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ORIGINAL ARTICLE

Investigation of thyroid function and blood pressure in school-aged subjects without overt thyroid disease

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Abstract This study was performed to ascertain whether a relationship exists between thyroid function and blood pressure in school-aged Chinese subjects without overt thyroid disease. A cross-sectional survey of 880 subjects (541 females and 339 males) aged 7–18 years in Bengbu, Anhui province was conducted. The investigation, which was based on a stratified random cluster sampling method, included a questionnaire and measurements of blood pressure, height, and body weight. Fasting blood samples were taken for measurements of thyroid-stimulating hormone (TSH), free 3,5,3′-triiodothyronine (FT_3) and free thyroxine (FT_4). Serum TSH and FT_3 were positively correlated with systolic and diastolic blood pressure *Z* scores (SBP-Z and DBP-Z) even after adjusting for body mass index (BMI) ($P < 0.05$) but no correlation was observed between FT_4 and SBP-Z or DBP-Z after comparable adjustments ($P > 0.05$). SBP-Z and DBP-Z in subjects with subclinical hypothyroidism were significant higher than in euthyroid subjects ($P < 0.05$). Both SBP-Z and DBP-Z increased linearly with TSH concentration in boys after adjusting BMI ($P < 0.05$); however, a similar linear trend was not observed in girls. Our findings support the hypothesis that elevated TSH and FT_3 concentrations increase blood pressure in school-aged Chinese subjects without overt thyroid disease; this increase may be even more significant in boys.

Keywords School-aged subjects · Thyroid-stimulating hormone · Free 3,5,3′-triiodothyronine/free thyroxine · Subclinical hypothyroidism · Systolic blood pressure/diastolic blood pressure

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Introduction

Thyroid hormones are recognized to exert profound effects on the myocardium [1] and to function importantly in the regulation of vascular reactivity [2]. Findings of previous studies reveal that clinically overt hyperthyroidism and hypothyroidism both increase the risk of hypertension [3–5]. In general, overt hyperthyroidism is associated with the induction of increased systolic blood pressure and pulse pressure as a result of augmented cardiac output and reduced systemic vascular resistance. On the other hand, increased diastolic blood pressure is routinely observed in overt hypothyroidism as a consequence of changes in cardiovascular hemodynamics and function, especially those contributing to development of atherosclerosis. However, subclinical hypothyroid function, which is characterized by thyroid hormone concentrations within the reference range combined with elevated thyroid-stimulating hormone (TSH) concentrations, is also reported to be associated with hypertension [6, 7]. Consistent with this

association, results of a recent population-based study including 30,728 individuals indicate a modest, but significant, linear positive correlation between serum TSH and blood pressure, even when TSH concentrations are within the normal range [8]. However, these findings remain controversial as other studies have failed to demonstrate an association between blood pressure and subclinical hypo- or hyperthyroidism [9, 10]. Because maintenance of a healthy blood pressure is a major goal for all subjects, potential associations between TSH and blood pressure in subjects without overt thyroid disease require further investigation.

To the best of our knowledge, no investigations have been conducted that explore the relationship between thyroid function and blood pressure in school-aged subjects. This study, which was based on a cross-sectional epidemiological survey, was undertaken to explore such relationships in participants aged 7–18 years with subclinical thyroid disease or with euthyroidism.

Subjects and methods

Participants

A cross-sectional study was performed in four districts of Bengbu, Anhui province from November 2008 to May 2009. Local school-aged subjects aged 7–18 years were enrolled. A total of 880 participants completed the questionnaire, underwent a physical examination, and provided blood samples. Individuals with known severe disorders such as renal failure, liver dysfunction, or congenital heart disease and subjects with overt thyroid disease were not enrolled. Nobody took medications with the potential to influence thyroid function or blood pressure, such as iodine or compound glycyrrhize mixture. Approval of this study was granted by the local ethics committees. All participants and their respective guardians gave informed consent for inclusion in this study, which was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Data collection and physical examination

Data were collected in examination centers located in local health stations. During subject visits, trained research staff administered a standard questionnaire in Chinese. Demographic characteristics, including age, gender, education, life habits and duration of time living in the district, 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. During the physical examination, blood pressure and anthropometric measurements were obtained by trained and certified observers using standard protocols and techniques. Subjects were asked to avoid drinking any beverage except water, and heavy exercise at least 1 h before measurements. Blood pressure was measured at the right upper arm brachial artery with the subject in a seated position and using a standard mercury sphygmomanometer with an appropriate cuff size after at least 15 min of rest. Three measurements were performed at 1-min intervals, and the mean value of the second and third measurements was used. Pulse pressure was calculated as the difference between systolic and diastolic blood pressures. Body weight and height were measured twice during the examination. Weight was measured to the nearest kg with the subjects wearing light clothes and no shoes, and height was determined to the nearest cm. BMI was calculated as weight divided by squared height.

Collection of blood samples

A venous blood sample was drawn from each individual in the morning following a 12 h fast.

No subject was involved in intensive or competitive physical activity prior to enrollment. Samples were stored at −80°C and tested at the same time after thawing.

Laboratory measurements

Thyroid function was measured using a chemiluminescence immunoassay system (Roche Diagnostics GmbH, Manheim, Germany). The reference for serum TSH concentration was 0.27–4.20 mIU/l, and references for 3,5,3′-triiodothyronine (FT_3) and thyroxine (FT_4) concentrations were 2.8–7.1 pmol/l and 12.0–22.0 pmol/l, respectively. Thyroid peroxidase antibodies (TPO-Abs) were measured by a chemiluminescent immunometric assay (Immulite 2000) with values of 0 to 34.0 IU/ml considered as normal. The intra-assay coefficients of variation were <6.5%, and the inter-assay coefficients of variation were <10%.

Definitions

SBP and DBP were also expressed in SBP-Z and DBP-Z related to age, gender and height for every individuals and 90th percentile (P_{90}) was termed as the cut point of "blood pressure elevation" according to "the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents"[11]. Subclinical hypothyroidism (SCH) was defined as >4.20 mIU/L TSH levels with normal FT_3 and FT_4, whereas subclinical hyperthyroidism was defined as <0.27 mIU/L TSH levels with normal FT_3 and FT_4.

Statistical analysis

Data were imput into a double-track system using the EpiData 3.0 software. Statistical analyses were performed by the SPSS 13.0 software package (SPSS, Inc., Chicago, IL). Continuous data were presented as $\bar{x} \pm s$ and categorical data were expressed as numbers with percentages. Comparisons of measured variables such as blood pressure *Z* scores (BP-*Z*) between groups were analyzed by the *t* test and one-way ANOVA. Spearman correlation analysis and linear regression models were applied to examine the relationships between BP-Z and serum concentrations of log-transformed TSH, FT_3, and FT_4. Both SBP-Z and DBP-Z for groups with different TSH values were compared using the multivariate analysis of variance. A two-tailed *P* value <0.05 was considered statistically significant.

Results

General characteristics of participants

The 880 participants in this study included 541 males and 339 females, with a mean age of 11.15 ± 2.34 years (range 7–18 years). No subject smoked or used alcohol. Subjects were divided into three groups according to thyroid status: the euthyroid group, the subclinical hyperthyroid group, and the SCH. The euthyroid group included 462 males and 292 females, and the SCH group was comprised of 77 males and 47 females. Two males, aged 10.90 and 11.30 years, were included in the subclinical hyperthyroid group; TSH levels were 0.053 and 0.131 mIU/l, and blood pressures were 82/58 and 110/70 mm Hg, respectively.

Characteristics of participants in the euthyroid and SCH groups

Considering the small number of subjects in the subclinical hyperthyroid group, only the basic characteristics of euthyroid and SCH groups were determined (Table 1). The mean age of subjects in the SCH group was 10.59 ± 2.03 years and was significantly younger than the euthyroid group (mean age of 11.25 ± 2.38 years; $P = 0.001$). Other characteristics of the two groups, including gender, BMI, pulse pressure and pulse, were similar (corresponding *P* values were 0.526, 0.524, 0.683, 0.294, respectively).

An initial comparison of blood pressures indicated that SBP was 2.6 mm Hg higher in the SCH than in euthyroid group and DBP was 2.2 mm Hg higher in the SCH group than in the euthyroid group as well, corresponding *P* values were 0.009 and 0.006, respectively. Both SBP-Z and DBP-Z were also higher in the SCH group than in the euthyroid group as well, corresponding *P* values were less than 0.001 and equal to 0.001, respectively (Table 1). To exclude the potential effects of autoimmune thyroiditis on the blood pressure elevations observed for subjects with SCH, sub-groups that were positive and negative for TPO Abs were compared for SBP-Z and DBP-Z; no difference in BP-Z was observed between these sub-groups (findings not shown).

Correlations of TSH, FT_3, and FT_4 with blood pressure

For the 880 individuals in this study, a positive correlation was found between serum TSH concentration and BP-Z, including both SBP-Z and DBP-Z (corresponding *P* values were all <0.001). A similar positive correlation

Table 1 Baseline characteristics of participants

	Total	EUT	SCH
Subjects (*N*)	880	754	124
Male (*N*%)	541 (61.48%)	462 (61.27%)	77 (62.10%)
Age (year)	11.15 ± 2.34	11.25 ± 2.38	10.59 ± 2.03*
BMI (kg/m^2)	21.79 ± 4.28	21.75 ± 4.30	22.02 ± 4.14
SBP (mm/Hg)	107.63 ± 12.47	107.29 ± 12.81	109.90 ± 9.76*
SBP-Z	0.1888 ± 1.0848	0.1391 ± 1.1032	0.5068 ± 0.8972*
DBP (mmHg)	69.54 ± 9.33	69.24 ± 9.49	71.47 ± 8.07*
DBP-Z	0.6352 ± 0.7758	0.6012 ± 0.7841	0.8486 ± 0.6918*
PP (mmHg)	38.09 ± 9.68	38.05 ± 9.84	38.44 ± 8.63
Pulse (beat/min)	80.98 ± 11.42	81.16 ± 11.47	80.00 ± 11.16
TSH (mIU/l)	2.92 ± 1.38	2.50 ± 0.84	5.47 ± 1.27*
FT_3 (pmol/l)	6.24 ± 0.78	6.23 ± 0.78	6.30 ± 0.79
FT_4 (pmol/l)	16.74 ± 2.02	16.80 ± 2.02	16.40 ± 1.95*

BMI body mass index, *DBP* diastolic blood pressure, *DBP-Z* diastolic blood pressure *Z* score, *EUT* euthyroid group, *FT_3* free 3,5,3′-triiodothyronine, *FT_4* free thyroxin, *PP* pulse pressure, *SBP* systolic blood pressure, *SBP-Z* systolic blood pressure *Z* score, *SCH* subclinical hypothyroidism, *TSH* thyroid-stimulating hormone. * $P < 0.05$, compared with euthyroid group

Table 2 Correlation analyze of TSH, FT_3, FT_4, and blood pressure *Z* score in total subjects, male and female groups

BP-Z	TSH				FT_3				FT_4			
	R1	*P*	R2	*P*	R1	*P*	R2	*P*	R1	*P*	R2	*P*
SBP-Z (total)	0.159	<0.001*	0.1465	<0.001*	0.129	<0.001*	0.0991	0.003*	−0.037	0.277	0.0051	0.879
DBP-Z (total)	0.127	<0.001*	0.1098	0.001*	0.129	<0.001*	0.0900	0.008*	−0.097	0.004*	−0.0454	0.178
SBP-Z (male)	0.172	<0.001*	0.1596	<0.001*	0.166	<0.001*	0.1061	0.014*	−0.044	0.306	−0.0047	0.914
DBP-Z (male)	0.139	0.001*	0.1243	0.004*	0.165	<0.001*	0.0927	0.031*	−0.107	0.013*	−0.0635	0.141
SBP-Z (female)	0.132	0.015*	0.1234	0.023*	0.007	0.893	0.0307	0.574	−0.050	0.359	−0.0075	0.891
DBP-Z (female)	0.104	0.055	0.0869	0.111	0.069	0.205	0.1208	0.026*	−0.083	0.126	0.0022	0.967

BP-Z blood pressure *Z* score, *DBP-Z* diastolic blood pressure *Z* score, *FT_3* free 3,5,3′-triiodothyronine, *FT_4* free thyroxin, *SBP-Z* systolic blood pressure *Z* score, *TSH* thyroid-stimulating hormone, *R1* correlation coefficients of crude, *R2* correlation coefficients after adjustment for BMI. * $P < 0.05$

was observed between FT_3 and SBP-Z as well as FT_3 and DBP-Z (corresponding *P* values were all <0.001). In contrast, negative correlation was found between FT_4 and DBP-Z (corresponding *P* values were 0.004) (Table 2, Fig. 1). After adjusting for BMI, the positive relationships between TSH or FT_3 and blood pressure were retained (corresponding *P* values were <0.001, 0.001, 0.003, 0.008, respectively). However, the negative correlation between FT_4 and DBP-Z was not sustained (corresponding *P* values was 0.178) after adjustment (Table 2).

Thyroid function and blood pressure as a function of gender

When the subjects in this study were divided into groups according to gender, both TSH and FT_3 concentrations were found to correlate positively with SBP-Z and DBP-Z in males, these correlations were sustained even after adjusting for BMI (corresponding *P* values were <0.001, 0.004, 0.014, 0.031, respectively). In contrast, negative correlations was found between FT_4 and DBP-Z (corresponding *P* values was 0.013), however, this correlation was not sustained (corresponding *P* values was 0.141) after adjustment. In the female group, the only correlations observed were the positive correlations between TSH and SBP-Z ($P = 0.023$) as well as FT_3 and DBP-Z ($P = 0.026$) after adjustment of BMI (Table 2). When sub-groups with cut-offs of 2.5 mIU/l and 4.2 mIU/l for TSH concentration were examined for correlations of TSH with BP-Z, both SBP-Z and DBP-Z were found to increase linearly with increasing TSH concentration in males after adjusting for BMI (corresponding *P* values were 0.002, 0.005, respectively, Table 3). However, this linear trend was not observed in females (Table 3).

Comparison of thyroid function between different blood pressure levels

According to the BP-Z, we defined SBP percentile or DBP percentile $\geq P_{90}$ as SBP elevation (SBPE) or DBP elevation (DBPE), and SBP or DBP percentile less than P_{90} as normal SBP (NSBP) or normal DBP (NDBP), respectively. Then we compared thyroid function between blood pressure elevation and normal groups, found that both FT_3 and TSH concentrations were higher in SBPE than NSBP group and also higher in DBPE than NDBP group (Table 4).

Discussion

To the best of our knowledge, this study is the first of its kind to explore the relationships between thyroid status and blood pressure in school-aged children without overt thyroid disease. In this cross-sectional study of 880 school-aged subjects, both SBP-Z and DBP-Z were found to be significantly higher in children with SCH as compared to euthyroid children. Serum TSH and FT_3 were positively correlated with BP-Z even after adjusting for BMI. Both FT_3 and TSH concentrations were also higher in SBPE and DBPE.

Recent literature searches reveal that cardiovascular disorders are found in adult subjects with SCH. Luboshitzky et al. [6], who examined a population of middle-aged women, found that the presence of SCH is associated with hypertension and that DBP is higher in women with, as compared to without, SCH. Other investigators [12] observed that diastolic brachial and aortic blood pressures in subjects with SCH decrease significantly after treatment with levothyroxine. In an epidemiological investigation involving 1,534 inhabitants of Shenyang, China who were 18–85 years of age, the prevalence of hypertension in those

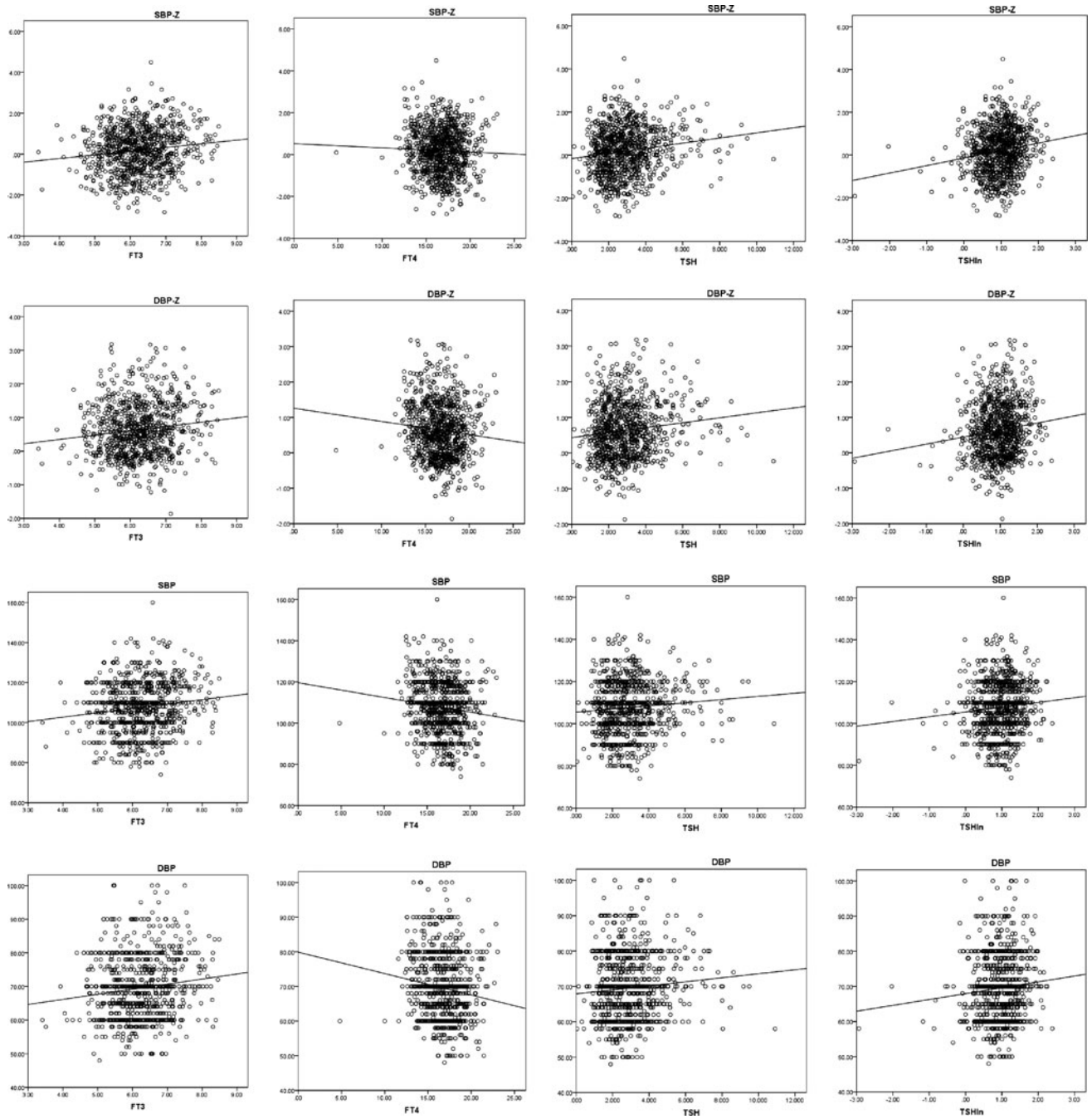

Fig. 1 Linear correlations between blood pressure, blood pressure *Z* score and thyroid function (TSH values were log-transformed because of non-normal distribution)

with SCH was found to be significantly higher than in those who were euthyroid [9]. Findings of a previous survey by our team disclosed that SCH is an independent predictor of increased SBP and pulse pressure in females [13]. In addition, Asvold et al. [8] reported that, within the reference range of TSH values, a linear positive association between TSH and both SBP and DBP exists, predictive of longer term implications for cardiovascular health. Findings of Gumieniak et al. [14] confirmed that TSH is higher in hypertensive, as compared with normotensive, euthyroid subjects. Collectively these findings establish that thyroid status influences blood pressure in subjects with SCH and implicate thyroid status in the regulation of blood pressure in euthyroid subjects. Although controversy remains regarding the relationship between SCH and hypertension [15–18], findings of this study strongly support a relationship between SCH and elevated blood pressure in school-aged subjects.

Table 3 Comparison of blood pressure *Z* score among different TSH level groups

	TSH	*N*	SBP	SBP-Z	*F*	*P*	DBP	DBP-Z	*F*	*P*
Male	≤2.50	223	107.95 ± 13.42	0.0873 ± 1.1208	6.199	0.002*	69.00 ± 9.90	0.5470 ± 0.7897	5.293	0.005*
	2.51–4.20	241	109.00 ± 13.56	0.3195 ± 1.1608			69.76 ± 9.65	0.6462 ± 0.8032		
	>4.20	77	111.10 ± 9.97	0.6109 ± 0.8955			72.09 ± 8.72	0.8953 ± 0.7283		
Female	≤2.50	167	104.90 ± 11.14	−0.0510 ± 1.008	2.596	0.076	69.12 ± 8.93	0.5985 ± 0.7595	0.855	0.426
	2.51–4.20	125	105.82 ± 11.89	0.1230 ± 1.0454			68.74 ± 9.20	0.6086 ± 0.7698		
	>4.20	47	107.94 ± 9.18	0.3362 ± 0.8832			70.45 ± 6.84	0.7719 ± 0.6276		

DBP diastolic blood pressure, *DBP-Z* diastolic blood pressure *Z* score, *SBP* systolic blood pressure, *SBP-Z* systolic blood pressure *Z* score, *TSH* thyroid-stimulating hormone. * $P < 0.05$: after adjustment for BMI

Table 4 Comparison of thyroid function between different blood pressure levels

	SBP-*Z*				DBP-*Z*			
	$\geq P_{90}$ (146)	$<P_{90}$ (734)	*t*	*P*	$\geq P_{90}$ (190)	$<P_{90}$ (690)	*t*	*P*
FT_3	6.45 ± 0.79	6.20 ± 0.77	3.503	<0.001*	6.43 ± 0.85	6.19 ± 0.75	3.649	<0.001*
FT_4	16.76 ± 2.26	16.74 ± 1.97	0.077	0.939	16.54 ± 2.24	16.80 ± 1.95	1.452	0.148
TSH	3.15 ± 1.38	2.87 ± 1.38	2.230	0.026*	3.18 ± 1.47	2.84 ± 1.35	2.824	0.005*

DBP-Z diastolic blood pressure *Z* score, FT_3 free 3,5,3′-triiodothyronine, FT_4 free thyroxin, P_{90} 90th percentile of blood pressure, *SBP-Z* systolic blood pressure *Z* score, *TSH* thyroid-stimulating hormone. * $P < 0.05$

In this study, Both SBP-Z and DBP-Z were found to increase linearly with increasing TSH and increasing FT_3, while DBP-Z decrease with increasing FT_4. The positive associations of TSH and FT_3 with BP-Z were observed even after adjusting for BMI and were more significant in males. Although in females these associations were not obvious, we still found the positive correlations between TSH and SBP-Z as well as FT_3 and DBP-Z. Change of thyroid function may increase the risk of blood pressure elevation. Although the mechanisms underpinning these associations have not been identified, several explanations for these associations can be advanced. Gumieniak et al. [14] proposed that an insufficiency of thyroid hormones may alter the sensitivity of blood pressure controls to salt concentration, a factor considered physiologically relevant to the onset of hypertension. In fact, FT_3 induces changes in cardiac function via direct and indirect actions and promotes dilation of vascular smooth muscle cells by multiple mechanisms [19] while potentiating norepinephrine-induced constriction of resistance vessels [20]. By contrast, T_4 directly promotes relaxation of skeletal muscle resistance arterioles [21]. Lastly, genetic variation may explain the observed relationship between increased serum TSH concentrations and elevated blood pressures. Accordingly, in families with a high prevalence of hypertension, concentrations of TSH tend to be in the upper part of the reference range [22]. It may also be relevant that the gene encoding the thyrotropin-releasing hormone receptor (THRH) has been found to be associated with essential hypertension [23]. Recent findings of experiments with animals also reveal that TRH overexpression induces hypertension and that silencing of the TRHR gene results in decreased arterial blood pressure [23–25]. The findings of Asvold et al. [8] agree with those of the present study regarding the increasing prevalence of hypertension with increasing TSH concentrations within the reference range; this association is stronger in males than in females.

The association of thyroid function with blood pressure in children should have been paid close attention to as considerable evidence has been provided to support the premise that hypertension has its antecedents during childhood. Blood pressure in adults often correlates with that in childhood. Hypertension in children also constitutes a significant risk factor for the development of cardiovascular disease in adulthood [26] and a high TSH level ever within normal range is associated with the metabolic syndrome [27]. Early intervention in children and adolescents with risk factors should reduce the overall incidence of hypertension and metabolic syndrome in adults.

In conclusion, findings of this study with school-aged children and adolescents confirm that both SBP-Z and DBP-Z are higher in subjects with SCH than in euthyroid subjects. In addition, BP-Z was found to increase linearly with increasing TSH and FT_3, especially in males. Both

SBP-Z and DBP-Z increased linearly with TSH concentration in males. However, these findings must be interpreted in the context of study design, and these associations are relatively weak. The analyses were exploratory, and findings should be confirmed for subjects in different districts and for different populations of subjects. In addition, the observed indicators in our study were relationships between thyroid function and clinic blood pressure, others studies had shown both overt and subclinical hypothyroidism were not only associated with the clinic blood pressure but also related to ambulatory blood pressure [28–30]. To the best of our knowledge, few studies have been performed to examine the relationship of blood pressure to thyroid function in children and adolescents. These subjects deserve further study in order to ascertain whether they should be screened routinely for the presence of hypertension and whether treatment of those with SCH is indicated.

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