ORIGINAL RESEARCH

Development of Predictive Equations for Nocturnal Hypertension and Nondipping Systolic Blood Pressure

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***Background*—**Nocturnal hypertension, defined by a mean asleep systolic blood pressure (SBP)/diastolic blood pressure (BP) ≥120/70 mm Hg, and nondipping SBP, defined by an awake-to-asleep decline in SBP <10%, are each associated with increased risk for cardiovascular disease.

***Methods and Results*—**We developed predictive equations to identify adults with a high probability of having nocturnal hypertension or nondipping SBP using data from the CARDIA (Coronary Artery Risk Development in Young Adults) study (n=787), JHS (Jackson Heart Study) (n=1063), IDH (Improving the Detection of Hypertension) study (n=395), and MHT (Masked Hypertension) study (n=772) who underwent 24-hour ambulatory BP monitoring. Participants were randomized to derivation (n=2511) or validation (n=506) data sets. The prevalence rates of nocturnal hypertension and nondipping SBP were 39.7% and 44.9% in the derivation data set, respectively, and 36.6% and 44.5% in the validation data set, respectively. The predictive equation for nocturnal hypertension included age, race/ethnicity, smoking status, neck circumference, height, high-density lipoprotein cholesterol, albumin/creatinine ratio, and clinic SBP and diastolic BP. The predictive equation for nondipping SBP included age, sex, race/ethnicity, waist circumference, height, alcohol use, high-density lipoprotein cholesterol, and albumin/creatinine ratio. Concordance statistics (95% CI) for nocturnal hypertension and nondipping SBP predictive equations in the validation data set were 0.84 (0.80–0.87) and 0.73 (0.69–0.78), respectively. Compared with reference models including antihypertensive medication use and clinic SBP and diastolic BP as predictors, the continuous net reclassification improvement (95% CI) values for the nocturnal hypertension and nondipping SBP predictive equations were 0.52 (0.35–0.69) and 0.51 (0.34–0.69), respectively.

***Conclusions*—**These predictive equations can direct ambulatory BP monitoring toward adults with high probability of having nocturnal hypertension and nondipping SBP. **(*J Am Heart Assoc*. 2020;9:e013696. DOI: 10.1161/JAHA.119.013696.)**

Key Words: ambulatory • blood pressure • nocturnal hypertension • nondipping • predictive equation • validation

Blood pressure (BP) in humans varies over a 24-hour period, with the lowest levels typically occurring during sleep.[1] Nocturnal hypertension and nondipping systolic BP (SBP) have each been associated with an increased risk for cardiovascular disease events, independent of SBP and diastolic BP (DBP) measured in the clinic setting.[2–6] Clinicians and researchers may seek to screen adults for nocturnal hypertension and nondipping SBP. Clinicians may recommend lifestyle modification or drug therapy to their patients with nocturnal hypertension or nondipping BP.[7] Researchers may seek to enroll a cohort of participants with nocturnal hypertension to test interventions that lower asleep BP.[8] Ambulatory BP monitoring (ABPM) is the primary approach used to identify nocturnal hypertension and nondipping SBP. However, it is not practical to conduct ABPM in all adults to identify those with nocturnal hypertension and nondipping

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Accompanying Data S1, Tables S1 through S13, and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013696

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Clinical Perspective

What Is New?

- Nocturnal hypertension and nondipping systolic blood pressure (BP) can be identified using ambulatory BP monitoring, but it is not practical to screen all adults for these phenotypes.
- We developed predictive equations to identify adults with a high probability of having nocturnal hypertension or nondipping systolic BP.

What Are the Clinical Implications?

- Compared with screening methods based on clinic BP and antihypertensive medication use, the predictive equations we developed exhibited superior classification characteristics in a validation data set.
- The equations developed in the current analysis may direct ambulatory BP monitoring to adults with a high probability of having nocturnal hypertension and nondipping systolic BP.

SBP.[9,10] A more feasible approach is to conduct ABPM screening among adults with a high probability of having these BP phenotypes. Therefore, we developed predictive equations to identify adults with a high probability of having nocturnal hypertension or nondipping SBP.

Methods

We pooled data from participants in the JHS (Jackson Heart Study) (n=1063), the CARDIA (Coronary Artery Risk Development in Young Adults) study (n=787), the IDH (Improving the Detection of Hypertension) study (n=395), and the MHT (Masked Hypertension) study (n=772) study who underwent 24-hour ABPM and had ≥10 SBP and DBP readings while awake and ≥5 SBP and DBP readings while asleep (Figure S1).[11–15] Additional details on each study are available in Data S1. All studies were approved by institutional review boards, and all participants provided written informed consent.

Requests to access JHS and CARDIA study data from qualified researchers trained in human subject confidentiality protocols may be submitted to BioLINCC, the National Heart, Lung, and Blood Institute repository (https://biolincc.nhlbi.nih.gov/home/). Alternatively, investigators may submit manuscript proposals to the CARDIA study or the JHS at https://www.cardia.dopm.uab.edu and https://www.jacksonheartstudy.org, respectively. Deidentified data from the IDH and MHT studies for the purpose of replicating this analysis may be made available on request to Dr Joseph Schwartz (E-mail: JES222@cumc.columbia.edu).

Ambulatory BP Monitoring

The JHS and IDH and MHT studies used a SpaceLabs model 90207 monitor (Snoqualmie, WA) to conduct 24-hour ABPM. The CARDIA study used a SpaceLabs OnTrak model 90227 monitor.[16,17] SBP and DBP were measured every 20 minutes (JHS), 28 to 30 minutes (MHT study), or 30 minutes (CARDIA and IDH studies).[18] In the current analysis, BP measurements outside of preset limits (SBP 70–250 mm Hg and DBP 40–150 mm Hg while awake; SBP ≥60 mm Hg and DBP ≥30 mm Hg while asleep) were excluded. In the CARDIA, IDH, and MHT studies, actigraphy data and sleep diaries were used to determine awake and asleep periods. JHS participants were only asked to complete a sleep diary. We identified 123 JHS participants who did not provide a valid sleep diary but did record ≥10 and ≥5 BP readings during daytime (10 AM–8 PM) and nighttime (12 AM–6 AM) hours, respectively. For these participants, we computed mean awake and asleep BP during daytime and nighttime hours, respectively.

Nocturnal Hypertension and Nondipping SBP

Awake and asleep BP levels were computed as the mean of all readings during each period. Nocturnal hypertension was defined as an asleep SBP/DBP ≥120/70 mm Hg. Nondipping SBP was defined as a decline in SBP from wakefulness to sleep <10% (ie, ratio of mean asleep SBP/mean awake SBP >0.90).

Candidate Predictor Variables

We reviewed a list of variables measured under similar conditions and protocols in each study and selected a subset as candidate predictor variables for the nocturnal hypertension and nondipping SBP prediction equations. Candidate predictors were selected on the basis of routine availability, clinical knowledge, and variables associated with asleep BP in prior studies.[19,20] Variables selected as candidate predictors were age (years), sex (men/women), race/ethnicity (white/black/Asian or Pacific Islander/other), smoking (current/former/never), alcohol consumption (yes/no), sleep duration (hours), height (centimeters), weight (kg), body mass index (kg/m^2), neck and waist circumference (centimeters), urinary albumin (mg/dL), urinary creatinine (g/dL), log-transformed urinary albumin/creatinine ratio (ACR; no units), estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (yes/no), fasting blood glucose (mg/dL), diabetes mellitus (yes/no), high- and low-density lipoprotein cholesterol (mg/dL), clinic-measured SBP and DBP (mm Hg), and antihypertensive medication use (yes/no).[21] Additional details about these variables are provided in Table S1.

Statistical Analyses

Derivation and validation data sets

All analyses were conducted using R version ≥3.6.0. Participants in the pooled JHS and CARDIA, IDH, and MHT study data were randomized to derivation (n=2511) or validation (n=506) data sets. Pooling all data sets versus keeping one out was applied to maximize the diversity of the derivation data set and, in turn, the generalizability of the predictive equations.[22] Summary statistics for characteristics were calculated for participants in the derivation and validation data sets, separately.

Development of the predictive equations

We developed a set of prediction equations using the derivation data and subsequently validated those equations in the validation data set (Figure 1). We compared 7 candidate modeling algorithms to create a predictive equation for nocturnal hypertension and nondipping SBP, separately, using a 5-step resampling process to internally validate predictive equations using the derivation data set (Figure 2 and Data S1).[23,24] Each candidate modeling algorithm was ranked by its discrimination, calibration, and overall goodness of fit using a concordance statistic (C-statistic), the Hosmer and Lemeshow χ^2 statistic, and the scaled Brier score, respectively.[25] The candidate modeling algorithm with the highest mean ranking was selected to create the predictive equations using the full set of derivation data. We applied bootstrap resampling to estimate the probability of inclusion into each predictive equation for each candidate predictor variable. To compare the selected predictive equations with a less complex predictive equation, we fit reference models to the derivation data set for nocturnal hypertension and nondipping SBP, separately, using logistic regression. Each reference model included clinic-measured SBP and DBP and antihypertensive medication use as predictors. Each reference model was formally compared with the selected predictive equations in the validation data set to determine whether the predictive equations outperformed a simpler set of equations outside of the derivation data set.

After developing predictive equations, we identified 4 cut points for categorizing participants as having a high probability of nocturnal hypertension and nondipping SBP, separately, that provided the following: (1) the closest number of predicted and observed cases (ie, maximizing calibration), (2) the maximum specificity with a sensitivity ≥0.80, (3) the maximum negative predictive value with a positive predictive value ≥0.80, and (4) the maximum Youden index (ie, sensitivity+specificity). The closest number of predicted and observed cases occurs when we chose a cut point that provided the same proportion of participants with the outcome as are defined as testing positive on the basis of the predictive equations.

Validation of the predictive equations

Using the validation data set, we assessed the predictive equations' discrimination using a C-statistic. C-statistics were also computed for the reference models for nocturnal hypertension and nondipping SBP. We applied bootstrap resampling to test the null hypothesis of equivalence between the C-statistics of each predictive equation and the reference model. We assessed the calibration of the predictive equations using a calibration slope curve, the Hosmer and Lemeshow goodness-of-fit test, and the Harrell unreliability test.[26,27] We computed C-statistics and conducted Hosmer and Lemeshow goodness-of-fit tests in subgroups based on age, race, sex, medication use, and high school graduation status for each predictive equation. For each of the 4 probability cut points identified using the derivation data, we computed the sensitivity, specificity, and positive and negative predictive values of the predictive equations in the validation data. These test characteristics were also calculated for 4 alternative methods that may be used to identify suitable candidates for ABPM screening: (I) clinic-measured SBP/DBP ≥120/70 mm Hg, (II) clinic-measured SBP/DBP ≥130/80 mm Hg, (III) clinic-measured SBP/DBP ≥140/90 mm Hg, or (IV) antihypertensive medication use. Categorical net reclassification improvement (NRI) was computed by initially classifying participants as having a low or high probability for nocturnal hypertension or nondipping SBP using screening methods (I–IV) listed above, separately, and then reclassifying participants on the basis of probability cut point 4 (ie, the cut point maximizing the Youden index) of the corresponding predictive equation.[28–31] Cut point 4 was chosen on the basis of the assumption that it would provide better overall classification characteristics than the other 3 cut points. Continuous NRI and integrated discrimination improvement index were computed by comparing predicted probabilities from the predictive equations versus reference models for nocturnal hypertension and nondipping SBP. Additional details on validation and the NRI are provided in Data S1.

Missing data

Albuminuria and neck circumference had the highest missing rates (9.9% and 5.0%, respectively). All other candidate predictors had <5.0% missing rates. Random forests were applied to impute missing values in the derivation and validation data sets, separately.[32]

Exploratory analyses

Prior studies that examined nocturnal BP patterns have focused on SBP versus DBP nondipping. We conducted

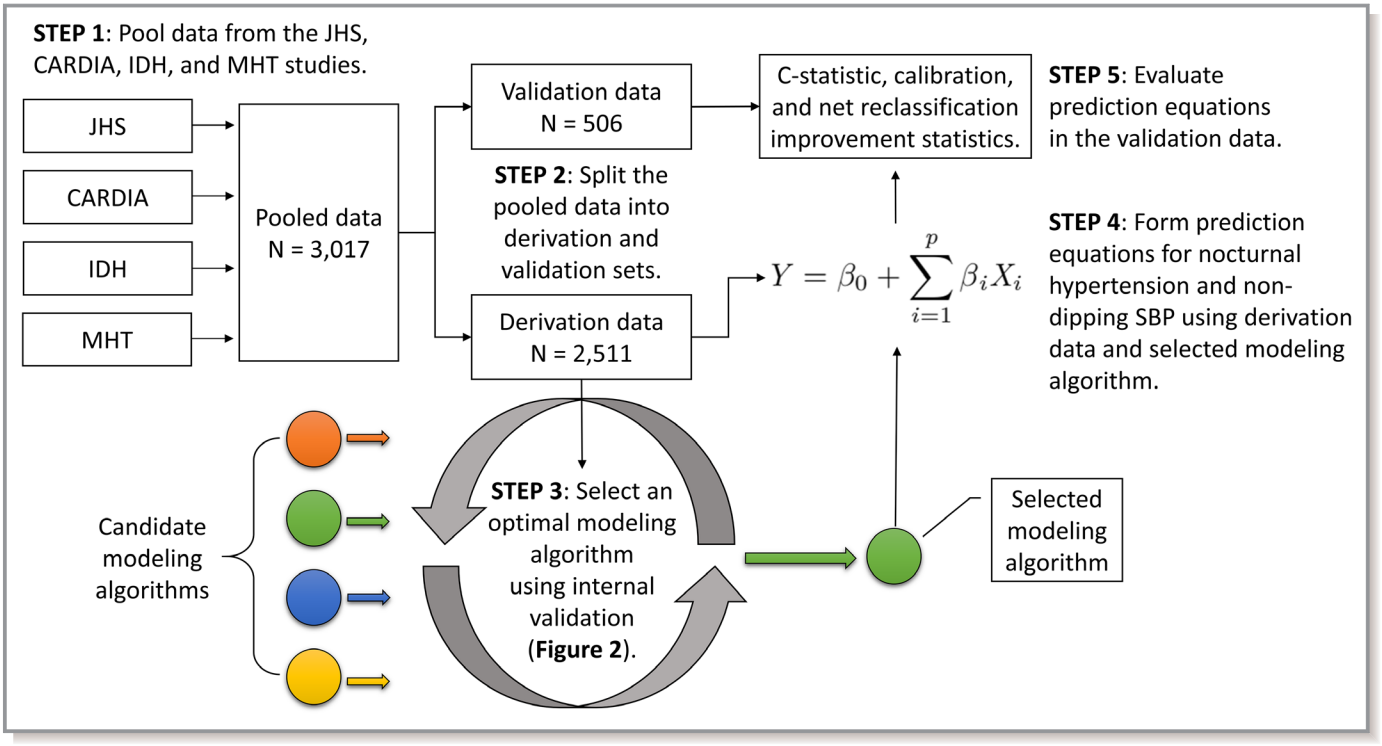

Figure 1. Description of the main steps taken to complete the current analysis. Candidate modeling algorithms comprise the sequence of steps taken to develop a prediction equation and were evaluated in step 3. CARDIA indicates Coronary Artery Risk Development in Young Adults; C-statistic, concordance statistic; IDH, Improving the Detection of Hypertension; JHS, Jackson Heart Study; MHT, Masked Hypertension; SBP, systolic blood pressure.

exploratory analyses developing and evaluating predictive equations for nondipping DBP.

Results

Characteristics of Participants

There was minimal evidence of a difference between the characteristics of participants in the derivation versus the validation data sets (Table 1; 2 $P<0.05$ in 26 comparisons). The prevalence rates of nocturnal hypertension and nondipping SBP were 39.7% and 44.9% in the derivation data set, respectively, and 36.6% and 44.5% in the validation data set, respectively. Participants from the CARDIA study who were included in the current study were more likely to be women and have prevalent diabetes mellitus compared with their counterparts in the CARDIA study who were not included (Table S2). Participants from the JHS who were included in the current study were older and more likely to have albuminuria compared with their counterparts in the JHS who were not included (Table S3). Participants in the CARDIA study exhibited a more narrow age range compared with participants in the JHS and the IDH and MHT studies (Table S4).

Development of the Predictive Equations

On the basis of the concordance error, the Hosmer-Lemeshow χ^2 statistic, and scaled Brier score, generalized additive logistic regression with forward variable selection was chosen to develop predictive equations for nocturnal hypertension and nondipping SBP (Table S5). Variables included in the predictive equation for nocturnal hypertension were age, race/ethnicity, smoking status, neck circumference, height, high-density lipoprotein cholesterol, ACR, and clinic SBP and DBP (Table 2; middle column). Variables included in the predictive equation for nondipping SBP were age, sex, race/ethnicity, waist circumference, height, alcohol use, high-density lipoprotein cholesterol, and ACR (Table 2; right column). Predictors based on race, age, and ACR were selected in >85% bootstrapped replicates of the derivation data (Tables S6 and S7). Height and clinic-measured SBP and DBP were selected as nonlinear predictors for nocturnal hypertension (Figure S2; top panel). Age, height, and ACR were selected as nonlinear predictors for nondipping SBP (Figure S2; bottom panel). The probability cut points associated with closest number of predicted and observed cases, maximum specificity with sensitivity ≥0.80, and maximum negative predictive value with positive

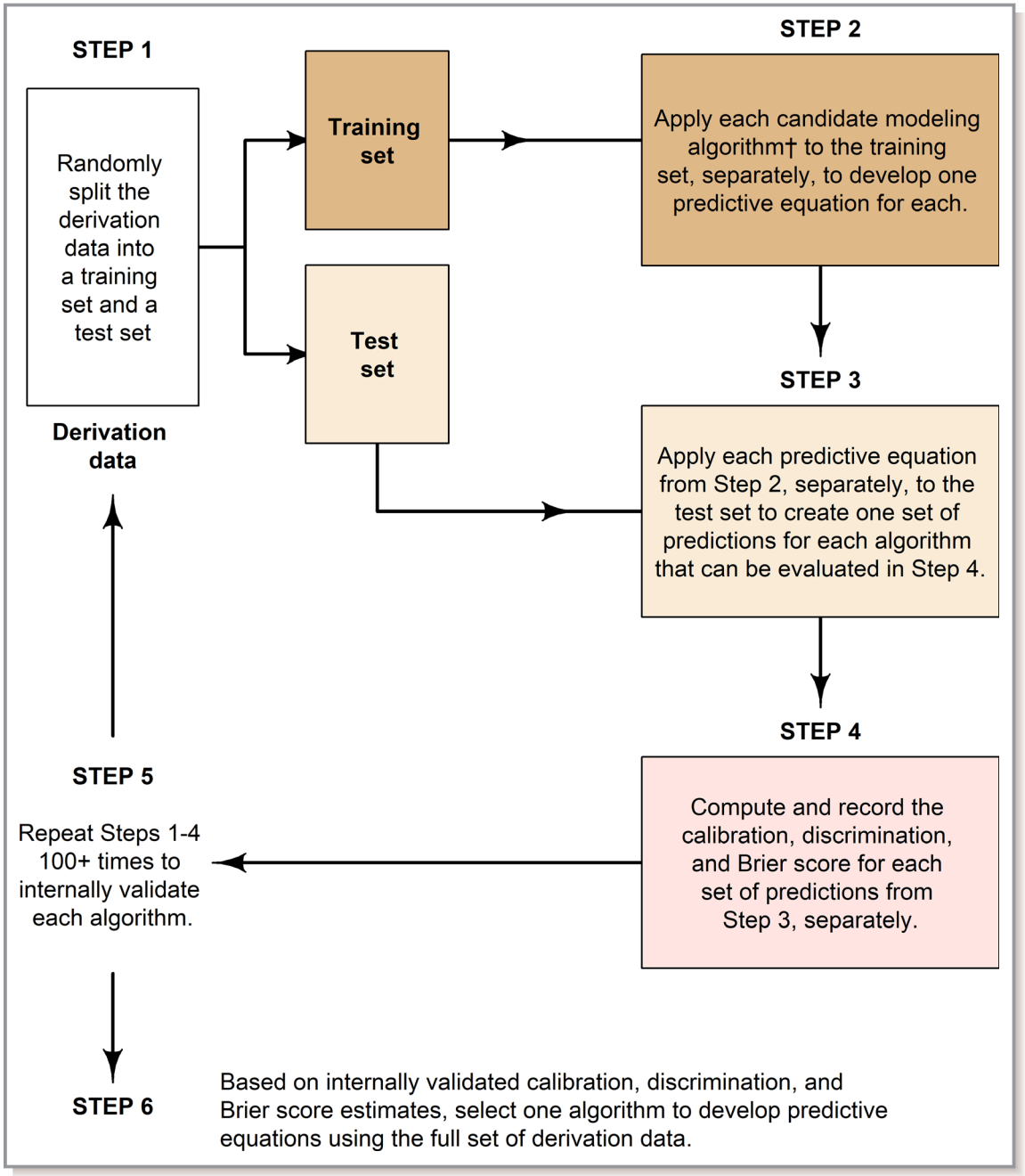

Figure 2. Five steps for the development and internal validation of candidate modeling algorithm. †A modeling algorithm is the collection of steps that translate data into a predictive equation. This process only uses the derivation data set. The validation data set is not used until a final modeling algorithm is selected and applied to the full derivation data set. Candidate modeling algorithms for the current analysis were as follows: (1) logistic regression using forward variable selection, (2) logistic regression using backwards variable selection, (3) generalized additive logistic regression using forward variable selection, (4) penalized logistic regression with a lasso penalty, (5) penalized logistic regression with a ridge penalty, (6) random forests, and (7) gradient boosted decision trees.

predictive value ≥0.80 and to maximize Youden index were 0.46, 0.37, 0.65, and 0.34, respectively, for the nocturnal hypertension predictive equation and 0.48, 0.35, 0.71, and 0.43, respectively, for the nondipping SBP predictive equation (Figure 3).

Validation of the Predictive Equations

For nocturnal hypertension, the predictive equation had a C-statistic of 0.84 (95% CI, 0.80–0.87) versus the reference model C-statistic of 0.82 (95% CI, 0.78–0.86; *P* value for

Table 1. Participant Characteristics Stratified by Assignment Into the Derivation or Validation Data Set

Characteristics*	Data Set†		*P* Value
	Derivation (n=2511)	Validation (n=506)	
Study cohort, %			0.977
CARDIA study	25.9	26.9	
JHS	35.3	35.0	
IDH study	13.1	12.8	
MHT study	25.6	25.3	
Age, y	51.9 (11.8)	51.6 (12.5)	0.587
Men, %	37.4	37.7	0.908
Race/ethnicity, %			0.598
White	34.9	37.2	
Black	56.7	55.9	
Asian or Pacific Islander	2.15	1.58	
Other	6.25	5.34	
High school graduate, %	90.3	91.2	0.568
Smoking habits, %			0.125
Current	11.0	8.38	
Former	20.7	23.4	
Never	68.3	68.3	
Alcohol use, %	65.2	69.5	0.073
Sleep duration, h	7.53 (1.68)	7.56 (1.59)	0.662
Neck circumference, cm	37.2 (4.27)	37.1 (4.16)	0.663
Waist circumference, cm	95.2 (15.8)	94.5 (15.9)	0.346
Weight, kg	84.8 (19.9)	84.14 (20.3)	0.510
Height, cm	168.3 (9.41)	168.4 (9.89)	0.883
Body mass index, kg/m^2	29.9 (6.46)	29.6 (6.28)	0.341
Albumin/creatinine ratio, mg/g	2.00 (0.94)	1.93 (0.84)	0.120
Albuminuria, %†	6.82	5.90	0.535
eGFR <60 mL/min per 1.73 m^2, %	3.10	4.62	0.113
Blood glucose, mg/dL	98.5 (32.1)	95.6 (27.0)	0.037
Diabetes mellitus, %	16.3	15.5	0.672
High-density lipoprotein cholesterol, mg/dL	56.1 (16.6)	57.5 (16.0)	0.071
Low-density lipoprotein cholesterol, mg/dL	117.9 (35.5)	113.9 (33.2)	0.019
Total cholesterol, mg/dL	195.1 (39.6)	191.8 (37.1)	0.079
Heart rate while awake, beats/min	78.3 (10.4)	77.3 (10.4)	0.055
Antihypertensive medication use, %	31.7	31.3	0.899
Conventional hypertension‡	37.4	37.5	36.7
Systolic blood pressure, mm Hg			
Clinic	121.8 (16.4)	121.6 (15.7)	0.832
Sleep	113.8 (15.3)	112.6 (15.2)	0.129
Diastolic blood pressure, mm Hg			
Clinic	75.1 (9.55)	75.4 (9.75)	0.451
Sleep	65.9 (9.23)	65.6 (9.54)	0.648

Continued

Table 1. Continued

Characteristics*	Data Set†		*P* Value
	Derivation (n=2511)	Validation (n=506)	
Nocturnal hypertension, %§	39.7	36.6	0.209
Nondipping systolic blood pressure, %‖	44.9	44.5	0.902

CARDIA indicates Coronary Artery Risk Development in Young Adults; eGFR, estimated glomerular filtration rate; IDH, Improving the Detection of Hypertension; JHS, Jackson Heart Study; MHT, Masked Hypertension.
*Table values are mean (SD) and percentage for continuous and categorical variables, respectively.
†Albuminuria was defined as a urinary albumin/urinary creatinine ratio ≥30 mg/g.
‡Conventional hypertension was defined as having a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or currently taking antihypertensive medication.
§Nocturnal hypertension was defined as having a mean systolic blood pressure ≥120 mm Hg or mean diastolic blood pressure ≥70 mm Hg while asleep.
‖Nondipping systolic blood pressure was defined as decline in mean systolic blood pressure from wakefulness to asleep <10%.

nonzero difference=0.089). For nondipping SBP, the predictive equation's C-statistic was 0.73 (95% CI, 0.69–0.78) compared with the reference model's C-statistic of 0.65 (95% CI, 0.60–0.70) (*P* value for nonzero difference <0.001). There was no evidence of miscalibration for the nocturnal hypertension or nondipping SBP equations overall (Figure 4) or in subgroups based on age, race, sex, medication use, and education (Table S8).

Test characteristics

Using the predictive equations for nocturnal hypertension and nondipping SBP resulted in higher values of Youden's index

Table 2. Odds Ratios for Variables Selected for Inclusion in the Predictive Equations for Nocturnal Hypertension and Nondipping SBP

Variable	Odds Ratio (95% CI)	
	Nocturnal Hypertension	Nondipping Systolic Blood Pressure
Age, 12 y	1.47 (1.29–1.67)	1.74 (1.40–2.00)*
Men	…	0.60 (0.47–0.78)
Race		
White	1 (Reference)	1 (Reference)
Black	2.64 (2.09–3.34)	3.08 (2.50–3.78)
Asian	1.26 (0.50–3.16)	1.22 (0.63–2.38)
Other race/ethnicity	2.28 (1.45–3.58)	1.37 (0.93–2.01)
Smoking status		
Current	1 (Reference)	…
Former	0.72 (0.50–1.03)	…
Never	0.68 (0.50–0.93)	…
Neck circumference, 4 cm	1.16 (1.03–1.32)	…
Waist circumference, 16 cm	…	1.19 (1.07–1.32)
Height, 10 cm	1.20 (1.06–1.35)*	1.10 (0.96–1.26)*
Alcohol use	…	0.64 (0.53–0.78)
HDL cholesterol, 17 mg/dL	0.87 (0.77–0.98)	0.81 (0.73–0.91)
Log(ACR), 1 log g/24 h	1.44 (1.28–1.63)	1.18 (1.03–1.40)*
Clinic SBP, 16 mm Hg	2.48 (2.15–2.87)*	…
Clinic DBP, 10 mm Hg	1.26 (1.12–1.45)*	…

Table values were computed using the derivation data. The odds ratios for the following predictor variables are presented for a 1-SD higher level of the exposure value: age, neck circumference, waist circumference, height, high-density lipoprotein cholesterol, clinic SBP, and clinic DBP. ACR indicates albumin/creatinine ratio; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; …, a variable was not selected for inclusion in the corresponding equation.
*This is a nonlinear variable in the predictive equation. The odds ratio is presented using the mean as a reference value.

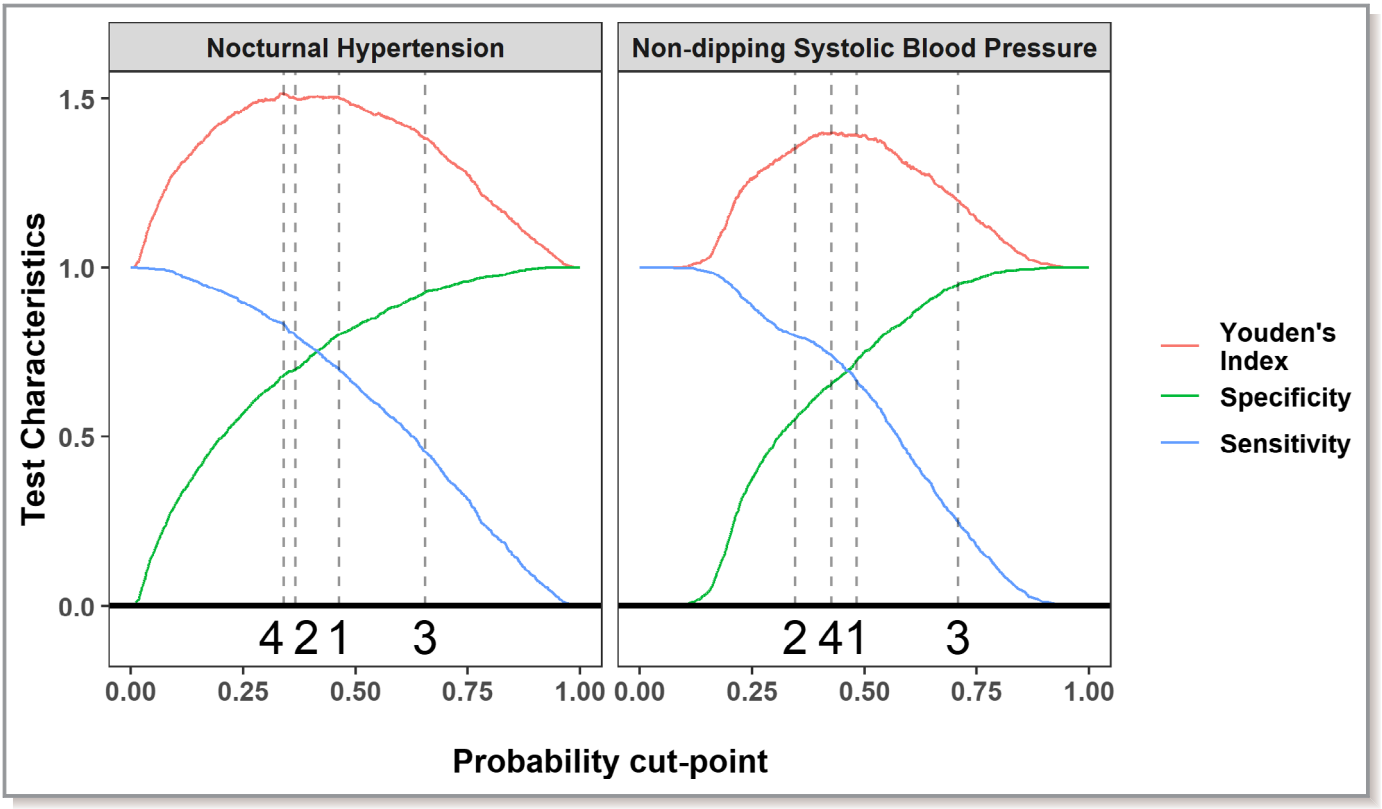

Figure 3. Sensitivity, specificity, and Youden index of the nocturnal hypertension and nondipping systolic blood pressure predictive equations. Results are based on the derivation data. Probability cut points selected for validation (bottom of each panel): (1) Closest number of predicted and observed cases with nocturnal hypertension and nondipping systolic blood pressure. (2) The maximum specificity with a sensitivity ≥0.80. (3) The maximum negative predictive value with a positive predictive value ≥0.80. (4) The maximum sum of sensitivity and specificity.

compared with clinic-measured SBP/DBP ≥120/70 mm Hg, ≥130/80 mm Hg, or ≥140/90 mm Hg, or antihypertensive medication use (Table 3).

Net reclassification improvement

Compared with screening methods based on clinic SBP and DBP or antihypertensive medication use, using the predictive equations resulted in overall categorical NRI values ranging from 0.11 (95% CI, 0.02–0.19) to 0.29 (95% CI, 0.20–0.40) (Table 4). Comparing the predictive equations with the reference models with the outcome of nocturnal hypertension and nondipping SBP resulted in continuous NRI values of 0.52 (95% CI, 0.35–0.69) and 0.51 (95% CI, 0.34–0.69), respectively, and integrated discrimination improvement indexes of 0.10 (95% CI, 0.07–0.12) and 0.07 (95% CI, 0.04–0.09), respectively.

Deployment of the Predictive Equations

A website automating the application of predictive equations developed in this research is available at https://bcjaeger.shinyapps.io/DPE4NHTN_WebApp/. Source codes are available from the corresponding author's GitHub site (https://github.com/bcjaeger/DPE-for-NHTN-and-NDSBP). Written instructions to compute the predicted probability of nocturnal hypertension and nondipping SBP using the equations developed in the current study by hand are provided in Table S9.

Exploratory Analyses

Results from exploratory analyses are presented in Data S1 and Tables S10 through S13.

Discussion

In the current analysis, we developed predictive equations for nocturnal hypertension and nondipping SBP. For each equation, 4 probability cut points were selected on the basis of the equation's test characteristics in a derivation data set. Calibration of the predictive equations in a validation data set was acceptable, as indicated by a calibration slope plot, the Hosmer and Lemeshow goodness-of-fit test, and the Harrell unreliability test. The predictive equations demonstrated superior discrimination, as indicated by C-statistics, the NRI, and the integrated discrimination improvement index

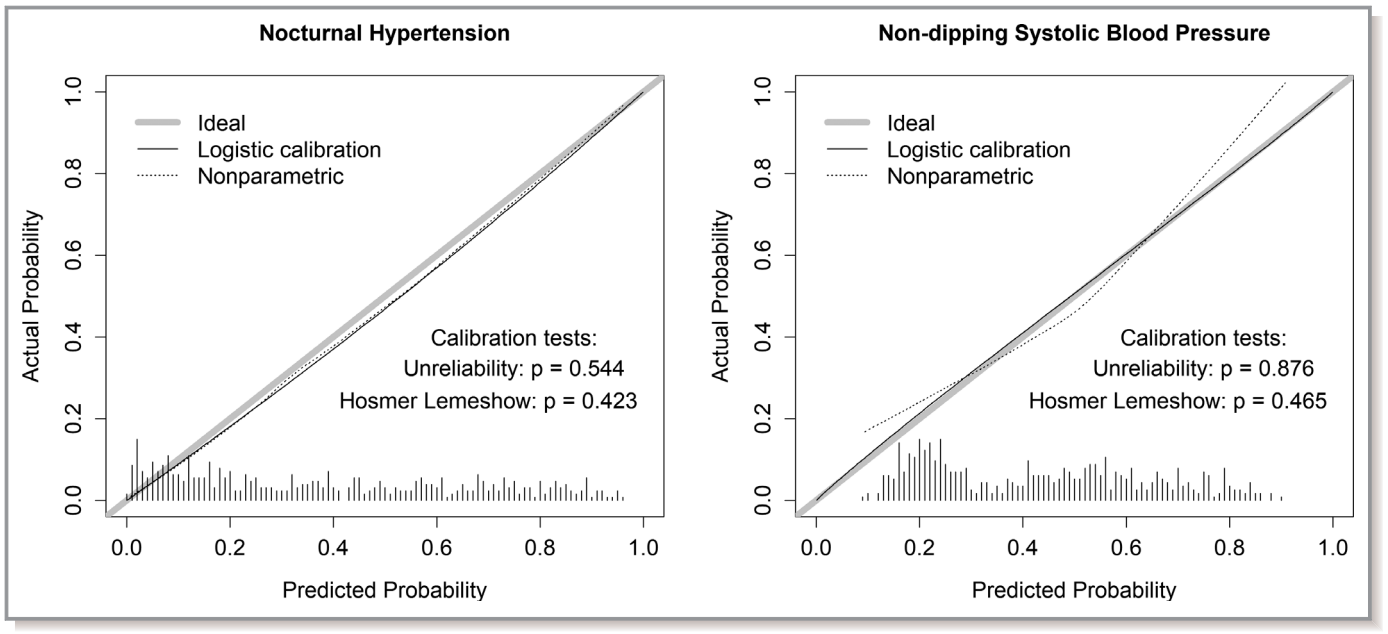

Figure 4. Calibration slope plots for nocturnal hypertension and nondipping systolic blood pressure. Results are based on the validation data. The ideal calibration curve shows the slope of a perfectly calibrated model. Histograms at the base of the panels show the distribution of predicted probabilities in the validation data. The logistic and nonparametric calibration slopes estimate the calibration of a predicted equation by fitting a logistic model and a locally estimated scatterplot smoothing model, with predicted probability and observed status playing the role of independent and dependent variables, respectively.

in comparison to reference models using SBP and DBP measured in a clinic setting and antihypertensive medication use. In addition, using the 4 probability cut points from the derivation data, the predictive equations provided superior test characteristics in comparison to screening methods based on antihypertensive medication use and clinic-measured SBP and DBP.

There were differences between participants in the JHS and CARDIA, IDH, and MHT studies with respect to age, race, and sex. These characteristics have been associated with nocturnal hypertension and nondipping SBP in prior studies.[33,34] The prediction equations developed in the current analysis account for these differences by incorporating these variables. Although sex is not included in the prediction equation for nocturnal hypertension, neck circumference and height, which have strong correlations with sex, are each included. Although the superior test characteristics of the prediction equations compared with screening methods based on SBP, DBP, and antihypertensive medication use may be attributed to the increased number of variables leveraged in the equations, the improved prognostic accuracy of the prediction equations suggests that their use in practice could substantially improve decisions related to ABPM screening.

High asleep BP and nondipping SBP have each been associated with an increased risk for cardiovascular disease events. In an analysis of the International Database of ABPM and Cardiovascular Outcomes, the hazard ratios for cardiovascular disease events associated with a 20–mm Hg increase in nighttime SBP and a 0.10 increase in night-to-day SBP ratio were 1.36 (95% CI, 1.30–1.43) and 1.14 (95% CI, 1.08–1.19), respectively, after multivariable adjustment.[35]

Recommendations on who to screen for nocturnal hypertension and nondipping SBP vary across guidelines. The 2018 European Society of Cardiology/European Society of Hypertension BP guideline recommends patients with sleep apnea, chronic kidney disease, diabetes mellitus, endocrine hypertension, or autonomic dysfunction undergo 24-hour ABPM to screen for nocturnal hypertension and nondipping SBP. Results from the current study were consistent with these recommendations as the predictive equations we developed included variables related to chronic kidney disease (ie, log of 1 plus ACR). The 2017 American College of Cardiology/American Heart Association BP guideline does not provide specific recommendations on who to screen for nocturnal hypertension or nondipping SBP.[36] However, the guideline mentions several areas of inquiry related to ABPM, including the importance of nocturnal hypertension.

The equations we developed can direct ABPM screening to patients who are most likely to have nocturnal hypertension and nondipping SBP, which can be helpful in both clinical and research settings. ABPM is recommended by the 2017 American College of Cardiology/American Heart Association BP guideline for >100 million US adults, but it is not widely implemented in the United States. Although home BP monitoring is an alternative to ABPM, it does not provide measurement of nocturnal BP. The equations developed in the

Table 3. Test Characteristics of the Predictive Equations and Alternative Screening Methods for Identifying Adults With a High Probability of Nocturnal Hypertension and Nondipping SBP

	Methods of Identifying Who Should Undergo 24-h Ambulatory Blood Pressure Monitoring							
	Predictive Equation Probability Cut Points				SBP/Diastolic Blood Pressure Cut Points, mm Hg			Current Use of Antihypertensive Medication
Characteristics	1	2	3	4	I	II	III	IV
	Nocturnal hypertension							
Classification cut points	≥0.46	≥0.37	≥0.65	≥0.34	≥120/70	≥130/80	≥140/90	Yes
Screened, %	37.7	47.2	22.9	50.0	78.5	42.1	14.6	31.6
Sensitivity	0.69	0.79	0.50	0.83	0.95	0.68	0.32	0.49
Specificity	0.80	0.71	0.93	0.69	0.31	0.73	0.96	0.79
Positive predictive value	0.67	0.62	0.79	0.61	0.44	0.59	0.81	0.57
Negative predictive value	0.82	0.86	0.76	0.88	0.92	0.80	0.71	0.73
Youden index	1.50	1.51	1.42	1.52	1.26	1.40	1.28	1.28
	Nondipping systolic blood pressure							
Classification cut points	≥0.48	≥0.35	≥0.71	≥0.43	≥120/70	≥130/80	≥140/90	Yes
Screened, %	43.5	58.9	12.8	50.6	78.5	42.1	14.6	31.6
Sensitivity	0.62	0.76	0.25	0.70	0.82	0.49	0.21	0.45
Specificity	0.72	0.55	0.97	0.65	0.24	0.63	0.90	0.79
Positive predictive value	0.64	0.58	0.88	0.62	0.46	0.52	0.64	0.64
Negative predictive value	0.70	0.75	0.62	0.73	0.62	0.61	0.59	0.64
Youden index	1.34	1.32	1.22	1.35	1.06	1.12	1.11	1.25

Table values were computed using the validation data. Participants with values greater than or equal to classification cut point values are recommended to undergo 24-hour ambulatory blood pressure monitoring. The following probability cut points of the predictive equations for nocturnal hypertension and nondipping systolic blood pressure were chosen on the basis of the derivation data:

1. Closest number of predicted and observed cases with nocturnal hypertension and nondipping systolic blood pressure.
2. The maximum specificity with a sensitivity ≥0.80.
3. The maximum negative predictive value with a positive predictive value ≥0.80.
4. The maximum sum of sensitivity and specificity. SBP indicates systolic blood pressure.

current study could be used to identify nocturnal hypertension and nondipping SBP among patients using home BP monitoring. Also, these equations may be useful in research settings. Future studies may aim to enroll participants with nocturnal hypertension or nondipping SBP to evaluate interventions designed to lower nocturnal BP. Study investigators could use the predictive equations developed in the current analysis to identify participants with a high likelihood of having these phenotypes, and this in turn would reduce the cost and time needed for recruitment. As an illustrative example, 79% of participants in the validation data set with a predicted probability for nocturnal hypertension ≥0.65 had nocturnal hypertension, compared with 39.7% of all participants in this data set. If a study aimed to recruit 800 people with nocturnal hypertension from a population where the prevalence of nocturnal hypertension is 40% (rounded up from 39.7%), investigators would expect to conduct ABPM for ≈2000 adults (ie, 2000×0.4=800). However, if the investigators only conducted ABPM for adults with a predicted probability of nocturnal hypertension ≥0.65, they could expect to conduct ABPM on ≈1013 adults to identify 800 participants with nocturnal hypertension (ie, 1013×0.79≈800). These results illustrate one way in which the predictive equations developed in the current analysis could substantially increase the efficiency and decrease the cost of recruitment for future studies.

The current analysis has several strengths. The JHS and CARDIA, IDH, and MHT studies were conducted following standardized protocols that included rigorous procedures for data collection. The use of a validation data set provided an unbiased assessment of the predictive equations. The application of multiple performance metrics (eg, C-statistic, Hosmer-Lemeshow goodness-of-fit statistic, Brier scores, and categorical and continuous NRI) provided a comprehensive and robust analysis for the performance of the predictive equations. The development and deployment of a public

Table 4. NRI and Integrated Discriminative Improvement Using Predictive Equations From the Current Analysis Versus Screening Methods Based on Clinic Blood Pressure and Antihypertensive Medication Use

Methods of Identifying Who Should Undergo 24-h Ambulatory Blood Pressure Monitoring	Net Reclassification Index (95% CI)	
	Nocturnal Hypertension	Nondipping Systolic Blood Pressure
	Overall categorical net reclassification index	
Clinic SBP/DBP ≥120/70 mm Hg	0.29 (0.20 to 0.40)	0.26 (0.18 to 0.34)
Clinic SBP/DBP ≥130/80 mm Hg	0.23 (0.12 to 0.34)	0.12 (0.03 to 0.21)
Clinic SBP/DBP ≥140/90 mm Hg	0.24 (0.14 to 0.34)	0.24 (0.15 to 0.33)
Antihypertensive medication use	0.11 (0.02 to 0.19)	0.25 (0.16 to 0.34)
	Negative categorical net reclassification index	
Clinic SBP/DBP ≥120/70 mm Hg	0.41 (0.34 to 0.48)	0.38 (0.32 to 0.44)
Clinic SBP/DBP ≥130/80 mm Hg	0.02 (−0.06 to 0.09)	−0.03 (−0.09 to 0.02)
Clinic SBP/DBP ≥140/90 mm Hg	−0.25 (−0.31 to −0.19)	−0.26 (−0.32 to −0.22)
Antihypertensive medication use	−0.14 (−0.20 to −0.10)	−0.09 (−0.15 to −0.05)
	Positive categorical net reclassification index	
Clinic SBP/DBP ≥120/70 mm Hg	−0.12 (−0.19 to −0.04)	−0.12 (−0.17 to −0.06)
Clinic SBP/DBP ≥130/80 mm Hg	0.21 (0.12 to 0.30)	0.16 (0.08 to 0.24)
Clinic SBP/DBP ≥140/90 mm Hg	0.49 (0.42 to 0.57)	0.51 (0.43 to 0.58)
Antihypertensive medication use	0.25 (0.19 to 0.32)	0.34 (0.27 to 0.42)
	Continuous net reclassification index	
Models using SBP, DBP, and antihypertensive medication use*	0.52 (0.35 to 0.69)	0.51 (0.34 to 0.69)
	Integrated discriminative improvement index	
Models using SBP, DBP, and antihypertensive medication use	0.10 (0.07 to 0.12)	0.07 (0.04 to 0.09)

Table values were computed using the validation data. For categorical net reclassification indexes, the probability cut points maximizing the Youden index for the predictive equations (0.34 and 0.43 for nocturnal hypertension and nondipping systolic blood pressure, respectively) were used. These cut points were chosen assuming that they provide better overall classification characteristics than the other 3 cut points. DBP indicates diastolic blood pressure; NRI, net reclassification improvement; SBP, systolic blood pressure.
*Predicted probabilities were obtained from equations formed for nocturnal hypertension and nondipping systolic blood pressure, separately, using logistic regression in the derivation data set with clinic SBP and DBP and antihypertensive medication use as independent variables.

website ensures that researchers can seamlessly incorporate these predictive equations into study recruitment protocols and validate the equations using an external data set. Results from the current analysis should be interpreted in the context of certain limitations. All ABPM data used in the current analysis were based on a single 24-hour monitoring period. Although the reproducibility of nocturnal hypertension is moderately high, it is lower for nondipping SBP.[37–39] Some variables that may be associated with nocturnal hypertension or nondipping (eg, glycated hemoglobin) were not measured in all of the studies and, therefore, were not considered as candidates for the predictive equations.

In conclusion, we developed predictive equations that can be used to identify who to screen for nocturnal hypertension and nondipping SBP. These equations outperformed screening methods based on antihypertensive medication use and SBP and DBP measured in a clinic setting. We have developed publicly available tools for the application of these predictive equations. Application of the predictive equations may increase the efficiency and decrease the cost of ABPM screening for nocturnal hypertension and nondipping SBP.

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Disclosures

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

The JHS is a community-based prospective cohort study designed to examine the etiology of CVD and related risk factors among blacks.[1] CARDIA is a prospective cohort study designed to examine the development, determinants, and risk factors of clinical and subclinical CVD.[2] The IDH study was designed to compare strategies for diagnosing hypertension among a community-based sample.[3] The MHT study was designed to evaluate the prevalence, predictors, and prognosis of masked hypertension.[4]

The Jackson Heart Study (JHS)

The JHS, a population-based prospective cohort study, was designed to evaluate the etiology of cardiovascular disease among African Americans. The JHS enrolled a total of 5,301 non-institutionalized African Americans ≥ 21 years old between 2000 and 2004 from the Atherosclerosis Risk in the Community site in Jackson, Mississippi, and a representative sample of urban and rural Jackson, Mississippi metropolitan tri-county (Hinds, Madison and Rankin counties) residents, volunteers, randomly contacted individuals and secondary family members. As part of an ancillary study, 1,148 JHS participants underwent 24-hour ABPM during their baseline examination. For the current analysis, we included 1,046 JHS participants who had ≥ 10 SBP and DBP valid readings while awake and ≥ 5 SBP and DBP valid readings while asleep. The JHS protocol was approved by the institutional review boards at the University of Mississippi Medical Center, Jackson State University, and Tougaloo College.

The Coronary Artery Risk Development in Young Adults (CARDIA) study

The CARDIA study was designed to examine the development and determinants of clinical and subclinical cardiovascular disease and its risk factors. The CARDIA study recruited 5,115 white and black men and women aged 18 to 30 years at four field centers in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) from 1985 to 1986. Participants have completed nine study examinations including a baseline exam at year 0 and follow-up exams at 2, 5, 7, 10, 15, 20, 25 and 30 years following baseline. The details of these examinations are available on the CARDIA study website at www.cardia.dopm.uab.edu. As part of an ancillary study at the Year 30 Exam (2015-2016), 825 non-pregnant participants at the Birmingham and Chicago Field Centers underwent 24-hour ABPM. For the current analysis, we included 781 CARDIA participants who had ≥ 10 SBP and DBP valid readings while awake and ≥ 5 SBP and DBP valid readings while asleep. Institutional review boards at the coordinating center and each field center approved all aspects of the CARDIA study.

The Improving the Detection of Hypertension (IDH) Study

The IDH Study recruited adults, primarily from the upper Manhattan community surrounding Columbia University Medical Center, who did not have any of the following conditions: (1) clinic systolic blood pressure (SBP) $\underline{\geq}$ 160 mm Hg or diastolic blood pressure (DBP) $\underline{\geq}$ 105 mm Hg, (2) evidence of secondary hypertension, (3) current use of antihypertensive medications or other medications that are known to affect SBP or DBP (i.e. steroids, tricyclic antidepressants, etc.), (4) history of overt cardiovascular disease, chronic kidney failure, or organ transplantation, (5) current liver disease, adrenal disease, thyroid disease, rheumatologic disease, hematologic disease, or cancer (not in remission for at least 6 months), (6) currently pregnant, or (7) currently

diagnosed with dementia. The IDH study recruited 408 eligible participants, all of whom underwent 24-hour ABPM twice, between March 2011 and August 2013. For consistency with the other studies, we only used ABPM data from the first 24-hour monitoring period. For the current analysis, we included 395 IDH study participants with ≥ 10 SBP and DBP valid readings while awake and ≥ 5 SBP and DBP valid readings while asleep. The IDH study protocol was approved by Columbia University's institutional review board.

The Masked Hypertension (MHT) Study

The MHT study recruited adults who were employed and maintained > 20 work hours per week and worked on two or more consecutive days per week. Participants were recruited from Stony Brook University, University Hospital at Stony Brook, Columbia University Medical Center, and a private hedge fund management organization. Participants with any of the following conditions were not eligible for the MHT study: (1) screening systolic blood pressure (SBP) ≥ 160 mm Hg or diastolic blood pressure (DBP) ≥ 105 mm Hg, (2) evidence of secondary hypertension, (3) current use of antihypertensive medications or other medications that are known to affect BP (i.e. steroids, tricyclic antidepressants, etc.), (4) a history of overt cardiovascular disease or chronic renal failure, (5) current liver disease, adrenal disease, thyroid disease, rheumatologic disease, hematologic disease, or cancer (not in remission for at least 6 months), (6) currently pregnant, (7) currently engaged in active substance abuse, or (8) currently diagnosed with a serious mental health illness. The MHT Study enrolled 1,010 eligible participants between February 2005 and July 2012, and 893 of the enrolled participants underwent 24-hour ambulatory blood pressure monitoring (ABPM). For the current analysis, we included 772 participants with ≥ 10 SBP and DBP valid readings while awake and ≥ 5 SBP and DBP valid readings while asleep. The

institutional review boards at the participating research centers—Stony Brook University and Columbia University—approved the conduct of the MHT.

Candidate Modeling Algorithms

The modeling algorithms we included as candidates to create predictive equations included (1) logistic regression using forward variable selection, (2) logistic regression using backwards variable selection, (3) generalized logistic regression using forward variable selection, (4) penalized logistic regression with a lasso penalty, (5) penalized logistic regression with a ridge penalty, (6) random forests, and (7) gradient boosted decision trees.[5,6] Generalized additive logistic regression incorporates non-linear effects into the framework of logistic regression by simultaneously fitting locally weighted smoothing curves and linear regression coefficients using a back-fitting algorithm. This algorithm is described in detail by the authors of the generalized additive model.[6] Forward variable selection incorporates variables into a statistical model one by one and the variable added at each step is the one that optimizes some model goodness-of-fit criteria. Additionally, forward variable selection for the generalized additive logistic regression model incorporates non-linear effects for continuous variables in the model by comparing the model's goodness-of-fit with and without a non-linear effect for each continuous predictor variable. We used Akaike's information criteria to evaluate model goodness-of-fit and guide decisions to include additional terms into the predictive model. To avoid over-fitting, we implemented a maximum of 15 steps in the forward variable selection algorithms. Penalized logistic regression minimizes the usual deviance of the model, with a constraint on the sum of the absolute values (lasso penalty) or squared values (ridge penalty) of the regression coefficients. Random forests and gradient boosted decision trees are each ensemble learning

techniques based on classification and regression trees. Trees in the random forest can be fit in parallel and are de-correlated from each other, whereas gradient boosted trees are fit sequentially and each new tree attempts to correct the errors of the previous trees.

Development and internal validation of predictive equations

We applied resampling to develop and internally validate predictive equations using the derivation dataset. Optimistic estimates of generalization error occur when the same data set that is used to develop a predictive equation is also used to evaluate the accuracy of the equation. We applied the following procedure to avoid optimistic errors: (1) Using the derivation dataset, split the data randomly into a training and test set. Note that validation dataset is not used. (2) Apply each candidate modeling algorithm to the training dataset, separately, to develop one predictive equation for each candidate modeling algorithm. A modeling algorithm is the collection of steps that are applied to translate data into a predictive equation. (3) Apply each predictive equation to the test set, separately, to compute one set of predictions using each equation. (4) Evaluate each set of predicted probabilities based on their similarity to the observed outcomes in the test set by computing the calibration error, concordance error, and scaled Brier score for each set of predictions. (5) Repeat steps 1-4 at least 100 times. We used 250 replications of steps 1-4 to achieve stabilized distributions of concordance error, calibration error, and scaled Brier scores.

Validation of predictive equations

It is recommended that prediction equations are validated in an external sample. Three commonly used metrics that assess different aspects of a prediction equation are calibration, discrimination, and net reclassification improvement (NRI).[7–11] Calibration estimates the

accuracy of a prediction equation for estimating the absolute probability of the outcome while discrimination assesses whether an equation will assign higher predicted probability to those with, versus their counterparts without, the outcome.[12] An equation with good calibration but poor discrimination or good discrimination but poor calibration may not be useful. The NRI estimates how well a prediction equation classifies a population when a given probability cut-point is applied. The NRI statistics (i.e., positive NRI and negative NRI) are each based on a comparison between a current prediction equation and a new prediction equation. Positive NRI is the proportion of people with the outcome who have a higher predicted probability using a new equation versus an existing equation. Analogously, the negative NRI is the proportion of people without the outcome who have a lower predicted probability using a new equation versus an existing equation. Overall continuous NRI is the sum of its positive and negative components. Categorical NRI statistics have similar interpretations to their continuous counterparts.

Supplemental results

Exploratory analyses

The predictive equation for non-dipping diastolic blood pressure included age, race/ethnicity, waist circumference, alcohol use, high density lipoprotein-cholesterol, and log of the albumin-to-creatinine ratio as predictors (**Table S10**). In the validation data, there was no evidence of miscalibration overall for the non-dipping diastolic blood pressure predictive equations (**Table S11**). However, Hosmer and Lemeshow's goodness of fit test indicated miscalibration for these predictive equations among participants not taking antihypertensive medication. The value of Youden's index for these predictive equations exceeded those of ambulatory blood pressure screening methods based on clinic blood pressure (**Table S12**). However, screening for

ambulatory blood pressure monitoring with antihypertensive medication use provided a similar value for Youden's index in comparison to the predictive equations for non-dipping diastolic blood pressure. Categorical and continuous net reclassification indices also indicated that the predictive equation for non-dipping diastolic blood pressure improved upon screening methods based on clinic blood pressure (**Table S13**).

Table S1. Description of candidate variables in the Jackson Heart, Coronary Artery Risk Development in Young Adults, Improving the Detection of Hypertension, and Masked Hypertension studies.

Variable	Units or Categories	Description			
		JHS	**CARDIA**	**MHT**	**IDH**
Age	Years	Self-reported at baseline interview.	Collected by questionnaire at baseline and verified at the Year 2 exam.	Collected by questionnaire	
Race	Black or white				
Sex	Male or female				
Education	Years of formal education		Collected by questionnaire at Year 30 exam.		
Family Income	Above or below $25,000 / year				
Current Smoker	Yes or no	Participants were asked the following questions:			
		(1) Have you smoked more than 400 cigarettes in your lifetime?	(1) Have you ever used any tobacco product such as cigarettes, cigars, tobacco pipe, chewing tobacco,	(1) Have you ever smoked cigarettes regularly for at least 3 months? By "regularly" we mean 5 or more	

			snuff, e-cigarettes (e.g., electronic cigarettes, vape pens, e-hookahs, etc.), nicotine chewing gum, or a nicotine patch?	cigarettes per week
		(2) Do you now smoke cigarettes?	(2) Have you ever smoked cigarettes regularly for at least three months?" ("Regularly" meant at least 5 cigarettes per week almost every week.)	(2) Do you currently smoke cigarettes?
		(3) How long has it been since you last smoked cigarettes?	(a) Do you still smoke cigarettes regularly? If response was "No", then participants were asked about time since they smoked cigarettes	(3) When did you stop smoking cigarettes regularly?

			regularly. (b) Have you started smoking regularly in the last three months?	
		Participants who were currently smoking or had quit less than 1 year ago were given a value of 'Yes' for this variable.		
Antihypertensive Medication Use	Yes or no	Defined as Yes if participant's self-reported antihypertensive medication use at baseline interview.	Defined as Yes if participant's self-reported antihypertensive medication use during Year 30 exam.	NONE, antihypertensive medication use was an exclusion criterion
Alcohol Consumption	Yes or No	Participants were asked: "Did you drink any alcoholic beverages in the past year?" at baseline interview	Participants were asked: "During the past 12 months, on average, how many days per week, month, or year did you drink any alcoholic beverage?"	Participants were asked "Did you drink any alcoholic beverages in the past year?"

			by questionnaire during Year 30 exam.	
		Participants who indicated consumption of alcohol in the past year had a value of 'Yes' for this variable and 'No' otherwise.		
Sleep Duration	Hours	Participants provided sleep diaries indicating when they went to sleep and when they woke up. Sleep duration was defined using these sleep diaries.	Participants wore actigraphy watches (Actiwatch, Philips-Respironics, Bend, OR) that monitored movement and indicated when participants were awake and asleep. Sleep duration was defined using the actigraphy data supplemented with self-reported sleep/wake times from a sleep diary.	
Clinic systolic and diastolic Blood Pressure	mm Hg	After participants had sat quietly for at least 5 minutes in an upright position with their back and arms supported, feet flat on the floor, legs uncrossed, and an appropriate-sized cuff was fitted, trained staff conducted blood pressure measurements using their **right** arm. Cuff		After participants had sat quietly for at least 5 minutes in an upright position with their back and arms supported, feet

		size was determined from an arm circumference measurement.		flat on the floor, legs uncrossed, and an appropriate-sized cuff was fitted, trained staff conducted blood pressure measurements using their **left** arm. Cuff size was determined from an arm circumference measurement.
		One to two minutes elapsed between the measurements. Two measurements were taken and averaged for	Three blood pressure measurements, each separated by at least 30 seconds, were recorded. The second and third BP measurements were averaged for	One to two minutes elapsed between the measurements. Three blood pressure measurements were obtained

		analysis. A random-zero sphygmomanometer (Hawksley and Sons, Ltd) was used and blood pressure values were later calibrated using an Omron device.	analysis. An automated oscillometric device (Omron model® HEM907XL) was used to conduct blood pressure measurements.	using a mercury sphygmomanometer and averaged for analysis.
Diabetes	Yes or no	Participants with fasting (≥ 8 hours) glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or taking anti-diabetes medication were given a value of 'Yes' for this variable.	Participants with fasting (≥ 8 hours) glucose ≥ 126 mg/dL or current use of antidiabetes medication were given a value of 'Yes' for this variable.	Participants with 1) self-reported diagnosis, 2) fasting (≥ 8 hours) glucose ≥ 126 mg/dL, 3) HbA1c ≥ 6.5% or 4) taking anti-diabetes medication were given a valye of 'Yes' for this variable.

Estimated glomerular filtration rate	< 60 or ≥ 60 ml/min/1.73 m^2	Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.		
High density lipoproteins	mg/dL	Measured by trained staff using blood samples after an overnight fast. Serum samples were sent on dry ice via overnight express to the testing laboratory (Atherotech in Birmingham, AL), where they were kept at −70°C until measurement.	Measured by trained staff and quantified by precipitation with dextran sulfate-magnesium chloride	Enzymatic colorimetric test using cholesterol esterase and cholesterol oxidase coupled with PEG on a Roche modular test or Hitachi system
Low density lipoproteins	mg/dL		Measured by trained staff and calculated using the Friedewald equation.	
Total cholesterol	mg/dL		Measured by trained staff and quantified using cholesterol in lipoprotein fractions performed by in vitro enzymatic tests using Roche reagents on a Roche	Enzymatic colorimetric test using cholesterol esterase and cholesterol oxidase on a Roche modular

			Double Modular P Analytical Automated Analyzer.	test or Hitachi system
Albuminuria	Urine albumin to urine creatinine ratio >30 or ≤ 30 mg/g	Urinary albumin and creatinine were quantified from a 24-hour urine collection or from a spot urine sample using the nephelometric immunoassay and enzymatic methods, respectively	Measured by trained staff using spot urine samples. Urinary albumin and creatinine were quantified using the nephelometric immunoassay and enzymatic methods.	Urinary albumin and creatinine were quantified using the nephelometric immunoassay and enzymatic methods, respectively from an overnight urine collection (sleep onset up to and including first morning void).
Height	cm	Measured by trained staff using a standardized protocol		
Weight	kg			
Waist Circumference	cm			

Neck Circumference	cm	
Body Mass Index	kg/m^2	Computed as weight in kilograms divided by height in meters squared

Table S2. **Characteristics of participants in the Coronary Artery Risk Development In young Adults (CARDIA) study stratified by inclusion in the current analysis.**

		Included in current analysis		
Characteristic*	**Overall (N = 5114)**	**No (N = 4327)**	**Yes (N = 787)**	**P-value**
Age, years	54.8 (3.63)	54.8 (3.62)	54.6 (3.68)	0.251
Male	45.5	46.5	40.2	0.001
Smoking Habits				0.154
Never	62.8	62.6	63.3	
Former	23.2	23.9	21.1	
Current	14.0	13.5	15.5	
Waist circumference, cm	96.2 (16.3)	95.9 (16.6)	97.2 (15.4)	0.039
Weight, lbs	194.1 (48.3)	193.2 (49.0)	196.7 (45.7)	0.069
Height, cm	169.9 (9.41)	170.2 (9.42)	168.9 (9.32)	< 0.001
Albumin-to-creatinine ratio, mg/g	27.2 (200.0)	26.0 (201.1)	30.8 (196.7)	0.552
Albuminuria†	8.34	8.16	8.91	0.557
eGFR < 60 ml/min/1.73 m2	3.14	2.89	3.95	0.170
Blood glucose, mg/dL	102.6 (31.8)	101.9 (29.6)	104.9 (37.8)	0.040
Diabetes	14.3	13.4	17.3	0.006
HDL, mg/dL	59.8 (18.9)	60.0 (18.9)	59.3 (18.9)	0.415
LDL, mg/dL	110.3 (33.2)	109.8 (33.1)	111.7 (33.6)	0.168
Total cholesterol, mg/dL	191.3 (38.1)	191.0 (37.9)	192.2 (38.7)	0.420
Blood pressure, mm Hg				
Clinic systolic	120.8 (16.7)	120.5 (16.5)	121.8 (17.4)	0.069
Clinic diastolic	74.1 (11.1)	73.9 (11.1)	74.5 (11.0)	0.157

*Table values are presented as mean (standard deviation) or percent.
†Albuminuria: urinary albumin to urinary creatinine ratio ≥ 30 mg/g.
eGFR = estimated glomerular filtration rate

Table S3. Characteristics of participants in the Jackson Heart Study (JHS) stratified by inclusion in the current analysis.

		Included in current analysis		
Characteristic*	**Overall (N = 5306)**	**No (N = 4243)**	**Yes (N = 1063)**	**P-value**
Age, years	54.8 (12.9)	53.9 (13.1)	58.7 (11.0)	< 0.001
Male	36.5	37.7	32.1	< 0.001
Smoking Habits				< 0.001
Never	67.6	67.7	67.2	
Former	19.3	18.5	22.7	
Current	13.1	13.8	10.1	
Waist circumference, cm	100.7 (16.2)	100.8 (16.3)	100.2 (15.7)	0.274
Weight, lbs	199.5 (47.2)	200.8 (47.9)	194.5 (43.5)	< 0.001
Height, cm	168.9 (9.28)	169.1 (9.32)	168.2 (9.10)	0.003
Albumin-to-creatinine ratio, mg/g	12.5 (125.4)	6.07 (111.0)	31.7 (159.2)	< 0.001
Albuminuria†	3.48	1.26	10.1	< 0.001
eGFR < 60 ml/min/1.73 m2	6.22	6.22	6.20	> 0.999
Blood glucose, mg/dL	100.0 (33.4)	99.5 (34.1)	102.1 (30.2)	0.022
Diabetes	23.7	22.9	26.8	0.010
HDL-cholesterol, mg/dL	51.8 (14.6)	51.2 (14.5)	53.9 (15.0)	< 0.001
LDL-cholesterol, mg/dL	126.6 (36.6)	126.8 (36.8)	125.9 (35.8)	0.460
Total cholesterol, mg/dL	199.3 (40.1)	198.8 (40.2)	201.3 (39.8)	0.074
Blood pressure, mm Hg				
Clinic systolic	127.5 (16.9)	127.4 (17.2)	127.6 (15.8)	0.710
Clinic diastolic	75.7 (8.77)	76.0 (8.82)	74.3 (8.47)	< 0.001

*Table values are presented as mean (standard deviation) or percent.
†Albuminuria: urinary albumin to urinary creatinine ratio ≥ 30 mg/g.
eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein

Table S4. Age, sex, and prevalence of nocturnal blood pressure phenotypes stratified by study.

		Age, years			Prevalence, %	
Study	**Number of participants**	**Mean +/- SD**	**Range**	**% Women**	**NHTN**	**NDSBP**
CARDIA	787	54.6 +/- 3.7	47.0 - 60.0	59.8	41.2	32.3
JHS	1063	58.7 +/- 11.0	21.0 - 84.0	67.9	57.1	72.8
IDH	395	41.2 +/- 13.2	18.3 - 81.8	60.0	26.8	33.7
MHT	772	45.1 +/- 10.4	21.3 - 81.3	59.3	18.7	24.7

CARDIA = Coronary Artery Risk Development in Young Adults, IDH = Improving Detection of Hypertension, JHS = Jackson Heart Study, MHT = Masked Hypertension, NDSBP = non-dipping systolic blood pressure, NHT = nocturnal hypertension, SD = standard deviation, % = percent

Table S5. **Bootstrapped means of performance metrics and overall ranks of competing modeling algorithms for prediction of nocturnal hypertension and non-dipping systolic blood pressure.**

Modeling Algorithm	**Concordance Error (95% CI)**	**Hosmer-Lemeshow X^2 Statistic (95% CI)**	**Scaled Brier Score (95% CI)**	**Mean Rank**
	Prediction of nocturnal hypertension			
Generalized additive regression	16.9 (16.7, 17.1)	12.2 (11.5, 12.9)	31.3 (30.8, 31.7)	1.3
Forward stepwise regression	17.1 (16.9, 17.3)	13.7 (12.9, 14.4)	30.7 (30.3, 31.2)	3.0
Random forest	17.3 (17.0, 17.5)	10.8 (10.3, 11.4)	30.2 (29.8, 30.6)	3.3
Backward stepwise regression	17.2 (16.9, 17.4)	13.2 (12.5, 13.9)	30.6 (30.2, 31.1)	3.3
Lasso penalized regression	17.1 (16.8, 17.3)	17.9 (17.1, 18.8)	29.7 (29.3, 30.0)	4.3
Gradient boosted decision trees	17.4 (17.2, 17.6)	16.9 (15.1, 18.6)	29.1 (28.5, 29.6)	6.3
Ridge penalized regression	17.3 (17.0, 17.5)	19.0 (18.2, 19.8)	29.2 (28.9, 29.6)	6.3
	Prediction of non-dipping systolic blood pressure			

Generalized additive regression	27.3 (27.1, 27.6)	12.8 (12.0, 13.5)	15.0 (14.6, 15.3)	1.7
Random forest	27.4 (27.1, 27.6)	11.8 (11.2, 12.5)	14.7 (14.4, 15.1)	2.0
Backward stepwise regression	27.9 (27.6, 28.1)	13.4 (12.6, 14.1)	14.3 (13.9, 14.7)	4.0
Forward stepwise regression	27.9 (27.7, 28.2)	12.9 (12.1, 13.6)	14.2 (13.8, 14.6)	4.3
Ridge penalized regression	27.8 (27.5, 28.1)	17.7 (16.8, 18.6)	13.3 (13.1, 13.5)	5.0
Gradient boosted decision trees	27.1 (26.9, 27.4)	25.9 (23.9, 27.9)	12.2 (11.7, 12.7)	5.0
Lasso penalized regression	28.1 (27.8, 28.3)	16.7 (15.9, 17.6)	13.1 (12.9, 13.4)	6.0

Table values were computed using the derivation data.

For clarity, concordance error, Brier scores, and calibration error were multiplied by 100.

Mean ranks were determined by taking the average of the order of the modeling algorithms from best (i.e., 1^{st}) to worst (i.e., 7^{th}) for concordance, calibration, and scaled Brier scores, separately.

Concordance error was measured one minus the concordance (C) statistic.

For concordance error and the Hosmer-Lemeshow X^2 Statistic, lower values indicate better fit. For the scaled Brier score, higher values indicate better fit.

CI = confidence interval.

Table S6. Proportions of bootstrap replicates where candidate variables were selected for inclusion in predictive equations for nocturnal hypertension.

Variable	Nocturnal hypertension
Included in predictive equations	
Race/ethnicity	100.0
Clinic SBP	100.0
Albumin-to-creatinine ratio	99.9
Age	98.3
Height	75.6
Neck circumference	64.8
Smoking status	57.0
High density lipoprotein-cholesterol	53.1
Clinic DBP	40.1
Not included in predictive equations	
Blood glucose	45.9
Sex	45.0
eGFR	27.0
Alcohol use	24.1
eGFR < 60 ml/min/1.73 m2	23.4
Low density lipoprotein-cholesterol	10.2
High school graduate	10.0
Body mass index	7.4
Waist circumference	6.8
Antihypertensive medication use	5.4
Diabetes	5.4
Total cholesterol	5.1

eGFR = estimated glomerular filtration rate; DBP = diastolic blood pressure; SBP = systolic blood pressure

Table S7. Proportions of bootstrap replicates where candidate variables were selected for inclusion in predictive equations for non-dipping systolic blood pressure.

Variable	Non-dipping systolic blood pressure
Included in predictive equations	
Race/ethnicity	100.0
Alcohol use	98.9
Age	91.5
High density lipoprotein-cholesterol	89.8
Albumin-to-creatinine ratio	86.3
Sex	75.8
Waist circumference	57.9
Height	27.5
Not included in predictive equations	
Blood glucose	32.9
Smoking status	29.4
Clinic DBP	28.0
Neck circumference	25.6
Low density lipoprotein-cholesterol	24.0
Antihypertensive medication use	21.5
Body mass index	20.2
Total cholesterol	17.6
eGFR < 60 ml/min/1.73 m2	15.8
Clinic SBP	13.7
Diabetes	11.1
eGFR	11.5
High school graduate	10.0

eGFR = estimated glomerular filtration rate; DBP = diastolic blood pressure; SBP = systolic blood pressure

Table S8. Calibration and discrimination of predictive equations for nocturnal hypertension and non-dipping systolic blood pressure overall and in sub-groups determined by race, sex, and antihypertensive medication use.

	Prevalence, %		P-value from Hosmer and Lemeshow's goodness of fit test		Concordance Statistic (95% Confidence Interval)	
	NHT	**NDSBP**	**NHT**	**NDSBP**	**NHT**	**NDSBP**
Race						
Non-white, N = 318 (62.8%)	46.2	57.2	0.310	0.158	0.82 (0.78, 0.87)	0.70 (0.64, 0.75)
White, N = 188 (37.2%)	20.2	22.9	0.143	0.560	0.81 (0.72, 0.89)	0.53 (0.43, 0.63)
Sex						
Female, N = 315 (62.3%)	30.2	43.8	0.152	0.925	0.83 (0.78, 0.87)	0.76 (0.71, 0.82)
Male, N = 191 (37.7%)	47.1	45.5	0.983	0.209	0.84 (0.79, 0.90)	0.69 (0.61, 0.77)
Antihypertensive medication use						
No, N = 346 (68.4%)	27.2	35.5	0.381	0.557	0.83 (0.78, 0.88)	0.66 (0.60, 0.73)
Yes, N = 160 (31.6%)	56.9	63.7	0.799	0.307	0.79 (0.72, 0.86)	0.76 (0.68, 0.84)
High school graduate						
Yes, N = 462 (91.3%)	34.0	42.9	0.382	0.558	0.84 (0.80, 0.88)	0.73 (0.68, 0.77)
No, N = 44 (8.7%)	63.6	61.4	0.395	0.344	0.73 (0.58, 0.89)	0.76 (0.61, 0.91)
All participants in validation data						
Overall, N = 506 (100.0%)	36.6	44.5	0.423	0.465	0.84 (0.80, 0.87)	0.73 (0.69, 0.78)

Table values were computed using the validation data.
NDSBP = non-dipping systolic blood pressure, NHT = nocturnal hypertension

Table S9. **Predictive equations for nocturnal hypertension and non-dipping systolic blood pressure.**

Equation	Formula
Nocturnal hypertension	Linear predictor = -33.055454 + 0.032777*(age in years) + 0.031443*(neck circumference in cm) + 1.014224*(1 if black, 0 otherwise) + 0.254249*(1 if asian, 0 otherwise) + 0.956609*(1 if other race, 0 otherwise) - 0.321403*(1 if former smoker, 0 otherwise) - 0.457890*(1 if never smoked, 0 otherwise) + 0.349868*(height in cm) - 0.000964*(height in cm)^2 - 0.118164*(clinic SBP in mm Hg) + 0.001829*(clinic SBP in mm Hg)^2 - 0.000006*(clinic SBP in mm Hg)^3 - 0.132077*(clinic DBP in mm Hg) + 0.000990*(clinic DBP in mm Hg)^2 - 0.008802*(HDL in mg/dL) + 0.321093*log(ACR + 1) Predicted probability = exp(linear predictor) / (1 + exp(linear predictor))
Non-dipping systolic blood pressure	Linear predictor = -13.284558 + 0.027831*(age in years) - 0.001952*(age in years)^2 + 0.000024*(age in years)^3 - 0.611072*(1 if male, 0 otherwise) + 1.099851*(1 if black, 0 otherwise) + 0.182960*(1 if asian, 0 otherwise) + 0.470218*(1 if other race, 0 otherwise) - 0.437195*(1 if drinks alcohol, 0 otherwise) + 0.145586*(height in cm) - 0.000382*(height in cm)^2 + 0.010166*(waist circumference in cm) - 0.011492*(HDL in mg/dL) - 1.061997*log(ACR + 1) + 0.346205*log(ACR + 1)^2 - 0.026371*log(ACR + 1)^3

	Predicted probability = exp(linear predictor) / (1 + exp(linear predictor))

exp(x) represents application of the exponential function to x.
The predictive equations shown here apply polynomials to model non-linear effects. These polynomials are approximately equal to the non-parametric smoothing functions used by the predictive equations developed in the current analysis.
ACR = albumin-to-creatinine ratio; DBP = diastolic blood pressure; HDL = high density lipoproteins; SBP = systolic blood pressure.

Table S10. Odds ratios for variables selected for inclusion in the predictive equations for non-dipping diastolic blood pressure.

Variable	Non-dipping Diastolic Blood Pressure
Age, 12 years	1.48 (1.31, 1.67)
Race/ethnicity	
White	1 (ref)
Black	2.76 (2.12, 3.60)
Asian	0.23 (0.03, 1.67)
Other race	1.30 (0.76, 2.23)
Waist circumference, 16 cm	1.17 (1.04, 1.32)*
Alcohol use	0.81 (0.66, 1.01)
HDL-cholesterol, 17 mg/dL	0.82 (0.73, 0.93)
Log(1+ACR), g/24hr	1.22 (1.10, 1.35)

Table values were computed using the derivation data.
* This is a non-linear variable in the predictive equation. The odds ratio is presented using the mean as a reference value.
The odds ratios for the following predictor variables are presented for a one standard deviation higher level of the exposure value: age, waist circumference, and high-density lipoprotein-cholesterol.
ACR = albumin-to-creatinine ratio; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table S11. **Calibration and discrimination of predictive equations for non-dipping diastolic blood pressure overall and in sub-groups determined by race, sex, and antihypertensive medication use.**

	P-value from Hosmer and Lemeshow's goodness of fit test	Concordance Statistic (95% Confidence Interval)
Race		
Non-white, N = 318 (62.8%)	0.912	0.70 (0.63, 0.76)
White, N = 188 (37.2%)	0.637	0.66 (0.53, 0.79)
Sex		
Female, N = 315 (62.3%)	0.973	0.72 (0.65, 0.78)
Male, N = 191 (37.7%)	0.135	0.73 (0.64, 0.82)
Antihypertensive medication use		
No, N = 346 (68.4%)	0.042	0.65 (0.56, 0.73)
Yes, N = 160 (31.6%)	0.644	0.69 (0.60, 0.77)
High school graduate		
Yes, N = 462 (91.3%)	0.526	0.72 (0.66, 0.78)
No, N = 44 (8.7%)	0.810	0.70 (0.53, 0.87)
All participants in validation data		
Overall, N = 506 (100.0%)	0.640	0.72 (0.67, 0.78)

Table values were computed in the validation data.

Table S12. **Test characteristics of the predictive equations for non-dipping diastolic blood pressure versus alternative screening methods for identifying adults with a high probability of non-dipping diastolic blood pressure.**

	Methods of identifying who should undergo 24-hour ambulatory blood pressure monitoring.							
	Predictive equation for non-dipping diastolic blood pressure probability cut-points				**Systolic/Diastolic blood pressure cut-points, mm Hg**			**Currently using anti-hypertensive medication**
	1	**2**	**3**	**4**	**I**	**II**	**III**	**IV**
Classification cut-point	≥0.36	≥0.19	≥0.44	≥0.19	≥120/70	≥130/80	≥140/90	Yes
Percent screened	21.5	51.2	9.68	52.2	78.5	42.1	14.6	31.6
Sensitivity	0.45	0.76	0.25	0.76	0.81	0.47	0.24	0.55
Specificity	0.86	0.56	0.95	0.55	0.22	0.60	0.88	0.76
Positive Predictive Value	0.49	0.35	0.59	0.34	0.24	0.26	0.38	0.41
Negative Predictive Value	0.84	0.89	0.81	0.88	0.80	0.79	0.79	0.85
Youden's Index	1.30	1.33	1.19	1.31	1.04	1.07	1.12	1.31

Table values were computed using the validation data.
Participants with values ≥ classification cut-point values are recommended to undergo 24-hour ambulatory blood pressure monitoring.
The following probability cut points of the predictive equation for non-dipping diastolic blood pressure were chosen based on the derivation data:

1. Closest number of predicted and observed cases with nocturnal hypertension and non-dipping systolic blood pressure.
2. The maximum specificity with a sensitivity ≥0.80;
3. The maximum negative predictive value with a positive predictive value ≥0.60,
4. The maximum sum of sensitivity and specificity.

Notably, cut-point 3 in our main analysis was selected as the maximum negative predictive value with a positive predictive value ≥0.60. However, the distribution of predicted probabilities from the predictive equations for non-dipping diastolic blood pressure could only meet the adjusted criteria used above, i.e., maximum negative predictive value with a positive predictive value ≥0.60.

Table S13. **Net reclassification improvement and integrated discriminative improvement using a predictive equation for non-dipping diastolic blood pressure versus screening methods based on clinic blood pressure and antihypertensive medication use.**

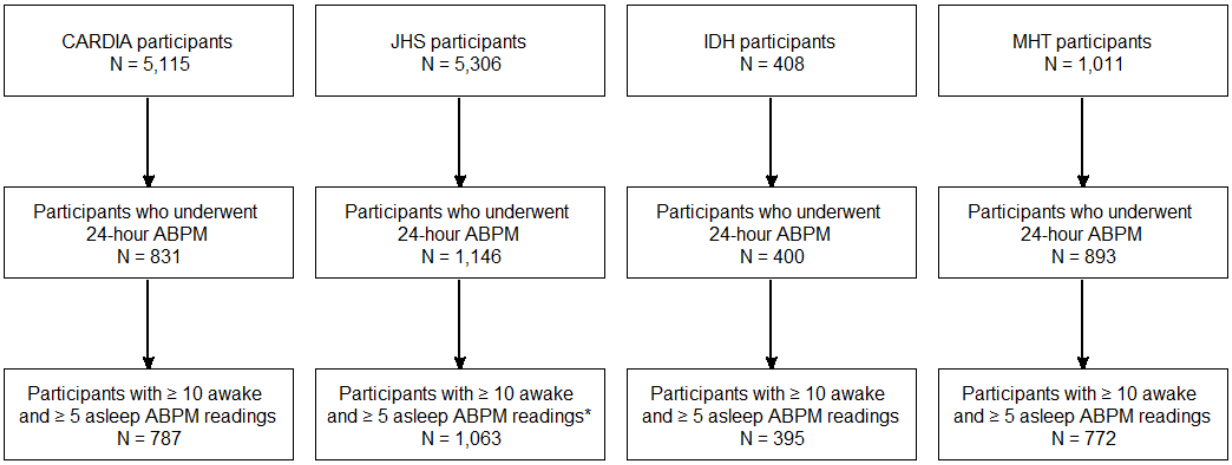
Methods of identifying who should undergo 24-hour ambulatory blood pressure monitoring	**Reclassification improvement using predictive equations (95% confidence interval) for non-dipping diastolic blood pressure**
Overall categorical net reclassification index*	
Clinic SBP/DBP ≥ 120/70 mm Hg	0.28 (0.17, 0.40)
Clinic SBP/DBP ≥ 130/80 mm Hg	0.24 (0.12, 0.38)
Clinic SBP/DBP ≥ 140/90 mm Hg	0.20 (0.09, 0.30)
Antihypertensive medication use	0.01 (-0.09, 0.11)
Negative categorical net reclassification index	
Clinic SBP/DBP ≥ 120/70 mm Hg	0.33 (0.27, 0.39)
Clinic SBP/DBP ≥ 130/80 mm Hg	-0.04 (-0.11, 0.02)
Clinic SBP/DBP ≥ 140/90 mm Hg	-0.33 (-0.39, -0.28)
Antihypertensive medication use	-0.20 (-0.25, -0.16)
Positive categorical net reclassification index	
Clinic SBP/DBP ≥ 120/70 mm Hg	-0.05 (-0.15, 0.05)
Clinic SBP/DBP ≥ 130/80 mm Hg	0.29 (0.18, 0.40)
Clinic SBP/DBP ≥ 140/90 mm Hg	0.53 (0.42, 0.62)
Antihypertensive medication use	0.21 (0.12, 0.30)
Continuous net reclassification index	
Models using SBP, DBP and antihypertensive medication use†	0.42 (0.21, 0.62)
Integrated discriminative improvement index	
Models using SBP, DBP and antihypertensive medication use†	0.04 (0.02, 0.06)

Table values were computed using the validation data.

* For categorical net reclassification indices, the probability cut-points maximizing Youden's index for the predictive equations (0.19) was used. This cut-point was chosen assuming that it would provide better overall classification characteristics than the other three cut-points.

† Predicted probabilities were obtained from equations formed for non-dipping diastolic blood pressure using logistic regression in the derivation data set with clinic systolic and diastolic blood pressure and antihypertensive medication use as independent variables.

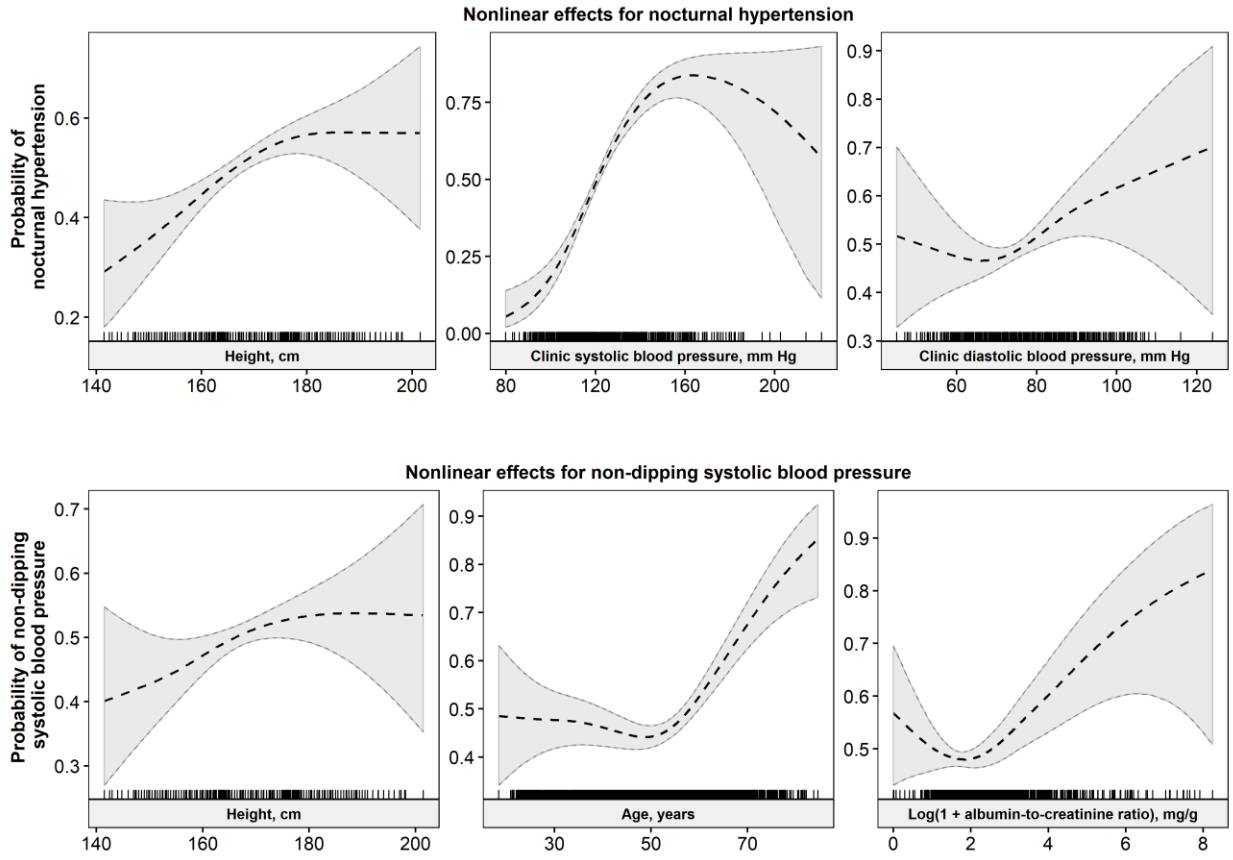
Figure S1. Inclusion cascade of participants from four studies that contributed data to the current analysis.



*For participants in the Jackson Heart Study who provided valid sleep diaries, we included those with ≥ 10 awake and ≥ 5 asleep blood pressure readings during self-reported awake and asleep periods. For Jackson Heart Study participants who did not provide valid sleep diaries, we included those with ≥ 10 daytime (10AM-8PM) and ≥ 5 nighttime (12AM-6AM) blood pressure readings.

ABPM = ambulatory blood pressure monitoring; CARDIA = Coronary Artery Risk Development in Young Adults; IDH = Improving Detection of Hypertension; JHS = Jackson Heart Study; MHT = Masked Hypertension Study

Figure S2. Predicted probability of nocturnal hypertension (top panels) and non-dipping systolic blood pressure (bottom panels) according to non-linear variables in the predictive equations.



Results are based on the derivation data.

Tick marks in the bottom of each panel indicate the distribution of observed values for a given variable.

Black curves are the predicted probability of nocturnal hypertension and non-dipping BP, relative to the given predictor variable, holding other predictors in the equation fixed.

Gray areas drawn around black curves are 95% confidence intervals for the predicted probability.

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