to 22 years (median 12.9 years, IQR 8.5-17.9), H2000 (n=6605) with the median follow-up of 13.9 (IQR 13.6-14.2) and T2D patients from the Botnia Study (n=1405) with the median follow up of 15.3 years (IQR 10.8-21.34). Altogether we had 6248 T2D patients (16.9%).

We used the Finnish nationwide health registry data to construct diagnosis events. To evaluate the performance of the diagnostic events, we compared the main risk factor distributions between OSA cases and the rest of the population. In Figure 1. we show that BMI and systolic blood pressure are on average higher and HDL lower in the OSA group compared to the rest of the population. Table 1. presents a more thorough comparison of the groups.

Cardiovascular outcomes

We first tested if OSA is associated with risk of incident coronary heart disease. In a model adjusted for age, sex and geographical region, OSA diagnosis elevates the risk of coronary heart disease (HR=1.54, CI=1.28-1.86, p=4.43×10^{-6}; Table 2, Supplementary Figure 1,2).

	Number of events / Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	2129/27948	1.43 [1.17-1.75]	7.34×10^{-4}	1.25 [1.01-1.54]	0.037
H2000	565/6267	2.13 [1.40-3.24]	4.08×10^{-4}	1.91 [1.25-2.92]	2.80×10^{-3}
Combined	2694/34215	1.54 [1.28-1.86]	4.43×10^{-6}	1.36 [1.12-1.64]	1.40×10^{-3}
Men					
FINRISK	1480/13066	1.33 [1.06-1.67]	0.015	1.18 [0.94-1.49]	0.157
H2000	306/2748	1.81 [1.13-2.91]	0.014	1.57 [0.97-2.55]	0.069
Combined	1786/15814	1.41 [1.15-1.73]	1.10×10^{-3}	1.25 [1.01-1.54]	0.039
Women					
FINRISK	649/14882	1.99 [1.24-3.19]	4.11×10^{-4}	1.66[1.03-2.68]	0.036
H2000	259/3519	4.12 [1.68-10.18]	2.06×10^{-3}	4.03 [1.62-10.01]	2.64×10^{-3}
Combined	908/18401	2.33 [1.53-3.53]	7.19×10^{-5}	2.01 [1.31-3.07]	1.20×10^{-3}

Table 2. Hazard ratios between individuals with OSA and the population for incident coronary heart disease events. The FINRISK raw model is adjusted for age, cohort year, geographical area and gender. The adjusted model is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension, prevalent type 2 diabetes and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 raw model is adjusted for geographical area and gender. H2000 adjusted model is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension and prevalent type 2 diabetes in addition to covariates of the raw model.

When adjusting for coronary heart disease risk factors (age, sex, region, HDL and total cholesterol, current cigarette smoking, BMI, hypertension, T2D baseline, and family history of stroke or myocardial infarction), the HR attenuated to 1.36 (CI=1.12-1.64,

p=1.40×10^{-3}). The estimates were similar across these cohorts and were slightly higher for females (adjusted HR=2.01, CI=1.31-3.07, p=1.20×10^{-3}) than for males (adjusted HR=1.25, CI=1.01-1.54, p=0.039). OSA did not, however, associate with stroke risk (Supplementary Table 2).

The effect of OSA on T2D and its complications

We next tested if OSA modifies the risk for T2D. Among OSA patients this risk was elevated (HR=2.52, p=1.91×10^{-32}, CI=2.16-2.93). After further adjustment for BMI, the risk remained at 1.48-fold (p=9.11×10^{-7}, CI=1.26-1.73) showing a similar effect in both cohorts (Supplementary Figure 2,3). Again, the effect was more prominent in females (adjusted HR = 1.63, CI=1.20-2.23, p=2.20×10^{-3}) than in males (HR = 1.44, CI=1.27-2.21, p=9.62×10^{-5}), (Table 3).

	Number of events/ Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	2435/27161	2.40 [2.03-2.84]	1.53×10^{-24}	1.38 [1.16-1.64]	2.74×10^{-4}
H2000	455/6181	3.18 [2.20-4.59]	7.03×10^{-10}	2.05 [1.42-2.97]	1.41×10^{-4}
Combined	2890/33342	2.52 [2.16-2.93]	1.91×10^{-32}	1.48 [1.26-1.73]	9.11×10^{-7}
Men					
FINRISK	1372/12880	2.21 [1.81-2.69]	2.55×10^{-15}	1.28 [1.05-1.57]	0.017
H2000	257/2772	3.65 [2.44-5.44]	2.23×10^{-10}	2.27 [1.51-3.41]	8.08×10^{-5}
Combined	1629/15652	2.43 [2.04-2.90]	4.16×10^{-23}	1.44 [1.27-2.21]	9.62×10^{-5}
Women					
FINRISK	1063/14281	3.14 [2.28-4.33]	3.12×10^{-12}	1.65 [1.18-2.29]	2.98×10^{-3}
H2000	198/3409	2.16 [0.80-5.87]	0.13	1.48 [0.55-4.02]	0.44
Combined	1261/17690	3.03 [2.23-4.12]	1.25×10^{-15}	1.63 [1.20-2.23]	2.20×10^{-3}

Table 3. Hazard ratios between individuals with OSA and the population for incident type 2 diabetes. The FINRISK raw model is adjusted for age, cohort year, geographical area and gender. The adjusted model is adjusted for BMI in addition to covariates of the raw model. The H2000 raw model is adjusted for geographical area and gender. The adjusted model is adjusted for BMI in addition to covariates of the raw model.

To analyze T2D complications more in detail we included the Botnia cohort into the meta-analysis. H2000 lacked incident diabetic kidney disease events among OSA patients.

Among T2D patients OSA elevated the risk for diabetic kidney disease (HR=2.16, CI=1.40-3.34, p=5.00×10^{-4}; Table 4).

	Number of events / Subjects at risk	Raw model		Adjusted model	
DKD		HR [95% CI]	p	HR [95% CI]	p
FINRISK	147/3932	2.15 [1.27-3.62]	4.10×10^{-3}	1.72[1.01-2.93]	0.044
Botnia	91/1380	2.19 [1.003-4.79]	0.049	1.80 [0.82-3.96]	0.143
Combined	238/5312	2.16 [1.40-3.34]	5.00×10^{-4}	1.75 [1.13-2.71]	0.013
CHD		HR [95% CI]	p	HR [95% CI]	p
FINRISK	640/3710	1.44 [1.07-1.95]	0.016	1.40 [1.04-1.90]	0.028
H2000	152/761	1.46 [0.74-2.82]	0.272	1.46 [0.74-2.89]	0.274
Botnia	236/1253	1.18 [0.60-2.31]	0.630	1.07 [0.54-2.11]	0.840
Combined	1028/5724	1.40 [1.10-1.81]	8.50×10^{-3}	1.36 [1.05-1.76]	0.019

Table 4. Hazard ratios for type 2 diabetes complications. The FINRISK raw models are adjusted for age, cohort year, geographical area and gender. The H2000 raw models are adjusted for age, geographical area and gender. The Botnia raw models are adjusted for age and gender. The adjusted models for DKD are adjusted for BMI and hypertension in all cohorts in addition to covariates of the raw model. The FINRISK adjusted model for CHD is adjusted for HDL and total cholesterol, current cigarette smoking,

BMI, hypertension and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 and Botnia adjusted models for CHD are adjusted for HDL and total cholesterol, current cigarette smoking, BMI and hypertension in addition to covariates of the raw model.

When adjusted for the known risk factors for diabetic kidney disease (BMI and hypertension) the HR was slightly reduced to 1.75 (CI=1.13-2.71, p=0.013), Supplementary Figure 4,5). The effects were similar in both cohorts.

Among T2D patients OSA alone increased the risk for coronary heart disease by 1.40 (CI=1.10-1.81, p=8.50×10^{-3}; Table 4). This was almost unaffected by adding the following risk factors: HDL and total cholesterol, current cigarette smoking, BMI, hypertension, and family history of stroke or myocardial infarction (HR=1.36, CI=1.05-1.76, p=0.019, Supplementary Figure 4,5).

The effect of OSA to mortality risk

We also examined whether OSA was an independent risk factor for all-cause mortality. OSA increased the risk in the raw model (HR=1.18, CI = 1.00-1.40, p = 0.057) and this risk attenuated after adjustment for other risk factors. Among T2D individuals OSA increased the all-cause mortality risk in the raw model (HR=1.40, CI=1.21-1.62, p=2.03×10^{-6}) and after adjustments (HR=1.35, CI=1.06-1.71, p=0.016; Table 5, Supplementary Figure 6).

	Number of events / Subjects at Risk	Raw model		Adjusted model	
General population		HR [95% CI]	p	HR [95% CI]	p
FINRISK	3228/28666	1.08 [0.89-1.31]	0.438	1.01 [0.83-1.22]	0.949
H2000	1286/6498	1.65 [1.14-2.39]	7.91×10^{-3}	1.74 [1.20-2.52]	3.68×10^{-3}
Combined	4514/35164	1.18 [1.00-1.40]	0.057	1.13 [0.95-1.34]	0.161
T2DM		HR [95% CI]	p	HR [95% CI]	p
FINRISK	719/3940	1.37 [1.01-1.84]	0.041	1.23 [0.91-1.67]	0.179
H2000	284/820	1.35 [0.68-2.71]	0.390	1.48 [0.74-2.98]	0.267
Botnia	348/1309	1.84 [1.14-2.99]	1.44×10^{-4}	1.62 [1.00-2.65]	0.052
Combined	1351/6069	1.40 [1.21-1.62]	2.03×10^{-6}	1.35 [1.06-1.71]	0.016

Table 5. Hazard ratios for all-cause mortality among general population and type 2 diabetes individuals. The FINRISK raw models are adjusted for age, cohort year, geographical area and gender. The H2000 raw models are adjusted for age, geographical area and gender. The Botnia raw models are adjusted for age and gender. The FINRISK adjusted model is adjusted for HDL and total cholesterol, current cigarette smoking, BMI, hypertension and family history of stroke or myocardial infarction in addition to covariates of raw model. The H2000 and Botnia adjusted models are adjusted for HDL and total cholesterol, current cigarette smoking, BMI and hypertension in addition to covariates of the raw model. Adjusted models for general population are also adjusted for prevalent type 2 diabetes.

DISCUSSION

Our results from three prospective population-based cohorts found a severe impact of OSA on cardiovascular health, T2D and mortality during a life course. We demonstrate that OSA is an independent risk factor for coronary heart disease and T2D in the general population. Using a combination of population cohorts and a T2D cohort, Botnia, we present evidence for the role of OSA in the risk of T2D complications. To our knowledge this is the largest study of the role of OSA in coronary heart disease and T2D

diseases, combining sample size of over 36,000 individuals with up to 20+ years of follow-up.

These results allow us to draw several conclusions. First, our results illustrate that nationwide health registry data can successfully be used to identify cases of obstructive sleep apnea. Second, the registry-based obstructive sleep apnea cases revealed an increased risk for future coronary heart disease events and T2D. This risk was surprisingly high in females, even after adjusting for risk factors, sheading new light to the potential sex differences in OSA. This finding may provide tools to identify particularly women in high risk of coronary heart disease and T2D. Third, we observed convincing evidence indicating that T2D accumulated to OSA patients independent of obesity.

OSA seems to increase the risk for coronary heart disease to the same extent in diabetic and non-diabetic individuals but the risk of diabetic kidney disease was 75% higher among OSA patients compared to diabetic individuals without OSA diagnosis. All-cause-mortality was increased by OSA among T2D patients but not significantly in the general population. The main cause of mortality was coronary heart disease both in diabetics (33.8%) and in the general population (30.8%).

While previous studies mostly lacked the longitudinal dimension, also our study has limitations: 1) Registry-based ascertainment through hospitalization may miss non-hospitalized cases (false negatives) and 2) treatment information such as CPAP compliance, and 3) OSA severity, emphasizing more severe OSA cases affecting the hazard estimates. However, in spite of these limitations the study design provides

comprehensive estimates of the adverse effects of OSA on coronary heart disease and T2D disorders. This is supported by a recent meta-analysis reporting an RR of 1.49 for the association of OSA and T2D,[28] which is well in line with the results from our study.

It is being increasingly recognized that OSA can accelerate loss of kidney function,[29] but OSA usually presents with other risk factors of kidney function like obesity, T2D and hypertension.[30, 31] It has been hypothesized that there is a bidirectional relationship between OSA and kidney disease, where kidney disease promotes OSA and OSA kidney disease.[29] Our study supports the latter hypothesis that in diabetic patients OSA increased the risk for kidney disease by 1.75-fold after adjustment for other risk factors. This is in line with previous, smaller studies.[19, 29]

An important advantage of our large sample size, was that we could investigate gender differences in the coronary heart disease and T2D risk associated with OSA. While we did not observe a significantly higher risk in females than in males, our data opposite to previous studies clearly show that the severe outcome of OSA is as severe in females as in men (if not more severe).[3, 32] It is possible explanation for this finding may be delayed diagnosis of OSA in women compared with men.

Taken together, our longitudinal study with up to 523,372 person years of follow-up demonstrates that OSA is an independent risk factor not only for coronary heart disease and T2D but also markedly increase risk for diabetic kidney disease. This emphasizes the need to search for signs of OSA in T2D patients with rapid progression of T2D and evaluate whether this progression can be halted by CPAP therapy.

NOTES:

We would like to thank Sari Kivikko, Mervi Kinnunen, and Elina Kilpeläinen for management assistance. The FINRISK data used for the research were obtained from THL Biobank and the Health 2000 data from THL. The skillful assistance of the Botnia Study Group is gratefully acknowledged. We thank all study participants and their advisers for their generous participation in the FINRISK, the Health 2000 and the Botnia studies.

Contributions: TP, AP and SR conceived the study and designed the study protocol. SS conducted the literature review, statistical analysis and drafted the manuscript. ASH contributed statistical analysis and phenotyped study samples. VS acquired the FINRISK data, TT and LG acquired the Botnia data and SK acquired the Health 2000 data. SS, TP, SR, AP, ASH, LG, TT, AM, VS, SK and AB reviewed the manuscript for intellectual content, made revisions as needed and approved the final version for publication. TP, SR and AP supervised the study.

Funding: This work was supported by Finnish Woman Dentists' Association, the Finnish Dental Society Apollonia, the Helsinki University Central Hospital Research Funds (HUS 369/2017), Academy of Finland Center of Excellence in Complex Disease Genetics (312062), Academy of Finland (251217 and 285380), The Finnish Foundation for

Cardiovascular Research, the Sigrid Juselius Foundation and HiLIFE Fellows grants 2017-2020. The sources of funding had no role in study design, data collection, analyses, interpretation, and decision to submit the article for publication.

FINRISK surveys have been funded mainly by budgetary funds of the National Institute for Health and Welfare. Additional funding has been obtained as research grants from the Finnish Academy and several domestic foundations. VS was supported by the Finnish Foundation for Cardiovascular Research.

The Health 2000 Study is funded by the National Institute for Health and Welfare (THL), the Finnish Centre for Pensions (ETK), The Social Insurance Institution of Finland (KELA), The Local Government Pensions Institution (KEVA) and other organizations listed on the website of the survey (http://www.terveys2000.fi).

The Botnia and The PPP-Botnia studies (L.G., T.T.) have been financially supported by grants from Folkhälsan Research Foundation, the Sigrid Juselius Foundation, The Academy of Finland (grants no. 263401, 267882, 312063 to LG, 312072 to TT), Nordic Center of Excellence in Disease Genetics, EU (EXGENESIS, EUFP7-MOSAIC FP7-600914), Ollqvist Foundation, Swedish Cultural Foundation in Finland, Finnish Diabetes Research Foundation, Foundation for Life and Health in Finland, Signe and Ane Gyllenberg Foundation, Finnish Medical Society, Paavo Nurmi Foundation, Helsinki University Central Hospital Research Foundation, Perklén Foundation, Närpes Health Care Foundation and Ahokas Foundation. The study has also been supported by the Ministry of Education in Finland, Municipal Heath Care Center and Hospital in Jakobstad and Health Care Centers in Vasa, Närpes and Korsholm.

No Competing Interests: *All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.*

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Ethical approval: FINRISK data is stored in the THL Biobank which distributes it to researchers on the basis of written applications. The Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital District has approved the THL Biobank with the decision # 238/13/03/00/2014. H2000 Study protocol is approved by the Ethical Committee of the National Public Health Institute (decision number 8/99). The Botnia/PPP Botnia Study protocols were approved by the Ethics Committee of the Helsinki University Central Hospital, Finland, with the decision #574/E5/03.

Data sharing: Data has been acquired from THL Biobank and is obtainable through National Institute of Welfare, Finland. Additional information https://thl.fi/en/web/thl-biobank.

REFERENCES:

1 Kapur V, Strohl KP, Redline S, et al. Underdiagnosis of sleep apnea syndrome in U.S. communities, *Sleep Breath* 2002;6:49-54 doi:10.1007/s11325-002-0049-5 [doi] [published Online First: Jun].

2 Wang X, Bi Y, Zhang Q, et al. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013;18:140-6 doi:https://dx.doi.org/10.1111/j.1440-1843.2012.02267.x [published Online First: Jan].

3 Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-60 doi:https://dx.doi.org/10.1161/CIRCULATIONAHA.109.901801 [published Online First: Jul 27].

4 Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population, *Lancet* 1984;2:1005-8 doi:S0140-6736(84)91107-3 [pii] [published Online First: Nov 3].

5 Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension, *Am Heart J* 1984;108:373-6 [published Online First: Aug].

6 Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest* 2014;146:982-90 doi:https://dx.doi.org/10.1378/chest.13-2403 [published Online First: Oct].

7 Varvarigou V, Dahabreh IJ, Malhotra A, et al. A review of genetic association studies of obstructive sleep apnea: field synopsis and meta-analysis, *Sleep* 2011;34:1461-8 doi:10.5665/sleep.1376 [doi] [published Online First: Nov 1].

8 Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;31:1071-8 [published Online First: Aug].

9 Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *American Journal of Respiratory & Critical Care Medicine* 2002;166:159-65 [published Online First: Jul 15].

10 Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study, *The Lancet* 2005;365:1046-53 doi:https://doi-org.libproxy.helsinki.fi/10.1016/S0140-6736(05)71141-7 [published Online First: 3/19–25].

11 Beck MK, Westergaard D, Jensen AB, et al. Temporal Order of Disease Pairs Affects Subsequent Disease Trajectories: the Case of Diabetes and Sleep Apnea, *Pac Symp Biocomput* 2016;22:380-9 doi:9789813207813_0036 [pii].

12 Botros N, Concato J, Mohsenin V, et al. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009;122:1122-7 doi:https://dx.doi.org/10.1016/j.amjmed.2009.04.026 [published Online First: Dec].

13 Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. *Thorax* 2009;64:834-9 doi:https://dx.doi.org/10.1136/thx.2009.115105 [published Online First: Oct].

14 Kendzerska T, Gershon AS, Hawker G, et al. Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med* 2014;190:218-25 doi:https://dx.doi.org/10.1164/rccm.201312-2209OC [published Online First: Jul 15].

15 Reichmuth KJ, Austin D, Skatrud JB, et al. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005;172:1590-5 doi:https://dx.doi.org/10.1164/rccm.200504-637OC [published Online First: Dec 15].

16 Ozol D, Carlioglu A, Karamanli H, et al. Influence of snoring on microalbuminuria in diabetic patients. *Sleep Breath* 2011;15:295-300 doi:https://dx.doi.org/10.1007/s11325-010-0380-1 [published Online First: Sep].

17 Leong WB, Nolen M, Thomas GN, et al. The impact of hypoxemia on nephropathy in extremely obese patients with type 2 diabetes mellitus. *J Clin Sleep Med* 2014;10:773-8 doi:https://dx.doi.org/10.5664/jcsm.3870 [published Online First: Jul 15].

18 Hwu DW, Lin KD, Lin KC, et al. The association of obstructive sleep apnea and renal outcomes-a systematic review and meta-analysis, *BMC Nephrol* 2017;18:313,017-0731-2 doi:10.1186/s12882-017-0731-2 [doi] [published Online First: Oct 16].

19 Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes Care* 2013;36:3718-25 doi:https://dx.doi.org/10.2337/dc13-0450 [published Online First: Nov].

20 Borodulin K, Vartiainen E, Peltonen M, et al. Forty-year trends in cardiovascular risk factors in Finland, *Eur J Public Health* 2015;25:539-46 doi:10.1093/eurpub/cku174 [doi] [published Online First: Jun].

21 Kattainen A, Salomaa V, Harkanen T, et al. Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s, *Eur Heart J* 2006;27:296-301 doi:ehi630 [pii] [published Online First: Feb].

22 Groop L, Forsblom C, Lehtovirta M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects, *Diabetes* 1996;45:1585-93 [published Online First: Nov].

23 Isomaa B, Forsen B, Lahti K, et al. A family history of diabetes is associated with reduced physical fitness in the Prevalence, Prediction and Prevention of Diabetes (PPP)-Botnia study, *Diabetologia* 2010;53:1709-13 doi:10.1007/s00125-010-1776-y [doi] [published Online First: Aug].

24 Tolonen H, Salomaa V, Torppa J, et al. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil* 2007;14:380-5 doi:https://dx.doi.org/10.1097/01.hjr.0000239466.26132.f2 [published Online First: Jun].

25 Pajunen P, Koukkunen H, Ketonen M, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease, *Eur J Cardiovasc Prev Rehabil* 2005;12:132-7 doi:00149831-200504000-00007 [pii] [published Online First: Apr].

26 Laitinen LA, Anttalainen U, Pietinalho A, et al. Sleep apnoea: Finnish National guidelines for prevention and treatment 2002-2012, *Respir Med* 2003;97:337-65 [published Online First: Apr].

27 Anonymous . https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf.

28 Anothaisintawee T, Reutrakul S, Van Cauter E, et al. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis, *Sleep Med Rev* 2016;30:11-24 doi:S1087-0792(15)00146-X [pii] [published Online First: Dec].

29 Abuyassin B, Sharma K, Ayas NT, et al. Obstructive Sleep Apnea and Kidney Disease: A Potential Bidirectional Relationship? *J Clin Sleep Med* 2015;11:915-24 doi:10.5664/jcsm.4946 [doi] [published Online First: Aug 15].

30 Tada T, Kusano KF, Ogawa A, et al. The predictors of central and obstructive sleep apnoea in haemodialysis patients, *Nephrol Dial Transplant* 2007;22:1190-7 doi:gfl748 [pii] [published Online First: Apr].

31 Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences, *Nutr Metab Cardiovasc Dis* 2007;17:233-40 doi:S0939-4753(06)00266-3 [pii] [published Online First: Mar].

32 Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study, *PLoS Med* 2009;6:e1000132 doi:10.1371/journal.pmed.1000132 [doi] [published Online First: Aug].

Figure legends

Figure 1. Distributions of age at OSA diagnosis (mean 55.31 years) (A) and significant differences in BMI ($p = 3.49\times10^{-96}$) (B), systolic blood pressure ($p = 7.78\times10^{-3}$) (C) and HDL ($p = 8.98\times10^{-53}$) (D) among OSA patients and non-OSA individuals in FINRISK.

Supplementary Figure 1. Kaplan-Meier curves for coronary heart disease events with OSA vs. without OSA. The model for coronary heart disease is adjusted for cohort, age, gender, current smoking, total cholesterol, HDL, hypertension, BMI and prevalent type 2 diabetes.

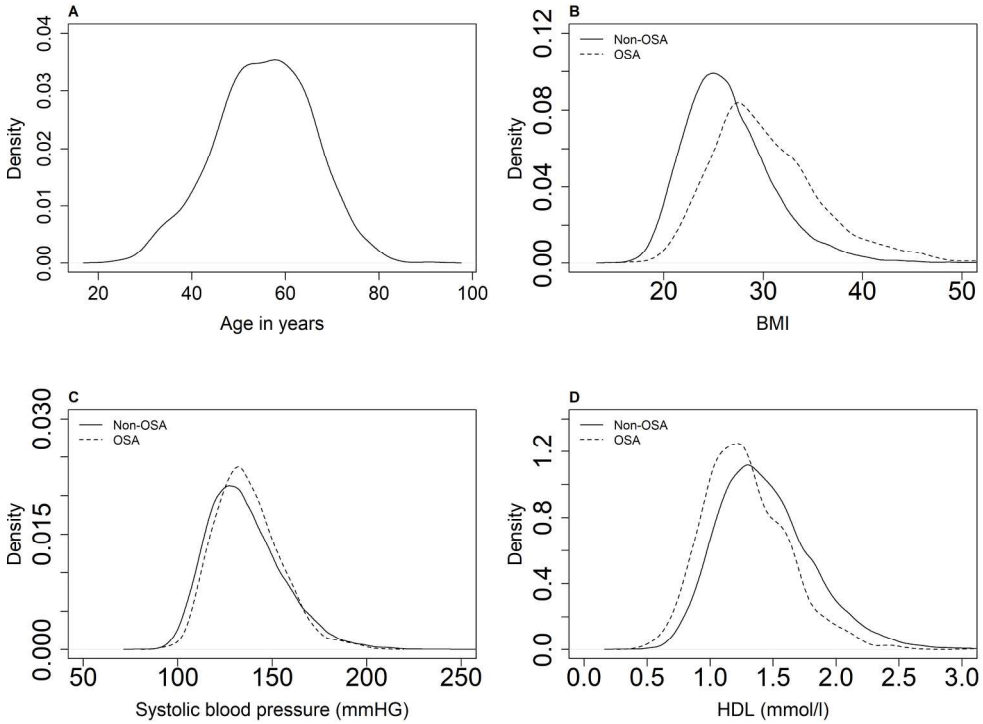
Supplementary Figure 2. Flow-chart showing the process for arriving at the final sample sizes (CHD=coronary heart disease, T2D=type 2 diabetes).

Supplementary Figure 3. Kaplan-Meier curves for type 2 diabetes with OSA vs. without OSA. The model for type 2 diabetes is adjusted for cohort, age, gender and BMI.

Supplementary Figure 4. Kaplan-Meier curves of diabetic kidney disease and coronary heart disease events among type 2 diabetes patients with OSA vs. without OSA. The model for diabetic kidney disease is adjusted for cohort, age, gender, hypertension and BMI. The model for coronary heart disease is adjusted for cohort, age, gender, current smoking, total cholesterol, HDL, hypertension and BMI.

Supplementary Figure 5. Flow-chart showing the process for arriving at the final sample sizes (DKD=diabetic kidney disease, CHD=coronary heart disease).

Supplementary Figure 6. Kaplan-Meier survival curves for all-cause mortality in the general population and in type 2 diabetes individuals with OSA vs. without OSA. The models are adjusted for cohort, age, gender, HDL and total cholesterol, current cigarette smoking, BMI and hypertension. The model for general population is also adjusted for prevalent type 2 diabetes.



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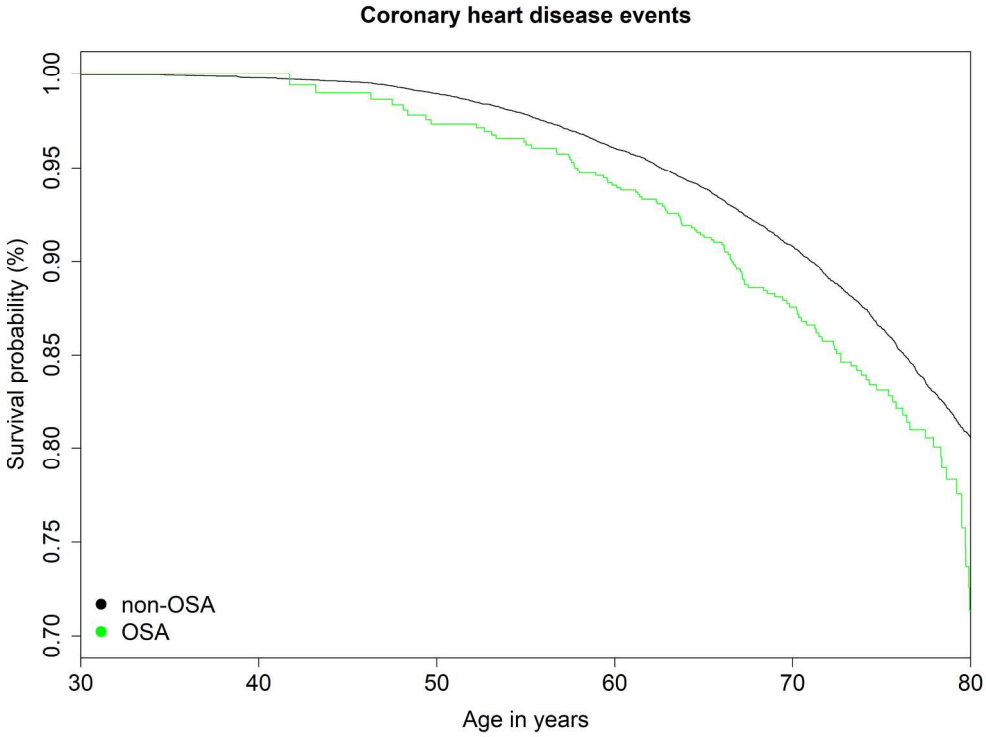

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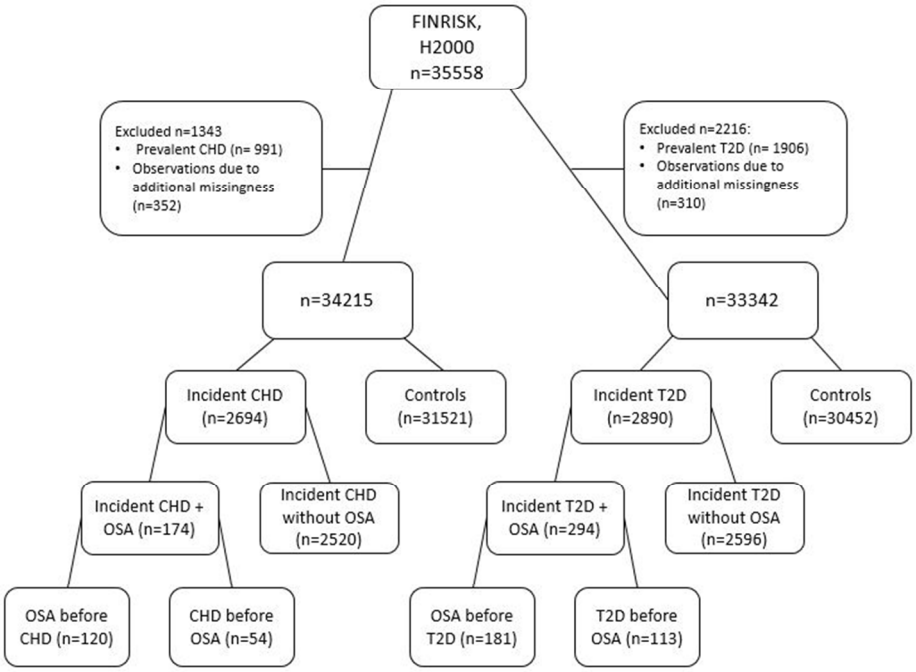

Supplementary Figure 2. Flow-chart showing the process for arriving at the final sample sizes (CHD=coronary heart disease, T2D=type 2 diabetes).

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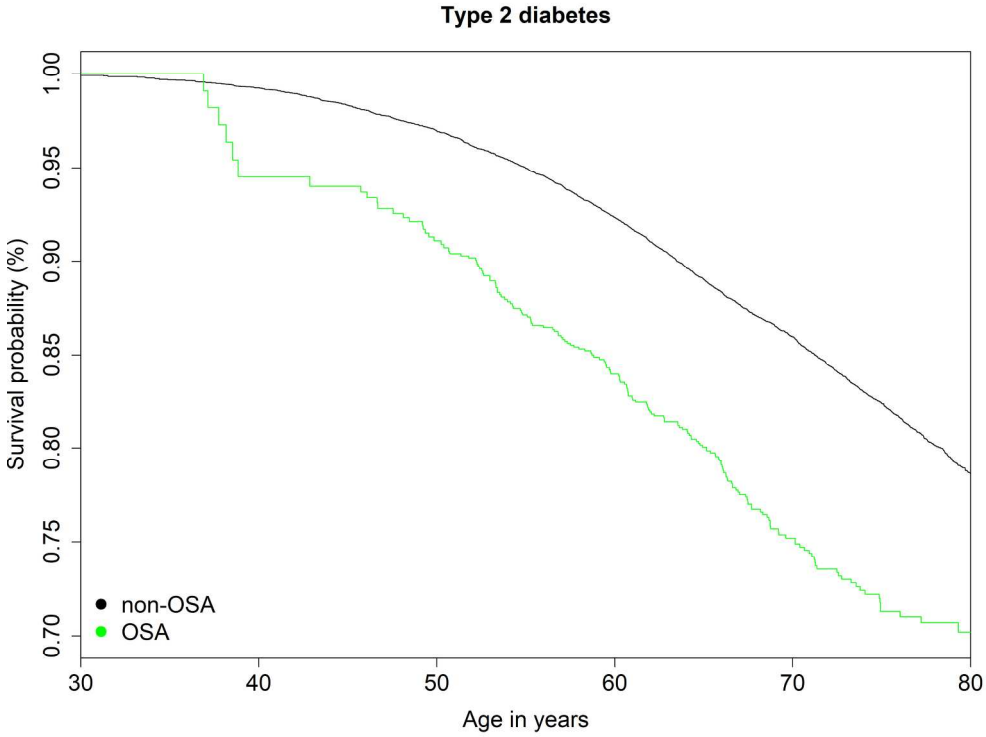

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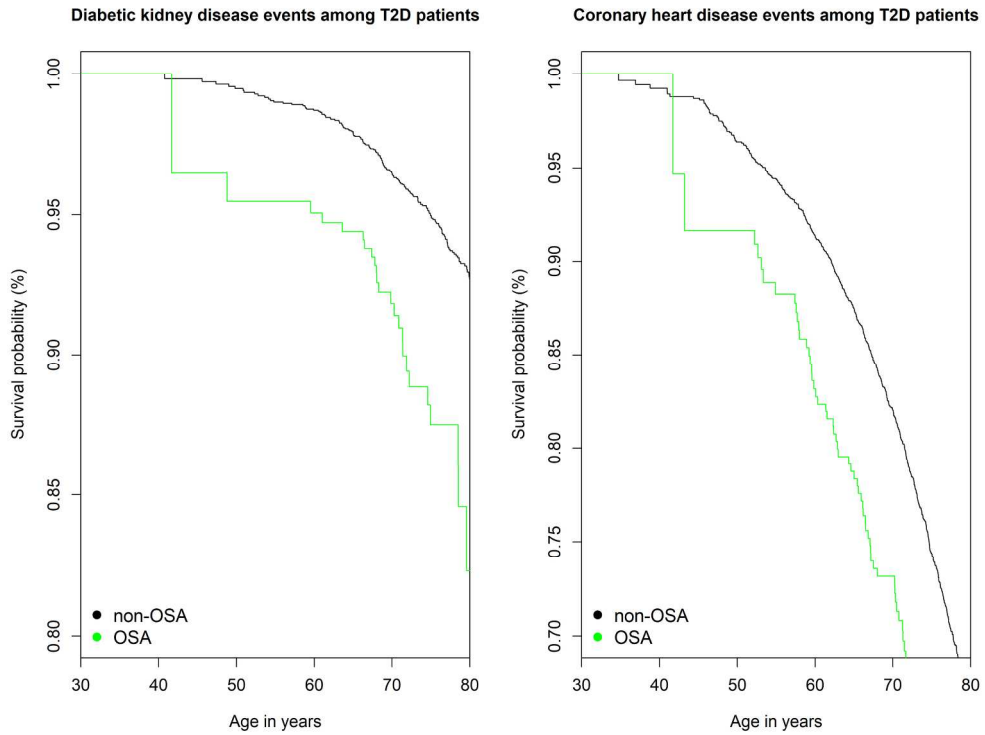

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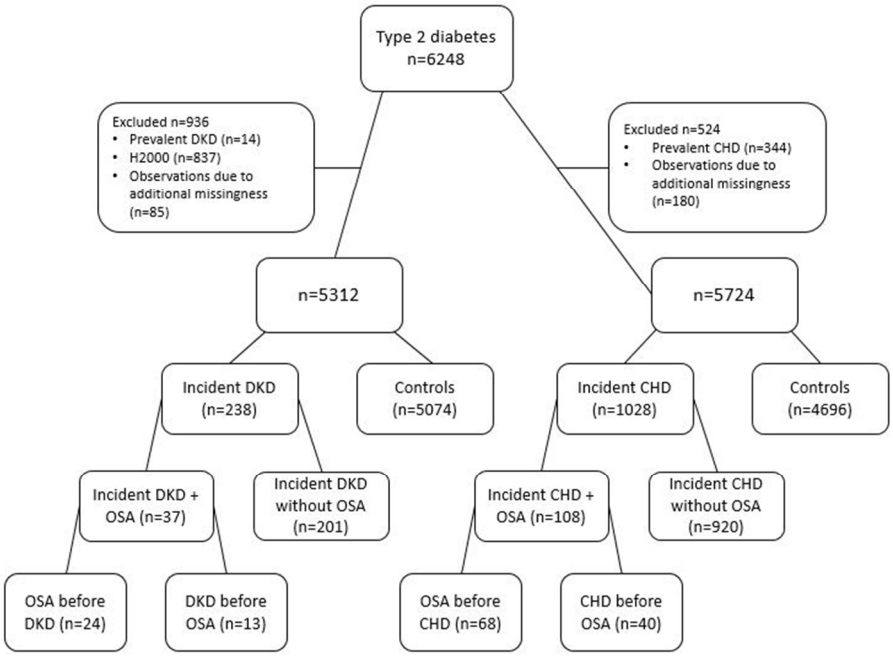

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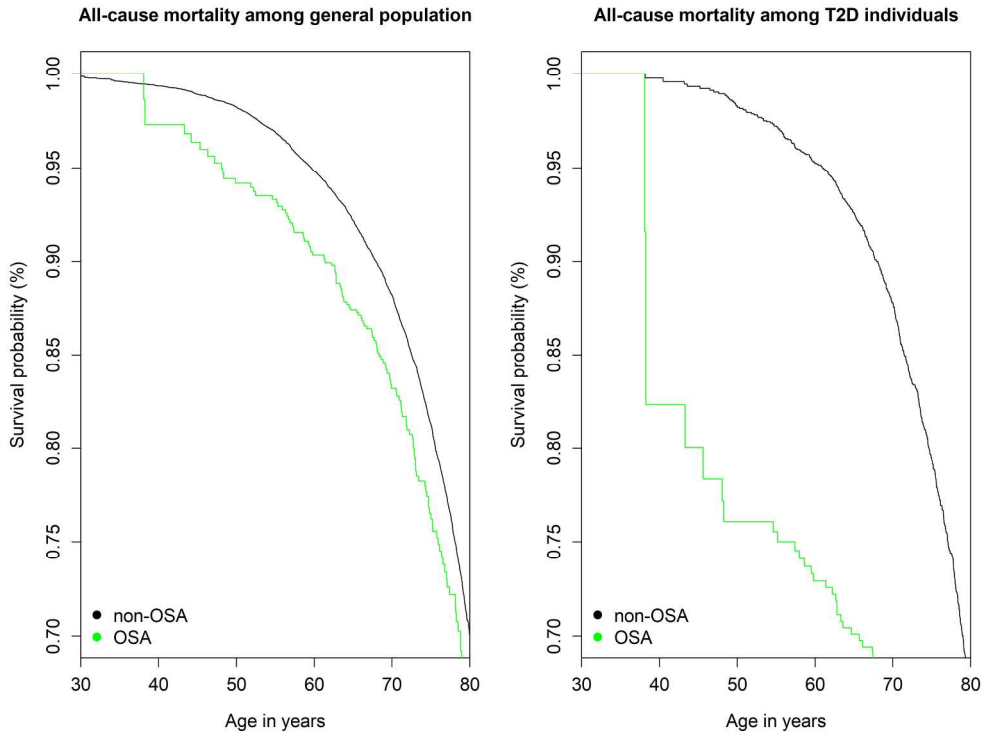

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Supplementary Material

	ICD 8	ICD 9	ICD 10
OSA	-	3472A	G47.3
CHD	410|4110	410|4110	I200|I21|I22
STR	431|433|434|436	431|4330A|4331A|4339A|4340A|4341A|4349A|436	I61|I63|I64
T2DM	250	250	E11|E12|E13|E14
DKD	58200|25004	585|2503A|2503B	N18|N19|E102|E112

Supplementary Table 1. ICD-codes (Finnish national version) for each endpoint definition. OSA=obstructive sleep apnea. CHD=coronary heart disease. STR=stroke. T2DM= type 2 diabetes. DKD=diabetic kidney disease.

	Number of events/ Subjects at risk	Raw model		Adjusted model	
		HR [95% CI]	p	HR [95% CI]	p
FINRISK	1285/28367	0.99 [0.73-1.36]	0.981	0.92 [0.67-1.26]	0.602
H2000	345/6350	1.41 [0.71-2.76]	0.320	1.44 [0.73-2.84]	0.288
Combined	1630/34717	1.06 [0.80-1.41]	0.689	0.99 [0.75-1.33]	0.981

Supplementary Table 2. Hazard ratios between individuals with OSA and the population for incident stroke events. The FINRISK raw model is adjusted with age, cohort year, geographical area and gender. The adjusted model is adjusted with HDL and total cholesterol, current cigarette smoking, BMI, hypertension, prevalent type 2 diabetes and family history of stroke or myocardial infarction in addition to covariates of the raw model. The H2000 raw model is adjusted with geographical area. The adjusted model is adjusted with HDL and total cholesterol, current cigarette smoking, BMI, hypertension and prevalent type 2 diabetes in addition to covariates of the raw model.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2-5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19-20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.