

ASSOCIATION OF PSG INDICES WITH BLOOD PRESSURE

A Systematic Assessment of the Association of Polysomnographic Indices with Blood Pressure: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Study Objective: Blood pressure (BP) may be adversely affected by a variety of sleep disturbances, including sleep fragmentation, hypoxemia, respiratory disturbances, and periodic limb movements. We aim to identify which polysomnography indices are most strongly and consistently associated with systolic and diastolic blood pressure (SBP, DBP) levels in a population-based sample.

Design: Cross-sectional analysis of data from 2,040 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who underwent polysomnography at MESA Exam 5 in 2011–2013.

Setting: Multisite cohort study.

Participants: Participants were mean age 68 y (54% females; 28% African American, 24% Hispanic, 11% Chinese).

Measurements: Thirty-two candidate polysomnography predictors were identified representing the domains of breathing disturbance frequency, hypoxemia, sleep architecture, and periodic limb movements. Cluster analysis was used for variable reduction. Statistical models, adjusted for potential confounders, were derived using stepwise regression. Final models were selected using cross-validation techniques.

Results: The apnea-hypopnea index (AHI) defined using a 4% desaturation hypopnea criterion (AHI4P) was most consistently associated with SBP level. The AHI and periodic limb movement index (associated with arousals; PLMIA) were significantly associated with DBP. Estimated adjusted differences in SBP and DBP levels between an individual with no sleep apnea (AHI4P = 0) and one with moderately severe sleep apnea (AHI4P = 30) were 2.2 mm Hg and 1.1 mm Hg, respectively. Each 10-unit increase in the PLMIA was associated with an increase in DBP of 1.2 mm Hg.

Conclusion: Our results support the use of a currently recommended apnea-hypopnea index definition as a marker of blood pressure risk and indicate that measurement of limb movements with arousals is also independently associated with diastolic blood pressure.

Keywords: cluster analysis, cohort study, cross validation, diastolic blood pressure, hypertension, imputation, multiethnic, sleep exposure, systolic blood pressure

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INTRODUCTION

Hypertension is prevalent in the United States, with a third of adults having a hypertension diagnosis.^{1–4} Untreated hypertension is associated with an increased risk of cardiovascular disease, ischemic heart disease, stroke, and congestive heart failure.⁵ There are a number of well-established risk factors for hypertension, such as advanced age, obesity, sodium intake, reduced physical activity, alcohol intake, diabetes mellitus, elevated low-density lipoprotein, smoking, psychological factors, and family history.^{6–9} Additionally, recent data point to sleep disturbances as novel and potentially modifiable risk factors for hypertension. During healthy sleep, blood pressure decreases by 10% or more, a condition known as nocturnal dipping. During disturbed sleep, with or without hypoxemia occurring secondary to disordered breathing, the normal parasympathetic-sympathetic nervous system balance may be altered, contributing to non-dipping or reverse nocturnal dipping, as well as sustained daytime hypertension.^{10,11} Experimental

exposures to episodes of airway occlusion or arousal¹² or to selective deprivation of slow wave sleep,¹³ or to a single night of sleep deprivation¹⁴ lead to acute blood pressure elevations. Prospective studies also indicate that incident hypertension is increased in association with untreated sleep disordered breathing (SDB),^{15–21} periodic limb movements (PLMs),^{22–28} and curtailed sleep duration,²⁹ as well as reduced slow wave sleep duration.³⁰ However, prior research has not systematically or comprehensively addressed the independent relationships of these varied sleep disturbances to hypertension in population samples. Understanding which sleep exposures are most consistently associated with elevated blood pressure could provide physiological insights into hypertension mechanisms as well as help inform the choice of sleep parameters for measurement in clinical or research settings.

In this study, we aimed to systematically evaluate the association of measures of breathing disturbances, sleep fragmentation, sleep duration, hypoxemia, limb movements, and sleep stage distribution with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a large, ethnically diverse population, the Multi-Ethnic Study of Atherosclerosis (MESA).³¹ To address the analytical challenges that arise when modeling multiple measures, many of which are highly correlated (Tables S1–S6, supplemental material), we use a rigorous four-stage statistical modeling procedure. Looking across five sleep exposure domains—sleep structure, arousals, breathing event frequency, oxygen saturation and

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limb movements—we specifically sought to identify which sleep measures associate with elevated blood pressure. We hypothesized that one or more sleep exposures would be selected by the analysis procedure and that the selected sleep measure may differ by SBP and DBP.

METHODS

Sample and Protocol

The current report is based on data collected from MESA, a multicenter prospective study designed to investigate the progression from subclinical to clinical cardiovascular disease.³¹ In total, 6,814 participants free of cardiovascular disease were recruited from July 2000 to August 2002 from six sites (Baltimore, MD; Chicago, IL, Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St. Paul, MN) and underwent assessment of a wide range of cardiovascular disease risk factors and measures of subclinical cardiovascular disease as described previously.³¹ Four subsequent examinations occurred after median 1.5, 3.2, 5, and 9.7 y. At Exam 5 (2010–2012), participants underwent standardized measurements of height, weight, and blood pressure and other measurements at a research clinic exam. Resting blood pressure was measured in triplicate using a Dinamap automated device (Model PRO 100, GE Healthcare) in a sitting position from the right arm during a morning examination (average measurement time 08:54 ± 48 min). The first blood pressure measurement was recorded after 5 min in the sitting position. Subsequent measurements were 5 min apart. Anthropometry was performed as previously described.³² Medical history, personal history, medication use, and physical activity were obtained using standardized questionnaires.³¹

Participants in Exam 5 were invited to participate in a sleep examination for collection of polysomnography (PSG), actigraphy, and sleep questionnaire data during a subsequent in-home examination. Sleep habits and sleep symptoms were collected with a sleep questionnaire adapted from the Hispanic Community Health Study Sleep Questionnaire³³ and which includes questions from validated instruments.^{22,34–37} Unattended PSG was conducted in the participants' homes or other convenient location by certified staffed members who followed procedures similar to those described for the Sleep Heart Health Study.³⁵ PSG data were collected using a 15-channel monitor (Compumedics Somte System; Compumedics Ltd., Abbotsville, AU). The recoding montage included central, frontal, and occipital electroencephalography (EEG) sampled at 256 Hz, bilateral electrooculograms, a chin electromyogram, bipolar echocardiography, thoracic and abdominal respiratory inductance plethysmography, airflow measured by thermocouple and nasal pressure cannula, finger pulse oximetry, and bilateral limb movements measured using piezoelectric sensors. The median time between the Exam 5 clinic examination and the sleep study was 300 days. Institutional Review Board approval was obtained at each study site and written informed consent was obtained from all participants.

PSG Scoring

Each sleep study was reviewed for quality and scored by registered polysomnologists according to standardized criteria,³⁸

using similar approaches as for the Sleep Heart Health Study at a centralized reading center (Brigham and Women's Hospital, Boston, MA).^{39,40} Sleep stages and arousals were scored according to American Academy of Sleep Medicine scoring guidelines.⁴¹ Apneas were scored when the thermocouple signal flattened or nearly flattened for greater than 10 sec. Hypopneas were scored when the amplitude of the sum of the abdominal and thoracic inductance signals or the nasal pressure flow signal decreased by 30% or more for greater than or equal to 10 sec. Events were classified as either “central” or “obstructive” according to the presence of absence of respiratory effort. Specialized software link apnea and hypopnea with data from the oxygen saturation and EEG signals, allowing each event to be characterized according to the degree of associated desaturation and arousal. PLMs were identified by the number and pattern of limb movements (greater than four movements each separated by 5–90 seconds). Software provide summary measures of apnea-hypopnea indices (AHIs) computed using different degrees of associated desaturation and arousal, arousal indices, and PLM index computed with all limb movements or limb movements with EEG arousals, with all indices stratified by rapid eye movement (REM) and nonrapid eye movement (NREM) sleep (Table 1). Given the multiple ways to derive these various indices, in total, over 2,500 PSG variables were available for potential analysis.

Definitions

The average of the second and third blood pressure measurements taken from Exam 5 were used to calculate SBP and DBP. Hypertension is defined as SBP > 140 mm Hg, SBP > 90, or use of hypertension medication. For statistical modeling, measured values of SBP and DBP values were adjusted for hypertension medication use by an imputation technique described in the literature.^{42,43} This imputation approach used data from the subset of new drug users throughout the MESA study to build a parametric model to estimate the underlying untreated variable of interest as a function of observed treated value, type of medication, and patient characteristics, assuming that the most recent pretreatment value is the underlying unobserved untreated value at the time when the first posttreatment value was measured. This is a reasonable assumption because the model was built based on the subset of new drug users and their pretreatment value and “unobserved untreated values” are not too far apart in time. The specific imputation model used included the following variables: observed on-treatment SBP or DBP, indicators for each class of antihypertensive medication (beta blockers, calcium channel blockers, diuretics, ace inhibitors/angiotensin II receptor blockers, vasodilators), age, sex, race/ethnicity, body mass index, diabetes, high-density lipoprotein and total cholesterol, smoking status (never/former/current), all two-way interactions between different medication types, and two-way interactions between each of sex and race/ethnicity with each medication type. To incorporate the variability in the imputed values, we generated 10 imputed SBP and DBP datasets and pooled the results using standard multiple imputation methods.⁴⁴ Medication use was assessed from review of the participants' medication containers. Smoking and alcohol status was determined by a personal history questionnaire.

Table 1—Candidate sleep exposures.

Arousal Index (per hour of sleep)

Arousal index	Overall arousal index
Arousal (NREM)	Arousal index during NREM
Arousal (REM)	Arousal index during REM sleep

Breathing Disturbance Index (per hour of sleep)

Central apnea (All desat)	Central apnea index, all central events regardless of I desaturation
Central apnea (4% desat)	Central apnea index; central events with $\geq 4\%$ desaturation
AHI4P	All obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation
AHI4PA	All obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation or arousal
OAHI3P	Obstructive apneas (all desaturations), hypopneas with a $\geq 3\%$ desaturations
OAHI3PA	Obstructive apneas (all desaturations), hypopnea with a $\geq 3\%$ desaturation or arousal
OAHI4PA	Obstructive apnea (all desaturation), hypopnea with a $\geq 4\%$ desaturation or arousal
AHI_AII_3P	Central apneas, obstructive apneas, and hypopneas, each with a $> 3\%$ desaturation
AHI_AII_PA	Central apneas, obstructive apneas, and hypopneas, each with a $> 3\%$ desaturation or arousal
AHI_AII_4P	Central apneas, obstructive apneas, and hypopneas, each with a $> 4\%$ desaturation
AHI_AII_4PA	Central apneas, obstructive apneas, and hypopneas, each with a $> 4\%$ desaturation or arousal
AHI_AII_3P-NREM	Central apneas, obstructive apneas, and hypopneas, each with a $> 3\%$ desaturation, in NREM sleep
AHI_AII_4P-NREM	Central apneas, obstructive apneas, and hypopneas, each with a $> 3\%$ desaturation, in NREM sleep obstructive apnea ($> 4\%$ desaturation) or Hypopnea ($> 4\%$ desaturation) or central Apnea ($> 4\%$ desaturation, during NREM
AHI_AII_3P-REM	Central apneas, obstructive apneas, and hypopneas, each with a $> 3\%$ desaturation, in REM sleep
AHI_AII_4P-REM	Central apneas, obstructive apneas, and hypopneas, each with a $> 4\%$ desaturation, in REM sleep

Hypoxemia (%)

Average SaO ₂	Average SaO ₂ in sleep
Minimum SaO ₂	Minimum SaO ₂ in sleep
%SaO ₂ < 90%	Percent sleep time at < 90% desaturation

Limb Movement (per hour of sleep)

PLMI	Number of PLM per hour of sleep
PLMIA	Number of PLM with arousal per hour of sleep
PLMI-REM	Number of PLM per hour of REM sleep
PLMI-NREM	Number of PLM per hour of NREM sleep

Sleep Structure

Sleep efficiency (%)	Proportion of sleep period A sleep (%)
Sleep maintenance (%)	Percentage of time between sleep onset and lights on that was spent sleeping
Sleep duration (min)	Sleep time (min)
REM (%)	Percent sleep time in REM
Slow wave (%)	Percent sleep time in stage N3
N1 (%)	Percent sleep time in stage N1
N2 (%)	Percent time in stage N2

AHI, apnea-hypopnea index; NREM, nonrapid eye movement; PLM, periodic limb movement; REM, rapid eye movement; SaO₂, saturated oxygen.

Smoking status was defined as having ever smoked (yes/no) and the variable was dichotomized from the current smoking status question. Alcohol use was defined as a positive response to the statement, “Presently Drink Alcohol.” Information on potential cardiovascular disease (CVD) events was obtained during each cohort exam and follow-up calls to each participant that occurred every 10–12 mo. Reported events were confirmed by a centralized endpoint committee based on medical record abstractions, death certificates, autopsy reports, and/or obituaries. CVD events included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), stroke,

stroke death, coronary heart disease death, other atherosclerotic death, and other CVD death.⁴⁵ Diabetes was defined as fasting glucose ≥ 126 ml/dL and/or use of antidiabetes medications, a definition based on the 2003 American Diabetes Association criteria.^{46,47} Congestive heart failure (CHF) was adjudicated and required one or more criteria, such as pulmonary edema/congestion by chest x-ray, dilated ventricle, reduced left ventricular function, or diastolic dysfunction by an imaging study. CHF events required physician diagnosis, supporting clinical evidence and symptoms such as shortness of breath or edema.⁴⁸ Covariates were derived from MESA Exam 5 and follow-up of 10 measurements.

to identify those variables that were most strongly and consistently associated with blood pressure.⁵²

Exposure Selection (Variable Reduction)

Each sleep study included 2,687 scored sleep variables across 11 groupings (Figure 1), including indices specific for REM/NREM sleep and indices with and without different degrees of oxygen desaturation and/or arousal. The first data reduction was accomplished by reviewing commonly used sleep terms in the literature and reviewing the selected variables with practicing sleep clinicians. The variable selection process was designed to ensure that variables across arousals, breathing disturbances, hypoxemia, limb movements, and sleep structure domain were included. The primary objective of the data selection step was to ensure that the generated models were clinically relevant and interpretable. The initial data reduction step resulted in 32 polysomnographic indices that represented indices from each of the aforementioned five domains^{49–51} (Table 1). Second, cluster analysis was used to reduce this variable set to a smaller representative subset. This approach first found groups of variables that were as correlated as possible among themselves and as uncorrelated as possible with variables in other clusters, then chose one variable from each group with a high correlation with its own cluster and a low correlation with the other clusters.^{49,51}

Statistical Modeling

The group of candidate sleep measurements selected by the data reduction method were evaluated for their association with SBP and DBP adjusted for hypertension medication use using a tenfold cross-validated stepwise variable selection procedure.⁵² In the stepwise procedure, variables were included at $P \leq 0.05$ and removed at $P \geq 0.1$. The P value was computed based on an F-test of the change in the sum of squared error by adding or removing the term. The cross validation procedure generated 10 models by first randomly dividing the dataset into 10 approximately equal partitions. The stepwise procedure was applied to nine tenths of the data, resulting in a model that was validated in the remaining one tenth of data not used during the model fitting procedure. Of the 10 generated models, the model with the lowest mean square error was selected as the final model. The final model was fit to the entire dataset. All models were adjusted for ethnicity, age, sex, alcohol use, smoking, body mass index (BMI), and waist circumference. Each of the 10 SBP and DBP imputed data sets were fit; model parameter estimates were obtained by averaging the estimates from each imputed dataset using the

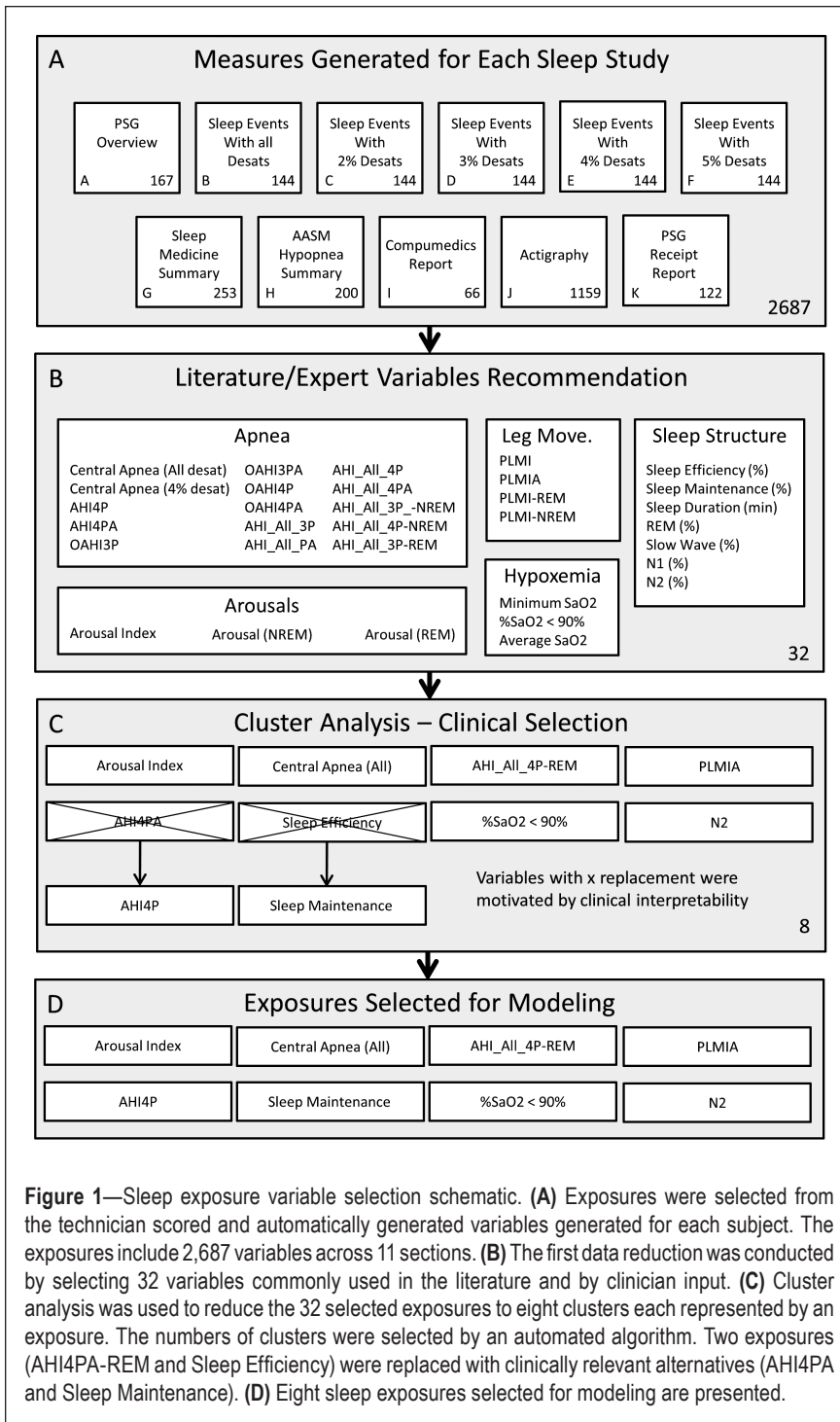


Figure 1—Sleep exposure variable selection schematic. (A) Exposures were selected from the technician scored and automatically generated variables generated for each subject. The exposures include 2,687 variables across 11 sections. (B) The first data reduction was conducted by selecting 32 variables commonly used in the literature and by clinician input. (C) Cluster analysis was used to reduce the 32 selected exposures to eight clusters each represented by an exposure. The numbers of clusters were selected by an automated algorithm. Two exposures (AHI4PA-REM and Sleep Efficiency) were replaced with clinically relevant alternatives (AHI4PA and Sleep Maintenance). (D) Eight sleep exposures selected for modeling are presented.

Statistical Methods

Overview

A cross section analysis aimed at identifying sleep exposures predictive of SBP and DBP is undertaken. A four-stage procedure was used to prioritize polysomnographic indices for subsequent statistical modeling from five domains (breathing disturbance frequency, overnight hypoxemia, sleep fragmentation, sleep stage distribution, and PLMs) through use of variable reduction procedures.^{49–51} After reducing the set of exposure variables, stepwise regression modeling and cross validation of the reduced set of exposure variables were conducted

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Table 2—Sample characteristics by median blood pressure.

Characteristic	Systolic Blood Pressure			Diastolic Blood Pressure		
	62–120 mm Hg Median (IQR)	120–250 mm Hg Median (IQR)	P	41–68 mm Hg Median (IQR)	68–113 mm Hg Median (IQR)	P
Age (y)	65.00 (15.00)	71.00 (14.00)	< 0.0001	71.00 (16.00)	65.00 (13.00)	< 0.0001
BMI (kg/m ²)	27.32 (7.19)	28.56 (7.29)	< 0.0001	27.54 (7.53)	28.29 (6.87)	0.0007
Waist (cm)	97.00 (18.93)	99.90 (18.38)	< 0.0001	97.50 (19.45)	99.40 (17.50)	0.0014
Race	N (%)	N (%)		N (%)	N (%)	
White	463 (55.9)	366 (44.1)	0.0002	459 (55.4)	370 (44.6)	0.0006
Chinese	146 (55.1)	119 (44.9)	0.0872	115 (43.4)	150 (56.6)	0.0265
Black	235 (38.2)	380 (61.8)	< 0.0001	269 (43.7)	346 (56.3)	0.0008
Hispanic	263 (50.0)	263 (50.0)	1.0000	260 (49.4)	266 (50.6)	0.7806
Sex						
Female	580 (48.5)	617 (51.5)	0.2116	709 (59.2)	488 (40.8)	< 0.0001
Male	527 (50.8)	511 (49.2)	0.5710	394 (38.0)	644 (62.0)	< 0.0001
HTN Meds, Yes	505 (41.9)	699 (58.1)	< 0.0001	619 (51.4)	585 (48.6)	0.2518
Smoking status, Smoked	515 (51.4)	486 (48.6)	0.2982	490 (49.0)	511 (51.0)	0.4513
Current alcohol use, Yes	511 (53.4)	446 (46.6)	0.0178	444 (46.4)	513 (53.6)	0.0119
Diabetes, Yes	133 (41.6)	187 (58.4)	0.0017	164 (51.25)	156 (48.7)	0.6426
Congestive heart failure, Yes	11 (33.3)	22 (66.7)	0.0546	21 (63.6)	12 (36.4)	0.1158
Cardiovascular disease, Yes	34 (33.3)	68 (66.7)	0.0006	60 (58.8)	42 (41.2)	0.0714

The study population was dichotomized by median (systolic and diastolic blood pressure) measurement and sample characteristic for each dichotomized group is presented. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. BMI, body mass index; HTN, hypertension; IQR, interquartile range.

multiple imputation method.^{44,53} The linearity assumptions was assessed graphically and using nonparametric regression.^{54,55} In sensitivity analyses, the final models were alternatively fit by adjusting SBP and DBP for hypertension medications by using a fixed constant (10 and 5 mm Hg, respectively, for SBP and DBP) rather than using the imputed values; and models were further adjusted for diabetes, CHF, and CVD. SAS 9.3 (Gary, IN) and MATLAB 2013a (MathWorks, Natick, MA) were used to perform analyses.

RESULTS

Sample Characteristics

PSG data were available for 2,040 MESA participants. They were age 68.0 (13.0) y (mean; standard deviation) and included 54% females, 28% African Americans, 24% Hispanics, and 12% Chinese. Of this sample, 57.5% were classified as hypertensive and 54% reporting using antihypertensive medications. The population is on average overweight (mean BMI 27.9 kg/m²). The prevalence of CVD and CHF was 4.6% and 2.5%, respectively. The average SBP and DBP are respectively 120.0 (interquartile range [IQR] = 26.0) and 68.0 (IQR = 13.0) mm Hg. Compared to participants in the Exam 5 who did not undergo the sleep examination, examination participants were younger, less likely to be hypertensive, and more likely to be Hispanic (Table S7, supplemental material).

Sample Characteristics by Level of Blood Pressure

Sample characteristics for the upper and lower 50th percentile for SBP and DBP are presented in Table 2. Higher

SBP is associated with older age, higher BMI and waist circumference, increased hypertension medication use, lower alcohol use, and African American race. Higher DBP is associated with male sex, African American race, younger age, increased BMI and waist circumference, and an increase in alcohol use.

Sleep Characteristics by Blood Pressure Level

Sleep characteristics for the upper and lower 50th percentiles of SBP and DBP are presented in Table 3. In unadjusted analyses, both overall and NREM-specific arousal indices and indices of the various apnea hypopnea indices were higher in participants with elevated SBP or DBP. However, the arousal index in REM and central apnea indices were only higher in association with elevated DBP. Additionally, measures of hypoxemia and sleep efficiency and duration were more disturbed in association with SBP than DBP, whereas PLM indices and sleep stage distributions were more abnormal in association with DBP.

Sleep Indices Selected by Cluster Analysis

The cluster procedure identified eight clusters. The sleep exposures that explained the highest proportion of variance within each cluster were: arousal index, AHI4PA (defined as all central and obstructive apneas and hypopneas with 4% desaturation or arousal), AHI_All_4P-REM (central apneas, obstructive apneas, and hypopneas, each with a > 4% desaturation, in REM sleep), central apnea (all desat), percent sleep time in oxygen saturation of less than 90%, PLM with associated arousal (PLMIA), sleep efficiency, and percentage of sleep time in stage N2. Each of the initial five sleep exposure domains represented

Table 3—Sleep exposures by median blood pressure.

Sleep Exposure	Systolic Blood Pressure			Diastolic Blood Pressure		
	62–120 mm Hg Median (IQR)	120–250 mm Hg Median (IQR)	P	41–68 mm Hg Median (IQR)	68–113 mm Hg Median (IQR)	P
Arousal indices (per hour of sleep)						
Overall arousal index	19.20 (13.32)	20.17 (14.72)	0.0838	19.04 (13.40)	20.38 (14.49)	0.0014
Arousal (NREM)	19.84 (14.59)	21.07 (16.47)	0.0253	19.91 (14.94)	20.92 (15.57)	0.0050
Arousal (REM)	15.40 (14.40)	14.59 (15.29)	0.1036	13.95 (13.78)	16.00 (15.49)	0.0002
Breathing disturbance (per hour of sleep)						
Central apnea index (All desat)	0.00 (0.27)	0.00 (0.31)	0.6626	0.00 (0.24)	0.00 (0.35)	0.0213
Central apnea index (4% desat)	0.00 (0.13)	0.00 (0.15)	0.0642	0.00 (0.13)	0.00 (0.15)	0.0277
AHI4P	7.45 (15.47)	10.26 (17.32)	0.0000	7.46 (14.81)	10.53 (17.25)	0.0000
AHI4PA	13.46 (18.67)	15.68 (21.01)	0.0006	13.24 (18.94)	15.92 (21.26)	0.0000
OAHI3P	6.33 (10.87)	7.87 (11.84)	0.0004	6.27 (10.74)	8.16 (11.91)	0.0000
OAHI3PA	9.52 (12.17)	10.63 (12.84)	0.0023	9.07 (12.17)	11.07 (13.11)	0.0001
OAH4PA	7.08 (9.74)	8.39 (10.18)	0.0025	6.92 (9.70)	8.31 (10.13)	0.0003
AHI_ALL_3P	12.19 (21.18)	15.23 (22.20)	0.0002	11.68 (20.67)	15.70 (22.91)	0.0000
AHI_ALL_3PA	16.59 (21.96)	19.64 (24.07)	0.0003	16.26 (21.87)	20.05 (24.30)	0.0000
AHI_ALL_4P	6.60 (14.66)	9.21 (16.52)	0.0001	6.52 (14.43)	9.37 (16.47)	0.0000
AHI_ALL_4PA	12.88 (18.27)	15.00 (20.58)	0.0003	12.68 (17.95)	15.31 (20.84)	0.0000
AHI_ALL_3P-NREM	8.86 (19.64)	11.00 (22.92)	0.0003	8.60 (19.41)	11.72 (23.20)	0.0000
AHI_ALL_4P-NREM	4.19 (12.26)	5.31 (15.51)	0.0003	3.96 (12.13)	5.85 (15.85)	0.0000
AHI_ALL_3P-REM	22.12 (34.65)	28.31 (35.97)	0.0000	22.24 (35.92)	28.32 (34.93)	0.0002
AHI_ALL_4P-REM	12.86 (29.25)	18.40 (33.09)	0.0000	13.64 (29.02)	17.67 (32.55)	0.0001
Hypoxemia (%)						
%SaO ₂ < 90%	0.43 (2.72)	0.83 (3.73)	0.0000	0.52 (3.20)	0.73 (3.18)	0.0635
Average SaO ₂	94.83 (2.05)	94.70 (2.22)	0.0101	94.76 (2.11)	94.77 (2.09)	0.4004
Minimum SaO ₂	86.00 (9.00)	85.00 (9.00)	0.0001	86.00 (9.00)	85.00 (8.00)	0.0322
Limb movement indices (per hour of sleep)						
Limb movement avg.	2.79 (16.36)	2.21 (19.46)	0.7863	3.42 (20.00)	1.74 (15.59)	0.0026
Limb movement avg. (arousal)	0.15 (1.42)	0.13 (1.58)	0.7106	0.21 (1.77)	0.00 (1.29)	0.0007
Limb movement avg. (REM)	0.00 (1.88)	0.00 (0.90)	0.5523	0.00 (2.30)	0.00 (0.00)	0.0165
Limb movement avg. (NREM)	2.70 (18.40)	2.05 (22.70)	0.6555	3.50 (22.70)	1.40 (17.78)	0.0034
Sleep structure						
Sleep efficiency (%)	79.03 (16.75)	77.42 (16.88)	0.0196	78.52 (16.64)	77.80 (16.65)	0.3974
Sleep maintenance (%)	83.09 (15.43)	81.44 (15.44)	0.0004	82.36 (16.16)	82.00 (15.45)	0.4221
Sleep duration (min)	374.00 (105.75)	363.00 (102.00)	0.0015	371.00 (107.00)	365.00 (102.25)	0.1582
REM (%)	19.00 (8.60)	17.90 (8.70)	0.0003	18.50 (8.45)	18.20 (8.78)	0.1909
Slow wave (%)	8.56 (13.24)	7.83 (13.80)	0.5304	8.82 (13.28)	7.91 (13.58)	0.0344
N1 (%)	11.75 (9.61)	12.40 (9.33)	0.0701	11.75 (9.64)	12.50 (9.36)	0.0146
N2 (%)	57.65 (12.55)	58.40 (13.28)	0.0956	57.80 (12.80)	58.20 (13.00)	0.2083

The study population was dichotomized by median (systolic and diastolic blood pressure) measurement and sleep exposures characteristic for each dichotomized group is presented. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. CA, central apnea; OA, obstructive apnea; IQR, interquartile range; SaO₂, saturated oxygen.

in the complete sleep exposure data set are represented in the reduced dataset of selected exposures. The selected variables were reviewed for clinical relevance and potential replacement. It was noted that the variance explained by the AHI4PA and AHI4 (all central and obstructive apneas and hypopneas with a 4% desaturation) were nearly identical. Therefore, the simpler measurement was selected, which corresponds to the American Academy of Sleep Medicine recommended definition.

SBP Model

The SBP model is depicted in Table 4. Each of the 10 cross-validated models was evaluated using the mean square error (MSE), which ranged from 228.3 to 319.6. The model with the smallest MSE was selected as the final model. All 10 models generated by the cross-validation procedure included the AHI4P and seven of 10 models included the PLMIA. The cross-validation procedure identified the AHI4P as significantly

Table 4—Systolic blood pressure models.

	Cross-Validated Model		
	Estimate (β)	SE	P
Age (y)	0.84	0.05	0.0000
Male	-2.19	0.89	0.0142
Chinese American	3.27	1.43	0.0219
African American	7.91	1.04	0.0000
Hispanic	2.58	1.09	0.0181
Alcohol use	-1.54	0.86	0.0752
Smoker	0.26	0.48	0.5968
BMI (kg/m ²)	0.39	0.16	0.0132
Waist (cm)	0.08	0.06	0.1740
AHI4P (per hour of sleep)	0.07	0.03	0.0053
PLMIA (per hour of sleep)	0.20	0.11	0.0825

Sleep exposure selected by tenfold cross validation; stepwise regression: P in = 0.05, P out = 0.10 out; model fit on entire data set is shown. Sleep exposures are selected separately for systolic and diastolic blood pressure models. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, all obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation; BMI, body mass index; PLMIA, periodic limb movement index associated with arousal per hour of sleep; SE, standard error.

Table 5—Diastolic blood pressure models.

	Cross-Validated Model		
	Estimate (β)	SE	P
Age (y)	-0.09	0.02	0.0001
Male	5.10	0.42	0.0000
Chinese American	1.55	0.68	0.0227
African American	4.78	0.50	0.0000
Hispanic	1.14	0.52	0.0285
Alcohol use	0.25	0.41	0.5475
Smoker	< 0.00	0.23	0.9959
BMI (kg/m ²)	0.04	0.08	0.6326
Waist (cm)	0.03	0.03	0.2238
AHI4P (per hour of sleep)	0.04	0.01	0.0035
PLMIA (per hour of sleep)	0.12	0.05	0.0219

Sleep exposure selected by tenfold cross validation; stepwise regression: P in = 0.05, P out = 0.10 out; model fit on entire data set is shown. Sleep exposures are selected separately for systolic and diastolic blood pressure models. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, all obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation; BMI, body mass index; PLMIA, periodic limb movement index associated with arousal per hour of sleep; SE, standard error.

associated with SBP when adjusted for age, sex, race, alcohol use, smoking, BMI, and waist ($\beta = 0.0735$ events/h/mm Hg, $P = 0.0053$). SBP model parameters variances that take into account within and between imputed dataset variance are presented in the supplementary materials (Table S8, supplemental material).

DBP Model

The DBP model is depicted in Table 5. Each of the 10 cross-validated models was evaluated using the MSE, which ranged from 45.3 to 77.5. The model with the smallest MSE was selected as the final model. All 10 models generated by the cross-validation procedure included PLMIA and eight of 10 models included the AHI4P. The best model selected by MSE included AHI4P ($\beta = 0.037$ events/h/mm Hg, $P = 0.004$) and PLMIA ($\beta = 0.123$ events/h/mm Hg, $P = 0.022$) as associated with DBP when adjusted by age, sex, race, alcohol use, smoking, BMI, and waist. DBP model parameter variances that take into account within and between imputed dataset variance are presented in the supplementary materials (Table S8).

Sensitivity Analyses

The final models for continuously measured SBP and DBP outcomes shown in Tables 3 and 4 were re-fit to the measured SBP and DBP adjusted for medication use by adding a fixed constant (10 and 5 mm Hg, respectively, for SBP and DBP) (Tables S9 and S10, supplemental material) rather than with use-imputed BP values. The SBP model resulted in comparable parameter estimates for PLMAI but had larger standard errors. The SBP model also had comparable parameters estimates for AHI4P but had larger standard errors. Similarly, the DBP models had comparable parameters for both PLMIA and

AHI4P, but with larger standard errors. Final cross-validated SBP and DBP models further adjusted for diabetes, CHF, and CVD (possible confounders or outcomes of hypertension) were consistent with the models presented in the manuscript and are provided in the supplement (Tables S11 and S12, supplemental material).

DISCUSSION

PSG provides the ability to collect numerous types of physiological data, which when processed can result in thousands of potential metrics to use for research and clinical purposes. Dissecting the relative contributions of numerous and often correlated measures poses numerous challenges. In this analysis, we attempted to overcome these challenges by applying a structured and comprehensive assessment of the association of a wide range of polysomnographic indices with blood pressure (BP) levels in a well-characterized and ethnically diverse sample. Through a rigorous cross-validated variable selection procedure, we identified two commonly used PSG metrics as providing the most consistent associations with BP. Of note, among 16 possible derivations of the AHI (using different degrees of desaturation, arousal, and inclusion or not of central events) this analysis identified the AHI4P—corresponding to the currently recommended AHI definition—as the AHI derivation that most consistently was associated with SBP and DBP. Notably, AHI metrics that used hypopnea definitions that required an arousal with or without a desaturation did not provide superior information compared to the simpler AHI4P. The selection of AHI by the methods described in this article is supported by previous findings.^{20,21,56} Of note, the utility of using an AHI at 4% oxygen desaturation has been identified using data from the Sleep Heart Health Study²⁰ and the Wisconsin Sleep

Cohort Study.²¹ After AHI was included in the models considered, there was little added predictive information for SBP attributable to consideration of arousal frequency, hypoxemia, or sleep stage distribution. The PLMIA (i.e., PLM associated with arousals) was significantly associated with DBP, and marginally associated with SBP. These analyses support the clinical utility of a commonly measured AHI^{20,21,56} as well as the PLM index (with arousals) for characterizing physiological sleep disturbances associated with outcomes such as hypertension.

A major challenge in analyzing the association between measures of sleep disturbances and BP relates to the frequent use of antihypertensive medication in older adults. Because of this, most prior research studies have not analyzed continuously measured BP values, but rather have analyzed binary outcomes that have combined measured BP values with self-reported medication use.^{20,29,57–59} This approach has numerous limitations and does not address the potential effect of sleep disturbances on BP level. Through use of a rigorous imputation procedure that estimated BP level with use of longitudinal study data, we were able to estimate the incremental influence of variation in AHI and PLMIA on BP level. After adjusting for key confounders, we estimate that each 10-unit increment in the AHI corresponds to a 0.74 mm Hg increase in SBP and a 0.37 mm Hg increase in DBP. In other words, the estimated adjusted differences in SBP and DBP levels between an individual with no sleep apnea (AHI4P = 0) and moderately severe sleep apnea (AHI4P = 30) is 2.2 and 1.1 mm Hg, respectively. Similarly, comparing those without sleep apnea to those with severe sleep apnea (AHI4P = 60) yields estimated average adjusted differences in SBP and DBP of 4.4 and 1.2 mm Hg, respectively. The estimated BP differences between individuals without and with moderate to severe sleep apnea are similar in magnitude to the reported differences in BP level after sleep apnea intervention with continuous positive airway pressure observed in clinical trials.^{60,61} In aggregate, these data support the growing consensus that sleep apnea contributes to elevations in BP and our findings quantify the average increase in SBP and DBP across a range of the AHI.

For DBP, we also identified a strong association between the PLMIA and elevations in BP. Our model estimated that for each 10-unit per hour increase in the number of PLMs associated with arousals, DBP was increased by 1.2 mm Hg. A similar association was observed for SBP, but with a wider standard error. This finding has potentially large implications for individuals with PLM disorder who may experience hundreds of limb movements per night, and also indicates that individuals with a lower frequency of nocturnal limb movements may have BP elevations. An adverse effect of PLMs on BP is supported by recent population and clinical research. PLMs are associated with bursts of sympathetic activity, increased heart rate, and acute surges in BP,²³ which may provide a basis for sustained daytime hypertension. PLMs with arousals are also more likely to disturb sleep quality than are leg movements unassociated with arousals.⁶² The finding of a stronger association between BP and PLMs associated with arousals compared to all PLMs is similar to the strong association observed for the PLMIA with peripheral vascular disease in the Outcomes of Sleep Disorders in Older Men (MrOS) Study.⁶³ PLMS also may co-occur with restless legs syndrome, which

has been associated with an increased odds ratio for hypertension in the Nurse's Health Study II.⁶⁴ Our findings, based on a rigorous assessment of sleep disturbances across five domains, indicate that measurement of leg movement frequency may be important in understanding vascular risk.

Identifying the best predictors of hypertension in sleep-monitoring data is challenging because of multiple interacting physiological pathways that result in correlated physiological signals. Prior research has compared selective sleep measures. In the Sleep Heart Health Study, cross-validation procedures implemented to identify PSG predictors of BP produced less consistent results compared with the current study, possibly because of differences in modeling and the adjustment procedures for BP medications.⁶⁵ Sulit et al.⁶⁶ identified the arousal index as a stronger predictor of hypertension than AHI in 394 subjects in the Cleveland Family Study (CFS). Study differences may relate to the consideration of a dichotomous hypertension outcome of because of the younger age in the CFS.

Although the AHI has been criticized because of the limitations of a "count" in quantifying sleep disturbances, the current findings suggest that after AHI is considered other measures of hypoxemia and sleep fragmentation may not appreciably improve the prediction of BP. This may be because the AHI reflects influences related to changes in inspiratory effort, pleural pressure swings, oxygen saturation, and sleep fragmentation that together may contribute to changes in BP level.

We faced several data analysis challenges related to the number of sleep exposures of interest and their known inter-correlations. We addressed this by first identifying variables that represent five classes of sleep disturbances and then applied a systematic variable selection approach which avoided overfitting of highly correlated measures. For data reduction, we chose the variable clustering method instead of principal component analysis or factor analysis because of the ability to easily interpret individual variables that each represented a cluster of correlated indices. Furthermore, the use of a cross-validated model building strategy provided an objective way to select statistical models, reducing the chance of identifying spurious or nonreplicable associations. In addition, we used a sophisticated approach for imputing BP level in individuals on medications, which accounts for additional uncertainty associated with imputing unobserved blood pressure values compared to an alternative strategy of adding a constant to the BP values. These statistical approaches may be adapted to future studies that share some of these challenges related to multiple correlated variables or to interest in modeling continuous outcomes that can be affected by medication use.

The study strengths include the analysis of highly standardized data with available longitudinal data, enabling imputation of BP levels. The cohort provided a broad ethnic representation. The sleep data were both comprehensive and rigorously analyzed. Well-delineated statistical methods provided a systematic methodology for selecting candidate sleep exposures; the cross-validation technique reduced the likelihood that the models are spurious or over fitted.

There are also several study limitations. The cross-sectional analysis limits causal inferences. Although consistent with the goal of generating clinically interpretable models, it is possible that in the process of reducing the dataset to 32 candidate

variables, several predictive variables may have been missed. Further application of the cluster analysis technique in other cohort studies is warranted to better understand the generalizability of our findings, including sensitivity to population and measurement differences. As with any imputation-based approaches, the accuracy of imputed blood pressure values relies on the underlying assumptions. The key assumption of treating the last pretreatment value as the first unobserved untreated value posttreatment appeared to be reasonable because the imputation model was built based on the subset of new drug users whose last pretreatment value and first unobserved untreated values posttreatment are not too far apart in time.

In summary, this study found that AHI and limb movements with arousals to be consistently associated with elevations in BP. The estimated effects for individuals with frequent breathing disturbances or limb movements are in the range considered clinically significant. Furthermore, our results supported a commonly used definition for the AHI. Although linking hypopneas with arousals did not strengthen the association between AHI and BP, linking arousals to limb movements did result in a PLM index that was strongly associated with DBP. Thus, future PSG montages may benefit from including sensors that allow reliable derivation of both the AHI as well as the PLMIA. Last, our findings suggest that PLMIA may be an addressable risk for hypertension, which warrants future study.

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Table S1—Sleep exposure Spearman rank correlation coefficients for arousals.

	Arousals		
	Arousal Index	Arousal (NREM)	Arousal (REM)
Arousals (per hour of sleep)			
Arousal index	1.00	0.98	0.57
Arousal (NREM)	0.98	1.00	0.44
Arousal (REM)	0.57	0.44	1.00
Breathing disturbance (per hour of sleep)			
Central apnea (All desat)	0.15	0.16	0.03
Central apnea (4% desat)	0.18	0.19	0.05
AHI4P	0.48	0.46	0.36
AHI4PA	0.65	0.63	0.45
OAHI3P	0.46	0.44	0.31
OAHI3PA	0.57	0.56	0.38
OAH4PA	0.62	0.60	0.42
AHI_ALL_3P	0.49	0.48	0.35
AHI_ALL_3PA	0.62	0.60	0.42
AHI_ALL_4P	0.46	0.44	0.34
AHI_ALL_4PA	0.66	0.63	0.45
AHI_ALL_3P-NREM	0.52	0.52	0.31
AHI_ALL_4P-NREM	0.49	0.48	0.29
AHI_ALL_3P-REM	0.31	0.26	0.40
AHI_ALL_4P-REM	0.31	0.26	0.40
Hypoxemia (%)			
Average SaO ₂	-0.18	-0.18	-0.09
Minimum SaO ₂	-0.24	-0.22	-0.24
%SaO ₂ < 90%	0.28	0.26	0.22
Limb movement (per hour of sleep)			
PLMI	0.06	0.08	-0.05
PLMIA	0.17	0.19	-0.01
PLMI-REM	-0.02	-0.01	-0.03
PLMI-NREM	0.06	0.08	-0.06
Sleep structure			
Sleep efficiency (%)	-0.32	-0.32	-0.11
Sleep maintenance (%)	-0.35	-0.35	-0.12
Sleep duration (min)	-0.19	-0.19	-0.09
REM (%)	-0.32	-0.29	-0.17
Slow wave (%)	-0.17	-0.18	-0.05
N1 (%)	0.65	0.66	0.29
N2 (%)	-0.16	-0.18	-0.09

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMI, periodic limb movement index; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S2—Sleep exposure Spearman rank correlation coefficients breathing disturbances I.

	Breathing Disturbances						
	Central apnea (All desat)	Central apnea (4% desat)	AHI4P	AHI4PA	OAHI3P	OAHI3PA	OAH4PA
Arousals (per hour of sleep)							
Arousal index	0.15	0.18	0.48	0.65	0.46	0.57	0.62
Arousal (NREM)	0.16	0.19	0.46	0.63	0.44	0.56	0.60
Arousal (REM)	0.03	0.05	0.36	0.45	0.31	0.38	0.42
Breathing disturbance (per hour of sleep)							
Central apnea (All desat)	1.00	0.81	0.26	0.26	0.19	0.18	0.18
Central apnea (4% desat)	0.81	1.00	0.35	0.33	0.29	0.26	0.25
AHI4P	0.26	0.35	1.00	0.94	0.89	0.82	0.81
AHI4PA	0.26	0.33	0.94	1.00	0.86	0.88	0.89
OAHI3P	0.19	0.29	0.89	0.86	1.00	0.95	0.91
OAHI3PA	0.18	0.26	0.82	0.88	0.95	1.00	0.98
OAH4PA	0.18	0.25	0.81	0.89	0.91	0.98	1.00
AHI_ALL_3P	0.23	0.35	0.97	0.94	0.90	0.84	0.80
AHI_ALL_3PA	0.24	0.34	0.95	0.99	0.88	0.89	0.87
AHI_ALL_4P	0.21	0.33	0.98	0.92	0.88	0.80	0.78
AHI_ALL_4PA	0.24	0.32	0.94	1.00	0.85	0.88	0.88
AHI_ALL_3P-NREM	0.27	0.36	0.93	0.92	0.88	0.83	0.80
AHI_ALL_4P-NREM	0.25	0.36	0.94	0.90	0.86	0.80	0.77
AHI_ALL_3P-REM	0.02	0.15	0.77	0.71	0.69	0.64	0.60
AHI_ALL_4P-REM	0.02	0.15	0.79	0.72	0.70	0.63	0.61
Hypoxemia (%)							
Average SaO ₂	-0.02	-0.14	-0.52	-0.45	-0.55	-0.48	-0.41
Minimum SaO ₂	-0.05	-0.18	-0.75	-0.65	-0.66	-0.58	-0.56
%SaO ₂ < 90%	0.05	0.19	0.76	0.67	0.70	0.61	0.58
Limb movement (per hour of sleep)							
PLMI	0.01	0.00	-0.07	-0.04	-0.08	-0.06	-0.06
PLMIA	0.01	0.02	-0.08	-0.03	-0.09	-0.07	-0.06
PLMI-REM	-0.02	-0.04	-0.07	-0.05	-0.09	-0.08	-0.08
PLMI-NREM	0.01	0.01	-0.06	-0.03	-0.07	-0.05	-0.05
Sleep structure							
Sleep efficiency (%)	-0.02	-0.03	-0.16	-0.23	-0.16	-0.20	-0.22
Sleep maintenance (%)	-0.04	-0.05	-0.20	-0.26	-0.18	-0.22	-0.24
Sleep duration (min)	0.03	0.00	-0.12	-0.16	-0.10	-0.12	-0.14
REM (%)	-0.01	-0.04	-0.21	-0.25	-0.23	-0.25	-0.25
Slow wave (%)	-0.05	-0.05	-0.14	-0.17	-0.10	-0.10	-0.11
N1 (%)	0.12	0.16	0.42	0.52	0.38	0.44	0.48
N2 (%)	-0.07	-0.06	-0.10	-0.13	-0.10	-0.12	-0.14

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S3—Sleep exposure Spearman rank correlation coefficients for breathing disturbances II.

	Breathing Disturbances							
	AHI_ALL_3P	AHI_ALL_3PA	AHI_ALL_4P	AHI_ALL_4PA	AHI_ALL_3P-NREM	AHI_ALL_4P-NREM	AHI_ALL_3P-REM	AHI_ALL_4P-REM
Arousals (per hour of sleep)								
Arousal index	0.49	0.62	0.46	0.66	0.52	0.49	0.31	0.31
Arousal (NREM)	0.48	0.60	0.44	0.63	0.52	0.48	0.26	0.26
Arousal (REM)	0.35	0.42	0.34	0.45	0.31	0.29	0.40	0.40
Breathing disturbance (per hour of sleep)								
Central apnea (All desat)	0.23	0.24	0.21	0.24	0.27	0.25	0.02	0.02
Central apnea (4% desat)	0.35	0.34	0.33	0.32	0.36	0.36	0.15	0.15
AHI4P	0.97	0.95	0.98	0.94	0.93	0.94	0.77	0.79
AHI4PA	0.94	0.99	0.92	1.00	0.92	0.90	0.71	0.72
OAHI3P	0.90	0.88	0.88	0.85	0.88	0.86	0.69	0.70
OAHI3PA	0.84	0.89	0.80	0.88	0.83	0.80	0.64	0.63
OAH4PA	0.80	0.87	0.78	0.88	0.80	0.77	0.60	0.61
AHI_ALL_3P	1.00	0.96	0.98	0.94	0.96	0.94	0.79	0.79
AHI_ALL_3PA	0.96	1.00	0.93	0.99	0.94	0.91	0.74	0.74
AHI_ALL_4P	0.98	0.93	1.00	0.92	0.93	0.95	0.79	0.81
AHI_ALL_4PA	0.94	0.99	0.92	1.00	0.92	0.90	0.71	0.73
AHI_ALL_3P-NREM	0.96	0.94	0.93	0.92	1.00	0.98	0.63	0.65
AHI_ALL_4P-NREM	0.94	0.91	0.95	0.90	0.98	1.00	0.62	0.64
AHI_ALL_3P-REM	0.79	0.74	0.79	0.71	0.63	0.62	1.00	0.98
AHI_ALL_4P-REM	0.79	0.74	0.81	0.73	0.65	0.64	0.98	1.00
Hypoxemia (%)								
Average SaO ₂	-0.57	-0.50	-0.56	-0.46	-0.54	-0.52	-0.52	-0.51
Minimum SaO ₂	-0.73	-0.66	-0.78	-0.66	-0.65	-0.67	-0.73	-0.77
%SaO ₂ < 90%	0.76	0.69	0.80	0.68	0.69	0.71	0.72	0.75
Limb Movement (per h sleep)								
PLMI	-0.07	-0.04	-0.08	-0.04	-0.05	-0.05	-0.07	-0.07
PLMIA	-0.07	-0.03	-0.09	-0.03	-0.05	-0.06	-0.07	-0.07
PLMI-REM	-0.07	-0.05	-0.08	-0.05	-0.05	-0.06	-0.10	-0.10
PLMI-NREM	-0.06	-0.03	-0.07	-0.03	-0.04	-0.04	-0.06	-0.06
Sleep structure								
Sleep efficiency (%)	-0.17	-0.22	-0.15	-0.24	-0.18	-0.17	-0.12	-0.11
Sleep maintenance (%)	-0.20	-0.24	-0.19	-0.26	-0.21	-0.20	-0.14	-0.13
Sleep duration (min)	-0.12	-0.15	-0.12	-0.16	-0.13	-0.13	-0.09	-0.09
REM (%)	-0.22	-0.25	-0.21	-0.25	-0.27	-0.25	-0.22	-0.22
Slow wave (%)	-0.13	-0.16	-0.13	-0.16	-0.14	-0.14	-0.04	-0.05
N1 (%)	0.41	0.50	0.39	0.52	0.46	0.44	0.21	0.22
N2 (%)	-0.10	-0.12	-0.09	-0.13	-0.09	-0.09	-0.01	-0.01

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S4—Sleep exposure Spearman rank correlation coefficients for hypoxemia.

	Hypoxemia		
	Average SaO ₂	Minimum SaO ₂	%SaO ₂ < 90%
Arousals (per hour of sleep)			
Arousal index	-0.18	-0.24	0.28
Arousal (NREM)	-0.18	-0.22	0.26
Arousal (REM)	-0.09	-0.24	0.22
Breathing disturbance (per hour of sleep)			
Central apnea (All desat)	-0.02	-0.05	0.05
Central apnea (4% desat)	-0.14	-0.18	0.19
AHI4P	-0.52	-0.75	0.76
AHI4PA	-0.45	-0.65	0.67
OAHI3P	-0.55	-0.66	0.70
OAHI3PA	-0.48	-0.58	0.61
OAH4PA	-0.41	-0.56	0.58
AHI_ALL_3P	-0.57	-0.73	0.76
AHI_ALL_3PA	-0.50	-0.66	0.69
AHI_ALL_4P	-0.56	-0.78	0.80
AHI_ALL_4PA	-0.46	-0.66	0.68
AHI_ALL_3P-NREM	-0.54	-0.65	0.69
AHI_ALL_4P-NREM	-0.52	-0.67	0.71
AHI_ALL_3P-REM	-0.52	-0.73	0.72
AHI_ALL_4P-REM	-0.51	-0.77	0.75
Hypoxemia (%)			
Average SaO ₂	1.00	0.58	-0.74
Minimum SaO ₂	0.58	1.00	-0.91
%SaO ₂ < 90%	-0.74	-0.91	1.00
Limb movement (per hour of sleep)			
PLMI	0.01	0.07	-0.05
PLMIA	0.01	0.07	-0.05
PLMI-REM	0.02	0.08	-0.06
PLMI-NREM	0.00	0.06	-0.04
Sleep structure			
Sleep efficiency (%)	0.08	0.04	-0.10
Sleep maintenance (%)	0.09	0.07	-0.12
Sleep duration (min)	0.06	0.00	-0.07
REM (%)	0.12	0.14	-0.16
Slow wave (%)	0.05	0.04	-0.07
N1 (%)	-0.17	-0.21	0.25
N2 (%)	0.02	0.06	-0.05

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S5—Sleep exposure Spearman rank correlation coefficients for limb movements.

	Limb Movements			
	PLMI	PLMIA	PLMI-REM	PLMI-NREM
Arousals (per hour of sleep)				
Arousal index	0.06	0.17	-0.02	0.06
Arousal (NREM)	0.08	0.19	-0.01	0.08
Arousal (REM)	-0.05	-0.01	-0.03	-0.06
Breathing disturbance (per hour of sleep)				
Central apnea (All desat)	0.01	0.01	-0.02	0.01
Central apnea (4% desat)	0.00	0.02	-0.04	0.01
AHI4P	-0.07	-0.08	-0.07	-0.06
AHI4PA	-0.04	-0.03	-0.05	-0.03
OAHI3P	-0.08	-0.09	-0.09	-0.07
OAHI3PA	-0.06	-0.07	-0.08	-0.05
OAH4PA	-0.06	-0.06	-0.08	-0.05
AHI_ALL_3P	-0.07	-0.07	-0.07	-0.06
AHI_ALL_3PA	-0.04	-0.03	-0.05	-0.03
AHI_ALL_4P	-0.08	-0.09	-0.08	-0.07
AHI_ALL_4PA	-0.04	-0.03	-0.05	-0.03
AHI_ALL_3P-NREM	-0.05	-0.05	-0.05	-0.04
AHI_ALL_4P-NREM	-0.05	-0.06	-0.06	-0.04
AHI_ALL_3P-REM	-0.07	-0.07	-0.10	-0.06
AHI_ALL_4P-REM	-0.07	-0.07	-0.10	-0.06
Hypoxemia (%)				
Average SaO ₂	0.01	0.01	0.02	0.00
Minimum SaO ₂	0.07	0.07	0.08	0.06
%SaO ₂ < 90%	-0.05	-0.05	-0.06	-0.04
Limb movement (per hour of sleep)				
PLMI	1.00	0.90	0.56	0.98
PLMIA	0.90	1.00	0.47	0.90
PLMI-REM	0.56	0.47	1.00	0.47
PLMI-NREM	0.98	0.90	0.47	1.00
Sleep structure				
Sleep efficiency (%)	-0.01	-0.04	0.04	-0.02
Sleep maintenance (%)	-0.01	-0.05	0.04	-0.02
Sleep duration (min)	-0.02	-0.03	0.02	-0.01
REM (%)	0.00	-0.02	0.15	-0.01
Slow wave (%)	-0.10	-0.08	-0.14	-0.08
N1 (%)	0.07	0.11	0.09	0.06
N2 (%)	0.04	0.01	-0.03	0.04

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S6—Sleep exposure Spearman rank correlation coefficients for sleep structure.

	Sleep Structure						
	Sleep efficiency	Sleep maintenance	Sleep duration	REM %	Slow wave %	N1 %	N2 %
Arousals (per hour of sleep)							
Arousal index	-0.32	-0.35	-0.19	-0.32	-0.17	0.65	-0.16
Arousal (NREM)	-0.32	-0.35	-0.19	-0.29	-0.18	0.66	-0.18
Arousal (REM)	-0.11	-0.12	-0.09	-0.17	-0.05	0.29	-0.09
Breathing disturbance (per hour of sleep)							
Central apnea (All desat)	-0.02	-0.04	0.03	-0.01	-0.05	0.12	-0.07
Central apnea (4% desat)	-0.03	-0.05	0.00	-0.04	-0.05	0.16	-0.06
AHI4P	-0.16	-0.20	-0.12	-0.21	-0.14	0.42	-0.10
AHI4PA	-0.23	-0.26	-0.16	-0.25	-0.17	0.52	-0.13
OAHI3P	-0.16	-0.18	-0.10	-0.23	-0.10	0.38	-0.10
OAHI3PA	-0.20	-0.22	-0.12	-0.25	-0.10	0.44	-0.12
OAH4PA	-0.22	-0.24	-0.14	-0.25	-0.11	0.48	-0.14
AHI_ALL_3P	-0.17	-0.20	-0.12	-0.22	-0.13	0.41	-0.10
AHI_ALL_3PA	-0.22	-0.24	-0.15	-0.25	-0.16	0.50	-0.12
AHI_ALL_4P	-0.15	-0.19	-0.12	-0.21	-0.13	0.39	-0.09
AHI_ALL_4PA	-0.24	-0.26	-0.16	-0.25	-0.16	0.52	-0.13
AHI_ALL_3P-NREM	-0.18	-0.21	-0.13	-0.27	-0.14	0.46	-0.09
AHI_ALL_4P-NREM	-0.17	-0.20	-0.13	-0.25	-0.14	0.44	-0.09
AHI_ALL_3P-REM	-0.12	-0.14	-0.09	-0.22	-0.04	0.21	-0.01
AHI_ALL_4P-REM	-0.11	-0.13	-0.09	-0.22	-0.05	0.22	-0.01
Hypoxemia (%)							
Average SaO ₂	0.08	0.09	0.06	0.12	0.05	-0.17	0.02
Minimum SaO ₂	0.04	0.07	0.00	0.14	0.04	-0.21	0.06
%SaO ₂ < 90%	-0.10	-0.12	-0.07	-0.16	-0.07	0.25	-0.05
Limb movement (per hour of sleep)							
PLMI	0.04	0.04	0.02	0.15	-0.14	0.09	-0.03
PLMIA	-0.01	-0.01	-0.02	0.00	-0.10	0.07	0.04
PLMI-REM	-0.04	-0.05	-0.03	-0.02	-0.08	0.11	0.01
PLMI-NREM	-0.02	-0.02	-0.01	-0.01	-0.08	0.06	0.04
Sleep structure							
Sleep efficiency (%)	1.00	0.85	0.59	0.23	0.19	-0.34	0.00
Sleep maintenance (%)	0.85	1.00	0.48	0.22	0.18	-0.37	0.02
Sleep duration (min)	0.59	0.48	1.00	0.17	0.13	-0.19	-0.03
REM (%)	0.23	0.22	0.17	1.00	0.01	-0.26	-0.38
Slow wave (%)	0.19	0.18	0.13	0.01	1.00	-0.45	-0.50
N1 (%)	-0.34	-0.37	-0.19	-0.26	-0.45	1.00	-0.18
N2 (%)	0.00	0.02	-0.03	-0.38	-0.50	-0.18	1.00

AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; NREM, nonrapid eye movement; PLMIA, periodic limb movement index associated with arousals; REM, rapid eye movement; SaO₂, saturation of oxygen.

Table S7—Characteristics of Multi-Ethnic Study of Atherosclerosis sleep participants with MESA exam 5 subjects not studied.

	MESA Sleep Participants n = 2,240	MESA Sleep Non-Participants from Exam 5 n = 2,279	P
Age (y)	68.0 (13.0)	71.0 (15.0)	< 0.0001
Male	1,039 (46.4%)	1,163 (46.9%)	0.7477
Asian	265 (11.8%)	276 (11.1%)	0.4431
Black	616 (27.5%)	634 (25.6%)	0.1274
Hispanic	526 (23.5%)	473 (19.1%)	0.0002
BMI (kg/m ²)	27.9 (7.3)	27.4 (7.1)	0.0002
CHF	33 (1.5%)	45 (1.8%)	0.3574
CVD	103 (4.6%)	143 (5.8%)	0.0709
Hypertension	1,285 (57.5%)	1,493 (61.7%)	0.0031
SBP (mm Hg)	120.0 (26.0)	121.0 (28.5)	0.0011
DBP (mm Hg)	68.0 (13.0)	68.0 (13.5)	0.9040

Values expressed as mean (IQR) or N (%). Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table S8—Blood pressure models, predictor mean and between-imputation variance for 10 imputed blood pressure datasets.

	Systolic Blood Pressure		Diastolic Blood Pressure	
	Mean (β)	Variance	Mean (β)	Variance
Age (y)	0.84	0.0035	-0.09	0.0007
Male	-2.19	0.9468	5.10	0.1256
Chinese American	3.27	1.5887	1.55	0.2476
African American	7.91	2.4047	4.78	0.3834
Hispanic	2.58	0.5586	1.14	0.1824
Alcohol use	-1.54	0.2246	0.25	0.0778
Smoker	0.25	0.0541	< 0.01	0.0195
BMI (kg/m ²)	0.39	0.0203	0.04	0.0046
Waist (cm)	0.08	0.0024	0.03	0.0006
AHI4P (per hour of sleep)	0.07	0.0004	0.04	0.0001
PLMIA (per hour of sleep)	0.20	0.0070	0.12	0.0021

Statistically significant predictors identified during the model building process are bolded. AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; BMI, body mass index; PLMIA, periodic limb movement index associated with arousals.

Table S9—Comparison of systolic blood pressure models when adjusting for blood pressure medication with imputed blood pressure values and with blood pressure adjusted with a constant.

	Systolic Blood Pressure		
	Estimate (β)	tStat	P
Imputed BP			
AHI4P (per hour of sleep)	0.07	0.03	0.0053
PLMIA (per hour of sleep)	0.20	0.11	0.0825
BP adjusted by constant			
AHI4P (per hour of sleep)	0.06	0.03	0.0413
PLMIA (per hour of sleep)	0.18	0.13	0.1624

Systolic and diastolic blood pressure adjusted for blood pressure medication use by adding 10 and 5 mm Hg respectively. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; BP, blood pressure; PLMIA, periodic limb movement index associated with arousals.

Table S10—Comparison of diastolic blood pressure models when adjusting for blood pressure medication with imputed blood pressure values and with blood pressure adjusted with a constant.

	Diastolic Blood Pressure		
	Estimate (β)	tStat	P
Imputed BP			
AHI4P (per hour of sleep)	0.04	0.01	0.0035
PLMIA (per hour of sleep)	0.12	0.05	0.0219
BP adjusted by constant			
AHI4P (per hour of sleep)	0.03	0.01	0.0543
PLMIA (per hour of sleep)	0.10	0.06	0.0929

Systolic and diastolic blood pressure adjusted for blood pressure medication use by adding 10 and 5 mm Hg respectively. Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, apnea-hypopnea index defined using a 4% desaturation hypopnea criterion; BP, blood pressure; PLMIA, periodic limb movement index associated with arousals.

Table S11—Systolic blood pressure model further adjusted for diabetes, congestive heart failure, and cardiovascular disease.

	Systolic Blood Pressure		
	Estimate (β)	SE	P
Age (y)	0.84	0.05	0.0000
Male	-1.80	0.96	0.0598
Chinese American	2.40	1.49	0.1074
African American	7.74	1.11	0.0000
Hispanic	1.16	1.21	0.3353
Alcohol use	-1.41	0.92	0.1277
Smoker	0.07	0.52	0.8901
BMI (kg/m ²)	0.39	0.17	0.0229
Waist (cm)	0.06	0.06	0.3409
Diabetes	3.79	1.04	0.0003
CHF	3.54	3.94	0.3693
CVD	7.13	2.10	0.0007
AHI4P (per hour of sleep)	0.05	0.03	0.0557
PLMIA (per hour of sleep)	0.20	0.12	0.0890

Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; PLMIA, periodic limb movement index associated with arousals; SE, standard error.

Table S12—Diastolic blood pressure model further adjusted for diabetes, congestive heart failure, and cardiovascular disease.

	Diastolic Blood Pressure		
	Estimate (β)	SE	P
Age (y)	-0.08	0.02	0.0017
Male	5.36	0.46	0.0000
Chinese American	1.36	0.71	0.0559
African American	4.74	0.53	0.0000
Hispanic	0.59	0.58	0.3060
Alcohol use	0.35	0.44	0.4237
Smoker	0.02	0.25	0.9387
BMI (kg/m ²)	0.04	0.08	0.5922
Waist (cm)	0.03	0.03	0.2873
Diabetes	0.34	0.49	0.4901
CHF	1.10	1.88	0.5589
CVD	2.26	1.00	0.0243
AHI4P (per hour of sleep)	0.03	0.01	0.0487
PLMIA (per hour of sleep)	0.11	0.06	0.0433

Sleep exposure entries for dichotomized populations (systolic and diastolic blood pressure) that show a statistically significant difference (χ^2 test; $p < 0.05$) are bolded. AHI4P, obstructive apneas, all central apneas, and hypopneas with a $\geq 4\%$ desaturation; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; PLMIA, periodic limb movement index associated with arousals; SE, standard error.