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Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Abstract

Objectives: Obesity has been found to be associated with an elevated risk of thyroid nodule(s), mainly in adults; however, evidence for this association in children was limited. The objective of this study was to investigate the association of adiposity and thyroid nodule(s) in children living in iodine-sufficiency areas.

Setting and participants: We examined the associations of a number of anthropometric measurements with thyroid nodule(s) using a cross-sectional study data from 1,403 Chinese children living in the East Coast of China in 2014.

Outcome measures: Anthropometric measures, including height, weight, and waist and hip circumferences were collected and body mass index (BMI), body surface area (BSA), and waist-hip-ratio (WHR) were then calculated. Thyroid ultrasonography was performed to assess thyroid volume and nodules.

Results: Based on BMI, 255(18.17%) children were overweight and 174(12.40%) were obese. Thyroid nodule(s) was detected in 18.46% of all participants and showed little age- and sex-variations. As compared with normal weight children, obese children, but not overweight ones, experienced significantly higher risks for solitary (OR: 2.07 (95% CI: 1.16, 3.71)) and multiple (OR:1.67(95%CI:1.03, 2.70)) thyroid nodules. Similar associations were observed with waist circumference (WC) and BSA, while WHR showed no association with thyroid(s). There were no notable differences in the associations between children consuming iodized and non-iodized salt.

Conclusions: These findings provide further evidence that childhood obesity is associated with the risk for thyroid nodule(s).

Strengths and limitations of this study:

- Used large sample size, directly measured thyroid ultrasonography and anthropometric measurements following a standardized protocol.
- Permitted analysis of a large number of children with detailed information distinguishing solitary and multiple nodules and household iodized salt consumption status on the individual level.
- Lack of information on thyroid function and then unable to further evaluate potential mechanisms.

INTRODUCTION

Thyroid nodule (TN) is a common thyroid disorder that has a global influence[1 2]. Thyroid ultrasound investigations have documented very high prevalences (approaching 50%) of thyroid nodules worldwide [3-5]. Potential risk factors for thyroid nodules included age, sex, iodine intake[3 6-8], demographic parameters, clinical history and waist circumference (WC) [2 9].

Obesity is a known risk factor for a number of chronic conditions, and may also increase the risk of thyroid cancer [10-14]. The recent increase in thyroid nodules and thyroid cancer may partly be due to the epidemic of obesity[9 15 16]. Elevated thyroid stimulating hormone (TSH) levels and declined free thyroxin (FT4) levels have been observed in obese patients [15]. However, previous studies explored the associations between obesity and thyroid mainly in adults and the results were not entirely consistent. Whether these data from adults can be applied to children is not clear, particularly because the body weight and body surface area (BSA) of children are rather different (smaller) from those of adults[15].

In the current study, we conducted a large-scale epidemiological study to determine the associations of a number of anthropometric measurements including body mass index (BMI), BSA, WC and waist-hip ratio (WHR) with solitary or multiple thyroid nodules in school age children.

METHODS

Study population

Details of the study methodologies have been reported previously[17]. Briefly, three primary schools were selected from Minhang District in Shanghai, Haimen City in Jiangsu Province and Taizhou City in Zhejiang Province, respectively. Four classes in each grade from grade 3 to grade 5 in these schools were randomly selected and all students without preexisting thyroid conditions in selected classes were enrolled into this study. Among 1444 children enrolled, 1343 provided first morning urine samples and 1403 students completed routine physical examinations. An ultra-sound test for thyroid gland volume was performed on 1429 students. After excluding those with no physical examinations or thyroid test, we included 1403 students in the current analysis. Written consent from parents or guardians of all participants were received and the study was approved by the Ethical Review Board of the School of Public Health of Fudan University.

Anthropometric measurements

Anthropometric measurements, including standing height (cm), weight (kg), and circumferences of the waist, hip and chest (cm) were taken by trained health professionals according to a standard protocol. The standing height was measured to the nearest 0.1cm without shoes. Weight was measured to the nearest 0.1kg using a digital weight scale. Body mass index was calculated as weight in kilograms divided by the square of height in meters and overweight/obese status were assessed using the BMI growth reference values for Chinese children[18]. The cutoffs for overweight and obesity in boys were 17.8 and 20.1 for age 8, 18.5 and 21.1 for age 9, 19.5 and 22.2 for age 10, and 20.1 and 23.2 for age 11. The corresponding cutoffs for girls were

17.3 and 19.5, 17.9 and 20.4, 18.7 and 21.5, 19.6 and 22.7, respectively. Body surface area was calculated by using the following formula: $BSA=(Weight^{0.425})*(Height^{0.725})*0.007184$. Waist-hip-ratio was calculated as waist circumference divided by hip circumference.

Test for thyroid nodules

All participants received thyroid ultrasonography performed by experienced examiners at school using a real-time sector scanner with a 7.5-MHz/40-mm probe linear transducer. The ultrasonographic examination was carried out on the children lying on a desk with the neck extended. Standardized thyroid ultrasound technique was adopted according to the method described by Fuse et al[19]. Discrete lesion(s) within the thyroid gland that is palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma were defined as thyroid nodule(s)[20]. In case of abnormality in the sonographic examination of the thyroid, parents of the children would receive a written note describing the abnormal results of the examination.

Urine and salt samples collection and iodine concentration analyses

First morning urine samples were collected for each participant. Students were also asked to bring a salt sample of more than 20g from home for iodine measurement.

Urinary iodine concentrations (UICs) were determined following the method proposed by the Ministry of Health of the People's Republic of China (WS / T107. 2006, and GB/T13025.7—1999)[21]. Salt iodine content was also measured using a national standard method with a proper quality control[22] (GB/T 13025.7-1999) . 10% urine samples were assayed in duplicate.

Iodine nutrition was determined according to WHO/UNICEF/ICCIDD: insufficient (UIC ≤100 μg/L), sufficient (100-200 μg/L), and more than adequate (UIC >200 μg/L). Iodized salt consumption status was categorized by using salt iodine concentration: non-iodized salt (<5 mg/kg) and iodized salt (⩾5 mg/kg).

Statistical analysis

All participants were categorized as having no nodule, solitary nodule, and multiple nodules according to their thyroid nodule detection status, and into three groups of under/normal weight, overweight and obesity status according to BMI. WC, WHR and BSA were categorized into quintiles to assess their relations with thyroid nodules. Chi-square analysis was performed to test the distribution of thyroid nodules in relation to sex, age, BMI, iodized salt consumption status, urinary iodine level and study area. Multinomial logistic regression analysis was used to examine the associations of various anthropometric measurements with the frequency of thyroid nodules (no, solitary nodule, and multiple nodules). Due to a considerable day-to-day variation in iodine excretion, one-spot urinary iodine level was not a proper indicator of iodine status for individuals [23]. Therefore, in current analysis, iodized salt consumption instead of iodine concentration in urine, was included in the multivariate models. We also assessed the correlation between urinary iodine concentration (UIC) and iodized salt consumption and observed a significantly higher level of UIC in children who consumed iodized salt at home, suggesting that iodized salt consumption status could be a good proxy for iodine nutrition at a population level. Multivariable logistic regression models were then used to adjust for age, sex, and iodized salt consumption. Potential effect modifications by sex, age and iodized salt consumption on the associations of interest were also examined.

All analyses were performed by using SAS, version 9.3 software (SAS Institute, Inc., Cary, NC, USA), and all tests of statistical significance were base on two-side probability.

RESULTS

Table 1 shows the demographic characteristics as well as iodine nutrition status for the 1403 participants included in the analysis. The mean age was 9.54(±0.98) years, the median BMI was 17.05(IQR: 15.55, 19.35) kg/m2, and the median UIC was 184.90μg/l.

Table 1. General characteristics for children from Shanghai, Haimen and Taizhou, China, 2014

		Male		Female			
		No.	%	No.	%	X^2	P
Total		739	52.67	664	47.33		
Age (years)						0.788	0.852
	8	116	15.70	111	16.72		
	9	246	33.29	215	32.38		
	10	237	32.07	204	30.72		
	11	140	18.94	134	20.18		
BMI						11.56	0.003
	Normal	531	71.85	443	66.72		
	Overweight	110	14.88	145	21.84		
	Obese	98	13.26	76	11.45		
Area						6.182	0.046
	Minhang	294	39.78	226	34.04		
	Haimen	234	31.66	214	32.23		
	Yuhuan	211	28.55	224	33.73		
UIC(μg/L)*						4.118	0.128
	<100	122	17.35	132	20.63		
	100-200	282	10.11	226	35.31		
	>200	299	42.53	282	44.06		

Iodized salt consumption**						0.015	0.901
	No	250	36.39	235	36.72		
	Yes	437	63.61	405	63.28		

*60 missing

** 76 missing

Thyroid nodule(s) were detected in 259 children, accounting for 18.46% of all the participants. Most nodules were accompanied by hypoechogenicity. The prevalence of multiple thyroid nodules was 12.54% (176/1403), which was twice of the proportion of solitary nodule (5.92% (83/1403)). The frequency of thyroid nodules showed no age or sex related difference(Table 2). The median UIC in children without nodules, with single nodule and multiple nodule were 187.80 μg/L, 195.55 μg/L, and 160.45 μg/L, respectively. UIC was significantly lower in children with multiple nodules than those in the other two groups (X^2=7.44, P=0.024). The prevalence of multiple thyroid nodules was much higher in children consuming non-iodized salt than those consuming iodized salt.

Table 2. Comparison of the prevalence of thyroid nodules in different subgroups for children from Shanghai, Haimen and Taizhou, China, 2014

		Thyroid nodules				
Characteristics	No.	No nodule (N (%))	Solitary nodule (N (%))	Multiple nodules (N (%))	*χ2*	*P*-value
All	1403	1144(81.54%)	83(5.92%)	176(12.54%)		
Sex					4.264	0.119
Male	739	617(83.49%)	37(5.01)	85(11.50%)		
Female	664	527(79.37%)	46(6.93%)	91(13.70%)		
Age (years)					11.61	0.071
8	227	192(84.58%)	12(5.29%)	23(10.13%)		
9	461	359(77.87%)	34(7.38%)	68(14.75%)		
10	441	374(84.81%)	24(5.44%)	43(9.75%)		
11	274	219(79.93%)	13(4.74%)	42(15.33%)		
Iodized salt consumption*					12.46	0.002
No	485	380(78.35%)	26(5.36%)	79(16.29%)		
Yes	842	708(84.09%)	52(6.18%)	82(9.74%)		
Urinary iodine(μg/l)**					13.20	0.010
<100	254	204(80.31%)	12(4.72%)	38(14.96%)		
100-200	508	400(78.74%)	31(6.10%)	77(15.16%)		
>200	581	493(84.85%)	37(6.37%)	51(8.78%)		
Area					155.80	<0.001
Shanghai	520	344(66.15%)	49(9.42%)	127(24.42%)		
Haimen	448	426(95.09%)	20(4.46%)	2(0.45%)		
Taizhou	435	374(85.95%)	14(3.22%)	47(10.80%)		

* 76 missing

** 60 missing

Based on BMI, 255(18.17%) were overweight and 174(12.40%) were obese. Girls were more likely to be overweight/obese than boys and the prevalence of overweight/obese decreased with age in both sexes.

Both univariate and multivariable analysis revealed an association of obesity with thyroid nodules (Table 3). As compared with normal weight children, obese children experienced significantly higher risks for solitary and multiple thyroid nodules. The association between obesity and multiple nodules tended to be more evident in girls (OR: 2.10 (95% CI: 0.89, 4.89)) than in boys (OR: 1.29 (95% CI: 0.62, 2.70)) and in children aged 9 years than the other age groups. In contrast, the association between obesity and solitary nodule was more evident in children aged 10. Overweight was not significantly associated with thyroid nodules in general, except an association with multiple nodules in children aged 8.

Table 3. Multinomial logistic regression analysis of obesity and thyroid nodules for children from Shanghai, Haimen and Taizhou, China, 2014

		Overweight		Obesity	
		Solitary nodule	Multiple nodules	Solitary nodule	Multiple nodules
		OR (95%CI) [a]	OR (95%CI) [a]	OR (95%CI) [a]	OR (95%CI) [a]
All subjects	Model 1	0.62(0.30, 1.26)	1.37(0.92, 2.03)	1.84(1.04, 3.25)	1.44(0.91, 2.30)
	Model 2	0.58(0.28, 1.20)	1.35(0.90, 2.00)	1.82(1.02, 3.24)	1.47(0.92, 2.35)
	Model 3	0.53(0.25, 1.13)	1.33(0.88, 2.03)	1.82(0.99, 3.36)	1.62(0.98, 2.70)
	Model 4	0.54(0.25, 1.16)	1.24(0.82, 1.88)	2.07(1.16, 3.71)	1.67(1.03, 2.70)
Sex	Male (Model 3)	0.17(0.02, 1.28)	1.18(0.61, 2.26)	1.53(0.63, 3.71)	1.29(0.62, 2.70)
	Female (Model 3)	0.77(0.33, 1.82)	1.49(0.86, 2.59)	2.09(0.89, 4.89)	2.10(1.03, 4.31)
Age (years)	8 (Model 3)	0.91(0.18, 4.53)	3.12(1.13, 8.61)	0.67(0.08, 5.67)	1.76(0.44, 7.02)
	9 (Model 3)	0.48(0.14, 1.67)	1.58(0.79, 3.18)	1.96(0.81, 4.76)	2.09(1.01, 4.31)
	10 (Model 3)	0.44(0.10, 1.98)	0.70(0.28, 1.80)	3.86(1.36, 10.98)	1.66(0.53, 5.21)
	11 (Model 3)	0.44(0.06, 3.56)	1.18(0.47, 2.94)	-	0.61(0.13, 2.80)
Iodized salt consumption	Yes (Model 3)	0.48(0.18, 1.27)	1.76(1.03, 3.02)	1.76(0.88, 3.54)	1.50(0.78, 2.90)
	No (Model 3)	0.59(0.17, 2.08)	0.88(0.45, 1.75)	1.84(0.50, 6.79)	1.97(0.86, 4.48)

Model 1: Univariate analysis

Model 2: Adjusted for sex and age

Model 3: Adjusted for sex, age, and urinary iodine concentration

Model 4: Adjusted for sex, age, and iodized salt consumption status

Figures 1 presents multivariate-adjusted ORs and 95% confidence intervals for solitary and multiple thyroid nodules associated with the quintiles of BMI, BSA, WC, and WHR, respectively. After adjustment for potential confounders, greater BSA and WC were significantly related to elevated risks of both solitary and multiple nodules (p values for trend were 0.015 and 0.013, respectively). As compared with children in the lowest quintile, ORs of solitary and multiple nodules were 2.45 (95% CI: 1.24, 4.87) and 2.76 (95% CI: 1.54, 4.97) for those in the highest quintile of BSA and 3.46 (95% CI: 1.54, 7.80) and 2.18 (95% CI: 1.27, 3.74) for those in the highest quintile of WC, respectively.

The results for BMI and WHR were less consistent. BMI was positively associated with the risk of multiple nodules, while WHR showed no association with either solitary or multiple nodules.

When stratified by sex and iodized salt consumption status, the associations of BSA and WC with multiply nodules were comparable between boys and girls. However, the association of BSA with solitary nodule seemed stronger in boys (OR=5.34 (95% CI: 1.64, 17.31)) than in girls (1.47 (95% CI: 0.60, 3.61)). Those associations above were similar between children consuming iodized salt and non-iodized salt.

DISCUSSION

In this large cross-sectional study of children living in an iodine sufficient area in East China, we observed a high prevalence of thyroid nodules and positive associations of obesity with both solitary and multiple thyroid nodules. Among several anthropometric measurements, BSA and WC were related to the risks for both solitary and multiple thyroid nodules. These findings were generally consistent across sex groups and independent of iodized salt consumption status.

Thyroid nodule(s) is common in adults and its impact on thyroid cancer risk is still unclear[15]. The prevalence of incidental thyroid nodules detected by ultrasound examinations is high in adults (close to 50%) even in iodine-deficient countries[3-5 24]. However, few studies have investigated the prevalence, and the spectrum of appearance of ultrasound-detected findings in children. Thyroid nodules were identified in 1.65% of children aged 3 to 18 years in three Japanese prefectures, and the prevalence increased with age with a female predominance[25]. The information released by Fukushima Prefecture indicated that 2014 (1.15%) of 75216 children aged 0-18 showed thyroid nodules[26]. Avula et al. conducted a retrospective analysis in 287 Canadian children (mean age=6.2) and detected only 1 child with multiple thyroid nodules[27]. In healthy Greek children living in an iodine-replete area, one or more nodules were observed in 5.1% of them[28]. For 2410 children aged 6-17 years living in Hangzhou, thyroid nodules were detected in 10.66% of them[29]. These results showed much lower frequencies than those observed in our current study, in which thyroid nodules existed in 18.46% of in 1433 Chinese children with little age- and sex-variations. Influencing factors include age composition, inter-observer variation, iodine intake, socio-ecological status and individual and family history, as well as detection sensitivity and image quality of ultrasound machine [25].

Thyroid nodule has multiple known risk factors, which include demographic parameters, clinical history, age, sex [6-8] and urinary iodine excretion[3]. The association of thyroid nodule(s) with obesity has been explored mostly in adults with inconsistent results (2)(16)[30 31].

Obesity is a risk factor for several chronic conditions, as well as goiter in adults[32]. Its impact on thyroid nodules has also been investigated by using different anthropometric parameters in adults. Among various parameters, BMI was most frequently used as a measure of general adiposity. It has been increasingly recognized that the adverse effects of obesity relate not only to the amount but also to the distribution of excess body fat. Therefore, the use of BMI alone to infer health risks in Asians may underestimate excess adiposity's detrimental health effects[33]. WHR and WC were good proxy measures of central adiposity. It has been suggested that WC is a better marker for total body adiposity than it is for visceral fat [34]. Another study has shown that both WC and BMI appear to perform equally well for estimating children and adolescents total and abdominal visceral fat[35]. BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI [30] and has been shown to be the best independent predictor of the thyroid volume in both sexes.

Several studies have found significant associations between measures of obesity and risk of thyroid nodules. For example, a study conducted in Hangzhou, China observed a prevalence of TN being 34.97% (33.97 for men and 36.92% for women) and concluded that great WC was risk factor for new TN in this iodine-adequate area[2]. Another study of postmenopausal women also revealed that WC and BMI were associated with thyroid nodules[36]. A higher BMI was associated with nodule growth among older patients with multiple nodules and larger dominant nodules [16], which was consistent with recent reports linking thyroid nodular disease to obesity and insulin resistance [37]. The presence of insulin resistance (IR) was associated with larger thyroid gland volume and an increased prevalence of thyroid nodules[38 39], which might be explained by obesity-related subclinical inflammation and an associated increase in levels of insulin-like growth factor-1(IGF-1)[38]. However, some other study yielded conflicting results, which suggested that patients with normal weight or overweight based on BMI tended to have an increased risk of thyroid nodules, as compared with obese people[31].

Our findings of increased risk for thyroid nodules in obese children are generally consistent with those in obese adults of other studies. The association of BSA with thyroid volume in children has been well established[28], while its relation to thyroid nodules has seldom been explored. Kim et al. [31] examined 7763 healthy Korean population and observed a significantly smaller BSA in those with thyroid nodules compared to the others, which was opposite to our findings. Considering the great difference in BSA between adults and children, it need to be cautious to generalize the results to children [15]. Xu et.al[29] conducted a cross-sectional study in Hangzhou, China, and reported an OR of 2.97 (95% CI: 1.85 to 4.77) for thyroid nodules for children with median BSA level or above as compared with those with less than median BSA. However, the number of thyroid nodules was not recorded in the study.

The strengths of our study include large sample size, directly measured thyroid ultrasonography and anthropometric measurements following a standardized protocol, and the abilities to distinguish solitary and multiple nodules and to adjust for household iodized salt consumption status. Our study also has several limitations. We did not have any information on thyroid function. Therefore, we were unable to further evaluate potential mechanisms that may explain the observed associations. In addition, the current analysis examined thyroid and physical measurement assessed only once; changes in physical measurement and thyroid nodules overtime were not taken into account.

CONCLUSION

By this cross-sectional study in a relatively lean children population, we found that increasing levels of general or abdominal adiposity, measured by BMI, BSA and WC, were associated with a significant increase in the risk of thyroid nodule(s), especially for multiple nodules in girls and solitary nodule in boys. Our findings, along with those observed from mostly adult populations, emphasize the importance of preventing excess adiposity for primary prevention of thyroid nodules.

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Competing interests None declared.

Ethics approval The study was approved by the Ethical Review Board of the School of Public Health of Fudan University (#2012-03-0350S).

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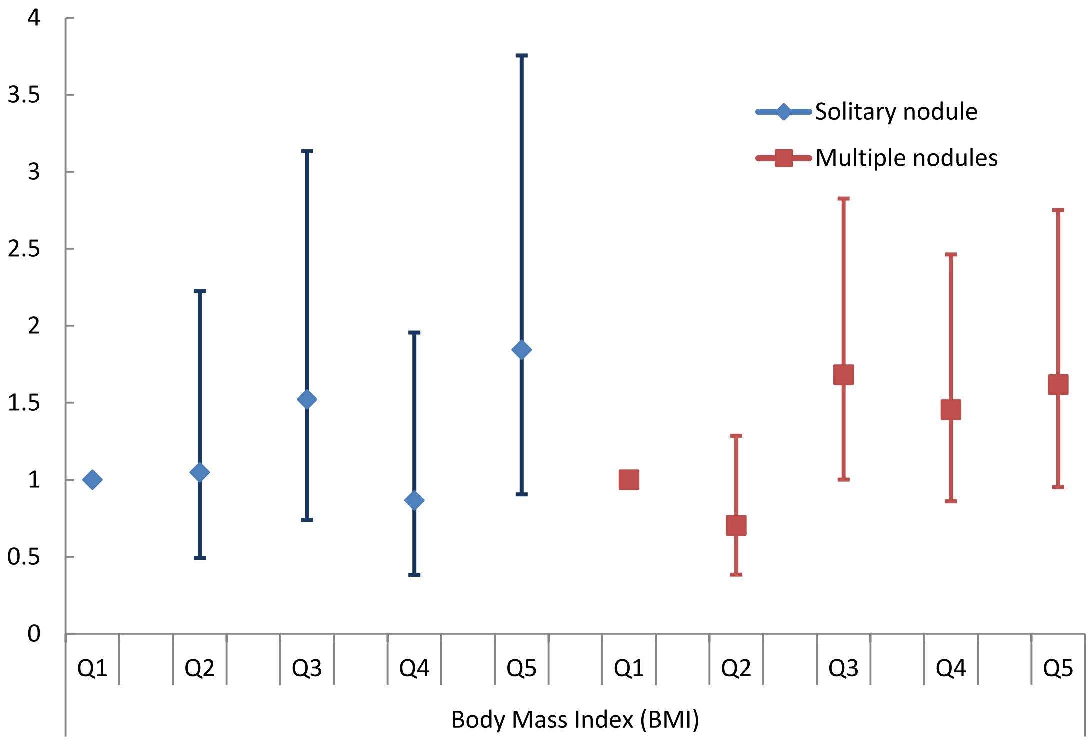
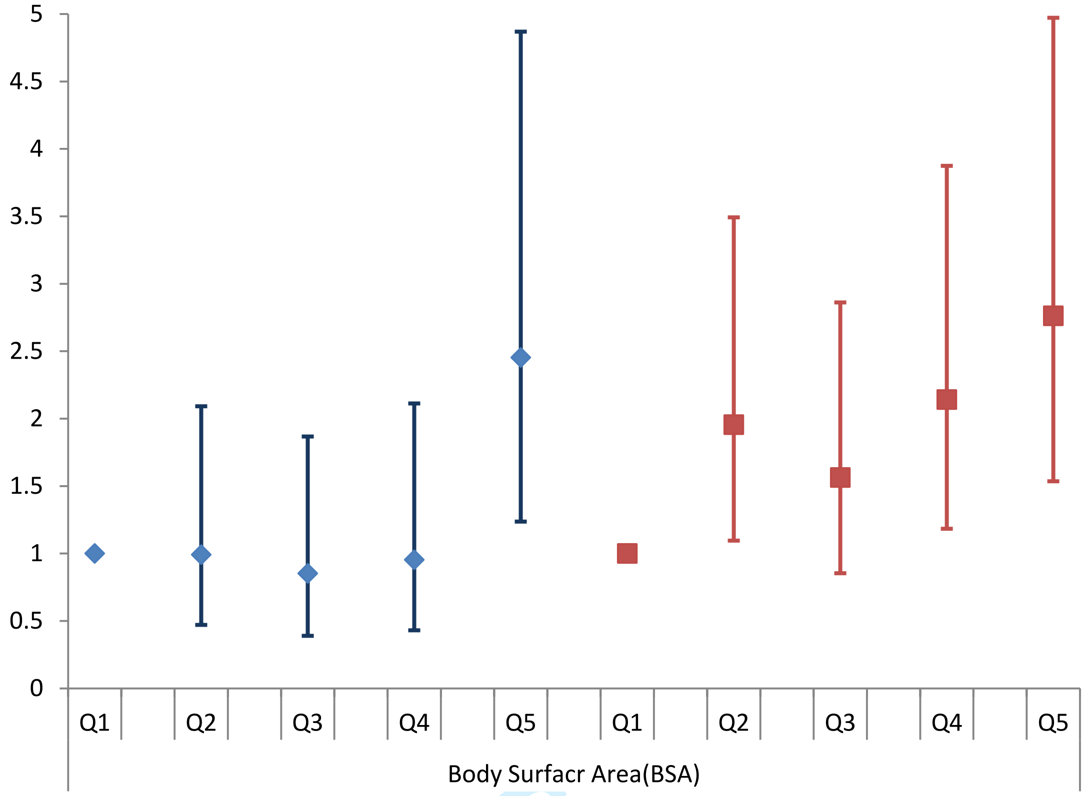
Figure1. Associations of Different Physical Measurements (BMI, BSA, WC, and WHR) with Thyroid Nodules for children from Shanghai, Haimen and Taizhou, China, 2014


4
3.5
3
2.5
2
1.5
1
0.5
0
Solitary nodule
Multiple nodules
Q1
Q2
Q3
Q4
Q5
Q1
Q2
Q3
Q4
Q5
Body Mass Index (BMI)


5
4.5
4
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3
2.5
2
1.5
1
0.5
0
Q1
Q2
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Q1
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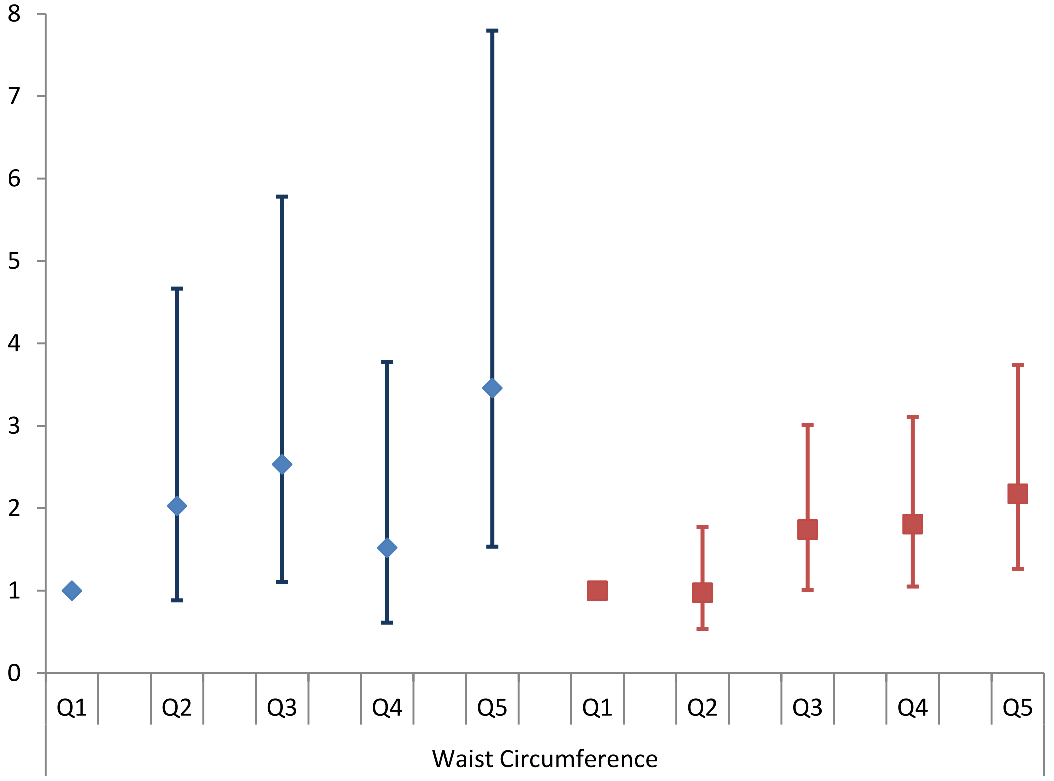
Q3
Q4
Q5
Body Surfacr Area(BSA)


8
7
6
5
4
3
2
1
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Q1
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Q4
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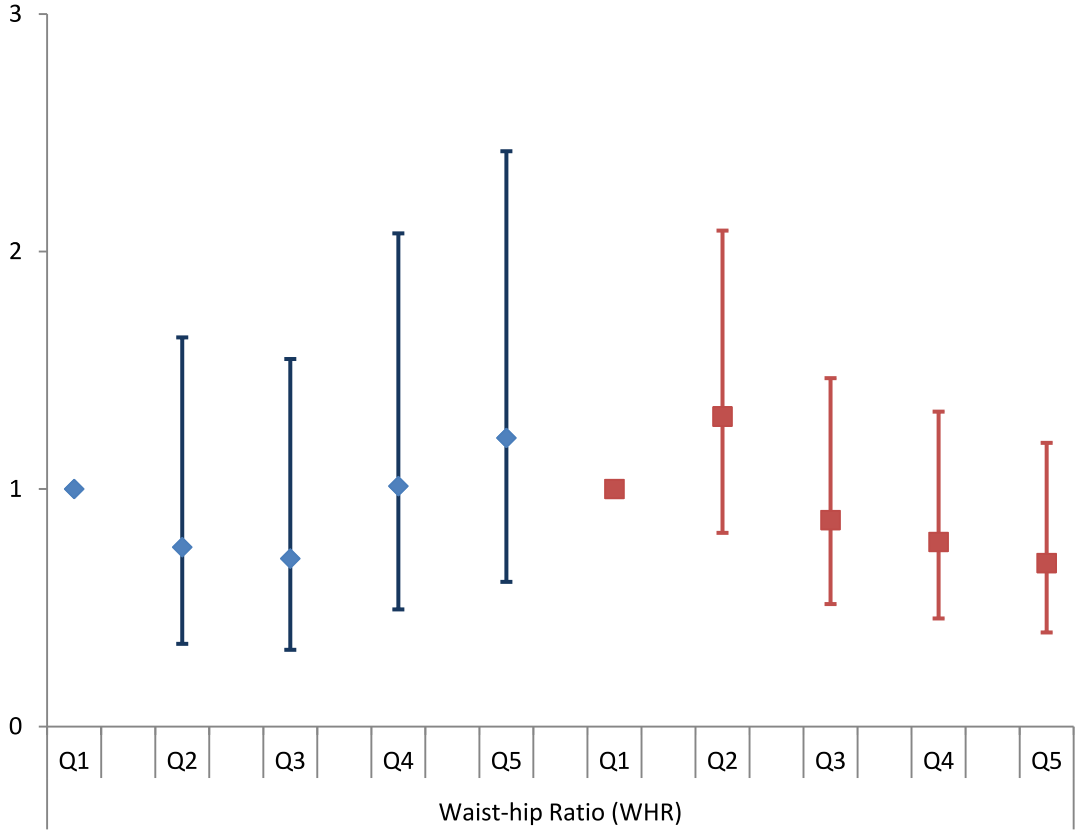
Q3
Q4
Q5
Waist Circumference


3
2
1
0
Q1
Q2
Q3
Q4
Q5
Q1
Q2
Q3
Q4
Q5
Waist-hip Ratio (WHR)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			8

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	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	10
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	12
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
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	19

*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.

BMJ Open

Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Keywords:	adiposity, thyroid nodule(s), children, iodine

Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Word Count: 2853 **Figures**: 2 **Tables**:3

Keywords: adiposity, thyroid nodule(s), children, iodine

Abstract

Objectives: Obesity has been found to be associated with an elevated risk of thyroid nodule(s), mainly in adults; however, evidence for this association in children was limited. The objective of this study was to investigate the association of adiposity and thyroid nodule(s) in children living in iodine-sufficiency areas.

Setting and participants: We conducted a cross-sectional study of 1,403 Chinese children living in the East Coast of China in 2014.

Outcome measures: Anthropometric measures, including height, weight, and waist and hip circumferences were taken and body mass index (BMI), body surface area (BSA), and waist-hip-ratio (WHR) were then calculated. Thyroid ultrasonography was performed to assess thyroid volume and nodules.

Results: Based on BMI, 255 (18.17%) children were overweight and 174 (12.40%) were obese. Thyroid nodule(s) was detected in 18.46% of all participants and showed little age- and sex-variations. As compared with normal weight children, obese children experienced significantly higher risks for solitary (OR: 2.07 (95% CI: 1.16, 3.71)) and multiple (OR: 1.67 (95%CI: 1.03, 2.70)) thyroid nodules. Similar associations with thyroid nodule(s) were observed with adiposity measured by waist circumference (WC) and BSA, but not WHR. There were no notable differences in the associations between children consuming iodized and non-iodized salt.

Conclusions: These findings provide further evidence that childhood obesity is associated with the risk for thyroid nodule(s).

Strengths and limitations of this study:

- Large sample size, directly measured thyroid ultrasonography and various anthropometric measurements following a standardized protocol.
- Detailed information distinguishing solitary and multiple nodules and household iodized salt consumption status at the individual level.
- Lack of information on thyroid function.

INTRODUCTION

Thyroid nodule (TN) is a common thyroid disorder globally and the incidence has been increasing in recent decades[1-2]. Thyroid ultrasound investigations have documented very high prevalences (approaching 50%) of thyroid nodules worldwide [3-5]. Potential risk factors for thyroid nodules include age, sex, iodine intake[3 6-8], demographic parameters, clinical history and waist circumference (WC) [2 9]. Both mildly deficient iodine intake and excessive iodine intake are risk factors for thyroid nodule(s) in normal subjects[10].

Obesity is a known risk factor for a number of chronic conditions, and may also increase the risk of thyroid cancer [11-15]. The recent increase in thyroid nodules and thyroid cancer may partly be due to the epidemic of obesity[9 16-17]. Elevated thyroid stimulating hormone (TSH) levels and declined free thyroxin (FT4) levels have been observed in obese patients [16]. However, previous studies of the associations between obesity and thyroid were mainly conducted in adults and the results were not entirely consistent. Whether these observations from adults can be applied to children is not clear, particularly because the incidence of thyroid nodules is lower but the risk for malignancy is greater in children as compared to adults[18].

In the current study, we conducted a large-scale epidemiological study to determine the associations of a number of anthropometric measurements including body mass index (BMI), body surface area (BSA), WC and waist-hip ratio (WHR) with solitary or multiple thyroid nodules in school age children.

METHODS

Study population

Randomized cluster sampling was used to selected subjects. Similar study methodologies have been reported for an earlier study[19]. Briefly, three coastal cities in east China (Minhang District in Shanghai, Haimen City in Jiangsu Province and Taizhou City in Zhejiang Province) were selected by purposive sampling. Previous studies have revealed an iodine sufficient status[20-22] along with distinguished iodized salt consumption proportions among three sites. One primary school (students were mainly local residents) was selected from each city to ensure a good representativeness. Four classes in each grade from grade 3 to grade 5 in these schools were randomly selected in 2014 and all students in 12 selected classes in each school were enrolled into this study (Figure 1). Among 1444 eligible children, 1343 provided first morning urine samples and 1403 students completed routine physical examinations. An ultra-sound test for thyroid gland volume was performed on 1429 students. After excluding those with no physical examinations or thyroid test, we included 1403 students in the current analysis. Written consent from parents or guardians of all participants were received and the study was approved by the Ethical Review Board of the School of Public Health of Fudan University.

Study variables

The outcome variables in this study were having thyroid nodule(s) (no, yes) and number of thyroid nodules (no nodule, solitary nodule, multiple nodules). Adiposity measurements were explanatory variables, including body mass index, body surface area, waist circumferences and waist-hip-ratio. Sex, age, urinary iodine concentrations, and iodized salt consumption status were covariates in the multivariate regression models.

Anthropometric measurements

Anthropometric measurements, including standing height (cm), weight (kg), and circumferences of the waist, hip and chest (cm) were taken by trained health professionals according to a standard protocol. The standing height was measured to the nearest 0.1cm without shoes. Weight was measured to the nearest 0.1kg using a digital weight scale. BMI was calculated as weight in kilograms divided by the square of height in meters and all participants were categorized into three groups of under/normal weight, overweight and obesity status according to the BMI growth reference values for Chinese children[23]. The cutoffs for overweight and obesity in boys were 17.8 and 20.1 for age 8, 18.5 and 21.1 for age 9, 19.5 and 22.2 for age 10, and 20.1 and 23.2 for age 11. The corresponding cutoffs for girls were 17.3 and 19.5, 17.9 and 20.4, 18.7 and 21.5, 19.6 and 22.7, respectively. Body surface area was calculated by using the following formula: $BSA=(Weight^{0.425})*(Height^{0.725})*0.007184$ [24]. Waist-hip-ratio was calculated as waist circumference divided by hip circumference. BSA, WC, and WHR were categorized into quintiles to assess their

relations with thyroid nodules.

Thyroid ultrasonography

All participants received thyroid ultrasonography performed by experienced examiners at school using a real-time sector scanner with a 7.5-MHz/40-mm probe linear transducer. The ultrasonographic examination was carried out on the children lying on a desk with the neck extended. Standardized thyroid ultrasound technique was adopted according to the method described by Fuse et al[25]. Discrete lesion(s) within the thyroid gland that wass palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma were defined as thyroid nodule(s)[26]. In case of abnormality in the sonographic examination of the thyroid, parents of the children would receive a written note describing the abnormal results of the examination and be advised to take their children to visit a physician. All participants were categorized as having no nodule, having nodule(s) (solitary nodule, and multiple nodules) according to their thyroid nodule detection status.

Urine and salt samples collection and iodine concentration analyses

First morning urine sample was collected for each participant. Students were also asked to bring a salt sample of more than 20g from home for iodine measurement.

Urinary iodine concentration (UIC) was determined following the method proposed by the Ministry of Health of the People's Republic of China (WS / T107．2006, and GB/T13025.7—1999)[27]. Salt iodine content was also measured using a national standard method with a proper quality control[28] (GB/T 13025.7-1999). 10% urine samples were assayed in duplicate and no statistical differences were observed as

compared with the primary results.

Iodine nutrition status was determined at a population level according to WHO/UNICEF/ICCIDD: insufficient (UIC <100 μg/L), sufficient (100-199 μg/L), more than adequate (200-299 μg/L), and excessive (≥300 μg/L). Iodized salt consumption status was grouped into two categories: non-iodized salt (<5 mg/kg) and iodized salt (≥5 mg/kg)[29].

Statistical analysis

,Chi-square test was used to examine thyroid nodules in relation to sex, age, BMI, iodized salt consumption status, urinary iodine level and study area. Multinomial logistic regression analysis was used to examine the associations of various anthropometric measurements with the frequency of thyroid nodules (no nodule, solitary nodule, and multiple nodules). Due to a considerable day-to-day variation in iodine excretion, one-spot urinary iodine level was not a proper indicator of iodine status for individuals [30-31]. Therefore, in current analysis, iodized salt consumption instead of iodine concentration in urine, was included in the multivariate models. We also assessed the correlation between urinary iodine concentration (UIC) and iodized salt consumption and observed a significantly higher level of UIC in children who consumed iodized salt at home, suggesting that iodized salt consumption status could be a good proxy for iodine nutrition at a population level. Multivariable logistic regression models were then used to adjust for age, sex, and iodized salt consumption. Potential effect modifications by sex, age and iodized salt consumption on the associations of interest were also examined by including associated interaction terms

into the multivariate analysis.

All analyses were performed by using SAS, version 9.3 software (SAS Institute, Inc., Cary, NC, USA), and all statistical significance was based on two-side probability.

RESULTS

Table 1 shows the demographic characteristics as well as iodine nutrition status for the 1403 participants included in the analysis. The mean age was 9.54 (±0.98) years, the median BMI was 17.05 (IQR: 15.55, 19.35) kg/m2, and the median UIC was 184.90μg/l.

Table 1. General characteristics for children from Shanghai, Haimen and Taizhou, China, 2014

		Male		Female			
		No.	%	No.	%	X^2	P
Total		739	52.67	664	47.33		
Age (years)						0.788	0.852
	8	116	15.70	111	16.72		
	9	246	33.29	215	32.38		
	10	237	32.07	204	30.72		
	11	140	18.94	134	20.18		
BMI						11.56	0.003
	Normal	531	71.85	443	66.72		
	Overweight	110	14.88	145	21.84		
	Obese	98	13.26	76	11.45		
Area						6.182	0.046
	Minhang	294	39.78	226	34.04		
	Haimen	234	31.66	214	32.23		
	Yuhuan	211	28.55	224	33.73		
UIC(μ g/L)*						4.198	0.241
	<100	122	17.35	132	20.63		
	100-199	282	40.11	226	35.31		

	200-299	171	23.14	158	24.69		
	⩾300	128	17.32	124	19.38		
Iodized salt consumption**						0.015	0.901
	No	250	36.39	235	36.72		
	Yes	437	63.61	405	63.28		

*60 missing: 36(60.00%) were male and 24(40.00%) were female.

** 76 missing: 52(68.42%) were male and 24(31.58%) were female.

Thyroid nodule(s) were detected in 259 children, accounting for 18.46% of all the participants. Most nodules were accompanied by hypoechogenicity. Of the participants, 5.92% (83/1403) had solitary nodule and 12.54% (176/1403) had multiple thyroid nodules. The frequency of thyroid nodules showed no age or sex related difference (Table 2). The median UIC in children without nodules, with single nodule and multiple nodules were 187.80 μ g/L, 195.55 μ g/L, and 160.45 μ g/L, respectively. UIC was significantly lower in children with multiple nodules than those in the other two groups (X^2=7.44, P=0.024). The prevalence of multiple thyroid nodules was much higher in children consuming non-iodized salt than those consuming iodized salt.

Table 2. Comparison of the prevalence of thyroid nodules in different subgroups for children from Shanghai, Haimen and Taizhou, China, 2014

		No nodule	Nodule(s)				
Characteristics	No.	N (%)	Solitary nodule (N (%))	Multiple nodules (N (%))	Total	$\chi2$, *P*-value[#]	$\chi2$, *P*-value[##]
All	1403	1144(81.54)	83(5.92)	176(12.54)	259(18.46)		
Sex						3.95, 0.047	4.264, 0.119
Male	739	617(83.49)	37(5.01)	85(11.50)	122(16.51)		
Female	664	527(79.37)	46(6.93)	91(13.70)	137(20.63)		
Age (years)						9.11, 0.028	11.61, 0.071
8	227	192(84.58)	12(5.29)	23(10.13)	35(15.42)		
9	461	359(77.87)	34(7.38)	68(14.75)	102(22.13)		
10	441	374(84.81)	24(5.44)	43(9.75)	67(15.19)		
11	274	219(79.93)	13(4.74)	42(15.33)	55(20.07)		
Iodized salt consumption*						6.85, 0.009	12.46, 0.002
No	485	380(78.35)	26(5.36)	79(16.29)	105(21.65)		
Yes	842	708(84.09)	52(6.18)	82(9.74)	134(15.91)		
Urinary iodine(µg/l)**						13.00, 0.005	13.20, 0.010
≤100	254	204(80.31)	12(4.72)	38(14.96)	50(19.69)		
100-200	508	400(78.74)	31(6.10)	77(15.16)	108(21.26)		
200-300	329	268(81.46)	37(6.37)	51(8.78)	61(18.54)		
>300	252	225(89.29)			27(10.71)		
Area						142.11, <0.001	155.80, <0.001
Shanghai	520	344(66.15)	49(9.42)	127(24.42)	176(33.85)		
Haimen	448	426(95.09)	20(4.46)	2(0.45)	22(4.91)		
Taizhou	435	374(85.95)	14(3.22)	47(10.80)	61(14.02)		

* 76 missing

** 60 missing

Comparison between participants with/without thyroid nodule(s)

Comparison among participants without nodule/ with solitary nodule/ with multiple nodules

Based on BMI, 255(18.17%) were overweight and 174(12.40%) were obese. Girls were more likely to be overweight than boys and the prevalence of overweight/obese decreased with age in both sexes (P-trend: 0.033 for boys and 0.010 for girls). The prevalences of solitary and multiple nodules in overweight subjects were 3.53% (9/255) and 15.29% (39/255), while the corresponding prevalence were 20.48% (17/174) and 14.77% (26/174) in obese ones, respectively.

Multivariable analysis revealed significant associations of obesity with both solitary nodule and multiple thyroid nodules (Table 3). As compared with normal weight children, obese children experienced significantly higher risks for solitary and multiple thyroid nodules. The association between obesity and multiple nodules tended to be more evident in girls (OR: 2.10, 95% CI: 0.89, 4.89) than in boys (OR: 1.29, 95% CI: 0.62, 2.70) although both were not statistically significant. Associations of multiple nodules with overweight (OR: 1.87, 95% CI: 1.07, 3.29) and obesity (OR: 2.00, 95%CI: 1.05, 3.78) were observed in children aged 8 or 9 years, but not in older ones. Overweight was not significantly associated with solitary thyroid nodule in general, which might be due to small number of children with this thyroid condition. However, overweight children had an increased risk for multiple thyroid nodules (OR: 1.76, 95% CI :1.03, 3.02) only in iodized salt consumers.

Table 3. Multinomial logistic regression analysis of obesity and thyroid nodules for children from Shanghai, Haimen and Taizhou, China, 2014

		Normal					Overweight				Obesity			
		No nodule	Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules	
		N	N	OR	N	OR	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]
All subjects [*]		806	57		111		9		39		39		26	
	Model 1			1.00		1.00		0.62(0.30, 1.26)		1.37(0.92, 2.03)		1.84(1.04, 3.25)		1.44(0.91, 2.30)
	Model 2			1.00		1.00		0.53(0.25, 1.13)		1.33(0.88, 2.03)		1.82(0.99, 3.36)		1.62(0.98, 2.70)
	Model 3			1.00		1.00		0.54(0.25, 1.16)		1.24(0.82, 1.88)		2.07(1.16, 3.71)		1.67(1.03, 2.70)
Sex [**]	Male	617	28	1.00	58	1.00	2	0.17(0.02, 1.28)	15	1.18(0.61, 2.26)	7	1.53(0.63, 3.71)	12	1.29(0.62, 2.70)
	Female	527	29	1.00	53	1.00	7	0.77(0.33, 1.82)	24	1.49(0.86, 2.59)	10	2.09(0.89, 4.89)	14	2.10(1.03, 4.31)
Age (years) [#]	8-9	551	31	1.00	49	1.00	5	0.63(0.24,1.68)	24	1.87(1.07,3.29)	10	1.60(0.71,3.57)	18	2.00(1.05,3.78)
	10-11	593	26	1.00	62	1.00	4	0.46(0.14,1.55)	15	0.95(0.50,1.82)	7	2.05(0.80,5.25)	8	1.05(0.43,2.60)
Iodized salt consumption [##]	Yes	708	35	1.00	46	1.00	5	0.48(0.18, 1.27)	23	1.76(1.03, 3.02)	12	1.76(0.88, 3.54)	13	1.50(0.78, 2.90)
	No	380	20	1.00	58	1.00	3	0.59(0.17, 2.08)	12	0.88(0.45, 1.75)	3	1.84(0.50, 6.79)	9	1.97(0.86, 4.48)

[*] Model 1: univariate analysis

Model 2: adjustment for sex, age, iodized salt consumption

Model 3: adjustment for sex, age, urinary iodine concentration

[**] Adjustment for age and iodized salt consumption

[#] Adjustment for sex and iodized salt consumption

[##] Adjustment for sex, and age

Figures 2 presents multivariate-adjusted ORs and 95% confidence intervals for solitary and multiple thyroid nodules associated with the quintiles of BSA, WC, BMI, and WHR, respectively. After adjustment for sex, age, and iodized salt consumption status, BSA and WC were positively related to the risks of solitary and multiple nodules (p values for trend were 0.015 and 0.013, respectively). As compared with children in the lowest quintile, the ORs of solitary and multiple nodules were 2.45 (95% CI: 1.24, 4.87) and 2.76 (95% CI: 1.54, 4.97) for those in the highest quintile of BSA and 3.46 (95% CI: 1.54, 7.80) and 2.18 (95% CI: 1.27, 3.74) for those in the highest quintile of WC, respectively. The interaction between BSA and sex on thyroid nodules was not statistically significant (p-interaction: 0.785 for solitary nodule and 0.600 for multiple nodules).

The results for BMI and WHR were less consistent. BMI was positively associated with the risk of multiple nodules (p-trend=0.005), while WHR showed no association with either solitary or multiple nodules.

DISCUSSION

In this large cross-sectional study of children living in iodine sufficient areas in East China, we observed a high prevalence of thyroid nodules and positive associations of obesity with both solitary and multiple thyroid nodules. Among several anthropometric measurements, BSA and WC were related to the risks for both solitary and multiple thyroid nodules. These findings were generally consistent across sex groups and independent of iodized salt consumption status.

Thyroid nodule(s) is common in adults and its impact on thyroid cancer risk is still unclear[16]. The prevalence of incidental thyroid nodules detected by ultrasound examinations is high in adults (close to 50%) as well asin iodine-deficient countries[3-5]. However, few studies have investigated the prevalence, and the spectrum of appearance of ultrasound-detected findings in children. Thyroid nodules were identified in 1.65% of children aged 3 to 18 years in three Japanese prefectures, and the prevalence increased with age with a female predominance[32]. The information released by Fukushima Prefecture indicated that 2014 (1.15%) of 75216 Japanese children aged 0-18 had thyroid nodules[33]. Avula et al. conducted a retrospective analysis in 287 Canadian children (mean age=6.2) and detected only 1 child with multiple thyroid nodules but 52(18%) children with thyroid abnormalities [34]. In healthy Greek children living in an iodine-replete area, one or more nodules were observed in 5.1% of them[35]. For 2410 children aged 6-17 years living in Hangzhou, China, thyroid nodules were detected in 10.66% of them[36]. These results showed much lower frequencies than those observed in the current study, in which thyroid nodules existed in 18.46% of 1433 Chinese children with little age- and sex-variations. Influencing factors include age composition, inter-observer variation, iodine intake, socio-economic status and individual and/or family history, as well as detection sensitivity and image quality of ultrasound machine[32].

Thyroid nodule has multiple known risk factors, including demographic parameters, clinical history, age, sex [6-8] , iodine deficiency[3] and potentially milk consumption[36]. The association between thyroid nodule(s) and obesity has been explored mostly in

adults with inconsistent results[37-38].

Obesity is a risk factor for several chronic conditions, as well as goiter in adults[39]. Its impact on thyroid nodules has also been investigated by using different anthropometric parameters in adults. Among various parameters, BMI was most frequently used as a measure of general adiposity. It has been increasingly recognized that the adverse effects of obesity relate not only to the amount but also to the distribution of excess body fat. Therefore, the use of BMI alone to infer health risks in Asians may underestimate the detrimental health effects of excess adiposity [40]. WHR and WC were good proxy measures of central adiposity. It has been suggested that WC is a better marker for total body adiposity than it is for visceral fat [41]. Another study has shown that both WC and BMI appear to perform equally well for estimating children and adolescents's total adiposity[42]. BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI [37] and has been shown to be the best independent predictor of the thyroid volume in both sexes.

Several studies have found significant associations between measures of obesity and the risk of thyroid nodules. For example, a study conducted in Hangzhou, China observed a prevalence of TN being 34.97% (33.97 for men and 36.92% for women) and great WC as a risk factor for new TN in this iodine-adequate area[2]. Similar trends were observed for females and males, but the association was not statistically significant in men[2], which was similar to our findings in children. Another study of postmenopausal women also revealed that WC and BMI were associated with thyroid

nodules[43]. Large BMI was associated with nodule growth among older patients with multiple nodules and larger dominant nodules[17]. Study conducted by Shin et al linked thyroid nodular disease to WC for males and glycated hemoglobin for females[44], suggesting potential sex disparity. The presence of insulin resistance (IR) was associated with larger thyroid gland volume and an increased prevalence of thyroid nodules[45-46], which might be explained by obesity-related subclinical inflammation and an associated increase in levels of insulin-like growth factor-1(IGF-1)[45]. However, another study yielded conflicting results, which suggested that adult patients with normal weight or overweight based on BMI tended to have an increased risk of thyroid nodules, as compared with underweight or obese people[38]. Evidence in children had been relatively limited.

The prevalence of obesity and overweight in our study population was slightly higher than that in students from four Chinese megacities (25.6%) [47] but lower than urban students of similar age groups in the National Surveys on Chinese Students' Constitution and Health (37.0% for overweight and 20.3% for obesity)[48]. Our findings of increased risk for thyroid nodules in obese children are generally consistent with those in obese adults of other studies. The association of BSA with thyroid volume in children has been well established[35], while its relation to thyroid nodules has been seldom explored. Kim et al. [38] examined 7763 healthy Korean individuals and observed a significantly smaller BSA in those with thyroid nodules compared to the others, which was opposite to our findings. Considering the great difference in BSA between adults and children, it need to be cautious to generalize the results to children

[16]. Xu et.al[36] conducted a cross-sectional study in Hangzhou, China, and reported an OR of 2.97 (95% CI: 1.85 to 4.77) for thyroid nodules for children with average BSA or above as compared with those with less than average BSA. However, they did not collect the information on waist and hip circumferences and number of thyroid nodules. Therefore, it was not possible to determine different associations between WC, WHR and different kinds of nodules in that study. The potential effect of iodized salt consumption, and sex on the association of overweight and multiple nodules also needs further investigations.

The strengths of our study include large sample size, directly measured thyroid ultrasonography and anthropometric measurements following a standardized protocol, and the abilities to distinguish solitary and multiple nodules and to adjust for household iodized salt consumption status. Our studyhas several limitations. Firstly, we did not have any information on thyroid function. Therefore, we were unable to further search potential mechanisms that might explain the observed associations. Secondly, there were no information on the amount of salt, and milk consumption. In addition, the cross-sectional design prevents us from making causal inferences.

CONCLUSION

In this cross-sectional study of a relatively lean children population, we found that elevated levels of general or abdominal adiposity, measured by BMI, BSA and WC, were associated with a significant increase in the risk of thyroid nodule(s), especially multiple nodules in girls and solitary nodule in boys. Our findings, along with those observed from adult populations, emphasize the importance of preventing excess adiposity for primary prevention of thyroid nodules.

Contributors NW, HF, CWF, PXH, MFS, QZ, and QWJ contributed to the study design; NW, HF, CWF, PXH, MFS, FJ, QZ and QWJ contributed to data acquisition and collection; NW, QZ, YC contributed to data analysis and interpretation; NW, QZ and YC drafted the manuscript; all authors contributed to the preparation of the final document, read and approved the final manuscript.

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Competing interests None declared.

Ethics approval The study was approved by the Ethical Review Board of the School of Public Health of Fudan University (#2012-03-0350S).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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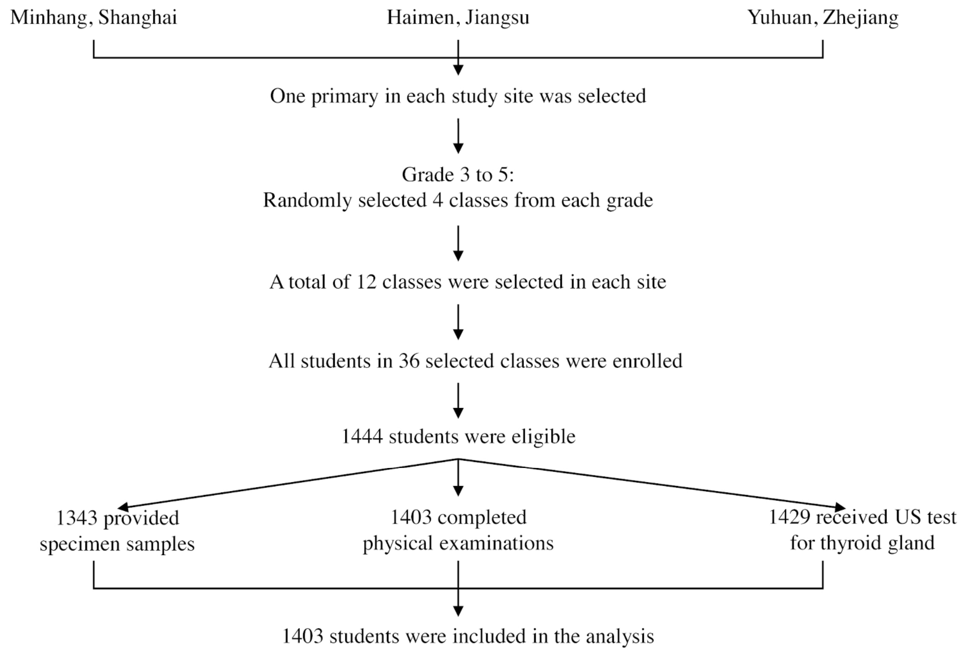
Figure 1.Flow chart for the study design

Figure 2. Associations of Different Physical Measurements (BSA, WC, BMI, and WHR) with Thyroid Nodules for children from Shanghai, Haimen and Taizhou, China, 2014



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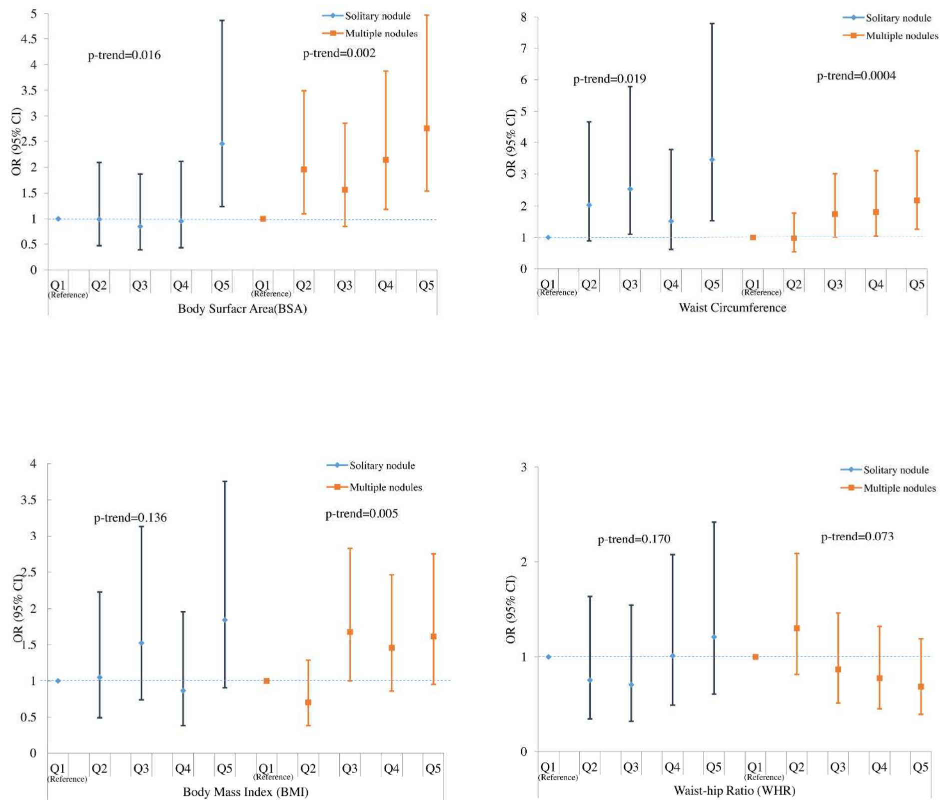

*: Adjustment for age, sex, and iodized salt consumption status

330x299mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			8

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	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	10
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	12
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
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	19

*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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Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Keywords: adiposity, thyroid nodule(s), children, iodine

Abstract

Objectives: Obesity has been found to be associated with an elevated risk of thyroid nodule(s), mainly in adults; however, evidence for this association in children was limited. The objective of this study was to investigate the association of adiposity and thyroid nodule(s) in children living in iodine-sufficiency areas.

Setting and participants: We conducted a cross-sectional study of 1,403 Chinese children living in the East Coast of China in 2014.

Outcome measures: Anthropometric measures, including height, weight, and waist and hip circumferences were taken and body mass index (BMI), body surface area (BSA), and waist-hip-ratio (WHR) were then calculated. Thyroid ultrasonography was performed to assess thyroid volume and nodules.

Results: Based on BMI, 255 (18.17%) children were overweight and 174 (12.40%) were obese. Thyroid nodule(s) was detected in 18.46% of all participants and showed little age- and sex-variations. As compared with normal weight children, obese children experienced significantly higher risks for solitary (OR: 2.07 (95% CI: 1.16, 3.71)) and multiple (OR: 1.67 (95%CI: 1.03, 2.70)) thyroid nodules. Similar associations with thyroid nodule(s) were observed with adiposity measured by waist circumference (WC) and BSA, but not WHR. There were no notable differences in the associations between children consuming iodized and non-iodized salt.

Conclusions: These findings provide further evidence that childhood obesity is associated with the risk for thyroid nodule(s).

Strengths and limitations of this study:

- Large sample size, directly measured thyroid ultrasonography and various anthropometric measurements following a standardized protocol.
- Detailed information distinguishing solitary and multiple nodules and household iodized salt consumption status at the individual level.
- Lack of information on thyroid function.

INTRODUCTION

Thyroid nodule (TN) is a common thyroid disorder globally and the incidence has been increasing in recent decades[1-2]. Thyroid ultrasound investigations have documented very high prevalences (approaching 50%) of thyroid nodules worldwide [3-5]. Potential risk factors for thyroid nodules include age, sex, iodine intake[3 6-8], demographic parameters, clinical history and waist circumference (WC) [2 9]. Both mildly deficient iodine intake and excessive iodine intake are risk factors for thyroid nodule(s) in normal subjects[10].

Obesity is a known risk factor for a number of chronic conditions, and may also increase the risk of thyroid cancer [11-15]. The recent increase in thyroid nodules and thyroid cancer may partly be due to the epidemic of obesity[9 16-17]. Elevated thyroid stimulating hormone (TSH) levels and declined free thyroxin (FT4) levels have been observed in obese patients [16]. However, previous studies of the associations between obesity and thyroid were mainly conducted in adults and the results were not entirely consistent. Whether these observations from adults can be applied to children is not clear, particularly because the incidence of thyroid nodules is lower but the risk for malignancy is greater in children as compared to adults[18].

In the current study, we conducted a large-scale epidemiological study to determine the associations of a number of anthropometric measurements including body mass index (BMI), body surface area (BSA), WC and waist-hip ratio (WHR) with solitary or multiple thyroid nodules in school age children.

METHODS

Study population

Randomized cluster sampling was used to selected subjects. Similar study methodologies have been reported for an earlier study[19]. Briefly, three coastal cities in east China (Minhang District in Shanghai, Haimen City in Jiangsu Province and Taizhou City in Zhejiang Province) were selected by purposive sampling. Previous studies have revealed an iodine sufficient status[20-22] along with distinguished iodized salt consumption proportions among three sites. One primary school (students were mainly local residents) was selected from each city to ensure a good representativeness. Four classes in each grade from grade 3 to grade 5 in these schools were randomly selected in 2014 and all students in 12 selected classes in each school were enrolled into this study (Figure 1). Among 1444 eligible children, an ultra-sound test for thyroid gland volume was performed on 1429 students and 1403 of them completed routine physical examinations. 1375 students provided first morning urine samples. Based on data from 1403 students who completed physical examinations and thyroid test, we determined the prevalence of thyroid nodule(s) and the influences of overweight and obesity. Written consent from parents or guardians of all participants were received and the study was approved by the Ethical Review Board of the School of Public Health of Fudan University.

Study variables

The outcome variables in this study were having thyroid nodule(s) (no, yes) and number of thyroid nodules (no nodule, solitary nodule, multiple nodules). Adiposity measurements were explanatory variables, including body mass index, body surface area, waist circumferences and waist-hip-ratio. Sex, age, urinary iodine concentrations, and iodized salt consumption status were covariates in the multivariate regression models.

Anthropometric measurements

Anthropometric measurements, including standing height (cm), weight (kg), and circumferences of the waist, hip and chest (cm) were taken by trained health professionals according to a standard protocol. The standing height was measured to the nearest 0.1cm without shoes. Weight was measured to the nearest 0.1kg using a digital weight scale. BMI was calculated as weight in kilograms divided by the square of height in meters and all participants were categorized into three groups of under/normal weight, overweight and obesity status according to the BMI growth reference values for Chinese children[23]. The cutoffs for overweight and obesity in boys were 17.8 and 20.1 for age 8, 18.5 and 21.1 for age 9, 19.5 and 22.2 for age 10, and 20.1 and 23.2 for age 11. The corresponding cutoffs for girls were 17.3 and 19.5, 17.9 and 20.4, 18.7 and 21.5, 19.6 and 22.7, respectively. Body surface area was calculated by using the following formula: BSA=$(\text{Weight}^{0.425})*(\text{Height}^{0.725})*0.007184$ [24]. Waist-hip-ratio was calculated as waist circumference divided by hip circumference. BSA, WC, and WHR were categorized into quintiles to assess their

relations with thyroid nodules.

Thyroid ultrasonography

All participants received thyroid ultrasonography performed by experienced examiners at school using a real-time sector scanner with a 7.5-MHz/40-mm probe linear transducer. The ultrasonographic examination was carried out on the children lying on a desk with the neck extended. Standardized thyroid ultrasound technique was adopted according to the method described by Fuse et al[25]. Discrete lesion(s) within the thyroid gland that wass palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma were defined as thyroid nodule(s)[26]. In case of abnormality in the sonographic examination of the thyroid, parents of the children would receive a written note describing the abnormal results of the examination and be advised to take their children to visit a physician. All participants were categorized as having no nodule, having nodule(s) (solitary nodule, and multiple nodules) according to their thyroid nodule detection status.

Urine and salt samples collection and iodine concentration analyses

First morning urine sample was collected for each participant. Students were also asked to bring a salt sample of more than 20g from home for iodine measurement.

Urinary iodine concentration (UIC) was determined following the method proposed by the Ministry of Health of the People's Republic of China (WS / T107．2006, and GB/T13025.7—1999)[27]. Salt iodine content was also measured using a national standard method with a proper quality control[28] (GB/T 13025.7-1999). 10% urine samples were assayed in duplicate and no statistical differences were observed as

compared with the primary results.

Iodine nutrition status was determined at a population level according to WHO/UNICEF/ICCIDD: insufficient (UIC <100 μ g/L), sufficient (100-199 μ g/L), more than adequate (200-299 μ g/L), and excessive (⩾300 μ g/L). Iodized salt consumption status was grouped into two categories: non-iodized salt (<5 mg/kg) and iodized salt (⩾5 mg/kg)[29].

Statistical analysis

,Chi-square test was used to examine thyroid nodules in relation to sex, age, BMI, iodized salt consumption status, urinary iodine level and study area. Multinomial logistic regression analysis was used to examine the associations of various anthropometric measurements with the frequency of thyroid nodules (no nodule, solitary nodule, and multiple nodules). Due to a considerable day-to-day variation in iodine excretion, one-spot urinary iodine level was not a proper indicator of iodine status for individuals [30-31]. Therefore, in current analysis, iodized salt consumption instead of iodine concentration in urine, was included in the multivariate models. We also assessed the correlation between urinary iodine concentration (UIC) and iodized salt consumption and observed a significantly higher level of UIC in children who consumed iodized salt at home, suggesting that iodized salt consumption status could be a good proxy for iodine nutrition at a population level. Multivariable logistic regression models were then used to adjust for age, sex, and iodized salt consumption. Potential effect modifications by sex, age and iodized salt consumption on the associations of interest were also examined by including associated interaction terms

into the multivariate analysis. We also re-analyzed the data by using mixed-effects with survey schools as random effect and observed no statistical significance of random effect in the GLMM (p=0.320).

All analyses were performed by using SAS, version 9.3 software (SAS Institute, Inc., Cary, NC, USA), and all statistical significance was based on two-side probability.

RESULTS

Table 1 shows the demographic characteristics as well as iodine nutrition status for the 1403 participants included in the analysis. The mean age was 9.54 (±0.98) years, the median BMI was 17.05 (IQR: 15.55, 19.35) kg/m2, and the median UIC was 184.90μg/l.

Table 1. General characteristics for children from Shanghai, Haimen and Taizhou, China, 2014

		Male		Female			
		No.	%	No.	%	X^2	P
Total		739	52.67	664	47.33		
Age (years)						0.788	0.852
	8	116	15.70	111	16.72		
	9	246	33.29	215	32.38		
	10	237	32.07	204	30.72		
	11	140	18.94	134	20.18		
BMI						11.56	0.003
	Normal	531	71.85	443	66.72		
	Overweight	110	14.88	145	21.84		
	Obese	98	13.26	76	11.45		
Area						6.182	0.046
	Minhang	294	39.78	226	34.04		
	Haimen	234	31.66	214	32.23		
	Yuhuan	211	28.55	224	33.73		
UIC(μg/L)*						4.198	0.241
	<100	122	17.35	132	20.63		
	100-199	282	40.11	226	35.31		

	200-299	171	23.14	158	24.69		
	≥300	128	17.32	124	19.38		
Iodized salt consumption**						0.015	0.901
	No	250	36.39	235	36.72		
	Yes	437	63.61	405	63.28		

*60 missing: 36(60.00%) were male and 24(40.00%) were female.

** 76 missing: 52(68.42%) were male and 24(31.58%) were female.

Thyroid nodule(s) were detected in 259 children, accounting for 18.46% of all the participants. Most nodules were accompanied by hypoechogenicity. Of the participants, 5.92% (83/1403) had solitary nodule and 12.54% (176/1403) had multiple thyroid nodules. The frequency of thyroid nodules showed no age or sex related difference (Table 2). The median UIC in children without nodules, with single nodule and multiple nodules were 187.80 μ g/L, 195.55 μ g/L, and 160.45 μ g/L, respectively. UIC was significantly lower in children with multiple nodules than those in the other two groups (X^2=7.44, P=0.024). The prevalence of multiple thyroid nodules was much higher in children consuming non-iodized salt than those consuming iodized salt.

Table 2. Comparison of the prevalence of thyroid nodules in different subgroups for children from Shanghai, Haimen and Taizhou, China, 2014

Characteristics	No.	No nodule	Nodule(s)				
		N (%)	Solitary nodule (N (%))	Multiple nodules (N (%))	Total	$\chi2$, *P*-value#	$\chi2$, *P*-value##
All	1403	1144(81.54)	83(5.92)	176(12.54)	259(18.46)		
Sex						3.95, 0.047	4.264, 0.119
Male	739	617(83.49)	37(5.01)	85(11.50)	122(16.51)		
Female	664	527(79.37)	46(6.93)	91(13.70)	137(20.63)		
Age (years)						9.11, 0.028	11.61, 0.071
8	227	192(84.58)	12(5.29)	23(10.13)	35(15.42)		
9	461	359(77.87)	34(7.38)	68(14.75)	102(22.13)		
10	441	374(84.81)	24(5.44)	43(9.75)	67(15.19)		
11	274	219(79.93)	13(4.74)	42(15.33)	55(20.07)		
Iodized salt consumption*						6.85, 0.009	12.46, 0.002
No	485	380(78.35)	26(5.36)	79(16.29)	105(21.65)		
Yes	842	708(84.09)	52(6.18)	82(9.74)	134(15.91)		
Urinary iodine(μg/l)**						13.00, 0.005	18.65, 0.005
≤100	254	204(80.31)	12(4.72)	38(14.96)	50(19.69)		
100-200	508	400(78.74)	31(6.10)	77(15.16)	108(21.26)		
200-300	329	268(81.46)	37(6.37)	51(8.78)	61(18.54)		
>300	252	225(89.29)	12(4.76)	15(5.95)	27(10.71)		
Area						142.11, <0.001	155.80, <0.001
Shanghai	520	344(66.15)	49(9.42)	127(24.42)	176(33.85)		
Haimen	448	426(95.09)	20(4.46)	2(0.45)	22(4.91)		
Taizhou	435	374(85.95)	14(3.22)	47(10.80)	61(14.02)		

* 76 missing: 52(68.42%) were male and 24(31.58%) were female.

** 60 missing: 36(60.00%) were male and 24(40.00%) were female.

Comparison between participants with/without thyroid nodule(s)

Comparison among participants without nodule/ with solitary nodule/ with multiple nodules

Based on BMI, 255(18.17%) were overweight and 174(12.40%) were obese. Girls were more likely to be overweight than boys and the prevalence of overweight/obese decreased with age in both sexes (P-trend: 0.033 for boys and 0.010 for girls). The prevalences of solitary and multiple nodules in overweight subjects were 3.53% (9/255) and 15.29% (39/255), while the corresponding prevalence were 20.48% (17/174) and 14.77% (26/174) in obese ones, respectively.

Multivariable analysis revealed significant associations between obesity and the risk of thyroid nodule(s) (Table 3). As compared with normal weight children, obese children experienced a significantly higher risks of thyroid nodule(s) ((OR: 1.71 (95% CI: 1.13, 2.59)). We observed a similar association of obesity with the risk of either solitary nodule or multiple nodules (Table 4). When stratified by sex, only obese girls experienced an increased risk for multiple nodules (OR: 2.10 (95% CI: 1.03, 4.31)) but the interaction of obesity with sex was not significant (p=0.494). Associations of multiple nodules with overweight (OR: 1.87, 95% CI: 1.07, 3.29) and obesity (OR: 2.00, 95%CI: 1.05, 3.78) were observed in children aged 8 or 9 years, but not in older ones. Overweight was not significantly associated with solitary thyroid nodule in general, which might be due to small number of children with this thyroid condition. Overweight children had an increased risk for multiple thyroid nodules (OR: 1.76, 95% CI: 1.03, 3.02) only in iodized salt consumers.

Table 3 Multinomial logistic regression analysis of obesity and thyroid nodule(s) for children from Shanghai, Haimen and Taizhou, China, 2014

		No nodule	Thyroid Nodule(s)					
			Normal		Overweight		Obesity	
		N	N	OR	N	OR (95%CI) [a]	N	OR (95%CI) [a]
All subjects*		1144	168		48		43	
	Model 1			1.00		1.11(0.78, 1.59)		1.58(1.07, 2.31)
	Model 2			1.00		1.00(0.69, 1.45)		1.82(1.22, 2.70)
	Model 3			1.00		1.04(0.71, 1.51)		1.71(1.13, 2.59)
Sex**	Male	576	80	1.00	14	0.83(0.45, 1.54)	17	1.39(0.77, 2.52)
	Female	512	79	1.00	29	1.21(0.75, 1.96)	20	2.10(1.17, 3.79)
Age (years)#	8-9	519	76	1.00	27	1.37(0.83, 2.25)	25	1.87(1.10, 3.19)
	10-11	569	83	1.00	16	0.77(0.43, 1.38)	12	1.39(0.70, 2.75)
Iodized salt consumption##	Yes	708	81	1.00	28	1.20(0.75, 1.93)	25	1.62(0.98, 2.68)
	No	380	78	1.00	15	0.81(0.43, 1.50)	12	1.94(0.92, 4.09)

* Model 1: univariate analysis

Model 2: adjustment for sex, age, iodized salt consumption

Model 3: adjustment for sex, age, urinary iodine concentration

** Adjustment for age and iodized salt consumption

\# Adjustment for sex and iodized salt consumption

\## Adjustment for sex, and age

Table 4. Multinomial logistic regression analysis of obesity and solitary and multiple thyroid nodules for children from Shanghai, Haimen and Taizhou, China, 2014

		Normal					Overweight				Obesity			
		No nodule	Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules	
		N	N	OR	N	OR	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]
All subjects*		1144	57		111		9		39		17		26	
	Model 1			1.00		1.00		0.62(0.30, 1.26)		1.37(0.92, 2.03)		1.84(1.04, 3.25)		1.44(0.91, 2.30)
	Model 2			1.00		1.00		0.53(0.25, 1.13)		1.33(0.88, 2.03)		1.82(0.99, 3.36)		1.62(0.98, 2.70)
	Model 3			1.00		1.00		0.54(0.25, 1.16)		1.24(0.82, 1.88)		2.07(1.16, 3.71)		1.67(1.03, 2.70)
Sex**	Male	576	26	1.00	54	1.00	1	0.17(0.02, 1.28)	13	1.18(0.61, 2.26)	7	1.53(0.63, 3.71)	10	1.29(0.62, 2.70)
	Female	512	29	1.00	50	1.00	7	0.77(0.33, 1.82)	22	1.49(0.86, 2.59)	8	2.09(0.89, 4.89)	12	2.10(1.03, 4.31)
Age (years)#	8-9	519	29	1.00	47	1.00	5	0.63(0.24,1.68)	22	1.87(1.07,3.29)	9	1.60(0.71,3.57)	16	2.00(1.05,3.78)
	10-11	569	26	1.00	57	1.00	3	0.46(0.14,1.55)	13	0.95(0.50,1.82)	6	2.05(0.80,5.25)	6	1.05(0.43,2.60)
Iodized salt consumption##	Yes	708	35	1.00	46	1.00	5	0.48(0.18, 1.27)	23	1.76(1.03, 3.02)	12	1.76(0.88, 3.54)	13	1.50(0.78, 2.90)
	No	380	20	1.00	58	1.00	3	0.59(0.17, 2.08)	12	0.88(0.45, 1.75)	3	1.84(0.50, 6.79)	9	1.97(0.86, 4.48)

* Model 1: univariate analysis

Model 2: adjustment for sex, age, iodized salt consumption

Model 3: adjustment for sex, age, urinary iodine concentration

** Adjustment for age and iodized salt consumption

\# Adjustment for sex and iodized salt consumption

\## Adjustment for sex, and age

Figures 2 presents multivariate-adjusted ORs and 95% confidence intervals for solitary and multiple thyroid nodules associated with the quintiles of BSA, WC, BMI, and WHR, respectively. After adjustment for sex, age, and iodized salt consumption status, BSA and WC were positively related to the risks of solitary and multiple nodule(s) (p values for trend for all the nodules together were 0.0001 and <0.0001, respectively). As compared with children in the lowest quintile, the ORs of solitary and multiple nodules were 2.45 (95% CI: 1.24, 4.87) and 2.76 (95% CI: 1.54, 4.97) for those in the highest quintile of BSA and 3.46 (95% CI: 1.54, 7.80) and 2.18 (95% CI: 1.27, 3.74) for those in the highest quintile of WC, respectively. The interaction between BSA and sex on thyroid nodules was not statistically significant (p-interaction: 0.785 for solitary nodule and 0.600 for multiple nodules).

The results for BMI and WHR were less consistent. BMI was positively associated with the risk of multiple nodules (p-trend=0.005), while WHR showed no association with either solitary or multiple nodules.

DISCUSSION

In this large cross-sectional study of children living in iodine sufficient areas in East China, we observed a high prevalence of thyroid nodules and positive associations of obesity with both solitary and multiple thyroid nodules. Among several anthropometric measurements, BSA and WC were related to the risks for both solitary and multiple thyroid nodules. These findings were generally consistent across sex groups and independent of iodized salt consumption status.

Thyroid nodule(s) is common in adults and its impact on thyroid cancer risk is still unclear[16]. The prevalence of incidental thyroid nodules detected by ultrasound examinations is high in adults (close to 50%) as well asin iodine-deficient countries[3-5]. However, few studies have investigated the prevalence, and the spectrum of appearance of ultrasound-detected findings in children. Thyroid nodules were identified in 1.65% of children aged 3 to 18 years in three Japanese prefectures, and the prevalence increased with age with a female predominance[32]. The information released by Fukushima Prefecture indicated that 2014 (1.15%) of 75216 Japanese children aged 0-18 had thyroid nodules[33]. Avula et al. conducted a retrospective analysis in 287 Canadian children (mean age=6.2) and detected only 1 child with multiple thyroid nodules but 52(18%) children with thyroid abnormalities [34]. In healthy Greek children living in an iodine-replete area, one or more nodules were observed in 5.1% of them[35]. For 2410 children aged 6-17 years living in Hangzhou, China, thyroid nodules were detected in 10.66% of them[36]. These results showed much lower frequencies than those observed in the current study, in which thyroid nodules existed in 18.46% of 1433 Chinese children with little age- and sex-variations. Influencing factors include age composition, inter-observer variation, iodine intake, socio-economic status and individual and/or family history, as well as detection sensitivity and image quality of ultrasound machine[32].

Thyroid nodule has multiple known risk factors, including demographic parameters, clinical history, age, sex [6-8] , iodine deficiency[3] and potentially milk consumption[36]. The association between thyroid nodule(s) and obesity has been explored mostly in

adults with inconsistent results[37-38].

Obesity is a risk factor for several chronic conditions, as well as goiter in adults[39]. Its impact on thyroid nodules has also been investigated by using different anthropometric parameters in adults. Among various parameters, BMI was most frequently used as a measure of general adiposity. It has been increasingly recognized that the adverse effects of obesity relate not only to the amount but also to the distribution of excess body fat. Therefore, the use of BMI alone to infer health risks in Asians may underestimate the detrimental health effects of excess adiposity [40]. WHR and WC were good proxy measures of central adiposity. It has been suggested that WC is a better marker for total body adiposity than it is for visceral fat [41]. Another study has shown that both WC and BMI appear to perform equally well for estimating children and adolescents's total adiposity[42]. BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI [37] and has been shown to be the best independent predictor of the thyroid volume in both sexes.

Several studies have found significant associations between measures of obesity and the risk of thyroid nodules. For example, a study conducted in Hangzhou, China observed a prevalence of TN being 34.97% (33.97 for men and 36.92% for women) and great WC as a risk factor for new TN in this iodine-adequate area[2]. Similar trends were observed for females and males, but the association was not statistically significant in men[2], which was similar to our findings in children. Another study of postmenopausal women also revealed that WC and BMI were associated with thyroid

nodules[43]. Large BMI was associated with nodule growth among older patients with multiple nodules and larger dominant nodules[17]. Study conducted by Shin et al linked thyroid nodular disease to WC for males and glycated hemoglobin for females[44], suggesting potential sex disparity. The presence of insulin resistance (IR) was associated with larger thyroid gland volume and an increased prevalence of thyroid nodules[45-46], which might be explained by obesity-related subclinical inflammation and an associated increase in levels of insulin-like growth factor-1(IGF-1)[45]. However, another study yielded conflicting results, which suggested that adult patients with normal weight or overweight based on BMI tended to have an increased risk of thyroid nodules, as compared with underweight or obese people[38]. Evidence in children had been relatively limited.

The prevalence of obesity and overweight in our study population was slightly higher than that in students from four Chinese megacities (25.6%) [47] but lower than urban students of similar age groups in the National Surveys on Chinese Students' Constitution and Health (37.0% for overweight and 20.3% for obesity)[48]. Our findings of increased risk for thyroid nodules in obese children are generally consistent with those in obese adults of other studies. The association of BSA with thyroid volume in children has been well established[35], while its relation to thyroid nodules has been seldom explored. Kim et al. [38] examined 7763 healthy Korean adults and observed a significantly smaller BSA in those with thyroid nodules compared to the others, which was opposite to our findings. Considering the great difference in BSA between adults and children, it need to be cautious to generalize the results to children [16]. Xu et.al[36] conducted a cross-sectional study in Hangzhou, China, and reported an OR of 2.97 (95% CI: 1.85 to 4.77) for thyroid nodules for children with average BSA or above as compared with those with less than average BSA. However, they did not collect the information on waist and hip circumferences and number of thyroid nodules. Therefore, it was not possible to determine different associations between WC, WHR and different kinds of nodules in that study. The potential interactive effects of iodized salt consumption, and sex on the association between overweight and multiple nodules also needs further investigations with a larger sample size. The strengths of our study include large sample size, directly measured thyroid ultrasonography and anthropometric measurements following a standardized protocol, and the abilities to distinguish solitary and multiple nodules and to adjust for household iodized salt consumption status. Our studyhas several limitations. Firstly, we did not have any information on thyroid function. Therefore, we were unable to further search potential mechanisms that might explain the observed associations. Secondly, there were no information on the amount of salt, and milk consumption. In the current study, the number of children with solitary or multiple nodules was small in some categories. In addition, the cross-sectional design prevents us from making causal inferences.

CONCLUSION

In this cross-sectional study of a relatively lean children population, we found that elevated levels of general or abdominal adiposity, measured by BMI, BSA and WC, were associated with a significant increase in the risk of thyroid nodule(s), especially multiple nodules in girls and solitary nodule in boys. Our findings, along with those observed from adult populations, emphasize the importance of preventing excess adiposity for primary prevention of thyroid nodules.

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Competing interests None declared.

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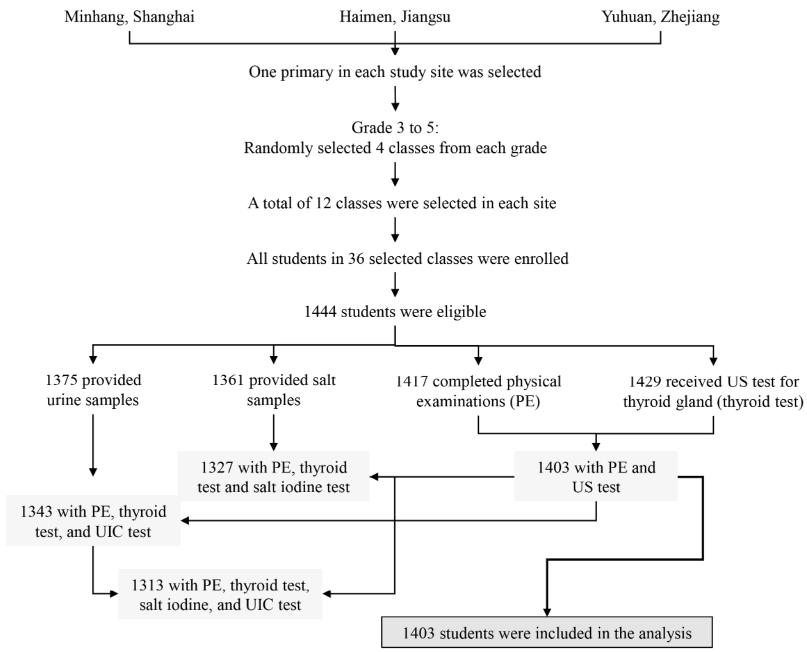
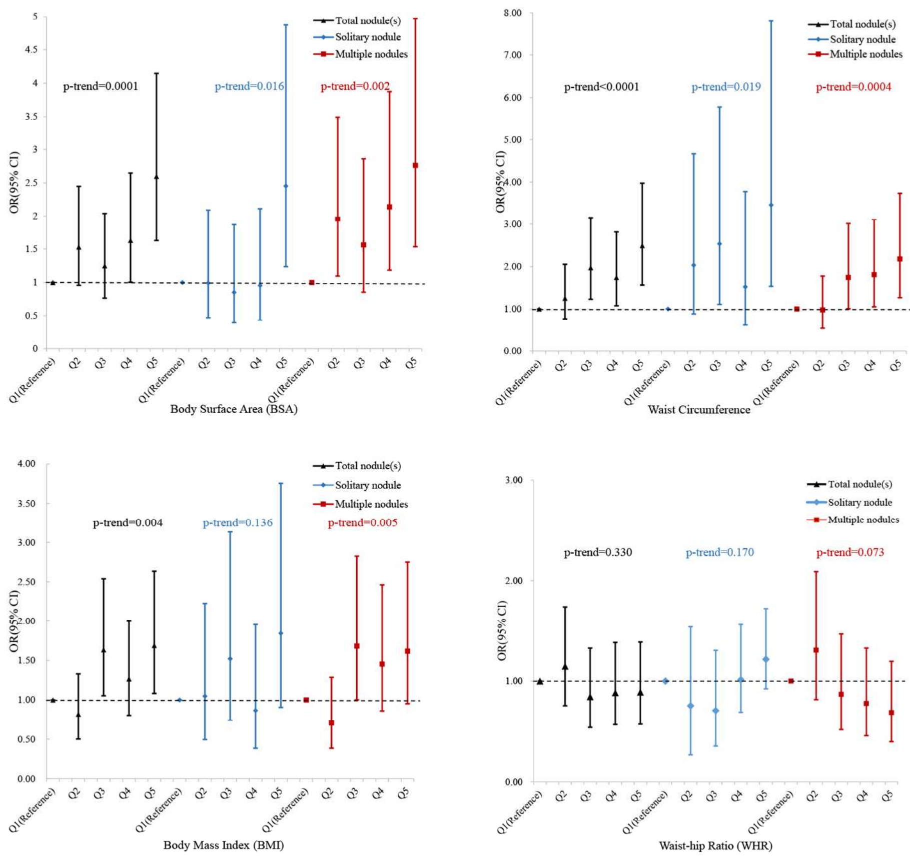
Figure 1.Flow chart for the study design

Figure 2. Associations of Different Physical Measurements (BSA, WC, BMI, and WHR) with Thyroid Nodule(s) for children from Shanghai, Haimen and Taizhou, China, 2014



flow chart

254x190mm (300 x 300 DPI)



*: Adjustment for age, sex, and iodized salt consumption status

140x140mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			8

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	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	10
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	12
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
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	19

*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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Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficiency areas: an observational study

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Word Count: 2940 **Figures**: 2 **Tables**:4

Keywords: adiposity, thyroid nodule(s), children, iodine

Abstract

Objectives: Obesity has been found to be associated with an elevated risk of thyroid nodule(s), mainly in adults; however, evidence for this association in children was limited. The objective of this study was to investigate the association of adiposity and thyroid nodule(s) in children living in iodine-sufficiency areas.

Setting and participants: We conducted a cross-sectional study of 1,403 Chinese children living in the East Coast of China in 2014.

Outcome measures: Anthropometric measures, including height, weight, and waist and hip circumferences were taken and body mass index (BMI), body surface area (BSA), and waist-hip-ratio (WHR) were then calculated. Thyroid ultrasonography was performed to assess thyroid volume and nodules.

Results: Based on BMI, 255 (18.17%) children were overweight and 174 (12.40%) were obese. Thyroid nodule(s) was detected in 18.46% of all participants and showed little age- and sex-variations. As compared with normal weight children, obese children experienced significantly higher risks for solitary (OR: 2.07 (95% CI: 1.16, 3.71)) and multiple (OR: 1.67 (95%CI: 1.03, 2.70)) thyroid nodules. Similar associations with thyroid nodule(s) were observed with adiposity measured by waist circumference (WC) and BSA, but not WHR. There were no notable differences in the associations between children consuming iodized and non-iodized salt.

Conclusions: These findings provide further evidence that childhood obesity is associated with the risk for thyroid nodule(s).

Strengths and limitations of this study:

- Large sample size, directly measured thyroid ultrasonography and various anthropometric measurements following a standardized protocol.
- Detailed information distinguishing solitary and multiple nodules and household iodized salt consumption status at the individual level.
- Lack of information on thyroid function.

INTRODUCTION

Thyroid nodule (TN) is a common thyroid disorder globally and the incidence has been increasing in recent decades[1-2]. Thyroid ultrasound investigations have documented very high prevalences (approaching 50%) of thyroid nodules worldwide [3-5]. Potential risk factors for thyroid nodules include age, sex, iodine intake[3 6-8], demographic parameters, clinical history and waist circumference (WC) [2 9]. Both mildly deficient iodine intake and excessive iodine intake are risk factors for thyroid nodule(s) in normal subjects[10].

Obesity is a known risk factor for a number of chronic conditions, and may also increase the risk of thyroid cancer [11-15]. The recent increase in thyroid nodules and thyroid cancer may partly be due to the epidemic of obesity[9 16-17]. Elevated thyroid stimulating hormone (TSH) levels and declined free thyroxin (FT4) levels have been observed in obese patients [16]. However, previous studies of the associations between obesity and thyroid were mainly conducted in adults and the results were not entirely consistent. Whether these observations from adults can be applied to children is not clear, particularly because the incidence of thyroid nodules is lower but the risk for malignancy is greater in children as compared to adults[18].

In the current study, we conducted a large-scale epidemiological study to determine the associations of a number of anthropometric measurements including body mass index (BMI), body surface area (BSA), WC and waist-hip ratio (WHR) with solitary or multiple thyroid nodules in school age children.

METHODS

Study population

Randomized cluster sampling was used to selected subjects. Similar study methodologies have been reported for an earlier study[19]. Briefly, three coastal cities in east China (Minhang District in Shanghai, Haimen City in Jiangsu Province and Taizhou City in Zhejiang Province) were selected by purposive sampling. Previous studies have revealed an iodine sufficient status[20-22] along with distinguished iodized salt consumption proportions among three sites. One primary school (students were mainly local residents) was selected from each city to ensure a good representativeness. Four classes in each grade from grade 3 to grade 5 in these schools were randomly selected in 2014 and all students in 12 selected classes in each school were enrolled into this study (Figure 1). Among 1444 eligible children, an ultra-sound test for thyroid gland volume was performed on 1429 students and 1403 of them completed routine physical examinations. 1375 students provided first morning urine samples. Based on data from 1403 students who completed physical examinations and thyroid test, we determined the prevalence of thyroid nodule(s) and the influences of overweight and obesity. Written consent from parents or guardians of all participants were received and the study was approved by the Ethical Review Board of the School of Public Health of Fudan University.

Study variables

The outcome variables in this study were having thyroid nodule(s) (no, yes) and number of thyroid nodules (no nodule, solitary nodule, multiple nodules). Adiposity measurements were explanatory variables, including body mass index, body surface area, waist circumferences and waist-hip-ratio. Sex, age, urinary iodine concentrations, and iodized salt consumption status were covariates in the multivariate regression models.

Anthropometric measurements

Anthropometric measurements, including standing height (cm), weight (kg), and circumferences of the waist, hip and chest (cm) were taken by trained health professionals according to a standard protocol. The standing height was measured to the nearest 0.1cm without shoes. Weight was measured to the nearest 0.1kg using a digital weight scale. BMI was calculated as weight in kilograms divided by the square of height in meters and all participants were categorized into three groups of under/normal weight, overweight and obesity status according to the BMI growth reference values for Chinese children[23]. The cutoffs for overweight and obesity in boys were 17.8 and 20.1 for age 8, 18.5 and 21.1 for age 9, 19.5 and 22.2 for age 10, and 20.1 and 23.2 for age 11. The corresponding cutoffs for girls were 17.3 and 19.5, 17.9 and 20.4, 18.7 and 21.5, 19.6 and 22.7, respectively. Body surface area was calculated by using the following formula: $BSA=(Weight^{0.425})*(Height^{0.725})*0.007184$ [24]. Waist-hip-ratio was calculated as waist circumference divided by hip circumference. BSA, WC, and WHR were categorized into quintiles to assess their

relations with thyroid nodules.

Thyroid ultrasonography

All participants received thyroid ultrasonography performed by experienced examiners at school using a real-time sector scanner with a 7.5-MHz/40-mm probe linear transducer. The ultrasonographic examination was carried out on the children lying on a desk with the neck extended. Standardized thyroid ultrasound technique was adopted according to the method described by Fuse et al[25]. Discrete lesion(s) within the thyroid gland that wass palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma were defined as thyroid nodule(s)[26]. In case of abnormality in the sonographic examination of the thyroid, parents of the children would receive a written note describing the abnormal results of the examination and be advised to take their children to visit a physician. All participants were categorized as having no nodule, having nodule(s) (solitary nodule, and multiple nodules) according to their thyroid nodule detection status.

Urine and salt samples collection and iodine concentration analyses

First morning urine sample was collected for each participant. Students were also asked to bring a salt sample of more than 20g from home for iodine measurement.

Urinary iodine concentration (UIC) was determined following the method proposed by the Ministry of Health of the People's Republic of China (WS / T107．2006, and GB/T13025.7—1999)[27]. Salt iodine content was also measured using a national standard method with a proper quality control[28] (GB/T 13025.7-1999). 10% urine samples were assayed in duplicate and no statistical differences were observed as

compared with the primary results.

Iodine nutrition status was determined at a population level according to WHO/UNICEF/ICCIDD: insufficient (UIC <100 μ g/L), sufficient (100-199 μ g/L), more than adequate (200-299 μ g/L), and excessive (⩾300 μ g/L). Iodized salt consumption status was grouped into two categories: non-iodized salt (<5 mg/kg) and iodized salt (⩾5 mg/kg)[29].

Statistical analysis

,Chi-square test was used to examine thyroid nodules in relation to sex, age, BMI, iodized salt consumption status, urinary iodine level and study area. Multinomial logistic regression analysis was used to examine the associations of various anthropometric measurements with the frequency of thyroid nodules (no nodule, solitary nodule, and multiple nodules). Due to a considerable day-to-day variation in iodine excretion, one-spot urinary iodine level was not a proper indicator of iodine status for individuals [30-31]. Therefore, in current analysis, iodized salt consumption instead of iodine concentration in urine, was included in the multivariate models. We also assessed the correlation between urinary iodine concentration (UIC) and iodized salt consumption and observed a significantly higher level of UIC in children who consumed iodized salt at home, suggesting that iodized salt consumption status could be a good proxy for iodine nutrition at a population level. Multivariable logistic regression models were then used to adjust for age, sex, and iodized salt consumption. Potential effect modifications by sex, age and iodized salt consumption on the associations of interest were also examined by including associated interaction terms

into the multivariate analysis. We also re-analyzed the data by using mixed-effects with survey schools as random effect and observed no statistical significance of random effect in the GLMM (p=0.320).

All analyses were performed by using SAS, version 9.3 software (SAS Institute, Inc., Cary, NC, USA), and all statistical significance was based on two-side probability.

RESULTS

Table 1 shows the demographic characteristics as well as iodine nutrition status for the 1403 participants included in the analysis. The mean age was 9.54 (±0.98) years, the median BMI was 17.05 (IQR: 15.55, 19.35) kg/m2, and the median UIC was 184.90μg/l.

Table 1. General characteristics for children from Shanghai, Haimen and Taizhou, China, 2014

		Male		Female			
		No.	%	No.	%	X^2	P
Total		739	52.67	664	47.33		
Age (years)						0.788	0.852
	8	116	15.70	111	16.72		
	9	246	33.29	215	32.38		
	10	237	32.07	204	30.72		
	11	140	18.94	134	20.18		
BMI						11.56	0.003
	Normal	531	71.85	443	66.72		
	Overweight	110	14.88	145	21.84		
	Obese	98	13.26	76	11.45		
Area						6.182	0.046
	Minhang	294	39.78	226	34.04		
	Haimen	234	31.66	214	32.23		
	Yuhuan	211	28.55	224	33.73		
UIC(μg/L)*						4.198	0.241
	<100	122	17.35	132	20.63		
	100-199	282	40.11	226	35.31		

	200-299	171	23.14	158	24.69		
	⩾300	128	17.32	124	19.38		
Iodized salt consumption**						0.015	0.901
	No	250	36.39	235	36.72		
	Yes	437	63.61	405	63.28		

*60 missing: 36(60.00%) were male and 24(40.00%) were female.

** 76 missing: 52(68.42%) were male and 24(31.58%) were female.

Thyroid nodule(s) were detected in 259 children, accounting for 18.46% of all the participants. Most nodules were accompanied by hypoechogenicity. Of the participants, 5.92% (83/1403) had solitary nodule and 12.54% (176/1403) had multiple thyroid nodules. The frequency of thyroid nodules showed no age or sex related difference (Table 2). The median UIC in children without nodules, with single nodule and multiple nodules were 187.80 μ g/L, 195.55 μ g/L, and 160.45 μ g/L, respectively (X^2=7.44, P=0.024). The prevalence of multiple thyroid nodules was much higher in children consuming non-iodized salt than those consuming iodized salt.

Table 2. Comparison of the prevalence of thyroid nodules in different subgroups for children from Shanghai, Haimen and Taizhou, China, 2014

		No nodule	Nodule(s)				
Characteristics	No.	N (%)	Solitary nodule (N (%))	Multiple nodules (N (%))	Total	χ2, *P*-value[#]	χ2, *P*-value[##]
All	1403	1144(81.54)	83(5.92)	176(12.54)	259(18.46)		
Sex						3.95, 0.047	4.264, 0.119
Male	739	617(83.49)	37(5.01)	85(11.50)	122(16.51)		
Female	664	527(79.37)	46(6.93)	91(13.70)	137(20.63)		
Age (years)						9.11, 0.028	11.61, 0.071
8	227	192(84.58)	12(5.29)	23(10.13)	35(15.42)		
9	461	359(77.87)	34(7.38)	68(14.75)	102(22.13)		
10	441	374(84.81)	24(5.44)	43(9.75)	67(15.19)		
11	274	219(79.93)	13(4.74)	42(15.33)	55(20.07)		
Iodized salt consumption*						6.85, 0.009	12.46, 0.002
No	485	380(78.35)	26(5.36)	79(16.29)	105(21.65)		
Yes	842	708(84.09)	52(6.18)	82(9.74)	134(15.91)		
Urinary iodine(μg/l)**						13.00, 0.005	18.65, 0.005
≤100	254	204(80.31)	12(4.72)	38(14.96)	50(19.69)		
100-200	508	400(78.74)	31(6.10)	77(15.16)	108(21.26)		
200-300	329	268(81.46)	25(7.60)	36(10.94)	61(18.54)		
>300	252	225(89.29)	12(4.76)	15(5.95)	27(10.71)		
Area						142.11, <0.001	155.80, <0.001
Shanghai	520	344(66.15)	49(9.42)	127(24.42)	176(33.85)		
Haimen	448	426(95.09)	20(4.46)	2(0.45)	22(4.91)		
Taizhou	435	374(85.95)	14(3.22)	47(10.80)	61(14.02)		

* 76 missing: 52(68.42%) were male and 24(31.58%) were female.

** 60 missing: 36(60.00%) were male and 24(40.00%) were female.

Comparison between participants with/without thyroid nodule(s)

Comparison among participants without nodule/ with solitary nodule/ with multiple nodules

Based on BMI, 255(18.17%) were overweight and 174(12.40%) were obese. Girls were more likely to be overweight than boys and the prevalence of overweight/obese decreased with age in both sexes (P-trend: 0.033 for boys and 0.010 for girls). The prevalences of solitary and multiple nodules in overweight subjects were 3.53% (9/255) and 15.29% (39/255), while the corresponding prevalence were 20.48% (17/174) and 14.77% (26/174) in obese ones, respectively.

Multivariable analysis revealed significant associations between obesity and the risk of thyroid nodule(s) (Table 3). As compared with normal weight children, obese children experienced a significantly higher risks of thyroid nodule(s) (OR: 1.82 (95% CI: 1.22, 2.70)). We observed a similar association of obesity with the risk of either solitary nodule or multiple nodules (Table 4). When stratified by sex, only obese girls experienced an increased risk for multiple nodules (OR: 2.10 (95% CI: 1.03, 4.31)) but the interaction of obesity with sex was not significant (p=0.494). Associations of multiple nodules with overweight (OR: 1.87, 95% CI: 1.07, 3.29) and obesity (OR: 2.00, 95%CI: 1.05, 3.78) were observed in children aged 8 or 9 years, but not in older ones. Overweight was not significantly associated with solitary thyroid nodule in general, which might be due to small number of children with this thyroid condition. Overweight children had an increased risk for multiple thyroid nodules (OR: 1.76, 95% CI: 1.03, 3.02) only in iodized salt consumers.

Table 3 Multinomial logistic regression analysis of obesity and thyroid nodule(s) for children from Shanghai, Haimen and Taizhou, China, 2014

		No nodule	Thyroid Nodule(s)					
			Normal		Overweight		Obesity	
		N	N	OR	N	OR (95%CI) [a]	N	OR (95%CI) [a]
All subjects*		1144	168		48		43	
	Model 1			1.00		1.11(0.78, 1.59)		1.58(1.07, 2.31)
	Model 2			1.00		1.00(0.69, 1.45)		1.82(1.22, 2.70)
	Model 3			1.00		1.04(0.71, 1.51)		1.71(1.13, 2.59)
Sex**	Male	576	80	1.00	14	0.83(0.45, 1.54)	17	1.39(0.77, 2.52)
	Female	512	79	1.00	29	1.21(0.75, 1.96)	20	2.10(1.17, 3.79)
Age (years)#	8-9	519	76	1.00	27	1.37(0.83, 2.25)	25	1.87(1.10, 3.19)
	10-11	569	83	1.00	16	0.77(0.43, 1.38)	12	1.39(0.70, 2.75)
Iodized salt consumption##	Yes	708	81	1.00	28	1.20(0.75, 1.93)	25	1.62(0.98, 2.68)
	No	380	78	1.00	15	0.81(0.43, 1.50)	12	1.94(0.92, 4.09)

* Model 1: univariate analysis (N=1403)

Model 2: adjustment for sex, age, iodized salt consumption (N=1327)

Model 3: adjustment for sex, age, urinary iodine concentration (N=1343)

** Adjustment for age and iodized salt consumption (N=1327)

\# Adjustment for sex and iodized salt consumption (N=1327)

\#\# Adjustment for sex, and age (N=1327)

Table 4. Multinomial logistic regression analysis of obesity and solitary and multiple thyroid nodules for children from Shanghai, Haimen and Taizhou, China, 2014

		Normal					Overweight				Obesity			
		No nodule	Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules		Solitary nodule		Multiple nodules	
		N	N	OR	N	OR	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]	N	OR (95%CI) [a]
All subjects*		1144	57		111		9		39		17		26	
	Model 1			1.00		1.00		0.62(0.30, 1.26)		1.37(0.92, 2.03)		1.84(1.04, 3.25)		1.44(0.91, 2.30)
	Model 2			1.00		1.00		0.53(0.25, 1.13)		1.33(0.88, 2.03)		1.82(0.99, 3.36)		1.62(0.98, 2.70)
	Model 3			1.00		1.00		0.54(0.25, 1.16)		1.24(0.82, 1.88)		2.07(1.16, 3.71)		1.67(1.03, 2.70)
Sex**	Male	576	26	1.00	54	1.00	1	0.17(0.02, 1.28)	13	1.18(0.61, 2.26)	7	1.53(0.63, 3.71)	10	1.29(0.62, 2.70)
	Female	512	29	1.00	50	1.00	7	0.77(0.33, 1.82)	22	1.49(0.86, 2.59)	8	2.09(0.89, 4.89)	12	2.10(1.03, 4.31)
Age (years)#	8-9	519	29	1.00	47	1.00	5	0.63(0.24,1.68)	22	1.87(1.07,3.29)	9	1.60(0.71,3.57)	16	2.00(1.05,3.78)
	10-11	569	26	1.00	57	1.00	3	0.46(0.14,1.55)	13	0.95(0.50,1.82)	6	2.05(0.80,5.25)	6	1.05(0.43,2.60)
Iodized salt consumption##	Yes	708	35	1.00	46	1.00	5	0.48(0.18, 1.27)	23	1.76(1.03, 3.02)	12	1.76(0.88, 3.54)	13	1.50(0.78, 2.90)
	No	380	20	1.00	58	1.00	3	0.59(0.17, 2.08)	12	0.88(0.45, 1.75)	3	1.84(0.50, 6.79)	9	1.97(0.86, 4.48)

* Model 1: univariate analysis (N=1403)

Model 2: adjustment for sex, age, iodized salt consumption (N=1327)

Model 3: adjustment for sex, age, urinary iodine concentration (N=1343)

** Adjustment for age and iodized salt consumption (N=1327)

Adjustment for sex and iodized salt consumption (N=1327)

Adjustment for sex, and age (N=1327)

Figures 2 presents multivariate-adjusted ORs and 95% confidence intervals for solitary and multiple thyroid nodules associated with the quintiles of BSA, WC, BMI, and WHR, respectively. After adjustment for sex, age, and iodized salt consumption status, BSA and WC were positively related to the risks of solitary and multiple nodule(s) (p values for trend for all the nodules together were 0.0001 and <0.0001, respectively). As compared with children in the lowest quintile, the ORs of solitary and multiple nodules were 2.45 (95% CI: 1.24, 4.87) and 2.76 (95% CI: 1.54, 4.97) for those in the highest quintile of BSA and 3.46 (95% CI: 1.54, 7.80) and 2.18 (95% CI: 1.27, 3.74) for those in the highest quintile of WC, respectively. The interaction between BSA and sex on thyroid nodules was not statistically significant (p-interaction: 0.785 for solitary nodule and 0.600 for multiple nodules).

The results for BMI and WHR were less consistent. BMI was positively associated with the risk of multiple nodules (p-trend=0.005), while WHR showed no association with either solitary or multiple nodules.

DISCUSSION

In this large cross-sectional study of children living in iodine sufficient areas in East China, we observed a high prevalence of thyroid nodules and positive associations of obesity with both solitary and multiple thyroid nodules. Among several anthropometric measurements, BSA and WC were related to the risks for both solitary and multiple thyroid nodules. These findings were generally consistent across sex groups and independent of iodized salt consumption status.

Thyroid nodule(s) is common in adults and its impact on thyroid cancer risk is still unclear[16]. The prevalence of incidental thyroid nodules detected by ultrasound examinations is high in adults (close to 50%) as well asin iodine-deficient countries[3-5]. However, few studies have investigated the prevalence, and the spectrum of appearance of ultrasound-detected findings in children. Thyroid nodules were identified in 1.65% of children aged 3 to 18 years in three Japanese prefectures, and the prevalence increased with age with a female predominance[32]. The information released by Fukushima Prefecture indicated that 2014 (1.15%) of 75216 Japanese children aged 0-18 had thyroid nodules[33]. Avula et al. conducted a retrospective analysis in 287 Canadian children (mean age=6.2) and detected only 1 child with multiple thyroid nodules but 52(18%) children with thyroid abnormalities [34]. In healthy Greek children living in an iodine-replete area, one or more nodules were observed in 5.1% of them[35]. For 2410 children aged 6-17 years living in Hangzhou, China, thyroid nodules were detected in 10.66% of them[36]. These results showed much lower frequencies than those observed in the current study, in which thyroid nodules existed in 18.46% of 1433 Chinese children with little age- and sex-variations. Influencing factors include age composition, inter-observer variation, iodine intake, socio-economic status and individual and/or family history, as well as detection sensitivity and image quality of ultrasound machine[32].

Thyroid nodule has multiple known risk factors, including demographic parameters, clinical history, age, sex [6-8] , iodine deficiency[3] and potentially milk consumption[36]. The association between thyroid nodule(s) and obesity has been explored mostly in

adults with inconsistent results[37-38].

Obesity is a risk factor for several chronic conditions, as well as goiter in adults[39]. Its impact on thyroid nodules has also been investigated by using different anthropometric parameters in adults. Among various parameters, BMI was most frequently used as a measure of general adiposity. It has been increasingly recognized that the adverse effects of obesity relate not only to the amount but also to the distribution of excess body fat. Therefore, the use of BMI alone to infer health risks in Asians may underestimate the detrimental health effects of excess adiposity [40]. WHR and WC were good proxy measures of central adiposity. It has been suggested that WC is a better marker for total body adiposity than it is for visceral fat [41]. Another study has shown that both WC and BMI appear to perform equally well for estimating children and adolescents's total adiposity[42]. BSA is a better indicator of the circulating blood volume, oxygen consumption, and basal energy expenditure than BMI [37] and has been shown to be the best independent predictor of the thyroid volume in both sexes.

Several studies have found significant associations between measures of obesity and the risk of thyroid nodules. For example, a study conducted in Hangzhou, China observed a prevalence of TN being 34.97% (33.97 for men and 36.92% for women) and great WC as a risk factor for new TN in this iodine-adequate area[2]. Similar trends were observed for females and males, but the association was not statistically significant in men[2], which was similar to our findings in children. Another study of postmenopausal women also revealed that WC and BMI were associated with thyroid

nodules[43]. Large BMI was associated with nodule growth among older patients with multiple nodules and larger dominant nodules[17]. Study conducted by Shin et al linked thyroid nodular disease to WC for males and glycated hemoglobin for females[44], suggesting potential sex disparity. The presence of insulin resistance (IR) was associated with larger thyroid gland volume and an increased prevalence of thyroid nodules[45-46], which might be explained by obesity-related subclinical inflammation and an associated increase in levels of insulin-like growth factor-1(IGF-1)[45]. However, another study yielded conflicting results, which suggested that adult patients with normal weight or overweight based on BMI tended to have an increased risk of thyroid nodules, as compared with underweight or obese people[38]. Evidence in children had been relatively limited.

The prevalence of obesity and overweight in our study population was slightly higher than that in students from four Chinese megacities (25.6%) [47] but lower than urban students of similar age groups in the National Surveys on Chinese Students' Constitution and Health (37.0% for overweight and 20.3% for obesity)[48]. Our findings of increased risk for thyroid nodules in obese children are generally consistent with those in obese adults of other studies. The association of BSA with thyroid volume in children has been well established[35], while its relation to thyroid nodules has been seldom explored. Kim et al. [38] examined 7763 healthy Korean adults and observed a significantly smaller BSA in those with thyroid nodules compared to the others, which was opposite to our findings. Considering the great difference in BSA between adults and children, it need to be cautious to generalize the results to children [16]. Xu et.al[36] conducted a cross-sectional study in Hangzhou, China, and reported an OR of 2.97 (95% CI: 1.85 to 4.77) for thyroid nodules for children with average BSA or above as compared with those with less than average BSA. However, they did not collect the information on waist and hip circumferences and number of thyroid nodules. Therefore, it was not possible to determine different associations between WC, WHR and different kinds of nodules in that study. The potential interactive effects of iodized salt consumption, and sex on the association between overweight and multiple nodules also needs further investigations with a larger sample size. The strengths of our study include large sample size, directly measured thyroid ultrasonography and anthropometric measurements following a standardized protocol, and the abilities to distinguish solitary and multiple nodules and to adjust for household iodized salt consumption status. Our studyhas several limitations. Firstly, we did not have any information on thyroid function. Therefore, we were unable to further search potential mechanisms that might explain the observed associations. Secondly, there were no information on the amount of salt, and milk consumption. In the current study, the number of children with solitary or multiple nodules was small in some categories. In addition, the cross-sectional design prevents us from making causal inferences.

CONCLUSION

In this cross-sectional study of a relatively lean children population, we found that elevated levels of general or abdominal adiposity, measured by BMI, BSA and WC, were associated with a significant increase in the risk of thyroid nodule(s), especially multiple nodules in girls and solitary nodule in boys. Our findings, along with those observed from adult populations, emphasize the importance of preventing excess adiposity for primary prevention of thyroid nodules.

Contributors NW, HF, CWF, PXH, MFS, QZ, and QWJ contributed to the study design; NW, HF, CWF, PXH, MFS, FJ, QZ and QWJ contributed to data acquisition and collection; NW, QZ, YC contributed to data analysis and interpretation; NW, QZ and YC drafted the manuscript; all authors contributed to the preparation of the final document, read and approved the final manuscript.

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Competing interests None declared.

Ethics approval The study was approved by the Ethical Review Board of the School of Public Health of Fudan University (#2012-03-0350S).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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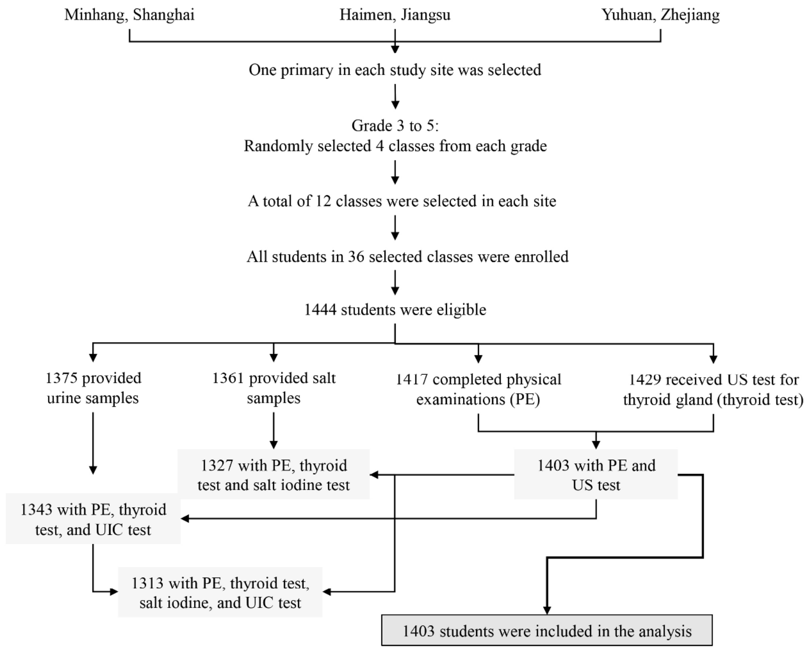
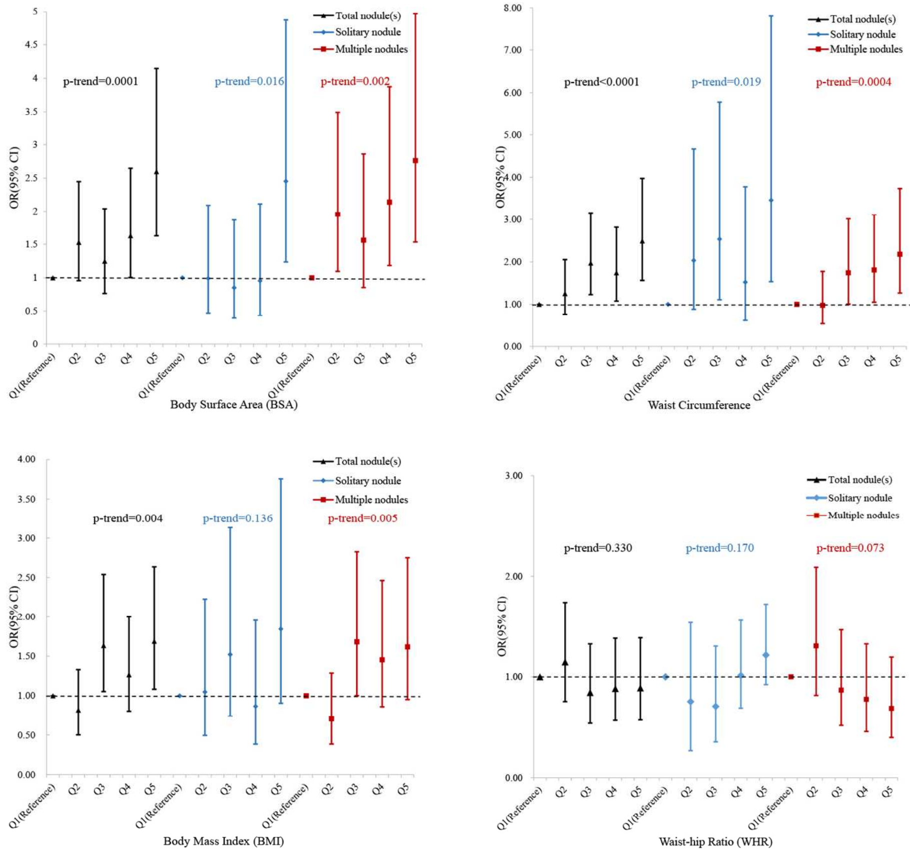
Figure 1.Flow chart for the study design

Figure 2. Associations of Different Physical Measurements (BSA, WC, BMI, and WHR) with Thyroid Nodule(s) for children from Shanghai, Haimen and Taizhou, China, 2014



flow chart

254x190mm (300 x 300 DPI)



*: Adjustment for age, sex, and iodized salt consumption status

140x140mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			8

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	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	10
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	12
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
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	19

*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.