Research Square

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Association of longitudinal hypoxic burden with cardiovascular mortality depends on apnea–hypopnea index adjustment: a Sleep Heart Health Study analysis

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Abstract

Background Hypoxic burden (HB) captures respiratory event-related hypoxic exposure, but its longitudinal association with mortality may depend on how changes in event frequency are accounted for. We examined whether the association between HB change and cardiovascular mortality depends on apnea–hypopnea index (AHI) definition and adjustment for concurrent AHI change.

Methods This post hoc Sleep Heart Health Study reanalysis used paired polysomnography and follow-up from the second examination. Five Cox models compared no AHI adjustment, baseline AHI adjustment, and baseline-plus-change adjustment using 3% and 4% desaturation-threshold indices. Samples, clinical adjustment and HB scaling were fixed within each outcome. Cardiovascular models were stratified by race. Paired participant bootstrap resampling quantified the difference between HB-change coefficients under full AHI3 and AHI4 adjustment.

Results Among 2,485 participants, 104 cardiovascular deaths occurred. Per fixed standard deviation of log-HB change, hazard ratios were 1.227 (95% confidence interval 0.987–1.525) without AHI adjustment, 1.685 (0.964–2.948) with full AHI3 adjustment, and 1.012 (0.611–1.679) with full AHI4 adjustment. The paired coefficient difference was 0.510 (1,000-replicate bootstrap interval 0.119–0.913). HB-change variance inflation factors were 7.66 and 5.31. Single-record omission and selected time-varying effects produced similar contrasts. The all-cause mortality contrast interval included zero.

Conclusions The conditional HB-change estimate depended on AHI definition and concurrent-change adjustment. These exploratory findings support transparent specification of adjustment targets; they establish neither a causal HB effect nor superiority of either AHI definition.

Background

Obstructive sleep apnea has been investigated in relation to mortality, coronary heart disease, heart failure and stroke in prospective SHHS analyses [1, 2, 3]. Event frequency remains a common severity measure, but it does not fully characterize the physiological consequences of individual events [4].

Respiratory event-related hypoxic burden integrates the depth and duration of desaturations that are incompletely represented by event frequency. Associations between HB and cardiovascular mortality have been reported in SHHS and other cohorts [5]. HB has also been examined in relation to incident heart failure and adverse cardiovascular outcomes in clinical cohorts [6, 7]. Subsequent work has examined physiological burdens and the consequences of alternative desaturation-area algorithms [8, 9]. These studies establish the relevance of hypoxic exposure while highlighting the importance of how respiratory metrics are defined and analyzed.

Respiratory scoring rules are relevant to this question. Alternative hypopnea definitions change AHI values, severity classification and the population identified as having sleep apnea [10, 11, 12]. SHHS

work using a 3% desaturation-or-arousal definition has also examined cardiovascular associations [13]. That definition differs from the desaturation-only indices used here.

Longitudinal analyses introduce an additional interpretive problem. Repeat SHHS examinations have demonstrated changes in sleep-disordered breathing associated with changes in weight [14]. HB and AHI may change together, and a coefficient for HB change adjusted for AHI change describes a conditional association. Changing the AHI definition can change what is held constant. Recent longitudinal SHHS research and methodological correspondence already motivate the study of changing sleep apnea and hypoxic exposure [15, 16]. We therefore compared adjustment specifications within the same participants using a fixed HB scale.

We investigated whether adding concurrent AHI change, and choosing a 3% versus 4% desaturation-threshold AHI, altered the association between HB change and subsequent cardiovascular mortality. This methodological question arose after exploratory screening of longitudinal clinical associations. It was not a prospectively registered primary hypothesis. All-cause mortality was retained as a companion analysis to show the limits of outcome consistency.

Methods

Design and study population

SHHS was designed as a multicenter prospective study with standardized unattended polysomnography [17, 18]. We performed a secondary analysis of SHHS data distributed through the National Sleep Research Resource (NSRR) [19], using the second polysomnographic examination as the follow-up landmark. Signal data were available for 2,639 participants at both examinations (5,278 PSG records). Clinical linkage and eligibility requiring positive follow-up and available AHI3 at both visits yielded 2,634 records. Signal and reconstruction quality criteria retained 2,569 participants, of whom 2,486 had complete clinical covariates. One additional participant did not meet cardiovascular outcome validity criteria, leaving 2,485 in that analysis (Fig. 1). We did not impute missing clinical variables. Among signal-eligible participants, missing values affected BMI at the second visit and BMI change (24 each), smoking (7), diabetes (47), and antihypertensive medication (7); these counts overlap.

Exposure construction and quality control

HB was reconstructed from oxygen saturation and respiratory-event annotations using a Python implementation based on the publicly available HB reference code [20]. The implementation used event-related desaturation areas and a participant-specific whole-night search window, with a fallback window when estimation failed. Eligible annotated apnea and hypopnea events were included irrespective of whether they met the AHI3 or AHI4 desaturation threshold. Oxygen saturation was processed at 1 Hz, with plausible values of 50–100% and exclusion of annotated artifacts. Sleep comprised stages 1–5; movement epochs were excluded from the valid-sleep normalization denominator. Two PSG records

required a small correction to exclude movement epochs from the normalization denominator. Independent Python reimplementation was checked in 136 PSG records from 71 participants; the maximum absolute HB difference was 6.58×10^{-11}. This was a technical check within the same runtime, not cross-engine or external-cohort validation (Additional file 1).

Both examinations required successful HB computation, finite HB, at least 95% valid sleep oxygen saturation, at least 90% window coverage, and an absolute difference no greater than 1 event/h between reconstructed total-event AHI and the corresponding database index. Endpoint, window and overlap conventions are specified in Additional file 1.

AHI3 and AHI4 denoted the SHHS rdi3p and rdi4p fields, respectively. These indices count central and obstructive apneas and hypopneas associated with at least 3% or 4% oxygen desaturation per hour of sleep. Thus, the desaturation threshold applies to apneas as well as hypopneas. Arousal alone does not qualify an event for either index. Change was calculated as log(1 + value at visit 2) minus log(1 + value at visit 1), without annualizing. HB-change effects used the original fixed standard deviation of 0.6952283 throughout the comparison. Baseline HB was also included. Holding scaling constant ensured that changes in the HB coefficient did not arise from outcome-specific rescaling.

Outcomes and statistical analysis

Cardiovascular mortality was analyzed with cause-specific Cox regression [21, 22]. Non-cardiovascular deaths were censored at death; surviving participants were censored at recorded follow-up. A cardiovascular death required a valid cause code, death status, and a cardiovascular death date after the second examination and within observed follow-up. All-cause mortality was analyzed separately. These models estimate hazards, not cumulative cardiovascular death probabilities.

Within each outcome, all five models used identical participants and clinical covariates: age and BMI at visit 2, BMI change, sex, smoking and diabetes at visit 1, antihypertensive medication at visit 2, and prior myocardial infarction, heart failure, or stroke by visit 2. Cardiovascular models used race strata; all-cause models included race indicators. Efron handling of ties was used. The five AHI specifications were no AHI terms, baseline AHI3, baseline plus change in AHI3, baseline AHI4, and baseline plus change in AHI4. The fully adjusted cardiovascular model contained 13 regression coefficients.

The focal comparison was the difference between the HB-change log-hazard coefficients from the AHI3 and AHI4 baseline-plus-change models. We used a nonparametric bootstrap [23], resampling participants with replacement 1,000 times (seed 20261006), fitting both models to the same resampled participants in each replicate. Percentile intervals describe exploratory within-sample uncertainty and do not account for the preceding research-direction selection. We evaluated correlations, variance inflation, log-time proportional-hazards score diagnostics, and influence. The time-effect checks addressed departures from the constant-coefficient assumption, a central concern in Cox-model diagnostics [24]. Influence refitting omitted each cardiovascular death and the union of records with the ten largest

approximate standardized influences in each model, yielding 105 unique omissions. No records were removed from the main analysis on this basis. A post hoc sensitivity analysis added current-smoking and diabetes interactions with log(t/5), where t is years since the second PSG. A further analysis added log-time interactions for age, current smoking and diabetes, followed by a two-term block for HB change and AHI change. Time-dependent covariate values were evaluated at each event time within its risk set, retaining Efron handling of ties. Nested likelihood-ratio tests assessed the added blocks; pointwise HB-change estimates were reported at 1, 3 and 5 years. These analyses were exploratory and were not used to replace the original model comparison. Analyses used Python and statsmodels PHReg; the custom time-dependent likelihood was numerically checked against the constant-effect implementation.

AI assistance

OpenAI ChatGPT/Codex was used to assist manuscript drafting and editing. Numerical results were checked against saved analysis outputs.

Results

Analysis population and adjustment sequence

The cardiovascular analysis included 2,485 participants and 104 cardiovascular deaths; the all-cause cohort included 2,486 participants and 304 deaths. The cardiovascular cohort had a median age of 68 years, and 1,349 participants (54.3%) were female. The median interval between examinations was 5.21 years. Median HB was 32.32 and 34.05 percent-minutes per hour of valid sleep at the first and second examinations, respectively (Table 1). All five model specifications are presented in Table 2 and Fig. 2a,b; paired coefficient comparisons are presented in Table 3 and Fig. 2c. In the all-cause cohort, observed follow-up had a median of 6.71 years (interquartile range, 6.00–7.38). Aggregate source data for the figures are provided in Additional file 2.

Table 1
Characteristics of the cardiovascular mortality cohort

Characteristic	Value
Age at second PSG, years	68.00 [60.00, 76.00]
BMI at second PSG, kg/m2	27.73 [24.88, 31.12]
BMI change, kg/m2	0.16 [-0.99, 1.26]
Interval between visits, years	5.21 [5.06, 5.37]
Observed follow-up from second PSG, years	6.71 [6.00, 7.38]
HB at first PSG, percent-min/h of valid sleep	32.32 [17.72, 55.44]
HB at second PSG, percent-min/h of valid sleep	34.05 [17.91, 63.21]
AHI3 at first PSG, events/h	8.49 [3.39, 17.45]
AHI3 at second PSG, events/h	10.75 [5.04, 21.31]
AHI4 at first PSG, events/h	3.87 [1.19, 10.13]
AHI4 at second PSG, events/h	5.83 [2.05, 13.51]
Female	1349 (54.3%)
Current smoking at first visit	222 (8.9%)
Former smoking at first visit	1079 (43.4%)
Diabetes at first visit	146 (5.9%)
Antihypertensive medication at second visit	1108 (44.6%)
Prior MI/CHF/stroke by second visit	303 (12.2%)

N = 2,485; cardiovascular deaths = 104. Continuous variables are median [25th, 75th percentile]; categorical variables are n (%). HB is expressed in percent-minutes per hour of valid sleep. MI, myocardial infarction; CHF, congestive heart failure; PSG, polysomnography.

Table 2
HB change and mortality under five AHI adjustment specifications

Mortality	AHI adjustment	HR (95% CI)	P value	VIF
Cardiovascular	No AHI terms	1.227 (0.987–1.525)	0.0657	1.19
Cardiovascular	Baseline AHI3	1.227 (0.987–1.525)	0.0658	1.20
Cardiovascular	Baseline + change AHI3	1.685 (0.964–2.948)	0.0672	7.66
Cardiovascular	Baseline AHI4	1.231 (0.990–1.531)	0.0614	1.21
Cardiovascular	Baseline + change AHI4	1.012 (0.611–1.679)	0.9619	5.31
All-cause	No AHI terms	0.926 (0.823–1.043)	0.2078	1.19
All-cause	Baseline AHI3	0.927 (0.823–1.044)	0.2111	1.20
All-cause	Baseline + change AHI3	0.780 (0.568–1.072)	0.1254	7.66
All-cause	Baseline AHI4	0.933 (0.828–1.051)	0.2519	1.21
All-cause	Baseline + change AHI4	0.674 (0.523–0.868)	0.0022	5.33

Cardiovascular: n = 2,485, 104 events; all-cause: n = 2,486, 304 events. HRs are per fixed SD (0.6952283) of log-HB change. All models include baseline HB and clinical covariates specified in Methods. Cardiovascular models use race strata; all-cause models include race indicators. Each outcome uses the same sample across all five specifications. VIF, variance inflation factor.

Table 3
Paired differences between HB change coefficients

Mortality	Difference in log-HR	Bootstrap 95% interval
Cardiovascular	0.510	0.119 to 0.913
All-cause	0.146	−0.083 to 0.379

Difference = beta under baseline-plus-change AHI3 adjustment minus beta under baseline-plus-change AHI4 adjustment. Both outcomes had 1,000 successful paired bootstrap replicates. Percentile intervals are exploratory and do not account for preceding research-direction selection. This contrast differs from testing either individual HB coefficient against zero.

Without AHI adjustment, the cardiovascular HR per fixed standard deviation of log-HB change was 1.227 (95% CI, 0.987–1.525). Adding baseline AHI alone changed this little: the HR was 1.227 (0.987–1.525)

with AHI3 and 1.231 (0.990–1.531) with AHI4. Adding concurrent AHI change produced different conditional estimates: 1.685 (0.964–2.948) for AHI3 and 1.012 (0.611–1.679) for AHI4. Both individual intervals included the null.

The corresponding log-hazard coefficients were 0.522 and 0.012, giving a paired difference of 0.510. All 1,000 bootstrap pairs converged. The difference had a percentile interval of 0.119–0.913. This comparison is distinct from testing either coefficient separately against zero and does not rank the models by causal validity.

Dependence and diagnostic analyses

In the cardiovascular cohort, log-HB change correlated 0.870 with log-AHI3 change and 0.815 with log-AHI4 change. The two AHI changes correlated 0.932. The HB-change variance inflation factor increased from 1.19 without AHI terms to 7.66 with full AHI3 adjustment and 5.31 with full AHI4 adjustment, consistent with substantial shared information and reduced coefficient precision.

Across 105 single-record omissions, the coefficient difference ranged from 0.466 to 0.553. This suggests that the difference was not attributable to any one of the examined observations, but it does not exclude broader model instability. Global log-time proportional-hazards score tests gave $p = 0.040$ for the AHI3 model and $p = 0.188$ for the AHI4 model. HB-change term-specific tests gave $p = 0.508$ and 0.474, respectively; failure to reject does not establish proportionality. Allowing selected smoking and diabetes effects to vary with log-time gave HB-change HRs of 1.700 (0.974–2.968) and 1.024 (0.617–1.698), with a coefficient difference of 0.507. This sensitivity does not resolve every possible time-varying effect. An additional analysis allowed age, current-smoking and diabetes effects to vary with log-time, then added a two-term block for HB-change and AHI-change time interactions. The additional block had likelihood-ratio p values of 0.654 and 0.652 in the AHI3 and AHI4 models, respectively. The resulting 18-coefficient models were imprecise, especially early in follow-up. All time-specific results are shown in Fig. 3 and reported in Additional file 1; absence of a clear interaction test result does not establish proportional hazards.

Companion outcome

For all-cause mortality, the fully adjusted HRs were 0.780 (0.568–1.072) with AHI3 and 0.674 (0.523–0.868) with AHI4. The paired coefficient difference was 0.146, with a bootstrap interval of − 0.083 to 0.379. Thus, the evidence for a difference did not extend clearly to all-cause mortality. The inverse conditional estimates must not be interpreted as evidence that increasing hypoxic exposure is protective. There was no observed sign reversal across the five all-cause specifications.

Discussion

This reanalysis identified sensitivity of the cardiovascular HB-change coefficient to the definition of concurrently adjusted AHI change. Baseline AHI adjustment alone had little effect. The contrast appeared when changes in highly correlated respiratory metrics were entered together. Paired resampling, selected influence refits, and a limited time-varying-covariate analysis supported persistence of the within-sample contrast. They did not provide independent replication.

The interpretation is conditional. Causal-diagram reasoning emphasizes that an adjustment set must follow the intended estimand and assumptions about variable relationships [25]. Adjustment may change bias or precision, and coefficients from the same multivariable model need not share a common causal interpretation [26, 27]. These principles motivate caution here; they do not establish that AHI change is a mediator or collider. Holding one AHI definition constant is not necessarily equivalent to holding another definition constant. An algebraic illustration of this conditioning issue is provided in Additional file 1. It does not establish a physiological mechanism or a causal decomposition of measured HB and AHI.

The practical implication is to specify the scientific target before choosing adjustment. A question about the association of overall changing hypoxic exposure is different from a question about HB change among people with the same modeled change in event frequency. Neither specification can be declared correct solely because it produces a larger HR or smaller p value. Measurement error, correlated change scores, residual confounding, and conditioning on shared physiological information may all contribute to the observed estimates. The present analysis cannot separate these explanations.

Prior work established associations between HB and mortality, compared HB algorithms, and motivated longitudinal analyses [5, 8, 9, 15, 16]. The present study complements these findings by isolating the contribution of AHI adjustment specification within a fixed analytical sample. This design separates changes caused by adjustment from changes caused by including different participants or rescaling HB. It does not identify which specification is closest to a causal effect. Prediction accuracy and clinical utility were not tested.

Clinical translation also requires evidence beyond an observational association. The SAVE trial did not show an overall reduction in recurrent cardiovascular events with CPAP in its enrolled population [28]. A post hoc ISAACC analysis explored whether baseline HB identified differential treatment response [29]. Those treatment questions differ from the present comparison of conditional longitudinal coefficients. Our findings cannot identify patients who will benefit from treatment or justify choosing one AHI threshold for clinical care.

Several limitations restrict inference. The hypothesis was selected after exploratory screening, and the bootstrap does not correct that selection. Only 104 cardiovascular deaths supported a 13-coefficient full model; confidence intervals were wide, and overfitting remains possible. Simulation work on events per variable supports caution about estimation with limited event information [30]. Repeat-visit survival and attendance, signal-quality exclusions, and complete-case selection may affect generalizability. Some clinical covariates came from the first visit, and changes in treatment, medication, and unmeasured

health status could confound associations. No independent cohort validation was performed. Algorithm implementation lacks cross-engine verification. The global proportional-hazards diagnostic raised concern in one model, and the selected time-varying sensitivity is incomplete. Finally, the all-cause contrast interval included zero, limiting claims of generality across outcomes.

These results justify transparent reporting of AHI definitions, concurrent-change adjustment, and the resulting conditional interpretation in longitudinal HB studies. Independent replication with a fixed analysis plan is needed before generalizing the magnitude or clinical significance of this model dependence.

Conclusions

In this SHHS repeat-PSG cohort, the estimated association of HB change with cardiovascular mortality varied with the AHI definition used to adjust for concurrent change. Reporting the adjustment specification and its conditional interpretation is essential. The magnitude and generalizability of this contrast require independent replication.

Abbreviations

AHI
apnea–hypopnea index
BMI
body mass index
CHF
congestive heart failure
CI
confidence interval
CPAP
continuous positive airway pressure
CVD
cardiovascular disease
EDF
European Data Format
HB
hypoxic burden
HR
hazard ratio
MI
myocardial infarction
NSRR
National Sleep Research Resource

PSG
polysomnography
SD
standard deviation
SHHS
Sleep Heart Health Study
VIF
variance inflation factor
XML
Extensible Markup Language.

Declarations

Ethics approval and consent to participate

The original Sleep Heart Health Study protocols were approved by the institutional review boards of the participating institutions, and all participants provided written informed consent. The present study was a secondary analysis of de-identified SHHS data and involved no additional participant recruitment or intervention.

Consent for publication

Not applicable. This manuscript contains no identifiable individual participant information.

Availability of data and materials

SHHS data are distributed through the National Sleep Research Resource (https://sleepdata.org/datasets/shhs) [19]. Access to participant-level data is subject to NSRR access policies and applicable data-use agreements; these data are not redistributed with this manuscript. Aggregate figure source data are included in Additional file 2.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Binbin Zhang: Conceptualization, methodology, formal analysis, and writing—original draft. Shinge SAU: Data curation, validation, and writing—review and editing. Men Yang: Data curation, methodology, and writing—review and editing. Xinyi Zhang: Validation, visualization, and writing—review and editing. Qingzhou Zhang: Software, formal analysis, and writing—review and editing. Kuan Zeng: Methodology, interpretation of results, and writing—review and editing. Yanqi Yang: Conceptualization, supervision, project administration, and writing—review and editing.All authors reviewed and approved the final manuscript and agree to be accountable for the work.

Clinical trial number

not applicable.

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Figures

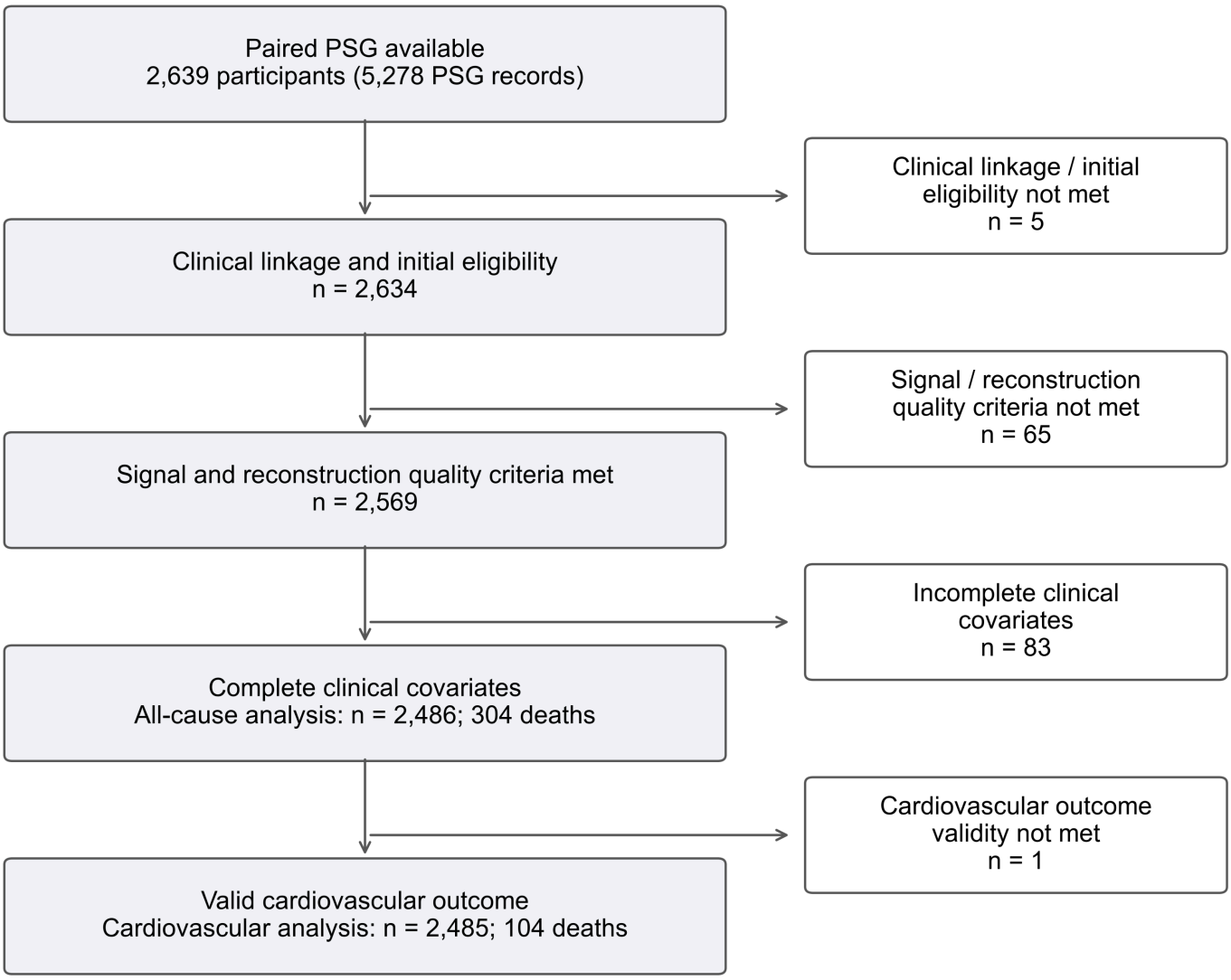


Figure 1

Participant selection and outcome-specific cohorts

The flow begins with participants with paired polysomnography. Counts denote participants except for the explicitly stated number of PSG records. Sequential exclusions yielded 2,486 participants for all-cause mortality and 2,485 for cardiovascular mortality. The one additional exclusion concerns cardiovascular outcome validity, not a separately removed all-cause death.

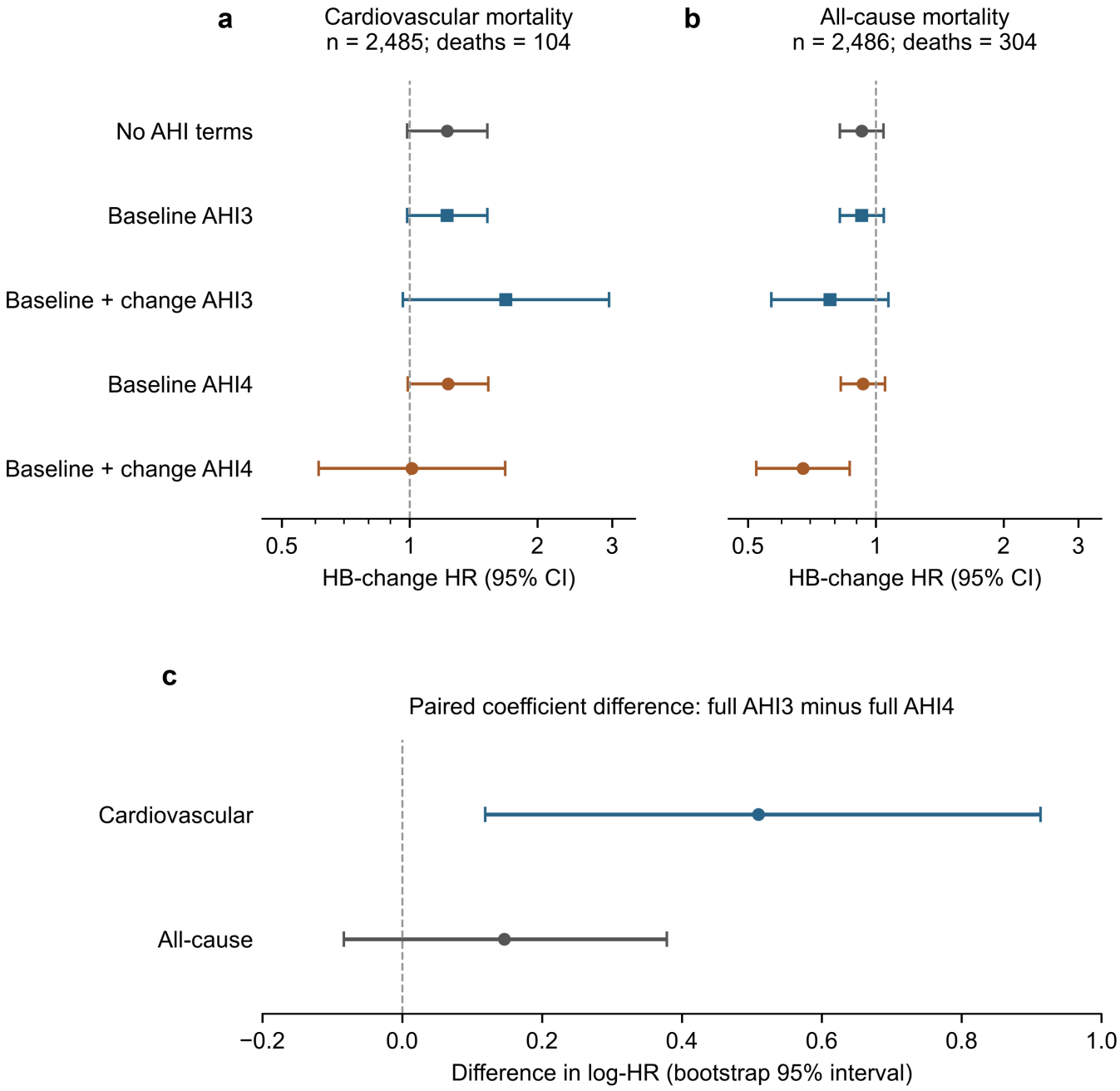
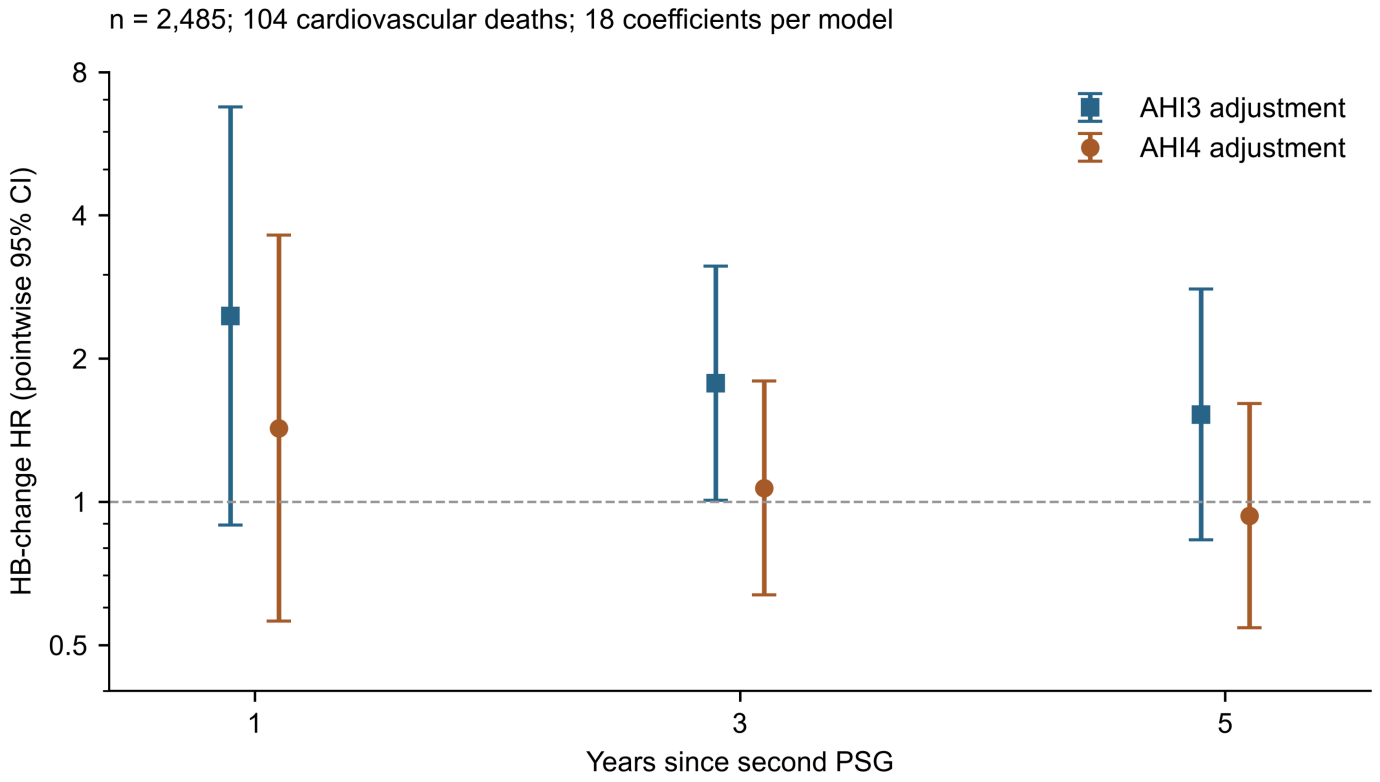


Figure 2

HB-change estimates across AHI adjustment specifications

a Cardiovascular mortality (n = 2,485; 104 deaths). b All-cause mortality (n = 2,486; 304 deaths). Points and bars show Cox-model HRs and 95% CIs per fixed SD of log-HB change (0.6952283). Each outcome uses identical participants and clinical adjustment across the five specifications, including baseline HB. Blue squares and orange circles distinguish AHI3 and AHI4 specifications; gray denotes no AHI terms. c Difference in the HB-change log-HR between the baseline-plus-change AHI3 and AHI4 models, with percentile 95% intervals from 1,000 paired participant bootstrap resamples per outcome. The bootstrap accounts for covariance between fits but not prior research-direction selection. Dashed lines mark HR =

1 in a,b and coefficient difference = 0 in c. These are exploratory conditional associations, not causal or treatment effects.



Year	1	3	5
At risk	2,459	2,382	2,183
CVD deaths through year	5	29	73

Figure 3

Exploratory time-specific HB-change estimates

Points show HB-change HRs per fixed SD and pointwise 95% CIs at 1, 3 and 5 years after the second PSG. Models additionally allow age, current-smoking, diabetes, HB-change and AHI-change effects to vary with log(t/5); each contains 18 coefficients and 104 cardiovascular deaths in 2,485 participants. The two-degree-of-freedom likelihood-ratio tests for the joint HB-change and AHI-change time-interaction block gave P = 0.654 for AHI3 and P = 0.652 for AHI4. These results neither establish proportional hazards nor demonstrate a temporal trend. All saved time points are shown; intervals are pointwise, without multiplicity adjustment. The lower rows report participants at risk and cumulative cardiovascular deaths through each year. Small horizontal offsets separate the two models at the same time point.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2.zip
- Additionalfile1.docx