Thresholds for Ambulatory Blood Pressure Monitoring Based on Maternal and Neonatal Outcomes in Late Pregnancy in a Southern Chinese Population

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Background—In contrast to the general population, outcome-derived thresholds for diagnosing ambulatory hypertension in pregnancy are not yet available. We aimed to identify and compare outcome-derived ambulatory blood pressure (BP) monitoring thresholds for adverse perinatal outcomes by using approaches related and not related to clinic BP in a southern Chinese population.

Methods and Results—Ambulatory BP monitoring was performed in a cohort of 1768 high-risk participants in late pregnancy who were not taking antihypertensive medications. Participants were followed for composite maternal (severe complications) and neonatal (pregnancy loss, advanced neonatal care, and small for gestational age) outcomes. Modeling of clinic BP–unrelated approaches revealed a nonlinear threshold effect of ambulatory diastolic BP on the composite outcome, with increased risk for daytime ≥79 mm Hg and 24-hour measurement ≥76 mm Hg. For other ambulatory BP components showing linear associations with outcome, the following thresholds were identified: 131 mm Hg for daytime systolic, 121 mm Hg for nighttime systolic, 130 mm Hg for 24-hour systolic, and 73 mm Hg for night-time diastolic BP. These thresholds unrelated to clinic BP were lower than the equivalents yielding a similar probability of outcome to clinic BP of 140/90 mm Hg and were comparable with equivalents to clinic BP of 130/80 mm Hg.

Conclusions—Using an outcome-derived approach unrelated to clinic BP, we identified rounded thresholds to define ambulatory hypertension in at-risk women in late pregnancy in a southern Chinese population as follows: 130/80 mm Hg for daytime, 120/75 mm Hg for nighttime, and 130/75 mm Hg for 24-hour measurement. For wider clinical applicability and to align both nonpregnancy and pregnancy ambulatory BP monitoring with an outcomes-based approach, prospective, multiethnic, international studies from early pregnancy onward will be required. (*J Am Heart Assoc.* 2019;8:e012027. DOI: 10.1161/JAHA.119.012027.)

Key Words: ambulatory blood pressure monitoring • hypertension • maternal outcome • neonatal outcome • pregnancy

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Ambulatory blood pressure monitoring (ABPM) provides a more comprehensive assessment of blood pressure (BP) than conventional clinic BP measurement in terms of information about BP diurnal pattern, evaluation of antihypertensive efficacy, and long-term prognosis in the general adult population.[1,2] In recent years, application of ABPM during

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Clinical Perspective

What Is New?

- By applying an outcome-derived approach unrelated to clinic blood pressure (BP), we identified ambulatory BP thresholds in late pregnancy in a southern Chinese population.
- The outcome-derived, clinic BP-unrelated thresholds are lower than the outcome-derived ambulatory BP monitoring equivalents to clinic BP of 140/90 mm Hg.
- There is a nonlinear association of daytime and 24-hour diastolic BP with composite maternal and neonatal outcomes in late pregnancy.

What Are the Clinical Implications?

- The outcome-derived thresholds unrelated to clinic BP in late pregnancy could provide reference values for risk evaluation in terms of maternal and neonatal outcomes and have implications for designing appropriate antihypertensive regimens for this population.

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pregnancy has identified new subgroups with hypertension in pregnancy, white-coat hypertension, and masked hypertension, with ABPM required for diagnosis and to guide appropriate management.[3–8] ABPM has improved our understanding of BP regulation during pregnancy and contributed to better care of patients with hypertensive disorders in pregnancy (HDP).

Several organizations have proposed BP thresholds for identifying hypertension using ABPM based on nonpregnant adult populations from Europe, Asia, and South America.[9,10] Slightly different thresholds for black adults have been proposed, reflecting the unique cardiovascular risk profiles in this population.[11] Two general approaches exist for identifying these thresholds: (1) the non–outcome-derived approach, which is based on data distribution of ambulatory BP measurements[12,13] or relies on the regression equations derived between clinic BP and ambulatory BP measurements[14,15], and (2) the outcome-derived approach related to clinic BP, which identifies the thresholds for ambulatory BP associated with cardiovascular outcomes and matched to a clinic BP cutoff value that yields similar probability of risk (eg, 140/90 mm Hg).[11,16–18] In the nonpregnant adult population, the latter approach (derived ambulatory BP equivalent to clinic BP) has been adopted in hypertension guidelines.[9,10] Considering the independent prognostic value of ABPM,[1] a preferable approach would be outcome-derived, regardless of clinic BP measurement, which directly addresses the associations between ambulatory BP levels and adverse outcomes.

Attempts to identify pregnancy-specific diagnostic thresholds for ambulatory BP measurement date from the early 1990s,[4,13,19–21] with the non–outcome-derived approach applied in all studies. The upper normal range of ambulatory BP values, derived in a gestational-age–specific manner during pregnancy,[13] was adopted in a recent position paper on ABPM.[22] However, this is at odds with the approach for nonpregnant adults of using outcome-derived thresholds. In addition to maternal complications secondary to high BP,[23–25] the potential risk of fetal safety due to placental hypoperfusion induced by BP lowering is another major concern and was the primary outcome in a recent randomized trial of pregnancy BP control.[26] Consequently, the "optimal" ABPM thresholds during pregnancy should be based on the balancing trade-offs between maternal and neonatal outcomes. In this study we aimed (1) to identify outcome-derived ABPM thresholds for women at high risk of adverse perinatal outcomes in a southern Chinese population and (2) to compare outcome- and non–outcome-derived thresholds both in relation to and independent of clinic BP.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Cohort

This retrospective cohort study assessed pregnant women with a live singleton fetus who were without major or urgent complications at study enrollment and receiving pregnancy care at Guangdong Women and Children Hospital (a tertiary referral hospital specializing in maternal and child health that performs $\approx 20,000$ births annually) in southern China. Inclusion criteria were either having at least one of the risk factors for HDP (advanced maternal age ≥35 years, primipara, HDP in a previous pregnancy, gestational diabetes mellitus, preexisting type 2 diabetes mellitus, family history of hypertension) or having been diagnosed with HDP (chronic hypertension and/or superimposed preeclampsia, gestational hypertension and preeclampsia) during this pregnancy. Exclusion criteria included multiple pregnancies, intolerance to ABPM, receipt of antihypertensive medications, and arrhythmias. All patients had a 24-hour ABPM assessment during the third trimester of pregnancy and were followed for the pregnancy outcome. The hospital ethics committee approved this study. Because ABPM was part of routine assessment of at-risk pregnant women in the hospital, the requirement of informed consent was unnecessary and was waived.

BP Measurements and Definitions

Conventional clinic BP was measured by trained research nurses using a mercury sphygmomanometer and auscultating

the Korotkoff sounds (phase 1 for systolic BP [SBP] and phase 5 for diastolic BP [DBP], respectively) with the patient in the sitting position and using an appropriate cuff size. Clinic hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg based on the average of at least 2 measurements taken at least 15 minutes apart.[27] ABPM was performed during hospitalization using an Oscar 2 ambulatory BP monitor (SunTech Medical). The device was programmed to take readings at intervals of 30 minutes starting from 7 AM for 24 hours. Bed rest was not prescribed during ABPM. Patient diaries were used to record and define awake and sleep times during ABPM. If BP data were missing for >2 hours, the first ABPM series was then excluded from further analysis and a second ABPM was performed. Mean daytime (awake), nighttime (sleep), and 24-hour levels of SBP, DBP and circadian rhythm of BP readings were computed. HDP was defined according to a recently published guideline from the American College of Obstetricians and Gynecologists.[28]

Study Outcomes

For the outcome-derived approach, we created a composite maternal and neonatal outcome. The following maternal outcomes were considered[23–25]:

1. Maternal death
2. Central nervous system: cerebrovascular accident/hemorrhage and/or new-onset, persistent visual symptoms or disturbance
3. Cardiorespiratory: positive inotropic support, myocardial ischemia or infarction, and/or pulmonary edema or effusion
4. Kidney: renal insufficiency (serum creatinine ≥100 μmol/L)
5. Liver: hepatic dysfunction (blood liver transaminase level twice the normal levels or higher) and hematoma/rupture
6. Thrombocytopenia ($\leq 100 \times 10^9$/L)
7. Placental abruption
8. Postpartum hemorrhage (>1000 mL)
9. Preterm delivery before 34 weeks.

The neonatal outcomes were as follows:

1. Pregnancy loss (pregnancy termination due to static fetal growth or fetal anomalies, perinatal death)
2. Prolonged advanced neonatal care (admission to the neonatal intensive care unit for ≥48 hours)
3. Small for gestational age: defined as birth weight <10th percentile birth weight for gestational age and adjusted for gender, according to a previously published global reference.[29]

A composite adverse outcome was considered to be present if at least one of the listed maternal and/or neonatal outcomes occurred.

Statistical Analysis

Data were initially analyzed descriptively and checked for normality. Continuous normally distributed data are presented as mean±SD, nonparametric continuous data are presented as median with interquartile range, and categorical data are presented as number and percentage.

To examine the relationship between clinic and ambulatory BP measurements and pregnancy outcome, we fit a univariate logistic regression model (model 1, without any adjustment). To assess whether the associations were independent of other BP measurements, additional adjustments were performed (model 2; odds ratios for clinic BP were adjusted for 24-hour BP, 24-hour BP was adjusted for clinic BP, daytime BP was adjusted for clinic and nighttime BP, and nighttime BP was adjusted for clinic and daytime BP).[2]

Four categories of ambulatory thresholds are mentioned in this study, depending on the methodology used to identify ambulatory thresholds:

1. Outcome derived and related to clinic BP: a threshold identified as the equivalent to a clinic BP level (ie, 140/90 mm Hg) that yields similar probability of risk for outcome
2. Outcome derived and unrelated to clinic BP: a threshold identified by direct modeling of the association between ambulatory BP (independent variable) and outcome (dependent variable)
3. Non–outcome derived and related to clinic BP: a threshold corresponding to a clinic BP level (ie, 140/90 mm Hg) calculated based on linear regression between clinic BP (independent variable) and ambulatory BP (dependent variable)
4. Non–outcome derived and unrelated to clinic BP: a threshold calculated as a certain cutoff value (ie, 95th percentile) based on the statistical distribution of the ambulatory BP level. Because our participants were all at-risk pregnant women, the thresholds for non–outcome derived and unrelated to clinic BP were not reported because these values should, ideally, be derived from an unselected population.

To identify non–outcome-derived thresholds, we used least squares linear regression and reduced major axis linear regression analysis between clinic and ambulatory BP values to generate ambulatory BP equivalents for specific clinic BP levels (120, 130, and 140 mm Hg for SBP; and 80, 85, and 90 mm Hg for DBP), using the intercept and coefficient derived from regression equations. Reduced major axis linear regression is suitable when both independent (clinic BP) and dependent (ambulatory BP) variables are subject to error. The analysis was performed using the R package "lmodel2."

To identify outcome–derived, clinic BP–related thresholds, we used a logistic regression model to identify thresholds for ambulatory BP that yielded a probability of the composite maternal and neonatal adverse events occurring that was similar to a specific clinic BP level.[11,18] We plotted incidence rates by fifths of the BP distribution. The linearity of a specific BP parameter was tested using a Box–Tidwell transformation with the STATA module "boxtid." If the linearity assumption was violated, the quadratic term of a BP parameter was added to the model to improve the fit. We then constructed logistic regression models using the composite outcome events with clinic SBP/DBP and ambulatory BP as the independent variable, sequentially. We next computed the incidence rate of the composite outcome associated with specific clinic SBP/DBP cutoffs (120, 130, and 140 mm Hg for SBP; 80, 85, and 90 mm Hg for DBP). We then computed the composite outcome associated with ambulatory BP levels using intervals of 0.1 mm Hg. Finally, we selected the ambulatory BP levels that were associated with similar incidence rates as the clinic BP values.

To identify thresholds that were outcome derived and unrelated to clinic BP, we used restricted cubic splines (STATA command "mkspline") with 4 knots, positioned at 5th, 35th, 65th, and 95th percentiles of the ambulatory BP distribution, in logistic regression models to examine the dose-response relationship between ABPM and pregnancy outcomes with and without adjustment for confounders. Notably, because we found statistical differences in serum creatinine levels between those with and without a composite outcome, and because the patients with isolated renal insufficiency accounted for only 3.37% (34/1009) of women with composite events, we treated serum creatinine (continuous variable) as a confounder for adjustment despite renal insufficiency (binary variable, defined as serum creatinine ≥100 μmol/L) being defined as one of the composite maternal outcomes. The STATA command "xblc" was used to estimate the odds ratio for association of ABPM with the risk of adverse pregnancy outcomes. The model effect and nonlinearity were assessed by Wald tests. *P* values for nonlinearity were calculated by comparing restricted cubic spline terms to linear models. For models where nonlinearity was rejected, a receiver operating characteristic (ROC) curve analysis was performed to identity the cutoff values based minimal Euclidean and Manhattan distance, respectively.

ROC curve–based cutoffs were determined by Cutoff Finder,[30] a freely available web tool using the R statistical language as the computing engine (http://molpath.cha rite.de/cutoff). To assess the performance of the thresholds in predicting adverse outcomes, we calculated area under receiver operating characteristic curve and sensitivity and specificity corresponding to a specific threshold using the STATA command "roctab." We used STATA v15.1 (StataCorp) and the R statistical software framework (http://www.

R-project.org) for analysis. All logistic regression analyses were performed using 1000 bootstrapping replications. Two-tailed *P*<0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 1973 women had ABPM performed after 28 weeks of gestation. After excluding 205 patients who were taking antihypertensive medications, 1768 patients were analyzed. Clinical characteristics of these participants are shown in Table 1. The median time delay between ABPM and delivery was 4.3 days (interquartile range: 3.4–7.2 days). The composite incidence rate of maternal and neonatal events was 57.1%. Notably, in our cohort, 29 cases of HELLP syndrome were diagnosed, all of which were classified as *≥2 complications* under maternal outcomes in Table 1. Compared with participants without composite outcome events (Table S1), those with adverse events were more likely to experience preterm delivery, lower offspring birth weight, higher BP levels, higher levels of triglycerides and low-density lipoprotein, and higher levels of serum creatinine and 24-hour urinary protein excretion. In terms of maternal or neonatal outcomes, statistical differences were also observed for baseline body mass index, hematocrit and glucose levels, and multipara (Tables S2 and S3). To make the thresholds comparable, 9 variables showing statistical significance in maternal, neonatal, or composite outcome events (body mass index, gestational age when ABPM was performed, multipara, glucose, hematocrit, triglycerides, LDL [low-density lipoprotein], serum creatinine, and 24-hour urinary protein excretion) were treated as confounding factors for adjustment in restricted cubic spline logistic regression.

Association Between Clinic and Ambulatory BP and Adverse Pregnancy Outcome

Univariate logistic regression analysis revealed that clinic and ambulatory BP measurements were all statistically associated with maternal, neonatal, and composite outcomes (model 1 in Table 2). However, after adjustment for ambulatory BP measurements, clinic BP lost its statistical associations; conversely, the odds ratio for ambulatory BP measurements did not change markedly after adjustment for clinic BP (model 2 in Table 2).

Non–Outcome-Derived ABPM Thresholds

Compared with a conventional least squares regression method (the green dotted lines in Figure 1), reduced major axis slopes were greater, and the regression lines closely

Table 1. Clinical Characteristics

Characteristic	Total Cohort (n=1768)
Maternal age at term, y	30.9±5.4
BMI, baseline, kg/m^2	21.5±3.0
Gestational weight gain, kg	13.3±3.4
Birth weight, g	2769±817
Gestational week at delivery	38.0 (36.0–39.4)
Gestational week at ABPM	37.3 (34.8–38.7)
Maternal status at enrollment	
Suspected HDP	898 (50.8)
Confirmed HDP with suspected preeclampsia	492 (27.8)
Confirmed preeclampsia	378 (21.4)
Multipara	1030 (58.3)
Preeclampsia, non-severe feature*	197 (11.1)
Preeclampsia, severe feature*	427 (24.2)
Neonatal outcomes	
Pregnancy termination	13 (0.74)
Perinatal death	62 (3.51)
NICU admission >48 h	596 (33.7)
Small for gestational age	434 (24.5)
Neonatal total incidence rate	808 (45.7)
Maternal outcomes	
Maternal death	0 (0)
Central nervous system	56 (3.17)
Cardiorespiratory	96 (5.43)
Renal insufficiency	34 (1.92)
Liver dysfunction	156 (8.82)
Thrombocytopenia	23 (1.30)
Placenta abruption	24 (1.36)
Postpartum hemorrhage	13 (0.74)
Preterm delivery ≤34 wk	146 (8.26)
≥2 Complications	102 (5.77)
Maternal total incidence rate	650 (36.8)
Composite incidence rate	1009 (57.1)
BP measurements, mm Hg	
SBP, clinic	132.1±15.3
DBP, clinic	82.1±11.7
SBP, daytime mean	129.5±15.3
SBP, nighttime mean	121.4±18.4
SBP, 24-h mean	127.4±15.6
DBP, daytime mean	79.1±11.8
DBP, nighttime mean	72.3±14.4
DBP, 24-h mean	77.3±12.2

Table 1. Continued

Characteristic	Total Cohort (n=1768)
Glucose, mmol/L	4.59±0.69
Triglycerides, mmol/L	2.84 (2.17–3.54)
Total cholesterol, mmol/L	5.83±1.24
HDL-C, mmol/L	1.65±0.42
LDL-C, mmol/L	3.14±1.00
Hematocrit, %	34.7±4.16
Creatinine, μmol/L	51.0±18.3
24-h urinary protein, mg	213 (95, 731)

Data are shown as mean±SD, median (interquartile range), or n (%). ABPM indicates ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HDP, hypertensive disorders in pregnancy; LDL-C, low-density lipoprotein cholesterol; NICU, neonatal intensive care unit; SBP, systolic blood pressure.
*Includes patients with chronic hypertension complicated by preeclampsia.

followed the major axis of the ellipse of data points (Figure 1). The ABPM equivalents to frequently used clinic SBP and DBP cutoffs are shown in Table 3. Daytime, nighttime, and 24-hour thresholds corresponding to clinic SBP/DBP of 140/90 mm Hg were 137.3/87.0 mm Hg, 130.9/82.1 mm Hg, and 135.5/85.6 mm Hg, respectively (Table 3).

Outcome-Derived, Clinic BP–Related Thresholds

The incidence of neonatal, maternal, and composite events increased across fifths of the distributions of clinic and ambulatory BP (Figure S1). Through visual inspection, the relationship between ambulatory DBP and composite incidence presented an obvious curvilinear shape that was further confirmed by Box–Tidwell transformation. Moreover, except for nighttime SBP, the nonlinear relationship between ambulatory SBP levels and composite event rates was also confirmed. Therefore, we introduced the quadratic term of all ambulatory DBP parameters as well as daytime and 24-hour SBP into the logistic models. The ambulatory equivalents that yielded the same risk of composite outcome events are shown in Table 3. The ambulatory BP equivalents corresponding to maternal and neonatal outcomes, which were calculated separately, are shown in Table S4. Notably, the ambulatory SBP thresholds corresponding to clinic SBP of 140 mm Hg were similar regardless of whether the neonatal-specific, maternal-specific, or composite events were used as the outcomes. In terms of ambulatory DBP equivalents to the clinic DBP of 90 mm Hg, the neonatal outcome-based threshold was ≈3.0 mm Hg higher than that derived from maternal outcomes in daytime, nighttime, and 24-hour ambulatory BP, with the composite outcome-derived value in the middle.

Table 2. Association of Clinic and Ambulatory BP With Pregnancy Outcome in Logistic Regression Models

	Model 1*		Model 2†	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Composite outcome				
Clinic SBP	1.29 (1.21–1.38)	<0.001	1.04 (0.96–1.13)	0.294
Clinic DBP	1.22 (1.17–1.38)	<0.001	1.04 (0.98–1.10)	0.163
Daytime SBP	1.46 (1.36–1.56)	<0.001	1.11 (0.97–2.28)	0.140
Nighttime SBP	1.39 (1.32–1.48)	<0.001	1.26 (1.13–1.41)	<0.001
24-h SBP	1.47 (1.38–1.58)	<0.001	1.44 (1.32–1.56)	<0.001
Daytime DBP	1.30 (1.24–1.36)	<0.001	1.05 (0.96–1.16)	0.267
Nighttime DBP	1.26 (1.21–1.30)	<0.001	1.18 (1.10–1.27)	<0.001
24-h DBP	1.30 (1.25–1.36)	<0.001	1.27 (1.20–1.34)	<0.001
Maternal outcome				
Clinic SBP	1.41 (1.32–1.51)	<0.001	1.05 (0.96–1.14)	0.290
Clinic DBP	1.30 (1.24–1.36)	<0.001	1.02 (0.96–1.08)	0.511
Daytime SBP	1.74 (1.61–1.88)	<0.001	1.28 (1.11–1.48)	0.001
Nighttime SBP	1.58 (1.49–1.69)	<0.001	1.30 (1.16–1.46)	<0.001
24-h SBP	1.75 (1.62–1.89)	<0.001	1.70 (1.56–1.86)	<0.001
Daytime DBP	1.46 (1.39–1.54)	<0.001	1.13 (1.03–1.25)	0.013
Nighttime DBP	1.38 (1.33–1.44)	<0.001	1.25 (1.16–1.35)	<0.001
24-h DBP	1.47 (1.40–1.54)	<0.001	1.45 (1.36–1.54)	<0.001
Neonatal outcome				
Clinic SBP	1.18 (1.11–1.26)	<0.001	1.02 (0.95–1.11)	0.539
Clinic DBP	1.16 (1.11–1.20)	<0.001	1.05 (0.99–1.11)	0.096
Daytime SBP	1.28 (1.20–1.36)	<0.001	1.04 (0.91–1.19)	0.596
Nighttime SBP	1.25 (1.19–1.32)	<0.001	1.20 (1.08–1.33)	0.001
24-h SBP	1.29 (1.21–1.37)	<0.001	1.27 (1.17–1.37)	<0.001
Daytime DBP	1.18 (1.13–1.23)	<0.001	0.98 (0.90–1.07)	0.692
Nighttime DBP	1.17 (1.13–1.21)	<0.001	1.15 (1.07–1.23)	<0.001
24-h DBP	1.19 (1.14–1.24)	<0.001	1.15 (1.09–1.22)	<0.001

ORs were estimated per 10 mm Hg for SBP and per 5 mm Hg for DBP. BP indicates blood pressure; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.
*Model 1 was univariate analysis.
†Model 2 was adjusted as follows: clinic BP was adjusted for 24-h pressure; 24-h BP was adjusted for clinic pressure; daytime BP was adjusted for clinic and nighttime pressures; and nighttime BP was adjusted for clinic and daytime pressures.

Outcome-Derived, Clinic BP–Unrelated Thresholds

The results of the logistic models with restricted cubic splines revealed nonlinear dose-response associations of ambulatory BP values with composite adverse outcome before adjustment for confounding factors, except for nighttime SBP (Figure S2). Notably, a J-shaped association was observed in daytime and 24-hour DBP, with inflection points of minimal risk for composite outcome at 71 and 70 mm Hg, respectively. However, after adjustment for confounders, nonlinear associations disappeared for ambulatory SBP (Figure 2).

Moreover, the increased risk for composite outcome below the inflection points in daytime and 24-hour DBP were no longer statistically significant (Figure 2). Using the BP values at the inflection points as references (71 and 67 mm Hg, respectively), daytime DBP >79 mm Hg and 24-hour DBP >76 mm Hg were associated with increased risk of the composite outcome (Figure 2). When maternal and neonatal outcomes were analyzed separately, after adjustment for confounding factors, the nonlinear associations remained only for daytime and 24-hour DBP (Figures S3–S6).

To determine the outcome-derived cutoffs for ambulatory SBP and nighttime DBP, we used ROC curve analysis. The
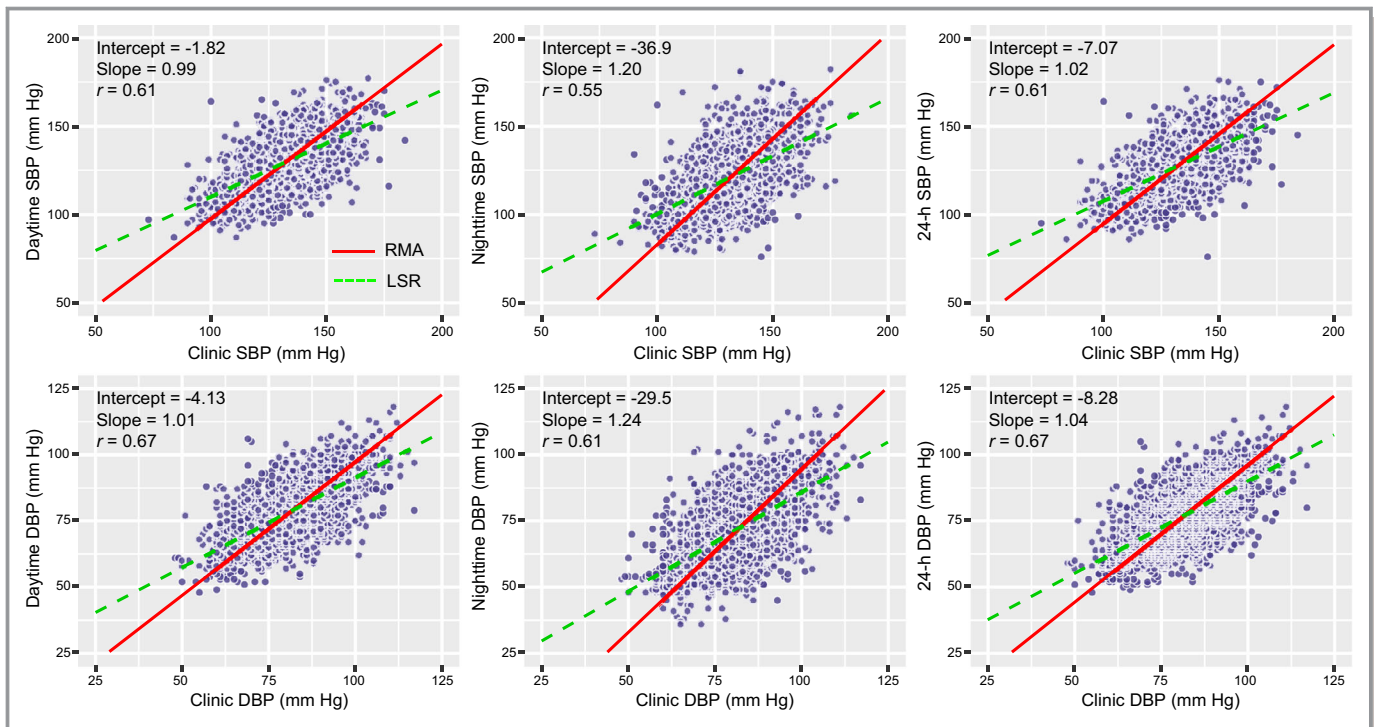
Figure 1. Linear correlation between clinic blood pressure measurement and ambulatory blood pressure monitoring. Green dashed lines indicate least squares linear regression, and red solid lines indicate reduced major axis (RMA) linear regression. The intercept, slope, and correlation coefficient (*r*) are shown for RMA regression. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

ROC curve–derived ambulatory thresholds using the composite, maternal, and neonatal outcomes are shown in Tables 4, S5, and S6, respectively. In general, the cutoffs derived from minimal Manhattan distance were higher than those derived from minimal Euclidean distance and thus contributed to increased specificity with reduced sensitivity. We then examined the associated risk for maternal and neonatal outcomes at ROC curve–derived cutoffs in logistic regression models after adjustment for baseline body mass index, gestational age when ABPM was performed, multipara, glucose, hematocrit, triglycerides, LDL, serum creatinine, and 24-hour urinary protein excretion. As shown in Figure 3, compared with Manhattan distance–derived cutoffs, the Euclidean distance–derived cutoffs were associated with reduced odds ratios for maternal and neonatal adverse outcomes.

Comparison of Outcome-Derived and Non–Outcome-Derived Thresholds

As shown in Table 5, the outcome-derived, clinic BP–unrelated thresholds were very close to ABPM equivalents achieved by clinic BP of 130/80 mm Hg and were slightly higher than a non–outcome-derived (reduced major axis regression) clinic BP equivalent at the same level. Compared with the most recommended normal upper limits in the third trimester (using the non–outcome-derived approach),[13] our

daytime thresholds were slightly lower (131/79 versus 135/86 mm Hg), whereas the nighttime thresholds were comparable (121/73 versus 123/72 mm Hg). In addition, our thresholds were close to a previous report using the 90th percentile as the upper normal limit.[4] Moreover, our daytime thresholds were lower and nighttime thresholds were higher than the recommended threshold corresponding to a clinic BP of 140/90 mm Hg for the nonpregnant population.[9,10]

Collectively, considering the clinic BP–independent value and the easiness for recall and interpretation, we identified the following outcome-derived thresholds unrelated to clinic BP in late pregnancy in a Southern Chinese population: 130/80 (131/79) mm Hg for daytime, 120/75 (121/73) mm Hg for nighttime, and 130/75 (130/76) for 24-hour measurement (Table 5) after rounding the point estimates to an integer BP value ending in 0 or 5, as suggested previously.[18]

Discussion

There is growing evidence demonstrating the clinical utility of ABPM in differential diagnosis and risk stratification of HDP. However, the diagnosis of ambulatory hypertension is either based on the non–outcome-derived cutoffs from normotensive pregnancies, or relies on thresholds used for non-pregnant adult populations. In the present study, we demonstrated the clinic BP–independent association of ABPM between

Table 3. Clinic BP–Related ABPM Threshold Equivalents

	Non–Outcome-Derived, RMA Regression–Based			Outcome-Derived, Clinic BP–Related		
	Daytime	Nighttime	24 h	Daytime	Nighttime	24 h
SBP						
120 mm Hg	117.5 (117.0–117.7)	107.0 (106.6–107.4)	115.1 (114.7–115.6)	124.0 (119.9–127.6)	111.5 (108.2–114.8)	121.9 (118.0–125.3)
Sensitivity, %	83.8	83.9	83.1	71.9	76.8	71.4
Specificity, %	28.1	31.4	29.4	47.4	42.2	50.0
130 mm Hg	127.4 (127.2–127.5)	119.0 (118.9–119.1)	125.3 (125.2–125.4)	131.0 (127.8–133.9)	119.2 (116.3–122.2)	128.7 (125.6–131.6)
Sensitivity, %	63.8	62.5	63.9	57.3	62.5	57.2
Specificity, %	55.6	59.2	56.4	65.1	59.2	66.0
140 mm Hg	137.3 (137.0–137.5)	130.9 (130.4–131.5)	135.5 (135.3–135.7)	136.7 (134.1–139.2)	127.0 (123.8–130.3)	134.4 (131.8–136.9)
Sensitivity, %	42.5	42.0	41.6	42.5	47.5	47.2
Specificity, %	81.3	81.4	83.3	81.3	75.4	78.7
DBP						
80 mm Hg	76.9 (76.9–77.0)	69.7 (69.5–69.9)	75.2 (75.1–75.2)	81.6 (79.7–83.2)	73.2 (70.2–75.8)	77.9 (75.4–80.1)
Sensitivity, %	66.6	64.4	67.7	53.8	58.7	60.3
Specificity, %	57.8	58.2	57.8	74.2	68.1	68.4
85 mm Hg	82.0 (82.0–82.1)	76.0 (75.9–76.1)	80.4 (80.2–80.5)	84.3 (82.7–85.8)	77.2 (74.8–79.5)	81.3 (79.3–83.2)
Sensitivity, %	53.8	51.9	56.1	47.7	49.7	52.5
Specificity, %	74.2	75.2	73.9	79.7	76.2	76.9
90 mm Hg	87.0 (86.9–87.3)	82.1 (81.9–82.4)	85.6 (85.3–85.9)	86.7 (85.4–88.2)	80.9 (78.7–83.0)	84.5 (82.7–86.3)
Sensitivity, %	38.8	38.7	37.8	38.8	40.8	40.9
Specificity, %	87.0	86.4	88.5	87.0	85.0	85.6

Data in parentheses indicate 95% CIs. ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; RMA, reduced major axis; SBP, systolic blood pressure.

maternal, neonatal and the composite outcome in late pregnancy. By using outcome-derived approaches, we identified ambulatory thresholds both related and unrelated to clinic BP that were associated with composite maternal and neonatal outcomes and compared those with cutoffs derived from non–outcome-derived approaches. Considering the clinic BP–independent value of ABPM and the tradeoff between sensitivity/specificity and maternal-/neonatal-specific risk, we identified the following cutoffs unrelated to clinic BP in late pregnancy in a southern Chinese population: 130/80 mm Hg for daytime, 120/75 mm Hg for nighttime, and 130/75 for 24-hour BP. To our knowledge, this work is the first to address the knowledge gap regarding outcome-derived ABPM thresholds during pregnancy.

Despite the fact that trimester-specific upper limits for ABPM have been proposed previously,[13,19,20] these thresholds were exclusively calculated by distribution-derived approaches from a reference population with "normal pregnancy," which may be influenced by the prevalence of hypertension and sample size. Given these limitations, the 2013 European Society of Hypertension position paper on ABPM proposes use of outcome-derived thresholds rather than thresholds relying on statistical distribution.[22] However, it is inappropriate to use major adverse cardiovascular events (ie, fatal and nonfatal cardiovascular events) to define maternal outcomes given their rare occurrence during pregnancy. Consequently, we adopted a composite adverse pregnancy outcome with 2 main components: (1) neonatal outcomes including pregnancy loss or prolonged high-level neonatal care, the outcome used in CHIPS (Control of Hypertension in Pregnancy Study),[26] and small for gestational age, an outcome known to be associated with increased BP levels and poor placental perfusion[31,32]; (2) maternal outcomes, mainly focused on maternal complications based on recent guideline and outcome prediction studies.[23–25]

An important finding from our work is that clinic BP–unrelated thresholds are lower than the clinic BP–related cutoffs matched to a clinic BP of 140/90 mm Hg in terms of similar probability of maternal and neonatal risk. This could be explained by the results from recent observational studies showing that BP values even within prehypertensive levels (120–139/80–89 mm Hg) confer risk with small for gestational age.[32–34] Another finding from the present study is that our results do not support an obvious J-shaped association
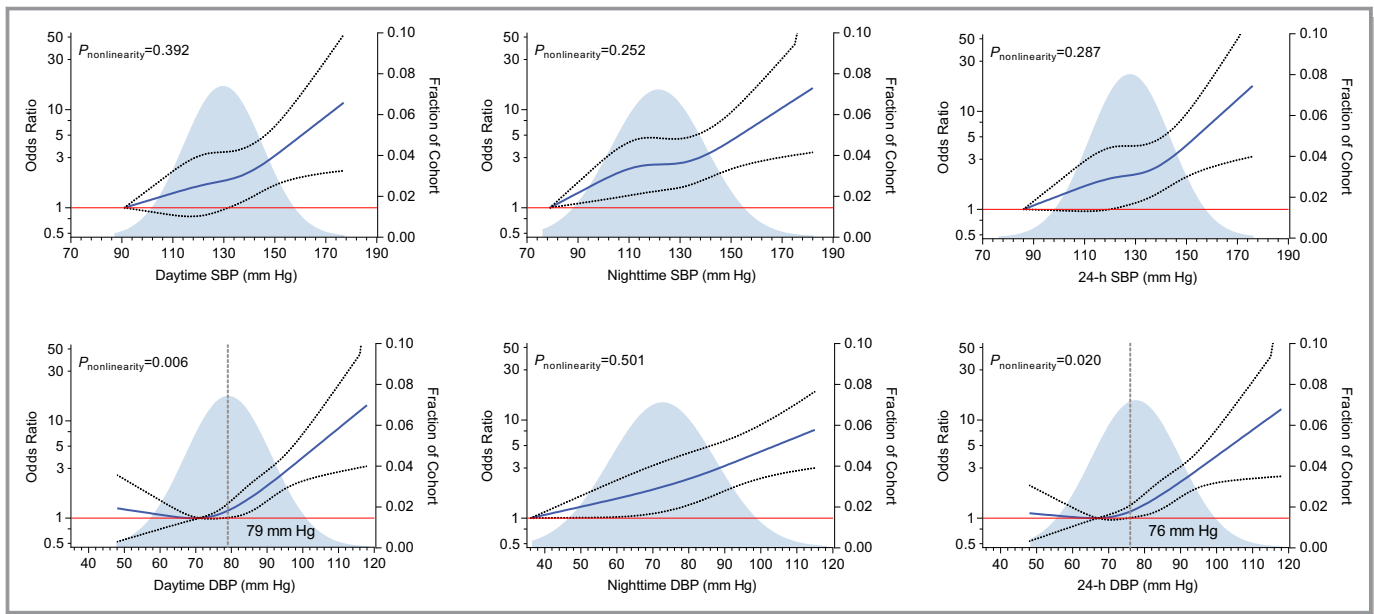
Figure 2. Associations of ambulatory blood pressure monitoring with composite maternal and neonatal adverse outcome in logistic models with restricted cubic splines after adjustment, with background distributional histogram of blood pressure level (blue area). Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% CIs. For systolic ambulatory measurements and nighttime DBP, the references were set at the lowest blood pressure level. For daytime and 24-hour DBP, the references were set at the inflection points at 71 and 67 mm Hg, respectively. The odds ratios are shown on the *y*-axis in log scale. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

between ambulatory DBP and pregnancy outcomes in late pregnancy after adjustment for confounding factors (ie, BP values below the inflection points are not associated with increased risk), especially for neonatal outcomes. This result is potentially important to clinical practice because it suggests that adverse perinatal outcome rates are similar to those in normotensive pregnancy, whereas ambulatory BP values remain below threshold. If validated in future studies, particularly if found to also hold true in women with medicated HDP, this finding may have implications for designing appropriate antihypertensive regimens in late pregnancy.

This study has the following strengths. First, to our knowledge, our study has the largest ABPM series in pregnant women, and it provides sufficient power to estimate ABPM thresholds using an outcome-derived approach. Second, considering the rare occurrence of adverse cardiovascular events in pregnant women, we used combined neonatal and maternal outcomes as an alternative to perform outcome-derived risk calculation.

Table 4. Clinic BP–Unrelated ABPM Thresholds Calculated by Cutoff Finder

	ROC Curve, Euclidean* (Composite Outcome-Derived)			ROC Curve, Manhattan[†] (Composite Outcome-Derived)			
	Cutoff (mm Hg)	Sensitivity (%)	Specificity (%)	Cutoff (mm Hg)	Sensitivity (%)	Specificity (%)	AUC
SBP							
Daytime	130.5	57.3	65.1	134.5	48.6	76.2	0.654
Nighttime	120.5	59.3	64.6	129.5	43.7	80.2	0.661
24 h	129.5	56.3	68.1	132.5	49.4	76.7	0.661
DBP							
Daytime	79.5	60.4	68.1	79.5	60.4	68.1	0.664
Nighttime	72.5	58.7	68.1	75.5	51.9	75.2	0.670
24 h	77.5	60.3	68.4	79.5	56.1	73.9	0.670

Cutoff Finder is available online (http://molpath.charite.de/cutoff). ABPM indicates ambulatory blood pressure monitoring; AUC, area under the curve; BP, blood pressure; DBP, diastolic blood pressure; ROC, receiver operating characteristic; SBP, systolic blood pressure.
*Determined by minimal Euclidean distance.
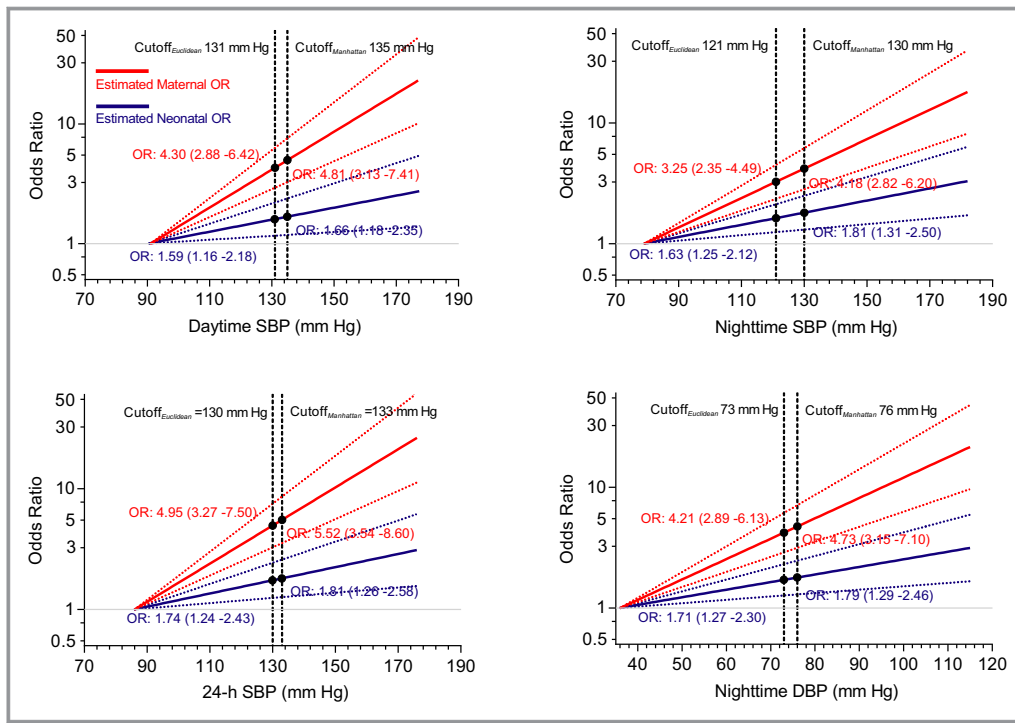[†]Determined by minimal Manhattan distance.

Figure 3. Comparisons of estimated OR for maternal (red lines) and neonatal (blue lines) adverse outcomes at receiver operating characteristic curve–derived ambulatory blood pressure cutoffs in logistic regression models after adjustment. The solid lines indicate estimated OR; dotted lines indicate 95% CI. The references were set at the lowest blood pressure level. The ORs are shown on the *y*-axis in log scale. DBP indicates diastolic blood pressure; OR, odds, ratio; SBP, systolic blood pressure.

This study has several limitations. First, our analysis was based on pregnant women in only a southern Chinese population and may not be representative for other ethnic populations. Second, because our analysis was based on a cohort in late pregnancy, considering the dynamic nature of BP change during pregnancy, further studies are warranted to establish trimester-specific ambulatory BP thresholds in a prospective manner. Given the recent evidence that a thorough evaluation of at-risk patients by routine clinical tests is helpful as a triage tool regarding need for transportation in the next 48 hours in late trimester,[24] we believe that ABPM performed even in the late third trimester could be a novel and important component that benefits patients. Third, our results are subject to potential bias given the lack of an Oscar 2 (SunTech Medical; ambulatory device used in this study) validation study. Few ABPM devices are validated for use in pregnancy generally, and among published studies, no ambulatory device passed validation in preeclampsia specifically.[35] Consequently, ABPM device validation in pregnancy and pregnancy complications, such as preeclampsia, is urgently needed for both research and clinical practice. Fourth, our cohort was based at a tertiary specialized hospital, which contributes to a higher proportion of high-risk pregnancies.[36] Therefore, our findings are particularly relevant for at-risk pregnant women, and the generalizability of these thresholds to low- and moderate-risk pregnancies remains to be

investigated. Fifth, because of the small sample size (n=205) of patients on antihypertensive medications during ABPM in this study, we excluded this subgroup for analysis. Future studies with sufficient sample sizes are warranted to identify and compare the ambulatory thresholds with those not on antihypertensive medications. Finally, despite the fact that our data support ABPM as a stronger predictor of pregnancy outcome than clinic BP, the prognostic accuracy of BP thresholds generated by all models, whether ABPM or clinic BP, did not reach the level used to define a clinically acceptable biomarker (ie, area under the ROC curve >0.7[37]; Table 3). This result further highlights the importance of BP-based multivariate models for outcome prediction during pregnancy,[24,25] which would increase prognostic accuracy by measuring the cumulative contribution of these risk factors/biomarkers to the estimated risk.[38] Notably, similar (low) prognostic accuracy of BP thresholds for clinical outcome prediction have been reported not only in nonpregnant adult populations but also in pregnant populations.[39–41]

In conclusion, by applying an outcome-derived approach unrelated to clinic BP, the current work identified ambulatory BP thresholds in late pregnancy in a southern Chinese population. Specifically, daytime, nighttime, and 24-hour mean thresholds to define ambulatory hypertension in at-risk women in late pregnancy for this population are 130/80,

Table 5. Comparisons of Outcome-Derived Thresholds With the Non–Outcome-Derived Thresholds for ABPM During Pregnancy and ABPM Thresholds for a Nonpregnant Population

Clinic BP	Daytime BP	Nighttime BP	24-h BP
Outcome-derived, clinic BP-unrelated thresholds			
NA	130/80 (131/79)	120/75 (121/73)	130/75 (130/76)
Outcome-derived, clinic BP–related thresholds (clinic BP equivalents)			
120/80 mm Hg	125/80 (124.0/81.6)	110/75 (111.5/73.2)	120/80 (121.9/77.9)
130/80 mm Hg	130/80 (131.0/81.6)	120/75 (119.2/73.2)	130/80 (128.7/77.9)
140/90 mm Hg	135/85 (136.7/86.7)	125/80 (127.0/80.9)	135/85 (134.4/84.5)
Non–outcome-derived (RMA regression), clinic BP–related thresholds (clinic BP equivalents)			
120/80 mm Hg	120/75 (117.4/76.9)	105/70 (107.0/69.7)	115/75 (115.1/75.2)
130/80 mm Hg	125/75 (127.4/76.9)	120/70 (119.0/69.7)	125/75 (125.3/75.2)
140/90 mm Hg	135/85 (137.3/87.0)	130/80 (130.9/82.1)	135/85 (135.5/85.6)
Non–outcome-derived upper limits in the third trimester (ABPM value distribution derived)			
Brown et al[13]	135/86*	123/72*	131/82*
Bellomo et al[4]	128/78†	121/70†	125/74†
Current hypertension guidelines for nonpregnant population[9,10]			
140/90 mm Hg	135/85 (138.2/86.4)‡	120/70 (119.5/70.8)‡	130/80 (131.0/79.4)‡

Data in parentheses indicate unrounded original data. ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; NA, not applicable; RMA, reduced major axis.
*Values derived from 276 normotensive pregnant women (mean+2 SD).
†Values derived from 132 normotensive pregnant women (90th percentile).
‡The unrounded BP levels were originally reported by Kikuya et al.[18]

120/75, and 130/75 mm Hg, respectively. For wider clinical applicability and to eventually align both nonpregnancy and pregnancy ABPM in an outcome-based approach, prospective multiethnic international studies are needed from early pregnancy onward using ABPM devices validated in HDP populations. Such studies are warranted to generate ABPM outcome-derived thresholds for the general pregnancy population and to provide sufficient sample sizes for important subgroups such as women on antihypertensive medication throughout pregnancy.

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None.

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Supplemental Material

Table S1. **Clinical characteristics between pregnant women with and without composite adverse outcomes.**

	No outcome events (n=759)		With outcome events (n=1009)	*P* Value
Maternal age, at term, y	31.0±5.2		30.8±5.5	0.371
BMI, baseline, kg/m^2	21.7±3.0		21.4±3.0	0.125
Gestational weight gain, kg	13.4±3.3		13.2±3.5	0.238
Gestational week, at delivery (median and interquartile intervals)	39.0 (38.1 to 40.0)		36.1 (33.7 to 38.7)	<0.001
Gestational week, at ABPM (median and interquartile intervals)	38.1 (37.2 to 39.2)		35.2 (32.7 to 37.8)	<0.001
Birth weight, g	3268±436		2393±835	<0.001
Multipara, n (%)	429 (56.5)		601 (59.6)	0.199
Blood pressure measurements				
SBP, clinic (mmHg)	128.8±14.8		134.6±15.3	<0.001
DBP, clinic (mmHg)	79.1±10.7		84.3±11.8	<0.001
SBP, daytime mean (mmHg)	124.8±13.6		132.9±15.5	<0.001
SBP, nighttime mean (mmHg)	115.5±16.4		125.9±18.6	<0.001
SBP, 24-h mean (mmHg)	122.4±14.0		131.2±15.8	<0.001
DBP, daytime mean (mmHg)	75.2±9.7		81.9±12.4	<0.001
DBP, nighttime mean (mmHg)	67.3±12.2		76.0±14.9	<0.001
DBP, 24-h mean (mm Hg)	73.2±10.0		80.4±12.7	<0.001
Glucose, mmol/L	4.56±0.56		4.61±0.78	0.184
Triglycerides, mmol/L (median and interquartile intervals)	2.66 (2.01, 3.35)		2.96 (2.28, 3.71)	<0.001
Total cholesterol, mmol/L	5.67±1.05		5.96±1.35	<0.001
HDL-C, mmol/L	1.65±0.37		1.65±0.45	0.955
LDL-C, mmol/L	3.02±0.90		3.24±1.08	<0.001
Hematocrit, %	34.7±3.86		34.7±4.35	0.880
24-h urinary protein, mg (median and interquartile intervals)	145 (73, 233)		346 (132, 2181)	<0.001
Creatinine, μmol/L	47.7±9.65		53.5±22.4	<0.001

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; ABP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table S2. Clinical characteristics between pregnant women with and without maternal adverse outcomes.

	No outcome events (n=1118)	With outcome events (n=650)	P Value
Maternal age, at term, y	31.0±5.4	30.7±5.4	0.266
BMI, baseline, kg/m^2	21.6±3.0	21.5±3.0	0.512
Gestational weight gain, kg	13.3±3.3	13.2±3.5	0.829
Gestational week, at delivery (median and interquartile intervals)	39.0 (37.9 to 39.9)	36.0 (33.0 to 38.0)	<0.001
Gestational week, at ABPM (median and interquartile intervals)	38.0 (36.6 to 39.1)	35.0 (32.2 to 37.3)	<0.001
Birth weight, g	3056±654	2275±834	<0.001
Multipara, n (%)	637 (57.0)	393 (60.5)	0.152
Blood pressure measurements			
SBP, clinic (mmHg)	129.3±14.7	137.0±15.2	<0.001
DBP, clinic (mmHg)	79.7±10.9	86.3±11.7	<0.001
SBP, daytime mean (mmHg)	125.3±13.7	136.7±15.1	<0.001
SBP, nighttime mean (mmHg)	116.3±16.4	130.3±18.2	<0.001
SBP, 24-h mean (mmHg)	123.0±14.0	135.0±15.3	<0.001
DBP, daytime mean (mmHg)	75.6±10.3	85.0±12.0	<0.001
DBP, nighttime mean (mmHg)	67.9±12.6	79.9±14.3	<0.001
DBP, 24-h mean (mmHg)	73.6±10.5	83.6±12.2	<0.001
Glucose, mmol/L	4.59±0.64	4.59±0.78	0.878
Triglycerides, mmol/L (median and interquartile intervals)	2.70 (2.03, 3.35)	3.15 (2.45, 3.90)	<0.001
Total cholesterol, mmol/L	5.71±1.12	6.04±1.40	<0.001
HDL-C, mmol/L	1.64±0.40	1.65±0.46	0.758
LDL-C, mmol/L	3.07±0.95	3.27±1.09	<0.001
Hematocrit, %	34.9±3.89	34.4±4.53	0.007
24-h urinary protein, mg (median and interquartile intervals)	150 (70, 249)	1150 (258, 3135)	<0.001
Creatinine, μmol/L	47.7±12.0	56.6±24.8	<0.001

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; ABP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table S3. **Clinical characteristics between pregnant women with and without neonatal adverse outcomes.**

	No outcome events (n=960)	With outcome events (n=808)	*P* Value
Maternal age, at term, y	31.0±5.2	30.7±5.5	0.288
BMI, baseline, kg/m^2	21.7±3.0	21.4±3.0	0.049
Gestational weight gain, kg	13.4±3.4	13.1±3.5	0.181
Gestational week, at delivery (median and interquartile intervals)	39.0 (38.0 to 39.9)	35.9 (33.0 to 38.4)	<0.001
Gestational week, at ABPM (median and interquartile intervals)	38.1 (36.9 to 39.1)	34.9 (32.2 to 37.6)	<0.001
Birth weight, g	3221±464	2231±820	<0.001
Multipara, n (%)	533 (55.5)	497 (61.5)	0.011
Blood pressure measurements			
SBP, clinic (mm Hg)	130.3±15.1	134.2±15.4	<0.001
DBP, clinic (mm Hg)	80.3±11.2	84.2±11.8	<0.001
SBP, daytime mean (mm Hg)	126.9±14.6	132.4±15.5	<0.001
SBP, nighttime mean (mm Hg)	118.1±17.6	125.3±18.6	<0.001
SBP, 24-h mean (mm Hg)	124.7±15.0	130.7±15.8	<0.001
DBP, daytime mean (mm Hg)	77.0±10.6	81.5±12.7	<0.001
DBP, nighttime mean (mm Hg)	69.5±13.0	75.7±15.3	<0.001
DBP, 24-h mean (mm Hg)	75.1±10.9	80.0±13.0	<0.001
Glucose, mmol/L	4.55±0.59	4.64±0.80	0.008
Triglycerides, mmol/L (median and interquartile intervals)	2.74 (2.06, 3.41)	2.97 (2.28, 3.72)	<0.001
Total cholesterol, mmol/L	5.70±1.08	5.99±1.39	<0.001
HDL-C, mmol/L	1.66±0.40	1.63±0.44	0.164
LDL-C, mmol/L	3.02±0.91	3.29±1.10	<0.001
Hematocrit, %	34.5±3.96	35.0±4.34	0.008
24-h urinary protein, mg (median and interquartile intervals)	167 (86, 300)	323 (124, 2194)	<0.001
Creatinine, μmol/L	48.7±10.8	53.7±24.1	<0.001

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; ABP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table S4. **Daytime, nighttime and 24-h systolic blood pressure and diastolic blood pressure thresholds corresponding to clinic systolic blood pressures of 120, 130 and 140 mm Hg, and clinic diastolic blood pressures of 80, 85 and 90 mm Hg in late pregnancy, using neonatal outcome and maternal outcome).**

	Neonatal Outcome-based			Maternal Outcome-based		
	Daytime	Nighttime	24-h	Daytime	Nighttime	24-h
Systolic blood pressure, mm Hg						
120	121.2 (116.4 to 125.9)	112.3 (107.1 to 117.4)	119.5 (115.2 to 123.7)	124.1 (121.0 to 126.8)	113.2 (110.4 to 115.8)	122.4 (119.5 to 125.0)
130	128.1 (124.0 to 132.1)	119.9 (115.4 to 124.4)	126.3 (122.3 to 129.9)	131.0 (128.5 to 133.3)	120.8 (118.4 to 123.1)	129.0 (126.5 to 131.3)
140	135.0 (130.8 to 139.2)	127.6 (123.0 to 132.2)	132.8 (128.8 to 136.8)	136.9 (134.8 to 138.9)	128.3 (126.0 to 130.6)	134.9 (132.8 to 136.9)
Diastolic blood pressure, mm Hg						
80	83.4 (80.4 to 85.8)	76.1 (71.8 to 79.6)	79.9 (76.1 to 83.0)	80.5 (78.6 to 82.1)	72.7 (70.3 to 74.9)	77.2 (75.5 to 78.8)
85	86.1 (83.7 to 88.1)	79.8 (76.4 to 82.8)	83.3 (80.3 to 85.9)	83.7 (82.1 to 85.1)	76.7 (74.6 to 78.7)	80.6 (79.0 to 82.1)
90	88.6 (86.5 to 90.5)	83.0 (80.0 to 85.7)	86.3 (83.8 to 88.6)	86.6 (85.2 to 87.9)	80.6 (78.7 to 82.4)	84.0 (82.5 to 85.5)

Data in parentheses indicate 95% confidence intervals.

For neonatal outcome-derived thresholds, the associations between ambulatory diastolic blood pressure measurements and the adverse events were fitted by adding a quadratic term of the blood pressure measurement. For maternal outcome-derived thresholds, the associations between daytime diastolic blood pressure and 24-h diastolic blood pressure, and the adverse events were fitted by adding a quadratic term of the blood pressure measurement.

Table S5. The ambulatory blood pressure monitoring thresholds calculated via Cutoff Finder (http://molpath.charite.de/cutoff) based on maternal outcome.

|	ROC Curve (Euclidean distance)			ROC Curve (Manhattan distance)		
	Cutoff (mmHg)	Sensitivity (%)	Specificity (%)	Cutoff (mmHg)	Sensitivity (%)	Specificity (%)
Systolic Blood Pressure						
Daytime	131.5	65.2	66.5	134.5	58.5	74
Nighttime	120.5	68.8	62.4	129.5	54.8	79.0
24-h	131.5	62	72.3	132.5	60.2	74.6
Diastolic Blood Pressure						
Daytime	81.5	65.1	71.7	81.5	65.1	71.7
Nighttime	74.5	65.5	70.4	78.5	56.5	80.1
24-h	79.5	67.7	71	79.5	67.7	71.0

ROC, receiver operating characteristic.

Table S6. **The ambulatory blood pressure monitoring thresholds calculated via Cutoff Finder (http://molpath.charite.de/cutoff) based on neonatal outcome.**

	ROC Curve (Euclidean distance)			ROC Curve (Manhattan distance)		
	Cutoff (mmHg)	Sensitivity (%)	Specificity (%)	Cutoff (mmHg)	Sensitivity (%)	Specificity (%)
Systolic Blood Pressure						
Daytime	130.5	55.9	59.3	134.5	46.8	69.5
Nighttime	120.5	57.9	58.4	131.5	40	76.9
24-h	129.5	54.5	61.5	136.5	39	79.2
Diastolic Blood Pressure						
Daytime	79.5	59	61	79.5	59	61
Nighttime	72.5	57.2	61.3	75.5	50.7	68.5
24-h	77.5	58.4	60.8	79.5	54	65.8

ROC, receiver operating characteristic.

Figure S1. Incidence rates of the composite maternal and neonatal outcome, the
maternal outcome and the neonatal outcome by fifths of the distribution of systolic
blood pressure (SBP, upper panel) and diastolic blood pressure (DBP, lower panel).
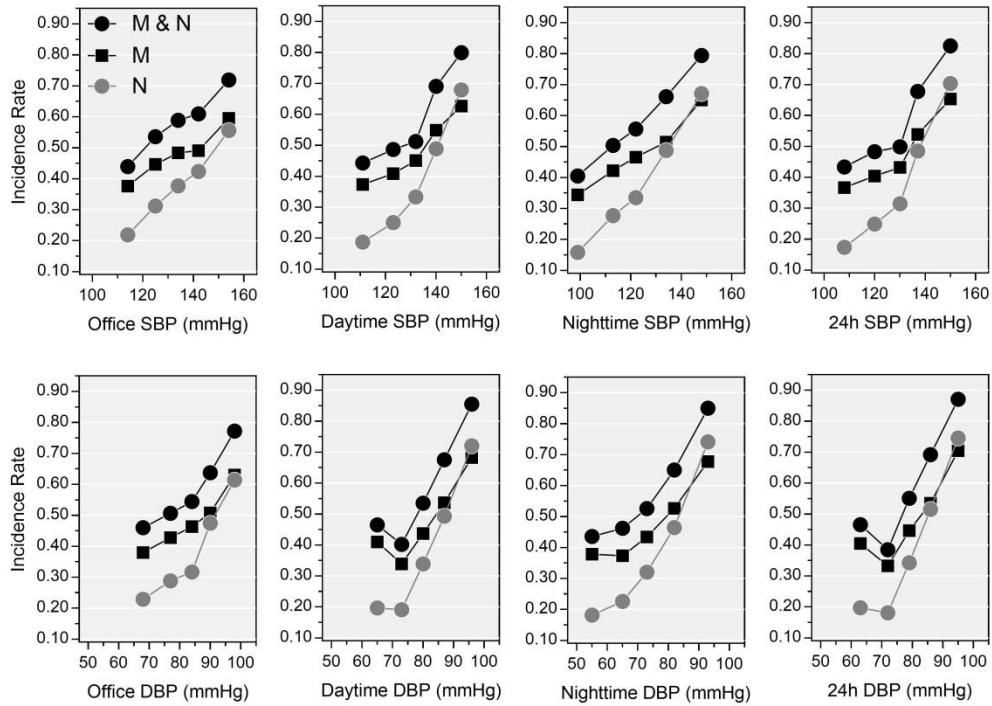
M denotes maternal outcome; N, neonatal outcome; M & N, maternal and neonatal outcome.

Figure S2. Associations of ambulatory blood pressure monitoring with composite maternal and neonatal adverse outcome in logistic models with restricted cubic splines before adjustment, with background distributional histogram of blood pressure level (blue area).
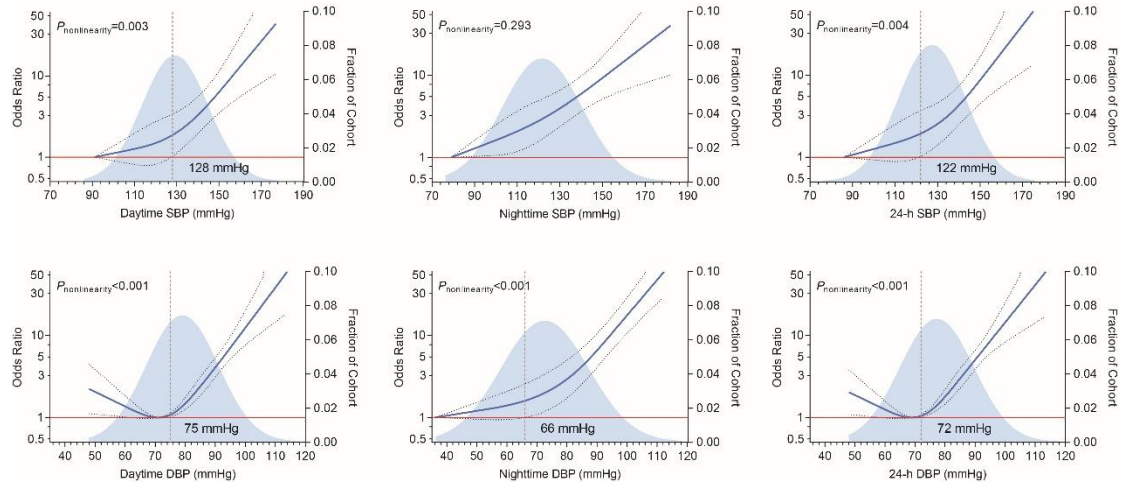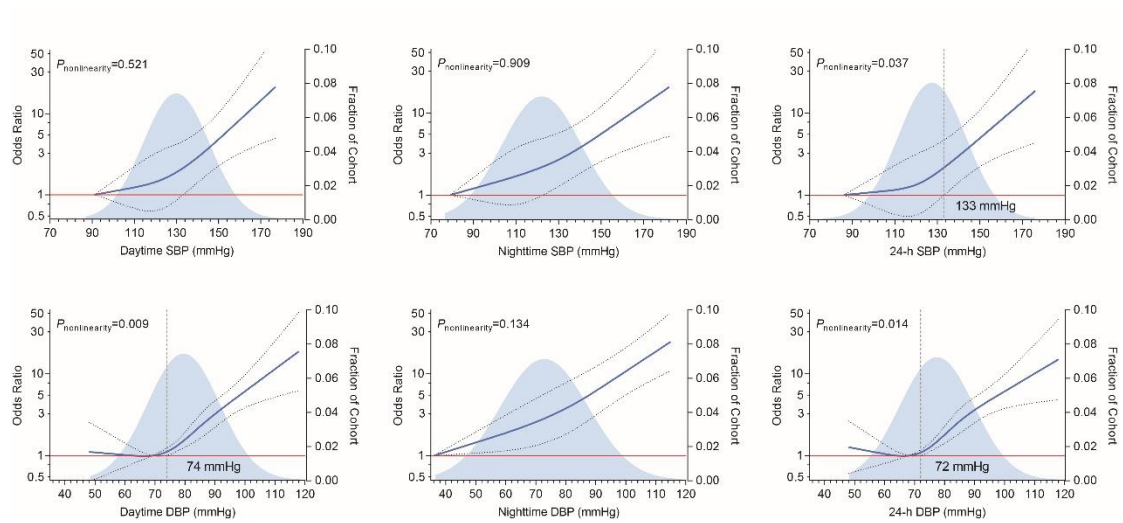

Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% confidence intervals. For systolic ambulatory measurements and nighttime diastolic blood pressure, the references were set at the lowest blood pressure level. For daytime and 24-h diastolic blood pressure, the references were set at the inflection points at 71 mmHg and 69 mmHg, respectively.

Figure S3. Associations of ambulatory blood pressure monitoring with maternal adverse outcome in logistic models with restricted cubic splines before adjustment, with background distributional histogram of blood pressure level (blue area).
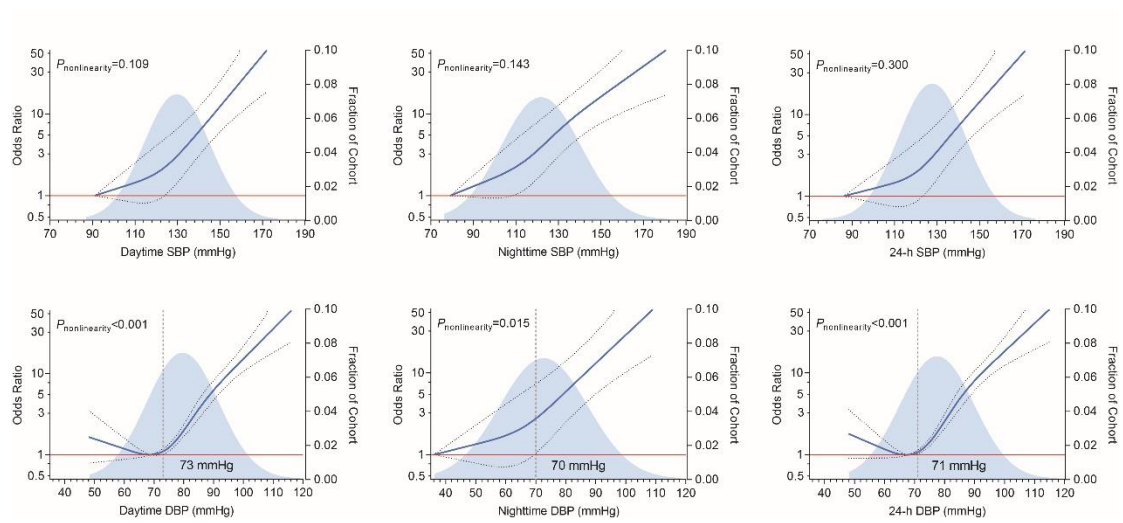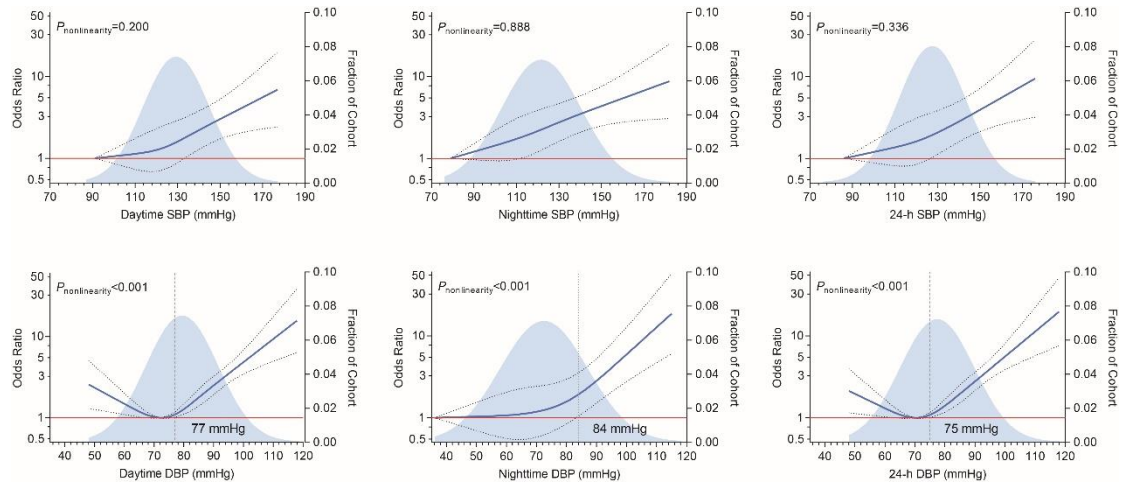

Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% confidence intervals. For systolic ambulatory measurements and nighttime diastolic blood pressure, the references were set at the lowest blood pressure level. For daytime and 24-h diastolic blood pressure, the references were set at the inflection points at 69 mmHg and 68 mmHg, respectively.

Figure S4. Associations of ambulatory blood pressure monitoring with maternal adverse outcome in logistic models with restricted cubic splines after adjustment, with background distributional histogram of blood pressure level (blue area).
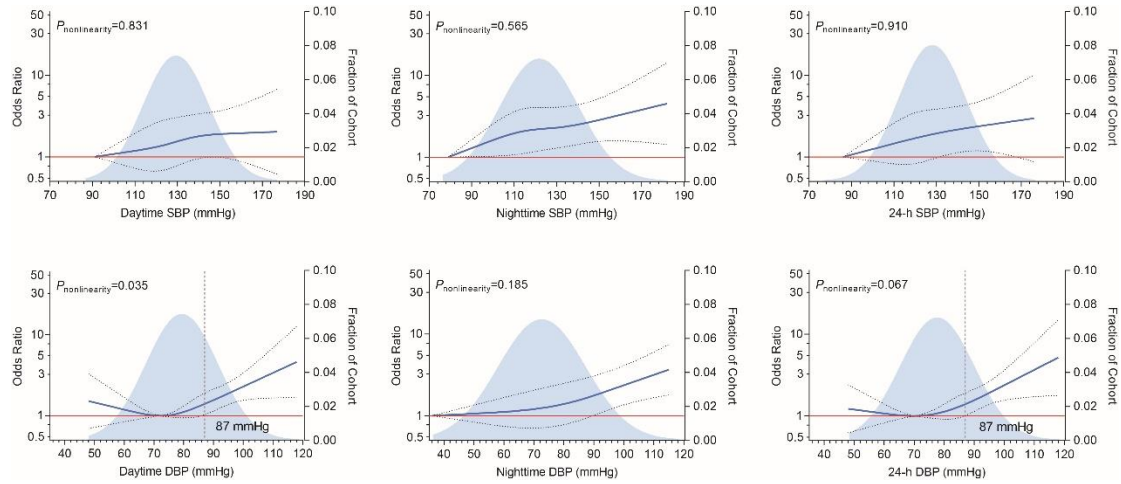

Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% confidence intervals. For systolic ambulatory measurements and nighttime diastolic blood pressure, the references were set at the lowest blood pressure level. For daytime and 24-h diastolic blood pressure, the references were set at the inflection points at 69 mmHg and 68 mmHg, respectively.

Figure S5. Associations of ambulatory blood pressure monitoring with neonatal adverse outcome in logistic models with restricted cubic splines before adjustment, with background distributional histogram of blood pressure level (blue area).

Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% confidence intervals. For systolic ambulatory measurements and nighttime diastolic blood pressure, the references were set at the lowest blood pressure level. For daytime and 24-h diastolic blood pressure, the references were set at the inflection points at 72 mmHg and 70 mmHg, respectively.

Figure S6. Associations of ambulatory blood pressure monitoring with neonatal adverse outcome in logistic models with restricted cubic splines after adjustment, with background distributional histogram of blood pressure level (blue area).

Blue solid lines indicate estimated odds ratio; dotted curves indicate 95% confidence intervals. For systolic ambulatory measurements and nighttime diastolic blood pressure, the references were set at the lowest blood pressure level. For daytime and 24-h diastolic blood pressure, the references were set at the inflection points at 72 mmHg and 70 mmHg, respectively.