Thyroid Function is Associated with Carotid Intima Media Thickness in Euthyroid Subjects

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Abstract

To investigate the relationship between thyroid function and carotid intima-media thickness in a relatively large general population with euthyroid status we initially enrolled 1,772 Japanese adults (421 men and 1,351 women) who participated in a medical screening program for the general population over 40 years old. To evaluate only euthyroid subjects without vascular diseases and/or its major risk factors, 1,129 were excluded and 643 participants (175 men and 468 women) were included for further analysis. Simple and multivariate linear regression analyses were performed to evaluate free thyroxine and thyroid-stimulating hormone levels and other existing parameters, including carotid intima-media thickness. By multivariate linear regression analysis adjusted for age and sex, free thyroxine was significantly correlated with triglycerides (β=0.07, p=0.015), carotid intima-media thickness (β=-0.091, p=0.049), and thyroid-stimulating hormone (β =-0.091, p=0.003). Thyroid-stimulating hormone was significantly correlated with HDL-C (β=-0.001, p=0.015), HbA1c (β=0.038, p=0.045), carotid intima-media thickness (β=0.27, p=0.001), and free thyroxine (β=-0.15, p=0.003). When adjusted for confounding factors, free thyroxine was significantly correlated only with carotid intima-media thickness (β=-0.13, p=0.043)

and thyroid-stimulating hormone was significantly correlated with HDL-C (β=-0.001, p<0.001), HbA_{1c} (β=0.04, p=0.021), and carotid intima-media thickness (β=0.29, p=0.001). We have demonstrated that carotid intima-media thickness is independently associated with thyroid function within the normal reference range, which suggests an increased cardiovascular risk in subjects with low normal thyroid function.

Keywords: cardiovascular risk; carotid intima-media thickness; euthyroid; free thyroxine (fT4); thyroid-stimulating hormone (TSH)

1. Introduction

It is well known that both hypothyroidism and hyperthyroidism have been associated with cardiovascular disease (CVD), and overt hypothyroidism is associated with dyslipidemia [1] and atherosclerosis [2,3]. Although an adverse influence of subclinical hypothyroidism on cardiac outcome is still controversial, mildly impaired thyroid function has been shown to be associated with dyslipidemia [1,4,5], enhanced low-grade inflammation [5], and endothelial function [6].

Recent technological advances in medical equipment have allowed non-invasive assessment of atherosclerosis in its early stages [7,8]. High-resolution B-mode ultrasonography provides a non-invasive method for quantifying arterial wall thickening and it has been shown that carotid intima-media thickness (CIMT) is a strong predictor of CVD [7]. Apart from the effects of age and sex, CIMT is determined by conventional risk factors such as blood pressure and dyslipidemia [8,9].

Several studies reported the effects of abnormalities in thyroid function on CIMT. Nagasaki *et al.* reported that CIMT is larger in subjects with overt hypothyroidism compared to euthyroid subjects and decreases after levothyroxine replacement [10,11]. Furthermore, Dullaart *et al.* performed a cross-sectional study of nonsmoking,

predominantly middle-aged, euthyroid subjects and showed that CIMT was found to be independently related to free thyroxine (fT4), but not to thyroid-stimulating hormone (TSH) and thyroid antibodies, which raises the possibility that even within the euthyroid ranges, low normal thyroid function may adversely affect cardiovascular risk [12]. Although the sample size of their study was relatively small (n=78), the extension of the study to such subjects is important, because most subjects at risk for CVD are euthyroid.

In the present study, we aimed to investigate the relationship between thyroid function and CIMT in a relatively large general population with euthyroid status.

2. Methods

2.1. Study population

Prior to this study, ethical approval was obtained from the special committee of Nagasaki University (project registration number 0501120073). The study was conducted during a medical screening program for the general population over 40 years old, living in Goto City (total population of 44,132 in 2008), Nagasaki Prefecture, Japan. Details of this screening program in Goto City have been described in elsewhere [13,14]. The data was collected by the staff of Nagasaki University, in cooperation with the staff of Goto City. After obtaining informed consent, we enrolled 1,772 Japanese adults (421 men and 1,351 women). To evaluate only euthyroid subjects without vascular diseases and/or its major risk factors, the following participants were excluded: 20 participants with current medication for thyroid disorders, 94 participants with current medication for diabetes mellitus, 161 participants with current smoking, 80 participants with current medication for cardiovascular diseases and/or past histories of ischemic heart disease, 23 participants with past histories of cerebral infarction or hemorrhage, 146 participants with current medication for dyslipidemia, 16 participants who showed severe

hypertriglycemia (>4.0 g/liter), 272 participants with current medication for hypertension, 117 participants who did not undergo measurement of CIMT, and 127 participants with insufficient volume of serum for the measurement of fT_4 and TSH. Additionally, 13 participants who showed overt or subclinical hyperthyroidism and 60 participants who showed overt or subclinical hypothyroidism were excluded. Finally, 643 participants (175 men and 468 women) were included for further analysis (Fig. 1).

2.2. Data collection and laboratory measurements

Height and weight were measured and body mass index (BMI; kilograms per meter squared) was calculated as an index of obesity. Waist circumference (WC) was measured horizontally at the umbilicus with a tape measure after normal expiration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at rest.

Blood samples were collected from each participant after fasting overnight. Serum was separated and stored at -20°C until assay. Serum concentration of TSH was assessed using a microparticle enzyme immunoassay (AxSYM; Abbott Laboratories, Abbott Park, IL). FT4 concentration was also measured using a microparticle enzyme immunoassay (Architect; Abbott Laboratories, Abbott Park, IL). Euthyroidism was

defined as TSH (reference range, 0.4-4.0 mIU/liter) and fT4 (reference range, 0.8-1.9 ng/liter) within the normal reference ranges while not taking any thyroid medication.

Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured by standard laboratory procedures, and low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation. Hemoglobin A_{1c} (HbA_{1c}) was measured by standard laboratory procedures. Highly sensitive C-reactive protein (hs-CRP) was measured by N-Latex CRP II assay (Dade Behring, Tokyo, Japan).

2.3. Measurement of CIMT

Measurement of CIMT by ultrasonography of the left and right carotid arteries was performed by two medical doctors (N.T. and M.N.), using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA). A detailed protocol has been described elsewhere [15]. Averages of left and right CIMTs were calculated and used in the analysis. Intra-observer variation of CIMT (N.T., n=32) was 0.91 ($p<0.01$) and inter-observer variation (N.T. *vs.* M.N., n=41) was 0.78 ($p<0.01$).

2.4. Statistical analysis

Results are expressed as mean ± standard deviation or median (25^{th}-75^{th} quartiles). Differences of laboratory values between women and men were evaluated using the *t*-test or Mann-Whitney's U test. Multivariate linear regression analysis was performed to evaluate fT4, TSH, and other existing parameters adjusted for age, and age and sex. Also, to confirm whether the relationship between CIMT and thyroid function is independent from circulation dynamics, lipid metabolism, and glucose metabolism, multivariate linear regression analysis was also performed adjusted for age, sex, and other confounding factors (SBP, HDL-C, and HbA_{1c}) in all subjects. Because TG, hs-CRP, and TSH levels were distributed in a skewed manner, logarithmic transformation was performed for the simple linear regression analysis and multivariate linear regression analysis. Probability values less than 0.05 were considered indicative of statistical significance. All statistical analyses were performed using SPSS v11.0 software (SPSS Japan, Tokyo, Japan).

3. Results

Characteristics of the study participants are shown in Table 1. The average age of the men was significantly younger than that of women (64.6 ± 10.5 years for women *vs.* 61.0 ± 11.9 years for men, $p<0.01$). Besides age, WC, DBP, HDL-C, and CIMT were significantly different between men and women.

By simple linear regression analysis, fT4 was correlated with TG in women ($r=0.11$, $p<0.023$) (Table 2). In addition, TSH was significantly correlated with HDL-C ($r=-0.10$, $p=0.035$), CIMT ($r=0.093$, $p=0.046$), and fT4 ($r=-0.12$, $p=0.009$) in women. In men, no factor was significantly correlated with fT4 and log TSH. In all participants, fT4 was significantly correlated with TG ($r=0.099$, $p=0.015$) and log TSH ($r=-0.12$, $p=0.002$), and log TSH was significantly correlated with HDL-C ($r=-0.08$, $p=0.048$) and fT4 ($r=-0.12$, $p=0.002$).

By multivariate linear regression analysis adjusted for age, fT4 and log TSH were relatively and significantly correlated with CIMT in women ($\beta=-0.13$, $p=0.08$ and $\beta=0.29$, $p=0.004$, respectively), whereas they were relatively, but not significantly correlated in men ($\beta=-0.12$, $p=0.09$ and $\beta=0.24$, $p=0.07$, respectively). Also, by multivariate linear regression analysis adjusted for age and sex, fT4 was significantly

correlated with log TG (β=-0.07, p=0.015), CIMT (β=-0.091, p=0.049), and log TSH (β =-0.091, p=0.003) and log TSH was significantly correlated with HDL-C (β=-0.001, p=0.015), HbA_{1c} (β=0.038, p=0.045), CIMT (β=0.27, p=0.001), and fT4 (β=-0.15, p=0.003; Table 3). Furthermore, by multivariate linear regression analysis adjusted for age, sex, SBP, HDL-C, and HbA_{1c}, fT4 was significantly correlated only with CIMT in all subjects (β=-0.13, p=0.043). In contrast, log TSH was significantly correlated with age (β=-0.002, p=0.047), sex (β=0.064, p=0.001), HDL-C (β=-0.001, p<0.001), HbA_{1c} (β=0.04, p=0.021), and CIMT (β=0.29, p=0.001).

Discussion

In this population-based study, we found that CIMT is negatively correlated with fT4 and positively correlated with log TSH after adjustment for age and sex. Furthermore, these relationships remained present after further adjustment for SBP, HDL-C, and HbA1c, which suggested that thyroid function may be associated with CIMT, independent from circulation dynamics, lipid metabolism, and glucose metabolism. Thus, in view of the contention that CIMT predicts CVD [16,17], our current results support the possibility that low normal thyroid function could contribute to an increased cardiovascular risk. Recently in the Hunt Study, Åsvold *et al.* prospectively studied the association between TSH levels and fatal chronic heart disease in 17,311 women and 8,002 men without known thyroid or cardiovascular disease or diabetes mellitus at baseline, and showed that TSH levels within the normal range were positively and linearly associated with chronic heart disease mortality in women [18]. This suggests that relatively low, but clinically normal thyroid function may increase the risk of CVD.

However, controversy still remains regarding the risk of CVD associated with subclinical thyroid abnormalities [19]. Takashima *et al.* categorized 3,607 study participants into five groups: normal, hyperthyroidism, hypothyroidism, subclinical

hypothyroidism, and subclinical hyperthyroidism. Their results showed that there was no significant association between thyroid function and CIMT [20]. Additionally, Jorde *et al.* categorized 1,850 subjects who were nonusers of thyroxine into three groups: a low serum TSH group (<0.48 mIU/l), a normal group (0.48-4.16 mIU/l), and a high serum TSH group (>4.16 mIU/l). From their results, they observed no significant differences between the three groups even after the adjustment for confounding factors [21]. However, in these studies, the numbers of subjects with subclinical hyperthyroidism, overt hyperthyroidism and hypothyroidism were much lower than the number of subjects in the normal thyroid group. Additionally, these researchers did not evaluate the association between thyroid function and CIMT in the euthyroid group and did not clearly state exclusion criteria, which might affect the results of the studies. Therefore, we introduced strict exclusion criteria into our current study and finally included 643 of 1,772 participants for statistical analysis.

Recently, Roos *et al.* screened 1,122 adults from the general population and demonstrated an association between fT4 levels within the normal reference range and lipids [22]. In addition, they showed that low normal fT4 levels were significantly associated with increased insulin resistance. Also, Dullaart *et al.* performed a cross-sectional study in 78 nonsmoking, predominantly middle-aged, euthyroid subjects

and showed that CIMT was found to be independently related to fT4, but not to TSH and thyroid antibodies [13]. In the present study, we showed a significant negative correlation between fT4 and CIMT, after adjustment for age and sex. In addition, we showed a strong positive correlation between TSH and CIMT, which is not consistent with the results of Dullaart *et al*. The discrepancy between the two studies might be simply caused by a difference in sample size. In addition, we performed logarithmic transformation for TSH before statistical analysis, because its levels were distributed in a skewed manner; this was not performed by Dullaart *et al*. Further studies will be needed to clarify the contribution of TSH itself to the cardiovascular risk in euthyroid subjects.

Interestingly, our study showed that TSH, as well as fT4, was significantly correlated with CIMT after adjustment for age, sex, SBP, HDL-C, and HbA_{1c}, suggesting that mechanisms other than these intermediate cardiovascular outcome variables and systemic hemodynamic factors *per se* may also be involved in the relationship between thyroid hormone status and CIMT in euthyroid subjects. Although it is difficult to identify the mechanism, variations in thyroid hormone status could affect lipoprotein quality and oxidation [13,23], vascular remodeling via an effect on local angiotension signaling [24,25], and endothelial function [26].

A limitation of this study is that it has a cross-sectional design, so a cause-and-effect relationship cannot be discerned. A future prospective design will be needed to determine whether the changes in CIMT that we found actually affect the future incidence of CVD. In addition, we could not measure fT3 and anti-thyroid antibodies in this study. We showed higher TSH in women than in men, which suggests the higher prevalence of early autoimmune thyroid disease in women. By multivariate linear regression analysis adjusted for age, fT4 and TSH were relatively and significantly correlated with CIMT in women, whereas they were not significantly correlated in men. This might be simply due to the insufficient number of men participating, or that a different mechanism may be associated with thyroid function and CIMT between euthyroid men and women. Also, we should clarify whether relatively higher thyroid function acts in a protective manner for future cardiovascular events. Furthermore, we showed a positive relationship between fT4 and log TG, which seems to be contrary to the other results. Further evaluation is needed to clarify the relationship between thyroid function and cardiovascular risk in euthyroid subjects.

In conclusion, we demonstrated that thyroid function and CIMT are associated even in subjects classified as being euthyroid, which suggests an increased cardiovascular risk in subjects with low normal thyroid function. Further prospective studies must be

1 performed to establish a guideline for the treatment of thyroid abnormalities at an earlier

2 stage.

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Figure Legend

Figure 1: Enrollment of the study participants

References

1. Duntas LH. Thyroid disease and lipids. Thyroid 2002;12:287-93.
2. Vanhaelst L, Neve P, Bastenie PA. Coronary-artery disease in myxoedema. Lancet 1967; 2:1257-8.
3. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003;88:2438-44.
4. Danese MD, Ladenson PW, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 2000;85:2993-3001.
5. Kventy J, Heldgaard PE, Bladbjerg EM, Gram J. Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in male below 50 years. Clin Endcrinol 2004;61:232-8.
6. Cikim AS, Oflaz H, Ozbey N, Cikim K, Ummnan S, Meric M, Sencer E, Molvalilar S. Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. Thyroid 2004;14:605-9.
7. Bots ML, Grobbee DE. Intima media thickness as a surrogate marker for generalised athrosclerosis. Cardiovasc Drugs Ther 2002;16:341-51.

8. Handa N, Matsumoto M, Maeda H, Hougaku H, Ogawa S, Fukunaga R, Yoneda S, Kimura K, Kamada T. Ultrasonic evaluation of early carotid atherosclerosis. Stroke 1990;21:1567-72.
9. Takamura N, Abe Y, Nakazato M, Maeda T, Wada M, Nakashima K, Kusano Y, Aoyagi K. Determinants of plasma homocysteine levels and carotid intima-media thickness in Japanese. Asia Pac J Clin Nutr 2007;16:698-703.
10. Nagasaki T, Inaba M, Henmi Y, Kumeda Y, Ueda M, Tahara H, Sugiguchi S, Fujiwara S, Emoto M, Ishimura E, Onoda N, Ishikawa T, Nishizawa Y. Decrease in carotid-intima media thickness in hypothyroid patients after normalization of thyroid function. Clin Endocrinol 2003;59:607-12.
11. Nagasaki T, Inaba M, Henmi Y, Kumeda Y, Ueda M, Tahara H, Ishimura E, Onoda N, Ishikawa T, Nishizawa Y. Change in von Willebrand factor and carotid intima-media thickness in hypothyroid patients with normal thyroid function after levothyroxine replacement therapy. Eur J Endocrinol 2004;150:125-31.
12. Dullaart RP, de Vries R, Roozendaal C, Kobold AC, Sluiter WJ. Carotid artery intima media thickness is inversely related to serum free thyroxine in euthyroid subjects. Clin Endocrinol (Oxf) 2007;67:668-73.
13. Ishibashi K, Takamura N, Aoyagi K, Yamasaki H, Abiru N, Nakazato M, Kamihira

S, Maeda T. Multimers and adiponectin gene 276G>T polymorphism in the Japanese population residing in rural areas. Clin Chem Lab Med 2007;45: 1457-63.

14. Kadota K, Takamura N, Aoyagi K, Yamasaki H, Usa T, Nakazato M, Maeda T, Wada M, Nakashima K, Abe K, Takeshima F, Ozono Y. Availability of cardio-ankle vascular index (CAVI) as a screening tool for atherosclerosis. Circ J 2008;72:304-8.
15. Hara T, Takamura N, Akashi S, Nakazato M, Maeda T, Wada M, Nakashima K, Abe Y, Kusano Y, Aoyagi K. Evaluation of clinical markers of atherosclerosis in young and elderly Japanese adults. Clin Chem Lab Med 2006;44:824-9.
16. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14-22.
17. de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, Kastelein JJ. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation 2004;109:III33-8.
18. Åsvlod B, Bjøro T, Nilsen TI, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease. Arch Intern Med 2008;168:855-60.
19. Duntas LH and Wartofsky L. Cardiovascular risk and subclinical hypothyroidism:

focus on lipids and new emerging risk factors. Thyroid 2007;17:1-10.

20. Takashima N, Niwa Y, Mannnami T, Tomoike H, Iwai N. Characterization of subclinical thyroid dysfunction from cardiovascular and metabolic viewpoints –The Suita Study. Circ J 2007;71:191-5.

21. Jorde R, Joakimsen O, Stensland E, Mathiesen EB. Lack of significant association between intima-media thickness in the carotid artery and serum TSH level. The Tromsø Study. Thyroid 2007;18:21-5.

22. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 2007;92:491-6.

23. Costantini F, Pierdomenico SD, De Cesare D, De Remigis P, Bucciarelli T, Bittolo-Bon G, Cazzolato G, Nubile G, Guagnano MT, Sensi S, Cuccurullo F, Mezzetti A. Effect of thyroid function on LDL oxidation. Arterioscler Thromb Vasc Biol 1998;18:732-7.

24. Fukuyama K, Ichiki T, Imayama I, Ohtsubo H, Ono H, Hashiguchi Y, Takeshita A, Sunagawa K. Thyroid hormone inhibits vascular remodeling through suppression of cAMP response element binding protein activity. Arterioscler Thromb Vasc Biol 2006;26:2049-55.

25. Fukuyama K, Ichiki T, Takeda K, Tokunou T, Iino N, Masuda S, Ishibashi M, Egashira K, Shimokawa H, Hirano K, Kanaide H, Takeshita A. Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertension 2003;41:598-603.

26. Xiang GD, He YS, Zhao LS, Hou J, Yue L, Xiang HJ. Impairment of endothelium-dependent arterial dilation in Hashimoto's thyroiditis patients with euthyroidism. Clin Endocrinol (Oxf) 2006;64:698-702.

Table 1. Characteristics of the Study Participants

	Men (n=175)	Women (n=468)	All (n=643)
Age (years)	64.6 ±10.5	61.0±11.9*	62.0±11.6
BMI (kg/m^2)	23.3±3.2	22.5±3.2	22.7±3.2
WC (cm)	83.7±8.6	78.7±3.2*	80.1±9.4
SBP (mmHg)	138.6±21.6	135.6±20.0	136.4±20.5
DBP (mmHg)	84.9±10.8	80.6±10.4*	81.8±10.6
TC (g/l)	2.0±0.3	2.1±0.3	2.1±0.3
TG (g/l)	1.0 (0.75-1.39)	1.0 (0.71-1.52)	1.0 (0.73-1.46)
HDL-C (g/l)	0.57±0.13	0.62±0.15*	0.60±0.15
LDL-C (g/l)	1.2±0.3	1.3±0.3*	1.2±0.3
HbA_{1c} (%)	5.2±0.5	5.3±0.3	5.3±0.5

hs-CRP (mg/ l)	0.34 (0.20-0.72)	0.35 (0.17-0.69)	0.34 (0.18-0.70)
CIMT (mm)	0.71±0.13	0.67±0.12*	0.68±0.12
fT4 (ng/liter)	11.9±1.7	11.8±1.6	11.8±1.6
TSH (mIU/l)	1.4 (1.0-2.0)	1.8 (1.2-2.3)*	1.7 (1.1-2.3)

Values are mean ± standard deviation or median (25^{th} – 75^{th} quartile)

*$p<0.01$ vs. men.

Abbreviations: body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin A_{1c} (HbA_{1c}), highly sensitive C-reactive protein (hs-CRP), carotid intima-media thickness (CIMT), free thyroxine (fT4) and thyroid-stimulating hormone (TSH)

Table 2. Simple linear regression analysis of fT4, TSH, and other variables.

	fT4			log TSH		
	Men	Women	All	Men	Women	All
Age	0.035	0.004	0.015	0.042	-0.035	-0.032
BMI	0.024	0.039	0.037	0.014	0.001	-0.010
WC	-0.022	0.052	0.037	0.003	-0.034	-0.052
SBP	-0.037	0.02	0.005	0.15	-0.046	0.003
DBP	-0.054	0.01	-0.004	0.15	0.016	0.032
TC	0.046	0.065	0.053	0.12	0.008	0.061
log TG	0.072	0.11*	0.099*	0.11	0.032	0.054
HDL-C	-0.065	-0.041	-0.050	-0.08	-0.10*	-0.08*
LDL-C	0.029	0.093	0.071	0.14	0.030	0.076

HbA_{1c}	0.009	-0.043	-0.03	-0.06	-0.091	-0.078
log hs-CRP	0.02	0.039	0.034	0.064	0.072	0.067
CIMT	-0.051	-0.063	-0.055	0.13	0.093*	0.083*
fT4	-	-	-	-0.11	-0.12**	-0.12**
log TSH	-0.11	-0.12**	-0.12**	-	-	-

Values presented are correlation coefficients.

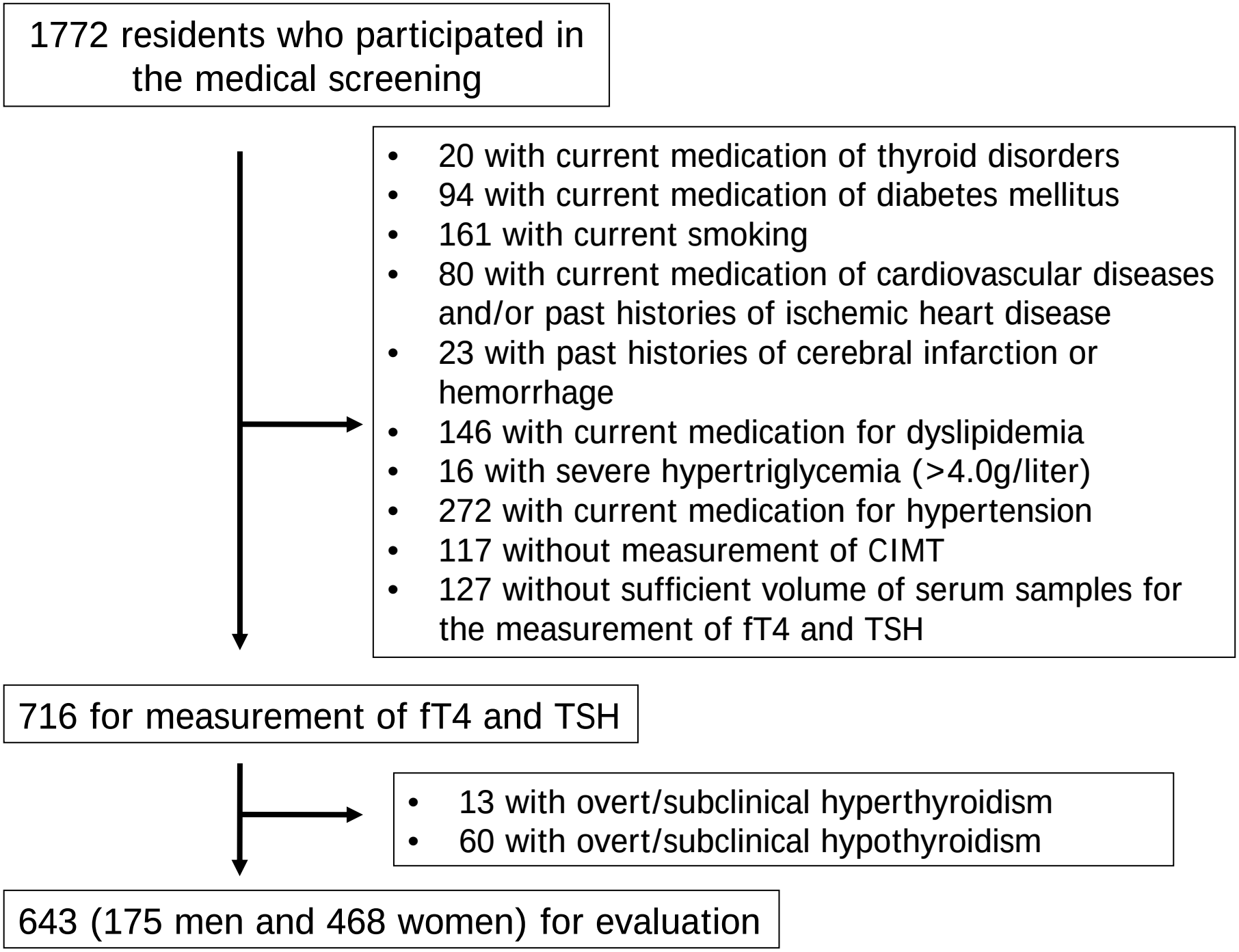
*p<0.05, **p<0.01

Table 3. Multivariate linear regression analysis of fT4 and TSH adjusted for age and sex

	fT4			log TSH		
Variables	β	95% CI	p	β	95% CI	p
BMI	0.002	-0.002, 0.006	0.38	0	-0.005, 0.005	0.92
WC	0.001	0, 0.002	0.35	0	-0.002, 0.001	0.59
SBP	0	0, 0.001	0.97	0	0, 0.001	0.97
DBP	0	-0.001, 0.001	0.80	0	-0.001, 0.001	0.80
TC	0	0, 0.001	0.14	0	0, 0.001	0.32
log TG	-0.07	-0.014, -0.13	0.015	0.05	-0.024, 0.12	0.18
HDL-C	0	-0.001, 0	0.27	-0.001	-0.003, 0	0.015
LDL-C	0	0, 0.001	0.064	0	0, 0.001	0.14
HbA_{1c}	-0.007	-0.037, 0.007	0.62	0.038	0, 0.076	0.045

log hs-CRP	0.010	-0.015, 0.035	0.44	0.12	-0.007, 0.24	0.064
CIMT	-0.13	-0.25, 0	0.049	0.27	0.11, 0.43	0.001
fT4	-	-	-	-0.15	-0.25, -0.052	0.003
log TSH	-0.091	-0.15, -0.03	0.003	-	-	-

β: standardized regression coefficient


1772 residents who participated in the medical screening
• 20 with current medication of thyroid disorders
• 94 with current medication of diabetes mellitus
• 161 with current smoking
• 80 with current medication of cardiovascular diseases and/or past histories of ischemic heart disease
• 23 with past histories of cerebral infarction or hemorrhage
• 146 with current medication for dyslipidemia
• 16 with severe hypertriglycemia (>4.0g/liter)
• 272 with current medication for hypertension
• 117 without measurement of CIMT
• 127 without sufficient volume of serum samples for the measurement of fT4 and TSH
716 for measurement of fT4 and TSH
• 13 with overt/subclinical hyperthyroidism
• 60 with overt/subclinical hypothyroidism
643 (175 men and 468 women) for evaluation