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The Relationship of Anthropometric Measurement with the Risk of Thyroid Nodule in Chinese Population

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ABSTRACT

Objective: Previous studies have found that overweight and obesity have been related to numerous diseases, including thyroid cancer and thyroid volume. This study is to evaluate the relationship of body size with the risk of thyroid nodule in Chinese population.

Methods: A total of 6,793 adults and 2,410 children who underwent thyroid ultrasonography were recruited in this cross-sectional study, Hangzhou, Zhejiang province, China, from March to October, 2010. The socio-demographic characteristics and potential risk factors of thyroid nodule were collected using questionnaire. The relationships of height, weight, Body Mass Index (BMI) and Body Surface Area (BSA) with thyroid nodule were evaluated using multiple logistic regression models.

Results: After adjusted potential risk factors, an increased risk of thyroid nodule was respectively associated with height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40, 95% CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) among adults, obviously in females. Similar trends of association between weight, BMI, BSA and the risk of thyroid nodule were observed in children, but not height. BSA was significantly associated with an increased risk of thyroid nodule among adult and children.

Conclusion: The present data identifies that thyroid nodule risk positively increased with weight, height, BMI and BSA among both adults and children, obviously in female adults and girls. It implies that individual with high height and obesity has

higher susceptibility for thyroid nodule.

Keywords: anthropometric measurement, thyroid nodule, Chinese population

Article summary:

Strengths and limitations of this study：

1) Including adult and children subjects.
2) Large sample size of subjects.
3) The weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report.
4) We adjusted for most main covariates, including cigarette smoking and alcohol drinking, two important factors influenced overweight
5) The number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished.

INTRODUCTION

Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Overweight and obesity are the fifth leading risk for global deaths. In addition, between 7% and 41% of certain cancer burdens are attributable to overweight and obesity[1]. Data from epidemiological studies demonstrate a direct correlation between BMI and the risk of medical complications and mortality rate[2 3]. The prevalence of overweight and obesity has been increasing in most economically developed countries for several decades, and there is evidence that the prevalence of overweight and obesity is also increasing in economically developing countries[4 5]. The prevalence of obesity has recently been dramatically increasing in China as a developing country. A national survey indicates that the prevalence of overweight and obesity were 24.1% and 2.8% in men and 26.1% and 5.0% in women, respectively [6]. Meanwhile, previous studies reported functional and morphological alterations of the thyroid gland in relation to obesity [7-11]. Due that thyroid hormones increase the basal metabolic rate, low thyroid function, even within the clinically normal range, could decrease metabolic speed and lead to obesity[11 12]. In addition, Mehmet Bastemir [10] found that serum TSH levels are positively correlated with the degree of obesity and some of its metabolic consequences in overweight people with normal thyroid function. Furthermore, S.Guth[13] reported that patient BMI were positively correlated with sizes of their thyroids. Through positive associations between height, weight and body mass index (BMI) and thyroid cancer have been reported in many studies and meta-analysis, other studies found no significant association between BMI and thyroid cancer [14-16].

Therefore, it is extremely important to understand the relationship of anthropometric measurements with thyroid nodule. But, to date, no study focuses on the relationship of anthropometric measurements with thyroid nodule in Chinese population. The aim of our study is to examine the relationship of anthropometric measurements with thyroid nodule in a large sample size of Chinese population.

MATERIALS AND METHODS

Population features

From March to October 2010, this large cross-sectional study was conducted in Hangzhou city, which is one of the leading commercial cities in eastern China. Hangzhou is the capital and largest city of Zhejiang Province in eastern China. This city covers eight districts and five counties. In 2010, the entire administrative division or prefecture had a registered population of 8.7 million residents. 73.25% of residents live in urban areas, only 26.75% in rural areas.

Subjects and study design

The detail description was shown in a published article of the same study[17]. The study participants were recruited based on following strategy: There are eight districts and five counties in big Hangzhou city. First, three sub-districts or towns were selected randomly from each district or county (except Binjiang district) respectively, so 36 sub-districts or towns were selected from big Hangzhou. Secondly, one community or village was randomly selected from each sub-district or town. Thirdly, 100 households from each community or village were randomly selected. Finally, we selected 3600 households for the interview. The family members of household were chosen based on the following criteria: (1) age at least 6 years; (2) living for above 5 years at present residence. The exclusion criteria: (1) the participants with coronary angiography (CAG) or endoscopic retrograde cholangiopancreatography (ERCP) in 6 months; (2) the participants taking amiodarone drug; (3) the participants with abnormal kidney function or serious illness.

The eligible family members of selected households were convened to village or community administration center. The researchers introduced the study protocol and obtained written informed consent form from each participant. Meanwhile, the interview schedule was appointed with participants. The study protocol was approved by Institutional Review Board of Hangzhou Center of Disease Control and Prevention. This survey was carried out by well-trained personnel (including community clinic physicians, nurses, public health doctors).

Collection of epidemiological data

The participants were invited to local community health center before 8:00 am after 8-hour fasting overnight. Firstly, each participant provided spot urine samples of at least 10 ml. Additionally, 5 ml venous blood was collected using vacuum blood collection tube. Secondly, the participants were interviewed for a structured questionnaire. The questionnaire covered the information about demographic characteristics and health status, including sex, age, nationality, physical activity, lifestyle, dietary habit, and personal or family history of thyroid disease (including time of diagnosis). Especially, information about type of salt, salt appetite and milk consumption was defined as following: the item--"Currently, which type of salt is consumed in your family?" was used for collecting information about type of salt. Three options for this item were provided: (1) only iodized salt; (2) non-iodized salt; (3) both of them. The question--"How about your appetite?" was used to evaluate salty appetite. Three options were provided: (1) salty; (2) moderate; (3) light.

Consuming milk ≤ 1 time per week was defined as having no habit of milk consumption, consuming milk ≥ 2 times per week was defined as having habit of milk consumption. In addition, diet pattern included three types: vegetarian, meat and moderate. Vegetarian defined as subjects mainly consumed vegetable diet, almost never ate meat food; meat defined as subjects mainly consumed meat food and uncommonly consumed vegetable; moderate defined as subjects consumed both vegetable and meat food. Eligible participants were interviewed face-to-face by well-trained investigators from Hangzhou Centers of Disease Control and Prevention.

Data collection of anthropometric measurements and thyroid nodule

Height and weight were measured using standard protocols, without shoes or outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer with a GMCS-I type height tester (Beijing). Weight was measured to the nearest 0.1 kg with the subjects standing motionless on a scale with a balance-beam scale (RGT-140, weighing Apparatus Co. Ltd. Wuxi). An ultrasound examination of thyroid was performed to detect thyroid nodules. The examination was performed with a Sonoline Versa Pro (Siemens, Munich, Germany) with a 7.5-MHz, 70-mm linear transducer (effective length, 62 mm). Thyroid nodule was defined as discrete lesion which was distinct from the surrounding thyroid parenchyma and which had solid portion regardless of having cystic portion.

Body Mass Index

The BMI is defined as the weight in kilograms divided by the square of the height in meters. Although the BMI calculation does not take into account factors such as frame size and body tissue compositions, BMI categories are generally used as a means of estimating adiposity and assessing how much an individual's body weight departs from what is normal or desirable for a person of the same height. Among adults, the classification of BMI was as follows: BMI < 24, group low (normal and underweight); 24 ≤ BMI, group high (overweight and obese). Among children, the reference BMI was calculated using the reference height and weight of each age group[18].

Body Surface Area (BSA)

BSA is a commonly used index in clinical practice to correct for patient size differences in various physiologic measurements and in calculating drug dosage. BSA is a better indicator of metabolic mass than body weight because it is less associated with excessive body fat. Various formulas have been proposed to estimate the BSA from a patient's weight and height, which may result in slightly different values [19-22]. The most commonly used formula in day-to-day clinical practice is the Mosteller formula: BSA (m^2) = (square root of product of weight [kg]×height [cm]) /60 [21]. This formula is simplified from a formula produced by Gehan and George [19], and has become a common standard because it is easy to memorize, and its use requires only a handheld calculator. So Mosteller formula was used in our study to calculate BSA.

Definition of variables

Diet pattern was classified as three groups: vegetarian, meat and moderate; vegetarian defined as subjects mainly consumed vegetable food; meat defined as subjects mainly consumed meat food; moderate defined as subjects consumed vegetable and meat food.

Among adults, the height, weight, BMI and BSA were dichotomized into high group and low group. The detailed criteria of each group were shown in Table 1. The classification of height and weight among adults refers to The Survey Report on National Physical Fitness of Chinese, 2005. In children, high group included subjects with height or weight ≥ reference standard of each age bracket (one year a bracket) in two genders. BMI was classified according to the reference calculated using the reference height and weight of each age bracket (one year a bracket) in two genders respectively. BSA was classified by the average value of each gender.

Statistical analysis

The comparison of height, weight and age between patients with and without thyroid nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test for qualitative data, including gender, education, marriage, resident location, cigarette smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of salt. Listwise deletion was used to address the missing data in the model.

The adjusted associations of height, weight, BMI and BSA with thyroid nodule were estimated respectively, using logistic regression model stratified by gender. The following variables were taken as covariates in logistic regression models: age, BMI, educational level, marital status, resident location, cigarette smoking, alcohol drinking, diet flavor, types of salt, dietary patterns, milk consumption. Among adults, age was classified as 5 classes: 18~29, 30~39, 40~49, 50~59, ≥ 60. Among children, age was classified as 4 classes: 6~8, 9~11, 12~14, 15~17. To account for the correlation of members in a same household, we calculated robust estimates of variances with generalized estimate equation (GEE) using SAS procedure GENMOD. All analyses were performed in SAS Version 9.0 (SAS Institute, Inc., Cary, NC, USA). A value of P<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of study population

A total of 12438 individuals were recruited in this investigation, but 3235 individuals were excluded for analyses, due to absence of anthropometic measurements. Final analyses included 9203 subject: 6,793 adults, and 2,410 children. The average age of adults was 47.93 years, 62.96% were females (Table 2); 4.39% were underweight, 66.13% were normal, 26.34% were overweight and 3.14% were obese. Out of 6,793 adults, 2,228 (32.80%) adults had thyroid nodule, of which women accounted for 71.01%. Among children, 47.55% were under the reference BMI, 52.45% were over the reference BMI. 257 (10.66%) children suffered from thyroid nodule, which more than half (57.98%) were girls (Table 4).

The relationship between anthropometric measurements and thyroid nodule among adults

The relationship between anthropometric measurements (height, weight, BMI, BSA) and an increased risk of thyroid nodule were estimated by gender (Table 3). Higher height (OR=1.15, 95% CL: 1.02-1.30), higher weight (OR=1.40, 95%CL: 1.24-1.58), higher BMI (OR=1.26, 95% CI: 1.11–1.42) and higher BSA (OR=1.43, 95% CI: 1.27–1.62) were significantly associated with an increased thyroid nodule among pooled samples, respectively. Similar trends were observed in females and males, but no significant association in males.

The relationship between anthropometric measurements and thyroid nodule among children

Similar relationship of anthropometric measurements with thyroid nodule was conducted among children (Table 5). Higher weight (OR=1.37, 95% CI: 1.03–1.81), higher BMI (OR=1.38, 95% CI: 1.04–1.83) and higher BSA (OR=2.97, 95% CI: 1.85–4.77) were significantly associated with an increased risk of thyroid nodule among pooled samples. The significant associations of BSA and an increased risk of thyroid nodule were observed in boys (OR=2.57, 95% CI: 1.25–5.28) and girls (OR=3.36, 95% CI: 1.82–6.20), but the relationship of BMI with an increased risk of thyroid nodule was only significant among boys. There is no significant association of height with risk of thyroid nodule among children.

DISCUSSION

This study, performed in a large Chinese population, demonstrates that height, weight, BMI and BSA were significantly associated with an increased risk of thyroid nodule among adults and children. More explicitly, in the present study, the significant association between high BSA and an increased risk of thyroid nodule was not obviously influenced by sex, age, resident location and iodine intake.

Thyroid nodule is very common disease in the general population. The present investigation showed that the prevalence of thyroid nodule was 32.80% in adults and 10.66% in children; but they are found clinically in 4-8% of cases[23]. The most of thyroid nodules are benign nodules[24], but 5-6.5% of them are malignant (carcinomas, CA)[25]. Because thyroid function is linked to development and growth, height and weight are seen as possible indicators of thyroid nodule risk. In our study, when the relationship of height, weight and thyroid nodule was examined among adults, the high height, heavy weight was significantly associated with an increased risk of thyroid nodule in pooled samples and females, respectively. But only significant relationship of weight with thyroid nodule was found in children population. To data, few study was focus on the relationship between anthropometric indexes and thyroid nodule. But, previous study showed that thyroid nodule may share similar risk factors with thyroid cancer: iodine deficiency is associated with an increased TC incidence, largely via benign thyroid conditions such as nodules, which are, in turn, strongly associated with TC. And, body size might be associated with the iodine requirementand, hence, indirectly related to thyroid nodule[26].

Our results were similar to the findings among 88,256 Canadian women in 2012. It is reported that height was positively associated with risk of all combined cancers and thyroid cancer, and height was significantly positively associated with risk of thyroid cancer in multivariable models [27]. Further, the European Prospective Investigation into Cancer and nutrition (EPIC), a large study including million subjects, also observed the positive association of height with thyroid cancer in female but not in male[28]. Beyond those findings from European population, a pooled analysis of individual data from 12 case-control studies conducted in eight countries (America, Asia, and Europe) suggests that height is moderately related to thyroid cancer risk[29]. In addition, similar association of height with thyroid nodule risk among Korean was observed in females but not males[30]. In our findings from Chinese, the sample size was large and the moderate association of height with thyroid nodule risk was also observed in females, which was consistent with those from Korea in Asia and even European population. However, the association was not significant among children, but we still can find an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90). It may due to the small case numbers of children, and the association between height and thyroid nodule among children need more studies to confirm.

Furthermore, similar to height, the pooled analysis conducted in eight countries also indicated the association of weight and risk of thyroid cancer in female rather than male[29]. In 2010, Clavel-Chapelon F[31] reported that there was a significant dose-effect relationship between thyroid cancer risk and weight in France. Additionally, in Asia, the significant association between weight and thyroid nodule in female was observed among Korean population[30]. Our data also confirmed these findings of adults in Chinese population after adjusted for possible covariates. Not only observed in adult, we also found a significant association of weight with risk of thyroid nodule in children. Present study lent further support to the possibility that increased height and weight of female may associated with increased risk of thyroid nodule. Altered thyroid status has well-known and profound effects on skeletal development and growth and on adult bone maintenance. The fact that thyroid hormones are associated with the regulation of the growth of long bones may be one possible explanation for the association between height and thyroid nodule[32]. Moreover, genetic or environmental factors (e.g., dietary factors, nutritious factors), correlate with adult height and weight, also influence thyroid function might be another possible explanation for this association[29].

Analogously, in our study, the significant associations between BMI and thyroid nodule were observed among pooled adult samples. Similar association was observed in women, but not in men. Among children, significant associations of BMI with thyroid nodule were also observed in pooled samples. Our findings in adult were consistent with that in German [33] and Italian [34], and similar findings were also observed among Korea population [30]. However, Results from previous prospective and case-control studies on the association of BMI with thyroid cancer risk have generally been more inconsistent in men than women. In a large Norwegian cohort of more than two million participants, the risk of thyroid cancer increased moderately with increased BMI in both sexes, but the results were unadjusted for smoking and other factors[15]. After adjusted for key covariates such as cigarette smoking, alcohol intake, physical activity and medical history of diabetes, the largest prospective study conducted in U.S. also observed a significant positive association between BMI and thyroid cancer risk in women [35]. Moreover, a systematic review conducted by Emily Peterson[36] in 2012 (including 37 studies) showed that most of studies supported a positive association of BMI with thyroid cancer in both sexes. The inconsistent results between men and women in previous studies is likely due to smaller numbers of cases in men, to the lack of control for important covariates (e.g. cigarette smoking, alcohol intake). Current smoking and alcohol intake are associated with BMI levels[37-40]. Unadjustment for smoking status or alcohol intake may be a important bias in the association between BMI and risk of thyroid nodule. Findings of present study cover adults and children, and the associations of BMI with risk of thyroid nodule were consistent in each population after adjusted for important covariates. Base on large samples and reducing important biases, our findings indicate that overweight and obesity increase the risk of thyroid nodule in both adult and children. The association between BMI and thyroid nodule may be the certain metabolic consequences of excess adipose tissue. Leptin produced by adipocytes has important influences on central regulation of thyroid function through stimulation of TRH. This seems to be important for down-regulation of thyroid function in states of energy deficits, but the importance for modulation of thyroid function under more physiological conditions is uncertain[41 42]. Additionally, thyroid hormones may be a significant determinant of sleeping energy expenditure in subjects without overt thyroid dysfunction[43]. Similarly, differences in thyroid function, within what is considered the normal range, are associated with differences in BMI, caused by longstanding minor alterations in energy expenditure[11]. What`s more, obesity is associated with insulin resistance and increased production of insulin and insulin-like growth factors which in turn have been reported to be associated to thyroid disorders[25 44 45].

Being similar with thyroid cancer[25 35], thyroid nodules are more common in women than in men[46-50]. Sex differences in the association between BMI and thyroid cancer have been confirmed in other studies[29 51 52]. Our findings of adult were consistent with the sex difference in association of BMI with thyroid nodule. The difference in incidence between two genders suggests that growth and progression of thyroid tumors is influenced by sex hormones, particularly estrogens[53 54]. Additionally, it was reported that the observed positive relation of overweight to thyroid cancer risk may be due to detection bias--more frequent examinations of thyroid gland among overweight young women than lean individuals[29]. However, sex difference of the correlation between body size and thyroid nodule was not obvious among children. It may due to the smaller difference of sex hormones in children, compared to adult. Few studies noted the correlation between body size and thyroid nodule in children, the findings from children population require furthermore studies to confirm.

BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI or weight[55]. In the present study, BSA was significantly associated with increased risk of thyroid nodule among adult and children. The association was not influenced by sex, age, resident location and iodine intake. Consistently, a positive association of thyroid cancer and current BSA in adult was found by Suzuki T in Japan in both sexes after adjusted for main covariates[56]. In addition, it was reported that BSA plays a dominant role in thyroid cancer risk and explains the apparent role of BMI in adult[55]. Muscle is more dense than fat, and BMI is not able to differentiate increased weight[57]. BSA is a more accurate measure of obesity, including central obesity, as it is a measurement of area and is able to account for the difference between muscle and fat better than BMI secondary to muscle versus fat[58]. In a way, the association between BSA and thyroid nodule more strongly and forcefully confirmed the increased risk of overweight and obesity with thyroid nodule than those of BMI.

Our study is novel for that it is performed in adult population and children population with a large sample size. Further, the weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report, reducing the bias of overestimation or underestimation of height and weight[59 60]. In addition, in order to reduce the possible bias, we adjusted for most main covariates, including cigarette smoking and alcohol drinking, two important factors influenced overweight[37-40]. Especially, salt type, salt appetite and diet patterns were taken as covariates in analysis models; the effect of iodine on risk of thyroid nodule was considered. Hence, the associations of anthropometric measurements were robust.

LIMITATION

There were several limitations in this study. Firstly, the circumferences of waist and hip were not measured. It hampered to examine the association of central adiposity with thyroid nodule. Secondly, the number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished. Thus, it is no way to find the different associations between anthropometric measurements and different kinds of thyroid nodule.

CONCLUSION

Our findings indicated that thyroid nodule risk increases with weight, height, BMI and BSA, especially in females. The similar trends of relationship between weight, BMI, BSA and thyroid nodule were observed in children. Among the four indicators, BSA was strongly associated with thyroid nodule. It implies that individual with high height and obesity has higher susceptibility for thyroid nodule.

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The authors gave the following different contribution on this manuscript: Yunxian Yu generated the idea, modified and edited the manuscript. Weimin Xu supervised the study field activities, prepared and managed the datasets. Zexin Chen did statistical analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and interviewed study subjects in the study field. All authors read and approved the final manuscript. None of the authors had a conflict of interest. The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. No additional unpublished data are available.

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Table 1. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group among adults.

Variables	Nodule (n=2228)	Non-nodule (n=4565)	*P*
Age(Mean ± SD)	53.49±13.80	44.93±13.72	<0.001
Height(Mean ± SD)	160.72±7.25	162.24±7.54	<0.001
Weight(Mean ± SD)	59.30±8.12	59.10±8.33	0.177
Gender			
male	646(28.99)	1870(40.96)	<0.001
female	1582(61.01)	2695(59.04)	
Education[a]			
primary school	922(42.10)	1317(29.15)	<0.001
Junior high school	647(29.54)	1440(31.87))	
senior high school	470(21.46)	1283(28.40)	
junior college and above	151(6.89)	478(10.58)	
Marriage			
single	78(3.51)	378(8.29)	<0.001
married	1980(88.98)	3981(87.30)	
divorce	22(0.99)	47(1.03)	
widowed	139(6.25)	140(3.07)	
others	6(0.27)	14(0.31)	
Resident location			
urban area	1214(54.49)	2125(46.55)	<0.001
rural area	1014(45.52)	2440(53.45)	
Cigarette smoking			
Never	1825(82.65)	3508(77.46)	<0.001
Ever	69(3.13)	121(2.67)	
Current	314(14.22)	900(19.87)	
Alcohol drinking			
No	1822(83.27)	3608(80.55)	0.027
Yes	366(16.73)	871(19.45)	
Salt appetite			
moderate	1135(51.24)	2479(54.52)	0.036
salty	469(21.17)	916(20.15)	
light	611(27.58)	1152(25.34)	
Milk consuming			
Yes	837(42.02)	1965(45.55)	0.009
No	1155(57.98)	2349(54.45)	
Diet patterns[b]			
balanced	1662(74.73)	3484(76.32)	0.043
vegetarian	403(18.12)	722(15.82)	

meat	159(7.15)	359(7.89)	
Types of salt[c]			
Iodized salt	2082(94.38)	4385(96.65)	<0.001
Non-iodized	124(5.62)	152(3.35)	

[a:] Educational status: primary school group includes illiteracy, senior high school group is made of senior high school and technical secondary school

[b:] Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[c:] Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

Table 2. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults.

Variables	Nodule	Non-nodule	OR(95%CI)	*P*
		Pooled*		
Height(cm)[a]				
low	1334(59.87)	2576(56.43)	1.00	
high	894(40.13)	1989(43.57)	1.15(1.02,1.30)	0.0245
Weight(kg)[b]				
low	1222(54.85)	2760(60.46)	1.00	
high	1006(45.15)	1805(39.54)	1.40(1.24,1.58)	<0.0001
BMI[c]				
low	1438(64.54)	3351(73.41)	1.00	
high	790(35.46)	1214(26.59)	1.26(1.11,1.42)	0.0003
BSA(m^2)[d]				
low	1068(47.94)	2675(58.60)	1.00	
high	1160(52.06)	1890(41.40)	1.43(1.27,1.62)	<0.0001
		Females		
Height(cm)[a]				
low	968(61.19)	1596(59.22)	1.00	
high	614(38.81)	1099(40.78)	1.24(1.07,1.44)	0.0050
Weight(kg)[b]				
low	946(59.80)	1960(72.73)	1.00	
high	636(40.20)	735(27.27)	1.71(1.47,1.98)	<0.0001
BMI[c]				
low	1002(63.64)	2048(75.99)	1.00	
high	580(36.66)	647(24.01)	1.47(1.26,01.72)	<0.0001
BSA(m^2)[d]				
low	627(39.63)	1366(50.69)	1.00	
high	955(60.37)	1329(49.31)	1.53(1.32,1.77)	<0.0001
		Males		
Height(cm)[a]				
Low	366(56.66)	980(52.41)	1.00	
high	280(43.34)	890(47.59)	1.00(0.82,1.24)	0.9699
Weight(kg)[b]				
low	276(42.72)	800(42.78)	1.00	
high	370(57.28))	1070(57.28)	1.00(0.80,1.20)	0.8690
BMI[c]				
low	436(67.49)	1303(69.68)	1.00	
high	210(32.51)	567(30.32)	1.00(0.81,1.23)	0.9892
BSA(m^2)[d]				
low	441(68.27)	1309(70.00)	1.00	
high	205(31.73)	561(30.00)	1.21(0.97,1.51)	0.0871

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**:** **Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**:** **Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

Table 3. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group in children.

Variables	Nodule (n=257)	Non-nodule (n=2153)	*P*
Age	12.01±2.73	11.06±3.56	<0.001
Gender			
male	108(42.02)	1083(50.30)	0.012
female	149(57.98)	1070(49.70)	
Resident location			
urban area	153(59.53)	1028(47.75)	0.0004
rural area	104(40.47)	1125(52.25)	
Diet pattern[a]			
Balanced	202(78.91)	1663(77.46)	0.519
vegetarian	30(11.72)	271(12.62)	
Meat	24(9.37)	213(9.92)	
Salt appetite			
Moderate	127(50.00)	1200(56.02)	0.042
Salty	61(24.02)	380(17.74)	
Light	66(25.98)	562(26.24)	
Milk consuming			
Yes	192(80.67)	1599(77.73)	0.300
No	46(19.33)	458(22.27)	
Types of salt[b]			
Iodized salt	236(94.02)	2063(96.58)	0.042
Non-iodized	15(5.98)	73(3.42)	

[a]: Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[b]: Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

Table 4. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children.

Variables	Nodule	Non-nodule	OR(95%CI)	*P*
		Pooled*		
Height(cm)[a]				
low	140(54.47)	1259(58.48)	1.00	
high	117(45.53)	894(41.52)	1.15(0.87,1.53)	0.3347
Weight(kg)[b]				
low	118(45.91)	1175(54.58)	1.00	
high	139(54.09)	978(45.42)	1.37(1.03,1.81)	0.0292
BMI[c]				
low	106(41.25)	1040(48.30)	1.00	
high	151(58.75)	1113(51.70)	1.38(1.04,1.83)	0.0248
BSA(m^2)[d]				
low	77(29.96)	1144(52.22)	1.00	
high	180(70.04)	1009(47.78)	2.97(1.85,4.77)	<0.0001
		Girls		
Height(cm)[a]				
low	79(53.02)	643(60.09)	1.00	
high	70(46.98)	427(39.91)	1.30(0.89,1.90)	0.1719
Weight(kg)[b]				
low	63(42.28)	555(51.87)	1.00	
high	86(57.72)	515(48.13)	1.55(1.07,2.25)	0.0218
BMI[c]				
low	63(42.28)	488(45.61)	1.00	
high	86(57.72)	582(54.39)	1.25(0.86,1.81)	0.2391
BSA(m^2)[d]				
low	43(28.86)	556(51.96)	1.00	
high	106(71.17)	514(48.04)	3.36(1.82,6.20)	0.0001
		Boys		
Height(cm)[a]				
low	61(56.48)	616(56.88)	1.00	
high	47(43.52)	467(43.12)	0.97(0.63,1.49)	0.8870
Weight(kg)[b]				
low	55(50.93)	620(57.25)	1.00	
high	53(49.07)	463(42.75)	1.15(0.75,1.77)	0.5120
BMI[c]				
low	43(39.81)	552(50.97)	1.00	
high	65(60.19)	531(49.03)	1.59(1.03,2.44)	0.0355
BSA(m^2)[d]				
low	34(31.48)	588(54.29)	1.00	
high	74(68.52)	495(45.71)	2.57(1.25,5.28)	0.0104

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2;

Mean of male′s BSA=1.26 m^2, Mean of female′s BSA=1.22 m^2.

Supplementary Table 1. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults without history of diseases related to thyroid.

Variables	Nodule	Non-nodule	OR(95%CI)	*P*
		Pooled*		
Height(cm)[a]				
low	1120(61.57)	2348(57.20)	1.00	
high	699(38.43)	1757(42.80)	1.15(1.01,1.30)	0.0388
Weight(kg)[b]				
low	997(54.81)	2485(60.54)	1.00	
high	822(45.19)	1620(39.46)	1.39(1.22,1.58)	<0.0001
BMI[c]				
low	1156(63.55)	3009(73.30)	1.00	
high	663(36.45)	1096(26.70)	1.31(1.15,1.50)	<0.0001
BSA(m^2)[d]				
low	897(49.31)	2415(58.83)	1.00	
high	922(50.69)	1690(41.17)	1.44(1.27,1.63)	<0.0001
		Females		
Height(cm)[a]				
low	797(62.81)	1449(60.10)	1.00	
high	472(37.19)	962(39.90)	1.23(1.04,1.44)	0.0147
Weight(kg)[b]				
low	753(59.34)	1758(72.92)	1.00	
high	516(40.66)	653(27.08)	1.68(1.44,1.97)	<0.0001
BMI[c]				
low	790(62.25)	1830(75.90)	1.00	
high	479(37.75)	581(24.10)	1.48(1.26,1.75)	<0.0001
BSA(m^2)[d]				
low	512(40.35)	1230(51.02)	1.00	
high	757(59.65)	1181(48.98)	1.56(1.34,1.81)	<0.0001
		Males		
Height(cm)[a]				
low	323(58.73)	899(53.07)	1.00	
high	227(41.27)	795(46.93)	0.99(0.80,1.23)	0.9473
Weight(kg)[b]				
low	244(44.36)	727(42.92)	1.00	
high	306(55.64)	967(57.08)	0.96(0.78,1.19)	0.7087
BMI[c]				
low	366(66.55)	1179(69.60)	1.00	
high	184(33.45)	515(30.40)	1.05(0.84,1.30)	0.6881
BSA(m^2)[d]				
low	385(70.00)	1185(69.95)	1.00	
high	165(30.00)	509(30.05)	1.18(0.93,1.48)	0.1705

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident

location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**: Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**: Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

Supplementary Table 2. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children without history of diseases related to thyroid.

Variables	Nodule	Non-nodule	OR(95%CI)	*P*
		Pooled*		
Height(cm)[a]				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight(kg)[b]				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI[c]				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA(m^2)[d]				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
		Girls		
Height(cm)[a]				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight(kg)[b]				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI[c]				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m^2)[d]				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
		Boys		
Height(cm)[a]				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight(kg)[b]				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI[c]				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA(m^2)[d]				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;
[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2; Mean of male′s BSA=1.26 m^2, Mean of female′s BSA=1.22 m^2.

Supplementary Table 3. Stratified criteria of height, weight, BMI and BSA among adults

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low	BMI<24.0	
High	BMI≥24	
BSA(m^2)		
low	BSA<1.80m^2	BSA<1.55m^2
high	BSA≥1.80m^2	BSA≥1.55m^2

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(line 32)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(line44-47)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(line 70-92)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(line 94-98)**
Methods		
Study design	4	Present key elements of study design early in the paper **(line 102-103)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection**(line 102-104)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **(line 109-130)**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(line 132-204)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(line 168-204)**
Bias	9	Describe any efforts to address potential sources of bias **(line 214-219)**
Study size	10	Explain how the study size was arrived at **(line 110-117)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(line 207-211)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(line 207-214, line 219-221)**
		(*b*) Describe any methods used to examine subgroups and interactions **(line213-214)**
		(*c*) Explain how missing data were addressed **(line211)**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **(N/A)**
		(*e*) Describe any sensitivity analyses **(N/A)**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(line227-229)**
		(b) Give reasons for non-participation at each stage **(line227)**
		(c) Consider use of a flow diagram **(N/A)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **（line 226-235）**
		(b) Indicate number of participants with missing data for each variable of interest **（Table 1）**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **（line 231-235）**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **（line -237-257）**
		(*b*) Report category boundaries when continuous variables were categorized **（line218-219）**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **（N/A）**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **（N/A）**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(line 260-264)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(line 397-403)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(line 265-385)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(line 260-262)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(line 424-429)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Relationship of Anthropometric Measurement with Thyroid Nodule in a Chinese Population

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

The Relationship of Anthropometric Measurement with Thyroid Nodule in a Chinese Population

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ABSTRACT

Objective: Previous studies have found that overweight and obesity have been related to numerous diseases, including thyroid cancer and thyroid volume. This study is to evaluate the relationship of body size with the risk of thyroid nodule in Chinese population.

Methods: A total of 6,793 adults and 2,410 children who underwent thyroid ultrasonography were recruited in this cross-sectional study, Hangzhou, Zhejiang province, China, from March to October, 2010. The socio-demographic characteristics and potential risk factors of thyroid nodule were collected using questionnaire. Height and weight were measured using standard protocols. The relationships of height, weight, Body Mass Index (BMI) and Body Surface Area (BSA) with thyroid nodule were evaluated using multiple logistic regression models.

Results: After adjusted potential risk factors, an increased risk of thyroid nodule was respectively associated with height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40, 95% CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) among adults, obviously in females. Similar trends of association between weight, BMI, BSA and the risk of thyroid nodule were observed in children, but not height. BSA was highest significantly associated with an increased risk of thyroid nodule among adult and children.

Conclusion: The present study identified that thyroid nodule risk was positively associated with weight, height, BMI and BSA among both adults and children,

obviously in female adults and girls. It implied that individual with high height and obesity increased the susceptibility for thyroid nodule.

Keywords: anthropometric measurement, thyroid nodule, adult, children, Chinese population

Article summary:

Strengths and limitations of this study：

1) Including adult and children subjects.
2) Large sample size of subjects.
3) The weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report.
4) The main results was presented after adjustment for many potential confounders, including cigarette smoking and alcohol drinking, two important factors influenced overweight
5) The number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished.

INTRODUCTION

Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Overweight and obesity are the fifth leading risk for global deaths. In addition, between 7% and 41% of certain cancer burdens are attributable to overweight and obesity[1]. Data from epidemiological studies demonstrate a direct correlation between BMI and the risk of medical complications and mortality rate[2 3]. The prevalence of overweight and obesity has been increasing in most economically developed countries for several decades, and there is evidence that the prevalence of overweight and obesity is also increasing in economically developing countries[4 5]. The prevalence of obesity has recently been dramatically increasing in China as a developing country. A national survey indicates that the prevalence of overweight and obesity were 24.1% and 2.8% in men and 26.1% and 5.0% in women, respectively [6]. Meanwhile, previous studies reported functional and morphological alterations of the thyroid gland in relation to obesity [7-11]. Due that thyroid hormones increase the basal metabolic rate, low thyroid function, even within the clinically normal range, could decrease metabolic speed and lead to obesity[11 12]. In addition, Mehmet Bastemir [10] found that serum TSH levels are positively correlated with the degree of obesity and some of its metabolic consequences in overweight people with normal thyroid function. Furthermore, S.Guth[13] reported that BMI were positively correlated with sizes of their thyroids. Though the vast majority of nodules are benign, the risk factors for thyroid nodules among euthyroid population have not yet been fully elucidated.

Previous study in Chinese population indicated overweight (OR = 1.199, 95% CI: 1.078 - 1.333) might be risk factor for thyroid nodules after adjusting for age and gender[14]. Similarly, S. Guth[13] observed that mean thyroid size was correlated strongly with body weight. However, Kim JY[15] reported that the patients with thyroid nodule had lower height, weight and body surface area (BSA) than those without thyroid nodule in Koreans. Especially, in the women, lower height and overweight were identified as independent risk factors for the presence of thyroid nodules.

Therefore, the association of anthropometric measurements with thyroid nodule is still unclear. Furthermore, few study focuses on the relationship of anthropometric measurements with thyroid nodule in Chinese population. The aim of our study was to examine the relationship of anthropometric measurements with thyroid nodule in a large sample size of Chinese population.

MATERIALS AND METHODS

Population features

From March to October 2010, this large cross-sectional study was conducted in Hangzhou city, which is one of the leading commercial cities in eastern China. The detail population feature was described in a published article [16].

Subjects and study design

The study participants were recruited based on following strategy: There are eight districts and five counties in big Hangzhou city. First, three sub-districts or towns were selected randomly from each district or county (except Binjiang district) respectively, so 36 sub-districts or towns were selected from big Hangzhou. Secondly, one community or village was randomly selected from each sub-district or town. Thirdly, 100 households from each community or village were randomly selected. Finally, we selected 3600 households for the interview. The family members of household were chosen based on the following criteria: (1) age at least 6 years; (2) living for above 5 years at present residence. The exclusion criteria: (1) the participants with coronary angiography (CAG) or endoscopic retrograde cholangiopancreatography (ERCP) in 6 months; (2) the participants taking amiodarone drug; (3) the participants with abnormal kidney function or serious illness.

The eligible family members of selected households were convened to village or community administration center. The researchers introduced the study protocol and obtained written informed consent form from each participant. Meanwhile, the interview schedule was appointed with participants. The study protocol was approved by Institutional Review Board of Hangzhou Center of Disease Control and Prevention. This survey was carried out by well-trained personnel (including community clinic physicians, nurses, public health doctors).

Collection of epidemiological data

The participants were interviewed for a structured questionnaire. The questionnaire covered the information about demographic characteristics and health status, including sex, age, nationality, physical activity, lifestyle, dietary habit, and personal or family history of thyroid disease (including time of diagnosis).

Data collection of anthropometric measurements and thyroid nodule

Height and weight were measured using standard protocols, without shoes or outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer with a GMCS-I type height tester (Beijing). Weight was measured to the nearest 0.1 kg with the subjects standing motionless on a scale with a balance-beam scale (RGT-140, weighing Apparatus Co. Ltd. Wuxi). An ultrasound examination of thyroid was performed to detect thyroid nodules by a Sonoline Versa Pro (Siemens, Munich, Germany) with a 7.5-MHz, 70-mm linear transducer (effective length, 62 mm). Thyroid nodule was defined as discrete lesion which was distinct from the surrounding thyroid parenchyma and which had solid portion regardless of having cystic portion.

Body Mass Index (BMI)

The BMI is defined as the weight in kilograms divided by the square of the height in meters. Although the BMI calculation does not take into account factors such as frame size and body tissue compositions, BMI categories are generally used as a means of estimating adiposity and assessing how much an individual's body weight departs from what is normal or desirable for a person of the same height. According to the criteria recommended by Working Group on Obesity in China[17], the classification of BMI for adults was as follows: BMI < 24, group low (normal and underweight); 24 ≤ BMI, group high (overweight and obese). Among children, the reference BMI was calculated using the reference height and weight of each age group[18].

Body Surface Area (BSA)

BSA is a commonly used index in clinical practice to correct for patient size differences in various physiologic measurements and in calculating drug dosage. BSA is a better indicator of metabolic mass than body weight because it is less affected by abnormal adipose mass[19]. Previous studies observed the association of BSA with thyroid volume and nodules[15 20].Various formulas have been proposed to estimate the BSA from a patient's weight and height, which may result in slightly different values [21-24]. The most commonly used formula in day-to-day clinical practice is the Mosteller formula: BSA (m^2) = (square root of product of weight [kg]×height [cm]) /60 [23]. This formula is simplified from a formula produced by Gehan and George [21], and has become a common standard because it is easy to memorize, and its use requires only a handheld calculator. So Mosteller formula was used in our study to calculate BSA.

Definition of variables

Among adults, the height, weight, BMI and BSA were dichotomized into high group and low group. The detailed criteria of each group were shown in Supplementary Table 3. The classification of height and weight among adults refers to The Survey Report on National Physical Fitness of Chinese, 2005. In children, high group included subjects with height or weight ≥ reference standard of each age bracket (one year a bracket) in two genders. BMI was classified according to the reference calculated using the reference height and weight of each age bracket (one year a bracket) in two genders respectively[18]. BSA was classified by the average value of each gender.

Statistical analysis

The comparison of height, weight and age between patients with and without thyroid nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test for qualitative data, including gender, education, marriage, resident location, cigarette smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of salt. Listwise deletion was used to address the missing data in the model.

The adjusted individual associations of height, weight, BMI and BSA with thyroid nodule were estimated, using logistic regression model stratified by gender. The variables showing significant difference between group with and without thyroid nodule were taken as covariates in logistic regression models: age, BMI, educational level, marital status, resident location, cigarette smoking, alcohol drinking, diet flavor, types of salt, dietary patterns, milk consumption. Among adults, age was classified as 5 classes: 18~29, 30~39, 40~49, 50~59, ≥ 60. Among children, age was classified as 4 classes: 6~8, 9~11, 12~14, 15~17. To account for the correlation of members in a same household, we calculated robust estimates of variances with generalized estimate equation (GEE) using SAS procedure GENMOD. All analyses were performed in SAS Version 9.0 (SAS Institute, Inc., Cary, NC, USA). A value of $P<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of study population

A total of 12438 individuals were recruited in this investigation, but 3235 individuals were excluded for analyses, due to absence of anthropometic measurements. Final analyses included 9203 subject: 6,793 adults, and 2,410 children. Among adults, the average age was 47.93 years; females accounted for 62.96%; the underweight, normal, overweight and obese was 4.39%, 66.13%, 26.34% and 3.14%, respectively. The socio-demographic characteristics among patients with thyroid nodule and non-nodule group for adults were shown in Table 1; Out of 6,793 adults, 2,228 (32.80%) adults had thyroid nodule, of which women accounted for 71.01%. Subjects with thyroid nodule was older, shorter, more females ($p<0.05$). Moreover, the distributions of education, marital status, resident location, smoking, drinking, salt appetite, milk consuming and diet patterns had significant difference between two groups (Table 1). The socio-demographic characteristics among patients with thyroid nodule and non-nodule group for children were shown in Table 3. Subjects with thyroid nodule was older, and more females ($p<0.05$). The distributions of resident location, salt appetite and type of salts had significant difference between two groups (Table 3). Among children, 47.55% were under the reference BMI, 52.45% over the reference BMI. 257 (10.66%) children suffered from thyroid nodule, which more than half (57.98%) were girls (Table 4).

The relationship between anthropometric measurements and thyroid nodule among adults

The relationship between anthropometric measurements (height, weight, BMI, BSA) and thyroid nodule were estimated by gender (Table 2). The height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40, 95%CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) were significantly associated with an increased risk of thyroid nodule among all adults, respectively. Similar trends were observed in females and males, but no significant association in males.

The relationship between anthropometric measurements and thyroid nodule among children

The relationship of anthropometric measurements with thyroid nodule was also conducted among children (Table 4). The weight (OR=1.37, 95% CI: 1.03–1.81), BMI (OR=1.38, 95% CI: 1.04–1.83) and BSA (OR=2.97, 95% CI: 1.85–4.77) were significantly positively associated with the risk of thyroid nodule among all children.

The significant association of BSA with thyroid nodule was observed in both boys (OR=2.57, 95% CI: 1.25–5.28) and girls (OR=3.36, 95% CI: 1.82–6.20); BMI and weight were also positively related with the risk of thyroid nodule among both genders, but significant association of BMI among boys and significant association of weight among girls was observed respectively. The significant association of height with risk of thyroid nodule was not observed among children.

DISCUSSION

This study, performed in a large Chinese population, demonstrated that height, weight, BMI and BSA were significantly associated with an increased risk of thyroid nodule among adults and children, respectively. More explicitly, in the present study, the significant association between high BSA and thyroid nodule was not obviously influenced by sex, age, resident location and iodine intake.

Thyroid nodule is very common disease in the general population. The present investigation showed that the prevalence of thyroid nodule was 32.80% in adults and 10.66% in children; but they are found clinically in 4-8% of cases[25]. The most of thyroid nodules are benign nodules[26], but 5-6.5% of them are malignant (carcinomas, CA)[27]. Because thyroid function is linked to development and growth, height and weight are seen as possible indicators of thyroid nodule risk. In our study, high height and heavy weight was significantly associated with thyroid nodule in all adults and females, respectively. But only significant relationship of weight with thyroid nodule was found in children population. To data, few study was focus on the relationship between anthropometric indexes and thyroid nodule. Previous study showed that thyroid nodule might share similar risk factors with thyroid cancer : iodine deficiency was associated with an increased TC incidence, largely via benign thyroid conditions such as nodules, which are, in turn, strongly associated with TC. Additionally, body size might be associated with the iodine requirement and, hence, indirectly related to thyroid nodule[28].

Our results were similar to the findings among 88,256 Canadian women in 2012. It is reported that height was positively associated with risk of all combined cancers and thyroid cancer, and height was significantly positively associated with risk of thyroid cancer in multivariable models [29]. Further, the European Prospective Investigation into Cancer and nutrition (EPIC), a large study including half-a-million subjects, also observed the positive association of height with thyroid cancer in female but not in male[30]. Beyond those findings from European population, a pooled analysis of individual data from 12 case-control studies conducted in eight countries (America, Asia, and Europe) suggests that height was moderately related to thyroid cancer risk[31]. In addition, similar association of height with thyroid nodule risk among Korean was observed in females but not males[15]. In our findings of Chinese population, the moderate association of height with thyroid nodule was also observed in females, which was consistent with those from Korea in Asia and even European population. However, the association was not significant among children, but we still found an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90). It may due to the small case numbers of children, and the association between height and thyroid nodule among children needs more future studies to confirm.

Furthermore, similar to height, the meta-analysis of data from eight countries also indicated the association of weight and risk of thyroid cancer in female rather than male[31]. In 2010, Clavel-Chapelon F[32] reported that there was a significant dose-effect relationship between thyroid cancer risk and weight in France. In Asia, the significant association between weight and thyroid nodule in female was observed among Korean population[15]. Our data also confirmed these findings after adjusted for possible covariates not only in adult, but also in children. Altered thyroid status has well-known that it has profound effects on skeletal development and growth and on adult bone maintenance. The fact that thyroid hormones are associated with the regulation of the growth of long bones may be one possible explanation for the association between height and thyroid nodule[33]. Moreover, genetic or environmental factors (e.g., dietary factors, nutritious factors), correlate with adult height and weight, also influence thyroid function might be another possible explanation for this association[31].

Analogously, the significant associations between BMI and thyroid nodule were observed among all adults. Similar association was observed in women, but not in men. Among children, significant associations of BMI with thyroid nodule were also observed. Our findings in adults were consistent with that in German [34] and Italian [35], and similar to those among Korean population [15]. However, Results from previous prospective and case-control studies on the association of BMI with thyroid cancer risk have generally been more inconsistent in men than women. In a large Norwegian cohort of more than two million participants, the risk of thyroid cancer increased moderately with increased BMI in both sexes, but the results were unadjusted for smoking and other potential confounders [36]. After adjusted for key covariates such as cigarette smoking, alcohol drinking, physical activity and medical history of diabetes, the largest prospective study conducted in U.S. also observed a significant positive association between BMI and thyroid cancer risk in women [37]. Moreover, a systematic review conducted by Emily Peterson[38] in 2012 (including 37 studies) showed that most of studies supported a positive association of BMI with thyroid cancer in both sexes. The inconsistent results between men and women in previous studies is likely due to smaller numbers of cases in men, to the lack of control for important covariates (e.g. cigarette smoking, alcohol intake). Current smoking and alcohol intake are associated with BMI [39-42]. Unadjustment for smoking status or alcohol drinking may be an important bias in the association between BMI and risk of thyroid nodule. Findings of present study covered adults and children, and the associations of BMI with thyroid nodule were consistent in two population after adjusted for important covariates. Base on large samples and reducing important biases, our findings indicate that overweight and obesity was associated with thyroid nodule in both adults and children. The association may be the certain metabolic consequences of excess adipose tissue. Leptin produced by adipocytes has important influences on central regulation of thyroid function through stimulation of TRH. This seems to be important for down-regulation of thyroid function in states of energy deficits, but the importance for modulation of thyroid function under more physiological conditions is uncertain[43 44]. Additionally, thyroid hormones may be a significant determinant of sleeping energy expenditure in subjects without overt thyroid dysfunction[45]. Similarly, differences in thyroid function, within what is considered the normal range, are associated with differences in BMI, caused by longstanding minor alterations in energy expenditure[11]. What`s more, obesity is associated with insulin resistance and increased production of insulin and insulin-like growth factors which in turn have been reported to be associated to thyroid disorders[27 46 47].

Being similar with thyroid cancer[27 37], thyroid nodules are more common in women than in men[48-52]. Sex differences in the association between BMI and thyroid cancer have been confirmed in other studies[31 53 54]. Similar results were observed in Korean[15]. The patients who were normal or overweight in BMI subgroup were identified to have higher frequency of thyroid nodules. However, the significant relationship between body size and thyroid nodule in the men were not observed. Our findings of adults were consistent with the sex difference in association of BMI with thyroid nodule. The difference in incidence between two genders suggests that growth and progression of thyroid tumors is influenced by sex hormones, particularly estrogens[55 56]. However, sex difference of the correlation between body size and thyroid nodule was not obvious among children. It may due to the smaller difference of sex hormones in children, compared to adults. Few studies noted the correlation between body size and thyroid nodule in children, the findings from children population require furthermore studies to confirm.

BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI or weight[57]. In the present study, BSA was significantly associated with thyroid nodule among adults and children. The association was not influenced by sex, age, resident location and iodine intake. Consistently, a positive association of thyroid cancer and current BSA in adults was found by Suzuki T in Japan in both sexes after adjusted for main covariates [58]. In addition, it was reported that BSA plays a dominant role in thyroid cancer risk and explains the apparent role of BMI in adults [57]. Muscle is more dense than fat, and BMI is not able to differentiate increased weight [59]. BSA is a more accurate measure of obesity, including central obesity, as it is a measurement of area and is able to account for the difference between muscle and fat better than BMI secondary to muscle versus fat [60]. In a way, the association between BSA and thyroid nodule more strongly and forcefully confirmed the increased risk of overweight and obesity with thyroid nodule than those of BMI.

Considering the potential selection bias introduced by subjects suffering from thyroid problems, we reevaluated the associations of height, weight, BMI and BSA with thyroid nodule after excluding subjects with diagnosed thyroid disease (Supplemental Table 1, Supplemental Table 2). Our analyses showed that the associations were very similar to our findings before excluding these subjects diagnosed thyroid diseases. Besides, we observed the similar associations of anthropometric measurement with thyroid nodule when considering quartile as cut-point (Supplemental Table 4). Our findings indicated that higher anthropometric measurement might be associate with thyroid nodule significantly among Chinese population. Further, our study performed in adult population and children population with a large sample size. Further, the weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report, reducing the bias of overestimation or underestimation of height and weight [61 62]. Moreover, all participants were screened for thyroid nodules via ultrasonography, reducing the p otential for screening bias. In addition, in order to reduce the possible bias, we adjusted for most main covariates, including cigarette smoking and alcohol drinking, two important factors influenced overweight [39-42]. Especially, salt type, salt appetite and diet patterns were taken as covariates in analysis models; the effect of iodine on risk of thyroid nodule was considered. Hence, the associations of anthropometric measurements were robust.

LIMITATION

There were several limitations in this study. Firstly, the circumferences of waist and hip were not measured. It hampered to examine the association of central adiposity with thyroid nodule. Secondly, the number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished. Thus, it is no way to find the different associations between anthropometric measurements and different kinds of thyroid nodule.

CONCLUSION

Our findings indicated that thyroid nodule risk increased with weight, height, BMI and BSA, especially in females. The similar trends of relationship between weight, BMI, BSA and thyroid nodule were observed in children. Among the four indicators, BSA was strongly associated with thyroid nodule. It implies that individual with high height and obesity has higher susceptibility for thyroid nodule.

CONTRIBUTORSHIP

The authors gave the following different contribution on this manuscript: Yunxian Yu generated the idea, modified and edited the manuscript. Weimin Xu supervised the study field activities, prepared and managed the datasets. Zexin Chen did statistical analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and interviewed study subjects in the study field. All authors read and approved the final manuscript. None of the authors had a conflict of interest. The manuscript has not been published and is not being considered for publication elsewhere, in whole or in

part, in any language, except as an abstract.

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COMPETING INTEREST

None

DATA SHARING

No additional unpublished data are available.

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TABLES

Table 1. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group among adults.

Variables	**Nodule (n=2228)**	**Non-nodule (n=4565)**	***P***
Age, year (Mean ± SD)	53.49±13.80	44.93±13.72	<0.001
Height, cm (Mean ± SD)	160.72±7.25	162.24±7.54	<0.001
Weight, kg (Mean ± SD)	59.30±8.12	59.10±8.33	0.177
BMI, kg/m^2 (Mean±SD)	23.07±2.69	22.52±2.65	<0.001
Gender, n(%)			
male	646(28.99)	1870(40.96)	<0.001
female	1582(61.01)	2695(59.04)	
Education[a], n(%)			
primary school	922(42.10)	1317(29.15)	<0.001
Junior high school	647(29.54)	1440(31.87))	
senior high school	470(21.46)	1283(28.40)	
junior college and above	151(6.89)	478(10.58)	
Marriage, n(%)			
single	78(3.51)	378(8.29)	<0.001
married	1980(88.98)	3981(87.30)	
divorce	22(0.99)	47(1.03)	
widowed	139(6.25)	140(3.07)	
others	6(0.27)	14(0.31)	
Resident location, n(%)			
urban area	1214(54.49)	2125(46.55)	<0.001
rural area	1014(45.52)	2440(53.45)	
Cigarette smoking, n(%)			
Never	1825(82.65)	3508(77.46)	<0.001
Ever	69(3.13)	121(2.67)	
Current	314(14.22)	900(19.87)	
Alcohol drinking, n(%)			
No	1822(83.27)	3608(80.55)	0.027
Yes	366(16.73)	871(19.45)	
Salt appetite, n(%)			
moderate	1135(51.24)	2479(54.52)	0.036
salty	469(21.17)	916(20.15)	

light	611(27.58)	1152(25.34)	
Milk consuming, n(%)			
Yes	837(42.02)	1965(45.55)	0.009
No	1155(57.98)	2349(54.45)	
Diet patterns[b], n(%)			
balanced	1662(74.73)	3484(76.32)	0.043
vegetarian	403(18.12)	722(15.82)	
meat	159(7.15)	359(7.89)	
Types of salt[c], n(%)			
Iodized salt	2082(94.38)	4385(96.65)	<0.001
Non-iodized	124(5.62)	152(3.35)	

[a:] Educational status: primary school group includes illiteracy, senior high school group is made of senior high school and technical secondary school

[b:] Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[c:] Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

Table 2. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	1334(59.87)	2576(56.43)	1.00	
high	894(40.13)	1989(43.57)	1.15(1.02,1.30)	0.0245
Weight[b]				
low	1222(54.85)	2760(60.46)	1.00	
high	1006(45.15)	1805(39.54)	1.40(1.24,1.58)	<0.0001
BMI[c]				
low	1438(64.54)	3351(73.41)	1.00	
high	790(35.46)	1214(26.59)	1.26(1.11,1.42)	0.0003
BSA[d]				
low	1068(47.94)	2675(58.60)	1.00	
high	1160(52.06)	1890(41.40)	1.43(1.27,1.62)	<0.0001
		Females		
Height[a]				
low	968(61.19)	1596(59.22)	1.00	
high	614(38.81)	1099(40.78)	1.24(1.07,1.44)	0.0050
Weight[b]				
low	946(59.80)	1960(72.73)	1.00	
high	636(40.20)	735(27.27)	1.71(1.47,1.98)	<0.0001
BMI[c]				
low	1002(63.64)	2048(75.99)	1.00	
high	580(36.66)	647(24.01)	1.47(1.26,01.72)	<0.0001
BSA[d]				
low	627(39.63)	1366(50.69)	1.00	
high	955(60.37)	1329(49.31)	1.53(1.32,1.77)	<0.0001
		Males		
Height[a]				
Low	366(56.66)	980(52.41)	1.00	
high	280(43.34)	890(47.59)	1.00(0.82,1.24)	0.9699
Weight[b]				
low	276(42.72)	800(42.78)	1.00	
high	370(57.28))	1070(57.28)	1.00(0.80,1.20)	0.8690

BMI[c]				
low	436(67.49)	1303(69.68)	1.00	
high	210(32.51)	567(30.32)	1.00(0.81,1.23)	0.9892
BSA[d]				
low	441(68.27)	1309(70.00)	1.00	
high	205(31.73)	561(30.00)	1.21(0.97,1.51)	0.0871

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**: Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**: Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

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Table 3. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group in children.

Variables	Nodule (n=257)	Non-nodule (n=2153)	*P*
Age, year (Mean ± SD)	12.01±2.73	11.06±3.56	<0.001
Height, cm (Mean ± SD)	150.50±15.84	142.90±19.68	<0.001
Weight, kg (Mean ± SD)	43.83±11.44	38.56±14.39	<0.001
Gender, n(%)			
male	108(42.02)	1083(50.30)	0.012
female	149(57.98)	1070(49.70)	
Resident location, n(%)			
urban area	153(59.53)	1028(47.75)	0.0004
rural area	104(40.47)	1125(52.25)	
Diet pattern[a], n(%)			
Balanced	202(78.91)	1663(77.46)	0.519
vegetarian	30(11.72)	271(12.62)	
Meat	24(9.37)	213(9.92)	
Salt appetite, n(%)			
Moderate	127(50.00)	1200(56.02)	0.042
Salty	61(24.02)	380(17.74)	
Light	66(25.98)	562(26.24)	
Milk consuming, n(%)			
Yes	192(80.67)	1599(77.73)	0.300
No	46(19.33)	458(22.27)	
Types of salt[b], n(%)			
Iodized salt	236(94.02)	2063(96.58)	0.042
Non-iodized	15(5.98)	73(3.42)	

[a:] Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[b:] Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

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Table 4. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	140(54.47)	1259(58.48)	1.00	
high	117(45.53)	894(41.52)	1.15(0.87,1.53)	0.3347
Weight[b]				
low	118(45.91)	1175(54.58)	1.00	
high	139(54.09)	978(45.42)	1.37(1.03,1.81)	0.0292
BMI[c]				
low	106(41.25)	1040(48.30)	1.00	
high	151(58.75)	1113(51.70)	1.38(1.04,1.83)	0.0248
BSA[d]				
low	77(29.96)	1144(52.22)	1.00	
high	180(70.04)	1009(47.78)	2.97(1.85,4.77)	<0.0001
		Girls		
Height[a]				
low	79(53.02)	643(60.09)	1.00	
high	70(46.98)	427(39.91)	1.30(0.89,1.90)	0.1719
Weight[b]				
low	63(42.28)	555(51.87)	1.00	
high	86(57.72)	515(48.13)	1.55(1.07,2.25)	0.0218
BMI[c]				
low	63(42.28)	488(45.61)	1.00	
high	86(57.72)	582(54.39)	1.25(0.86,1.81)	0.2391
BSA[d]				
low	43(28.86)	556(51.96)	1.00	
high	106(71.17)	514(48.04)	3.36(1.82,6.20)	0.0001
		Boys		
Height[a]				
low	61(56.48)	616(56.88)	1.00	
high	47(43.52)	467(43.12)	0.97(0.63,1.49)	0.8870
Weight[b]				
low	55(50.93)	620(57.25)	1.00	
high	53(49.07)	463(42.75)	1.15(0.75,1.77)	0.5120
BMI[c]				
low	43(39.81)	552(50.97)	1.00	

high	65(60.19)	531(49.03)	1.59(1.03,2.44)	0.0355
BSA[d]				
low	34(31.48)	588(54.29)	1.00	
high	74(68.52)	495(45.71)	2.57(1.25,5.28)	0.0104

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2;

Mean of male′s BSA=1.26 m^2, Mean of female′s BSA=1.22 m^2.

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Supplementary Table 1. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults without history of diseases related to thyroid.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	1120(61.57)	2348(57.20)	1.00	
high	699(38.43)	1757(42.80)	1.15(1.01,1.30)	0.0388
Weight[b]				
low	997(54.81)	2485(60.54)	1.00	
high	822(45.19)	1620(39.46)	1.39(1.22,1.58)	<0.0001
BMI[c]				
low	1156(63.55)	3009(73.30)	1.00	
high	663(36.45)	1096(26.70)	1.31(1.15,1.50)	<0.0001
BSA[d]				
low	897(49.31)	2415(58.83)	1.00	
high	922(50.69)	1690(41.17)	1.44(1.27,1.63)	<0.0001
		Females		
Height[a]				
low	797(62.81)	1449(60.10)	1.00	
high	472(37.19)	962(39.90)	1.23(1.04,1.44)	0.0147
Weight[b]				
low	753(59.34)	1758(72.92)	1.00	
high	516(40.66)	653(27.08)	1.68(1.44,1.97)	<0.0001
BMI[c]				
low	790(62.25)	1830(75.90)	1.00	
high	479(37.75)	581(24.10)	1.48(1.26,1.75)	<0.0001
BSA[d]				
low	512(40.35)	1230(51.02)	1.00	
high	757(59.65)	1181(48.98)	1.56(1.34,1.81)	<0.0001
		Males		
Height[a]				
low	323(58.73)	899(53.07)	1.00	
high	227(41.27)	795(46.93)	0.99(0.80,1.23)	0.9473
Weight[b]				
low	244(44.36)	727(42.92)	1.00	
high	306(55.64)	967(57.08)	0.96(0.78,1.19)	0.7087
BMI[c]				
low	366(66.55)	1179(69.60)	1.00	
high	184(33.45)	515(30.40)	1.05(0.84,1.30)	0.6881
BSA[d]				
low	385(70.00)	1185(69.95)	1.00	
high	165(30.00)	509(30.05)	1.18(0.93,1.48)	0.1705

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident

location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**: Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**: Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

Supplementary Table 2. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children without history of diseases related to thyroid.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight[b]				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI[c]				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA[d]				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
		Girls		
Height[a]				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight[b]				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI[c]				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m^2)[d]				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
		Boys		
Height[a]				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight[b]				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI[c]				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA[d]				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;
[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2; Mean of male's BSA=1.26 m^2, Mean of female's BSA=1.22 m^2.

Supplementary Table 3. Stratified criteria of height, weight, BMI and BSA among adults

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low	BMI<24.0	
High	BMI≥24	
BSA(m^2)		
low	BSA<1.80m^2	BSA<1.55m^2
high	BSA≥1.80m^2	BSA≥1.55m^2

Supplementary Table 4. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults without history of diseases related to thyroid.

Variables	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
	Pooled*		Female		Male	
Height(cm)[a]						
<156	1.00		1.00		1.00	
156-<161	1.19(1.01,1.40)	0.0363	1.21(1.02,1.44)	0.0260	1.13(0.48,2.65)	0.7843
161-<168	1.34(1.11,1.60)	0.0019	1.35(1.11,1.65))	0.0031	1.22(0.55,2.73)	0.6262
≥168	1.38(1.09,1.75)	0.0075	1.83(1.25,2.70)	0.0021	1.10(0.50,2.46)	0.8084
Weight(kg)[a]						
<54	1.00		1.00			
54-<60	1.20(1.02,1.43))	0.0330	1.13(0.94,1.35)	0.1936	1.00[&]	
60-<65	1.63(1.36,1.95)	<0.001	1.62(1.33,1.98)	<0.001	1.03(0.75,1.41)	0.8556
≥65	1.73(1.44,2.08)	<0.001	1.97(1.58,2.45)	<0.001	1.00(0.75,1.34)	0.9924
BMI[b]						
<18.5	1.00		1.00			
18.5-<24	1.50(1.09,2.04)	0.0116	1.41(1.02,1.93)	0.0350	/[#]	/
≥24	1.88(1.37,2.60)	0.0001	2.01(1.45,2.79)	<0.001	/	/
BSA(m^2)[a]						
<1.53	1.00		1.00		1.00	
1.53-<1.63	1.30(1.10,1.53)	0.0023	1.27(1.07,1.50)	0.0072	0.69(0.06,7.96)	0.7664
1.63-<1.74	1.78(1.49,2.12)	<0.001	1.78(1.47,2.16)	<0.001	0.75(0.07,8.43)	0.8120
≥1.74	1.86(1.51,2.29)	<0.001	2.15(1.63,2.83)	<0.001	0.72(0.06,8.12)	0.7892

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident location, types of salt, salt appetite, diet patterns, milk consuming;

a: 4 categories by quartile;

b: The criteria recommended by Working Group on Obesity in China;

&: No male`s weight <54kg;

#: the number of thyroid nodule patient BMI <18.5 is 0.

Dear editor,

Thank you very much for your comments and suggestions concerning our manuscript entitled“The Relationship of Anthropometric Measurement with the Risk of Thyroid Nodule in Chinese Population”. Those comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our researches. Based on reviewers’ comments, we have carefully modified manuscript. Revised portions are marked in red in the Manuscript. Meanwhile, the responses for all comments one by one as following:

Review 1

Comment 1:

The manuscript would benefit from some additional editing. There are several grammatical errors, and the Discussion section, in particular, appears unorganized and repetitive.

Response 1: We have carefully revised the manuscript.

Comment 2:

The rationale, as outlined in the Introduction, is not very convincing. What is the connection between thyroid nodules, thyroid function, and thyroid cancer? What biological or public health insights could be obtained through a greater understanding of the relationship for anthropometric factors and thyroid nodules? Why is a study based on a Chinese population needed, and how would this add to what is known from studies based in other populations? What is the rationale for examining these associations in both children and adults?

Response 2: As request, we have modified description in Introduction section.

Comment 3:

The authors should clarify the reason for examining BSA in this study. They state that BSA is “a better indicator of metabolic mass than body weight because it is less associa ted with excess body weight.” It is not clear what is meant by this statement, and no re ference is provided to refer to.

Response 3: We have revised the description in MATERIALS AND METHODS section (line 215-220).

Comment 4:

Height and weight were measured using a standardized protocol. This is an important detail that should be mentioned in the Abstract.

Response 4: We have added the detail description (line 34-35).

Comment 5:

All participants were screened for thyroid nodules via ultrasonography, thereby reducin g the potential for screening bias. This is an important strength that should be discusse d.

Response 5: We have added the strength to discussion section as request (line 426-427).

Comment 6:

The authors suggest that detection bias may explain the stronger association between b ody size and nodules in women, as has been suggested for thyroid cancer (page 18); ho wever, this population was screened for thyroid nodules, thereby reducing the potential for screening/detection biases. The findings from this study of thyroid nodules should primarily be compared with findings from studies with a similar design, which does no t include most studies of thyroid cancer. For instance, there are a few Korean studies p ublished of thyroid nodules based on populations that were screened for thyroid nodule s. How do the findings of this study compare with those?

Response 6: We have compared our finding with that of Korean study in

DISCUSSION (line 386-389).

Review 2

Materials and Methods:

Comment 1:

as the subjects and study design have been described in detail in a recent publication, t his part should be shortened giving more emphasis to the description of the variables of interest (anthropometry and thyroid nodule measurements)

Response 1: The description of subjects and study design has been shortened.

Comment 2:

The choice of a cut-point of 24 for BMI in adults should be justified.

Response 2: The cut-point of 24 for BMI is determined by the criteria recommended by Working Group on Obesity in China (line 186-187).

Comment 3:

Because of the large size of the population, it would be of interest to explore associatio ns with tertiles of exposures.

Response 3: We have added the results in Supplementary Table 4, and added the description to discussion section (line 381-384).

Comment 4:

How does the simplified formula used for the calculation of body surface area correlate to the formula by Boyd, in adults and children?

Response 4: Body surface area of both adults and children were calculated using the formula: $\mathrm{BSA} = \sqrt{\mathrm{Weight} * \mathrm{Height}}/60$.

Comment 5:

The description of the population as presented in Table 1 should be part of the Results s ection of the manuscript.

Response 5: The description of the population as presented in Table 1 has been added to result section (line 247-259).

-Statistical analyses:

Comment 1:

Justification to the choice of the variables retained for adjustment should be given

Response 1: The variables showing significant difference between two groups were taken as covariates in logistic regression models. We have added the description in Statistical analysis section (line 232)**.**

-Results:

Comment 1:

References to Tables should be checked. For example, pag 12, line 230, reference shou ld be to table 1. Line 240, reference should be made to table 2.

Response 1： We have checked all the references to tables and revised the mistakes as request.

-Tables:

Comment 1: Table 1: Mean and SD for BMI should be indicated.

Response 1: This point was done.

Comment 2:

Table 3: Mean and SD for anthropometric variables should be presented.

Response 2: We have added it in Table 3.

Comment 3:

For ease of comparisons, tables 1 and 3 could be combined by adding additional colum ns to Table 1.

Response 3: The adults and children are different population, and the socio-demographic characteristics of adult and children are different (education, marriage, smoking and drinking were not included in children). Hence, we still keep Table 1 and Table 3.

Comment 4: There is no reference to Supplementary tables in the text

Response 4: We have revised the reference to supplementary tables in discussion section (line 214, line 420).

-Discussion:

Comment 1:

As the study presented has a cross-sectional design, it would be important to state that no causality can be inferred. Some conclusions on associations in this section may ther efore be smoothened, and the title of the manuscript may be rephrased as "The relation ship of anthropometric measurements with thyroid nodules in a Chinese population"

Response 1: The title and conclusions were modified.

Comment 2: Pag 14, line 286: the EPIC study includes about half-a-million subjects.

Response 2: We have revised (line 313).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(line 32)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(line44-47)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(line 70-92)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(line 94-98)**
Methods		
Study design	4	Present key elements of study design early in the paper **(line 102-103)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection**(line 102-104)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **(line 109-130)**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(line 132-204)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(line 168-204)**
Bias	9	Describe any efforts to address potential sources of bias **(line 214-219)**
Study size	10	Explain how the study size was arrived at **(line 110-117)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(line 207-211)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(line 207-214, line 219-221)**
		(*b*) Describe any methods used to examine subgroups and interactions **(line213-214)**
		(*c*) Explain how missing data were addressed **(line211)**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **(N/A)**
		(*e*) Describe any sensitivity analyses **(N/A)**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(line227-229)**
		(b) Give reasons for non-participation at each stage **(line227)**
		(c) Consider use of a flow diagram **(N/A)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **（line 226-235）**
		(b) Indicate number of participants with missing data for each variable of interest **（Table 1）**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **（line 231-235）**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **（line -237-257）**
		(*b*) Report category boundaries when continuous variables were categorized **（line218-219）**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **（N/A）**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **（N/A）**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(line 260-264)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(line 397-403)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(line 265-385)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(line 260-262)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(line 424-429)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Relationship of Anthropometric Measurement with Thyroid Nodule in a Chinese Population

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, STATISTICS & RESEARCH METHODS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

The Relationship of Anthropometric Measurement with Thyroid Nodule in a Chinese Population

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ABSTRACT

Objective: Previous studies have found that overweight and obesity have been related to numerous diseases, including thyroid cancer and thyroid volume. This study is to evaluate the relationship between body size and thyroid nodule in Chinese population.

Methods: A total of 6,793 adults and 2,410 children who underwent thyroid ultrasonography were recruited in this cross-sectional study, Hangzhou, Zhejiang province, China, from March to October, 2010. The socio-demographic characteristics and potential risk factors of thyroid nodule were collected using questionnaire. Height and weight were measured using standard protocols. The associations of height, weight, Body Mass Index (BMI) and Body Surface Area (BSA) with thyroid nodule were evaluated using multiple logistic regression models.

Results: After adjusted potential risk factors, an increased risk of thyroid nodule was respectively associated with height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40, 95% CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) among all adults, obviously in females. Similar associations between weight, BMI, BSA and the risk of thyroid nodule were observed in children, but not height. BSA was highest significantly associated with thyroid nodule among both adult and children.

Conclusion: The present study identified that thyroid nodule was positively associated with weight, height, BMI and BSA among both female adults and girls. It implied that individual with high height and obesity increased the susceptibility for

thyroid nodule.

Keywords: anthropometric measurement, thyroid nodule, adult, children, Chinese population

Article summary:

Strengths and limitations of this study：

1) Including adult and children subjects.
2) Large sample size of subjects.
3) The weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report.
4) The main results was presented after adjustment for many potential confounders, including cigarette smoking and alcohol drinking, two important factors influenced overweight
5) The number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished.

INTRODUCTION

The most of thyroid nodules are benign nodules[1], but 5-6.5% of them are malignant (carcinomas, CA)[2]. Because thyroid function is linked to development and growth, height and weight are seen as possible indicators of thyroid nodule risk. Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Overweight and obesity are the fifth leading risk for global deaths. In addition, between 7% and 41% of certain cancer burdens are attributable to overweight and obesity[3]. Data from epidemiological studies demonstrate a direct correlation between BMI and the risk of medical complications and mortality rate[4 5]. The prevalence of overweight and obesity has been increasing in most economically developed countries for several decades, and there is evidence that the prevalence of overweight and obesity is also increasing in economically developing countries[6 7]. The prevalence of obesity has recently been dramatically increasing in China as a developing country. A national survey indicates that the prevalence of overweight and obesity were 24.1% and 2.8% in men and 26.1% and 5.0% in women, respectively [8]. Meanwhile, previous studies reported functional and morphological alterations of the thyroid gland in relation to obesity [9-13]. Due that thyroid hormones increase the basal metabolic rate, low thyroid function, even within the clinically normal range, could decrease metabolic speed and lead to obesity[13 14]. In addition, Mehmet Bastemir [12] found that serum TSH levels are positively correlated with the degree of obesity and some of its metabolic consequences in overweight people with normal thyroid function. Furthermore, S.Guth[15] reported that BMI were positively correlated with sizes of their thyroids. Though the vast majority of nodules are benign, the risk factors for thyroid nodules among euthyroid population have not yet been fully elucidated. Previous study in Chinese population indicated overweight (OR = 1.199, 95% CI: 1.078 - 1.333) might be a risk factor for thyroid nodules after adjusting for age and gender[16]. Similarly, S. Guth[15] observed that mean thyroid size was correlated strongly with body weight. However, Kim JY[17] reported that the patients with thyroid nodule had lower height, weight and body surface area (BSA) than those without thyroid nodule in Koreans. Especially, in the women, lower height and overweight were identified as independent risk factors for the presence of thyroid nodules.

Therefore, the association of anthropometric measurements with thyroid nodule is still unclear. Additionally, previous studies rarely focus on the relationship of anthropometric measurements with thyroid nodule in Chinese population. The aim of our study is to examine the relationship of anthropometric measurements with thyroid nodule in a large sample size of Chinese population.

MATERIALS AND METHODS

Population features

From March to October 2010, this large cross-sectional study was conducted in Hangzhou city, which is one of the leading commercial cities in eastern China. The detail population feature was described in a published article [18].

Subjects and study design

All participants were recruited based on following strategies: There are eight districts and five counties in big Hangzhou city. Firstly, three sub-districts or towns were selected randomly from each district or county (except Binjiang district) respectively, so 36 sub-districts or towns were selected from big Hangzhou. Secondly, one community or village was randomly selected from each sub-district or town. Thirdly, 100 households from each community or village were randomly selected. Finally, we selected 3600 households for the interview. The family members of household were chosen based on the following criteria: (1) age at least 6 years; (2) living for above 5 years at present residence. The exclusion criteria: (1) the participants with coronary angiography (CAG) or endoscopic retrograde cholangiopancreatography (ERCP) in 6 months; (2) the participants taking amiodarone drug; (3) the participants with abnormal kidney function or serious illness.

The eligible family members of selected households were convened to village or community administration center. The researchers introduced the study protocol and obtained written informed consent form from each participant. Meanwhile, the interview schedule was appointed with participants. The study protocol was approved by Institutional Review Board of Hangzhou Center of Disease Control and Prevention. This survey was carried out by well-trained personnel (including community clinic physicians, nurses, public health doctors).

Collection of epidemiological data

The participants were interviewed for a structured questionnaire. The questionnaire covered the information about demographic characteristics and health status, including sex, age, nationality, physical activity, lifestyle, dietary habit, and personal or family history of thyroid disease (including time of diagnosis).

Data collection of anthropometric measurements and thyroid nodule

Height and weight were measured using standard protocols, without shoes or outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer with a GMCS-I type height tester (Beijing). Weight was measured to the nearest 0.1 kg with the subjects standing motionless on a scale with a balance-beam scale (RGT-140, weighing Apparatus Co. Ltd. Wuxi). An ultrasound examination of thyroid was performed to detect thyroid nodules by a Sonoline Versa Pro (Siemens, Munich, Germany) with a 7.5-MHz, 70-mm linear transducer (effective length, 62 mm). Thyroid nodule was defined as discrete lesion which was distinct from the surrounding thyroid parenchyma and which had solid portion regardless of having cystic portion.

Body Mass Index (BMI)

The BMI is defined as the weight in kilograms divided by the square of the height in meters. Although the BMI calculation is not taken into account factors such as frame size and body tissue compositions, BMI categories are generally used as a means of estimating adiposity and assessing how much an individual's body weight departs from what is normal or desirable for a person of the same height. According to the criteria recommended by Working Group on Obesity in China[19], the classification of BMI for adults was as follows: BMI < 24, group low (normal and underweight); 24 ≤ BMI, group high (overweight and obese). Among children, the reference BMI was calculated using the reference height and weight of each age group[20].

Body Surface Area (BSA)

BSA is a commonly used index in clinical practice to correct for patient size differences in various physiologic measurements and in calculating drug dosage. BSA is a more accurate measure of obesity, including central obesity, as it is a measurement of area and is able to account for the difference between muscle and fat better than BMI secondary to muscle versus fat [21]. Previous studies observed the association of BSA with thyroid volume and nodules[17 22].Various formulas have been proposed to estimate the BSA from a patient's weight and height, which may result in slightly different values [23-26]. The most commonly used formula in day-to-day clinical practice is the Mosteller formula: BSA (m^2) = (square root of product of weight [kg]×height [cm]) /60 [25]. This formula is simplified from a formula produced by Gehan and George [23], and has become a common standard because it is easy to memorize, and its use requires only a handheld calculator. So Mosteller formula was used in our study to calculate BSA.

Definition of variables

Among adults, the height, weight, BMI and BSA were dichotomized into high group and low group. The detailed criteria of each group were shown in Supplementary Table 1. The classification of height and weight among adults refers to The Survey Report on National Physical Fitness of Chinese, 2005. In children, high group included subjects with height or weight ≥ reference standard of each age bracket (one year a bracket) in two genders. BMI was classified according to the reference calculated using the reference height and weight of each age bracket (one year a bracket) in two genders respectively[20]. BSA was classified by the average value of each gender.

Statistical analysis

The comparison of height, weight and age between patients with and without thyroid nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test for qualitative data, including gender, education, marriage, resident location, cigarette smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of salt. Listwise deletion was used to address the missing data in the model.

The adjusted associations of height, weight, BMI and BSA with thyroid nodule were estimated, using logistic regression model stratified by gender. The variables showing significant difference between group with and without thyroid nodule were taken as covariates in logistic regression models: age, BMI, educational level, marital status, resident location, cigarette smoking, alcohol drinking, diet flavor, types of salt, dietary patterns, milk consumption. Among adults, age was classified as 5 classes: 18~29, 30~39, 40~49, 50~59, ≥ 60. Among children, age was classified as 4 classes: 6~8, 9~11, 12~14, 15~17. To account for the correlation of members in a same household, we calculated robust estimates of variances with generalized estimate equation (GEE) using SAS procedure GENMOD. All analyses were performed in SAS Version 9.0 (SAS Institute, Inc., Cary, NC, USA). A value of P<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of study population

A total of 12,438 individuals were recruited in this investigation, but 3,235 individuals were excluded for analyses, due to absence of anthropometic measurements. Final analyses included 9,203 subjects: 6,793 adults, and 2,410 children. Among adults, the average age was 47.93 years; females accounted for 62.96%; the underweight, normal, overweight and obese was 4.39%, 66.13%, 26.34% and 3.14%, respectively. The socio-demographic characteristics among patients with thyroid nodule and non-nodule group for adults were shown in Table 1; Out of 6,793 adults, 2,228 (32.80%) adults had thyroid nodule, of which women accounted for 71.01%. Subjects with thyroid nodule was older, shorter, and more females (p<0.05). Moreover, the distributions of education, marital status, resident location, smoking, drinking, salt appetite, milk consuming and diet patterns had significant difference between two groups (Table 1). The socio-demographic characteristics among patients with thyroid nodule and non-nodule group for children were shown in Table 2. Subjects with thyroid nodule was older, and more females ($p<0.05$). The distributions of resident location, salt appetite and type of salts had significant difference between two groups (Table 2). Among children, 47.55% were under the reference BMI, 52.45% over the reference BMI. 257 (10.66%) children suffered from thyroid nodule, which more than half (57.98%) were girls (Table 2).

The relationship between anthropometric measurements and thyroid nodule among adults tertile

The relationship between anthropometric measurements (height, weight, BMI, BSA) and thyroid nodule were estimated by gender (Table 3). The height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40, 95%CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) were significantly associated with an increased risk of thyroid nodule among pooled adults, respectively. Similar trends were observed in females and males, but no significant association in males. The associations with tertiles of exposures (height, weight, BMI, BSA) were very similar to the previous findings when those subjects diagnosed thyroid diseases were excluded (Supplementary Table 2).

The relationship between anthropometric measurements and thyroid nodule

among children

The relationship of anthropometric measurements with thyroid nodule was also conducted among children (Table 4). The weight (OR=1.37, 95% CI: 1.03–1.81), BMI (OR=1.38, 95% CI: 1.04–1.83) and BSA (OR=2.97, 95% CI: 1.85–4.77) were significantly associated with thyroid nodule among all children. The significant association of BSA with thyroid nodule was observed in both boys (OR=2.57, 95% CI: 1.25–5.28) and girls (OR=3.36, 95% CI: 1.82–6.20); BMI and weight were also positively related with thyroid nodule among both genders, but significant association of BMI among boys and significant association of weight among girls was observed respectively. The significant association of height with thyroid nodule was not observed among children.

DISCUSSION

This study, performed in a large Chinese population, demonstrated that height, weight, BMI and BSA were positively associated with thyroid nodule among adults and children respectively, but only significantly in female adults and children. More explicitly, in the present study, the significant association between high BSA and thyroid nodule was not obviously influenced by sex, age, resident location and iodine intake.

Thyroid nodule is very common disease in the general population. The present investigation showed that the prevalence of thyroid nodule was 32.80% in adults and

10.66% in children; but they are found clinically in 4-8% of cases[27]. In our study, high height and heavy weight was significantly associated with thyroid nodule in all adults and female, respectively. But only significant relationship of weight with thyroid nodule was found in children population. To data, few study was focus on the relationship between anthropometric indexes and thyroid nodule. Previous study showed that thyroid nodule might share similar risk factors with thyroid cancer: iodine deficiency was associated with an increased TC incidence, largely via benign thyroid conditions such as nodules, which were, in turn, strongly associated with TC. Additionally, body size might be associated with the iodine requirement and, hence, indirectly related to thyroid nodule[28].

Our results were similar to the findings among 88,256 Canadian women in 2012. It is reported that height was positively associated with the risk of all combined cancers and thyroid cancer, and height was significantly positively associated with risk of thyroid cancer in multivariable models [29]. Further, the European Prospective Investigation into Cancer and nutrition (EPIC), a large study including half-a-million subjects, also observed the positive association of height with thyroid cancer in female but not in male[30]. Beyond those findings from European population, a pooled analysis of individual data from 12 case-control studies conducted in eight countries (America, Asia, and Europe) suggests that height was moderately related to thyroid cancer risk[31]. In addition, similar association of height with thyroid nodule risk among Korean was observed in females but not males[17]. In our findings of Chinese population, the moderate association of height with thyroid nodule was also observed in females, which was consistent with those from Korea in Asia and even European population. However, the association was not significant among children, but we still found an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90). It may due to the small case numbers of children, and the association between height and thyroid nodule among children needs more studies to confirm.

Furthermore, similar to height, the meta-analysis of data from eight countries also indicated the association of weight and risk of thyroid cancer in female rather than male[31]. In 2010, Clavel-Chapelon F[32] reported that there was a significant dose-effect relationship between thyroid cancer risk and weight in France. In Asia, the significant association between weight and thyroid nodule in female was observed among Korean population[17]. Our data confirmed these findings after adjusted for the relevant covariates. Altered thyroid status has profound effects on skeletal development and growth, and on adult bone maintenance. The fact that thyroid hormones are associated with the regulation of the growth of long bones may be one possible explanation for the association between height and thyroid nodule[33]. Moreover, genetic or environmental factors (e.g., dietary factors, nutritious factors), correlate with adult height and weight, also influence thyroid function might be another possible explanation for their association[31].

Analogously, the significant associations between BMI and thyroid nodule were observed among all adults. Similar association was observed in women, but not in men. Among children, significant associations of BMI with thyroid nodule were also observed. Our findings in adults were consistent with that in German [34] and Italian [35], and similar to those among Korean population [17]. However, Results from previous prospective and case-control studies on the association of BMI with thyroid cancer risk have generally been more inconsistent in men than women. In a large Norwegian cohort of more than two million participants, the risk of thyroid cancer increased moderately with increased BMI in both sexes, but the results were unadjusted for smoking and other potential confounders [36]. After adjusted for key covariates such as cigarette smoking, alcohol drinking, physical activity and medical history of diabetes, the largest prospective study conducted in U.S. also observed a significant positive association between BMI and thyroid cancer risk in women [37]. Moreover, a systematic review conducted by Emily Peterson[38] in 2012 (including 37 studies) showed that most of studies supported a positive association of BMI with thyroid cancer in both sexes. The inconsistent results between men and women in previous studies is likely due to smaller numbers of cases in men, to the lack of control for important covariates (e.g. cigarette smoking, alcohol intake). Current smoking and alcohol intake are associated with BMI [39-42]. Un-adjustment for smoking status or alcohol drinking may be an important bias in the association between BMI and risk of thyroid nodule. Findings of present study covered adults and children, and the associations of BMI with thyroid nodule were consistent in adult and children after adjusted for important covariates. Base on large samples and reducing important biases, our findings indicate that overweight and obesity was associated with thyroid nodule in both adults and children. The association may be the certain metabolic consequences of excess adipose tissue. Leptin produced by adipocytes has important influences on central regulation of thyroid function through stimulation of TRH. This seems to be important for down-regulation of thyroid function in states of energy deficits, but the importance for modulation of thyroid function under more physiological conditions is uncertain[43 44]. Additionally, thyroid hormones may be a significant determinant of sleeping energy expenditure in subjects without overt thyroid dysfunction[45]. Similarly, differences in thyroid function, within what is considered the normal range, are associated with differences in BMI, caused by longstanding minor alterations in energy expenditure[13]. What`s more, obesity is associated with insulin resistance and increased production of insulin and insulin-like growth factors which in turn have been reported to be associated to thyroid disorders[2 46 47].

Being similar with thyroid cancer[2 37], thyroid nodules are more common in women than in men[48-52]. Sex differences in the association between BMI and thyroid cancer have been confirmed in other studies[31 53 54]. Similar results were observed in Korean[17]. The patients who were normal or overweight in BMI subgroup were identified to have higher frequency of thyroid nodules. However, the significant relationship between body size and thyroid nodule in the men were not observed. Our findings of adults were consistent with the sex difference in association of BMI with thyroid nodule. The difference in incidence between two genders suggests that growth and progression of thyroid tumors is influenced by sex hormones, particularly estrogens[55 56]. However, sex difference of the correlation between body size and thyroid nodule was not obvious among children. It may due to the smaller difference of sex hormones in children, compared to adults. Few studies noted the correlation between body size and thyroid nodule in children, the findings from children population require furthermore studies to confirm.

BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI or weight[57]. In the present study, BSA was significantly associated with thyroid nodule among adults and children. The association was not influenced by sex, age, resident location and iodine intake. Consistently, a positive association of thyroid cancer and current BSA in adults was found by Suzuki T in Japan in both sexes after adjusted for main covariates [58]. In addition, it was reported that BSA plays a dominant role in thyroid cancer risk and explains the apparent role of BMI in adults [57]. Muscle is more dense than fat, and BMI is not able to differentiate increased weight [59]. BSA is a more accurate measure of obesity, including central obesity, as it is a measurement of area and is able to account for the difference between muscle and fat better than BMI secondary to muscle versus fat [21]. In a way, the association between BSA and thyroid nodule more strongly and forcefully confirmed the increased risk of overweight and obesity with thyroid nodule than those of BMI.

Considering the potential selection bias introduced by subjects suffering from thyroid problems, we reevaluated the associations of height, weight, BMI and BSA with thyroid nodule after excluding subjects with diagnosed thyroid disease (Supplemental Table 3, Supplemental Table 4). Our analyses showed that the associations were very similar to our findings before excluding these subjects diagnosed thyroid diseases. Besides, we observed the similar associations of anthropometric measurement with thyroid nodule when considering quartile as cut-point (Supplemental Table 2). Our findings indicated that higher anthropometric measurement might be associate with thyroid nodule significantly among Chinese population. Further, our study performed in adult population and children population with a large sample size. Further, the weight and standing height were measured in a standardized protocol by a trained examiner rather than self-report, reducing the bias of overestimation or underestimation of height and weight [60 61]. Moreover, all participants were screened for thyroid nodules via ultrasonography, reducing the potential for screening bias. In addition, in order to reduce the possible bias, we adjusted for most main covariates, including cigarette smoking and alcohol drinking, two important factors influenced overweight [39-42]. Especially, salt type, salt appetite and diet patterns were taken as covariates in analysis models; the effect of iodine on risk of thyroid nodule was considered. Hence, the associations of anthropometric measurements were robust.

LIMITATION

There were several limitations in this study. Firstly, the circumferences of waist and hip were not measured. It hampered to examine the association of central adiposity with thyroid nodule. Secondly, the number and mass size of thyroid nodule were not recorded in the investigation, and the classification of thyroid nodules was not distinguished. Thus, it is no way to find the different associations between anthropometric measurements and different kinds of thyroid nodule. Also, the age difference between the subjects with and without thyroid nodules may be a potential bias.

CONCLUSION

Our findings indicated that thyroid nodule risk increased with weight, height, BMI and BSA, especially in females. The similar trends of relationship between weight, BMI, BSA and thyroid nodule were observed in children. Among the four indicators, BSA was mostly strongly associated with thyroid nodule. It implies that individual with high height and obesity has higher susceptibility for thyroid nodule.

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Contribution statement

The authors gave the following different contribution on this manuscript: Yunxian Yu generated the idea, modified and edited the manuscript. Weimin Xu supervised the study field activities, prepared and managed the datasets. Zexin Chen did statistical

analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and interviewed study subjects in the study field.

Competing interests

All authors read and approved the final manuscript. None of the authors had a conflict of interest. The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract.

Data sharing statement

No additional unpublished data are available.

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TABLES

Table 1. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group among adults.

Variables	Nodule (n=2228)	Non-nodule (n=4565)	*P*
Age, year (Mean ± SD)	53.49±13.80	44.93±13.72	<0.001
Height, cm (Mean ± SD)	160.72±7.25	162.24±7.54	<0.001
Weight, kg (Mean ± SD)	59.30±8.12	59.10±8.33	0.177
BMI, kg/m^2 (Mean ± SD)	23.07±2.69	22.52±2.65	<0.001
Gender, n(%)			
male	646(28.99)	1870(40.96)	<0.001
female	1582(61.01)	2695(59.04)	
Education[a], n(%)			
primary school	922(42.10)	1317(29.15)	<0.001
Junior high school	647(29.54)	1440(31.87))	
senior high school	470(21.46)	1283(28.40)	
junior college and above	151(6.89)	478(10.58)	
Marriage, n(%)			
single	78(3.51)	378(8.29)	<0.001
married	1980(88.98)	3981(87.30)	
divorce	22(0.99)	47(1.03)	
widowed	139(6.25)	140(3.07)	
others	6(0.27)	14(0.31)	
Resident location, n(%)			
urban area	1214(54.49)	2125(46.55)	<0.001
rural area	1014(45.52)	2440(53.45)	
Cigarette smoking, n(%)			
Never	1825(82.65)	3508(77.46)	<0.001
Ever	69(3.13)	121(2.67)	
Current	314(14.22)	900(19.87)	
Alcohol drinking, n(%)			
No	1822(83.27)	3608(80.55)	0.027
Yes	366(16.73)	871(19.45)	
Salt appetite, n(%)			
moderate	1135(51.24)	2479(54.52)	0.036
salty	469(21.17)	916(20.15)	
light	611(27.58)	1152(25.34)	
Milk consuming, n(%)			
Yes	837(42.02)	1965(45.55)	0.009
No	1155(57.98)	2349(54.45)	
Diet patterns[b], n(%)			
balanced	1662(74.73)	3484(76.32)	0.043

vegetarian	403(18.12)	722(15.82)	
meat	159(7.15)	359(7.89)	
Types of salt[c], n(%)			
Iodized salt	2082(94.38)	4385(96.65)	<0.001
Non-iodized	124(5.62)	152(3.35)	

[a]: Educational status: primary school group includes illiteracy, senior high school group is made of senior high school and technical secondary school

[b]: Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[c]: Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

Table 2. The distributions of socio-demographic characteristics among patients with thyroid nodule and non-nodule group in children.

Variables	Nodule (n=257)	Non-nodule (n=2153)	*P*
Age, year (Mean ± SD)	12.01±2.73	11.06±3.56	<0.001
Height, cm (Mean ± SD)	150.50±15.84	142.90±19.68	<0.001
Weight, kg (Mean ± SD)	43.83±11.44	38.56±14.39	<0.001
Gender, n(%)			
male	108(42.02)	1083(50.30)	0.012
female	149(57.98)	1070(49.70)	
Resident location, n(%)			
urban area	153(59.53)	1028(47.75)	0.0004
rural area	104(40.47)	1125(52.25)	
Diet pattern[a], n(%)			
Balanced	202(78.91)	1663(77.46)	0.519
vegetarian	30(11.72)	271(12.62)	
Meat	24(9.37)	213(9.92)	
Salt appetite, n(%)			
Moderate	127(50.00)	1200(56.02)	0.042
Salty	61(24.02)	380(17.74)	
Light	66(25.98)	562(26.24)	
Milk consuming, n(%)			
Yes	192(80.67)	1599(77.73)	0.300
No	46(19.33)	458(22.27)	
Types of salt[b], n(%)			
Iodized salt	236(94.02)	2063(96.58)	0.042
Non-iodized	15(5.98)	73(3.42)	

[a:] Vegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

[b:] Iodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

Table 3. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	1334(59.87)	2576(56.43)	1.00	
high	894(40.13)	1989(43.57)	1.15(1.02,1.30)	0.0245
Weight[b]				
low	1222(54.85)	2760(60.46)	1.00	
high	1006(45.15)	1805(39.54)	1.40(1.24,1.58)	<0.0001
BMI[c]				
low	1438(64.54)	3351(73.41)	1.00	
high	790(35.46)	1214(26.59)	1.26(1.11,1.42)	0.0003
BSA[d]				
low	1068(47.94)	2675(58.60)	1.00	
high	1160(52.06)	1890(41.40)	1.43(1.27,1.62)	<0.0001
		Females		
Height[a]				
low	968(61.19)	1596(59.22)	1.00	
high	614(38.81)	1099(40.78)	1.24(1.07,1.44)	0.0050
Weight[b]				
low	946(59.80)	1960(72.73)	1.00	
high	636(40.20)	735(27.27)	1.71(1.47,1.98)	<0.0001
BMI[c]				
low	1002(63.64)	2048(75.99)	1.00	
high	580(36.66)	647(24.01)	1.47(1.26,01.72)	<0.0001
BSA[d]				
low	627(39.63)	1366(50.69)	1.00	
high	955(60.37)	1329(49.31)	1.53(1.32,1.77)	<0.0001
		Males		
Height[a]				
Low	366(56.66)	980(52.41)	1.00	
high	280(43.34)	890(47.59)	1.00(0.82,1.24)	0.9699
Weight[b]				
low	276(42.72)	800(42.78)	1.00	
high	370(57.28))	1070(57.28)	1.00(0.80,1.20)	0.8690
BMI[c]				
low	436(67.49)	1303(69.68)	1.00	
high	210(32.51)	567(30.32)	1.00(0.81,1.23)	0.9892
BSA[d]				
low	441(68.27)	1309(70.00)	1.00	
high	205(31.73)	561(30.00)	1.21(0.97,1.51)	0.0871

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**: Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**: Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

Table 4. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	140(54.47)	1259(58.48)	1.00	
high	117(45.53)	894(41.52)	1.15(0.87,1.53)	0.3347
Weight[b]				
low	118(45.91)	1175(54.58)	1.00	
high	139(54.09)	978(45.42)	1.37(1.03,1.81)	0.0292
BMI[c]				
low	106(41.25)	1040(48.30)	1.00	
high	151(58.75)	1113(51.70)	1.38(1.04,1.83)	0.0248
BSA[d]				
low	77(29.96)	1144(52.22)	1.00	
high	180(70.04)	1009(47.78)	2.97(1.85,4.77)	<0.0001
		Girls		
Height[a]				
low	79(53.02)	643(60.09)	1.00	
high	70(46.98)	427(39.91)	1.30(0.89,1.90)	0.1719
Weight[b]				
low	63(42.28)	555(51.87)	1.00	
high	86(57.72)	515(48.13)	1.55(1.07,2.25)	0.0218
BMI[c]				
low	63(42.28)	488(45.61)	1.00	
high	86(57.72)	582(54.39)	1.25(0.86,1.81)	0.2391
BSA[d]				
low	43(28.86)	556(51.96)	1.00	
high	106(71.17)	514(48.04)	3.36(1.82,6.20)	0.0001
		Boys		
Height[a]				
low	61(56.48)	616(56.88)	1.00	
high	47(43.52)	467(43.12)	0.97(0.63,1.49)	0.8870
Weight[b]				
low	55(50.93)	620(57.25)	1.00	
high	53(49.07)	463(42.75)	1.15(0.75,1.77)	0.5120
BMI[c]				
low	43(39.81)	552(50.97)	1.00	
high	65(60.19)	531(49.03)	1.59(1.03,2.44)	0.0355
BSA[d]				
low	34(31.48)	588(54.29)	1.00	
high	74(68.52)	495(45.71)	2.57(1.25,5.28)	0.0104

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;

[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2;

Mean of male′s BSA=1.26 m^2, Mean of female′s BSA=1.22 m^2.

Supplementary Table 1. Stratified criteria of height, weight, BMI and BSA among adults

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low	BMI<24.0	
High	BMI≥24	
BSA(m^2)		
low	BSA<1.80m^2	BSA<1.55m^2
high	BSA≥1.80m^2	BSA≥1.55m^2

Supplementary Table 2. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults without history of diseases related to thyroid.

Variables	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
	Pooled*		Female		Male	
Height(cm)[a]						
<156	1.00		1.00		1.00	
156-<161	1.19(1.01,1.40)	0.0363	1.21(1.02,1.44)	0.0260	1.13(0.48,2.65)	0.7843
161-<168	1.34(1.11,1.60)	0.0019	1.35(1.11,1.65))	0.0031	1.22(0.55,2.73)	0.6262
≥168	1.38(1.09,1.75)	0.0075	1.83(1.25,2.70)	0.0021	1.10(0.50,2.46)	0.8084
Weight(kg)[a]						
<54	1.00		1.00			
54-<60	1.20(1.02,1.43))	0.0330	1.13(0.94,1.35)	0.1936	1.00[&]	
60-<65	1.63(1.36,1.95)	<0.001	1.62(1.33,1.98)	<0.001	1.03(0.75,1.41)	0.8556
≥65	1.73(1.44,2.08)	<0.001	1.97(1.58,2.45)	<0.001	1.00(0.75,1.34)	0.9924
BMI[b]						
<18.5	1.00		1.00			
18.5-<24	1.50(1.09,2.04)	0.0116	1.41(1.02,1.93)	0.0350	/[#]	/
≥24	1.88(1.37,2.60)	0.0001	2.01(1.45,2.79)	<0.001	/	/
BSA(m^2)[a]						
<1.53	1.00		1.00		1.00	
1.53-<1.63	1.30(1.10,1.53)	0.0023	1.27(1.07,1.50)	0.0072	0.69(0.06,7.96)	0.7664
1.63-<1.74	1.78(1.49,2.12)	<0.001	1.78(1.47,2.16)	<0.001	0.75(0.07,8.43)	0.8120
≥1.74	1.86(1.51,2.29)	<0.001	2.15(1.63,2.83)	<0.001	0.72(0.06,8.12)	0.7892

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident location, types of salt, salt appetite, diet patterns, milk consuming;

a: 4 categories by quartile;

b: The criteria recommended by Working Group on Obesity in China;

&: No male`s weight <54kg;

#: the number of thyroid nodule patient BMI <18.5 is 0.

Supplementary Table 3. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among adults without history of diseases related to thyroid.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
		Pooled*		
Height[a]				
low	1120(61.57)	2348(57.20)	1.00	
high	699(38.43)	1757(42.80)	1.15(1.01,1.30)	0.0388
Weight[b]				
low	997(54.81)	2485(60.54)	1.00	
high	822(45.19)	1620(39.46)	1.39(1.22,1.58)	<0.0001
BMI[c]				
low	1156(63.55)	3009(73.30)	1.00	
high	663(36.45)	1096(26.70)	1.31(1.15,1.50)	<0.0001
BSA[d]				
low	897(49.31)	2415(58.83)	1.00	
high	922(50.69)	1690(41.17)	1.44(1.27,1.63)	<0.0001
		Females		
Height[a]				
low	797(62.81)	1449(60.10)	1.00	
high	472(37.19)	962(39.90)	1.23(1.04,1.44)	0.0147
Weight[b]				
low	753(59.34)	1758(72.92)	1.00	
high	516(40.66)	653(27.08)	1.68(1.44,1.97)	<0.0001
BMI[c]				
low	790(62.25)	1830(75.90)	1.00	
high	479(37.75)	581(24.10)	1.48(1.26,1.75)	<0.0001
BSA[d]				
low	512(40.35)	1230(51.02)	1.00	
high	757(59.65)	1181(48.98)	1.56(1.34,1.81)	<0.0001
		Males		
Height[a]				
low	323(58.73)	899(53.07)	1.00	
high	227(41.27)	795(46.93)	0.99(0.80,1.23)	0.9473
Weight[b]				
low	244(44.36)	727(42.92)	1.00	
high	306(55.64)	967(57.08)	0.96(0.78,1.19)	0.7087
BMI[c]				
low	366(66.55)	1179(69.60)	1.00	
high	184(33.45)	515(30.40)	1.05(0.84,1.30)	0.6881
BSA[d]				
low	385(70.00)	1185(69.95)	1.00	
high	165(30.00)	509(30.05)	1.18(0.93,1.48)	0.1705

*: Adjustment for age, sex, education, marriage, smoking, alcohol drinking, resident

location, types of salt, salt appetite, diet patterns, milk consuming;

[a]: **Male**: high: height≥170cm, low: height<170cm; **female**: high: height≥160cm, low: height<160cm;

[b]**: Male**: high: weight≥65kg, low: weight<65kg; **female**: high: weight≥60kg, low: weight<60kg;

[c]**:** Low=BMI<24.0; high: BMI≥24;

[d]**: Male**: high: BSA≥1.80m^2, low: BSA<1.80m^2; **female**: high: BSA≥1.55m^2, low: BSA<1.55m^2

Supplementary Table 4. Adjusted logistic regression* to identify the correlation between body size and thyroid nodule among children without history of diseases related to thyroid.

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	*P*
Pooled*				
Height[a]				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight[b]				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI[c]				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA[d]				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
Girls				
Height[a]				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight[b]				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI[c]				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m^2)[d]				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
Boys				
Height[a]				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight[b]				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI[c]				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA[d]				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

*:Adjustment for age, sex, resident location, types of salt, salt appetite, diet patterns, milk consuming;
[a,b]:High: height or weight ≥ reference standard, low: height or weight <reference standard;

[c]: The reference height and weight were used to calculate the BMI reference.

[d]:**Male**: high: BSA≥1.26m^2,low: BSA<1.26m^2;**female**: high: BSA≥1.22m^2,low: BSA<1.22m^2; Mean of male′s BSA=1.26 m^2, Mean of female′s BSA=1.22 m^2.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(line 32)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(line44-47)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(line 70-92)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(line 94-98)**
Methods		
Study design	4	Present key elements of study design early in the paper **(line 102-103)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection**(line 102-104)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **(line 109-130)**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(line 132-204)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(line 168-204)**
Bias	9	Describe any efforts to address potential sources of bias **(line 214-219)**
Study size	10	Explain how the study size was arrived at **(line 110-117)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(line 207-211)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(line 207-214, line 219-221)**
		(*b*) Describe any methods used to examine subgroups and interactions **(line213-214)**
		(*c*) Explain how missing data were addressed **(line211)**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **(N/A)**
		(*e*) Describe any sensitivity analyses **(N/A)**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(line227-229)**
		(b) Give reasons for non-participation at each stage **(line227)**
		(c) Consider use of a flow diagram **(N/A)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **（line 226-235）**
		(b) Indicate number of participants with missing data for each variable of interest **（Table 1）**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **（line 231-235）**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **（line -237-257）**
		(*b*) Report category boundaries when continuous variables were categorized **（line218-219）**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **（N/A）**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **（N/A）**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(line 260-264)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(line 397-403)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(line 265-385)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(line 260-262)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(line 424-429)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.