ORIGINAL ARTICLE

Gender-specific associations between subclinical hypothyroidism and blood pressure in Chinese adults

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Received: 11 May 2009/Accepted: 4 August 2009/Published online: 14 October 2009 © Humana Press 2009

Abstract Hypothyroidism is often related with increased blood pressure, yet, gender-specific associations between subclinical hypothyroidism (SCH) and hypertension have not been previously assessed. We conducted a large-scale, cross-sectional study from six districts of Jiangsu Province to investigate the association of SCH and blood pressure in female and male adults. In the studied population, 4725 participants (3034 women and 1691 men) aged 20-60 years were included. The prevalence of hypertension was significantly higher in males as compared to females (37.34% vs. 27.39%, P < 0.05), while the prevalence of SCH was much higher in women (9.36% vs. 5.32%, P < 0.05). Furthermore, the hypertension rate was significantly higher in female SCH group compared to euthyroid (EUT) group(P < 0.05), while no significant differences were observed between the two groups in male participants(P > 0.05). After adjusting for age and body mass index (BMI), SCH was an independent predictor for increased SBP (OR = 1.47, 95%CI 1.08–1.99, P = 0.015) and elevated pulse pressure (OR = 1.45, 95%CI 1.05–1.99, P = 0.024) in females, and serum thyroid stimulating hormone (TSH) was significantly higher in female hypertensive group as compared to normotensive group (2.09 vs. 1.92 mIU/l, P = 0.0004). In male participants, SCH was not independently correlated with blood pressure, and no significant difference in TSH levels between hypertensive and normotensive groups was observed (1.74 vs. 1.66 mIU/l, P = 0.12). We concluded that SCH is an independent predictor of increased SBP and pulse pressure in females. Thus, thyroid function may influence blood pressure to a greater extent in females compared to males.

Keywords Subclinical hypothyroidism · Blood pressure · Increased systolic blood pressure · Relationship · Male/female

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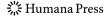
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Introduction

Thyroid hormones participate in the control of systemic arterial blood pressure homeostasis. Both overt hyperthyroidism and hypothyroidism can lead to hypertension [1, 2]. Hyperthyroidism may induce a widened pulse pressure [3], while hypothyroidism has been associated with increased systemic vascular resistance, which was thought to be the main pathophysiological mechanism of hypertension [4]. Recent studies have shown that overt hypothyroidism is related to increased risk of abnormal cardiovascular haemodynamics and dysfunction, especially contributing to atherosclerosis [5, 6]. In addition, accumulating evidence has suggested that patients with hypothyroidism are more likely to suffer from dyslipidemia and diastolic hypertension, which may lead to coronary heart disease [7–10].



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Subclinical hypothyroidism (SCH) is defined as an asymptomatic condition in which normal levels of free thyroxine (FT4) are detected in the presence of elevated serum thyroid stimulating hormone (TSH) concentrations [9]. The relationship between SCH and blood pressure has received insufficient attention; although some studies have reported a similar relationship between SCH and hypertension as well as overt hypothyroidism and blood pressure [11, 12], this issue remains controversial. For example, several authors reported that there was no correlation between SCH and hypertension in a population-based study [13, 14]. Up to now, very few investigations had explored gender-specific differences in the relationship between SCH and blood pressure, and, therfore, we conducted a large-scale, cross-sectional survey to assess the association between SCH and hypertension in both female and male adults.

Results

General characteristics and risk behaviors of investigated population

A total of 4725 people were enrolled in this survey, which consisted of 3034 females and 1691 males. The clinical characteristics of each gender are summarized in Table 1. In this population, males were more prone to be smokers and have larger body mass index (BMI) (P < 0.05). Serum levels of triglycerides (TG) and high density lipoprotein

cholesterol (HDL-C) were much higher in men (P < 0.05). Compared with females, the SBP and DBP were significantly higher in males, but TSH levels were much lower (P < 0.05). There was no difference in age, family history of hypertension, or pulse pressure between the genders (P > 0.05; Table 1).

In females, blood pressure, including SBP (125.40 \pm 19.91 mmHg), DBP (81.51 \pm 11.9 6 mmHg), and pulse pressure (43.89 \pm 12.64 mmHg) was significantly higher (P < 0.05, respectively) in SCH group compared to euthyroid (EUT) group (SBP 121.78 \pm 17.68 mmHg, DBP 79.79 \pm 10.83 mmHg, and pulse pressure 41.99 \pm 11.27 mmHg; Table 2). For males, the blood pressure was slightly higher, and no differences were found in the two groups (P > 0.05; Table 2).

The prevalence of SCH and hypertension in men and women of different ages

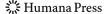
The prevalence of hypertension was significantly higher in males as compared to females (37.34 vs. 27.39%, P=0.000), while SCH prevalence was much higher in women (9.36 vs. 5.32%, P=0.000). The prevalence of both hypertension and SCH increased with age in males and females, but SCH prevalence in women aged 20–29 years was slightly higher than those aged 30–39 years (8.45 vs. 8.09%), which was not observed in men. Thus, it appeared that SCH was more commonly observed in women, and hypertension was more often observed in men (Table 3).

Table 1 Baseline characteristics in studied population

Total $(n = 4725)$	Women $(n = 3034)$	Men $(n = 1691)$	P
Age (years) ^a	43.76 ± 9.52	43.27 ± 10.60	0.11
HP family history (%)	692 (23.71)	397 (24.06)	0.79
BMI (kg/m ²) ^a	23.98 ± 4.46	24.83 ± 9.21	0.0005*
Smoking status (%)	221 (7.28)	917 (54.23)	0.0000*
TG(mmol/l) ^b	1.03 (0.74–1.53)	1.23 (0.82–1.91)	0.0000*
HDL-C(mmol/l) ^b	1.32 (1.14–1.54)	1.21 (1.05–1.43)	0.0000*
HP Prevelence (%)	831(27.39)	633 (37.43)	0.000*
Current SBP (mmHg) ^a	122.12 ± 17.92	125.73 ± 16.93	0.0000*
Current DBP (mmHg) ^a	79.95 ± 10.95	83.49 ± 11.11	0.0000*
Current Pulse pressure (mmHg) ^a	42.16 ± 11.42	42.23 ± 11.29	0.84
SCH prevelence (%)	284 (9.36)	90(5.32)	0.000#
Serum TSH (mIU/l) ^b	1.97 (1.34–3.13)	1.69 (1.20–2.51)	0.000#

HP hypertension, BMI body mass index, TG triglycerides, HDL-C high-density lipoprotein cholesterol, TSH thyroid stimulation hormone, SBP systolic blood pressure, DBP diastolic blood pressure, smoking status was defined as current smoker or non-current smoker

Continuous data are expressed as a mean \pm SD or b median(25th and 75th pecentile); categorical data are presented as numbers of percentage t test (t' test), chi-squared and Mann–Whitney's U-test were used as statistic method; Significance was set at P < 0.05; * comparison groups of women, P < 0.01; # comparison groups of men, P < 0.05



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Table 2 Correlations of blood pressure and thyroid function in men and women

Blood pressure	Women $(n = 3034)$	(1	P_1	OR	OR 95% CI P_3	P_3	Men $(n = 1691)$		P_2	OR	P_2 OR 95% CI P_4	P_4
	EUT $(n = 2750)$	EUT $(n = 2750)$ SCH $(n = 284)$					EUT $(n = 1601)$ SCH $(n = 90)$	SCH (n = 90)				
SBP(mmHg)	121.78 ± 17.68	125.40 ± 19.91 [#]	0.0034#	1.65	1.65 1.21–2.24	0.001*	125.53 ± 16.83	129.32 ± 18.48	0.060	1.26	0.060 1.26 0.80-1.99	0.32
DBP(mmHg)	79.79 ± 10.83	$81.51 \pm 11.96^{*}$	$0.021^{\#}$	1.23	0.91 - 1.66	0.18	83.37 ± 11.04	85.66 ± 12.04	0.082	1.28	0.83-1.96	0.26
Pulse pressure(mmHg)	41.99 ± 11.27	43.89 ± 12.64 [#]	0.015#		1.70 1.22–2.36	0.002**	42.15 ± 11.14	43.67 ± 13.63 0.300	0.300	1.12	0.73-1.73	0.61

SCH subclinical hypothyroidism, EUT euthyroid group, SBP systolic blood pressure, DBP diastolic blood pressure, OR odds ratio, CI confidence interval, Data excludes subjects with treatment

SD; Categorical data are presented as numbers; Mann–Whitney's U-tests, chi-squared test and t test were used for comparison of qualitative data: BMI, and smoking status; Significance was set at P < 0.05, and 95% CIs were calculated Logistic regression test were used for correlation analyses and adjusted for age, Continuous data are expressed as mean \pm for hypertension

as >50 mmHg, correlations between SCH and increased SBP, DBP and pulse pressure adjusted for age and BMI in women; P4, correlations between SCH and increased represents as independent correlation between SCH and EUT in men increased pulse pressure defined increased SBP; defined as ≥90 pressure adjusted for age, BMI, and smoking status in men; * represents as independent correlation between SCH and comparisons of blood mmHg, EUT in women; as defined groups of SCH euthyroid group; * represents P < 0.05 compared with evaluated above the 75th percentile; P_3 P_1 , comparisons of blood pressure pulse pressure poold

Correlation analysis between SCH and blood pressure

Increased blood pressure correlated with age and BMI in both men and women. Smoking status was associated with increased blood pressure in men (OR = 1.19,95%CI = 1.01–1.40, P = 0.041), while the same correlation was not found in women (OR = 1.46,95%CI = 0.97–2.19, P = 0.071). Moreover, SCH had no relationship with smoking status either in males (OR = 1.35, 95%CI = 0.88-2.07, P = 0.167) or females (OR = 1.12, 95%CI = 0.86-1.46, P = 0.393). Specifically, a weak correlation between SCH and increased SBP (OR = 1.65, 95%CI 1.21-2.24, P = 0.001) and elevated pulse pressure (OR = 1.70, 95%CI 1.22–2.36, P = 0.002) was observed in females while no similar correlations were detected in males (P > 0.05). Further, after adjusting for age and BMI, binary logistic regression revealed that SCH was an independent predictor of increased SBP (OR = 1.47, 95%CI 1.08-1.99, P = 0.015) and elevated pulse pressure (OR = 1.45, 95%CI 1.05-1.99, P = 0.024) in females only (Table 2).

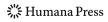
Correlation between TSH levels and blood pressure in normotensive and hypertensive participants

As shown in Table 4, elevated serum TSH levels were observed in the hypertensive group (2.09 mIU/l) as compared to the normotensive group (1.92 mIU/l, P=0.0004) in females. However, in males, serum TSH levels were not statistically different between the hypertensive and normotensive groups (1.74 vs. 1.66 mIU/l, P=0.12; Table 4).

Discussion

In this cross-sectional, community-based, large-scale survey, we analyzed associations between SCH and hypertension in Chinese men and women 20–60 years of age. The prevalence of hypertension was significantly higher in males than that in females (37.34 vs. 27.39%), while SCH was detected more often in females compared to males (9.36 vs. 5.32%). Also, the prevalence of hypertension and SCH increased with age in general, but SCH prevalence in women aged 20–29 years was slightly higher than those aged 30–39 years (8.45 vs. 8.09). Similar trends were not observed in men. Thus, more women seem to have SCH, while men are more prone to hypertension.

In 2002, Hollowell et al. [15] reported that the concentration of TSH and the prevalence of anti-thyroid antibodies were greater in women, especially higher in whites and Mexican Americans as compared with blacks [15]. Also, TSH values were slightly higher in children



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Table 3 The prevalence of SCH and hypertension in men and women with different ages

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	[n = 447 (9.46%)]	$\begin{bmatrix} 30 \\ [n = 1129 \ (23.89\%)] \end{bmatrix}$	[n = 1554 (32.89%)]	[n = 1595 (33.76%)]	Total $[n = 4725 (100\%)]$
SCH prevalence					
Female $(n = 3034)$	8.09 (19/235)	7.46 (57/764)	8.75 (89/1017)	11.69 (119/1018)	9.36 (284/3034)
Male $(n = 1691)$	3.77 (8/212)	4.11 (15/365)	4.66 (25/537)	7.28 (42/577)	5.32 (90/1691)
Total $(n = 4725)$	6.04 (27/447)	6.38 (72/1129)	7.34 (114/1554)	10.09 (161/1595)	7.92 (374/4725)
χ^2	3.65	4.65	8.67	7.89	24.29
P	0.056	0.031#	0.003#	0.005#	$0.000^{\#}$
HP prevalence					
Female $(n = 3034)$	7.23 (17/235)	13.48 (103/764)	27.53 (280/1017)	42.34 (431/1018)	27.39 (831/3034)
Male $(n = 1691)$	15.09 (32/212)	27.40 (100/365)	41.90 (225/537)	47.83 (276/577)	37.43 (633/1691)
Total $(n = 4725)$	10.96 (49/447)	17.98 (203/1129)	32.50 (505/1554)	44.33 (707/1595)	30.98 (1464/4725)
χ^2	7.06	32.43	33.07	4.51	51.22
P	0.008*	0.000*	0.000*	0.034*	0.000*

SCH subclinical hypothyroidism, HP hypertension; Data are presented as numbers and percentage; Comparative data between groups were derived from chi-squared test; # represents comparison groups of men, P < 0.01; * represents comparison groups of women, P < 0.01

Table 4 Comparison of serum TSH between hypertensive and normotensive groups in female and male population

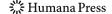
Serum TSH (mIU/l)	Women $(n = 3034)$		Men(n = 1691)	
	Hypertension $(n = 831)$	Normotension $(n = 2203)$	Hypertension $(n = 633)$	Normotension $(n = 1058)$
Median	2.09	1.92	1.74	1.655
25–75th percentile <i>P</i>	1.39–3.37 0.0004*	1.32–3.03	1.23–2.56 0.12	1.18–2.48

Continuous data are expressed as median (25th and 75th percentile); categorical data are presented as numbers of percentage; comparisons of serum TSH are made by Mann–Whitney's U-test; P represents comparison of hypertension with normotension; * means comparison of normotensive group, P < 0.05

aged 12–19 years than in young adults aged 20–29 years, although the reason was unknown [15]. Another UK survey observed that serum TSH levels did not vary with age in men, but increased markedly in women more than 45 years [16]. Furthermore, no increase in TSH with age was observed in women in the absence of anti-thyroid anti-bodies [17]. However, Takashima et al. [18] reported that the prevalence of SCH in an elderly Japanese population (>75 y) regardless of gender was not as high as other reports [18]. Therefore, differences in ethnic or environmental backgrounds of the subjects might account for these discrepancies.

In our study, the SBP, DBP, and pulse pressure were significantly higher in SCH females than in their EUT counterparts, while no such differences were detected in males. More importantly, in females, SCH was associated with increased SBP and pulse pressure, and SCH was an independent predictor of increased SBP after adjustment for confounding factors. However, SCH was not independently associated with increased blood pressure in males.

Few studies have assessed the association of blood pressure and SCH with regard to gender differences. Several investigated populations were only related to women. In a Kuwaiti study, it was found that women suffering from SCH exhibited elevated atherogenic parameters, including hyperinsulinemia, total cholesterol, and low-density lipoprotein-C (LDL-C) [17]. In addition, Kvetny et al. reported that patients with SCH have increased levels of triglycerides and signs of low-grade inflammation (i.e., raised C-reactive protein levels), and that subclinical hypothyroidism might be a risk factor for development of cardiovascular disease in younger males [19]. Other studies of the general population report conflicting results [12, 18, 20, 21]. Specifically, SCH was not associated with hypertension in an Australian population-based study [20] and a Japanese population-based study [18]. However, a small case-control study observed that SCH was associated with large BMI, DBP, high total cholesterol, and elevated triglycerides in women [21]. These discrepancies can be explained by differences in participants, iodine intake, and



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detection sensitivity of FT4 and TSH, as well as the prevalence rate of hypertension. Nonetheless, the relationship between SCH and hypertension remains controversial [12, 22].

We also found that serum TSH levels in hypertensive women were significantly higher than in normotensive women, while no statistical differences were found in men. Thus, the mechanism by which TSH influences hypertension or plays a role in increased blood pressure is still uncertain. Whether the gender-specific differences between SCH and blood pressure could be explained by the effects of estrogen should be further investigated in future studies. Some studies have observed that sex hormones, including follicle stimulating hormone (FSH), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), testosterone, and estradiol were not associated with TSH [23].

In addition, it was discovered that smoking status correlated with increased blood pressure in men, although the same result was not found in women. In fact, smoking also deteriorated blood pressure in the general population surveyed in this study. The differential effect of smoking on blood pressure in women may be because of fewer smokers in women.

In conclusion, in this study, it was found that SCH was an independent predictor of increased SBP and pulse pressure in females, and thyroid function had a more effect on blood pressure in female as compared to male participants.

Materials and methods

Study population

According to the stratified clustering sampling design, six districts of Jiangsu Province (Xuzhou, Huaian, Zhenjiang, Wuxi, Gaochun, and Nanjing) were selected for sample collection. From 2005 to 2006, 6992 residents >20 years of age (range 20–88 years) that lived for at least 5 years in the corresponding districts were included in this survey, and out of them, 6583 participants (4115 females and 2468 males) were investigated. Pregnant women and subjects taking contraceptive agents or estrogens were also excluded. Those who suffered from severe renal, liver, or heart failure or abdominal ascites were not recruited. Individuals taking medicines that influence thyroidal function and blood pressure were excluded. Hypertensive subjects receiving treatment (n = 415) were excluded from analyses of systolic blood pressure (SBP) and diastolic blood pressure (DBP) but included hypertension prevalence analysis. Among the total subjects, 4725 participants aged 20-60 years were included in this survey and completed physical examination and blood sample measurements. Local ethics committees and other relevant regulatory bodies in Jiangsu province approved the study. Written informed consent was obtained from all the participants before data collection.

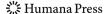
Data collection and physical examination

Data were collected in an examination center located in local health stations or community clinics within the participants' residential areas. During the visits, trained research staff administered a standard questionnaire in Chinese. Demographic characteristics, including age, gender, education, occupation, life habits, and income were collected. The interview included questions relevant to the diagnosis and treatment of thyroid diseases as well as other specific diseases such as hypertension, diabetes, dyslipidemia, cardiovascular disease, renal failure, and hepatic cirrhosis; inquiries into current treatment and medication usage were also made.

During the physical examination, blood pressure and anthropometric measurements were obtained by trained and certified observers using standard protocols and techniques [24]. Blood pressure was measured by a physician using a mercury sphygmomanometer after the subjects had rested for at least 5 min in the sitting position. Participants were advised to avoid cigarette smoking, alcohol, caffeinated beverages, and exercise for at least 30 min before their blood pressure examination. Three measurements were taken at 1-min intervals, and the average value was used to define the clinical SBP and DBP. Body weight and height were measured twice during the examination. Weight was measured in light indoor clothing without shoes to the nearest 100 g. Height was examined without shoes to the nearest 1 cm with a stadiometer. Waist circumference was measured to the nearest 1 cm midway between the lower costal margin and the iliac crest, and hip circumference at the level of maximum extension of the buttocks.

Laboratory methods

Overnight fasting blood specimens were processed at the examination center and shipped to a central clinical laboratory in Nanjing where they were stored at -70° C until analysis. Concentrations of high density lipoprotein-C (HDL-C) and triglycerides (TG) were assessed enzymatically with commercially available reagents. Serum TSH, FT3, and FT4 measurements were detected with an IM-MULITE 1000 Analyzer Device (Diagnostic Products Corporation, Los Angeles, CA, USA) using a solid-phase, two-site chemiluminescent immunometric assay and competitive, analog-based immunoassay method. If TSH levels



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were abnormal, FT3 and FT4 were measured as well. The analytical sensitivities for TSH, FT3, and FT4 were 0.004 $\mu IU/ml,~1.536$ pmol/l, and 3.861 pmol/l, respectively. The reference ranges were 0.4–4.5 $\mu IU/ml$ for TSH, 2.3–6.3 pmol/l for FT3 and 10.3–24.5 pmol/l for FT4 [25].

Definitions

SCH was defined as >4.5 μ IU/l TSH levels with normal FT3 and FT4. Patients with a SBP >130 mmHg, a DBP >85 mmHg, or those who received treatment for previously diagnosed hypertension were considered to have elevated blood pressure. Increased pulse pressure was defined as the value above the 75th percentile of the pulse pressure distribution (50 mmHg). Body mass index (BMI) was calculated as weight (kg)/height² (m²).

Statistical analysis

The data were input into the double-track system of EpiData 3.0 software. Statistical analyses were conducted using SPSS 13.0 statistical software (Chicago, IL, USA). Measurement data were represented as the mean \pm standard deviation. Intergroup comparisons of quantitative variables were assessed using One-Way ANOVA. Chisquare and Fischer's Exact tests were used to compare qualitative data. Multivariable analyses were performed using binary logistic regression to identify risk factors for hypertension. Adjusted means and odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Differences were considered statistically significant if the P value was <0.05.

Acknowledgments This study was supported by a Medical Key Subject grant from Jiangsu Province, China. Chao Liu was supported by grants, RC2002047and LJ200619, from Jiangsu Province, China. We are grateful to all the patients and medical staff who participated in the study.

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