METHODS

Participants and Study Design

The Osteoporotic Fractures in Men Study (MrOS) is a multi-center prospective observational study designed to determine risk factors for osteoporosis, fractures and prostate cancer in older men. The MrOS cohort was designed to be representative of community dwelling, ambulatory men aged 65 years or older. Participants met the following criteria: at least 65 years of age, able to consent, able to walk without the assistance of another person, did not have bilateral hip replacement, able to provide self-reported information, expected to reside near the clinical site for the duration of the study, and had no condition that in the judgment of the site investigator would make the individual unable to participate or survive the duration of the study, or for whom participation would be inappropriate. A total of 5,994 men were recruited between March 2000 to April 2002 from six centers in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; the Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA).[1,2] Study protocols were approved by the Institutional Review Board at each site (University of Alabama at Birmingham Institutional Review Board for Human Use, F030725004; Human Research Protection Program at the University of Minnesota, 0307M50161; Stanford University, Protocol ID 13647; University of Pittsburgh Institutional Review Board, IRB980305; Oregon Health & Science University Institutional Review Board, IRB00001296; University of California, San Diego Human Research Protections Program, Project #071795), and all participants provided written informed consent.

The Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study was an ancillary study with a target recruitment number of 3,000 men from the parent MrOS Study. The study was designed to test several hypotheses: 1) to characterize the associations between sleep disruption and subsequent cardiovascular disease events during 3.5 years of follow-up, 2) to determine if sleep disturbances are associated with an increased risk of total and cause-specific mortality in older men, 3) to test whether sleep disturbances are associated with increased risk of falls and decreased physical function, 4) to test whether sleep disturbances are associated with impaired cognitive function in older men, and 5) to test whether sleep disorders are associated with bone density and fracture risk in older men. To participate in the MrOS Sleep Study, men had to agree to a comprehensive sleep assessment that included wrist actigraphy and a single overnight in-home polysomnography study. The initial Sleep Visit (VS) for the MrOS Sleep

Study occurred on average 3.4 ± 0.5 years (range 1.9 – 4.9) after the baseline examination, between December 2003 and March 2005. A total of 3,135 men from the original cohort completed the MrOS Sleep examination. Of the 2,859 men who did not participate in this ancillary study, 1,997 refused, 349 died before the sleep study visit, 150 were ineligible due to exclusion criteria such as use of mechanical devices during sleep, including positive airway pressure devices, oral appliances for snoring or sleep apnea, or oxygen therapy, 324 were not screened because recruitment goals were met, and 39 terminated the MrOS study before the sleep study was offered.

The second MrOS Sleep Visit (VS2) occurred between November 2009 and March 2012 at the six MrOS centers. All participants who remained active in the MrOS study and had usable polysomnography and actigraphy data from the baseline Sleep Visit were eligible to be contacted to participate in VS2. A special emphasis was put on minority recruitment for VS2, so all active minority participants with usable polysomnography and actigraphy data from VS were contacted for participation in VS2. Non-minority participants were contacted in random order for enrollment in VS2 until study recruitment goals were met. A total of 1,055 participants were seen as part of VS2 (exceeding recruitment goal of 1,000). All participants completed a comprehensive sleep assessment that included validated sleep questionnaires, an in-clinic interview, a series of clinical measures including weight, height, neck and waist circumference, wrist actigraphy, and a single overnight in-home polysomnography study. Participants also underwent spirometry testing during VS2. Of the 2,080 men who did not participate in VS2, 856 refused, 537 died before the sleep study visit, 288 did not have polysomnography data from the initial sleep visit, 54 were ineligible, 308 were not screened as recruitment goals were met, and 37 terminated the MrOS study before the sleep study was offered.

Of the 1,055 participants seen for VS2, 145 did not have spirometry data (n=41 had poor quality spirometry, n=5 refused, n=40 were ineligible due to recent myocardial infarction, stroke or eye surgery within the past 3 months, n=18 had history of hemoptysis, pneumothorax, or thoracic aneurysm, n=1 had significant difficulty with spirometry in the past, n=33 had physical or medical limitation, n=7 had equipment problem or other issue) and 2 had missing data. We also excluded 23 participants who did not have polysomnography data from VS2. Participants 90 years of age or greater (n=32) were excluded from our primary analyses given no reference values for FEV_1 were available.

Compared to the remainder of participants from the initial MrOS cohort, participants in our study were slightly younger and had modest but significantly lower prevalence of ever smoking, self-reported OAD, and cardiovascular comorbidities, but similar BMI:

Variable	**Overall N=5994**	**Participants not in the present analysis N=5141**	**Participants in the present analysis N=853**	**P value**
Age, years	73.7 ± 5.9	74.1 ± 6.0	70.1 ± 4.1	<0.0001
BMI, kg/m^2	27.4 ± 3.8	27.4 ± 3.9	27.2 ± 3.6	0.1331
Smoking status, n (%)				0.0008
Never	2248 (37.5)	1881 (36.6)	367 (43.0)	
Past	3539 (59.1)	3074 (59.8)	465 (54.5)	
Current	206 (3.4)	185 (3.6)	21 (2.5)	
Self-reported OAD (COPD, bronchitis, emphysema, or asthma), n (%)	640 (10.7)	570 (11.1)	70 (8.2)	0.0116
Diabetes mellitus, n (%)	653 (10.9)	583 (11.3)	70 (8.2)	0.0065
Hypertension, n (%)	2581 (43.1)	2282 (44.4)	299 (35.1)	<0.0001
Myocardial infarction, n (%)	834 (13.9)	758 (14.7)	76 (8.9)	<0.0001
Congestive heart failure, n (%)	317 (5.3)	290 (5.6)	27 (3.2)	0.0028
Stroke, n (%)	344 (5.7)	312 (6.1)	32 (3.8)	0.0007

Categorical variables are presented as number (%). Continuous variables are presented as mean ± SD.

P values for continuous variables from a t-test for normally distributed variables or a Wilcoxon rank-sum test for nonnormally distributed data.

P values for categorical variables from a Chi-square test.

Data from original MrOS Visit.

Compared to the remainder of participants from the initial Sleep Visit who were active at the time of VS2, participants in our study were younger (mean 74.2 vs. 76.5 years), had greater waist circumference (mean 100.3 vs. 98.8 cm), had higher AHI (11.9 vs. 10.8) and lower nocturnal oxygenation, and a greater proportion of participants had poor sleep as assessed by the Pittsburgh Sleep Quality Index (45.3% vs. 39.5%). However, there were similar rates of smoking and self-reported history of obstructive airway disease.

Sleep Studies

The polysomnography recordings were gathered within 1 month of the clinic visit (mean 5.7 ± 9.7 days from visit), with 78% of recordings gathered within 1 week of the clinic visit. The recording montage consisted of C3/A2 and C4/A1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (by nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, lead I electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Trained certified staff members performed home visits for setup of the sleep study units. The studies were scored at the Sleep Reading Center (Boston, MA) by four trained research polysomnologists using previously described approaches.[3] Polysomnography data quality was excellent, with a failure rate of less than 3% and more than 77% of studies graded as being of excellent or outstanding quality. Quality codes for signals and studies were graded using previously described approaches, including coding of the duration of artifact-free data per channel and overall study quality (reflecting the combination of grades for each channel).[3] In addition to weekly informal review of studies and scoring exercises, each certified scoring staff participated in reliability assessments approximately every 6 months for the duration of the MrOS Sleep Study. The inter- and intra-scorer reliability for the apnea-hypopnea index exceeded 0.95. Apneas were classified as obstructive or central depending on the presence or absence of inspiratory effort on the thoracic and abdominal respiratory inductance plethysmography. The arousal index was defined as the number of arousals per hour of sleep. Sleep latency was defined as the time from lights out to the first three epochs of stage 1 or first epoch of any other stage of sleep. Total sleep time was calculated as the time per night spent sleeping while in bed after lights-out. Sleep efficiency was defined as the percent of the total sleep time divided by the time from lights-out until the final morning awakening.

Spirometry

Spirometry was performed using a SensorMedics model 1022 dry-rolling seal volume spirometer (SensorMedics; Yorba Linda, CA) during Sleep Visit 2. The spirometer was fitted by OMI (Occupational Marketing, Inc.; Houston, TX) with a digital volume encoder, temperature sensor, and RS232 serial computer interface. OMI spirometry software version 5.05.28 was used. Daily leak checks and calibrations checks were conducted with a calibrated 3-L syringe. Participants were instructed to refrain from use of tobacco for 2 hours before testing, or use of short acting bronchodilators for 4 hours before testing, and attempts were made to test at least 2 weeks after a respiratory illness ended. Centrally trained and certified staff members performed the testing according to American Thoracic Society (ATS) recommendations.[4] The goal of the spirometry test was to obtain a minimum of 3 acceptable Forced Vital Capacity (FVC) maneuvers that met ATS acceptability criteria and are reproducible (FVC within 150 mL of maximal). To obtain 3 acceptable curves, the participant performed a minimum of 5 maneuvers. If there were less than 3 acceptable curves, the participant may have attempted a maximum of 8 maneuvers. The start of the test and end of the test were also assessed for acceptability. Data collected was transferred to a central Reading Center (Boston, MA) for centralized review and quality control using ATS criteria.[4] The largest value from the 3 acceptable FVC maneuvers was selected for FEV_1 and FVC. The quality control and curve selection was reviewed and confirmed by a board certified pulmonologist (Dr. Susan Redline). Of the 910 spirometry records, 93% had at least 2 forced maneuvers that met ATS acceptability criteria.

FEV_1 and FVC % predicted were calculated using predicted normal values calculated based on the characteristics of gender, age, race, height, and weight.[5,6] The standard reference does not include reference values for the Asian race. To calculate the predicted values for Asians, a correction factor of 0.94 was applied to the formula used for Caucasians.[6] Recent work has suggested that a correction factor of 0.88 is preferable for Asians,[7] however, the current guidelines at the time of data collection was to use the correction factor of 0.94. No normal values are available for men 90 years of age or greater (n=32). We conducted additional sensitivity analyses using extrapolated values of FEV_1% predicted for those 90 years of age or older. These did not appreciably influence study findings (data not shown).

Other Measures

Self-administered questionnaires were used at the time of VS2 to ascertain participant demographic and lifestyle information and their personal and family medical history, including self-reported asthma, chronic obstructive pulmonary disease, bronchitis, or emphysema. Participants also reported tobacco use (current, past, or never) and race/ethnicity (Caucasian/White, African American/Black, Asian, Hispanic/Other). Interviews and examinations by trained study staff members included measures of functional status and anthropometric data. Body weight (kg) was measured with a calibrated balance beam or digital scale that was calibrated with standard weights, height (cm) was measured on a wall-mounted Harpenden stadiometer (Holtain Ltd, Crymych, Dyfed, Wales). Waist and neck circumference were measured using standard methods.[8]

REFERENCES:

1. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. Contemp Clin Trials 2005;26:569-85.

2. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials 2005;26:557-68.

3. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 1998;21:759–67.

4. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

5. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.

6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.

7. Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society recommended spirometry reference values in a multiethnic sample of adults: the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. Chest 2010;137:138-45.

8. Callaway CW, Chumlea WC, Bouchard C, et al. Circumferences. In: Lohman TG, Roche AF, Martorell R, editors. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics Books; 1988. pp. 41–5.

Table S1—Baseline characteristics of the study population by OAD [GOLD] severity.

		OAD (FEV_1/FVC ratio <0.7)			
	No OAD	**Mild**	**Moderate**	**Severe**	**P value**
		(FEV_1 ≥80% predicted)	(50% ≤FEV_1 <80% predicted)	(30% ≤FEV_1 <50% predicted)	
	(n=493)	**(n=249)**	**(n=97)**	**(n=14)**	
Demographics					
Age, years	80.2 ± 3.9	81.5 ± 4.5	81.0 ± 4.1	80.2 ± 2.4	0.0008
Race, n (%)					
Caucasian	421 (85.4)	225 (90.4)	82 (84.5)	12 (85.7)	0.2611
African-American	17 (3.5)	8 (3.2)	7 (7.2)	1 (7.1)	
Asian	27 (5.5)	11 (4.4)	3 (3.1)	--	
Hispanic/Other	28 (5.7)	5 92.0)	5 (5.2)	1 (7.1)	
BMI, kg/m^2	27.3 ± 3.7	26.0 ± 3.6	27.1 ± 4.5	27.3 ± 5.2	0.0002
Waist circumference, cm	100.8 ± 10.5	98.0 ± 10.0	102.0 ± 11.3	105.5 ± 12.7	0.0003
Neck circumference, cm	38.9 ± 2.7	38.5 ± 2.6	39.7 ± 3.1	39.2 ± 3.7	0.0038
Smoking status, n (%)					
Never	257 (52.2)	117 (47.0)	28 (28.9)	4 (28.6)	<0.0001
Past	228 (46.3)	131 (52.6)	67 (69.1)	8 (57.1)	
Current	7 (1.4)	1 (0.4)	2 (2.1)	2 (14.3)	
Self-reported asthma, n (%)	18 (3.7)	17 (6.8)	20 (20.6)	6 (42.9)	<0.0001
Self-reported obstructive lung disease (COPD, bronchitis, or emphysema), n (%)	28 (6.0)	24 (10.4)	20 (24.1)	7 (53.9)	<0.0001
Pittsburgh Sleep Quality Index >5, n (%)	214 (43.5)	89 (35.7)	49 (50.5)	5 (38.5)	0.0599
Epworth Sleepiness Scale >10, n (%)	87 (17.7)	44 (17.7)	21 (21.7)	3 (21.4)	0.7959
Spirometry Measures					
FEV_1/FVC, %	76.3 ± 4.6	65.0 ± 4.4	59.2 ± 8.6	48.7 ± 8.3	<0.0001
FEV_1, L	2.7 ± 0.5	2.6 ± 0.5	1.8 ± 0.4	1.2 ± 0.2	<0.0001
FEV_1 % predicted, %	105 ± 19	101 ± 15	68 ± 8	43 ± 5	<0.0001
FVC, L	3.6 ± 0.7	4.0 ± 0.7	3.1 ± 0.6	2.5 ± 0.3	<0.0001
FVC % predicted, %	98 ± 18	110 ± 15	83 ± 13	64 ± 7	<0.0001
Polysomnography Sleep Measures					
Sleep latency, min	20 (11, 33)	18 (11, 36)	23 (9.5, 36.5)	42 (19, 67)	0.1560
Total sleep time, min	342.8 ± 74.2	342.9 ± 81.6	348.4 ± 86.6	349.1 ± 58.7	0.9166
Sleep efficiency, %	74.0 ± 12.8	74.6 ± 13.4	74.8 ± 13.4	78.0 ± 11.1	0.6531
Arousal index	23.7 ± 12.6	24.0 ± 13.0	21.6 ± 13.1	21.0 ± 12.7	0.4177
Sleep time spent in REM, %	19.4 ± 7.0	19.9 ± 7.1	18.4 ± 7.8	15.8 ± 7.8	0.0885
Sleep time in stage 3 and 4 sleep, %	4.7 (1.4, 10.4)	4.3 (0.88, 10.2)	3.4 (0.6, 7.5)	4.9 (2.8, 7.7)	0.3748
AHI, events/h					
Mean ± SD	13.7 ± 14.5	10.8 ± 12	9.5 ± 12.2	3.8 ± 4.2	<0.0001
Median (IQR)	8.4 (2.9, 19.9)	6.3 (2.4, 15.9)	6.2 (1.4, 11.1)	3.2 (0.4, 5.3)	<0.0001
REM AHI, events/h	12.1 (3.8, 24.2)	7.9 (2.3, 20.8)	8.7 (1.4, 20.7)	5.5 (2.1, 13.7)	0.0120
Sleep time with SpO_2 <90%, %	0.9 (0.1, 5.0)	0.7 (0.0, 3.0)	0.8 (0.0, 6.4)	0.2 (0.0, 4.8)	0.4136
Average SpO_2 in REM, %	93.3 ± 2.2	93.5 ± 2.0	02.8 ± 2.7	92.9 ± 2.8	0.1091
Average SpO_2 in NREM, %	93.8 ± 1.7	93.9 ± 1.6	93.6 ± 2.2	93.6 ± 2.0	0.6627
Average hypopnea length, sec	22.9 ± 5.3	23.1 ± 5.7	21.4 ± 4.8	18.5 ± 3.4	0.0009
Average apnea length, sec	23.2 (12.6, 29.7)	24.2 (17.7, 31.4)	18.6 (0, 27.2)	13 (0, 26.9)	0.0003

Categorical variables are presented as number (%). Continuous variables are presented as mean ± SD or median (interquartile range). P values for continuous variables from an ANOVA for normally distributed variables or a Kruskal Wallis test for nonnormally distributed data. P values for categorical variables from a Chi-square test for homogeneity. *OAD defined using National Clinical Guidance Centre (NICE) definition (FEV_1/FVC <0.70 and FEV_1 <80% predicted). AHI, apnea-hypopnea index; BMI, body mass index (kg/m^2); COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second (L); FVC, forced vital capacity (L); NREM, non-rapid eye movement sleep; OAD, obstructive airway disease; REM, rapid eye movement sleep; SpO_2, average oxygen saturation.

Table S2—Baseline characteristics of the study population stratified by sleep apnea severity

	Sleep Apnea		P value
	AHI <15 (n=606)	**AHI ≥15 (n=247)**	
Demographics			
Age, years	80.5 ± 4.1	81.1 ± 4.1	0.0727
Race, n (%)			
Caucasian	523 (86.3)	217 (87.9)	0.8728
African-American	23 (3.8)	10 (4.1)	
Asian	31 (5.1)	10 (4.1)	
Hispanic/Other	29 (4.8)	10 (4.1)	
BMI, kg/m^2	26.4 ± 3.6	28.1 ± 4.0	<0.0001
Waist circumference, cm	99.1 ± 10.3	103.11 ± 10.8	<0.0001
Neck circumference, cm	38.6 ± 2.6	39.5 ± 3.0	<0.0001
Smoking status, n (%)			
Never	296 (48.9)	110 (44.5)	0.0301
Past	297 (49.1)	137 (55.5)	
Current	12 (2.0)	0 (0)	
Self-reported asthma, n (%)	53 (8.8)	8 (3.2)	0.0046
Self-reported obstructive lung disease (COPD, bronchitis, or emphysema), n (%)	60 (10.7)	19 (8.2)	0.2806
OAD*, n (%)	95 (15.7)	16 (6.5)	0.0003
Pittsburgh sleep quality index >5, n (%)	241 (39.9)	116 (47.0)	0.0581
Epworth sleepiness scale >10, n (%)	104 (17.2)	51 (20.7)	0.2311
Spirometry Measures			
FEV_1/FVC, %	69.7 ± 9.1	72.7 ± 7.7	<0.0001
FEV_1, L	2.5 ± 0.6	2.6 ± 0.6	0.6313
FEV_1 % predicted, %	98 ± 22	101 ± 20	0.0888
FVC, L	3.7 ± 0.8	3.5 ± 0.7	0.0558
FVC % predicted, %	99 ± 19	98 ± 19	0.3283
Polysomnography Sleep Measures			
Sleep latency, min	19.0 (11.0, 34.0)	21.0 (11.0, 34.5)	0.4953
Total sleep time, min	350.6 ± 72.9	326.3 ± 85.7	0.0001
Sleep efficiency, %	75.7 ± 12.4	71.0 ± 13.9	<0.0001
Arousal index, events/h	21.1 ± 11.7	29.7 ± 13.3	<0.0001
Sleep time in stage 3 and 4 sleep, %	4.9 (1.3, 10.5)	3.6 (0.8, 9.2)	0.0069†
Sleep time spent in REM, %	20.0 ± 6.8	17.7 ± 7.7	<0.0001
Sleep time with SpO_2 <90%, %	0.2 (0, 1.9)	5.0 (1.6, 11.2)	<0.0001
Average SpO_2 in REM, %	93.7 ± 2.0	92.2 ± 2.3	<0.0001
Average SpO_2 in NREM, %	94.0 ± 1.7	93.3 ± 1.7	<0.0001
Average hypopnea length, sec	21.8 ± 4.7	25.0 ± 6.2	<0.0001
Average apnea length, sec	20.4 (0, 28.2)	27.2 (22.1, 32.3)	<0.0001

Categorical variables are presented as number (%). Continuous variables are presented as mean ± SD for normally distributed data or median (interquartile range) for skewed data.

*OAD defined using National Clinical Guidance Centre (NICE) definition (FEV_1/FVC <0.70 and FEV_1 <80% predicted).

P values for continuous data are from a *t*-test for normally distributed data, Wilcoxon rank sum test for skewed data. P values for categorical data are from a chi-square test.

AHI, apnea-hypopnea index; BMI, body mass index (kg/m^2); COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second (L); FVC, forced vital capacity (L); NREM, non-rapid eye movement sleep; OAD, obstructive airway disease; REM, rapid eye movement sleep; SpO_2, average oxygen saturation.

Table S3—Association of sleep apnea (AHI ≥15) and various types of self-reported history of obstructive airway disease

	Odds Ratio (95% Confidence Interval)	
	Unadjusted	**Adjusted***
Asthma	0.35 (0.16, 0.75)	0.34 (0.15, 0.74)
Chronic bronchitis	1.00 (0.54, 1.87)	0.77 (0.40, 1.50)
Emphysema	0.82 (0.26, 2.58)	0.54 (0.16, 1.83)
COPD	0.60 (0.26, 1.40)	0.44 (0.18, 1.07)
COPD, chronic bronchitis, or emphysema	0.74 (0.43, 1.28)	0.55 (0.31, 0.98)

*Adjusted for age, race, study site, smoking status, body mass index, and neck circumference

AHI, apnea-hypopnea index; COPD, chronic obstructive pulmonary disease

STROBE Checklist

	Item No	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	1343
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1343
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1343
Objectives	3	State specific objectives, including any prespecified hypotheses	1343
Methods			
Study design	4	Present key elements of study design early in the paper	1344
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1344, supplemental material (methods)
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	1344, Figure 1, supplemental material (methods)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	1344
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	supplemental material (methods)
Bias	9	Describe any efforts to address potential sources of bias	1344
Study size	10	Explain how the study size was arrived at	1344, supplemental material (methods)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	1344
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	1344
		(*b*) Describe any methods used to examine subgroups and interactions	1344
		(*c*) Explain how missing data were addressed	1344
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	1344
		(*e*) Describe any sensitivity analyses	1344
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 analyzed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1, supplemental material (methods)
		(c) Consider use of a flow diagram	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, supplemental material Tables S1and S2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarize follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures	Table 1
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	1344, Tables 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	1344, Table 2, Figure 2, supplemental material Table S3
Discussion			
Key results	18	Summarize key results with reference to study objectives	1345, 1346
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	1347-1349
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	1349
Generalizability	21	Discuss the generalizability (external validity) of the study results	1349
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	1351

Reference:

Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007;147:W-163-194.