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DOI:10.4158/EP-2018-0061

Original Article EP-2018-0061

WAIST CIRCUMFERENCE AND SUBCLINICAL THYROID DYSFUNCTION IN A LARGE COHORT OF CHINESE MEN AND WOMEN

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Running title: Subclinical thyroid dysfunction and WC, Endocr Pract. 2018;24(No. 8)

Submitted for publication: February 4, 2018

Accepted for publication: May 27, 2018

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DOI:10.4158/EP-2018-0061
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Published as a Rapid Electronic Article in Press at: http://www.endocrinepractice.org on date?.

DOI:10.4158/EP-2018-0061

DOI:10.4158/EP-2018-0061

ABSTRACT

Objective: The association between subclinical thyroid dysfunction and waist circumference (WC) is still controversial, especially from the perspective of sex differences. We aimed to explore the impact of sex on this relationship in a large Chinese cohort.

Methods: This cross-sectional study recruited 13,505 healthy participants (8,346 males, 5,159 females) who were enrolled in a health check program. Clinical data were collected. The association between subclinical thyroid dysfunction and WC of both sexes was analyzed separately after dividing WC into quartiles. Odds ratios (ORs) were calculated by binary logistic regression models, and linear regression analysis was also performed.

Results: The prevalence rates of subclinical hyper- and hypothyroidism were significantly lower in males. Binary logistic regression models showed that WC in females with subclinical hypothyroidism had a detrimental effect with an OR of 1.011, but the effect disappeared when we included other covariates. The other ORs indicated no significant effects. The weak negative relationship between WC and thyrotropin was also indicated by linear regression analyses with very low R^2 values.

Conclusion: The current research did not show WC as a risk factor for subclinical thyroid dysfunction in either sex. Regional and ancestral origin differences may account for the variations with other studies. **(Endocr Pract. 2018;24:000-000)**

Keywords: Thyroid dysfunction, obesity, hypothyroidism.

DOI:10.4158/EP-2018-0061

Abbreviations:

ALT = alanine aminotransferase; **BMI** = body mass index; **FT3** = free triiodothyronine; **FT4** = free thyroxine; **TG** = triglycerides; **TSH** = thyroid-stimulating hormone; **UA** = uric acid; **WC** = waist circumference

INTRODUCTION

Subclinical thyroid dysfunction has a high prevalence among populations all around the world (1). According to Cooper and his colleagues, the prevalence of subclinical hypothyroidism varies from 5.0% to 13.2%, and the overall prevalence of subclinical hyperthyroidism in nodular goitrous disease is estimated at about 20% (2). There is evidence that a proportion of patients with subclinical hypothyroidism develop clinical hypothyroidism after several years (3).

Obesity is also a worldwide public problem; more than 1 billion adults worldwide are overweight, and about 400 million are obese (4). The prevalence of obesity in Chinese children is even more severe and continues to increase (5). Obesity is considered a risk factor for many diseases including diabetes, insulin resistance, hepatic steatosis, polycystic ovarian disease, hypertension, cardiovascular abnormalities, ischemic stroke, and several types of cancer (6-11). Epidemiologic surveys usually take body mass index (BMI) (11) as an indicator for whole body obesity, and waist circumference (WC) (12,13) for abdominal fat accumulation or central obesity (14).

Several studies have demonstrated that serum thyroid-stimulating hormone (TSH) is

DOI:10.4158/EP-2018-0061

relatively high in obese patients (9,10,12,13,15-20). The underlying mechanism between TSH and WC is not yet fully understood, but there are some postulations (7,12,16,21-26). Yet several different viewpoints exist. There is also research demonstrating that no relationship exists between TSH and WC (16,23,27,28). Park et al. proposed an opposite view: that increased TSH level is negatively associated with WC (24). These inconsistencies underscore the need for further studies. More importantly, very little research has explored the impact of sex on the relationship. The objectives of our cross-sectional study were to clarify the relationship between subclinical thyroid dysfunction and WC and to determine if there is an influence of sex on this relationship in a representative sample of the Tianjin municipality population.

METHODS

Design

This cross-sectional study was carried out at Tianjin Medical University General Hospital in China under collaboration from the departments of Health Management, Endocrinology & Metabolism, and Nuclear Medicine. From September 2011 to April 2014, a total of 13,855 subjects participated in this mainly community-based health check program as conducted previously by our group (29-32). All participants were asked to complete a questionnaire about medical history, lifestyle, alcohol intake, and smoking. To avoid the influence of confounding factors, the exclusion criteria were a disease history of the thyroid, any diseases or taking any medicine that might affect thyroid function, a history of excessive smoking and drinking, and participants with abnormal thyroid hormones (Fig. 1). In our study, the reference ranges for

DOI:10.4158/EP-2018-0061

free triiodothyronine (FT3) and free thyroxine (FT4) were 3.5 to 6.5 pmol/L and 11.5 to 23.5 pmol/L, respectively. Participants overtly hypothyroid or hyperthyroid were excluded. Finally, 13,505 eligible subjects (8,346 male, 5,159 female) were included.

Ethics

The institutional review board and ethic committee of Tianjin Medical University General Hospital approved the ethical, methodologic, and protocol aspects of this investigation. We confirm that all methods in the current study were carried out in accordance with the relevant guidelines and regulations. Informed consent was obtained from all participants.

Measurements

Anthropometric measurements and fasting blood tests of the participants were performed during their visits to our institution. Height and weight were measured in centimeters and kilograms. BMI was calculated by dividing weight (kg) by height squared (m^2). WC was measured midway between the lowest rib and the iliac crest in centimeters (33). Fasting blood samples were obtained between 7 and 10 AM. TSH, FT3, and FT4 were analyzed on a fully automated ADVIA Centaur analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) based on a chemiluminescent reaction principle. Triglycerides (TG), alanine aminotransferase (ALT), and uric acid (UA) were determined enzymatically by an auto-analyzer (Hitachi Model 7600 analyzer, Hitachi, Tokyo, Japan).

Definitions

Central obesity: WC >90 cm for males and >80 cm for females (34). The recommended normal range for FT3 was 3.5 to 6.5 pmol/L and for FT4 11.5 to 23.5 pmol/L. According to the

DOI:10.4158/EP-2018-0061

TSH and thyroid hormone references, our thyroid function states were classified into 3 groups (34): group I: subclinical hyperthyroidism (TSH <0.3 μIU/mL with normal thyroid hormone ranges); group II: euthyroidism (TSH 0.3-5.0 μIU/mL with normal thyroid hormone ranges); and group III: subclinical hypothyroidism (TSH >5.0 μIU/mL with normal thyroid hormone ranges).

Statistical Analysis

TSH values were generally analyzed based on sex and WC groups. WC was divided into 5 groups: <70 cm, 70 cm<WC≤ 80 cm, 80 cm<WC≤90 cm, 90 cm<WC≤100 cm, and WC>100 cm. All data are expressed as mean ± SD. We performed χ^2 tests to compare intergroup prevalence differences of central obesity and subclinical thyroid dysfunction in both sexes. Two-way analysis of variance (ANOVA) tests and subsequent Bonferroni *t* tests were used to analyze differences and interactions of TSH between sexes and different WC groups. After stratifying data by WC, age, BMI, TG, ALT, and UA, odds ratio (ORs) for subclinical thyroid dysfunction with 95% confidence intervals (CIs) were calculated by binary logistic regression. Further, binary logistic regression calculated ORs for subclinical hypothyroidism with 95% CIs by considering WC as a categorical and continuous variable in different models. Linear regression analysis was finally utilized to generate regression equations for TSH by including WC as a continuous variable. The analyses were performed with Statistical Package for Social Sciences (SPSS version 17.0; SPSS Inc, Chicago, IL). Differences were considered significant at $P<.05$.

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RESULTS

Prevalence of Central Obesity/Subclinical Thyroid Dysfunction by Sex

Overall, 48.25% participants had central obesity. The prevalence of central obesity in males was significantly higher than in females (51.40% vs. 43.17%, $P<.01$). Altogether, 0.46% had subclinical hyperthyroidism and 5.46% had subclinical hypothyroidism. The prevalence of subclinical hyperthyroidism was significantly lower in males than in females (0.26% vs. 0.79%, $P<.01$) and the prevalence of subclinical hypothyroidism in males was significantly lower than in females (2.86% vs. 9.67%, $P<.01$; Table 1).

In all WC quartiles, females had a significantly higher subclinical hypothyroidism prevalence than males ($P<.01$). There was a higher prevalence of subclinical hypothyroidism as WC increased in females (χ^2 value = 8.443, $P<.05$; Fig. 2 *A*). In all WC quartiles, females had significantly higher subclinical hyperthyroidism prevalence rates than males ($P<.01$, Fig. 2 *B*).

TSH Values Based on Sex and WC Groups

Two-way ANOVA (Table 2) showed the F-statistics for sex and WC subgroups were 130.209 ($P<.01$) and 1.561 ($P = .182$), respectively, and the F-statistic for interaction of gender × WC subgroups was 0.401 ($P = .808$). Bonferroni *t*-tests revealed significant differences ($P<.01$) in TSH between 2 groups of 70 cm<WC≤80 cm, 80 cm<WC≤90 cm, and 90 cm<WC≤100 cm; between WC<70 cm and 90 cm<WC≤100 cm; and between 70 cm<WC≤80 cm and WC>100 cm.

Risks of Having Subclinical Thyroid Dysfunction by Sex

DOI:10.4158/EP-2018-0061

We used binary logistic regression to model the risks of having subclinical hypothyroidism (Table 3) and subclinical hyperthyroidism (Table 4). WC, TG, and ALT had detrimental effects on the risk of subclinical hypothyroidism in females. Age had detrimental effect of subclinical hypothyroidism in both sexes (Table 3). For subclinical hyperthyroidism, only age had a detrimental effect in females (Table 4).

Furthermore, we calculated risks for subclinical hypothyroidism by stratifying data with WC as categorical and continuous variables in different models. Model 1 analyzed WC as a categorical variable. WC quartile was designated as the categorical variable, with the lowest quartile as the reference. Model 1 included WC quartiles, age, BMI, TG, and ALT as covariates, Models 2 and 3 analyzed WC as a continuous variable. Model 2 included WC as a covariate, and model 3 included WC, age, BMI, TG, and ALT. In model 2, WC in females with subclinical hypothyroidism exerted a detrimental effect with an OR of 1.011 (Table 5). This effect disappeared in other models when we included additional covariates. The other ORs indicated no significance. Therefore, the current study did not identify WC as a risk factor for subclinical thyroid dysfunction in either sex.

Relationship Between WC and TSH With Linear Regression Analysis

Linear regression models were used to analyze the relationships between TSH and WC, age, BMI, TG, ALT, and UA. A weakly negative relationship between WC and TSH could be expressed in the following 2 equations. For males: TSH = 1.397 – 0.004 × WC + 0.011 × age** + 0.011 × BMI – 0.001 × TG + 0.002 × ALT + 0.001 × UA* (WC R^2 = 0.4%). For females: TSH = 1.915 – 0.009 × WC + 0.014 × age** + 0.020 × BMI – 0.104 × TG** + 0.005 × ALT*

DOI:10.4158/EP-2018-0061

+ 0.001 × UA (WC R^2 = 1.3%)(*P<.05, **P<.01). There was no significant colinearity in our models because all the tolerances were >0.1 and all the variance inflation factors were <5.

DISCUSSION

Subclinical thyroid dysfunction is defined as an abnormal thyrotropin level in combination with normal thyroid hormone levels in a usually asymptomatic patient (1). Many studies have reported that subclinical thyroid dysfunction is related to several diseases such as polycystic ovary syndrome, nonalcoholic steatohepatitis, nonalcoholic fatty liver, and cardiovascular diseases (8,21,22,25,26). We previously demonstrated that subclinical thyroid dysfunction is associated with serum lipids and serum UA (31,35). In the current study, we studied the association between subclinical thyroid dysfunction and WC, with what is now the largest sample size for this topic. In fact, we were the first to study this association from the perspective of sex impact.

The prevalence of subclinical hyperthyroidism in our samples was 0.46%, which was lower than other population-based studies (2,34). We thought there may be 2 possible explanations: First, different regions and races have variable prevalence rates. The National Health and Nutrition Examination Survey found different prevalences of subclinical hyperthyroidism among different races (4% in Black, 1.4% in White, and 3% in Mexican American) (2). Data from Korea indicated that the prevalence of subclinical hyperthyroidism is between 0.64% and 4.6% (36). Second, we hypothesized that sufficient iodine intake might explain the discrepancy because Tianjin is a coastal municipality (37). Cooper and Kim

DOI:10.4158/EP-2018-0061

proposed that the prevalence of subclinical hyperthyroidism in iodine-sufficient regions was far lower than in iodine-deficient regions (2,36). The current study demonstrated that the prevalence of subclinical hypothyroidism increased with greater WC in females. Similarly, a Norwegian longitudinal study with 15,020 euthyroid participants found that TSH increased in those who gained weight during follow-up and decreased among women who lost weight (13). There is a widely accepted hypothesis that thyroid dysfunction is a consequence of body weight changes rather than its cause (10,12). Our binary logistic regression models stratified WC to calculate the risk of subclinical thyroid dysfunction. Two-way ANOVA showed the difference between sexes was significant, yet the differences between WC groups and the interaction of sex × WC subgroups were not significant. The effect of sex is similar for all WC categories in Figure 2, again showing that the interaction term is reflective of the effects. In binary logistic regression models, WC displayed a detrimental effect on subclinical hypothyroidism in females only when the model had no other covariates. The detrimental effect disappeared after other covariates were included. Linear regression models also showed no significant differences between TSH and WC in either sex. Based on these results, we could not identify WC as an explicit risk for subclinical thyroid dysfunction.

Other groups have considered the association between subclinical hypothyroidism and WC. Several studies found an association between TSH level and WC (10,12,15-20), but they had limitations. Their sample sizes were small (16,17), with some only including <100 cases (15,18). Others only examined one sex (12), while some only studied obese people (12,16) or children (17, 20), which limited the universality of their results.

DOI:10.4158/EP-2018-0061

There are also studies that support our findings. A Korean study (28) investigated 918 euthyroid aged participants and did not find differences in WC between the euthyroid and subclinical hypothyroidism groups. Two Korean (23,38) and a Japanese (27) study also found no association between TSH level and WC. There could be several reasons for this. First, these studies are all from Asia, so ethnicity may explain the different results between our cohort and studies from Western countries. Regional and ancestral origin differences may influence the results because people from different countries have variable genetic backgrounds and iodine intakes. People from Asia also have different dietary habits from Western countries, which could influence the degree of obesity. Age could be another influential factor. People of different ages have different serum TSH levels, so there should be variable recommended normal ranges for different age groups. We suggest that different grouping basis for age groups should be used in further research. Third, although opinions on the association between TSH and BMI are unified, there is disagreement over TSH and WC. Shen et al showed that WC is more related to subcutaneous fat, while BMI is more related to preperitoneal fat (39). Therefore, TSH may have a closer relationship with total body fat than visceral fat.

There are some limitations in our study that should be addressed in further research on this subject. First, since our samples came from volunteers participating in a community-based health check program, selection bias may have influenced our results. Second, although we tried to reduce measurement error as much as possible, it still existed due to the manual-derived measurement, which would result in information bias. Third, our questionnaire did not include thyroid antibodies, thyroid ultrasonography, or specific thyroid symptoms because our

DOI:10.4158/EP-2018-0061

investigation was a general health check-up, not a thyroid-only questionnaire. This may have led to the loss of some essential information related to our results, which might explain the differences with other studies. Fourth, we did not measure some confounding factors (e.g., sex hormones) in our study due to budget shortages. These indices may account for the sex-specific dissimilarities and influence the association between thyroid dysfunction and obesity. Fifth, the power of our study was not strong enough to a recruit a multi-ethnic population to clarify the exact relationship. Sixth, the cross-sectional design naturally limited our research, and prospective longitudinal studies should be conducted in the future.

CONCLUSION

Our study did not identify WC as an explicit risk for subclinical thyroid dysfunction in men or women. Some previous studies from Asia reached similar conclusions. Regional and ancestral origin differences may account for these results.

ACKNOWLEDGMENT

This study was supported by the National Key Clinical Specialty Project (awarded to the Departments of Nuclear Medicine and Radiology).

This study was supported by Tianjin Medical University General Hospital New Century Excellent Talent Program; Young and Middle-aged Innovative Talent Training Program from Tianjin Education Committee; and Talent Fostering Program (the 131 Project) from Tianjin

DOI:10.4158/EP-2018-0061

Education Committee, Tianjin Human Resources and Social Security Bureau (awarded to Zhaowei Meng).

This study was supported by China National Natural Science Foundation grant 81571709, Key Project of Tianjin Science and Technology Committee Foundation grant 16JCZDJC34300 (awarded to Zhaowei Meng).

This study was also supported by Tianjin Science and Technology Committee Foundation grants 11ZCGYSY05700, 12ZCZDSY20400, and 13ZCZDSY20200 (awarded to Qing Zhang, Qiyu Jia and Kun Song).

This manuscript was reviewed and modified by Andrew Murphy, BSEE, JD, Attorney at Law (P.C. 3601 N. Classen Blvd. #106, Oklahoma City, OK 73118) and Kai Jin (University of California, Davis, College of Letters and Science, Department of Statistics).

DISCLOSURE

The authors have no multiplicity of interest to disclose.

DOI:10.4158/EP-2018-0061

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DOI:10.4158/EP-2018-0061

Table 1

Prevalence of Central Obesity/Subclinical Thyroid Dysfunction by Sex

	Total	Male	Female	Pearson χ^2
Central obesity	48.25% (6,517/13,505)	51.40% (4,290/8,346)	43.17% (2,227/5,159)	85.581[a]
Subclinical hyperthyroidism	0.46% (63/13,505)	0.26% (22/8,346)	0.79% (41/5,159)	19.370[a]
Subclinical hypothyroidism	5.46% (738/13,505)	2.86% (239/8,346)	9.67% (499/5,159)	286.108[a]

[a] $P<.01$

DOI:10.4158/EP-2018-0061

Table 2

TSH Values Based on Sex and WC Groups[a]

WC groups (cm)	Total	Male	Female
WC≤70	2.60 ± 1.77	2.13 ± 1.35	2.65 ± 1.80
70<WC≤80	2.61 ± 2.17	2.06 ± 1.29	2.83 ± 2.40
80<WC≤90	2.40 ± 2.59	2.15 ± 2.78	2.93 ± 2.06
90<WC≤100	2.20 ± 1.42	2.09 ± 1.25	2.91 ± 2.03
WC>100	2.31 ± 1.55	2.22 ± 1.46	3.06 ± 2.02

Abbreviations: TSH = thyroid stimulating hormone; WC = waist circumference.

[a] Assessed by 2-way analysis of variance.

DOI:10.4158/EP-2018-0061

Table 3

Risk of Subclinical Hypothyroidism With Different Variables

Sex	Male		Female	
Variable	**OR (CI)**	***P***	**OR (CI)**	***P***
WC	0.993 (0.979-1.008)	.353	1.011 (1.001-1.020)	.026[a]
Age	1.038 (1.027-1.050)	.000[b]	1.027 (1.019-1.035)	.000[b]
BMI	0.969 (0.930-1.009)	.124	1.023 (0.997-1.050)	.082
TG	0.949 (0.859-1.049)	.305	1.140 (1.063-1.223)	.000[b]
ALT	0.998 (0.992-1.005)	.626	1.010 (1.004-1.016)	.001[b]
UA	1.001 (1.000-1.003)	.078	1.001 (1.000-1.003)	.096

Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; OR = odds ratio; TG = triglycerides; UA = uric acid; WC = waist circumference.

[a] $P<.05$

[b] $P<.01$

DOI:10.4158/EP-2018-0061

Table 4

Risk of Subclinical Hyperthyroidism Based on Different Variables

Sex	Male		Female	
Variable	**OR (CI)**	***P***	**OR (CI)**	***P***
WC	0.989 (0.943-1.037)	.645	0.990 (0.958-1.023)	.548
Age	1.017 (0.978-1.057)	.405	1.028 (1.001-1.055)	.042[a]
BMI	0.923 (0.806-1.057)	.247	0.976 (0.891-1.069)	.599
TG	0.735 (0.453-1.193)	.213	1.144 (0.984-1.330)	.079
ALT	1.002 (0.993-1.012)	.623	1.009 (0.991-1.062)	.330
UA	0.998 (0.993-1.004)	.514	1.003 (0.998-1.008)	.202

Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; OR = odds ratio; TG = triglycerides; UA = uric acid; WC = waist circumference.

[a] $P<.05$

DOI:10.4158/EP-2018-0061

Table 5

Risk of Subclinical Hypothyroidism by WC Quartile

Sex		**Male**			**Female**	
Model 1[a]	**Parameter values**	**OR (CI)**	***P***	**Parameter values**	**OR (CI)**	***P***
WC quartile	(cm)					
Quartile 1	WC≤85	Reference		WC≤73	Reference	
Quartile 2	85<WC≤91	0.919 (0.629-1.345)	.665	73<WC≤79	1.039 (0.777-1.391)	.795
Quartile 3	91<WC≤97	0.687 (0.429-1.098)	.117	79<WC≤86	0.940 (0.682-1.296)	.706
Quartile 4	WC>97	0.919 (0.520-1.623)	.771	WC>86	1.012 (0.673-1.524)	.953
Model 2[a]		0.993 (0.979-1.008)	.353		1.011 (1.001-1.020)	.026[b]
Model 3[a]		0.987 (0.960-1.016)	.379		0.988 (0.970-1.006)	.203

Abbreviations: ALT = alanine aminotransferase; BMI = triglycerides; CI = confidence interval; OR = odds ratio; TG = triglycerides; WC = waist circumference.

[a] Logistic regression model 1 included WC quartiles, age, BMI, TG and ALT as covariates. Model 2 and 3 analyzed WC as a continuous variable. Model 2 included WC as a covariate and model 3 included WC, age, BMI, TG and ALT as covariates.

[b] $P<.05$

DOI:10.4158/EP-2018-0061

FIGURE CAPTION

Fig. 1. Selection process of eligible participants. The exclusion criteria were subjects with: a history of thyroid disease, any diseases or taking any medicine that might affect thyroid function, a history of excessive smoking and drinking, and overtly hypo- or hyperthyroid. The reference ranges for free triiodothyronine and free thyroxine were 3.5 to 6.5 pmol/L and 11.5 to 23.5 pmol/L, respectively.

Fig. 2. Prevalence of subclinical hypothyroidism (*A*) and subclinical hyperthyroidism (*B*) in different WC quartiles in both genders. WC quartiles 1 to 4 in males referred to the following: WC≤85 cm, 85<WC≤91 cm, 91<WC≤97 cm, WC>97 cm. The corresponding values in females were: WC≤73 cm, 73<WC≤79 cm, 79<WC≤86 cm, WC>86 cm. *WC* = waist circumference.

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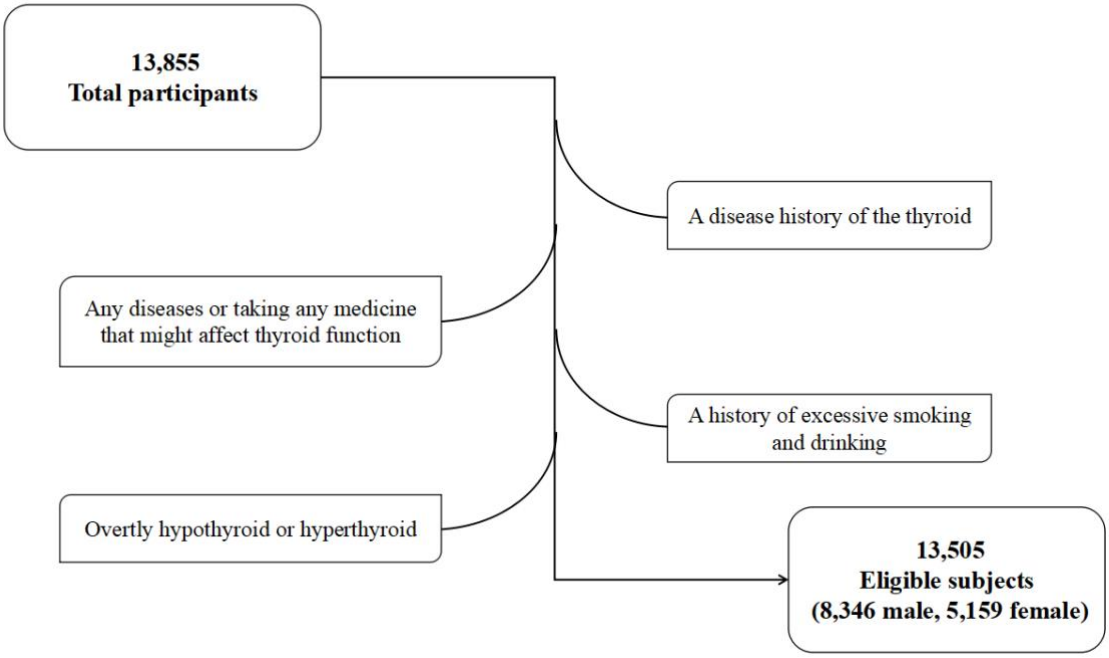

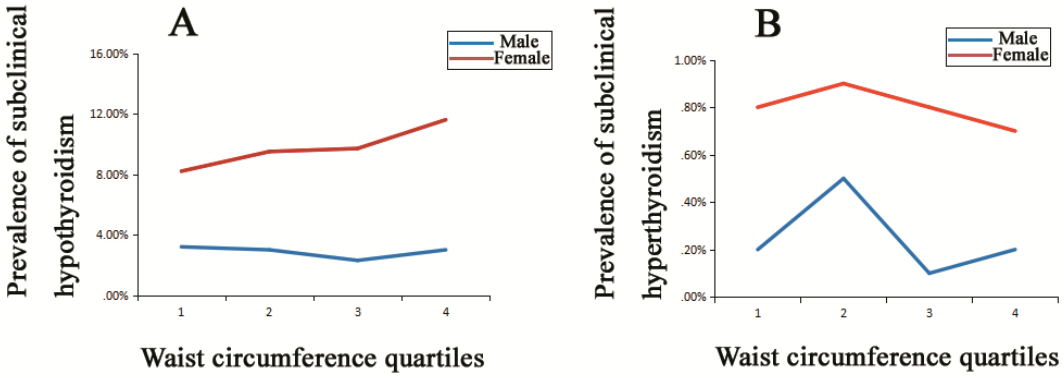

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