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# Isolated nocturnal hypertension in relation to host and environmental factors and clock genes

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## Abstract

Isolated nocturnal hypertension (INH) is a special type of out-of-office hypertension. Its determinants and pathophysiology remain unclear. In a nested case-control study, we intend to investigate the host, environmental, and genetic factors in relation to INH. Among 2030 outpatients screened from December 2008 till June 2015, 128 patients with INH were identified, and then 128 normotensives were matched according to sex and age. INH was an elevated nocturnal blood pressure (BP ≥120/70 mmHg) in the presence of a normal daytime BP (< 135/85 mmHg). Host factors included age, sex, body mass index, smoking and drinking, sleep time and duration, heart rate, serum lipids, and serum creatinine. Environmental cues encompassed season, ambient temperature, atmospheric pressure, humidity, and wind speed, and genetic cues 29 single-nucleotide polymorphisms (SNPs) in 12 clock genes. Daytime and nighttime BPs averaged 124.9/80.7 and 114.5/73.7 mmHg, respectively, in the INH patients and 121.0/76.5 and 101.8/63.3 mmHg in the normotensive controls. Stepwise logistic regression analyses revealed that INH was associated with nighttime heart rate ($P = .0018$), sleep duration ($P = .0499$), and relative humidity ($P = .0747$). The odds ratios (95% CI) for each 10 beats/min faster nighttime heart rate and 10% lower relative humidity were 1.82 (1.25-2.65) and 0.82 (0.67-1.00), respectively. Irrespective of the genetic models, no significant association was observed between INH and the SNPs ($P \geq .054$). In conclusion, INH was associated with host and environmental factors rather than genetic markers.

KEYWORDS
ambulatory blood pressure, clock genes, heart rate, humidity, isolated nocturnal hypertension, sleep duration

## 1 | INTRODUCTION

In 2007, isolated nocturnal hypertension (INH), defined as an abnormally elevated nocturnal blood pressure (BP) in the presence of normal daytime ambulatory BP, was first identified as a novel clinical identity in a Chinese population.[1] Subsequent investigations revealed that INH was prevalent (~10-20%) in east Asians, Blacks, Arabs, and South Americans, as well as in children and adult patients with chronic kidney diseases or diabetes mellitus.[2–9] INH was associated with left ventricular hypertrophy, arterial stiffness and impaired renal function, and with increased risks of all-cause mortality, cardiovascular complications and renal events.[10–14] Therefore, INH is not an innocent condition. However, as INH can only be diagnosed by ambulatory or home BP monitoring, it is often masked by office BP measurement and ignored by both patients and doctors. Until now, INH has been insufficiently investigated, and its pathophysiological basis remains incompletely understood.[15]

Hypertension is a complex trait determined by multiple genetic, host and environmental factors. As controlled by an internal clock, BP usually follows a "dipping" pattern, being higher during the awakening daytime than asleep nighttime. INH, however, often presents an abnormal "non-dipping" or "rising" pattern.[15] Previous studies showed that non-dippers had a higher weighted circadian genetic risk score than dippers.[16] Host and environmental factors, such as seasonality, ambient temperature, smoking and drinking, and sleep habits, may also play an important role in the maintenance of the 24-h BP profile.[17–19] Nonetheless, up to now no study comprehensively investigated the genetic, host, and environmental factors in relation to INH. We therefore designed a nested case-control study on INH and addressed this issue in the present analyses.

## 2 | METHODS

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

### 2.1 | Study population

As described elsewhere,[20] we recruited consecutive patients referred for ambulatory BP monitoring to the Hypertension Outpatient Clinic of Ruijin Hospital, Shanghai, China. We adhered to the principles of the Declaration of Helsinki. The Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine approved the study protocol. All patients gave informed written consent.

Of the patients referred from December 2008 until June 2015, 2030 were recruited, because they were not on antihypertensive drug treatment or off antihypertensive medication for at least 2 weeks, and because they had both their clinic and 24-h ambulatory BP measured.[20] Among these 2030 participants, 1368 recorded diary during the ambulatory BP monitoring, and then 155 (11.3%) with INH and 323 (23.6%) with day-night normotension were identified. For the present study, 27 patients with INH were excluded because of missing blood samples. Thus, 128 INH patients were included in the present analyses, with whom 128 control patients with day-night normotension were then matched according to sex and age (within 5 years).

### 2.2 | Ambulatory BP measurement

We programmed validated oscillometric SpaceLabs 90217 monitors (SpaceLabs Inc, Redmond, WA, USA) to obtain BP readings at 20-min intervals during daytime (6 AM–10 PM) and at 30-min intervals during nighttime (10 PM–6 AM).[17,20] Participants were asked to keep a diary during the monitoring and report the time when they went to sleep at night and got awakening in the morning. Sleep duration was then calculated, and daytime and nighttime were defined according to the diary. Patients were categorized into groups of sleep before or after 23:00 according to the reported sleeping time on the BP monitoring day. INH was an elevated nighttime BP of ≥120 mmHg systolic or ≥70 mmHg diastolic in the presence of a normal daytime BP of < 135 mmHg systolic and < 85 mmHg diastolic.[1]

### 2.3 | Other host factors

A standardized questionnaire was administered by trained researchers to obtain information on each patient's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by body height in meters squared. Venous blood samples were drawn after the participants had fasted overnight. Serum total and high-density lipoprotein cholesterol and triglycerides and plasma glucose were measured by automated enzymatic methods. Diabetes mellitus was a fasting plasma glucose level of ≥7.0 mmol/L, use of antidiabetic drugs, or a self-reported diagnosis in the questionnaire.

### 2.4 | Environmental factors

For each day in the study period, we obtained the mean daily temperature, relative humidity, wind speed and atmospheric pressure for Shanghai from http://www.wunderground.com (Weather Underground, Inc., San Francisco, CA, US).[17] Spring was defined as ranging from March 1 to May 31, summer from June 1 to August 31, autumn from September 1 to November 30, and winter from December 1 to the end of next year's February.[17]

### 2.5 | Genotyping

Based on literature relating variation in clock genes to BP, 29 single-nucleotide polymorphisms (SNPs) in 12 clock genes were selected. Genotyping was performed using multiplex PCR and sequencing on Illumina X-10,[21] a high-throughput genotyping platform in Shanghai

BioWing Applied Biotechnology Company. For all the 29 SNPs, 97.7% of the total samples were successfully genotyped.

## 2.6 | Statistical analysis

For database management and statistical analysis, we used SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Means and proportions were compared using the Student's *t* test and the $\chi^2$ statistic, respectively. Significance was a two-tailed $\alpha$-level of 0.05 or less.

We first searched for significant host and environmental factors associated with INH using stepwise logistic regression. We set the *p*-values for explanatory variables to enter and stay in the models at 0.10. The host factors considered for entry in the models were age, sex, body mass index, current smoking and drinking, diabetes mellitus, 24-h, daytime and nighttime heart rate, sleep before or after 23:00, sleep duration, serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides, and serum creatinine. The environmental cues encompassed seasons, mean daily outdoor temperature, atmospheric pressure, relative humidity and wind speed. In the genetic analyses, the Hardy-Weinberg equilibrium was tested using the exact statistics available in the PROC Allele procedure of the SAS package. The unadjusted associations of INH with the SNPs of clock genes were investigated using the dominant, recessive and additive models. In multivariable genetic analyses, we used only dominant models by contrasting minor allele carriers with major allele homozygotes, with adjustment for the host and environmental factors.

# 3 | RESULTS

## 3.1 | Characteristics of participants

The 256 participants included 158 women (61.7%) Age averaged (± SD) 54.0 ± 8.6 years. The mean body mass index was 24.0 kg/m$^2$. The median (interquartile range) number of readings averaged to estimate the daytime and nighttime BPs was 44 (40-46) and 16 (14-18), respectively.

Of all the 256 participants (Table 1), 72 (28.1%) performed ambulatory BP monitoring in spring, 57 (22.3%) in summer, 80 (31.3%) in autumn, and 47 (18.4%) in winter. As shown in the Supplemental Table S1, the daily outdoor temperature, relative humidity, and atmospheric pressure significantly differed between seasons ($P < .001$), except for the wind speed ($P = .09$). The median (interquartile range) sleep duration was 8.0 (7.3-9.0) hours. In unadjusted analyses, the sleep duration was negatively associated with temperature ($r = -0.24$, $P < .001$), and positively with atmospheric pressure ($r = 0.22$, $P < .001$), and differed between seasons, being shortest in summer and longest in winter (8.3 vs 7.7 vs 8.0 vs 8.5 h in spring, summer, autumn, and winter, respectively, $P = .0016$). Nonetheless, these associations with the sleep duration became non-significant if all these environmental factors being included in a single model or the analyses being restricted in the season of summer ($P \geq .24$).

**TABLE 1** Characteristics of the participants

| Characteristic | Normotension (no. = 128) | INH (no. = 128) | *P* |
|---|---|---|---|
| Host factors | | | |
| Age, years | 54.5 ± 8.8 | 53.6 ± 8.5 | .38 |
| Female, no. (%) | 78 (60.9) | 80 (62.5) | .80 |
| Body mass index (kg/m$^2$) | 23.8 ± 3.2 | 24.2 ± 3.1 | .22 |
| Smoking, no. (%) | 13 (10.2) | 16 (12.5) | .55 |
| Alcohol intake, no. (%) | 17 (13.3) | 20 (15.6) | .59 |
| Sleep duration, (hour) | 8.2 ± 1.0 | 8.0 ± 1.2 | .13 |
| Sleep after 23:00, no. (%) | 43 (33.6) | 43 (33.6) | 1.00 |
| Diabetes mellitus, no. (%) | 7 (5.5) | 8 (6.3) | .79 |
| Fasting plasma glucose, mmol/L | 5.04 ± 0.7 | 5.09 ± 0.9 | .64 |
| Serum creatinine, $\mu$mol/L | 63.9 ± 14.2 | 63.2 ± 15.1 | .70 |
| Total cholesterol (mmol/L) | 5.06 ± 0.78 | 5 ± 0.91 | .53 |
| 24 h SBP (mmHg) | 114.6 ± 7.8 | 121.5 ± 6.3 | <.001 |
| 24 h DBP (mmHg) | 72.1 ± 4.6 | 78.4 ± 3.3 | <.001 |
| 24 h heart rate (beats/min) | 68.9 ± 7.2 | 71.4 ± 7.1 | .007 |
| Daytime SBP (mmHg) | 121.0 ± 8.6 | 124.9 ± 6.5 | <.001 |
| Daytime DBP (mmHg) | 76.5 ± 5.6 | 80.7 ± 3.9 | <.001 |
| Daytime heart rate (beats/min) | 73.5 ± 7.9 | 75.7 ± 7.8 | .026 |
| Nighttime SBP (mmHg) | 101.8 ± 8.1 | 114.5 ± 8.3 | <.001 |
| Nighttime DBP (mmHg) | 63.3 ± 4.4 | 73.7 ± 3.9 | <.001 |
| Nighttime heart rate (beats/min) | 59.8 ± 6.8 | 62.6 ± 7.0 | .002 |
| Environmental factors | | | |
| Season, no. (%) | | | |
| Spring | 38 (29.7) | 34 (26.6) | .58 |
| Summer | 23 (18.0) | 34 (26.6) | .10 |
| Autumn | 43 (33.6) | 37 (28.9) | .42 |
| Winter | 24 (18.8) | 23 (18.0) | .87 |
| Daily temperature, °C | 16.7 ± 8.7 | 17.8 ± 8.5 | .29 |
| Relative humidity, % | 69.7 ± 12.2 | 66.7 ± 13.6 | .064 |
| Wind speed, Mph | 9.18 ± 2.9 | 8.68 ± 2.9 | .17 |
| Atmosphere pressure, Kpa | 101.5 ± 0.8 | 101.3 ± 0.9 | .21 |

Values are means (±SD) or number of participants (% of the column). Environmental factors refer to conditions on the day of ambulatory blood pressure monitoring. *p* values are for the significance of the difference between the two groups.

## 3.2 | Host and environmental factors in relation to INH

Daytime and nighttime BPs averaged 124.9/80.7 and 114.5/73.7 mmHg, respectively, in the INH patients and 121.0/76.5 and

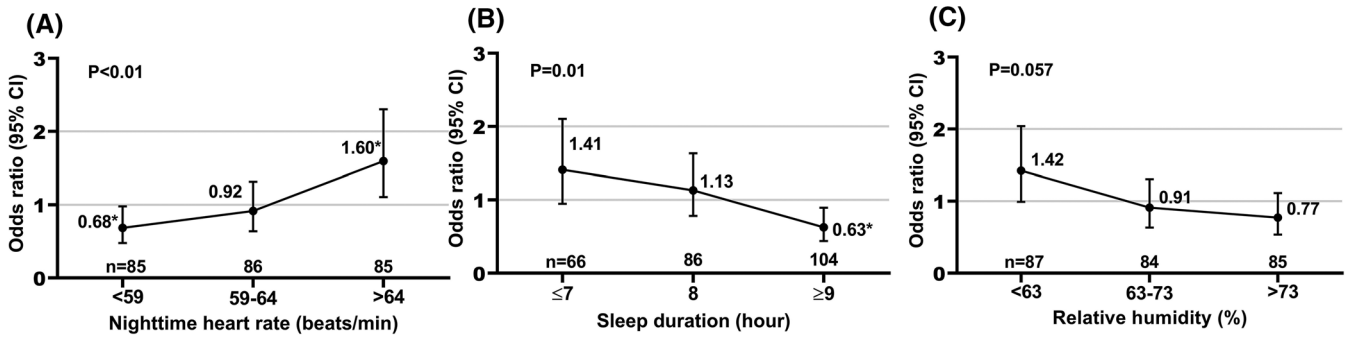


**FIGURE 1** Association of isolated nocturnal hypertension with nighttime heart rate, sleep duration and relative humidity. Plotted values are odds ratios (95% confidence intervals, CI) versus the average risk for each category of nighttime heart rate (A), sleep duration (B), and relative humidity (C). Persons were categorized according to the tertile distributions of the nighttime heart rate and relative humidity or rounded integers of sleep duration. The number of persons in each group is given along the horizontal axis. The covariables in the logistic regression models included age, sex, body mass index, nighttime heart rate, sleep duration, and relative humidity as appropriate. Significance of the odds ratio, $^*P < .05$

**TABLE 2** Isolated nocturnal hypertension in relation to host and environmental factors

| | Isolated nocturnal hypertension | |
|---|---|---|
| **Explanatory variable** | **Odds ratio (95%CI)** | ***P*** |
| Host factors | | |
| Nighttime heart rate (+10 beats/min) | 1.82 (1.25 to 2.65) | .0018 |
| Sleep duration, (+1 h) | 0.81 (0.65 to 1.02) | .0747 |
| Environmental factors | | |
| Relative humidity (+10%) | 0.82 (0.67 to 1.00) | .0499 |

In the stepwise logistic regression analyses, the p-values for explanatory variables to enter and stay in the model were set at 0.10. The host factors considered for entry in the model were age, sex, body mass index, current smoking and drinking, diabetes mellitus, sleep after 23:00, 24-h, daytime and nighttime heart rate, sleep duration, serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and creatinine. The environmental cues encompassed season, mean daily outdoor temperature, atmospheric pressure, relative humidity and wind speed. We first searched host factors in relation to isolated nocturnal hypertension, and then in the analyses on environmental factors, the identified two host factors were forced to be included in the model, from which the odds ratios and *P* values shown in the table were derived.

101.8/63.3 mmHg in the normo-tensive controls (Table 1). Among the 128 INH patients, 8 (6.3%) had isolated systolic hypertension, 100 (78.1%) isolated diastolic hypertension, and 20 (15.6%) systolic and diastolic hypertension. Compared to normotensive persons (Table 1), patients with INH had significantly higher 24-h, daytime and nighttime BPs ($P < .001$) and heart rate ($P \leq .026$), tended to have shorter sleep duration ($P = .13$), and were more likely identified in summer ($P = .10$) and days with a lower relative humidity ($P = .064$).

Among the possible host factors, multiple stepwise logistic regression analyses revealed that nighttime heart rate and sleep duration were associated with INH (Table 2). The odds ratios for each 10 beats/min faster of nighttime heart rate were 1.82 (95% CI, 1.25-2.65, $P = .0018$). When nighttime heart rate and sleep duration were forced into the stepwise regression model, among the four environmental factors considered, only relative humidity entered the model. The odds ratio for each 10% lower of relative humidity was 0.82 (95% CI, 0.67-1.00, $P = .0499$).

In further multivariate analyses, we contrasted each tertile group of the nighttime heart rate, sleep duration, and relative humidity with the average risk of INH in all participants. As shown in Figure 1, the trend of odds ratios between the tertile groups was significant for nighttime heart rate and sleep duration ($P \leq .01$), but not for relative humidity ($P = .057$), the upper tertile group of nighttime heart rate of > 64 beats/min, and the group of sleep duration of ≥ 9 h were significantly associated with INH. The corresponding odds ratios (95% CI) were 1.60 (1.11-2.30) and 0.63 (0.44-0.89), respectively.

## 3.3 | Clock genes in relation to INH

The 29 genotyped SNPs complied with the Hardy-Weinberg equilibrium ($P \geq .06$) except for two SNPs (rs9684900 and rs3888170). Table 3 shows the detailed information of the 29 SNPs. The minor allele frequency ranged from 8% of *CLOCK* rs11932595 and rs1801260 to 44% of *BMAL1* rs4757144.

In unadjusted analyses, no SNP of clock genes had any significant association with INH ($P \geq .054$, Supplemental table S2) irrespective of the genetic models used. With adjustments applied for sex, age, body mass index, nighttime heart rate, sleep duration, relative humidity and other covariables (Table 3), the associations of the SNPs of clock genes with INH remained non-significant ($P \geq .11$) in dominant models. There was also no significant ($P \geq .28$) interaction of the SNPs with the host and environmental factors on INH after Bonferroni corrections for multiple testing.

## 4 | DISCUSSION

During the seven years screening work at our Hypertension Outpatient Clinic, over 100 patients with untreated INH were identified, which

**TABLE 3** Isolated nocturnal hypertension in relation to clock genes in multivariate logistic regression

| Gene | Chr | SNP | Location | Allele (Minor/Major) | MAF | HWE | Genotype | Odds Ratio (95%CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|
| CRY1 | 12 | rs4964513 | Intron | C/T | 0.24 | 0.32 | CC+CT *vs* TT | 1.48 (0.85,2.60) | .17 |
| | | rs11613557 | Intron | T/C | 0.26 | 0.25 | TT+TC *vs* CC | 1.11 (0.64,1.91) | .72 |
| | | rs4964518 | Intron | T/C | 0.27 | 0.10 | TT+TC *vs* CC | 0.93 (0.54,1.61) | .79 |
| CRY2 | 11 | rs7121611 | upstream | A/T | 0.21 | 0.18 | AA+AT *vs* TT | 1.12 (0.63,1.97) | .70 |
| | | rs7945565 | Intron | G/A | 0.21 | 0.21 | GG+GA *vs* AA | 1.16 (0.65,2.05) | .62 |
| | | rs10838524 | Intron | G/A | 0.21 | 0.15 | GG+GA *vs* AA | 1.07 (0.61,1.89) | .81 |
| BMAL1 | 11 | rs6486121 | Intron | T/C | 0.17 | 0.82 | TT+TC *vs* CC | 0.76 (0.42,1.38) | .37 |
| | | rs3789327 | Intron | G/A | 0.27 | 0.71 | GG+GA *vs* AA | 1.04 (0.60,1.78) | .89 |
| | | rs969485 | Intron | A/G | 0.43 | 1.00 | AA+AG *vs* GG | 1.21 (0.67,2.19) | .53 |
| | | rs3816358 | Intron | A/C | 0.15 | 0.98 | AA+AC *vs* CC | 1.03 (0.57,1.87) | .92 |
| | | rs12363415 | Intron | G/A | 0.14 | 0.06 | GG+GA *vs* AA | 0.88 (0.47,1.63) | .68 |
| | | rs4757144 | Intron | A/G | 0.44 | 0.98 | AA+AG *vs* GG | 0.77 (0.43,1.38) | .38 |
| CLOCK | 4 | rs6811520 | Intron | T/C | 0.26 | 0.35 | TT+TC *vs* CC | 1.17 (0.67,2.05) | .58 |
| | | rs13124436 | Intron | G/A | 0.33 | 0.96 | GG+GA *vs* AA | 1.46 (0.82,2.60) | .20 |
| | | rs4580704 | Intron | G/C | 0.28 | 0.28 | GG+GC *vs* CC | 1.13 (0.64,1.98) | .67 |
| | | rs11932595 | Intron | G/A | 0.08 | 0.34 | GG+GA *vs* AA | 1.36 (0.64,2.88) | .42 |
| | | rs1801260 | Intron | G/A | 0.08 | 0.39 | GG+GA *vs* AA | 1.33 (0.61,2.89) | .47 |
| DEC2 | 12 | rs2291140 | Intron | C/T | 0.33 | 0.43 | CC+CT *vs* TT | 1.06 (0.61,1.85) | .84 |
| NOC | 4 | rs9684900 | Intron | A/G | 0.28 | 0.04 | AA+AG *vs* GG | 1.18 (0.65,2.15) | .59 |
| | | rs17050679 | Intron | C/G | 0.43 | 0.09 | CC+CG *vs* GG | 1.56 (0.85,2.86) | .15 |
| | | rs1112828 | Intron | G/T | 0.43 | 0.78 | GG+GT *vs* TT | 0.75 (0.42,1.33) | .32 |
| NPAS2 | 2 | rs3888170 | Intron | A/G | 0.43 | 0.02 | AA+AG *vs* GG | 0.66 (0.36,1.19) | .16 |
| PER2 | 2 | rs934945 | Exon | T/C | 0.30 | 0.56 | TT+TC *vs* CC | 1.47 (0.83,2.59) | .19 |
| | | rs6431590 | Intron | G/A | 0.29 | 0.66 | GG+GA *vs* AA | 0.99 (0.57,1.72) | .97 |
| RORA | 15 | rs10519096 | Intron | A/G | 0.09 | 0.88 | AA+AG *vs* GG | 1.37 (0.67,2.78) | .39 |
| | | rs16943453 | Intron | G/T | 0.21 | 0.41 | GG+GT *vs* TT | 0.81 (0.48,1.38) | .46 |
| RORB | 9 | rs1410225 | Downstream | A/G | 0.43 | 0.15 | AA+AG *vs* GG | 0.81 (0.45,1.45) | .47 |
| STK38L | 12 | rs16931815 | Intron | G/A | 0.42 | 0.57 | GG+GA *vs* AA | 1.31 (0.73,2.34) | .37 |
| TNFRSF9 | 1 | rs2453021 | Intron | T/C | 0.28 | 0.16 | TT+TC *vs* CC | 0.62 (0.34,1.12) | .11 |

The logistic regression analyses were adjusted for age, sex, body mass index, diabetes mellitus, current smoking and alcohol intake, nighttime heart rate, sleep duration, sleep after 23:00, seasons, average daily temperature, relative humidity, wind speed, and atmosphere pressure in a dominant model.
Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

allowed us to perform a nested case-control study on INH. The present analyses revealed that the host and environmental factors associated with untreated INH were nighttime heart rate, sleep duration and relative humidity, and the studied 29 SNPs of the 12 clock genes were not significantly associated with INH.

INH is a special type of out-of-office hypertension, which is often masked by normal office BP. In the Chinese Jingning population study, the prevalence of INH was 10.9%.[1] Of the 74 patients with INH, only 4 (5.4%) had office hypertension. The Chinese patients with INH, compared with normotensive persons, were older, more often reported alcohol intake, and had faster nighttime pulse rate and higher serum cholesterol and blood glucose level.[1] Among the 8711 individuals in the International Database of Ambulatory BP in relation to Cardiovascular Outcome (IDACO), 577 (6.6%) had INH, of whom 457 (79.2%) were normotensive on office BP measurement.[13] Compared with normotensives, patients with INH were older, more likely male, and more frequently reported alcohol intake, and had a higher body mass index, faster pulse rate at night, and higher serum cholesterol and blood glucose.[13] In the Jackson Heart Study,[9] among the 425 African-Americans not on antihypertensive medication, 19.1% had INH. The patients with INH were older, had a higher prevalence of metabolic syndrome or diabetes, higher level of total cholesterol and low-density lipoprotein cholesterol, higher daytime and nighttime pulse pressures, and higher proportions of left ventricular hypertrophy

and proteinuria.[9] In 20 773 Italian persons who performed ambulatory BP monitoring in local pharmacies, INH was more common (16%) than isolated daytime hypertension (9%) and occurred more often in persons treated with antihypertensive medications, older persons, and in those at high cardiovascular risk or with concomitant diseases.[22] In an Argentina study involving 1344 individuals, the prevalence of INH was 12.9%, similar across optimal, normal and high-normal office BP categories.[6] Patients with INH had a significantly higher neck circumference than normotensive persons.[6] In 428 Saudi patients who were referred to a hypertension clinic, INH was observed in 21%, and was more prevalent in masked hypertension versus sustained hypertension (70% vs 30%, $P < .001$) and in untreated versus treated patients (29% vs 18.7%, $P < .05$).[5] In a recent report from a Korean general population including 823 participants, INH was observed in 22.8% of patients, among whom 92.6% had normal office BP.[3] Compared to normotensive participants, the INH patients had an older age, greater body mass index, and higher levels of serum cholesterol and plasma glucose, and serum creatinine. INH was prevalent in patients with chronic kidney disease and sleep apnea. In a Chinese renal inpatients cohort, the prevalence of INH amounted to 20%, and was similar across 1–4 stages of chronic kidney disease.[8] In newly diagnosed patients with sleep apnea but without a history of office hypertension, 18% had INH on ambulatory BP monitoring.[23]

Although the pathophysiological pathways of INH remain incompletely understood, it is generally accepted that several mechanisms related to nocturnal hypertension might be involved, including activated sympathetic and renin-angiotensin systems, disturbed water and sodium metabolism, decreased baroreflex sensitivity, and insulin resistance.[15] These mechanisms, at least in part, explain why the prevalence of INH varied between populations of different characteristics,[1,3–6] and was common in patients complicated with sleep-related disorders, chronic kidney disease, diabetes mellitus, and metabolic syndrome.[2,8,9,22]

Our present findings that INH patients had a faster nighttime heart rate than normotensive persons were consistent with the results of the above-mentioned reports.[1,13] Elevated heart rate is an indicator of activated sympathetic activity,[24] and usually common in patients with sleep apnea. Unfortunately, we did not assess the possibility of sleep apnea in these patients. Nevertheless, the present study illustrated that INH was associated with short sleep duration. Independent of sleep apnea and other sleep disorders, insufficient sleep had been demonstrated to be associated with nocturnal hypertension and increased cardiovascular risk.[25,26] In a recently published randomized, controlled, cross-over study,[27] sleep restriction (4 h of sleep per night) for 9 days in women caused persistent and significant elevation in 24-h and sleep-time BP by 8.0 and 11.3 mmHg, respectively. Endothelial function was impaired and plasma norepinephrine increased during the phase of sleep restriction.[27]

Environmental factors including seasonality and atmospheric conditions also have impact on the diurnal BP profile.[17,18,28] In a meta-analysis involving 856 539 participants in 47 studies,[28] office, daytime and home BPs, but not nighttime BP, were significantly lower in summer than in winter. Indeed, the pooled summer minus winter systolic/diastolic BPs difference of the 19 included ambulatory BP studies was -3.4/-2.1 mmHg for daytime and 1.3/0.5 mmHg for nighttime.[28] In the present study, we observed that INH tended to be more prevalent than normotensive controls in summer (26.6% vs 18.0%, $P = .10$), although in multivariate analyses seasonality was not independently associated with INH. Changes in out-door temperature played a major role in the seasonal BP variation. However, other weather factors, such as daylight hours, relative humidity, and wind speed also had an independent effect.[29,30] Previous studies showed that nighttime BP was positively associated with daylight hours independent of ambient tempreature,[29] and increased on winter days characterized by high humidity and cloud cover, high ground level wind turbulence, and low atmospheric pressure.[30] In the present study, we observed a negative association of INH with relative humidity in both univariate and multivariate analyses, for which the mechanisms remained unclear. Future studies are needed to confirm these findings.

Clock genes were reported to be associated with diurnal BP variations in humans.[16,17] In 372 young hypertensive patients, Leu and associates[16] found that among the 23 tag SNPs in 11 clock genes, five tag SNPs within five loci, including rs3888170 in *NPAS2*, rs6431590 in *PER2*, rs1410225 in *RORB*, rs3816358 in *BMAL1*, and rs10519096 in *RORA*, were significantly associated with the non-dipping pattern. Along similar lines, we had previously studied 14 SNPs in 10 clock genes in patients not on antihypertensive treatment.[17] Two SNPs (rs6486121 and rs3816358) in *BMAL1* were weakly associated with the night-to-day ratio of BP. However, the associations lost statistical significance after Bonferroni correction for multiple testing. Season and temperature explained about 8% and 3%, respectively, of the variance of the night-to-day ratio, while the corresponding proportion for the SNPs of clock genes was less than 1%.[17] The null findings on the genetic cues of INH in the present study once more indicated a minor role of clock genes in the nocturnal hypertension.

Our study should be interpreted within the context of its strengths and limitations. The ambulatory BP recordings were in high quality, and possible confounding by antihypertensive treatment was avoided by recruiting only untreated patients. However, INH was diagnosed based only one 24-h ambulatory recording. Considering that the short-term reproducibility of INH was modest,[31] it is better to define INH based on repeated recordings in future studies. In addition, 94% of the untreated INH patients in the current study were diastolic hypertension, our findings have to be confirmed in studies on systolic INH. Furthermore, we only genotyped 29 SNPs in 12 clock genes, and did not account for many other important factors, such as salt intake, psychological stress, physical activity during the day, sleep quality, and so on, which were related to nocturnal hypertension and diurnal BP variations.[32]

In conclusion, INH was associated with host and environmental factors rather than genetic markers. Indeed, untreated INH was associated with faster nighttime heart rate, shorter sleep duration, and lower relative humidity, but not the studied genetic markers of clock genes.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## AUTHOR CONTRIBUTIONS

Yan Li contributed to the conception and design of the study. Jian-Feng Huang acquired the data, performed statistical analyses, and prepared the draft of the manuscript together with Yan Li. All authors critically commented and revised the manuscript and gave final approval.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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