Nocturnal Hypoxemia and Incident Coronary Artery Disease in Obstructive Sleep Apnea: Results from the Sleep Apnea Patients in Skaraborg Study

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Background: The relationship between obstructive sleep apnea (OSA) and coronary artery disease (CAD) remains controversial. Although observational studies have suggested that OSA is associated with an increased risk of coronary events, substantial confounding and neutral findings from treatment trials have raised uncertainty regarding which aspects of OSA are most strongly linked to CAD risk.

Aims: This study aimed to examine the association between nocturnal hypoxemia, assessed using the oxygen desaturation index (ODI), and incident CAD.

Study Design: Prospective cohort study.

Methods: Adults referred for evaluation of suspected OSA within the sleep apnea patients in Skaraborg study were prospectively followed for the occurrence of incident CAD. Associations between nocturnal hypoxemia, measured using the ODI, and incident CAD were investigated. Apnea-hypopnea index (AHI) categories were also analyzed for comparison. Multivariable Cox proportional hazards regression models were constructed, including models that evaluated AHI and ODI separately as well as simultaneously to determine their independent associations with CAD risk.

Results: The analytic cohort included 2,902 adults (1,012 women and 1,890 men) with a median follow-up duration of 8.7 years, during which 111 incident CAD events were identified. In fully adjusted Cox regression analyses, participants in the highest ODI category (≥ 30 events/h) had a significantly greater risk of incident CAD than those in the lowest category (hazard ratio, 1.99; 95% confidence interval, 1.08-3.65). In contrast, AHI categories were not independently associated with incident CAD. Moreover, when AHI and ODI were simultaneously included in the same model, ODI remained independently associated with incident CAD. In analyses restricted to adults with OSA, the association between ODI and CAD was attenuated and did not reach statistical significance, although the direction and magnitude of the association remained generally consistent with those observed in the primary analysis.

Conclusion: Among adults referred for OSA evaluation, nocturnal hypoxemia assessed using ODI, rather than event-based OSA severity, was associated with incident CAD. However, the absence of independent associations when both ODI and AHI were considered simultaneously suggests substantial overlap between these OSA severity metrics. These findings suggest that hypoxemia-related parameters may provide additional value for coronary risk stratification.

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INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder that is frequently accompanied by cardiometabolic comorbidities, including obesity, hypertension, and diabetes mellitus.[1-4] Over the past two decades, OSA has been associated with an increased risk of cardiovascular disease; however, the strength and causality of this association remain controversial, particularly with respect to coronary artery disease (CAD).[5-9]

Several large observational studies have reported higher rates of coronary events among individuals with OSA.[8,10-12] Nevertheless, interpretation of these findings is complicated by substantial confounding from shared cardiovascular risk factors that are highly prevalent in OSA populations. Even in well-adjusted prospective cohorts, residual confounding remains a major concern, making it difficult to distinguish the independent contribution of sleep-disordered breathing from underlying cardiometabolic risk.[13,14]

Randomized controlled trials evaluating OSA treatment have further challenged the causal interpretation of the relationship between OSA and CAD. Large trials investigating positive airway pressure (PAP) therapy have failed to demonstrate consistent reductions in coronary events despite improvements in sleep-related symptoms and intermediate physiological parameters.[15-18] These neutral findings have prompted renewed interest in whether conventional measures of OSA severity, such as the apnea-hypopnea index (AHI), adequately capture the aspects of sleep-disordered breathing that are most relevant to cardiovascular risk.[19]

Increasing evidence suggests that OSA is a heterogeneous disorder and that event frequency alone may not fully reflect its cardiovascular consequences.[2,20,21] Alternative phenotypic markers, including measures of nocturnal hypoxemia, have therefore been proposed as potentially more relevant indicators of vascular injury, inflammation, and atherosclerotic progression.[22,23] In particular, the oxygen desaturation index (ODI) and, more recently, hypoxic burden have emerged as candidate markers that may better discriminate cardiovascular risk than AHI.[24-26]

However, prospective data examining the relationship between nocturnal hypoxemia and incident CAD among adults referred for OSA evaluation remain limited. Therefore, the present study aimed to investigate the association between nocturnal hypoxemia, assessed using ODI, and incident CAD in a large, well-characterized cohort of adults referred to a sleep clinic for suspected OSA, with direct comparison to conventional AHI-based severity measures.

MATERIALS AND METHODS

Study design and population

This prospective cohort study included adults referred to a sleep clinic for evaluation of suspected OSA within the sleep apnea patients in Skaraborg (SIS) study.[27] The cohort comprised consecutive adults who underwent home sleep apnea testing (HSAT) as part of routine clinical care between January 1, 2005, and December 31, 2011. Follow-up continued until April 30, 2018. The SIS registry integrates clinical sleep data with longitudinal follow-up information obtained from medical records and national health registries.

For the present analysis, participants with prevalent CAD or other cardiac diseases at baseline were excluded, as were individuals with missing data for either AHI or ODI. The final study population consisted of 2,902 individuals (Figure 1).

The study was reviewed and approved by the Regionala Etikprövningsnämnden i Göteborg (approval number 579-13, December 8, 2013; amendment T779-18, September 12, 2018) and was conducted in accordance with the principles

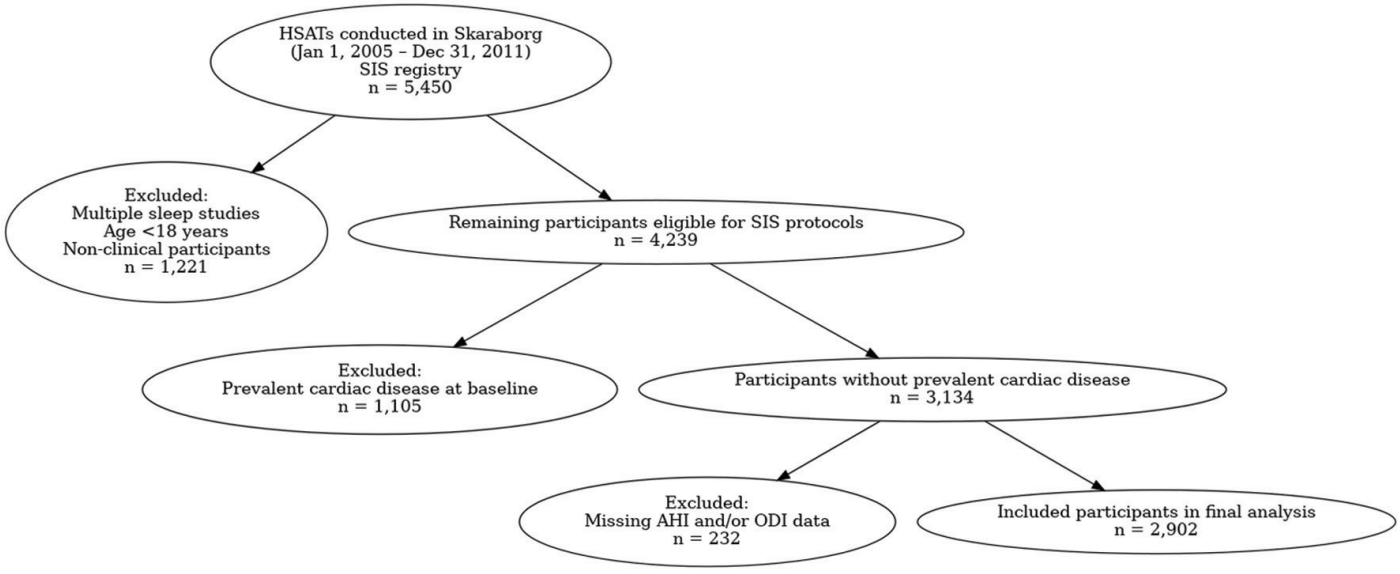

FIG. 1. Flowchart of participant selection for the incident coronary artery disease analysis.
AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SIS, sleep apnea patients in Skaraborg; HSATs, home sleep apnea tests.

of the Declaration of Helsinki. The analyses were based on pseudonymized clinical information linked to national health registries. In accordance with Swedish ethical legislation, the use of registry-linked pseudonymized data did not require written informed consent from individual participants. All data were handled under strict confidentiality, and no information enabling identification of individual participants was accessible at any stage of the analyses.

Sleep studies and definitions

OSA was assessed using unattended HSAT performed in accordance with routine clinical practice in Sweden, where HSAT represents the standard diagnostic approach, whereas in-laboratory polysomnography is reserved for selected cases. Apnea was defined as a reduction in airflow of at least 90% from baseline. Hypopneas were defined as a reduction of at least 50% in nasal pressure amplitude and/or thoracoabdominal movement lasting for at least 10 seconds.[28] AHI was calculated as the total number of apneas and hypopneas divided by the hours of recording time. ODI was defined as the number of oxygen desaturation events per hour, with desaturation specified as a decrease in oxygen saturation of at least 4% from baseline. Because HSAT was used, AHI was calculated on the basis of recording time rather than total sleep time and should therefore be interpreted as an estimate rather than a polysomnography-derived AHI.

For analytical purposes, both AHI and ODI were categorized into four clinically meaningful severity groups: < 5, 5-15, 15-30, and ≥ 30 events/h. These cut-off values were selected to facilitate direct comparison between traditional event-based indices and hypoxemia-based measures of OSA severity.

Clinical variables

Baseline clinical data were obtained from medical records and standardized clinical assessments. Variables included age, sex, body mass index (BMI), smoking status, hypertension, and diabetes mellitus. Excessive daytime sleepiness was evaluated using the Epworth sleepiness scale (ESS). Baseline initiation of treatment with PAP therapy or intraoral devices (IODs) was also recorded.

Outcome ascertainment

The primary outcome was incident CAD, defined as the first occurrence of myocardial infarction, coronary revascularization, or a documented diagnosis of CAD during follow-up according to ICD-10 codes I20-I25. Outcomes were identified through linkage with regional and national health registries and were verified using medical records when available. Participants were followed from the date of baseline sleep assessment until the first CAD event, relocation outside the Skaraborg region, death, or the end of follow-up.

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation (SD), median with interquartile range, or number and percentage, as appropriate. Incidence rates were calculated per 1,000 person-years, and 95% confidence intervals (CIs) were estimated using exact Poisson methods. Kaplan-Meier curves were constructed to illustrate CAD-free survival across AHI and ODI categories and compared using the log-rank test.

Associations between OSA indices and incident CAD were evaluated using Cox proportional hazards regression models. AHI and ODI were initially examined in separate multivariable models adjusted for age, sex, BMI, smoking status, hypertension, and diabetes mellitus. In addition, a combined model including both AHI and ODI was constructed to assess their independent associations with CAD risk. Pearson and Spearman correlation coefficients between AHI and ODI were calculated. Collinearity in the combined models was assessed using variance inflation factors (VIFs) and tolerance values for continuous models, and the scaled generalized variance inflation factors $[(GVIF)^{(1/(2\times Df)}]$ for categorical models. Covariates were selected a priori based on established cardiovascular risk factors and their known associations with both OSA and CAD.

Both categorical and continuous representations of AHI and ODI were evaluated. Continuous effects were estimated separately for AHI and ODI and jointly in a combined model, with hazard ratios (HRs) expressed per 1 event/h, per 10 events/h, and per 1 SD increase. Potential non-linearity in dose-response relationships was assessed using restricted cubic splines with 3, 4, and 5 knots placed at recommended quantiles (Harrell), and compared with corresponding linear models using likelihood ratio tests. Multivariable models were based on the subset of the analytic cohort with complete covariate data ($n = 2,849$; 110 events). HRs with 95% CIs are reported. The proportional hazards assumption was assessed using global and covariate-specific tests based on scaled Schoenfeld residuals (Grambsch-Therneau test). This assumption was further evaluated by including covariate-by-log(time) interaction terms, and sensitivity analyses were performed using Cox models stratified by early versus late follow-up (split at the median event time).

Additional analyses were conducted within the OSA subgroup, with further adjustment for baseline treatment with PAP or IOD therapy. Treatment was not modeled as a time-varying exposure due to the absence of longitudinal adherence data.

Participants with missing baseline AHI and/or ODI data were excluded from the analytic cohort. Among included participants, missingness in covariates was minimal (BMI 1.3%, current smoking 0.5%, all other covariates 0%), and a complete-case approach with listwise deletion was used for primary analyses. Included and excluded participants were compared on available baseline characteristics (Supplementary Table 1) to assess potential selection bias.

p values for trend across AHI and ODI categories were calculated by modeling the categorical variables as ordinal terms in Cox regression. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Participants with missing baseline AHI and ODI data (n = 232) were excluded from the final analytic cohort (Figure 1). Included and excluded participants were similar with respect to age, sex, ESS score, smoking status, hypertension, and diabetes prevalence, whereas the excluded group had marginally lower BMI and AHI values and a lower prevalence of baseline PAP or IOD therapy (Supplementary Table 1). The cumulative incidence of CAD during follow-up was essentially identical between the two groups (3.9% vs. 3.8%; $p = 1.00$), suggesting no meaningful outcome-related selection bias. The final analytic cohort comprised 2,902 adults referred for evaluation of suspected OSA who were free of known cardiac disease at baseline. Of these, 1,012 (34.9%) were women and 1,890 (65.1%) were men, with a mean age of 52.3 ± 12.9 years. Baseline characteristics of the study population are shown in Table 1. During a median follow-up of 8.7 years, 111 participants experienced an incident CAD event. During the same period, 216 participants died (198 without prior CAD and 18 after a CAD event). All-cause mortality by AHI category was 19, 50, 64, and 83 for < 5, 5-15, 15-30, and ≥ 30 events/h, corresponding to mortality rates of 6.9, 8.2, 7.4, and 11.0 per 1,000 person-years, respectively. By ODI category, the corresponding numbers were 50, 64, 56, and 46 deaths, with mortality rates of 6.5, 8.0, 11.0, and 10.5 per 1,000 person-years, respectively.

Baseline characteristics according to ODI categories are presented in Table 2. Participants with higher ODI values were older and had a higher burden of cardiometabolic risk factors. Specifically, age, BMI, hypertension, and diabetes mellitus increased progressively across ODI categories (all $p < 0.001$). In contrast, the proportion of current smokers did not differ significantly between groups. Female sex was less prevalent in higher ODI categories ($p < 0.001$).

The incidence of CAD across AHI categories is presented in Table 3. CAD incidence rates increased modestly with higher AHI categories, ranging from 2.93 to 6.84 per 1,000 person-years; however, no clear dose-response relationship was observed ($p = 0.20$). Kaplan-Meier analysis demonstrated only modest separation of CAD-free survival curves across AHI categories (Figure 2).

In contrast, CAD incidence across ODI categories showed a progressive increase (Table 3). Incidence rates rose from 2.75 per 1,000 person-years in the lowest ODI category to 7.90 per 1,000 person-years in the highest category (p for trend = 0.015).

TABLE 1. Baseline Characteristics of the Study Population.

Characteristic	Overall cohort (n = 2,902)
Age, years (mean ± SD)	52.3 ± 12.9
Female sex, n (%)	1,012 (34.9)
Male sex, n (%)	1,890 (65.1)
BMI, kg/m² (mean ± SD)	29.4 ± 5.5
Current smoker, n (%)	476 (16.5)
Hypertension, n (%)	903 (31.1)
Diabetes mellitus, n (%)	250 (8.6)
ESS score (median, IQR)	11 (7-14)
AHI, events/h (median, IQR)	20.0 (10.6-34.0)
ODI, events/h (median, IQR)	10.0 (3.7-22.0)
Baseline PAP or IOD therapy, n (%)	2006 (69.1)

Values are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. The analytic cohort included participants free of any known cardiac disease at baseline with complete AHI and ODI measurements. AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth sleepiness scale; IOD, intraoral device; PAP, positive airway pressure; SD, standard deviation; IQR, interquartile range.

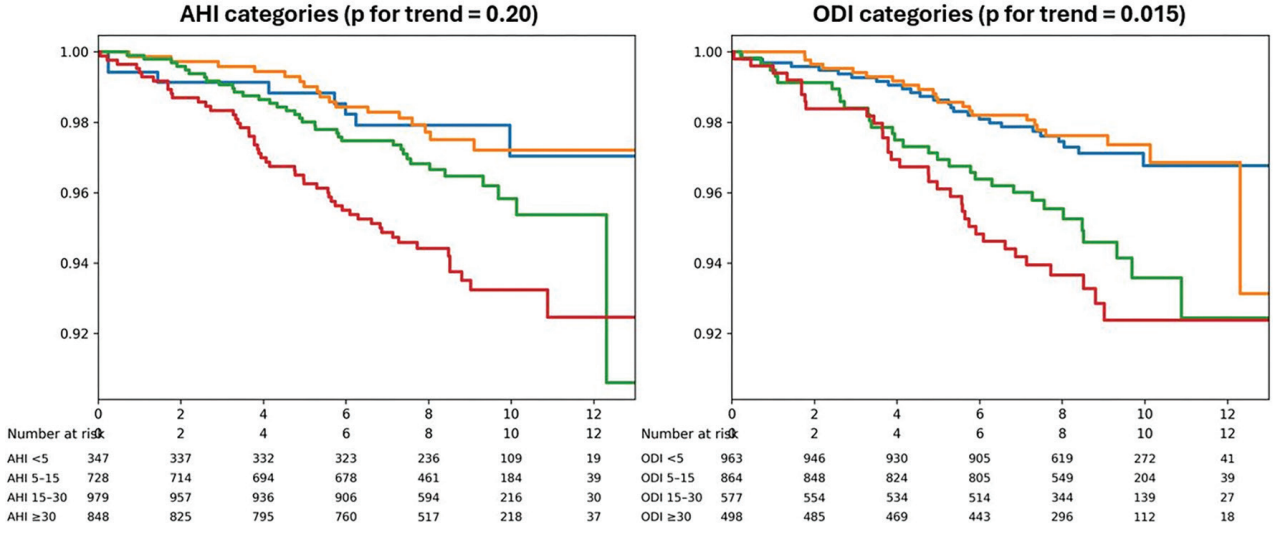

FIG. 2. Kaplan-Meier curves for incident coronary artery disease according to categories of apnea-hypopnea index (left panel) and oxygen desaturation index (right panel).

AHI, apnea-hypopnea index; ODI, oxygen desaturation index.

TABLE 2. Baseline Characteristics According to ODI Categories (events/h).

Variable	ODI < 5 (n = 864)	ODI 5-15 (n = 923)	ODI 15-30 (n = 600)	ODI ≥ 30 (n = 515)	*p* value
Age (years)	48.0 ± 13.9	52.9 ± 12.4	55.4 ± 11.5	54.5 ± 11.3	< 0.001
Female sex (%)	384 (44.4%)	329 (35.6%)	174 (29.0%)	125 (24.3%)	< 0.001
BMI (kg/m²)	27.1 ± 4.6	29.1 ± 5.2	30.1 ± 4.9	32.9 ± 6.1	< 0.001
Current smoker (%)	154 (17.9%)	146 (15.9%)	80 (13.4%)	96 (18.8%)	0.120
Hypertension (%)	151 (17.5%)	290 (31.4%)	233 (38.8%)	229 (44.5%)	< 0.001
Diabetes mellitus (%)	35 (4.1%)	81 (8.8%)	66 (11.0%)	68 (13.2%)	< 0.001

Values are mean ± SD or n (%). *p* values from ANOVA or chi-square test. BMI, body mass index; ODI, oxygen desaturation index; SD, standard deviation; ANOVA, analysis of variance.

TABLE 3. Incident Coronary Artery Disease Across Categories of AHI and ODI.

AHI category (events/h)	n	CAD events, n (%)	Person-years	Incidence rate (95% CI per 1,000 PY)
< 5	307	8 (2.6)	2728.2	2.93 (1.27-5.78)
5-< 15	700	15 (2.1)	6087.4	2.46 (1.38-4.06)
15-< 30	1011	37 (3.7)	8566.2	4.32 (3.04-5.95)
≥ 30	884	51 (5.8)	7458.6	6.84 (5.09-8.99)
p for trend				0.200
ODI category (events/h)	**n**	**CAD events, n (%)**	**Person-years**	**Incidence rate (95% CI, per 1,000 PY)**
< 5	864	21 (2.4)	7631.2	2.75 (1.70-4.21)
5-< 15	923	26 (2.8)	7890.7	3.3 (2.15-4.83)
15-< 30	600	30 (5.0)	5012.1	5.99 (4.04-8.54)
≥ 30	515	34 (6.6)	4306.4	7.90 (5.47-11.03)
p for trend				0.015

Incidence rates are expressed per 1,000 person-years with 95% confidence intervals calculated using exact Poisson methods. *p* values for trend were derived from Cox proportional hazards models. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; CAD, coronary artery disease; CI, confidence interval.

However, only the highest ODI category was significantly associated with increased risk in adjusted analyses. Kaplan-Meier curves demonstrated greater separation across ODI categories than across AHI categories (Figure 2).

In multivariable Cox regression models adjusted for age, sex, BMI, smoking status, hypertension, and diabetes mellitus, AHI categories were not independently associated with incident CAD (Table 4). In contrast, participants in the highest ODI category (≥ 30 events/h) had a significantly higher risk of CAD compared with those in the lowest category (HR: 1.99, 95% CI: 1.08-3.65; $p = 0.027$), whereas intermediate categories were not statistically significant. Tests based on scaled Schoenfeld residuals showed no evidence of violation of the proportional hazards assumption for either exposure. In the AHI model, the category-specific test yielded $\chi^2 = 2.08$ (df = 3, $p = 0.56$), with a global test $\chi^2 = 16.04$ (df = 9, $p = 0.07$); corresponding values for ODI were $\chi^2 = 0.78$ (df = 3, $p = 0.85$) and $\chi^2 = 14.87$ (df = 9, $p = 0.09$). Continuous and combined AHI-ODI specifications yielded qualitatively similar results (all exposure-specific $p \geq 0.40$; all global $p \geq 0.06$; Supplementary Table 2). A supplementary model including an ODI × log(time) interaction was not significant ($p = 0.54$), and a Cox model stratified at the median event time (4.9 years) showed an unchanged HR for the highest ODI category (HR: 1.99, 95% CI 1.08-3.65), with no significant ODI × time-period interactions (all $p \geq 0.48$). The proportional hazards assumption was also supported within the OSA-restricted subgroup (ODI Schoenfeld $p = 0.82$).

When AHI and ODI were included simultaneously in the same multivariable model (Table 5), neither was independently associated with incident CAD (AHI: HR: 1.005, $p = 0.580$; ODI: HR: 1.005, $p = 0.611$), consistent with the strong correlation between AHI and ODI (Pearson r = 0.89, 95% CI: 0.89-0.90; Spearman ρ = 0.88) and the substantial collinearity observed in the combined model (VIF 4.6 for AHI and 5.0 for ODI; tolerance 0.22 and 0.20, respectively; all other covariates VIF < 1.5).

When AHI and ODI were modeled as continuous predictors in separate multivariable Cox models, both showed associations with incident CAD that approached but did not reach statistical significance (Table 5): AHI HR: 1.10 per 10 events/h (95% CI: 1.00-1.22; $p = 0.057$) and ODI HR: 1.11 per 10 events/h (95% CI: 1.00-1.23; $p = 0.055$), with corresponding HRs per 1 SD of 1.22 (0.99-1.49) for AHI and 1.21 (1.00-1.48) for ODI. When both indices were entered simultaneously, the estimates attenuated toward the null, as noted above. Restricted cubic spline analyses (4 knots) showed no statistically significant non-linearity in either

the AHI–CAD or ODI–CAD relationship (non-linearity $p = 0.77$ and $p = 0.14$, respectively; Figure 3); results were consistent across 3-, 4-, and 5-knot specifications (Supplementary Table 3). Overall, the continuous analyses are consistent with a weak, approximately linear association, with categorical effects driven primarily by the highest ODI category.

In analyses restricted to participants with OSA, the association between ODI and incident CAD was attenuated and not statistically significant (HR: 2.06, 95% CI: 0.94-4.52; $p = 0.071$). The wide CI likely reflects the smaller sample size in this subgroup. The point estimate remained directionally consistent with the primary analysis; however, this finding should be interpreted as hypothesis-generating rather than confirmatory. Baseline treatment with PAP or IOD therapy was not independently associated with CAD risk.

In a sensitivity analysis excluding the nine incident CAD events occurring within the first year of follow-up (n = 2,840; 101 events), and using the same multivariable model as in the primary analysis (adjusted for age, sex, BMI, current smoking, hypertension, and diabetes; Table 4), the association between ODI and incident CAD remained consistent. The HR for the highest ODI category (≥ 30 events/h) versus the lowest (< 5 events/h) was 2.24 (95% CI: 1.17-4.28; $p = 0.015$), and the across-category ordinal trend remained statistically significant (per-category HR: 1.35, 95% CI: 1.10-1.67; $p = 0.005$). Continuous specifications showed borderline associations consistent in direction with the primary analysis (per 10 events/h: HR: 1.11, 95% CI: 0.99-1.23; $p = 0.067$; per 1 SD: HR: 1.21, 95% CI: 0.99-1.49; $p = 0.067$). The full sensitivity analysis results are presented in Table 6.

TABLE 4. Cox Proportional Hazards Models for Incident Coronary Artery Disease.

Variable	Model 1: AHI HR (95% CI)	*p* value	Model 2: ODI HR (95% CI)	*p* value
AHI < 5/ODI < 5	Reference		Reference	
AHI 5-< 15	0.51 (0.21-1.22)	0.132		
AHI 15-< 30	0.74 (0.34-1.60)	0.437		
AHI ≥ 30	0.93 (0.43-2.02)	0.856		
ODI 5-< 15			0.84 (0.47-1.52)	0.569
ODI 15-< 30			1.33 (0.74-2.40)	0.343
ODI ≥ 30			1.99 (1.08-3.65)	0.027
Age (per year)	1.08 (1.05-1.10)	< 0.001	1.08 (1.05-1.10)	< 0.001
Male sex	2.51 (1.57-4.01)	< 0.001	2.42 (1.51-3.86)	< 0.001
BMI	0.98 (0.94-1.02)	0.335	0.96 (0.92-1.01)	0.092
Current smoker	1.18 (0.66-2.08)	0.578	1.11 (0.63-1.96)	0.726
Hypertension	1.68 (1.12-2.51)	0.012	1.64 (1.10-2.46)	0.016
Diabetes	1.62 (0.97-2.71)	0.065	1.67 (1.00-2.79)	0.050

Hazard ratios (HRs) were derived from Cox proportional hazards models adjusted for age, sex, body mass index, smoking status, hypertension, and diabetes. AHI and ODI were evaluated in separate models. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; CI, confidence interval; BMI, body mass index.

TABLE 5. Continuous AHI and ODI as Predictors of Incident CAD.

Model	Predictor	Increment	HR (95% CI)	*p*
AHI alone	AHI	per 1 event/h	1.010 (1.000-1.020)	0.057
AHI alone	AHI	per 10 events/h	1.102 (0.997-1.219)	0.057
AHI alone	AHI	per 1 SD (20.0)	1.215 (0.994-1.485)	0.057
ODI alone	ODI	per 1 event/h	1.010 (1.000-1.021)	0.055
ODI alone	ODI	per 10 events/h	1.107 (0.998-1.228)	0.055
ODI alone	ODI	per 1 SD (19.1)	1.214 (0.996-1.479)	0.055
AHI + ODI together	AHI	per 1 event/h	1.005 (0.986-1.025)	0.581
AHI + ODI together	AHI	per 10 events/h	1.056 (0.870-1.283)	0.581
AHI + ODI together	ODI	per 1 event/h	1.005 (0.985-1.026)	0.611
AHI + ODI together	ODI	per 10 events/h	1.054 (0.860-1.293)	0.611

Multivariable Cox regression models adjusted for age, sex, BMI, current smoking, hypertension, and diabetes mellitus. n = 2,849; 110 events. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; CI, confidence interval; HR, hazard ratio; CAD, coronary artery disease.

TABLE 6. Sensitivity Analysis Excluding First-Year CAD Events.

Analysis	ODI specification	HR (95% CI)	*p*
Primary (n = 2,849; 110 events)	Highest (≥ 30 vs. < 5)	1.99 (1.08-3.65)	0.027
Sensitivity (n = 2,840; 101 events)	5-15 vs. < 5	1.02 (0.55-1.89)	0.960
Sensitivity	15-30 vs. < 5	1.48 (0.79-2.78)	0.220
Sensitivity	≥ 30 vs. < 5	2.24 (1.17-4.28)	0.015
Sensitivity	Ordinal trend (per category)	1.35 (1.10-1.67)	0.005
Sensitivity	Continuous (per 10 events/h)	1.11 (0.99-1.23)	0.067
Sensitivity	Continuous (per 1 SD = 19.0)	1.21 (0.99-1.49)	0.067

Multivariable Cox regression models with the same covariates as the primary analysis (age, sex, BMI, current smoking, hypertension, diabetes; Table 4). The first row shows the primary estimate for direct comparison. n = 2,840; 101 events; 9 events excluded. CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; ODI, oxygen desaturation index; SD, standard deviation; BMI, body mass index.

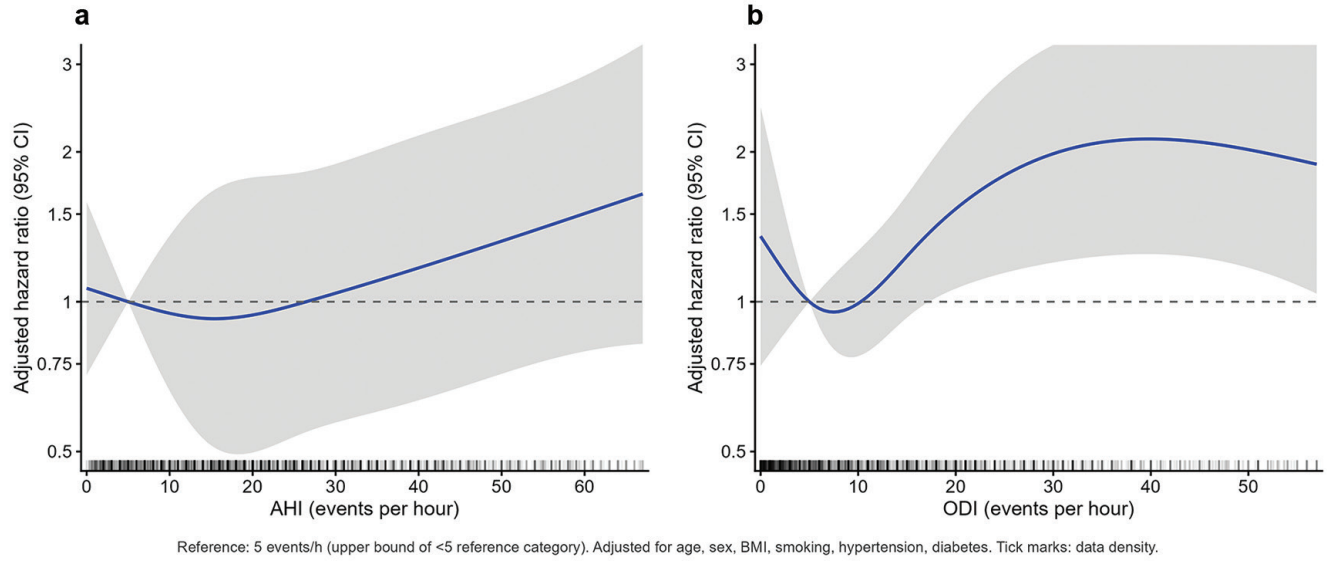

FIG. 3. Restricted cubic spline curves (4 knots) for the adjusted hazard ratio (HR) of incident coronary artery disease as a function of (a) apnea-hypopnea index (AHI) and (b) oxygen desaturation index (ODI). Solid lines show point estimates on a logarithmic HR scale; shaded bands show 95% CIs; the dashed horizontal line marks the reference (HR = 1). The reference value is 5 events per hour, corresponding to the upper bound of the < 5 events/h reference category in the categorical analysis. The x-axis is truncated at the 95th percentile of each index (AHI 67 events/h; ODI 57 events/h) to avoid displaying regions with sparse data. Tick marks at the lower edge of each panel indicate the distribution of observations. Models are adjusted for age, sex, BMI, current smoking, hypertension, and diabetes mellitus. No statistically significant non-linearity was detected for either index (non-linearity $p = 0.77$ for AHI; $p = 0.14$ for ODI). For ODI, the spline-derived HR at 30 events/h was 1.98 (95% CI 1.20-3.28), closely matching the categorical estimate for ODI ≥ 30 vs. < 5 (HR 1.99, 95% CI 1.08-3.65).

CAD, coronary artery disease; CI, confidence interval; BMI, body mass index.

DISCUSSION

In this prospective cohort of adults referred to a sleep clinic for evaluation of suspected OSA, nocturnal hypoxemia assessed by the ODI was associated with incident CAD in Cox models adjusted for established cardiovascular risk factors, whereas conventional event-based OSA severity measured by the AHI was not. However, when AHI and ODI were included simultaneously in the same model, neither metric remained independently associated with CAD, suggesting substantial overlap between event-based and hypoxemia-based measures of sleep-disordered breathing. These findings indicate that different OSA metrics capture related but not identical dimensions of disease severity, and that no single index fully accounts for cardiovascular risk. he association between OSA and CAD has been reported in several observational cohorts; however, interpretation of these findings has been complicated by substantial confounding from shared cardiometabolic risk factors, including obesity, hypertension, and diabetes mellitus.[3-7] Individuals referred for OSA evaluation frequently have a high burden of these comorbidities, making it difficult to disentangle the independent contribution of sleep-disordered breathing to CAD risk. Even in large prospective studies with extensive statistical adjustment, residual confounding remains a major concern.[8,10,11,13] In this context,

the lack of an independent association between AHI categories and incident CAD observed in the present study supports the notion that event frequency alone may be an insufficient surrogate marker of cardiovascular risk.

In contrast, nocturnal hypoxemia assessed by ODI showed an overall increasing trend across categories, although only the highest category reached statistical significance. This pattern is consistent with emerging evidence suggesting that hypoxemia-related metrics may better reflect pathophysiological processes implicated in vascular injury, including oxidative stress, systemic inflammation, and endothelial dysfunction.[22,23,25,29] Continuous analyses showed borderline associations for both AHI and ODI per 10 events/h (each $p = 0.06$), and restricted cubic spline analyses demonstrated no evidence of non-linearity. This suggests that the categorical signal at ODI ≥ 30 likely reflects accumulation of a weak monotonic effect at the upper end of the distribution rather than a discrete biological threshold (Table 5, Figure 3, Supplementary Table 3). Unlike AHI, which assigns equal weight to all respiratory events regardless of their physiological impact, ODI more directly reflects the frequency of oxygen desaturation episodes and may therefore better capture cumulative hypoxic vascular stress during sleep.[19,25,30] In addition, emerging evidence suggests that hypoxic burden—which incorporates both the depth and duration of oxygen desaturations—may provide an even more comprehensive measure of the physiological impact of sleep-disordered breathing. Prior studies have shown that hypoxic burden is more strongly associated with cardiovascular outcomes than conventional metrics such as AHI.[30] Although hypoxic burden was not available in the present dataset, its inclusion in future studies may further improve risk stratification and should be explored in subsequent research.

These findings may also help contextualize the neutral results of randomized controlled trials evaluating PAP therapy for the prevention of cardiovascular events in OSA.[15-17] While such trials have demonstrated improvements in sleep-related symptoms and intermediate physiological measures, they have not consistently shown reductions in incident coronary outcomes. One possible explanation is that conventional trial designs rely predominantly on AHI-based definitions of OSA severity, which may not adequately capture the hypoxemic burden most relevant to cardiovascular risk. In addition, trial populations often include patients with established cardiovascular disease, in whom modification of advanced atherosclerotic processes may be less responsive to treatment. In our cohort, baseline use of PAP or IOD therapy was not independently associated with incident CAD. Because treatment status was ascertained only at baseline and no data on adherence, discontinuation, or treatment initiation during follow-up were available, this finding cannot be interpreted as evidence of treatment efficacy and should not be considered directly comparable to results from randomized trials of OSA therapy.

In analyses restricted to participants with OSA, the association between ODI and CAD was attenuated and was no longer statistically significant (HR: 2.06, 95% CI: 0.94-4.52). The point estimate remained directionally consistent with the primary analysis; however, the wide CI suggests limited precision, and this subgroup analysis should be interpreted as exploratory rather than confirmatory. The attenuation may reflect reduced statistical power within the OSA subgroup, potential confounding from treatment initiation during follow-up, or heterogeneity in hypoxemic burden within AHI-defined OSA categories. Larger studies are needed to clarify whether nocturnal hypoxemia is associated with cardiovascular risk specifically among individuals with established OSA. Several biological mechanisms have been proposed to explain how OSA may contribute to the development of CAD. Intermittent nocturnal hypoxemia, a hallmark of OSA, promotes endothelial dysfunction, oxidative stress, systemic inflammation, and sympathetic nervous system activation.[2,3,22] Recurrent oxygen desaturations may induce repeated cycles of hypoxia-reoxygenation, leading to increased production of reactive oxygen species, reduced nitric oxide bioavailability, and vascular inflammation, all of which are central processes in atherogenesis.[31-33]

Experimental and clinical studies have further demonstrated associations between intermittent hypoxemia and increased arterial stiffness, enhanced platelet activation, and prothrombotic states, providing potential pathways through which sleep-disordered breathing may accelerate coronary plaque formation and instability.[2,3] Importantly, these mechanisms are more directly linked to the burden and frequency of hypoxemic episodes than to the mere number of respiratory events. This distinction may explain why hypoxemia-based metrics, such as the ODI, appear to be more closely associated with coronary outcomes than event-based measures such as the AHI.

The AHI assigns equal weight to respiratory events regardless of their physiological consequences, potentially obscuring meaningful heterogeneity in hypoxemic exposure among individuals with similar AHI values. As a result, the AHI may be less sensitive to the cumulative vascular stress imposed by sleep-disordered breathing, particularly in relation to CAD, which develops over long periods through progressive endothelial injury and inflammation. The observed association between ODI and incident CAD in the present study is therefore biologically plausible and aligns with current understanding of hypoxia-driven cardiovascular pathophysiology. Baseline characteristics showed a progressive increase in cardiometabolic risk factors across ODI categories, suggesting that individuals with more severe nocturnal hypoxemia represent a higher risk phenotype. Although this pattern raises the possibility of residual confounding, the association between ODI and incident CAD persisted after adjustment for major risk factors. Sensitivity analyses excluding early events yielded similar results, supporting the robustness of the findings and arguing against reverse causation.

Several limitations should be considered when interpreting these findings. First, as an observational study, causal inferences cannot be established, and residual confounding remains possible despite multivariable adjustment. Important factors such as lipid profiles, physical activity, socioeconomic status, and detailed medication use were not available and may have influenced the observed associations. Second, sleep-disordered breathing was assessed using HSAT, which reflects routine clinical practice in Sweden, where HSAT is the standard diagnostic approach and in-laboratory

polysomnography is reserved for selected cases. However, HSAT does not include electroencephalographic monitoring and may underestimate AHI because it relies on recording time rather than true sleep time. This limitation may have influenced comparisons between AHI and ODI and should be considered when interpreting the findings. Third, the number of incident CAD events was relatively modest, which may limit statistical power and the precision of effect estimates, particularly in subgroup analyses. Fourth, participants were recruited from a sleep clinic referral population, which may limit generalizability to community-based populations and introduce selection bias. In addition, undetected subclinical CAD at baseline cannot be excluded. The primary outcome was a composite of myocardial infarction, coronary revascularization, and documented CAD diagnosis (ICD-10 codes I20-I25), provided in the analytic dataset as a single binary indicator with the corresponding event date. Component-level information was not available; therefore, we were unable to report the distribution of individual outcome components or perform component-specific analyses. While this composite reflects real-world registry-based ascertainment, the relative contribution of each component cannot be determined from the present data, and associations may differ between harder outcomes (e.g., myocardial infarction) and softer outcomes (e.g., angina or elective revascularization). Fifth, information on PAP or IOD therapy was limited to baseline, and no data on treatment adherence, discontinuation, or changes during follow-up were available. Because OSA treatment is time-varying, modeling treatment as a baseline exposure may introduce bias, including potential immortal time bias. Accordingly, no conclusions regarding the efficacy of PAP or IOD therapy on incident CAD can be drawn from this study. Sixth, although 216 participants died during follow-up (198 without prior CAD), we did not perform a formal Fine-Gray competing-risk analysis. The HRs reported here are cause-specific and retain an etiologic interpretation, whereas subdistribution hazard models (Fine-Gray) are primarily used for estimating cumulative incidence in the presence of competing risks rather than causal inference. Mortality rates increased modestly across categories (from 6.9 to 11.0 per 1,000 person-years for AHI and from 6.5 to 10.5 per 1,000 person-years for ODI). Because competing-event risk was higher in categories with greater CAD risk, accounting for competing risks would be expected to attenuate rather than amplify cumulative incidence estimates; thus, the observed cause-specific associations are likely conservative. Nevertheless, given the long follow-up, death may have acted as a competing event and could have influenced the observed associations. Finally, the analytic cohort excluded 232 participants with missing baseline ODI. A comparison of included and excluded participants showed similar age, sex, ESS score, smoking status, and prevalence of hypertension and diabetes, with only slightly lower BMI and AHI and a marginally lower prevalence of PAP or IOD therapy in the excluded group. The cumulative incidence of CAD was essentially identical between groups (3.9% vs. 3.8%; Supplementary Table 1). Together with minimal missingness in covariates within the included cohort (BMI 1.3%, current smoking 0.5%, all other covariates 0%) handled by listwise deletion, the likelihood of substantial selection bias from the complete-case approach is considered low.

Strengths of the study include its prospective design, long follow-up duration, exclusion of participants with baseline cardiovascular disease, and the simultaneous evaluation of both event-based and hypoxemia-based measures of sleep-disordered breathing.

In conclusion, among adults referred for evaluation of suspected OSA, nocturnal hypoxemia assessed by ODI was associated with incident CAD in separately adjusted Cox models, whereas event-based OSA severity assessed by AHI was not. However, when AHI and ODI were modeled together, this association was attenuated and no longer statistically significant, consistent with substantial overlap between event-based and hypoxemia-based measures of sleep-disordered breathing. These findings suggest that hypoxemia-related metrics may provide complementary information for cardiovascular risk stratification, although no single index fully captures the complexity of OSA-related coronary risk.

Ethics Committee Approval: The study was reviewed and approved by the Regionala Etikprövningsnämnden i Göteborg (approval number 579-13, December 8, 2013; amendment T779-18, September 12, 2018) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: In accordance with Swedish Ethical Legislation, the use of registry-linked pseudonymized data did not require written informed consent from individual participants. All data were handled under strict confidentiality, and no information enabling identification of individual participants was accessible at any stage of the analyses.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Supplementary Tables: https://balkanmedicaljournal.org/img/files/BalkanMedJ-2026.2026-3-213-supplementary-tables.pdf

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