

Blood pressure characteristics of subclinical hypothyroidism: an observation study combined with office blood pressure and 24-h ambulatory blood pressure

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Objective: To investigate the characteristics of blood pressure in subclinical hypothyroidism by combining office blood pressure and 24-h ambulatory blood pressure.

Methods: A total of 3078 adults voluntarily participants were enrolled in this study between December 2017 and November 2019. Among 1431 of them who did not fit exclusion criteria, 104 patients were with subclinical hypothyroidism (S-HYPO group), and 1327 were euthyroid participants (euthyroid group). Office blood pressure measurement and 24-h ambulatory blood pressure monitoring were carried out to analyze the characteristics of blood pressure in subclinical hypothyroidism.

Results: There was no statistical difference in office SBP and DBP between the S-HYPO group and the euthyroid group ($P > 0.05$). On the ambulatory blood pressure level, the daytime SBP, night-time SBP, night-time DBP, 24-h SBP and DBP in the S-HYPO group were significantly higher than those in the euthyroid group ($P = 0.048$, $P = 0.002$, $P = 0.003$, $P = 0.014$, $P = 0.046$, respectively), and the proportion of nondipper blood pressure in the S-HYPO group was higher than that in the euthyroid group. Comprehensive analysis of blood pressure inside and outside the joint clinic revealed that the S-HYPO group was independently related to sustained hypertension and masked hypertension but not to white-coat hypertension ($P = 0.004$, $P = 0.002$, $P = 0.886$, respectively). After adjusting for age, sex, BMI, and other confounding factors, the above differences were still statistically significant ($P < 0.05$).

Conclusion: The characteristics of blood pressure in subclinical hypothyroidism can be more accurately understood by combining office blood pressure and ambulatory blood pressure.

Keywords: masked hypertension, nondipper blood pressure, subclinical hypothyroidism, sustained hypertension, white-coat hypertension

Abbreviations: ALT, alanine transaminase; Glu, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MHT, masked hypertension; NT, normotension; Scr, serum creatinine; SD,

standard deviation; SHT, sustained hypertension; S-HYPO, subclinical hypothyroidism; WCH, white-coat hypertension

INTRODUCTION

Subclinical hypothyroidism is characterized by elevated thyroid-stimulating hormone (TSH), while free triiodothyronine (FT3) and free thyroxine (FT4) are still in the normal range [1]. This disease is commonly found in women, middle-aged and older adults and people with high iodine diet and are considered as abnormal thyroid function with the highest incidence in the world [2–4]. A large number of clinical researches have shown that subclinical hypothyroidism is associated with a cardiovascular event and target organ damage [5]. However, the correlation between subclinical hypothyroidism and hypertension has always been controversial [6]. Velkoska Nakova *et al.* [7] studied 24 patients with subclinical hypothyroidism and 13 participants with normal thyroid function, reporting the increased prevalence rate of hypertension in subclinical hypothyroidism. In 2011, Cai *et al.* [8] conducted a meta-analysis of seven clinical studies, reporting that subclinical hypothyroidism was positively correlated with clinic SBP and DBP. Nevertheless, in 2014, another meta-analysis included a total of 50 147 study samples but it was impossible to obtain a research conclusion on the correlation between subclinical hypothyroidism and blood pressure

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level [9]. Since then, Gonzalez Gil and de la Sierra [10] examined 240 cases of subclinical hypothyroidism and 480 cases of normal thyroid function in a case–control study in 2017, finding no difference in the prevalence rate of hypertension between the two groups.

Previous research disputes mainly focused on office blood pressure. With the gradual application of ambulatory blood pressure monitoring technology, the medical profession found that office blood pressure alone could not reflect the real overall clinical characteristics of individual blood pressure [11]. It is one-sided to rely solely on office blood pressure to evaluate the body's blood pressure level. Moreover, because of the white-coat phenomenon or masked phenomenon in some people during office blood pressure measurement, the results may be unreliable. In contrast, office blood pressure cannot reflect the night-time blood pressure level. The relationship between subclinical hypothyroidism and hypertension has been debated in relation to the level of office blood pressure. It remained unclear whether combined out-of-office blood pressure could more precisely reflect the characteristics of blood pressure in subclinical hypothyroidism. Consequently, we designed the current study to explore the relationship between subclinical hypofunction and hypertension combined with office blood pressure and ambulatory blood pressure.

METHODS

Study participants

This study recruited 3078 adults who took part in routine physical examinations in Daping Hospital between December 2017 and November 2019. All participants completed 24-h ambulatory blood pressure monitoring. After detailed understanding of the participants' medical history and biochemical tests, such as liver function, kidney function, and thyroid function, the participants were screened step by step according to the following exclusion criteria: the use of antihypertensive drugs and drugs affecting thyroid function; patients with congenital heart disease, cardiomyopathy and moderate or above valvular heart disease; secondary hypertension; liver and kidney insufficiency (ALT \geq 80 IU/l, Scr \geq 133 μ mol/l) [12]; other thyroid abnormalities other than subclinical hypothyroidism. The study was reviewed and approved by the Ethics Committee of Daping Hospital of the Army Medical University and registered in the Chinese Clinical Trial Registry with the registration number ChiCTR1800015507. All participants gave informed consent to participate in the study.

Study groups

The participants were divided into subclinical hypothyroidism group (S-HYPO group) and euthyroid group according to the results of the thyroid function test. The division method was based on the standards of our laboratory. The thyroid function standard of S-HYPO group was TSH greater than 5.60 uIU/ml; FT3, 3.09–7.42 pmol/l; FT4, 7.64–16.03 pmol/l, and the thyroid function in euthyroid group was TSH, 0.34–5.60 uIU/ml; FT3, 3.09–7.42 pmol/l; FT4, 7.64–16.03 pmol/l [13].

General clinical Information

The age, sex, smoking history, drinking history, history of diabetes, and hyperlipidemia were collected from participants using questionnaires. The height and weight of the selected participants were measured on the spot, and the BMI was calculated using the formula: BMI = weight (kg) \div height² (m).

Blood pressure measurement

After the participants sat and rested in the clinic for 20 min, medical professionals used mercury sphygmomanometer to measure the right brachial artery blood pressure of participants in a quiet clinic. Clinic blood pressure was measured three times at intervals of not less than 12 h. The average value for blood pressure measurement was taken as the office blood pressure measurement result. Twenty-four hour ambulatory blood pressure monitoring was carried out by ambulatory ECG blood pressure recorder CB-2301-A (Wuxi, China), with 0600–2200 h as daytime blood pressure and 2200–0600 h as night-time blood pressure; participants were instructed to work and rest according to this timetable. Diurnal blood pressure measurement was conducted every 30 min, the number of effective blood pressure readings was to be above 80%, and night-time blood pressure required effective blood pressure every hour [14,15].

Normotension, white-coat hypertension (WCH), masked hypertension (MHT), and sustained hypertension (SHT) were distinguished according to office blood pressure measurement results and 24-h AMBP blood pressure monitoring results [16,17]. European Hypertension Practice Guideline Standard (2014 Edition) was adopted, and the blood pressure rise boundary point was set at office blood pressure at least 140/90 mmHg. The average ambulatory blood pressure was at least 135/85 mmHg during the day, at least 120/70 mmHg at night, and at least 130/80 mmHg during the whole day [18]. SHT group had elevated both office blood pressure and ambulatory blood pressure. WCH group had elevated office blood pressure and normal ambulatory blood pressure. MHT group had normal office blood pressure but elevated ambulatory blood pressure. In the normotension group, both office blood pressure and ambulatory blood pressure were normal [19,20]. A reduction of at least 10% in night-time blood pressure compared with daytime blood pressure was defined as dipper blood pressure, whereas no reduction in night-time blood pressure compared with daytime BP was defined as nondipper blood pressure [21].

Biochemical detection

After fasting for 12 h, the blood from the anterior elbow vein was collected at 0600–0800 h from participants by a professional medical staff, and immediately submitted for examination. Alanine transaminase (ALT), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood glucose (Glu), serum creatinine (Scr) and uric acid were determined by A5800 automatic biochemical analyzer (California, USA). Diabetes mellitus and hyperlipidemia (HLP) were defined according to the participants' past history and the

results of this blood lipid and blood glucose test. Diabetes mellitus referred to a participant who has been clearly diagnosed with diabetes in the past and whose fasting blood glucose was at least 7.0 mmol/l in this test. HLP referred to those who were diagnosed with hyperlipidemia and those who had total cholesterol at least 5.18 mmol/l, triglycerides at least 1.70 mmol/l, or LDL-C at least 3.37 mmol/l.

DXC800 Beckman automatic chemiluminescence analyzer (California, USA) was used to detect thyroid function indexes TSH, FT3, and FT4. The Beckman automatic chemiluminescence analyzer used a sandwich method to detect TSH and competition method to detect FT3 and FT4.

Time sequence

Blood pressure measurement and thyroid function test are completed in the following time sequence. On the first day, the office blood pressure was measured. Thyroid function was detected in the early morning of the next day, followed by the second office blood pressure measurement, and ambulatory blood pressure monitoring was started. After the 24-h ambulatory blood pressure monitoring was completed, the third office blood pressure measurement was carried out.

Statistical analysis

The research data were input by Epidata 3.1 software and analyzed by SPSS 22.0 software. Continuous data with quantitative characteristics were presented as mean \pm standard deviation (SD), whereas categorical data with qualitative characteristics were presented as numbers and percentages [22]. Pearson's chi-square test and contingency table analysis were used to read bilateral progressive significance. When a two-to-two comparison was involved, the Bonferroni method was used to correct *P* value to control the incidence of type I errors [23]. If the measurement data met the variance homogeneity and normal distribution, an independent sample *t*-test was selected. If the variance homogeneity and normal distribution were not satisfied, the Kruskal–Wallis rank-sum test was adopted. Univariate logistic regression analysis was further used to verify the correctness of chi-square test results. Unconditional logistic regression analysis was used to correct for age, sex, BMI, smoking history, drinking history, diabetes, and hyperlipidemia by forwarding method to further evaluate the correlation. The software of Graphpad Prism 8.0 was used for scientific mapping.

RESULTS

A total of 3078 adult participants were enrolled between December 2017 and November 2019. After detailed understanding of the participants' medical history and examination results, 1354 cases were excluded because of the use of antihypertensive drugs or drugs affecting thyroid function, 29 cases were patients with congenital heart disease, cardiomyopathy and moderate or above valvular heart disease, 17 cases were patients with secondary hypertension, 65 cases were patients with liver and kidney insufficiency, and 182 cases were patients with thyroid dysfunction other than subclinical hypothyroidism. Finally, a total of 104 cases

TABLE 1. Comparison of general clinical information between subclinical hypothyroidism group and euthyroid group

Parameters	S-HYPO	ET	<i>P</i> value
Individuals	104	1327	–
Female (%)	68 (65.4)	627 (47.2)	<0.001
Age (years)	65.3 \pm 11.2	61.6 \pm 11.7	0.005
BMI (kg/m ²)	23.4 \pm 3.2	23.8 \pm 3.2	0.211
Smoking (%)	20 (19.2)	404 (30.4)	0.016
Drinking (%)	13 (12.5)	318 (24.0)	0.008
Diabetes (%)	14 (13.5)	182 (13.7)	0.942
HLP (%)	37 (35.6)	566 (42.7)	0.159
ALT (IU/l)	21.7 \pm 12.8	23.1 \pm 13.7	0.340
Glu (mmol/l)	5.21 \pm 1.34	5.36 \pm 1.67	0.636
TC (mmol/l)	4.14 \pm 1.03	4.22 \pm 1.05	0.506
TG (mmol/l)	1.49 \pm 0.95	1.65 \pm 1.19	0.097
HDL-C (mmol/l)	1.20 \pm 0.33	1.16 \pm 0.31	0.208
LDL-C (mmol/l)	2.61 \pm 0.75	2.68 \pm 0.76	0.410
Scr (μ mol/l)	65.6 \pm 16.8	66.2 \pm 15.9	0.472
UA (μ mol/l)	318.8 \pm 99.0	329.0 \pm 88.6	0.059
TSH (uIU/ml)	8.40 \pm 5.58	2.17 \pm 1.10	<0.001
FT3 (pmol/l)	4.84 \pm 0.73	5.06 \pm 0.72	0.002
FT4 (pmol/l)	10.6 \pm 1.7	11.3 \pm 1.7	<0.001

ALT, glutamic pyruvic transaminase; ET, euthyroid; Glu, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; S-HYPO, subclinical hypothyroidism; TC, total cholesterol; TG, triglyceride; UA, serum uric acid.

of subclinical hypothyroidism group (S-HYPO group) and 1327 cases of normal thyroid function group (euthyroid group) were included. Among these, there were 736 men and 695 women with an average age of 61.9 \pm 11.7 years old.

General clinical information and test results

General clinical information and test results are shown in Table 1. The results of statistical analysis showed that the proportion of women in the S-HYPO group was higher than that in the euthyroid group (65.4 vs. 47.2%, *P* < 0.001). In addition, participants from the S-HYPO group were relatively older compared with those in the euthyroid group (65.3 \pm 11.2 vs. 61.6 \pm 11.7, *P* = 0.005). The proportion of smokers and drinkers in S-HYPO group was significantly lower than that in euthyroid group (19.2 vs. 30.4%, *P* = 0.016; 12.5 vs. 24.0%, *P* = 0.008) but there was no statistical difference between the groups in the prevalence of hyperlipidemia and diabetes, BMI, fasting blood glucose, total cholesterol, and other routine biochemical indicators (*P* > 0.05).

The concentration of TSH in S-HYPO group was significantly higher than that in euthyroid group (8.40 \pm 5.58 vs. 2.17 \pm 1.10, *P* < 0.001), whereas the concentration of FT3 and FT4 in S-HYPO group was lower than that in euthyroid group (4.84 \pm 0.73 vs. 5.06 \pm 0.72, *P* = 0.002; 10.6 \pm 1.7 vs. 11.3 \pm 1.7, *P* < 0.001).

Office blood pressure and 24-h ambulatory blood pressure

Statistical analysis showed that there was no statistical difference in clinic SBP and DBP between the S-HYPO group and euthyroid group (*P* > 0.05, Table 2). However, there were statistical differences in many ambulatory blood

TABLE 2. Comparison of clinic blood pressure level, ambulatory blood pressure level and rhythm between subclinical hypothyroidism group and euthyroid group

Parameters	S-HYPO	ET	P value
Clinic BP measurement			
Clinic SBP (mmHg)	127.4 ± 21.5	126.6 ± 20.0	0.792
Clinic DBP (mmHg)	77.7 ± 13.9	77.6 ± 12.4	0.999
Ambulatory blood pressure monitoring			
Daytime SBP (mmHg)	121.8 ± 13.3	119.2 ± 12.4	0.048
Daytime DBP (mmHg)	73.2 ± 7.5	72.3 ± 7.3	0.153
Night-time SBP (mmHg)	118.1 ± 15.1	113.7 ± 14.5	0.002
Night-time DBP (mmHg)	70.2 ± 9.3	67.7 ± 8.0	0.003
24-h SBP (mmHg)	121.0 ± 13.2	117.9 ± 12.4	0.014
24-h DBP (mmHg)	72.6 ± 7.5	71.2 ± 7.1	0.046
The rhythm of ambulatory blood pressure			
Nondipper BP (%)	97 (93.3)	1145 (86.3)	0.043

BP, blood pressure; ET, euthyroid; S-HYPO, subclinical hypothyroidism.

pressure parameters between the S-HYPO group and the euthyroid group. The daytime SBP, night-time SBP, night-time DBP, 24-h SBP and 24-h DBP in S-HYPO group were significantly higher than those in euthyroid group ($P=0.048$, $P=0.002$, $P=0.003$, $P=0.014$, $P=0.046$, respectively).

Dipper blood pressure and nondipper blood pressure

The proportion of nondipper blood pressure was 93.3% in the S-HYPO group and 86.3% in the euthyroid group. There was a significant difference in the proportion of nondipper blood pressure between the S-HYPO group and the euthyroid group ($P=0.043$, Table 2). After adjusting for the confounding factors of sex, age, BMI, smoking history, drinking history, diabetes mellitus, and hyperlipidemia by multivariate logistic regression analysis, the statistical results also showed that subclinical hypothyroidism was independently correlated with nondipper blood pressure (OR = 2.203, 95% CI 1.007–4.819, $P=0.048$, Table 4).

Normotension, white-coat hypertension, masked hypertension, and sustained hypertension

The prevalence rates of WCH, MHT, and SHT in the S-HYPO group were 8.7, 32.7, and 31.7%, respectively, whereas the prevalence rates of WCH, MHT, and SHT in euthyroid group were 13.9, 22.2, and 22.9%, respectively (Table 3 and Fig. 1). Chi-square test of contingency table showed that the distribution of normotension, WCH, MHT, and SHT between the S-HYPO group and euthyroid group was statistically different ($P=0.002$, Table 3, Fig. 1). After adjusting P value by the Bonferroni method, the distribution of subclinical hypothyroidism patients and normal

thyroid patients between the MHT group and normotension group was statistically different ($P=0.002$). There were also statistical differences in the distribution of subclinical hypothyroidism patients and normal thyroid function patients between SHT and normotension groups ($P=0.004$). However, no such statistical difference was found between WCH and normotension groups ($P=0.886$).

The odds ratio (OR) of MHT to normotension in univariate unconditional logistic regression analysis confirmed that patients with subclinical hypothyroidism had a significantly increased risk of MHT compared with those with normal thyroid function [OR = 2.247, 95% confidence interval (CI) 1.336–3.779, $P=0.002$, Table 4]. After adjusting for confounding factors of sex, age, BMI, smoking history, drinking history, diabetes mellitus, and hyperlipidemia, multivariate logistic regression analysis showed that subclinical hypothyroidism was an independent risk factor for MHT (OR = 2.197, 95% CI 1.298–3.719, $P=0.003$). The risk of SHT vs. normotension was verified by the same method. Univariate logistic regression analysis showed that the risk of SHT increased in patients with subclinical hypothyroidism (OR = 2.109, 95% CI 1.250–3.557, $P=0.005$). Multivariate logistic regression analysis also showed that subclinical hypothyroidism was an independent risk factor for SHT after adjusting for confounding factors of sex, age, BMI, smoking history, drinking history, diabetes, and hyperlipidemia (OR = 2.232, 95% CI 1.290–3.863, $P=0.004$).

DISCUSSION

The relation between subclinical hypothyroidism and hypertension has always been a controversial issue [9]. The previous meta-analyses have also reported inconsistent results on this matter [24]. Previous research disputes have

TABLE 3. Analysis of normotension, white-coat hypertension, masked hypertension, and sustained hypertension distribution differences between subclinical hypothyroidism group and euthyroid group

Groups	Samples (%)	NT (%)	WCH (%)	MHT (%)	SHT (%)	P value
S-HYPO	104 (100)	28 (26.9)	9 (8.7)	34 (32.7) ^a	33 (31.7) ^a	0.002
ET	1327 (100)	544 (41.0)	185 (13.9)	294 (22.2) ^a	304 (22.9) ^a	

ET, euthyroid; MHT, masked hypertension; NT, normal blood pressure; SHT, sustained hypertension; S-HYPO, subclinical hypothyroidism; WCH, white-coat hypertension.
^aCompared with normotension group, there was a statistical difference.

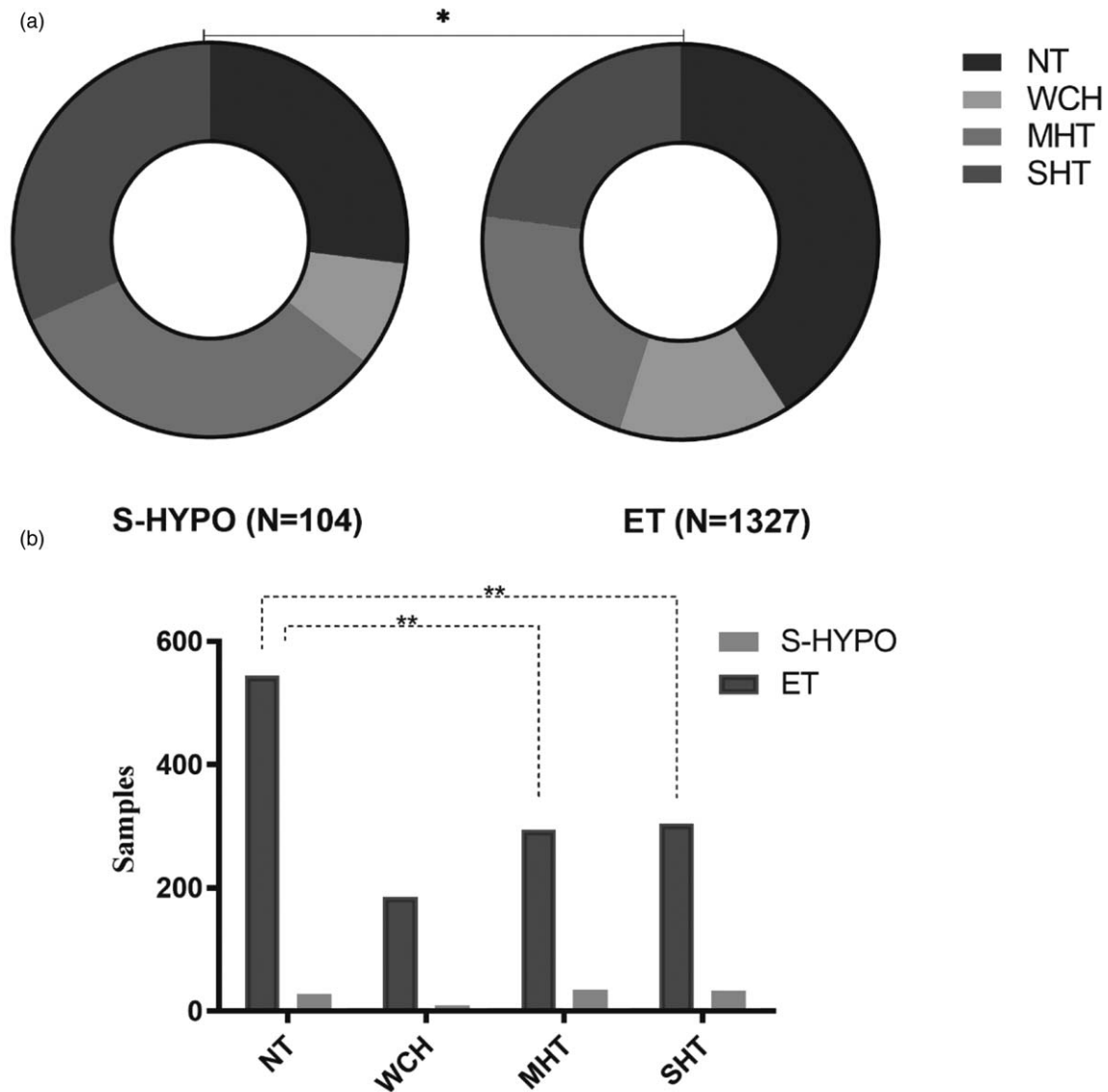


FIGURE 1 Comparison of white-coat hypertension, masked hypertension, and sustained hypertension distribution differences between S-HYPO group and euthyroid group. ET, euthyroid; MHT, masked hypertension; NT, normotension; SHT, sustained hypertension; S-HYPO, subclinical hypothyroidism; WCH, white-coat hypertension. * $P < 0.05$; ** $P < 0.008$, Bonferroni corrected chi-square test showed statistical difference.

TABLE 4. Logistic regression analysis of distribution difference of masked hypertension and sustained hypertension and blood pressure rhythm difference

Parameters	Univariate logistic regression		Parameters	Multivariate logistic regression	
	OR (95% CI)	P value		OR (95% CI)	P value
MHT vs. NT	2.247 (1.336–3.779)	0.002	S-HYPO	2.197 (1.298–3.719)	0.003
S-HYPO			Age	1.017 (1.005–1.030)	0.007
			BMI	1.100 (1.050–1.152)	<0.001
SHT vs. NT	2.109 (1.250–3.557)	0.005	S-HYPO	2.232 (1.290–3.863)	0.004
S-HYPO			Gender	0.706 (0.529–0.942)	0.018
			Age	1.026 (1.013–1.039)	<0.001
			BMI	1.170 (1.118–1.226)	<0.001
			HLP	1.393 (1.036–1.871)	0.028
Nondipper vs. dipper	2.203 (1.007–4.819)	0.048	S-HYPO	2.203 (1.007–4.819)	0.048
S-HYPO					

CI, confidence interval; ET, euthyroid; MHT, masked hypertension; OR, odds ratio; NT, normal blood pressure; SHT, sustained hypertension; S-HYPO, subclinical hypothyroidism.

focused on the level of office blood pressure [25]. Polat Canbolat *et al.* [26] found that subclinical hypothyroidism can lead to an increase in ambulatory blood pressure during the daytime and night-time, extending the correlation study between subclinical hypothyroidism and blood pressure status to the ambulatory blood pressure level outside the clinic. In the present study, we aimed to jointly explore the correlation between subclinical hypothyroidism and blood pressure status from the two levels of office blood pressure and blood pressure outside the clinic.

Our comparison results between the blood pressure groups inside and outside the clinic suggested that although the clinic SBP and DBP of subclinical hypothyroidism group are slightly higher than those in the normal thyroid function group: the observed difference was not statistically significant. However, the ambulatory blood pressure monitoring results showed significant differences among the daytime SBP, night-time SBP, night-time DBP, 24-h SBP and DBP outside the clinic, with these values being higher in subclinical hypothyroidism group compared with the normal thyroid function group. Previous studies have reported inconsistent results on the correlation between subclinical hypothyroidism and blood pressure inside and outside the clinic. A total of 6583 research samples were included in the large-scale clinical research results conducted by Duan *et al.*, including 806 cases of subclinical hypothyroidism and 5669 cases of normal thyroid function. Their research results suggested that subclinical hypothyroidism had a high prevalence among female patients of advanced age. At the same time, there was no difference in SBP and DBP between the two groups, which was consistent with our results at the office blood pressure level [27]. Previous research results suggested that subclinical hypothyroidism could induce increased arterial stiffness and increased peripheral vascular resistance [28]. These pathological changes may cause the body's blood pressure to rise; however, many clinical studies have not found that subclinical hypothyroidism is related to office blood pressure [29]. In our previous studies, we have found that white-coat hypertension, masked hypertension, and sustained hypertension have their own thyroid function characteristics in the euthyroid participants [13]. For example, among patients with euthyroid, elevated TSH was only found in those with sustained hypertension. This suggests that thyroid function is closely related to hypertension subtypes, such as sustained hypertension. Nevertheless, it remains unclear whether characteristics of blood pressure inside and outside the clinic in subclinical hypothyroidism are inconsistent as subclinical hypothyroidism has a special connection with a white-coat, masked, and sustained hypertension. Therefore, we further analyzed the respective correlations between subclinical hypothyroidism and white-coat, masked and sustained hypertension, hoping to explain these differences in the relationship between subclinical hypothyroidism and blood pressure inside and outside the clinic.

After dividing hypertension subtypes, such as WCH, MHT, and SHT according to the current European Hypertension Practice Guidelines, multivariate logistic regression analysis revealed that subclinical hypothyroidism was an independent risk factor for MHT and SHT, whereas the

proportion of WCH patients in S-HYPO group was lower than that in euthyroid group; however, the observed difference was not statistically significant. These results suggested that subclinical hypothyroidism is independently related to MHT and SHT, but not to WCH. Subclinical hypothyroidism has the pathological mechanism of increased peripheral vascular resistance and increased cardiac afterload [30]. In 2018, Yao *et al.* systematically reviewed the correlation between subclinical hypothyroidism and carotid intima-media thickness, pulse wave velocity, and brachial artery blood flow-mediated vasodilation among a total of 27 clinical studies. Their final results showed that subclinical hypothyroidism could increase carotid intima-media thickness and pulse wave velocity while reducing brachial artery blood flow-mediated vasodilation [31]. This suggests that subclinical hypothyroidism is related to increased arterial stiffness, impaired vascular endothelial function, and increased peripheral vascular resistance. The results of a MRI study have also shown that subclinical hypothyroidism is accompanied by increased cardiac afterload and increased systemic vascular resistance [32]. Subclinical hypothyroidism may also be related to renal function damage. Zhou *et al.* suggested that subclinical hypothyroidism is an independent risk factor for chronic kidney diseases in diabetic patients [33]. The above pathological changes, such as increased peripheral vascular resistance, can lead to increased blood pressure. SHT and MHT have both been shown to have the ability to increase peripheral vascular resistance, while WCH is different from them.

Whether WCH can lead to increased arterial stiffness and increased peripheral vascular resistance is still controversial [34]. It is currently believed that the mechanism underlying WCH is related to changes in cardiac autonomic nervous function [35]. Fagard *et al.* included 1485 study samples, recorded the time elapsing between two consecutive R-waves in the electrocardiogram in a supine position and standing position in the clinic, respectively, and calculated the low-frequency to a high-frequency ratio (LF/HF) [34]. The increase of the LF/HF ratio can reflect the rise of cardiac sympathetic nerve activity and the decrease of vagus nerve activity. Their results showed that an increase in LF/HF accompanied WCH. At the same time, MHT and SHT had no corresponding changes, thus suggesting that WCH was accompanied by an increase in cardiac sympathetic nerve activity. However, the effect of subclinical hypothyroidism on cardiac autonomic nerve function lies in its reduction of cardiac sympathetic nerve activity. In the ELSA-Brasil study, researchers examined 855 participants for heart rate variability in order to reflect the activity of cardiac autonomic nerve function. Their research results showed that the cardiac sympathetic and parasympathetic nerve activity in subclinical hypothyroidism patients was lower than that of normal thyroid function group in resting state [36]. When the participants changed posture, patients with subclinical hypothyroidism also showed a delay in sympathetic nerve function. The changes in cardiac autonomic nervous function between WCH and subclinical hypothyroidism are far from each other. No association between WCH and subclinical hypothyroidism was found in this study, which may also be related to the above differences.

All the above studies have confirmed that subclinical thyroid diseases are indeed closely related to blood pressure, but because of the existence of white-coat effect and masked effect, the correlation between subclinical hypothyroidism and office blood pressure is often not found at the office blood pressure level. Also, Inal *et al.* suggested that patients with subclinical hypothyroidism complicated with hypertension are more likely to show nondipper blood pressure [37]. The results of our study also indicated that the subclinical hypothyroidism population was closely related to nondipper blood pressure. The existence of nondipper blood pressure is an essential factor leading to masked hypertension, especially after the European Hypertension Practice Guidelines added diagnostic criteria for nocturnal blood pressure, where independent nocturnal hypertension was also grouped into masked hypertension [38]. The characteristics of blood pressure rhythm in subclinical hypothyroidism may also explain the controversy over the correlation between subclinical hypothyroidism and the office blood pressure level.

The results of this study suggest that subclinical hypothyroidism is related to the increase in ambulatory blood pressure. In contrast, the rise of office blood pressure (WCH) alone is not related to subclinical hypothyroidism. Literature reports show that the incidence of WCH and MHT is different in different regions and different races, which might explain the controversy over the correlation between office blood pressure and subclinical hypothyroidism [39]. In addition, putting the research results into clinical practice is the fundamental purpose of clinical research. Our research results may assist clinicians in judging the blood pressure status in subclinical hypothyroidism. For example, for patients with subclinical hypothyroidism patients in clinical practice, even if their office blood pressure is normal, the possibility of MHT should be highly suspected.

There are some limitations in this study. Not all participants in this study are healthy, and some participants suffer from hyperlipidemia and diabetes. We only used multivariate logistic regression analysis to correct the interference of hyperlipidemia and diabetes mellitus on the study results. In addition, we did not investigate salt intake and family history of hypertension, which is also the limitation of this study. In addition, although the combination of office blood pressure and ambulatory blood pressure is an innovative method to understand the blood pressure characteristics of subclinical hypothyroidism, this article does not discuss whether subclinical hypothyroidism caused by aging is inconsistent with subclinical hypothyroidism caused by thyroiditis and other diseases, which is also the limitation of this study.

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Conflicts of interest

There are no conflicts of interest.

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