

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2015-008452
Article Type:	Research
Date Submitted by the Author:	17-Apr-2015
Complete List of Authors:	Xu, Weimin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention chen, zexin; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics Li, Na; Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Liu, Hui; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics Huo, Liangliang; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Huang, Yangmei; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Jin, Xingyi; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Deng, Jin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Zhu, Sujuan; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention zhang, shanchun; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics yu, yunxian; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Weimin Xu, MD², Zexin Chen, MD¹, Na Li³, Hui Liu, MD¹, Liangliang Huo²,
Yangmei Huang, MD², Xingyi Jin, MD², Jin Deng, MD², Sujuan Zhu, MD²,
Shanchun Zhang, PhD¹, Yunxian Yu, PhD¹

1. Department of Epidemiology & Health Statistics, School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China
2. Department of Endemic Diseases Control and Prevention, Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China
3. Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China

Weimin Xu and Zexin Chen have equally contribution to the manuscript.

***Correspondence and reprint requests should be addressed to:**

Yunxian Yu, MD, PhD

Department of Epidemiology & Health Statistics, School of Public Health, Zhejiang

University, Hangzhou, Zhejiang, China

866 Yu-Hang-Tang Road, Xihu District, Hangzhou 310058, Zhejiang, China

Tel: +86-571-88208191

Fax: +86-571-88208194

E-mail: yunxianyu@zju.edu.cn

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**ABSTRACT**

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

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

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

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

1
2
3
4 47 higher susceptibility for thyroid nodule.
5
6

7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68

48 **Keywords:** anthropometric measurement, thyroid nodule, Chinese population

50 **Article summary:**

51 Strengths and limitations of this study:

52 1) Including adult and children subjects.

53 2) Large sample size of subjects.

54 3) The weight and standing height were measured in a standardized protocol by a
55 trained examiner rather than self-report.

56 4) We adjusted for most main covariates, including cigarette smoking and alcohol
57 drinking, two important factors influenced overweight

58 5) The number and mass size of thyroid nodule were not recorded in the
59 investigation, and the classification of thyroid nodules was not distinguished.

69 INTRODUCTION

70 Overweight and obesity are major risk factors for a number of chronic diseases,
71 including diabetes, cardiovascular diseases and cancer. Overweight and obesity are
72 the fifth leading risk for global deaths. In addition, between 7% and 41% of certain
73 cancer burdens are attributable to overweight and obesity[1]. Data from
74 epidemiological studies demonstrate a direct correlation between BMI and the risk of
75 medical complications and mortality rate[2 3]. The prevalence of overweight and
76 obesity has been increasing in most economically developed countries for several
77 decades, and there is evidence that the prevalence of overweight and obesity is also
78 increasing in economically developing countries[4 5]. The prevalence of obesity has
79 recently been dramatically increasing in China as a developing country. A national
80 survey indicates that the prevalence of overweight and obesity were 24.1% and 2.8%
81 in men and 26.1% and 5.0% in women, respectively [6]. Meanwhile, previous studies
82 reported functional and morphological alterations of the thyroid gland in relation to
83 obesity [7-11]. Due that thyroid hormones increase the basal metabolic rate, low
84 thyroid function, even within the clinically normal range, could decrease metabolic
85 speed and lead to obesity[11 12]. In addition, Mehmet Bastemir [10] found that serum
86 TSH levels are positively correlated with the degree of obesity and some of its
87 metabolic consequences in overweight people with normal thyroid function.
88 Furthermore, S.Guth[13] reported that patient BMI were positively correlated with
89 sizes of their thyroids. Through positive associations between height, weight and body
90 mass index (BMI) and thyroid cancer have been reported in many studies and

1
2
3
4 91 meta-analysis, other studies found no significant association between BMI and thyroid
5
6 92 cancer [14-16].
7
8
9 93

10
11 94 Therefore, it is extremely important to understand the relationship of anthropometric
12
13 95 measurements with thyroid nodule. But, to date, no study focuses on the relationship
14
15 96 of anthropometric measurements with thyroid nodule in Chinese population. The aim
16
17 97 of our study is to examine the relationship of anthropometric measurements with
18
19 98 thyroid nodule in a large sample size of Chinese population.
20
21
22
23
24 99

25 26 100 **MATERIALS AND METHODS**

27 28 29 101 **Population features**

30
31 102 From March to October 2010, this large cross-sectional study was conducted in
32
33 103 Hangzhou city, which is one of the leading commercial cities in eastern China.
34
35 104 Hangzhou is the capital and largest city of Zhejiang Province in eastern China. This
36
37 105 city covers eight districts and five counties. In 2010, the entire administrative division
38
39 106 or prefecture had a registered population of 8.7 million residents. 73.25% of residents
40
41 107 live in urban areas, only 26.75% in rural areas.
42
43
44
45
46
47 108

48 49 109 **Subjects and study design**

50
51 110 The detail description was shown in a published article of the same study[17]. The
52
53 111 study participants were recruited based on following strategy: There are eight districts
54
55 112 and five counties in big Hangzhou city. First, three sub-districts or towns were
56
57
58
59
60

1
2
3
4 113 selected randomly from each district or county (except Binjiang district) respectively,
5
6 114 so 36 sub-districts or towns were selected from big Hangzhou. Secondly, one
7
8 115 community or village was randomly selected from each sub-district or town. Thirdly,
9
10 116 100 households from each community or village were randomly selected. Finally, we
11
12 117 selected 3600 households for the interview. The family members of household were
13
14 118 chosen based on the following criteria: (1) age at least 6 years; (2) living for above 5
15
16 119 years at present residence. The exclusion criteria: (1) the participants with coronary
17
18 120 angiography (CAG) or endoscopic retrograde cholangiopancreatography (ERCP) in 6
19
20 121 months; (2) the participants taking amiodarone drug; (3) the participants with
21
22 122 abnormal kidney function or serious illness.
23
24
25
26
27
28
29
30

31 124 The eligible family members of selected households were convened to village or
32
33 125 community administration center. The researchers introduced the study protocol and
34
35 126 obtained written informed consent form from each participant. Meanwhile, the
36
37 127 interview schedule was appointed with participants. The study protocol was approved
38
39 128 by Institutional Review Board of Hangzhou Center of Disease Control and Prevention.
40
41 129 This survey was carried out by well-trained personnel (including community clinic
42
43 130 physicians, nurses, public health doctors).
44
45
46
47
48
49
50

51 132 **Collection of epidemiological data**

52
53 133 The participants were invited to local community health center before 8:00 am after
54
55 134 8-hour fasting overnight. Firstly, each participant provided spot urine samples of at
56
57
58
59
60

1
2
3
4 135 least 10 ml. Additionally, 5 ml venous blood was collected using vacuum blood
5
6 136 collection tube. Secondly, the participants were interviewed for a structured
7
8
9 137 questionnaire. The questionnaire covered the information about demographic
10
11 138 characteristics and health status, including sex, age, nationality, physical activity,
12
13 139 lifestyle, dietary habit, and personal or family history of thyroid disease (including
14
15 140 time of diagnosis). Especially, information about type of salt, salt appetite and milk
16
17 141 consumption was defined as following: the item--“Currently, which type of salt is
18
19 142 consumed in your family?” was used for collecting information about type of salt.
20
21 143 Three options for this item were provided: (1) only iodized salt; (2) non-iodized salt;
22
23 144 (3) both of them. The question--“How about your appetite?” was used to evaluate
24
25 145 salty appetite. Three options were provided: (1) salty; (2) moderate; (3) light.
26
27
28
29
30
31
32
33

34 147 Consuming milk ≤ 1 time per week was defined as having no habit of milk
35
36 148 consumption, consuming milk ≥ 2 times per week was defined as having habit of milk
37
38 149 consumption. In addition, diet pattern included three types: vegetarian, meat and
39
40 150 moderate. Vegetarian defined as subjects mainly consumed vegetable diet, almost
41
42 151 never ate meat food; meat defined as subjects mainly consumed meat food and
43
44 152 uncommonly consumed vegetable; moderate defined as subjects consumed both
45
46 153 vegetable and meat food. Eligible participants were interviewed face-to-face by
47
48 154 well-trained investigators from Hangzhou Centers of Disease Control and Prevention.
49
50
51
52
53
54
55

56 156 **Data collection of anthropometric measurements and thyroid nodule**
57
58
59
60

1
2
3
4 157 Height and weight were measured using standard protocols, without shoes or
5
6 158 outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer with
7
8
9 159 a GMCS-I type height tester (Beijing). Weight was measured to the nearest 0.1 kg
10
11 160 with the subjects standing motionless on a scale with a balance-beam scale (RGT-140,
12
13 161 weighing Apparatus Co. Ltd. Wuxi). An ultrasound examination of thyroid was
14
15 162 performed to detect thyroid nodules. The examination was performed with a Sonoline
16
17 163 Versa Pro (Siemens, Munich, Germany) with a 7.5-MHz, 70-mm linear transducer
18
19 164 (effective length, 62 mm). Thyroid nodule was defined as discrete lesion which was
20
21 165 distinct from the surrounding thyroid parenchyma and which had solid portion
22
23 166 regardless of having cystic portion.
24
25
26
27
28
29
30

31 168 **Body Mass Index**

32
33
34 169 The BMI is defined as the weight in kilograms divided by the square of the height in
35
36 170 meters. Although the BMI calculation does not take into account factors such as frame
37
38 171 size and body tissue compositions, BMI categories are generally used as a means of
39
40 172 estimating adiposity and assessing how much an individual's body weight departs
41
42 173 from what is normal or desirable for a person of the same height. Among adults, the
43
44 174 classification of BMI was as follows: BMI < 24, group low (normal and underweight);
45
46 175 24 ≤ BMI, group high (overweight and obese). Among children, the reference BMI
47
48 176 was calculated using the reference height and weight of each age group[18].
49
50
51
52
53
54
55

56 178 **Body Surface Area (BSA)**

57
58
59
60

1
2
3
4 179 BSA is a commonly used index in clinical practice to correct for patient size
5
6 180 differences in various physiologic measurements and in calculating drug dosage. BSA
7
8
9 181 is a better indicator of metabolic mass than body weight because it is less associated
10
11 182 with excessive body fat. Various formulas have been proposed to estimate the BSA
12
13 183 from a patient's weight and height, which may result in slightly different values
14
15 184 [19-22]. The most commonly used formula in day-to-day clinical practice is the
16
17 185 Mosteller formula: $BSA (m^2) = (\text{square root of product of weight [kg]}\times\text{height [cm]})$
18
19 186 /60 [21]. This formula is simplified from a formula produced by Gehan and George
20
21 187 [19], and has become a common standard because it is easy to memorize, and its use
22
23 188 requires only a handheld calculator. So Mosteller formula was used in our study to
24
25 189 calculate BSA.
26
27
28
29
30
31
32
33

34 191 **Definition of variables**

35
36 192 Diet pattern was classified as three groups: vegetarian, meat and moderate; vegetarian
37
38 193 defined as subjects mainly consumed vegetable food; meat defined as subjects mainly
39
40 194 consumed meat food; moderate defined as subjects consumed vegetable and meat
41
42 195 food.
43
44
45
46
47
48

49 197 Among adults, the height, weight, BMI and BSA were dichotomized into high group
50
51 198 and low group. The detailed criteria of each group were shown in Table 1. The
52
53 199 classification of height and weight among adults refers to The Survey Report on
54
55 200 National Physical Fitness of Chinese, 2005. In children, high group included subjects
56
57
58
59
60

1
2
3
4 201 with height or weight \geq reference standard of each age bracket (one year a bracket) in
5
6 202 two genders. BMI was classified according to the reference calculated using the
7
8
9 203 reference height and weight of each age bracket (one year a bracket) in two genders
10
11 204 respectively. BSA was classified by the average value of each gender.
12
13
14
15

16 206 **Statistical analysis**

17
18
19 207 The comparison of height, weight and age between patients with and without thyroid
20
21 208 nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test
22
23 209 for qualitative data, including gender, education, marriage, resident location, cigarette
24
25 210 smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of
26
27
28 211 salt. Listwise deletion was used to address the missing data in the model.
29
30
31
32

33
34 213 The adjusted associations of height, weight, BMI and BSA with thyroid nodule were
35
36 214 estimated respectively, using logistic regression model stratified by gender. The
37
38 215 following variables were taken as covariates in logistic regression models: age, BMI,
39
40 216 educational level, marital status, resident location, cigarette smoking, alcohol drinking,
41
42 217 diet flavor, types of salt, dietary patterns, milk consumption. Among adults, age was
43
44 218 classified as 5 classes: 18~29, 30~39, 40~49, 50~59, \geq 60. Among children, age was
45
46 219 classified as 4 classes: 6~8, 9~11, 12~14, 15~17. To account for the correlation of
47
48
49 220 members in a same household, we calculated robust estimates of variances with
50
51 221 generalized estimate equation (GEE) using SAS procedure GENMOD. All analyses
52
53
54
55
56
57
58
59
60

222 were performed in SAS Version 9.0 (SAS Institute, Inc., Cary, NC, USA). A value of
223 $P < 0.05$ was considered statistically significant.

224

225 **RESULTS**

226 **Baseline characteristics of study population**

227 A total of 12438 individuals were recruited in this investigation, but 3235 individuals
228 were excluded for analyses, due to absence of anthropometric measurements. Final
229 analyses included 9203 subject: 6,793 adults, and 2,410 children. The average age of
230 adults was 47.93 years, 62.96% were females (Table 2); 4.39% were underweight,
231 66.13% were normal, 26.34% were overweight and 3.14% were obese. Out of 6,793
232 adults, 2,228 (32.80%) adults had thyroid nodule, of which women accounted for
233 71.01%. Among children, 47.55% were under the reference BMI, 52.45% were over
234 the reference BMI. 257 (10.66%) children suffered from thyroid nodule, which more
235 than half (57.98%) were girls (Table 4).

236

237 **The relationship between anthropometric measurements and thyroid nodule**

238 **among adults**

239 The relationship between anthropometric measurements (height, weight, BMI, BSA)
240 and an increased risk of thyroid nodule were estimated by gender (Table 3). Higher
241 height (OR=1.15, 95% CL: 1.02-1.30), higher weight (OR=1.40, 95%CL: 1.24-1.58),
242 higher BMI (OR=1.26, 95% CI: 1.11–1.42) and higher BSA (OR=1.43, 95% CI:
243 1.27–1.62) were significantly associated with an increased thyroid nodule among

1
2
3
4 244 pooled samples, respectively. Similar trends were observed in females and males, but
5
6 245 no significant association in males.
7
8

9 246

11 247 **The relationship between anthropometric measurements and thyroid nodule**

14 248 **among children**

16 249 Similar relationship of anthropometric measurements with thyroid nodule was
17
18 250 conducted among children (Table 5). Higher weight (OR=1.37, 95% CI: 1.03–1.81),
19
20
21 251 higher BMI (OR=1.38, 95% CI: 1.04–1.83) and higher BSA (OR=2.97, 95% CI:
22
23
24 252 1.85–4.77) were significantly associated with an increased risk of thyroid nodule
25
26 253 among pooled samples. The significant associations of BSA and an increased risk of
27
28
29 254 thyroid nodule were observed in boys (OR=2.57, 95% CI: 1.25–5.28) and girls
30
31 255 (OR=3.36, 95% CI: 1.82–6.20), but the relationship of BMI with an increased risk of
32
33
34 256 thyroid nodule was only significant among boys. There is no significant association of
35
36 257 height with risk of thyroid nodule among children.
37
38

39 258

41 259 **DISCUSSION**

43
44
45 260 This study, performed in a large Chinese population, demonstrates that height, weight,
46
47 261 BMI and BSA were significantly associated with an increased risk of thyroid nodule
48
49
50 262 among adults and children. More explicitly, in the present study, the significant
51
52
53 263 association between high BSA and an increased risk of thyroid nodule was not
54
55 264 obviously influenced by sex, age, resident location and iodine intake.
56
57
58
59
60

1
2
3
4 265 Thyroid nodule is very common disease in the general population. The present
5
6 266 investigation showed that the prevalence of thyroid nodule was 32.80% in adults and
7
8
9 267 10.66% in children; but they are found clinically in 4-8% of cases[23]. The most of
10
11 268 thyroid nodules are benign nodules[24], but 5-6.5% of them are malignant
12
13
14 269 (carcinomas, CA)[25]. Because thyroid function is linked to development and growth,
15
16 270 height and weight are seen as possible indicators of thyroid nodule risk. In our study,
17
18
19 271 when the relationship of height, weight and thyroid nodule was examined among
20
21 272 adults, the high height, heavy weight was significantly associated with an increased
22
23
24 273 risk of thyroid nodule in pooled samples and females, respectively. But only
25
26 274 significant relationship of weight with thyroid nodule was found in children
27
28
29 275 population. To data, few study was focus on the relationship between anthropometric
30
31 276 indexes and thyroid nodule. But, previous study showed that thyroid nodule may
32
33
34 277 share similar risk factors with thyroid cancer: iodine deficiency is associated with an
35
36 278 increased TC incidence, largely via benign thyroid conditions such as nodules, which
37
38
39 279 are, in turn, strongly associated with TC. And, body size might be associated with the
40
41 280 iodine requirement and, hence, indirectly related to thyroid nodule[26].
42
43
44 281

45
46 282 Our results were similar to the findings among 88,256 Canadian women in 2012. It is
47
48
49 283 reported that height was positively associated with risk of all combined cancers and
50
51 284 thyroid cancer, and height was significantly positively associated with risk of thyroid
52
53
54 285 cancer in multivariable models [27]. Further, the European Prospective Investigation
55
56 286 into Cancer and nutrition (EPIC), a large study including million subjects, also
57
58
59
60

1
2
3
4 287 observed the positive association of height with thyroid cancer in female but not in
5
6 288 male[28]. Beyond those findings from European population, a pooled analysis of
7
8
9 289 individual data from 12 case-control studies conducted in eight countries (America,
10
11 290 Asia, and Europe) suggests that height is moderately related to thyroid cancer risk[29].
12
13
14 291 In addition, similar association of height with thyroid nodule risk among Korean was
15
16 292 observed in females but not males[30]. In our findings from Chinese, the sample size
17
18 293 was large and the moderate association of height with thyroid nodule risk was also
19
20
21 294 observed in females, which was consistent with those from Korea in Asia and even
22
23
24 295 European population. However, the association was not significant among children,
25
26 296 but we still can find an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90).
27
28
29 297 It may due to the small case numbers of children, and the association between height
30
31 298 and thyroid nodule among children need more studies to confirm.
32
33
34 299
35
36 300 Furthermore, similar to height, the pooled analysis conducted in eight countries also
37
38
39 301 indicated the association of weight and risk of thyroid cancer in female rather than
40
41 302 male[29]. In 2010, Clavel-Chapelon F[31] reported that there was a significant
42
43
44 303 dose-effect relationship between thyroid cancer risk and weight in France.
45
46 304 Additionally, in Asia, the significant association between weight and thyroid nodule in
47
48
49 305 female was observed among Korean population[30]. Our data also confirmed these
50
51 306 findings of adults in Chinese population after adjusted for possible covariates. Not
52
53
54 307 only observed in adult, we also found a significant association of weight with risk of
55
56 308 thyroid nodule in children. Present study lent further support to the possibility that
57
58
59
60

1
2
3
4 309 increased height and weight of female may associated with increased risk of thyroid
5
6 310 nodule. Altered thyroid status has well-known and profound effects on skeletal
7
8
9 311 development and growth and on adult bone maintenance. The fact that thyroid
10
11 312 hormones are associated with the regulation of the growth of long bones may be one
12
13 313 possible explanation for the association between height and thyroid nodule[32].
14
15 314 Moreover, genetic or environmental factors (e.g., dietary factors, nutritious factors),
16
17 315 correlate with adult height and weight, also influence thyroid function might be
18
19 316 another possible explanation for this association[29].
20
21
22
23
24 317

25
26 318 Analogously, in our study, the significant associations between BMI and thyroid
27
28 319 nodule were observed among pooled adult samples. Similar association was observed
29
30 320 in women, but not in men. Among children, significant associations of BMI with
31
32 321 thyroid nodule were also observed in pooled samples. Our findings in adult were
33
34 322 consistent with that in German [33] and Italian [34], and similar findings were also
35
36 323 observed among Korea population [30]. However, Results from previous prospective
37
38 324 and case-control studies on the association of BMI with thyroid cancer risk have
39
40 325 generally been more inconsistent in men than women. In a large Norwegian cohort of
41
42 326 more than two million participants, the risk of thyroid cancer increased moderately
43
44 327 with increased BMI in both sexes, but the results were unadjusted for smoking and
45
46 328 other factors[15]. After adjusted for key covariates such as cigarette smoking, alcohol
47
48 329 intake, physical activity and medical history of diabetes, the largest prospective study
49
50 330 conducted in U.S. also observed a significant positive association between BMI and
51
52
53
54
55
56
57
58
59
60

1
2
3
4 331 thyroid cancer risk in women [35]. Moreover, a systematic review conducted by
5
6 332 Emily Peterson[36] in 2012 (including 37 studies) showed that most of studies
7
8
9 333 supported a positive association of BMI with thyroid cancer in both sexes. The
10
11 334 inconsistent results between men and women in previous studies is likely due to
12
13 335 smaller numbers of cases in men, to the lack of control for important covariates (e.g.
14
15 336 cigarette smoking, alcohol intake). Current smoking and alcohol intake are associated
16
17 337 with BMI levels[37-40]. Unadjustment for smoking status or alcohol intake may be a
18
19 338 important bias in the association between BMI and risk of thyroid nodule. Findings of
20
21 339 present study cover adults and children, and the associations of BMI with risk of
22
23 340 thyroid nodule were consistent in each population after adjusted for important
24
25 341 covariates. Base on large samples and reducing important biases, our findings indicate
26
27 342 that overweight and obesity increase the risk of thyroid nodule in both adult and
28
29 343 children. The association between BMI and thyroid nodule may be the certain
30
31 344 metabolic consequences of excess adipose tissue. Leptin produced by adipocytes has
32
33 345 important influences on central regulation of thyroid function through stimulation of
34
35 346 TRH. This seems to be important for down-regulation of thyroid function in states of
36
37 347 energy deficits, but the importance for modulation of thyroid function under more
38
39 348 physiological conditions is uncertain[41 42]. Additionally, thyroid hormones may be a
40
41 349 significant determinant of sleeping energy expenditure in subjects without overt
42
43 350 thyroid dysfunction[43]. Similarly, differences in thyroid function, within what is
44
45 351 considered the normal range, are associated with differences in BMI, caused by
46
47 352 longstanding minor alterations in energy expenditure[11]. What's more, obesity is
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 353 associated with insulin resistance and increased production of insulin and insulin-like
5
6 354 growth factors which in turn have been reported to be associated to thyroid
7
8
9 355 disorders[25 44 45].
10

11 356
12
13 357 Being similar with thyroid cancer[25 35], thyroid nodules are more common in
14
15 358 women than in men[46-50]. Sex differences in the association between BMI and
16
17 359 thyroid cancer have been confirmed in other studies[29 51 52]. Our findings of adult
18
19 360 were consistent with the sex difference in association of BMI with thyroid nodule.
20
21

22 361 The difference in incidence between two genders suggests that growth and
23
24 362 progression of thyroid tumors is influenced by sex hormones, particularly
25
26 363 estrogens[53 54]. Additionally, it was reported that the observed positive relation of
27
28 364 overweight to thyroid cancer risk may be due to detection bias--more frequent
29
30 365 examinations of thyroid gland among overweight young women than lean
31
32 366 individuals[29]. However, sex difference of the correlation between body size and
33
34 367 thyroid nodule was not obvious among children. It may due to the smaller difference
35
36 368 of sex hormones in children, compared to adult. Few studies noted the correlation
37
38 369 between body size and thyroid nodule in children, the findings from children
39
40 370 population require furthermore studies to confirm.
41
42
43
44
45
46
47
48

49 371
50
51 372 BSA is a better indicator of the circulating blood volume, oxygen consumption, and
52
53 373 basal energy expenditure than BMI or weight[55]. In the present study, BSA was
54
55 374 significantly associated with increased risk of thyroid nodule among adult and
56
57
58
59
60

1
2
3
4 375 children. The association was not influenced by sex, age, resident location and iodine
5
6 376 intake. Consistently, a positive association of thyroid cancer and current BSA in adult
7
8
9 377 was found by Suzuki T in Japan in both sexes after adjusted for main covariates[56].
10
11 378 In addition, it was reported that BSA plays a dominant role in thyroid cancer risk and
12
13 379 explains the apparent role of BMI in adult[55]. Muscle is more dense than fat, and
14
15 380 BMI is not able to differentiate increased weight[57]. BSA is a more accurate measure
16
17 381 of obesity, including central obesity, as it is a measurement of area and is able to
18
19 382 account for the difference between muscle and fat better than BMI secondary to
20
21 383 muscle versus fat[58]. In a way, the association between BSA and thyroid nodule
22
23 384 more strongly and forcefully confirmed the increased risk of overweight and obesity
24
25 385 with thyroid nodule than those of BMI.
26
27 386
28
29
30
31
32
33
34 387 Our study is novel for that it is performed in adult population and children population
35
36 388 with a large sample size. Further, the weight and standing height were measured in a
37
38 389 standardized protocol by a trained examiner rather than self-report, reducing the bias
39
40 390 of overestimation or underestimation of height and weight[59 60]. In addition, in
41
42 391 order to reduce the possible bias, we adjusted for most main covariates, including
43
44 392 cigarette smoking and alcohol drinking, two important factors influenced
45
46 393 overweight[37-40]. Especially, salt type, salt appetite and diet patterns were taken as
47
48 394 covariates in analysis models; the effect of iodine on risk of thyroid nodule was
49
50 395 considered. Hence, the associations of anthropometric measurements were robust.
51
52
53
54
55
56 396
57
58
59
60

397 **LIMITATION**

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

404

405 **CONCLUSION**

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

411

412 **ACKNOELEDGMENTS**

413 The authors gave the following different contribution on this manuscript: Yunxian Yu
414 generated the idea, modified and edited the manuscript. Weimin Xu supervised the
415 study field activities, prepared and managed the datasets. Zexin Chen did statistical
416 analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei
417 Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and
418 interviewed study subjects in the study field. All authors read and approved the final

1
2
3
4 419 manuscript. None of the authors had a conflict of interest. The manuscript has not
5
6 420 been published and is not being considered for publication elsewhere, in whole or in
7
8
9 421 part, in any language, except as an abstract. No additional unpublished data are
10
11 422 available.

12
13
14 423
15
16 424 The study was funded in part by grants from Hangzhou Science and Technology
17
18 425 Bureau (Grant number: 200908033B27), the Ministry of Science and Technology
19
20 426 (Grant number: 2011CB503706) and we thank the staff of Hangzhou Center for
21
22 427 Disease Control and Prevention collecting the epidemiological data and blood
23
24 428 specimen. We would like to particularly thank all participants and their family for
25
26 429 their contributions and supports.

27
28
29
30 430
31
32 431
33
34 432
35
36 433
37
38 434
39
40 435
41
42 436
43
44 437
45
46 438
47
48 439
49
50 440
51
52
53
54
55
56
57
58
59
60

441 REFERENCE

442

- 443 1. WHO. Media Center: Obesity and overweight. Secondary Media Center: Obesity and overweight
444 2012.
- 445 2. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes
446 mellitus in women. *Ann Intern Med* 1995;**122**(7):481-6
- 447 3. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a
448 prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**(15):1097-105 doi:
449 10.1056/nejm199910073411501[published Online First: Epub Date]].
- 450 4. Saw SM, Rajan U. The epidemiology of obesity: a review. *Ann Acad Med Singapore*
451 1997;**26**(4):489-93
- 452 5. WHO. Obesity: preventing and managing the global epidemic—report of a WHO consultation. World
453 Health Organization 2000
- 454 6. Reynolds K, Gu D, Whelton PK, et al. Prevalence and risk factors of overweight and obesity in
455 China. *Obesity (Silver Spring)* 2007;**15**(1):10-8 doi: 10.1038/oby.2007.527[published Online
456 First: Epub Date]].
- 457 7. Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid
458 volume and function in obese women. *Clinical Endocrinology* 2003;**59**(2):258-62 doi:
459 10.1046/j.1365-2265.2003.01836.x[published Online First: Epub Date]].
- 460 8. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity.
461 *Thyroid* 2006;**16**(1):73-8 doi: 10.1089/thy.2006.16.73[published Online First: Epub Date]].
- 462 9. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid
463 stimulating hormone are directly associated with waist circumference, independently of
464 insulin resistance, metabolic parameters and blood pressure in overweight and obese women.
465 *Clin Endocrinol (Oxf)* 2007;**67**(2):265-9 doi: 10.1111/j.1365-2265.2007.02874.x[published
466 Online First: Epub Date]].
- 467 10. Bastemir M, Akin F, Alkis E, Kaptanoglu B. Obesity is associated with increased serum TSH level,
468 independent of thyroid function. *Swiss Med Wkly* 2007;**137**(29-30):431-4 doi:
469 2007/29/smw-11774[published Online First: Epub Date]].
- 470 11. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be
471 important for body mass index and the occurrence of obesity in the population. *J Clin*
472 *Endocrinol Metab* 2005;**90**(7):4019-24 doi: 10.1210/jc.2004-2225[published Online First:
473 Epub Date]].
- 474 12. al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in
475 patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab*
476 1997;**82**(4):1118-25
- 477 13. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules
478 detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest*
479 2009;**39**(8):699-706 doi: 10.1111/j.1365-2362.2009.02162.x[published Online First: Epub
480 Date]].
- 481 14. Mack WJ, Preston-Martin S, Bernstein L, Qian D. Lifestyle and other risk factors for thyroid cancer
482 in Los Angeles County females. *Ann Epidemiol* 2002;**12**(6):395-401

- 1
2
3 483 15. Engeland A, Tretli S, Akslen LA, Bjorge T. Body size and thyroid cancer in two million Norwegian
4 484 men and women. *Br J Cancer* 2006;**95**(3):366-70 doi: 10.1038/sj.bjc.6603249[published
5 485 Online First: Epub Date]].
- 6
7 486 16. Paes JE, Hua K, Nagy R, Kloos RT, Jarjoura D, Ringel MD. The relationship between body mass
8 487 index and thyroid cancer pathology features and outcomes: a clinicopathological cohort study.
9 488 *J Clin Endocrinol Metab* 2010;**95**(9):4244-50 doi: 10.1210/jc.2010-0440[published Online
10 489 First: Epub Date]].
- 11
12 490 17. Chen Z, Xu W, Huang Y, et al. Associations of noniodized salt and thyroid nodule among the
13 491 Chinese population: a large cross-sectional study. *Am J Clin Nutr* 2013;**98**(3):684-92 doi:
14 492 10.3945/ajcn.112.054353[published Online First: Epub Date]].
- 15
16 493 18. Ya-qin LHJC-yZX-nZ. Height and weight standardized growth charts for Chinese children and
17 494 adolescents aged 0 to 18 years. *CHINESE JOURNAL OF PEDIATRICS* 2009;**47**(7)
- 18
19 495 19. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer*
20 496 *Chemother Rep* 1970;**54**(4):225-35
- 21
22 497 20. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a
23 498 height-weight formula validated in infants, children, and adults. *J Pediatr* 1978;**93**(1):62-6
- 24
25 499 21. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;**317**(17):1098 doi:
26 500 10.1056/NEJM198710223171717[published Online First: Epub Date]].
- 27
28 501 22. Livingston EH, Lee S. Body surface area prediction in normal-weight and obese patients. *Am J*
29 502 *Physiol Endocrinol Metab* 2001;**281**(3):E586-91
- 30
31 503 23. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules
32 504 discovered incidentally on thyroid imaging. *Ann Intern Med* 1997;**126**(3):226-31
- 33
34 505 24. Leitzmann MF, Brenner A, Moore SC, et al. Prospective study of body mass index, physical
35 506 activity and thyroid cancer. *Int J Cancer* 2010;**126**(12):2947-56 doi:
36 507 10.1002/ijc.24913[published Online First: Epub Date]].
- 37
38 508 25. Tae HJ, Lim DJ, Baek KH, et al. Diagnostic value of ultrasonography to distinguish between benign
39 509 and malignant lesions in the management of thyroid nodules. *Thyroid* 2007;**17**(5):461-6
- 40
41 510 26. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an
42 511 epidemiological review focused on nutritional factors. *Cancer Causes Control*
43 512 2009;**20**(1):75-86 doi: 10.1007/s10552-008-9219-5[published Online First: Epub Date]].
- 44
45 513 27. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in
46 514 a cohort of Canadian women. *International Journal of Cancer* 2012:n/a-n/a doi:
47 515 10.1002/ijc.27704[published Online First: Epub Date]].
- 48
49 516 28. Rinaldi S, Lise M, Clavel-Chapelon F, et al. Body size and risk of differentiated thyroid carcinomas:
50 517 Findings from the EPIC study. *International Journal of Cancer* 2012;**131**(6):E1004-E14 doi:
51 518 10.1002/ijc.27601[published Online First: Epub Date]].
- 52
53 519 29. Dal Maso L, La Vecchia C, Franceschi S, et al. A pooled analysis of thyroid cancer studies. V.
54 520 Anthropometric factors. *Cancer Causes Control* 2000;**11**(2):137-44
- 55
56 521 30. Kim JY, Jung EJ, Park ST, et al. Body size and thyroid nodules in healthy Korean population. *J*
57 522 *Korean Surg Soc* 2012;**82**(1):13-7 doi: 10.4174/jkss.2012.82.1.13[published Online First:
58 523 Epub Date]].
- 59
60 524 31. Clavel-Chapelon F, Guillas G, Tondeur L, Kernaleguen C, Boutron-Ruault MC. Risk of
525 526 differentiated thyroid cancer in relation to adult weight, height and body shape over life: the
French E3N cohort. *Int J Cancer* 2010;**126**(12):2984-90 doi: 10.1002/ijc.25066[published

- 1
2
3 527 Online First: Epub Date]].
4 528 32. Gogakos AI, Duncan Bassett JH, Williams GR. Thyroid and bone. Arch Biochem Biophys
5 529 2010;**503**(1):129-36 doi: 10.1016/j.abb.2010.06.021[published Online First: Epub Date]].
6
7 530 33. Karger S, Schotz S, Stumvoll M, Berger F, Fuhrer D. Impact of pregnancy on prevalence of goitre
8 531 and nodular thyroid disease in women living in a region of borderline sufficient iodine supply.
9 532 Horm Metab Res 2010;**42**(2):137-42 doi: 10.1055/s-0029-1241861[published Online First:
10 533 Epub Date]].
11 534 34. Trimboli P, Rossi F, Thorel F, et al. One in five subjects with normal thyroid ultrasonography has
12 535 altered thyroid tests. Endocr J 2012;**59**(2):137-43
13 536 35. Kitahara CM, Platz EA, Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and
14 537 women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev
15 538 2011;**20**(3):464-72 doi: 10.1158/1055-9965.epi-10-1220[published Online First: Epub Date]].
16 539 36. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer: a
17 540 systematic review. PLoS One 2012;**7**(1):e29177 doi: 10.1371/journal.pone.0029177[published
18 541 Online First: Epub Date]].
19 542 37. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat
20 543 distribution, and insulin resistance. Am J Clin Nutr 2008;**87**(4):801-9
21 544 38. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking
22 545 cessation on the prevalence of overweight in the United States. N Engl J Med
23 546 1995;**333**(18):1165-70 doi: 10.1056/nejm199511023331801[published Online First: Epub
24 547 Date]].
25 548 39. Wannamethee SG, Shaper AG. Alcohol, body weight, and weight gain in middle-aged men. Am J
26 549 Clin Nutr 2003;**77**(5):1312-7
27 550 40. Hou X, Jia W, Bao Y, et al. Risk factors for overweight and obesity, and changes in body mass
28 551 index of Chinese adults in Shanghai. BMC Public Health 2008;**8**:389 doi:
29 552 10.1186/1471-2458-8-389[published Online First: Epub Date]].
30 553 41. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the
31 554 neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest
32 555 2003;**111**(9):1409-21 doi: 10.1172/jci17490[published Online First: Epub Date]].
33 556 42. LaMarca A, Volpe A. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl
34 557 J Med 2004;**351**(22):2343; author reply 43 doi: 10.1056/nejm200411253512221[published
35 558 Online First: Epub Date]].
36 559 43. Astrup A, Buemann B, Christensen NJ, et al. The contribution of body composition, substrates, and
37 560 hormones to the variability in energy expenditure and substrate utilization in premenopausal
38 561 women. J Clin Endocrinol Metab 1992;**74**(2):279-86
39 562 44. Volzke H, Friedrich N, Schipf S, et al. Association between serum insulin-like growth factor-I
40 563 levels and thyroid disorders in a population-based study. J Clin Endocrinol Metab
41 564 2007;**92**(10):4039-45 doi: 10.1210/jc.2007-0816[published Online First: Epub Date]].
42 565 45. Vella V, Sciacca L, Pandini G, et al. The IGF system in thyroid cancer: new concepts. Mol Pathol
43 566 2001;**54**(3):121-4
44 567 46. Mazzaferri EL, de los Santos ET, Rofagha-Keyhani S. Solitary thyroid nodule: diagnosis and
45 568 management. The Medical clinics of North America 1988;**72**(5):1177-211
46 569 47. Mazzaferri EL. Management of a Solitary Thyroid Nodule. New England Journal of Medicine
47 570 1993;**328**(8):553-59 doi: doi:10.1056/NEJM199302253280807[published Online First: Epub
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 571 Date]].
4 572 48. Hurtado-Lopez LM, Basurto-Kuba E, Montes de Oca-Duran ER, Pulido-Cejudo A, Vazquez-Ortega
5 573 R, Athie-Gutierrez C. Prevalence of thyroid nodules in the Valley of Mexico. *Cir Cir*
6 574 2011;**79**(2):114-7
7
8 575 49. Yoon DY, Chang SK, Choi CS, et al. The prevalence and significance of incidental thyroid nodules
9 576 identified on computed tomography. *J Comput Assist Tomogr* 2008;**32**(5):810-5 doi:
10 577 10.1097/RCT.0b013e318157fd38[published Online First: Epub Date]].
11
12 578 50. Bartolotta TV, Midiri M, Runza G, et al. Incidentally discovered thyroid nodules: incidence, and
13 579 greyscale and colour Doppler pattern in an adult population screened by real-time compound
14 580 spatial sonography. *Radiol Med* 2006;**111**(7):989-98 doi:
15 581 10.1007/s11547-006-0097-1[published Online First: Epub Date]].
16
17 582 51. Guignard R, Truong T, Rougier Y, Baron-Dubourdieu D, Guenel P. Alcohol drinking, tobacco
18 583 smoking, and anthropometric characteristics as risk factors for thyroid cancer: a countrywide
19 584 case-control study in New Caledonia. *Am J Epidemiol* 2007;**166**(10):1140-9 doi:
20 585 10.1093/aje/kwm204[published Online First: Epub Date]].
21
22 586 52. Brindel P, Doyon F, Rachedi F, et al. Anthropometric factors in differentiated thyroid cancer in
23 587 French Polynesia: a case-control study. *Cancer Causes Control* 2009;**20**(5):581-90 doi:
24 588 10.1007/s10552-008-9266-y[published Online First: Epub Date]].
25
26 589 53. Negri E, Ron E, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer. I.
27 590 Methods. *Cancer Causes Control* 1999;**10**(2):131-42
28 591
29 592 54. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer:
30 593 a systematic review and meta-analysis of prospective observational studies. *Lancet*
31 594 2008;**371**(9612):569-78 doi: 10.1016/s0140-6736(08)60269-x[published Online First: Epub
32 595 Date]].
33 596 55. Clero E, Leux C, Brindel P, et al. Pooled analysis of two case-control studies in New Caledonia and
34 597 French Polynesia of body mass index and differentiated thyroid cancer: the importance of
35 598 body surface area. *Thyroid* 2010;**20**(11):1285-93 doi: 10.1089/thy.2009.0456[published
36 599 Online First: Epub Date]].
37
38 599 56. Suzuki T, Matsuo K, Hasegawa Y, et al. Anthropometric factors at age 20 years and risk of thyroid
39 600 cancer. *Cancer Causes Control* 2008;**19**(10):1233-42 doi:
40 601 10.1007/s10552-008-9194-x[published Online First: Epub Date]].
41
42 602 57. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and
43 603 subcutaneous fat. *Curr Diabetes Rev* 2006;**2**(4):367-73
44 604
45 605 58. Roy SK, Zeb I, Kadakia J, Li D, Budoff MJ. Body surface area is a predictor of coronary artery
46 606 calcium, whereas body mass index is not. *Coron Artery Dis* 2012;**23**(2):113-7 doi:
47 607 10.1097/MCA.0b013e32834f1b72[published Online First: Epub Date]].
48
49 608 59. Gunnell D, Berney L, Holland P, et al. How accurately are height, weight and leg length reported by
50 609 the elderly, and how closely are they related to measurements recorded in childhood? *Int J*
51 610 *Epidemiol* 2000;**29**(3):456-64
52 611
53 612 60. Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A. Validity of self-reported weight and
54 613 height in the French GAZEL cohort. *Int J Obes Relat Metab Disord* 2000;**24**(9):1111-8
55
56
57
58
59
60

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

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

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

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

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

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

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

Variables	Nodule	Non-nodule	OR(95%CI)	P
Pooled*				
Height(cm)^a				
low	1334(59.87)	2576(56.43)	1.00	
high	894(40.13)	1989(43.57)	1.15(1.02,1.30)	0.0245
Weight(kg)^b				
low	1222(54.85)	2760(60.46)	1.00	
high	1006(45.15)	1805(39.54)	1.40(1.24,1.58)	<0.0001
BMI^c				
low	1438(64.54)	3351(73.41)	1.00	
high	790(35.46)	1214(26.59)	1.26(1.11,1.42)	0.0003
BSA(m²)^d				
low	1068(47.94)	2675(58.60)	1.00	
high	1160(52.06)	1890(41.40)	1.43(1.27,1.62)	<0.0001
Females				
Height(cm)^a				
low	968(61.19)	1596(59.22)	1.00	
high	614(38.81)	1099(40.78)	1.24(1.07,1.44)	0.0050
Weight(kg)^b				
low	946(59.80)	1960(72.73)	1.00	
high	636(40.20)	735(27.27)	1.71(1.47,1.98)	<0.0001
BMI^c				
low	1002(63.64)	2048(75.99)	1.00	
high	580(36.66)	647(24.01)	1.47(1.26,01.72)	<0.0001
BSA(m²)^d				
low	627(39.63)	1366(50.69)	1.00	
high	955(60.37)	1329(49.31)	1.53(1.32,1.77)	<0.0001
Males				
Height(cm)^a				
Low	366(56.66)	980(52.41)	1.00	
high	280(43.34)	890(47.59)	1.00(0.82,1.24)	0.9699
Weight(kg)^b				
low	276(42.72)	800(42.78)	1.00	
high	370(57.28))	1070(57.28)	1.00(0.80,1.20)	0.8690
BMI^c				
low	436(67.49)	1303(69.68)	1.00	
high	210(32.51)	567(30.32)	1.00(0.81,1.23)	0.9892
BSA(m²)^d				
low	441(68.27)	1309(70.00)	1.00	
high	205(31.73)	561(30.00)	1.21(0.97,1.51)	0.0871

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

^a: **Male**: high: height \geq 170cm, low: height $<$ 170cm; **female**: high: height \geq 160cm, low: height $<$ 160cm;

^b: **Male**: high: weight \geq 65kg, low: weight $<$ 65kg; **female**: high: weight \geq 60kg, low: weight $<$ 60kg;

^c: Low=BMI $<$ 24.0; high: BMI \geq 24;

^d: **Male**: high: BSA \geq 1.80m², low: BSA $<$ 1.80m²; **female**: high: BSA \geq 1.55m², low: BSA $<$ 1.55m²

For peer review only

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

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

^aVegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

^bIodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

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

Variables	Nodule	Non-nodule	OR(95%CI)	P
Pooled*				
Height(cm)^a				
low	140(54.47)	1259(58.48)	1.00	
high	117(45.53)	894(41.52)	1.15(0.87,1.53)	0.3347
Weight(kg)^b				
low	118(45.91)	1175(54.58)	1.00	
high	139(54.09)	978(45.42)	1.37(1.03,1.81)	0.0292
BMI^c				
low	106(41.25)	1040(48.30)	1.00	
high	151(58.75)	1113(51.70)	1.38(1.04,1.83)	0.0248
BSA(m²)^d				
low	77(29.96)	1144(52.22)	1.00	
high	180(70.04)	1009(47.78)	2.97(1.85,4.77)	<0.0001
Girls				
Height(cm)^a				
low	79(53.02)	643(60.09)	1.00	
high	70(46.98)	427(39.91)	1.30(0.89,1.90)	0.1719
Weight(kg)^b				
low	63(42.28)	555(51.87)	1.00	
high	86(57.72)	515(48.13)	1.55(1.07,2.25)	0.0218
BMI^c				
low	63(42.28)	488(45.61)	1.00	
high	86(57.72)	582(54.39)	1.25(0.86,1.81)	0.2391
BSA(m²)^d				
low	43(28.86)	556(51.96)	1.00	
high	106(71.17)	514(48.04)	3.36(1.82,6.20)	0.0001
Boys				
Height(cm)^a				
low	61(56.48)	616(56.88)	1.00	
high	47(43.52)	467(43.12)	0.97(0.63,1.49)	0.8870
Weight(kg)^b				
low	55(50.93)	620(57.25)	1.00	
high	53(49.07)	463(42.75)	1.15(0.75,1.77)	0.5120
BMI^c				
low	43(39.81)	552(50.97)	1.00	
high	65(60.19)	531(49.03)	1.59(1.03,2.44)	0.0355
BSA(m²)^d				
low	34(31.48)	588(54.29)	1.00	
high	74(68.52)	495(45.71)	2.57(1.25,5.28)	0.0104

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

^{a,b}:High: height or weight \geq reference standard, low: height or weight $<$ reference standard;

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

^d:**Male**: high: $BSA \geq 1.26 \text{ m}^2$, low: $BSA < 1.26 \text{ m}^2$; **female**: high: $BSA \geq 1.22 \text{ m}^2$, low: $BSA < 1.22 \text{ m}^2$;

Mean of male's $BSA = 1.26 \text{ m}^2$, Mean of female's $BSA = 1.22 \text{ m}^2$.

For peer review only

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

Variables	Nodule	Non-nodule	OR(95%CI)	P
Pooled*				
Height(cm)^a				
low	1120(61.57)	2348(57.20)	1.00	
high	699(38.43)	1757(42.80)	1.15(1.01,1.30)	0.0388
Weight(kg)^b				
low	997(54.81)	2485(60.54)	1.00	
high	822(45.19)	1620(39.46)	1.39(1.22,1.58)	<0.0001
BMI^c				
low	1156(63.55)	3009(73.30)	1.00	
high	663(36.45)	1096(26.70)	1.31(1.15,1.50)	<0.0001
BSA(m²)^d				
low	897(49.31)	2415(58.83)	1.00	
high	922(50.69)	1690(41.17)	1.44(1.27,1.63)	<0.0001
Females				
Height(cm)^a				
low	797(62.81)	1449(60.10)	1.00	
high	472(37.19)	962(39.90)	1.23(1.04,1.44)	0.0147
Weight(kg)^b				
low	753(59.34)	1758(72.92)	1.00	
high	516(40.66)	653(27.08)	1.68(1.44,1.97)	<0.0001
BMI^c				
low	790(62.25)	1830(75.90)	1.00	
high	479(37.75)	581(24.10)	1.48(1.26,1.75)	<0.0001
BSA(m²)^d				
low	512(40.35)	1230(51.02)	1.00	
high	757(59.65)	1181(48.98)	1.56(1.34,1.81)	<0.0001
Males				
Height(cm)^a				
low	323(58.73)	899(53.07)	1.00	
high	227(41.27)	795(46.93)	0.99(0.80,1.23)	0.9473
Weight(kg)^b				
low	244(44.36)	727(42.92)	1.00	
high	306(55.64)	967(57.08)	0.96(0.78,1.19)	0.7087
BMI^c				
low	366(66.55)	1179(69.60)	1.00	
high	184(33.45)	515(30.40)	1.05(0.84,1.30)	0.6881
BSA(m²)^d				
low	385(70.00)	1185(69.95)	1.00	
high	165(30.00)	509(30.05)	1.18(0.93,1.48)	0.1705

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

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

^a: **Male**: high: height \geq 170cm, low: height<170cm; **female**: high: height \geq 160cm, low: height<160cm;

^b: **Male**: high: weight \geq 65kg, low: weight<65kg; **female**: high: weight \geq 60kg, low: weight<60kg;

^c: Low=BMI<24.0; high: BMI \geq 24;

^d: **Male**: high: BSA \geq 1.80m², low: BSA<1.80m²; **female**: high: BSA \geq 1.55m², low: BSA<1.55m²

For peer review only

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

Variables	Nodule	Non-nodule	OR(95%CI)	P
Pooled*				
Height(cm)^a				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight(kg)^b				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI^c				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA(m²)^d				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
Girls				
Height(cm)^a				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight(kg)^b				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI^c				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m²)^d				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
Boys				
Height(cm)^a				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight(kg)^b				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI^c				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA(m²)^d				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

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

^{a,b} :High: height or weight \geq reference standard, low: height or weight <reference standard;

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

^d: **Male**: high: $BSA \geq 1.26 \text{ m}^2$, low: $BSA < 1.26 \text{ m}^2$; **female**: high: $BSA \geq 1.22 \text{ m}^2$, low: $BSA < 1.22 \text{ m}^2$;
Mean of male's $BSA = 1.26 \text{ m}^2$, Mean of female's $BSA = 1.22 \text{ m}^2$.

For peer review only

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

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low		BMI<24.0
High		BMI≥24
BSA(m²)		
low	BSA<1.80m ²	BSA<1.55m ²
high	BSA≥1.80m ²	BSA≥1.55m ²

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

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

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (line 227-229) (b) Give reasons for non-participation at each stage (line 227) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (line 226-235) (b) Indicate number of participants with missing data for each variable of interest (Table 1) (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures (line 231-235)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (line -237-257) (b) Report category boundaries when continuous variables were categorized (line 218-219) (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (N/A)
Discussion		
Key results	18	Summarise key results with reference to study objectives (line 260-264)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (line 397-403)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (line 265-385)
Generalisability	21	Discuss the generalisability (external validity) of the study results (line 260-262)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (line 424-429)

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

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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-008452.R1
Article Type:	Research
Date Submitted by the Author:	13-Jul-2015
Complete List of Authors:	Xu, Weimin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention chen, zexin; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics Li, Na; Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Liu, Hui; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics Huo, Liangliang; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Huang, Yangmei; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Jin, Xingyi; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Deng, Jin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention Zhu, Sujuan; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention zhang, shanchun; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics yu, yunxian; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Weimin Xu, MD², Zexin Chen, MD¹, Na Li³, Hui Liu, MD¹, Liangliang Huo²,
Yangmei Huang, MD², Xingyi Jin, MD², Jin Deng, MD², Sujuan Zhu, MD²,
Shanchun Zhang, PhD¹, Yunxian Yu, PhD¹

1. Department of Epidemiology & Health Statistics, School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China
2. Department of Endemic Diseases Control and Prevention, Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China
3. Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China

Weimin Xu and Zexin Chen have equally contribution to the manuscript.

***Correspondence and reprint requests should be addressed to:**

Yunxian Yu, MD, PhD

Department of Epidemiology & Health Statistics, School of Public Health, Zhejiang

University, Hangzhou, Zhejiang, China

866 Yu-Hang-Tang Road, Xihu District, Hangzhou 310058, Zhejiang, China

Tel: +86-571-88208191

Fax: +86-571-88208194

E-mail: yunxianyu@zju.edu.cn

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**ABSTRACT**

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

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

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

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

1
2
3
4 47 obviously in female adults and girls. It implied that individual with high height and
5
6 48 obesity increased the susceptibility for thyroid nodule.
7

8
9 49 **Keywords:** anthropometric measurement, thyroid nodule, adult, children, Chinese
10
11 50 population
12

13
14
15
16 52 **Article summary:**

17
18
19 53 Strengths and limitations of this study:

- 20
21 54 1) Including adult and children subjects.
22
23 55 2) Large sample size of subjects.
24
25
26 56 3) The weight and standing height were measured in a standardized protocol by a
27
28 57 trained examiner rather than self-report.
29
30
31 58 4) The main results was presented after adjustment for many potential confounders,
32
33 59 including cigarette smoking and alcohol drinking, two important factors
34
35 60 influenced overweight
36
37
38 61 5) The number and mass size of thyroid nodule were not recorded in the
39
40 62 investigation, and the classification of thyroid nodules was not distinguished.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

69 INTRODUCTION

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

1
2
3
4 91 Previous study in Chinese population indicated overweight (OR = 1.199, 95% CI:
5
6 92 1.078 - 1.333) might be risk factor for thyroid nodules after adjusting for age and
7
8 93 gender[14]. Similarly, S. Guth[13] observed that mean thyroid size was correlated
9
10 94 strongly with body weight. However, Kim JY[15] reported that the patients with
11
12 95 thyroid nodule had lower height, weight and body surface area (BSA) than those
13
14 96 without thyroid nodule in Koreans. Especially, in the women, lower height and
15
16 97 overweight were identified as independent risk factors for the presence of thyroid
17
18 98 nodules.
19
20
21
22
23
24
25

26 100 Therefore, the association of anthropometric measurements with thyroid nodule is still
27
28 101 unclear. Furthermore, few study focuses on the relationship of anthropometric
29
30 102 measurements with thyroid nodule in Chinese population. The aim of our study was to
31
32 103 examine the relationship of anthropometric measurements with thyroid nodule in a
33
34 104 large sample size of Chinese population.
35
36
37
38
39
40

41 106 **MATERIALS AND METHODS**

42 107 **Population features**

43
44 108 From March to October 2010, this large cross-sectional study was conducted in
45
46 109 Hangzhou city, which is one of the leading commercial cities in eastern China. The
47
48 110 detail population feature was described in a published article [16].
49
50
51
52
53
54

55 112 **Subjects and study design**

56
57
58
59
60

1
2
3
4 113 The study participants were recruited based on following strategy: There are eight
5
6 114 districts and five counties in big Hangzhou city. First, three sub-districts or towns
7
8
9 115 were selected randomly from each district or county (except Binjiang district)
10
11 116 respectively, so 36 sub-districts or towns were selected from big Hangzhou. Secondly,
12
13 117 one community or village was randomly selected from each sub-district or town.
14
15 118 Thirdly, 100 households from each community or village were randomly selected.
16
17 119 Finally, we selected 3600 households for the interview. The family members of
18
19 120 household were chosen based on the following criteria: (1) age at least 6 years; (2)
20
21 121 living for above 5 years at present residence. The exclusion criteria: (1) the
22
23 122 participants with coronary angiography (CAG) or endoscopic retrograde
24
25 123 cholangiopancreatography (ERCP) in 6 months; (2) the participants taking
26
27 124 amiodarone drug; (3) the participants with abnormal kidney function or serious
28
29 125 illness.

30
31
32
33
34
35
36 126
37
38 127 The eligible family members of selected households were convened to village or
39
40 128 community administration center. The researchers introduced the study protocol and
41
42 129 obtained written informed consent form from each participant. Meanwhile, the
43
44 130 interview schedule was appointed with participants. The study protocol was approved
45
46 131 by Institutional Review Board of Hangzhou Center of Disease Control and Prevention.
47
48 132 This survey was carried out by well-trained personnel (including community clinic
49
50 133 physicians, nurses, public health doctors).

51
52
53
54
55
56 134
57
58
59
60

135 **Collection of epidemiological data**

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

140

141 **Data collection of anthropometric measurements and thyroid nodule**

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

152

153 **Body Mass Index (BMI)**

154 The BMI is defined as the weight in kilograms divided by the square of the height in
155 meters. Although the BMI calculation does not take into account factors such as frame
156 size and body tissue compositions, BMI categories are generally used as a means of

1
2
3
4 157 estimating adiposity and assessing how much an individual's body weight departs
5
6 158 from what is normal or desirable for a person of the same height. According to the
7
8
9 159 criteria recommended by Working Group on Obesity in China[17], the classification
10
11 160 of BMI for adults was as follows: BMI < 24, group low (normal and underweight); 24
12
13 161 ≤ BMI, group high (overweight and obese). Among children, the reference BMI was
14
15
16 162 calculated using the reference height and weight of each age group[18].
17
18
19 163

164 **Body Surface Area (BSA)**

165 BSA is a commonly used index in clinical practice to correct for patient size
166 differences in various physiologic measurements and in calculating drug dosage. BSA
167 is a better indicator of metabolic mass than body weight because it is less affected by
168 abnormal adipose mass[19]. Previous studies observed the association of BSA with
169 thyroid volume and nodules[15 20]. Various formulas have been proposed to estimate
170 the BSA from a patient's weight and height, which may result in slightly different
171 values [21-24]. The most commonly used formula in day-to-day clinical practice is
172 the Mosteller formula: $BSA (m^2) = (\text{square root of product of weight [kg]}\times\text{height$
173 $[\text{cm}]) / 60$ [23]. This formula is simplified from a formula produced by Gehan and
174 George [21], and has become a common standard because it is easy to memorize, and
175 its use requires only a handheld calculator. So Mosteller formula was used in our
176 study to calculate BSA.

177 **Definition of variables**

1
2
3
4 178 Among adults, the height, weight, BMI and BSA were dichotomized into high group
5
6 179 and low group. The detailed criteria of each group were shown in Supplementary
7
8
9 180 Table 3. The classification of height and weight among adults refers to The Survey
10
11 181 Report on National Physical Fitness of Chinese, 2005. In children, high group
12
13 182 included subjects with height or weight \geq reference standard of each age bracket (one
14
15 183 year a bracket) in two genders. BMI was classified according to the reference
16
17 184 calculated using the reference height and weight of each age bracket (one year a
18
19 185 bracket) in two genders respectively[18]. BSA was classified by the average value of
20
21
22 186 each gender.
23
24
25
26
27
28

29 188 **Statistical analysis**

30
31 189 The comparison of height, weight and age between patients with and without thyroid
32
33 190 nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test
34
35 191 for qualitative data, including gender, education, marriage, resident location, cigarette
36
37 192 smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of
38
39 193 salt. Listwise deletion was used to address the missing data in the model.
40
41
42
43
44

45
46 195 The adjusted individual associations of height, weight, BMI and BSA with thyroid
47
48 196 nodule were estimated, using logistic regression model stratified by gender. The
49
50 197 variables showing significant difference between group with and without thyroid
51
52 198 nodule were taken as covariates in logistic regression models: age, BMI, educational
53
54 199 level, marital status, resident location, cigarette smoking, alcohol drinking, diet flavor,
55
56
57
58
59
60

1
2
3
4 200 types of salt, dietary patterns, milk consumption. Among adults, age was classified as
5
6 201 5 classes: 18~29, 30~39, 40~49, 50~59, ≥ 60 . Among children, age was classified as 4
7
8 202 classes: 6~8, 9~11, 12~14, 15~17. To account for the correlation of members in a
9
10 203 same household, we calculated robust estimates of variances with generalized
11
12 204 estimate equation (GEE) using SAS procedure GENMOD. All analyses were
13
14 205 performed in SAS Version 9.0 (SAS Institute, Inc., Cary, NC, USA). A value of
15
16 206 $P < 0.05$ was considered statistically significant.
17
18
19
20
21
22

23 208 **RESULTS**

24 209 **Baseline characteristics of study population**

25
26 210 A total of 12438 individuals were recruited in this investigation, but 3235 individuals
27
28 211 were excluded for analyses, due to absence of anthropometric measurements. Final
29
30 212 analyses included 9203 subject: 6,793 adults, and 2,410 children. Among adults, the
31
32 213 average age was 47.93 years; females accounted for 62.96%; the underweight, normal,
33
34 214 overweight and obese was 4.39%, 66.13%, 26.34% and 3.14%, respectively. The
35
36 215 socio-demographic characteristics among patients with thyroid nodule and non-nodule
37
38 216 group for adults were shown in Table 1; Out of 6,793 adults, 2,228 (32.80%) adults
39
40 217 had thyroid nodule, of which women accounted for 71.01%. Subjects with thyroid
41
42 218 nodule was older, shorter, more females ($p < 0.05$). Moreover, the distributions of
43
44 219 education, marital status, resident location, smoking, drinking, salt appetite, milk
45
46 220 consuming and diet patterns had significant difference between two groups (Table 1).
47
48
49
50
51
52
53
54
55
56
57 221 The socio-demographic characteristics among patients with thyroid nodule and
58
59
60

1
2
3
4 222 non-nodule group for children were shown in Table 3. Subjects with thyroid nodule
5
6 223 was older, and more females ($p < 0.05$). The distributions of resident location, salt
7
8
9 224 appetite and type of salts had significant difference between two groups (Table 3).
10
11 225 Among children, 47.55% were under the reference BMI, 52.45% over the reference
12
13 226 BMI. 257 (10.66%) children suffered from thyroid nodule, which more than half
14
15 227 (57.98%) were girls (Table 4).
16
17
18
19
20

21 229 **The relationship between anthropometric measurements and thyroid nodule**
22
23
24 230 **among adults**

25
26 231 The relationship between anthropometric measurements (height, weight, BMI, BSA)
27
28 232 and thyroid nodule were estimated by gender (Table 2). The height (OR=1.15, 95%
29
30 233 CL: 1.02-1.30), weight (OR=1.40, 95%CL: 1.24-1.58), BMI (OR=1.26, 95% CI:
31
32 234 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) were significantly associated
33
34 235 with an increased risk of thyroid nodule among all adults, respectively. Similar trends
35
36 236 were observed in females and males, but no significant association in males.
37
38
39
40

41 237
42
43
44 238 **The relationship between anthropometric measurements and thyroid nodule**
45
46 239 **among children**

47
48 240 The relationship of anthropometric measurements with thyroid nodule was also
49
50 241 conducted among children (Table 4). The weight (OR=1.37, 95% CI: 1.03–1.81), BMI
51
52 242 (OR=1.38, 95% CI: 1.04–1.83) and BSA (OR=2.97, 95% CI: 1.85–4.77) were
53
54 243 significantly positively associated with the risk of thyroid nodule among all children.
55
56
57
58
59
60

1
2
3
4 244 The significant association of BSA with thyroid nodule was observed in both boys
5
6 245 (OR=2.57, 95% CI: 1.25–5.28) and girls (OR=3.36, 95% CI: 1.82–6.20); BMI and
7
8
9 246 weight were also positively related with the risk of thyroid nodule among both
10
11 247 genders, but significant association of BMI among boys and significant association of
12
13 248 weight among girls was observed respectively. The significant association of height
14
15 249 with risk of thyroid nodule was not observed among children.
16
17
18
19 250
20

21 **DISCUSSION**

22
23
24
25 252 This study, performed in a large Chinese population, demonstrated that height, weight,
26
27 253 BMI and BSA were significantly associated with an increased risk of thyroid nodule
28
29 254 among adults and children, respectively. More explicitly, in the present study, the
30
31 255 significant association between high BSA and thyroid nodule was not obviously
32
33 256 influenced by sex, age, resident location and iodine intake.
34
35
36
37

38 257 Thyroid nodule is very common disease in the general population. The present
39
40 258 investigation showed that the prevalence of thyroid nodule was 32.80% in adults and
41
42 259 10.66% in children; but they are found clinically in 4-8% of cases[25]. The most of
43
44 260 thyroid nodules are benign nodules[26], but 5-6.5% of them are malignant
45
46 261 (carcinomas, CA)[27]. Because thyroid function is linked to development and growth,
47
48 262 height and weight are seen as possible indicators of thyroid nodule risk. In our study,
49
50 263 high height and heavy weight was significantly associated with thyroid nodule in all
51
52 264 adults and females, respectively. But only significant relationship of weight with
53
54
55
56
57
58
59
60

1
2
3
4 265 thyroid nodule was found in children population. To data, few study was focus on the
5
6 266 relationship between anthropometric indexes and thyroid nodule. Previous study
7
8
9 267 showed that thyroid nodule might share similar risk factors with thyroid cancer :
10
11 268 iodine deficiency was associated with an increased TC incidence, largely via benign
12
13
14 269 thyroid conditions such as nodules, which are, in turn, strongly associated with TC.
15
16 270 Additionally, body size might be associated with the iodine requirement and, hence,
17
18
19 271 indirectly related to thyroid nodule[28].
20

21
22 272
23
24 273 Our results were similar to the findings among 88,256 Canadian women in 2012. It is
25
26 274 reported that height was positively associated with risk of all combined cancers and
27
28
29 275 thyroid cancer, and height was significantly positively associated with risk of thyroid
30
31 276 cancer in multivariable models [29]. Further, the European Prospective Investigation
32
33
34 277 into Cancer and nutrition (EPIC), a large study including half-a-million subjects, also
35
36 278 observed the positive association of height with thyroid cancer in female but not in
37
38
39 279 male[30]. Beyond those findings from European population, a pooled analysis of
40
41 280 individual data from 12 case-control studies conducted in eight countries (America,
42
43
44 281 Asia, and Europe) suggests that height was moderately related to thyroid cancer
45
46 282 risk[31]. In addition, similar association of height with thyroid nodule risk among
47
48
49 283 Korean was observed in females but not males[15]. In our findings of Chinese
50
51 284 population, the moderate association of height with thyroid nodule was also observed
52
53
54 285 in females, which was consistent with those from Korea in Asia and even European
55
56 286 population. However, the association was not significant among children, but we still
57
58
59
60

1
2
3
4 287 found an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90). It may due to
5
6 288 the small case numbers of children, and the association between height and thyroid
7
8
9 289 nodule among children needs more future studies to confirm.

10
11 290

12
13
14 291 Furthermore, similar to height, the meta-analysis of data from eight countries also
15
16 292 indicated the association of weight and risk of thyroid cancer in female rather than
17
18
19 293 male[31]. In 2010, Clavel-Chapelon F[32] reported that there was a significant
20
21 294 dose-effect relationship between thyroid cancer risk and weight in France. In Asia, the
22
23
24 295 significant association between weight and thyroid nodule in female was observed
25
26 296 among Korean population[15]. Our data also confirmed these findings after adjusted
27
28
29 297 for possible covariates not only in adult, but also in children. Altered thyroid status
30
31 298 has well-known that it has profound effects on skeletal development and growth and
32
33
34 299 on adult bone maintenance. The fact that thyroid hormones are associated with the
35
36 300 regulation of the growth of long bones may be one possible explanation for the
37
38
39 301 association between height and thyroid nodule[33]. Moreover, genetic or
40
41 302 environmental factors (e.g., dietary factors, nutritious factors), correlate with adult
42
43
44 303 height and weight, also influence thyroid function might be another possible
45
46 304 explanation for this association[31].

47
48
49 305

50
51 306 Analogously, the significant associations between BMI and thyroid nodule were
52
53
54 307 observed among all adults. Similar association was observed in women, but not in
55
56 308 men. Among children, significant associations of BMI with thyroid nodule were also
57
58
59
60

1
2
3
4 309 observed. Our findings in adults were consistent with that in German [34] and Italian
5
6 310 [35], and similar to those among Korean population [15]. However, Results from
7
8
9 311 previous prospective and case-control studies on the association of BMI with thyroid
10
11 312 cancer risk have generally been more inconsistent in men than women. In a large
12
13 313 Norwegian cohort of more than two million participants, the risk of thyroid cancer
14
15
16 314 increased moderately with increased BMI in both sexes, but the results were
17
18 315 unadjusted for smoking and other potential confounders [36]. After adjusted for key
19
20 316 covariates such as cigarette smoking, alcohol drinking, physical activity and medical
21
22 317 history of diabetes, the largest prospective study conducted in U.S. also observed a
23
24 318 significant positive association between BMI and thyroid cancer risk in women [37].
25
26 319 Moreover, a systematic review conducted by Emily Peterson[38] in 2012 (including
27
28 320 37 studies) showed that most of studies supported a positive association of BMI with
29
30 321 thyroid cancer in both sexes. The inconsistent results between men and women in
31
32 322 previous studies is likely due to smaller numbers of cases in men, to the lack of
33
34 323 control for important covariates (e.g. cigarette smoking, alcohol intake). Current
35
36 324 smoking and alcohol intake are associated with BMI [39-42]. Unadjustment for
37
38 325 smoking status or alcohol drinking may be an important bias in the association
39
40 326 between BMI and risk of thyroid nodule. Findings of present study covered adults and
41
42 327 children, and the associations of BMI with thyroid nodule were consistent in two
43
44 328 population after adjusted for important covariates. Base on large samples and
45
46 329 reducing important biases, our findings indicate that overweight and obesity was
47
48 330 associated with thyroid nodule in both adults and children. The association may be the
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 331 certain metabolic consequences of excess adipose tissue. Leptin produced by
5
6 332 adipocytes has important influences on central regulation of thyroid function through
7
8
9 333 stimulation of TRH. This seems to be important for down-regulation of thyroid
10
11 334 function in states of energy deficits, but the importance for modulation of thyroid
12
13 335 function under more physiological conditions is uncertain[43 44]. Additionally,
14
15 336 thyroid hormones may be a significant determinant of sleeping energy expenditure in
16
17 337 subjects without overt thyroid dysfunction[45]. Similarly, differences in thyroid
18
19 338 function, within what is considered the normal range, are associated with differences
20
21 339 in BMI, caused by longstanding minor alterations in energy expenditure[11]. What's
22
23 340 more, obesity is associated with insulin resistance and increased production of insulin
24
25 341 and insulin-like growth factors which in turn have been reported to be associated to
26
27 342 thyroid disorders[27 46 47].
28
29
30
31
32
33

34
35
36 344 Being similar with thyroid cancer[27 37], thyroid nodules are more common in
37
38 345 women than in men[48-52]. Sex differences in the association between BMI and
39
40 346 thyroid cancer have been confirmed in other studies[31 53 54]. Similar results were
41
42 347 observed in Korean[15]. The patients who were normal or overweight in BMI
43
44 348 subgroup were identified to have higher frequency of thyroid nodules. However, the
45
46 349 significant relationship between body size and thyroid nodule in the men were not
47
48 350 observed. Our findings of adults were consistent with the sex difference in association
49
50 351 of BMI with thyroid nodule. The difference in incidence between two genders
51
52 352 suggests that growth and progression of thyroid tumors is influenced by sex hormones,
53
54
55
56
57
58
59
60

1
2
3
4 353 particularly estrogens[55 56]. However, sex difference of the correlation between
5
6 354 body size and thyroid nodule was not obvious among children. It may due to the
7
8
9 355 smaller difference of sex hormones in children, compared to adults. Few studies noted
10
11 356 the correlation between body size and thyroid nodule in children, the findings from
12
13
14 357 children population require furthermore studies to confirm.
15

16
17 358

18
19 359 BSA is a better indicator of the circulating blood volume, oxygen consumption, and
20
21 360 basal energy expenditure than BMI or weight[57]. In the present study, BSA was
22
23
24 361 significantly associated with thyroid nodule among adults and children. The
25
26 362 association was not influenced by sex, age, resident location and iodine intake.
27
28
29 363 Consistently, a positive association of thyroid cancer and current BSA in adults was
30
31 364 found by Suzuki T in Japan in both sexes after adjusted for main covariates [58]. In
32
33
34 365 addition, it was reported that BSA plays a dominant role in thyroid cancer risk and
35
36 366 explains the apparent role of BMI in adults [57]. Muscle is more dense than fat, and
37
38
39 367 BMI is not able to differentiate increased weight [59]. BSA is a more accurate
40
41 368 measure of obesity, including central obesity, as it is a measurement of area and is
42
43
44 369 able to account for the difference between muscle and fat better than BMI secondary
45
46 370 to muscle versus fat [60]. In a way, the association between BSA and thyroid nodule
47
48
49 371 more strongly and forcefully confirmed the increased risk of overweight and obesity
50
51 372 with thyroid nodule than those of BMI.
52

53
54 373

55
56 374 Considering the potential selection bias introduced by subjects suffering from thyroid
57
58
59
60

1
2
3
4 375 problems, we reevaluated the associations of height, weight, BMI and BSA with
5
6 376 thyroid nodule after excluding subjects with diagnosed thyroid disease (Supplemental
7
8
9 377 Table 1, Supplemental Table 2). Our analyses showed that the associations were very
10
11 378 similar to our findings before excluding these subjects diagnosed thyroid diseases.
12
13
14 379 Besides, we observed the similar associations of anthropometric measurement with
15
16 380 thyroid nodule when considering quartile as cut-point (Supplemental Table 4). Our
17
18 381 findings indicated that higher anthropometric measurement might be associate with
19
20 382 thyroid nodule significantly among Chinese population. Further, our study performed
21
22
23 383 in adult population and children population with a large sample size. Further, the
24
25 384 weight and standing height were measured in a standardized protocol by a trained
26
27 385 examiner rather than self-report, reducing the bias of overestimation or
28
29 386 underestimation of height and weight [61 62]. Moreover,
30
31 387 all participants were screened for thyroid nodules via ultrasonography, reducing the p
32
33 388 otential for screening bias. In addition, in order to reduce the possible bias, we
34
35 389 adjusted for most main covariates, including cigarette smoking and alcohol drinking,
36
37 390 two important factors influenced overweight [39-42]. Especially, salt type, salt
38
39 391 appetite and diet patterns were taken as covariates in analysis models; the effect of
40
41 392 iodine on risk of thyroid nodule was considered. Hence, the associations of
42
43 393 anthropometric measurements were robust.
44
45
46
47
48
49
50

394

395 **LIMITATION**

396 There were several limitations in this study. Firstly, the circumferences of waist and

1
2
3
4 397 hip were not measured. It hampered to examine the association of central adiposity
5
6 398 with thyroid nodule. Secondly, the number and mass size of thyroid nodule were not
7
8
9 399 recorded in the investigation, and the classification of thyroid nodules was not
10
11 400 distinguished. Thus, it is no way to find the different associations between
12
13
14 401 anthropometric measurements and different kinds of thyroid nodule.
15
16
17 402

18 19 403 **CONCLUSION**

20
21 404 Our findings indicated that thyroid nodule risk increased with weight, height, BMI
22
23 405 and BSA, especially in females. The similar trends of relationship between weight,
24
25
26 406 BMI, BSA and thyroid nodule were observed in children. Among the four indicators,
27
28
29 407 BSA was strongly associated with thyroid nodule. It implies that individual with high
30
31 408 height and obesity has higher susceptibility for thyroid nodule.
32
33
34 409

35 36 410 **CONTRIBUTORSHIP**

37
38
39 411 The authors gave the following different contribution on this manuscript: Yunxian Yu
40
41 412 generated the idea, modified and edited the manuscript. Weimin Xu supervised the
42
43
44 413 study field activities, prepared and managed the datasets. Zexin Chen did statistical
45
46 414 analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei
47
48
49 415 Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and
50
51 416 interviewed study subjects in the study field. All authors read and approved the final
52
53
54 417 manuscript. None of the authors had a conflict of interest. The manuscript has not
55
56 418 been published and is not being considered for publication elsewhere, in whole or in
57
58
59
60

1
2
3
4 419 part, in any language, except as an abstract.
5
6 420
7
8
9 421 The study was funded in part by grants from Hangzhou Science and Technology
10
11 422 Bureau (Grant number: 200908033B27), the Ministry of Science and Technology
12
13 423 (Grant number: 2011CB503706) and we thank the staff of Hangzhou Center for
14
15 424 Disease Control and Prevention collecting the epidemiological data and blood
16
17 425 specimen. We would like to particularly thank all participants and their family for
18
19 426 their contributions and supports.
20
21
22
23
24 427

25
26 428 **COMPETING INTEREST**
27

28
29 429 None
30
31 430

32
33
34 431 **DATA SHARING**
35

36 432 No additional unpublished data are available.
37
38
39 433
40
41 434
42
43 435
44
45 436
46
47 437
48
49 438
50
51 439
52
53 440
54
55
56
57
58
59
60

441

442

443

444 **REFERENCE**

445

- 446 1. WHO. Media Center: Obesity and overweight. Secondary Media Center: Obesity and overweight
447 2012.
- 448 2. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes
449 mellitus in women. *Ann Intern Med* 1995;**122**(7):481-6
- 450 3. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a
451 prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**(15):1097-105 doi:
452 10.1056/nejm199910073411501[published Online First: Epub Date]].
- 453 4. Saw SM, Rajan U. The epidemiology of obesity: a review. *Ann Acad Med Singapore*
454 1997;**26**(4):489-93
- 455 5. WHO. Obesity: preventing and managing the global epidemic—report of a WHO consultation. World
456 Health Organization 2000
- 457 6. Reynolds K, Gu D, Whelton PK, et al. Prevalence and risk factors of overweight and obesity in
458 China. *Obesity (Silver Spring)* 2007;**15**(1):10-8 doi: 10.1038/oby.2007.527[published Online
459 First: Epub Date]].
- 460 7. Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid
461 volume and function in obese women. *Clinical Endocrinology* 2003;**59**(2):258-62 doi:
462 10.1046/j.1365-2265.2003.01836.x[published Online First: Epub Date]].
- 463 8. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity.
464 *Thyroid* 2006;**16**(1):73-8 doi: 10.1089/thy.2006.16.73[published Online First: Epub Date]].
- 465 9. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid
466 stimulating hormone are directly associated with waist circumference, independently of
467 insulin resistance, metabolic parameters and blood pressure in overweight and obese women.
468 *Clin Endocrinol (Oxf)* 2007;**67**(2):265-9 doi: 10.1111/j.1365-2265.2007.02874.x[published
469 Online First: Epub Date]].
- 470 10. Bastemir M, Akin F, Alkis E, Kaptanoglu B. Obesity is associated with increased serum TSH level,
471 independent of thyroid function. *Swiss Med Wkly* 2007;**137**(29-30):431-4 doi:
472 2007/29/smw-11774[published Online First: Epub Date]].
- 473 11. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be
474 important for body mass index and the occurrence of obesity in the population. *J Clin*
475 *Endocrinol Metab* 2005;**90**(7):4019-24 doi: 10.1210/jc.2004-2225[published Online First:
476 Epub Date]].
- 477 12. al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in
478 patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab*
479 1997;**82**(4):1118-25

- 1
2
3 480 13. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules
4 481 detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest*
5 482 2009;**39**(8):699-706 doi: 10.1111/j.1365-2362.2009.02162.x[published Online First: Epub
6 483 Date]].
- 7
8 484 14. Zhu HF, Yang Y, Li JY, Li XM, Ma AG. [Prevalence of thyroid nodules and influencing factors
9 485 among employees of a company in Qingdao]. *Zhonghua Yu Fang Yi Xue Za Zhi*
10 486 2012;**46**(3):228-32
- 11 487 15. Kim JY, Jung EJ, Park ST, et al. Body size and thyroid nodules in healthy Korean population. *J*
12 488 *Korean Surg Soc* 2012;**82**(1):13-7 doi: 10.4174/jkss.2012.82.1.13[published Online First:
13 489 Epub Date]].
- 14 490 16. Chen Z, Xu W, Huang Y, et al. Associations of noniodized salt and thyroid nodule among the
15 491 Chinese population: a large cross-sectional study. *Am J Clin Nutr* 2013;**98**(3):684-92 doi:
16 492 10.3945/ajcn.112.054353[published Online First: Epub Date]].
- 17 493 17. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive
18 494 values of body mass index and waist circumference for risk factors of certain related diseases
19 495 in Chinese adults--study on optimal cut-off points of body mass index and waist
20 496 circumference in Chinese adults. *Biomed Environ Sci* 2002;**15**(1):83-96
- 21 497 18. Ya-qin LHJC-yZX-nZ. Height and weight standardized growth charts for Chinese children and
22 498 adolescents aged 0 to 18 years. *CHINESE JOURNAL OF PEDIATRICS* 2009;**47**(7)
- 23 499 19. Parsons S. *Pharmaceutical Calculations*: Lulu.com, 2012.
- 24 500 20. Mickuviene N, Krasauskiene A, Kazanavicius G. [The results of thyroid ultrasound examination in
25 501 randomly selected schoolchildren]. *Medicina (Kaunas)* 2006;**42**(9):751-8
- 26 502 21. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer*
27 503 *Chemother Rep* 1970;**54**(4):225-35
- 28 504 22. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a
29 505 height-weight formula validated in infants, children, and adults. *J Pediatr* 1978;**93**(1):62-6
- 30 506 23. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;**317**(17):1098 doi:
31 507 10.1056/NEJM198710223171717[published Online First: Epub Date]].
- 32 508 24. Livingston EH, Lee S. Body surface area prediction in normal-weight and obese patients. *Am J*
33 509 *Physiol Endocrinol Metab* 2001;**281**(3):E586-91
- 34 510 25. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules
35 511 discovered incidentally on thyroid imaging. *Ann Intern Med* 1997;**126**(3):226-31
- 36 512 26. Leitzmann MF, Brenner A, Moore SC, et al. Prospective study of body mass index, physical
37 513 activity and thyroid cancer. *Int J Cancer* 2010;**126**(12):2947-56 doi:
38 514 10.1002/ijc.24913[published Online First: Epub Date]].
- 39 515 27. Tae HJ, Lim DJ, Baek KH, et al. Diagnostic value of ultrasonography to distinguish between benign
40 516 and malignant lesions in the management of thyroid nodules. *Thyroid* 2007;**17**(5):461-6
- 41 517 28. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an
42 518 epidemiological review focused on nutritional factors. *Cancer Causes Control*
43 519 2009;**20**(1):75-86 doi: 10.1007/s10552-008-9219-5[published Online First: Epub Date]].
- 44 520 29. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in
45 521 a cohort of Canadian women. *International Journal of Cancer* 2012:n/a-n/a doi:
46 522 10.1002/ijc.27704[published Online First: Epub Date]].
- 47 523 30. Rinaldi S, Lise M, Clavel-Chapelon F, et al. Body size and risk of differentiated thyroid carcinomas:

- 1
2
3 524 Findings from the EPIC study. *International Journal of Cancer* 2012;**131**(6):E1004-E14 doi:
4 525 10.1002/ijc.27601[published Online First: Epub Date]].
- 5 526 31. Dal Maso L, La Vecchia C, Franceschi S, et al. A pooled analysis of thyroid cancer studies. V.
6 527 Anthropometric factors. *Cancer Causes Control* 2000;**11**(2):137-44
- 7 528 32. Clavel-Chapelon F, Guillas G, Tondeur L, Kernalguen C, Boutron-Ruault MC. Risk of
8 529 differentiated thyroid cancer in relation to adult weight, height and body shape over life: the
9 530 French E3N cohort. *Int J Cancer* 2010;**126**(12):2984-90 doi: 10.1002/ijc.25066[published
10 531 Online First: Epub Date]].
- 11 532 33. Gogakos AI, Duncan Bassett JH, Williams GR. Thyroid and bone. *Arch Biochem Biophys*
12 533 2010;**503**(1):129-36 doi: 10.1016/j.abb.2010.06.021[published Online First: Epub Date]].
- 13 534 34. Karger S, Schotz S, Stumvoll M, Berger F, Fuhrer D. Impact of pregnancy on prevalence of goitre
14 535 and nodular thyroid disease in women living in a region of borderline sufficient iodine supply.
15 536 *Horm Metab Res* 2010;**42**(2):137-42 doi: 10.1055/s-0029-1241861[published Online First:
16 537 Epub Date]].
- 17 538 35. Trimboli P, Rossi F, Thorel F, et al. One in five subjects with normal thyroid ultrasonography has
18 539 altered thyroid tests. *Endocr J* 2012;**59**(2):137-43
- 19 540 36. Engeland A, Tretli S, Akslen LA, Bjorge T. Body size and thyroid cancer in two million Norwegian
20 541 men and women. *Br J Cancer* 2006;**95**(3):366-70 doi: 10.1038/sj.bjc.6603249[published
21 542 Online First: Epub Date]].
- 22 543 37. Kitahara CM, Platz EA, Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and
23 544 women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev*
24 545 2011;**20**(3):464-72 doi: 10.1158/1055-9965.epi-10-1220[published Online First: Epub Date]].
- 25 546 38. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer: a
26 547 systematic review. *PLoS One* 2012;**7**(1):e29177 doi: 10.1371/journal.pone.0029177[published
27 548 Online First: Epub Date]].
- 28 549 39. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat
29 550 distribution, and insulin resistance. *Am J Clin Nutr* 2008;**87**(4):801-9
- 30 551 40. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking
31 552 cessation on the prevalence of overweight in the United States. *N Engl J Med*
32 553 1995;**333**(18):1165-70 doi: 10.1056/nejm199511023331801[published Online First: Epub
33 554 Date]].
- 34 555 41. Wannamethee SG, Shaper AG. Alcohol, body weight, and weight gain in middle-aged men. *Am J*
35 556 *Clin Nutr* 2003;**77**(5):1312-7
- 36 557 42. Hou X, Jia W, Bao Y, et al. Risk factors for overweight and obesity, and changes in body mass
37 558 index of Chinese adults in Shanghai. *BMC Public Health* 2008;**8**:389 doi:
38 559 10.1186/1471-2458-8-389[published Online First: Epub Date]].
- 39 560 43. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the
40 561 neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *J Clin Invest*
41 562 2003;**111**(9):1409-21 doi: 10.1172/jci17490[published Online First: Epub Date]].
- 42 563 44. LaMarca A, Volpe A. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl*
43 564 *J Med* 2004;**351**(22):2343; author reply 43 doi: 10.1056/nejm200411253512221[published
44 565 Online First: Epub Date]].
- 45 566 45. Astrup A, Buemann B, Christensen NJ, et al. The contribution of body composition, substrates, and
46 567 hormones to the variability in energy expenditure and substrate utilization in premenopausal

- 1
2
3 568 women. *J Clin Endocrinol Metab* 1992;**74**(2):279-86
- 4 569 46. Volzke H, Friedrich N, Schipf S, et al. Association between serum insulin-like growth factor-I
5 570 levels and thyroid disorders in a population-based study. *J Clin Endocrinol Metab*
6 571 2007;**92**(10):4039-45 doi: 10.1210/jc.2007-0816[published Online First: Epub Date]].
- 7 572 47. Vella V, Sciacca L, Pandini G, et al. The IGF system in thyroid cancer: new concepts. *Mol Pathol*
8 573 2001;**54**(3):121-4
- 9 574 48. Mazzaferri EL, de los Santos ET, Rofagha-Keyhani S. Solitary thyroid nodule: diagnosis and
10 575 management. *The Medical clinics of North America* 1988;**72**(5):1177-211
- 11 576 49. Mazzaferri EL. Management of a Solitary Thyroid Nodule. *New England Journal of Medicine*
12 577 1993;**328**(8):553-59 doi: doi:10.1056/NEJM199302253280807[published Online First: Epub
13 578 Date]].
- 14 579 50. Hurtado-Lopez LM, Basurto-Kuba E, Montes de Oca-Duran ER, Pulido-Cejudo A, Vazquez-Ortega
15 580 R, Athie-Gutierrez C. Prevalence of thyroid nodules in the Valley of Mexico. *Cir Cir*
16 581 2011;**79**(2):114-7
- 17 582 51. Yoon DY, Chang SK, Choi CS, et al. The prevalence and significance of incidental thyroid nodules
18 583 identified on computed tomography. *J Comput Assist Tomogr* 2008;**32**(5):810-5 doi:
19 584 10.1097/RCT.0b013e318157fd38[published Online First: Epub Date]].
- 20 585 52. Bartolotta TV, Midiri M, Runza G, et al. Incidentally discovered thyroid nodules: incidence, and
21 586 greyscale and colour Doppler pattern in an adult population screened by real-time compound
22 587 spatial sonography. *Radiol Med* 2006;**111**(7):989-98 doi:
23 588 10.1007/s11547-006-0097-1[published Online First: Epub Date]].
- 24 589 53. Guignard R, Truong T, Rougier Y, Baron-Dubourdieu D, Guenel P. Alcohol drinking, tobacco
25 590 smoking, and anthropometric characteristics as risk factors for thyroid cancer: a countrywide
26 591 case-control study in New Caledonia. *Am J Epidemiol* 2007;**166**(10):1140-9 doi:
27 592 10.1093/aje/kwm204[published Online First: Epub Date]].
- 28 593 54. Brindel P, Doyon F, Rachedi F, et al. Anthropometric factors in differentiated thyroid cancer in
29 594 French Polynesia: a case-control study. *Cancer Causes Control* 2009;**20**(5):581-90 doi:
30 595 10.1007/s10552-008-9266-y[published Online First: Epub Date]].
- 31 596 55. Negri E, Ron E, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer. I.
32 597 Methods. *Cancer Causes Control* 1999;**10**(2):131-42
- 33 598 56. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer:
34 599 a systematic review and meta-analysis of prospective observational studies. *Lancet*
35 600 2008;**371**(9612):569-78 doi: 10.1016/s0140-6736(08)60269-x[published Online First: Epub
36 601 Date]].
- 37 602 57. Clero E, Leux C, Brindel P, et al. Pooled analysis of two case-control studies in New Caledonia and
38 603 French Polynesia of body mass index and differentiated thyroid cancer: the importance of
39 604 body surface area. *Thyroid* 2010;**20**(11):1285-93 doi: 10.1089/thy.2009.0456[published
40 605 Online First: Epub Date]].
- 41 606 58. Suzuki T, Matsuo K, Hasegawa Y, et al. Anthropometric factors at age 20 years and risk of thyroid
42 607 cancer. *Cancer Causes Control* 2008;**19**(10):1233-42 doi:
43 608 10.1007/s10552-008-9194-x[published Online First: Epub Date]].
- 44 609 59. Hamdy O, Porrmatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and
45 610 subcutaneous fat. *Curr Diabetes Rev* 2006;**2**(4):367-73
- 46 611 60. Roy SK, Zeb I, Kadakia J, Li D, Budoff MJ. Body surface area is a predictor of coronary artery

- 1
2
3 calcium, whereas body mass index is not. *Coron Artery Dis* 2012;**23**(2):113-7 doi:
4 10.1097/MCA.0b013e32834f1b72[published Online First: Epub Date].
5
6 61. Gunnell D, Berney L, Holland P, et al. How accurately are height, weight and leg length reported by
7 the elderly, and how closely are they related to measurements recorded in childhood? *Int J*
8 *Epidemiol* 2000;**29**(3):456-64
9
10 62. Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A. Validity of self-reported weight and
11 height in the French GAZEL cohort. *Int J Obes Relat Metab Disord* 2000;**24**(9):1111-8
12
13
14 620
15
16
17 621
18
19 622
20
21 623
22
23
24 624
25
26 625
27
28
29 626
30
31 627
32
33
34 628
35
36 629
37
38
39 630
40
41 631
42
43
44 632
45
46 633
47
48
49 634
50
51 635
52
53
54 636
55
56 637
57
58
59
60

638

639

640

641 TABLES

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

Variables	Nodule (n=2228)	Non-nodule (n=4565)	P
Age, year (Mean ± SD)	53.49±13.80	44.93±13.72	<0.001
Height, cm (Mean ± SD)	160.72±7.25	162.24±7.54	<0.001
Weight, kg (Mean ± SD)	59.30±8.12	59.10±8.33	0.177
BMI, kg/m² (Mean±SD)	23.07±2.69	22.52±2.65	<0.001
Gender, n(%)			
male	646(28.99)	1870(40.96)	<0.001
female	1582(61.01)	2695(59.04)	
Education^a, n(%)			
primary school	922(42.10)	1317(29.15)	<0.001
Junior high school	647(29.54)	1440(31.87)	
senior high school	470(21.46)	1283(28.40)	
junior college and above	151(6.89)	478(10.58)	
Marriage, n(%)			
single	78(3.51)	378(8.29)	<0.001
married	1980(88.98)	3981(87.30)	
divorce	22(0.99)	47(1.03)	
widowed	139(6.25)	140(3.07)	
others	6(0.27)	14(0.31)	
Resident location, n(%)			
urban area	1214(54.49)	2125(46.55)	<0.001
rural area	1014(45.52)	2440(53.45)	
Cigarette smoking, n(%)			
Never	1825(82.65)	3508(77.46)	<0.001
Ever	69(3.13)	121(2.67)	
Current	314(14.22)	900(19.87)	
Alcohol drinking, n(%)			
No	1822(83.27)	3608(80.55)	0.027
Yes	366(16.73)	871(19.45)	
Salt appetite, n(%)			
moderate	1135(51.24)	2479(54.52)	0.036
salty	469(21.17)	916(20.15)	

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

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

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

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

642

643

644

645

646

647

648

649

650

651

652

653

654

655

656

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

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

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

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

^a: **Male**: high: height \geq 170cm, low: height $<$ 170cm; **female**: high: height \geq 160cm, low: height $<$ 160cm;

^b: **Male**: high: weight \geq 65kg, low: weight $<$ 65kg; **female**: high: weight \geq 60kg, low: weight $<$ 60kg;

^c: Low=BMI $<$ 24.0; high: BMI \geq 24;

^d: **Male**: high: BSA \geq 1.80m², low: BSA $<$ 1.80m²; **female**: high: BSA \geq 1.55m², low: BSA $<$ 1.55m²

657

658

659

660

661

662

663

664

665

666

667

668

669

670

671

672

673

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

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

^aVegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

^bIodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

674

675

676

677

678

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

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

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

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

^{a,b}:High: height or weight \geq reference standard, low: height or weight $<$ reference standard;

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

^d:**Male**: high: $BSA \geq 1.26m^2$,low: $BSA < 1.26m^2$;**female**: high: $BSA \geq 1.22m^2$,low: $BSA < 1.22m^2$;

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

679

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

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

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

1
2
3
4 location, types of salt, salt appetite, diet patterns, milk consuming;

5 ^a: **Male**: high: height \geq 170cm, low: height $<$ 170cm; **female**: high: height \geq 160cm, low:
6 height $<$ 160cm;

7 ^b: **Male**: high: weight \geq 65kg, low: weight $<$ 65kg; **female**: high: weight \geq 60kg, low:
8 weight $<$ 60kg;

9 ^c: Low=BMI $<$ 24.0; high: BMI \geq 24;

10 ^d: **Male**: high: BSA \geq 1.80m², low: BSA $<$ 1.80m²; **female**: high: BSA \geq 1.55m², low:
11 BSA $<$ 1.55m²
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	P
Pooled*				
Height^a				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight^b				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI^c				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA^d				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
Girls				
Height^a				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight^b				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI^c				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m²)^d				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
Boys				
Height^a				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight^b				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI^c				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA^d				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

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

^{a,b}:High: height or weight \geq reference standard, low: height or weight $<$ reference standard;

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

^d: **Male**: high: $BSA \geq 1.26 \text{ m}^2$, low: $BSA < 1.26 \text{ m}^2$; **female**: high: $BSA \geq 1.22 \text{ m}^2$, low: $BSA < 1.22 \text{ m}^2$;
Mean of male's $BSA = 1.26 \text{ m}^2$, Mean of female's $BSA = 1.22 \text{ m}^2$.

For peer review only

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

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low		BMI<24.0
High		BMI≥24
BSA(m²)		
low	BSA<1.80m ²	BSA<1.55m ²
high	BSA≥1.80m ²	BSA≥1.55m ²

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

Variables	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
	Pooled*		Female		Male	
Height(cm)^a						
<156	1.00		1.00		1.00	
156-<161	1.19(1.01,1.40)	0.0363	1.21(1.02,1.44)	0.0260	1.13(0.48,2.65)	0.7843
161-<168	1.34(1.11,1.60)	0.0019	1.35(1.11,1.65)	0.0031	1.22(0.55,2.73)	0.6262
≥168	1.38(1.09,1.75)	0.0075	1.83(1.25,2.70)	0.0021	1.10(0.50,2.46)	0.8084
Weight(kg)^a						
<54	1.00		1.00			
54-<60	1.20(1.02,1.43)	0.0330	1.13(0.94,1.35)	0.1936	1.00 ^{&}	
60-<65	1.63(1.36,1.95)	<0.001	1.62(1.33,1.98)	<0.001	1.03(0.75,1.41)	0.8556
≥65	1.73(1.44,2.08)	<0.001	1.97(1.58,2.45)	<0.001	1.00(0.75,1.34)	0.9924
BMI^b						
<18.5	1.00		1.00			
18.5-<24	1.50(1.09,2.04)	0.0116	1.41(1.02,1.93)	0.0350	/ [#]	/
≥24	1.88(1.37,2.60)	0.0001	2.01(1.45,2.79)	<0.001	/	/
BSA(m²)^a						
<1.53	1.00		1.00		1.00	
1.53-<1.63	1.30(1.10,1.53)	0.0023	1.27(1.07,1.50)	0.0072	0.69(0.06,7.96)	0.7664
1.63-<1.74	1.78(1.49,2.12)	<0.001	1.78(1.47,2.16)	<0.001	0.75(0.07,8.43)	0.8120
≥1.74	1.86(1.51,2.29)	<0.001	2.15(1.63,2.83)	<0.001	0.72(0.06,8.12)	0.7892

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

a: 4 categories by quartile;

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

&: No male's weight <54kg;

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

1
2
3 Dear editor,
4

5
6 Thank you very much for your comments and suggestions concerning our manuscript
7
8 entitled "The Relationship of Anthropometric Measurement with the Risk of Thyroid N
9
10odule in Chinese Population". Those comments are all valuable and very helpful for
11
12 revising and improving our manuscript, as well as the important guiding significance to
13
14 our researches. Based on reviewers' comments, we have carefully modified manuscript.
15
16 Revised portions are marked in red in the Manuscript. Meanwhile, the responses for all
17
18 comments one by one as following:
19
20
21
22
23
24

25 *Review 1*

26 **Comment 1:**

27
28 The manuscript would benefit from some additional editing. There are several gramma
29
30 tical errors, and the Discussion section, in particular, appears unorganized and repetitiv
31
32 e.
33
34

35
36 **Response 1:** We have carefully revised the manuscript.
37
38

39 **Comment 2:**

40
41 The rationale, as outlined in the Introduction, is not very convincing. What is the conn
42
43 ection between thyroid nodules, thyroid function, and thyroid cancer? What biological
44
45 or public health insights could be obtained through a greater understanding of the relat
46
47 ionship for anthropometric factors and thyroid nodules? Why is a study based on a Chi
48
49 nese population needed, and how would this add to what is known from studies based i
50
51 n other populations? What is the rationale for examining these associations in both chi
52
53 ldren and adults?
54

55
56 **Response 2:** As request, we have modified description in Introduction section.
57
58

59 **Comment 3:**

60

1
2
3
4 The authors should clarify the reason for examining BSA in this study. They state that
5 BSA is “a better indicator of metabolic mass than body weight because it is less associa
6 ted with excess body weight.” It is not clear what is meant by this statement, and no re
7 ference is provided to refer to.
8
9

10
11 **Response 3:** We have revised the description in MATERIALS AND METHODS
12 section (line 215-220).
13
14

15
16
17
18
19 **Comment 4:**

20 Height and weight were measured using a standardized protocol. This is an important
21 detail that should be mentioned in the Abstract.
22
23

24
25 **Response 4:** We have added the detail description (line 34-35).
26
27

28
29 **Comment 5:**

30 All participants were screened for thyroid nodules via ultrasonography, thereby reducin
31 g the potential for screening bias. This is an important strength that should be discusse
32 d.
33
34

35
36
37 **Response 5:** We have added the strength to discussion section as request (line
38 426-427).
39
40

41
42
43 **Comment 6:**

44 The authors suggest that detection bias may explain the stronger association between b
45 ody size and nodules in women, as has been suggested for thyroid cancer (page 18); ho
46 wever, this population was screened for thyroid nodules, thereby reducing the potential
47 for screening/detection biases. The findings from this study of thyroid nodules should
48 primarily be compared with findings from studies with a similar design, which does no
49 t include most studies of thyroid cancer. For instance, there are a few Korean studies p
50 ublished of thyroid nodules based on populations that were screened for thyroid nodule
51 s. How do the findings of this study compare with those?
52
53
54
55
56
57
58
59
60

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

1
2
3
4 DISCUSSION (line 386-389).
5
6
7

8 *Review 2*

9
10 Materials and Methods:
11

12 **Comment 1:**

13
14 as the subjects and study design have been described in detail in a recent publication, t
15
16 his part should be shortened giving more emphasis to the description of the variables of
17
18 interest (anthropometry and thyroid nodule measurements)
19

20 **Response 1:** The description of subjects and study design has been shortened.
21
22

23 **Comment 2:**

24
25 The choice of a cut-point of 24 for BMI in adults should be justified.
26
27

28 **Response 2:** The cut-point of 24 for BMI is determined by the criteria recommended
29
30 by Working Group on Obesity in China (line 186-187).
31
32

33 **Comment 3:**

34
35 Because of the large size of the population, it would be of interest to explore associatio
36
37 ns with tertiles of exposures.
38
39

40 **Response 3:** We have added the results in Supplementary Table 4, and added the
41
42 description to discussion section (line 381-384).
43
44

45 **Comment 4:**

46
47 How does the simplified formula used for the calculation of body surface area correlate
48
49 to the formula by Boyd, in adults and children?
50
51

52 **Response 4:** Body surface area of both adults and children were calculated using the
53
54 formula: $BSA = \sqrt{\text{Weight} * \text{Height}}/60$.
55
56

57 **Comment 5:**

58
59 The description of the population as presented in Table 1 should be part of the Results s
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ection of the manuscript.

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

-Statistical analyses:

Comment 1:

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

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

-Results:

Comment 1:

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

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

-Tables:

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

Response 1: This point was done.

Comment 2:

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

Response 2: We have added it in Table 3.

Comment 3:

1
2
3
4 For ease of comparisons, tables 1 and 3 could be combined by adding additional colum
5
6 ns to Table 1.

7
8 **Response 3:** The adults and children are different population, and the
9
10 socio-demographic characteristics of adult and children are different (education,
11
12 marriage, smoking and drinking were not included in children). Hence, we still keep
13
14 Table 1 and Table 3.

15
16
17
18 **Comment 4:** There is no reference to Supplementary tables in the text

19
20 **Response 4:** We have revised the reference to supplementary tables in discussion
21
22 section (line 214, line 420).

23
24
25
26 -Discussion:

27
28 **Comment 1:**

29
30 As the study presented has a cross-sectional design, it would be important to state that
31
32 no causality can be inferred. Some conclusions on associations in this section may ther
33
34 efore be smoothed, and the title of the manuscript may be rephrased as “The relation
35
36 ship of anthropometric measurements with thyroid nodules in a Chinese population”

37
38 **Response 1:** The title and conclusions were modified.

39
40
41 **Comment 2:** Pag 14, line 286: the EPIC study includes about half-a-million subjects.

42
43
44 **Response 2:** We have revised (line 313).

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

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

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (line 227-229) (b) Give reasons for non-participation at each stage (line 227) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (line 226-235) (b) Indicate number of participants with missing data for each variable of interest (Table 1) (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures (line 231-235)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (line -237-257) (b) Report category boundaries when continuous variables were categorized (line 218-219) (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (N/A)

Discussion

Key results	18	Summarise key results with reference to study objectives (line 260-264)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (line 397-403)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (line 265-385)
Generalisability	21	Discuss the generalisability (external validity) of the study results (line 260-262)

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (line 424-429)
---------	----	---

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

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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-008452.R2
Article Type:	Research
Date Submitted by the Author:	17-Sep-2015
Complete List of Authors:	<p>Xu, Weimin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>chen, zexin; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics</p> <p>Li, Na; Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China,</p> <p>Liu, Hui; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics</p> <p>Huo, Liangliang; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>Huang, Yangmei; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>Jin, Xingyi; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>Deng, Jin; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>Zhu, Sujuan; Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China, Department of Endemic Diseases Control and Prevention</p> <p>zhang, shanchun; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics</p> <p>yu, yunxian; School of Public Health, Zhejiang University, Hangzhou, Zhejiang, China, Department of Epidemiology & Health Statistics</p>
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, STATISTICS & RESEARCH METHODS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Weimin Xu, MD², Zexin Chen, MD¹, Na Li³, Hui Liu, MD¹, Liangliang Huo²,
Yangmei Huang, MD², Xingyi Jin, MD², Jin Deng, MD², Sujuan Zhu, MD²,
Shanchun Zhang, PhD¹, Yunxian Yu, PhD¹

1. Department of Epidemiology & Health Statistics, School of Public Health, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China
2. Department of Endemic Diseases Control and Prevention, Hangzhou Center for Disease Control and Prevention, Hangzhou, Zhejiang, China
3. Shangcheng Center for Disease Control and Prevention, Hangzhou, Zhejiang, China

Weimin Xu and Zexin Chen have equally contribution to the manuscript.

***Correspondence and reprint requests should be addressed to:**

Yunxian Yu, MD, PhD

Department of Epidemiology & Health Statistics, School of Public Health, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

866 Yu-Hang-Tang Road, Xihu District, Hangzhou 310058, Zhejiang, China

Tel: +86-571-88208191

Fax: +86-571-88208194

E-mail: yunxianyu@zju.edu.cn

1
2
3
4 26 **ABSTRACT**
5

6 27 **Objective:** Previous studies have found that overweight and obesity have been
7
8
9 28 related to numerous diseases, including thyroid cancer and thyroid volume. This study
10
11 29 is to evaluate the relationship between body size and thyroid nodule in Chinese
12
13
14 30 population.

15
16 31 **Methods:** A total of 6,793 adults and 2,410 children who underwent thyroid
17
18 32 ultrasonography were recruited in this cross-sectional study, Hangzhou, Zhejiang
19
20
21 33 province, China, from March to October, 2010. The socio-demographic characteristics
22
23
24 34 and potential risk factors of thyroid nodule were collected using questionnaire. Height
25
26 35 and weight were measured using standard protocols. The associations of height,
27
28
29 36 weight, Body Mass Index (BMI) and Body Surface Area (BSA) with thyroid nodule
30
31 37 were evaluated using multiple logistic regression models.

32
33
34 38 **Results:** After adjusted potential risk factors, an increased risk of thyroid nodule was
35
36 39 respectively associated with height (OR=1.15, 95% CL: 1.02-1.30), weight (OR=1.40,
37
38
39 40 95% CL: 1.24-1.58), BMI (OR=1.26, 95% CI: 1.11-1.42) and BSA (OR=1.43, 95%
41
42 41 CI: 1.27-1.62) among all adults, obviously in females. Similar associations between
43
44 42 weight, BMI, BSA and the risk of thyroid nodule were observed in children, but not
45
46 43 height. BSA was highest significantly associated with thyroid nodule among both
47
48
49 44 adult and children.

50
51 45 **Conclusion:** The present study identified that thyroid nodule was positively
52
53 46 associated with weight, height, BMI and BSA among both female adults and girls. It
54
55
56 47 implied that individual with high height and obesity increased the susceptibility for
57
58
59
60

1
2
3
4 48 thyroid nodule.
5

6 49 **Keywords:** anthropometric measurement, thyroid nodule, adult, children, Chinese
7
8 50 population
9
10

11 51

12
13
14 52 **Article summary:**

15
16 53 Strengths and limitations of this study:

- 17
18 54 1) Including adult and children subjects.
19
20 55 2) Large sample size of subjects.
21
22 56 3) The weight and standing height were measured in a standardized protocol by a
23
24 57 trained examiner rather than self-report.
25
26 58 4) The main results was presented after adjustment for many potential confounders,
27
28 59 including cigarette smoking and alcohol drinking, two important factors
29
30 60 influenced overweight
31
32 61 5) The number and mass size of thyroid nodule were not recorded in the
33
34 62 investigation, and the classification of thyroid nodules was not distinguished.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

70 INTRODUCTION

71 The most of thyroid nodules are benign nodules[1], but 5-6.5% of them are malignant
72 (carcinomas, CA)[2]. Because thyroid function is linked to development and growth,
73 height and weight are seen as possible indicators of thyroid nodule risk. Overweight
74 and obesity are major risk factors for a number of chronic diseases, including diabetes,
75 cardiovascular diseases and cancer. Overweight and obesity are the fifth leading risk
76 for global deaths. In addition, between 7% and 41% of certain cancer burdens are
77 attributable to overweight and obesity[3]. Data from epidemiological studies
78 demonstrate a direct correlation between BMI and the risk of medical complications
79 and mortality rate[4 5]. The prevalence of overweight and obesity has been increasing
80 in most economically developed countries for several decades, and there is evidence
81 that the prevalence of overweight and obesity is also increasing in economically
82 developing countries[6 7]. The prevalence of obesity has recently been dramatically
83 increasing in China as a developing country. A national survey indicates that the
84 prevalence of overweight and obesity were 24.1% and 2.8% in men and 26.1% and
85 5.0% in women, respectively [8]. Meanwhile, previous studies reported functional and
86 morphological alterations of the thyroid gland in relation to obesity [9-13]. Due that
87 thyroid hormones increase the basal metabolic rate, low thyroid function, even within
88 the clinically normal range, could decrease metabolic speed and lead to obesity[13 14].
89 In addition, Mehmet Bastemir [12] found that serum TSH levels are positively
90 correlated with the degree of obesity and some of its metabolic consequences in
91 overweight people with normal thyroid function. Furthermore, S.Guth[15] reported

1
2
3
4 92 that BMI were positively correlated with sizes of their thyroids. Though the vast
5
6 93 majority of nodules are benign, the risk factors for thyroid nodules among euthyroid
7
8
9 94 population have not yet been fully elucidated. Previous study in Chinese population
10
11 95 indicated overweight (OR = 1.199, 95% CI: 1.078 - 1.333) might be a risk factor
12
13
14 96 for thyroid nodules after adjusting for age and gender[16]. Similarly, S. Guth[15]
15
16 97 observed that mean thyroid size was correlated strongly with body weight. However,
17
18
19 98 Kim JY[17] reported that the patients with thyroid nodule had lower
20
21 99 height, weight and body surface area (BSA) than those without thyroid nodule in
22
23
24 100 Koreans. Especially, in the women, lower height and overweight were identified as
25
26
27 101 independent risk factors for the presence of thyroid nodules.
28
29
30

31 103 Therefore, the association of anthropometric measurements with thyroid nodule is still
32
33 104 unclear. Additionally, previous studies rarely focus on the relationship of
34
35
36 105 anthropometric measurements with thyroid nodule in Chinese population. The aim of
37
38
39 106 our study is to examine the relationship of anthropometric measurements with thyroid
40
41
42 107 nodule in a large sample size of Chinese population.
43
44
45

46 109 **MATERIALS AND METHODS**

47 110 **Population features**

48
49
50
51 111 From March to October 2010, this large cross-sectional study was conducted in
52
53
54 112 Hangzhou city, which is one of the leading commercial cities in eastern China. The
55
56
57 113 detail population feature was described in a published article [18].
58
59
60

1
2
3
4 1145
6 115 **Subjects and study design**
7

8 116 All participants were recruited based on following strategies: There are eight districts
9 117 and five counties in big Hangzhou city. Firstly, three sub-districts or towns were
10 118 selected randomly from each district or county (except Binjiang district) respectively,
11 119 so 36 sub-districts or towns were selected from big Hangzhou. Secondly, one
12 120 community or village was randomly selected from each sub-district or town. Thirdly,
13 121 100 households from each community or village were randomly selected. Finally, we
14 122 selected 3600 households for the interview. The family members of household were
15 123 chosen based on the following criteria: (1) age at least 6 years; (2) living for above 5
16 124 years at present residence. The exclusion criteria: (1) the participants with coronary
17 125 angiography (CAG) or endoscopic retrograde cholangiopancreatography (ERCP) in 6
18 126 months; (2) the participants taking amiodarone drug; (3) the participants with
19 127 abnormal kidney function or serious illness.

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39 128

40 129 The eligible family members of selected households were convened to village or
41 130 community administration center. The researchers introduced the study protocol and
42 131 obtained written informed consent form from each participant. Meanwhile, the
43 132 interview schedule was appointed with participants. The study protocol was approved
44 133 by Institutional Review Board of Hangzhou Center of Disease Control and Prevention.
45 134 This survey was carried out by well-trained personnel (including community clinic
46 135 physicians, nurses, public health doctors).

1
2
3
4 136
5
6

7 **137 Collection of epidemiological data**

8
9 138 The participants were interviewed for a structured questionnaire. The questionnaire
10
11 139 covered the information about demographic characteristics and health status,
12
13 140 including sex, age, nationality, physical activity, lifestyle, dietary habit, and personal
14
15 141 or family history of thyroid disease (including time of diagnosis).
16
17
18
19 142

20
21 **143 Data collection of anthropometric measurements and thyroid nodule**

22
23
24 144 Height and weight were measured using standard protocols, without shoes or
25
26 145 outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer with
27
28 146 a GMCS-I type height tester (Beijing). Weight was measured to the nearest 0.1 kg
29
30 147 with the subjects standing motionless on a scale with a balance-beam scale (RGT-140,
31
32 148 weighing Apparatus Co. Ltd. Wuxi). An ultrasound examination of thyroid was
33
34 149 performed to detect thyroid nodules by a Sonoline Versa Pro (Siemens, Munich,
35
36 150 Germany) with a 7.5-MHz, 70-mm linear transducer (effective length, 62 mm).
37
38 151 Thyroid nodule was defined as discrete lesion which was distinct from the
39
40 152 surrounding thyroid parenchyma and which had solid portion regardless of having
41
42 153 cystic portion.
43
44
45
46
47
48
49 154

50
51 **155 Body Mass Index (BMI)**

52
53
54 156 The BMI is defined as the weight in kilograms divided by the square of the height in
55
56 157 meters. Although the BMI calculation is not taken into account factors such as frame
57
58
59
60

1
2
3
4 158 size and body tissue compositions, BMI categories are generally used as a means of
5
6 159 estimating adiposity and assessing how much an individual's body weight departs
7
8
9 160 from what is normal or desirable for a person of the same height. According to the
10
11 161 criteria recommended by Working Group on Obesity in China[19], the classification
12
13 162 of BMI for adults was as follows: BMI < 24, group low (normal and underweight); 24
14
15
16 163 ≤ BMI, group high (overweight and obese). Among children, the reference BMI was
17
18
19 164 calculated using the reference height and weight of each age group[20].
20
21
22 165

23 166 **Body Surface Area (BSA)**

24
25
26 167 BSA is a commonly used index in clinical practice to correct for patient size
27
28 168 differences in various physiologic measurements and in calculating drug dosage. BSA
29
30
31 169 is a more accurate measure of obesity, including central obesity, as it is a
32
33
34 170 measurement of area and is able to account for the difference between muscle and fat
35
36
37 171 better than BMI secondary to muscle versus fat [21]. Previous studies observed the
38
39 172 association of BSA with thyroid volume and nodules[17 22]. Various formulas have
40
41
42 173 been proposed to estimate the BSA from a patient's weight and height, which may
43
44 174 result in slightly different values [23-26]. The most commonly used formula in
45
46 175 day-to-day clinical practice is the Mosteller formula: $BSA (m^2) = (\text{square root of}$
47
48
49 176 $\text{product of weight [kg]}\times\text{height [cm]}) /60$ [25]. This formula is simplified from a
50
51
52 177 formula produced by Gehan and George [23], and has become a common standard
53
54 178 because it is easy to memorize, and its use requires only a handheld calculator. So
55
56
57 179 Mosteller formula was used in our study to calculate BSA.
58
59
60

1
2
3
4 180

5
6 181 **Definition of variables**

7
8
9 182 Among adults, the height, weight, BMI and BSA were dichotomized into high group
10
11 183 and low group. The detailed criteria of each group were shown in Supplementary
12
13
14 184 Table 1. The classification of height and weight among adults refers to The Survey
15
16 185 Report on National Physical Fitness of Chinese, 2005. In children, high group
17
18 186 included subjects with height or weight \geq reference standard of each age bracket (one
19
20 187 year a bracket) in two genders. BMI was classified according to the reference
21
22 188 calculated using the reference height and weight of each age bracket (one year a
23
24 189 bracket) in two genders respectively[20]. BSA was classified by the average value of
25
26
27
28 190 each gender.

29
30
31 191

32
33
34 192 **Statistical analysis**

35
36 193 The comparison of height, weight and age between patients with and without thyroid
37
38 194 nodule was conducted by *t* test. Comparisons between groups were made using χ^2 test
39
40 195 for qualitative data, including gender, education, marriage, resident location, cigarette
41
42 196 smoking, alcohol drinking, salt appetite, milk consuming, diet patterns and types of
43
44 197 salt. Listwise deletion was used to address the missing data in the model.

45
46
47 198

48
49
50
51 199 The adjusted associations of height, weight, BMI and BSA with thyroid nodule were
52
53 200 estimated, using logistic regression model stratified by gender. The variables showing
54
55 201 significant difference between group with and without thyroid nodule were taken as

1
2
3
4 202 covariates in logistic regression models: age, BMI, educational level, marital status,
5
6 203 resident location, cigarette smoking, alcohol drinking, diet flavor, types of salt, dietary
7
8
9 204 patterns, milk consumption. Among adults, age was classified as 5 classes: 18~29,
10
11 205 30~39, 40~49, 50~59, ≥ 60 . Among children, age was classified as 4 classes: 6~8,
12
13
14 206 9~11, 12~14, 15~17. To account for the correlation of members in a same household,
15
16 207 we calculated robust estimates of variances with generalized estimate equation (GEE)
17
18
19 208 using SAS procedure GENMOD. All analyses were performed in SAS Version 9.0
20
21 209 (SAS Institute, Inc., Cary, NC, USA). A value of $P < 0.05$ was considered statistically
22
23
24 210 significant.
25
26
27 211

212 **RESULTS**

213 **Baseline characteristics of study population**

214 A total of 12,438 individuals were recruited in this investigation, but 3,235 individuals
215 were excluded for analyses, due to absence of anthropometric measurements. Final
216 analyses included 9,203 subjects: 6,793 adults, and 2,410 children. Among adults, the
217 average age was 47.93 years; females accounted for 62.96%; the underweight, normal,
218 overweight and obese was 4.39%, 66.13%, 26.34% and 3.14%, respectively. The
219 socio-demographic characteristics among patients with thyroid nodule and non-nodule
220 group for adults were shown in Table 1; Out of 6,793 adults, 2,228 (32.80%) adults
221 had thyroid nodule, of which women accounted for 71.01%. Subjects with thyroid
222 nodule was older, shorter, and more females ($p < 0.05$). Moreover, the distributions of
223 education, marital status, resident location, smoking, drinking, salt appetite, milk

1
2
3
4 224 consuming and diet patterns had significant difference between two groups (Table 1).
5
6 225 The socio-demographic characteristics among patients with thyroid nodule and
7
8 226 non-nodule group for children were shown in Table 2. Subjects with thyroid nodule
9
10 227 was older, and more females ($p < 0.05$). The distributions of resident location, salt
11
12 228 appetite and type of salts had significant difference between two groups (Table 2).
13
14 229 Among children, 47.55% were under the reference BMI, 52.45% over the reference
15
16 230 BMI. 257 (10.66%) children suffered from thyroid nodule, which more than half
17
18 231 (57.98%) were girls (Table 2).
19
20
21
22
23
24
25

26 233 **The relationship between anthropometric measurements and thyroid nodule**
27
28
29 234 **among adults tertile**

30
31 235 The relationship between anthropometric measurements (height, weight, BMI, BSA)
32
33 236 and thyroid nodule were estimated by gender (Table 3). The height (OR=1.15, 95%
34
35 237 CL: 1.02-1.30), weight (OR=1.40, 95%CL: 1.24-1.58), BMI (OR=1.26, 95% CI:
36
37 238 1.11–1.42) and BSA (OR=1.43, 95% CI: 1.27–1.62) were significantly associated
38
39 239 with an increased risk of thyroid nodule among pooled adults, respectively. Similar
40
41 240 trends were observed in females and males, but no significant association in males.
42
43 241 The associations with tertiles of exposures (height, weight, BMI, BSA) were very
44
45 242 similar to the previous findings when those subjects diagnosed thyroid diseases were
46
47 243 excluded (Supplementary Table 2).
48
49
50
51
52
53
54

55
56 245 **The relationship between anthropometric measurements and thyroid nodule**
57
58
59
60

1
2
3
4 246 **among children**

5
6 247 The relationship of anthropometric measurements with thyroid nodule was also
7
8
9 248 conducted among children (Table 4). The weight (OR=1.37, 95% CI: 1.03–1.81), BMI
10
11 249 (OR=1.38, 95% CI: 1.04–1.83) and BSA (OR=2.97, 95% CI: 1.85–4.77) were
12
13
14 250 significantly associated with thyroid nodule among all children. The significant
15
16 251 association of BSA with thyroid nodule was observed in both boys (OR=2.57, 95% CI:
17
18 252 1.25–5.28) and girls (OR=3.36, 95% CI: 1.82–6.20); BMI and weight were also
19
20
21 253 positively related with thyroid nodule among both genders, but significant association
22
23 254 of BMI among boys and significant association of weight among girls was observed
24
25
26 255 respectively. The significant association of height with thyroid nodule was not
27
28
29 256 observed among children.

30
31 257

32 33 34 258 **DISCUSSION**

35
36
37 259 This study, performed in a large Chinese population, demonstrated that height, weight,
38
39 260 BMI and BSA were positively associated with thyroid nodule among adults and
40
41 261 children respectively, but only significantly in female adults and children. More
42
43
44 262 explicitly, in the present study, the significant association between high BSA and
45
46
47 263 thyroid nodule was not obviously influenced by sex, age, resident location and iodine
48
49
50 264 intake.

51
52
53
54 265 Thyroid nodule is very common disease in the general population. The present
55
56 266 investigation showed that the prevalence of thyroid nodule was 32.80% in adults and
57
58
59
60

1
2
3
4 267 10.66% in children; but they are found clinically in 4-8% of cases[27]. In our study,
5
6 268 high height and heavy weight was significantly associated with thyroid nodule in all
7
8
9 269 adults and female, respectively. But only significant relationship of weight with
10
11 270 thyroid nodule was found in children population. To data, few study was focus on the
12
13 271 relationship between anthropometric indexes and thyroid nodule. Previous study
14
15 272 showed that thyroid nodule might share similar risk factors with thyroid cancer:
16
17 273 iodine deficiency was associated with an increased TC incidence, largely via benign
18
19 274 thyroid conditions such as nodules, which were, in turn, strongly associated with TC.
20
21 275 Additionally, body size might be associated with the iodine requirement and, hence,
22
23 276 indirectly related to thyroid nodule[28].
24
25
26
27
28
29
30

31 277
32 278 Our results were similar to the findings among 88,256 Canadian women in 2012. It is
33
34 279 reported that height was positively associated with the risk of all combined cancers
35
36 280 and thyroid cancer, and height was significantly positively associated with risk of
37
38 281 thyroid cancer in multivariable models [29]. Further, the European Prospective
39
40 282 Investigation into Cancer and nutrition (EPIC), a large study including half-a-million
41
42 283 subjects, also observed the positive association of height with thyroid cancer in female
43
44 284 but not in male[30]. Beyond those findings from European population, a pooled
45
46 285 analysis of individual data from 12 case-control studies conducted in eight countries
47
48 286 (America, Asia, and Europe) suggests that height was moderately related to thyroid
49
50 287 cancer risk[31]. In addition, similar association of height with thyroid nodule risk
51
52 288 among Korean was observed in females but not males[17]. In our findings of Chinese
53
54
55
56
57
58
59
60

1
2
3
4 289 population, the moderate association of height with thyroid nodule was also observed
5
6 290 in females, which was consistent with those from Korea in Asia and even European
7
8
9 291 population. However, the association was not significant among children, but we still
10
11 292 found an increased OR of higher height (OR=1.30, 95% CL: 0.89-1.90). It may due to
12
13 293 the small case numbers of children, and the association between height and thyroid
14
15 294 nodule among children needs more studies to confirm.
16
17
18
19 295

20
21 296 Furthermore, similar to height, the meta-analysis of data from eight countries also
22
23 297 indicated the association of weight and risk of thyroid cancer in female rather than
24
25 298 male[31]. In 2010, Clavel-Chapelon F[32] reported that there was a significant
26
27 299 dose-effect relationship between thyroid cancer risk and weight in France. In Asia, the
28
29 300 significant association between weight and thyroid nodule in female was observed
30
31 301 among Korean population[17]. Our data confirmed these findings after adjusted for
32
33 302 the relevant covariates. Altered thyroid status has profound effects on skeletal
34
35 303 development and growth, and on adult bone maintenance. The fact that thyroid
36
37 304 hormones are associated with the regulation of the growth of long bones may be one
38
39 305 possible explanation for the association between height and thyroid nodule[33].
40
41 306 Moreover, genetic or environmental factors (e.g., dietary factors, nutritious factors),
42
43 307 correlate with adult height and weight, also influence thyroid function might be
44
45 308 another possible explanation for their association[31].
46
47
48
49
50
51
52
53
54
55

56 310 Analogously, the significant associations between BMI and thyroid nodule were
57
58
59
60

1
2
3
4 311 observed among all adults. Similar association was observed in women, but not in
5
6 312 men. Among children, significant associations of BMI with thyroid nodule were also
7
8
9 313 observed. Our findings in adults were consistent with that in German [34] and Italian
10
11 314 [35], and similar to those among Korean population [17]. However, Results from
12
13
14 315 previous prospective and case-control studies on the association of BMI with thyroid
15
16 316 cancer risk have generally been more inconsistent in men than women. In a large
17
18
19 317 Norwegian cohort of more than two million participants, the risk of thyroid cancer
20
21 318 increased moderately with increased BMI in both sexes, but the results were
22
23
24 319 unadjusted for smoking and other potential confounders [36]. After adjusted for key
25
26 320 covariates such as cigarette smoking, alcohol drinking, physical activity and medical
27
28
29 321 history of diabetes, the largest prospective study conducted in U.S. also observed a
30
31 322 significant positive association between BMI and thyroid cancer risk in women [37].
32
33
34 323 Moreover, a systematic review conducted by Emily Peterson[38] in 2012 (including
35
36 324 37 studies) showed that most of studies supported a positive association of BMI with
37
38
39 325 thyroid cancer in both sexes. The inconsistent results between men and women in
40
41 326 previous studies is likely due to smaller numbers of cases in men, to the lack of
42
43
44 327 control for important covariates (e.g. cigarette smoking, alcohol intake). Current
45
46 328 smoking and alcohol intake are associated with BMI [39-42]. Un-adjustment for
47
48
49 329 smoking status or alcohol drinking may be an important bias in the association
50
51 330 between BMI and risk of thyroid nodule. Findings of present study covered adults and
52
53
54 331 children, and the associations of BMI with thyroid nodule were consistent in adult and
55
56 332 children after adjusted for important covariates. Base on large samples and reducing
57
58
59
60

1
2
3
4 333 important biases, our findings indicate that overweight and obesity was associated
5
6 334 with thyroid nodule in both adults and children. The association may be the certain
7
8
9 335 metabolic consequences of excess adipose tissue. Leptin produced by adipocytes has
10
11 336 important influences on central regulation of thyroid function through stimulation of
12
13
14 337 TRH. This seems to be important for down-regulation of thyroid function in states of
15
16 338 energy deficits, but the importance for modulation of thyroid function under more
17
18
19 339 physiological conditions is uncertain[43 44]. Additionally, thyroid hormones may be a
20
21 340 significant determinant of sleeping energy expenditure in subjects without overt
22
23
24 341 thyroid dysfunction[45]. Similarly, differences in thyroid function, within what is
25
26 342 considered the normal range, are associated with differences in BMI, caused by
27
28
29 343 longstanding minor alterations in energy expenditure[13]. What's more, obesity is
30
31 344 associated with insulin resistance and increased production of insulin and insulin-like
32
33
34 345 growth factors which in turn have been reported to be associated to thyroid
35
36 346 disorders[2 46 47].
37
38
39 347
40
41 348 Being similar with thyroid cancer[2 37], thyroid nodules are more common in women
42
43
44 349 than in men[48-52]. Sex differences in the association between BMI and thyroid
45
46
47 350 cancer have been confirmed in other studies[31 53 54]. Similar results were observed
48
49
50 351 in Korean[17]. The patients who were normal or overweight in BMI subgroup were
51
52 352 identified to have higher frequency of thyroid nodules. However, the significant
53
54
55 353 relationship between body size and thyroid nodule in the men were not observed. Our
56
57 354 findings of adults were consistent with the sex difference in association of BMI with
58
59
60

1
2
3
4 355 thyroid nodule. The difference in incidence between two genders suggests that growth
5
6 356 and progression of thyroid tumors is influenced by sex hormones, particularly
7
8
9 357 estrogens[55 56]. However, sex difference of the correlation between body size and
10
11 358 thyroid nodule was not obvious among children. It may due to the smaller difference
12
13
14 359 of sex hormones in children, compared to adults. Few studies noted the correlation
15
16 360 between body size and thyroid nodule in children, the findings from children
17
18
19 361 population require furthermore studies to confirm.

20
21 362
22
23
24 363 BSA is a better indicator of the circulating blood volume, oxygen consumption, and
25
26 364 basal energy expenditure than BMI or weight[57]. In the present study, BSA was
27
28
29 365 significantly associated with thyroid nodule among adults and children. The
30
31 366 association was not influenced by sex, age, resident location and iodine intake.
32
33
34 367 Consistently, a positive association of thyroid cancer and current BSA in adults was
35
36 368 found by Suzuki T in Japan in both sexes after adjusted for main covariates [58]. In
37
38
39 369 addition, it was reported that BSA plays a dominant role in thyroid cancer risk and
40
41 370 explains the apparent role of BMI in adults [57]. Muscle is more dense than fat, and
42
43
44 371 BMI is not able to differentiate increased weight [59]. BSA is a more accurate
45
46 372 measure of obesity, including central obesity, as it is a measurement of area and is
47
48
49 373 able to account for the difference between muscle and fat better than BMI secondary
50
51 374 to muscle versus fat [21]. In a way, the association between BSA and thyroid nodule
52
53
54 375 more strongly and forcefully confirmed the increased risk of overweight and obesity
55
56 376 with thyroid nodule than those of BMI.
57
58
59
60

377

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

398

399 **LIMITATION**

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

409 **CONCLUSION**

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

416 **ACKNOELEDGMENTS**

417 **Contribution statement**

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

1
2
3
4 421 analyses and made draft of manuscript. Hui Liu, Na Li, Liangliang Huo, Yangmei
5
6 422 Huang, Xingyi Jin, Jin Deng, Sujuan Zhu and Shanchun Zhang enrolled and
7
8
9 423 interviewed study subjects in the study field.
10
11
12
13
14

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

425 **Competing interests**

426 All authors read and approved the final manuscript. None of the authors had a conflict
427 of interest. The manuscript has not been published and is not being considered for
428 publication elsewhere, in whole or in part, in any language, except as an abstract.
429

430 **Data sharing statement**

431 No additional unpublished data are available.
432

433 **Funding**

434 The study was funded in part by grants from Hangzhou Science and Technology
435 Bureau (Grant number: 200908033B27), the Ministry of Science and Technology
436 (Grant number: 2011CB503706) and we thank the staff of Hangzhou Center for
437 Disease Control and Prevention collecting the epidemiological data and blood
438 specimen. We would like to particularly thank all participants and their family for
439 their contributions and supports.
440
441
442

443 **REFERENCE**

- 444 1. Leitzmann MF, Brenner A, Moore SC, et al. Prospective study of body mass index, physical activity
445 and thyroid cancer. *Int J Cancer* 2010;**126**(12):2947-56 doi: 10.1002/ijc.24913[published
446 Online First: Epub Date]].
- 447 2. Tae HJ, Lim DJ, Baek KH, et al. Diagnostic value of ultrasonography to distinguish between benign
448 and malignant lesions in the management of thyroid nodules. *Thyroid* 2007;**17**(5):461-6
- 449 3. WHO. Media Center: Obesity and overweight. Secondary Media Center: Obesity and overweight
450 2012.
- 451 4. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes
452 mellitus in women. *Ann Intern Med* 1995;**122**(7):481-6
- 453 5. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a
454 prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**(15):1097-105 doi:
455 10.1056/nejm199910073411501[published Online First: Epub Date]].
- 456 6. Saw SM, Rajan U. The epidemiology of obesity: a review. *Ann Acad Med Singapore*
457 1997;**26**(4):489-93
- 458 7. WHO. Obesity: preventing and managing the global epidemic—report of a WHO consultation. World
459 Health Organization 2000
- 460 8. Reynolds K, Gu D, Whelton PK, et al. Prevalence and risk factors of overweight and obesity in
461 China. *Obesity (Silver Spring)* 2007;**15**(1):10-8 doi: 10.1038/oby.2007.527[published Online
462 First: Epub Date]].
- 463 9. Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid
464 volume and function in obese women. *Clinical Endocrinology* 2003;**59**(2):258-62 doi:
465 10.1046/j.1365-2265.2003.01836.x[published Online First: Epub Date]].
- 466 10. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid
467 obesity. *Thyroid* 2006;**16**(1):73-8 doi: 10.1089/thy.2006.16.73[published Online First: Epub
468 Date]].
- 469 11. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid
470 stimulating hormone are directly associated with waist circumference, independently of
471 insulin resistance, metabolic parameters and blood pressure in overweight and obese women.
472 *Clin Endocrinol (Oxf)* 2007;**67**(2):265-9 doi: 10.1111/j.1365-2265.2007.02874.x[published
473 Online First: Epub Date]].
- 474 12. Bastemir M, Akin F, Alkis E, Kaptanoglu B. Obesity is associated with increased serum TSH level,
475 independent of thyroid function. *Swiss Med Wkly* 2007;**137**(29-30):431-4 doi:
476 2007/29/smw-11774[published Online First: Epub Date]].
- 477 13. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be
478 important for body mass index and the occurrence of obesity in the population. *J Clin
479 Endocrinol Metab* 2005;**90**(7):4019-24 doi: 10.1210/jc.2004-2225[published Online First:
480 Epub Date]].
- 481 14. al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in
482 patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab*
483 1997;**82**(4):1118-25
- 484 15. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules
485 detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest*

- 1
2
3 486 2009;**39**(8):699-706 doi: 10.1111/j.1365-2362.2009.02162.x[published Online First: Epub
4 487 Date]].
- 5 488 16. Zhu HF, Yang Y, Li JY, Li XM, Ma AG. [Prevalence of thyroid nodules and influencing factors
6 489 among employees of a company in Qingdao]. *Zhonghua Yu Fang Yi Xue Za Zhi*
7 490 2012;**46**(3):228-32
- 8 491 17. Kim JY, Jung EJ, Park ST, et al. Body size and thyroid nodules in healthy Korean population. *J*
9 492 *Korean Surg Soc* 2012;**82**(1):13-7 doi: 10.4174/jkss.2012.82.1.13[published Online First:
10 493 Epub Date]].
- 11 494 18. Chen Z, Xu W, Huang Y, et al. Associations of noniodized salt and thyroid nodule among the
12 495 Chinese population: a large cross-sectional study. *Am J Clin Nutr* 2013;**98**(3):684-92 doi:
13 496 10.3945/ajcn.112.054353[published Online First: Epub Date]].
- 14 497 19. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive
15 498 values of body mass index and waist circumference for risk factors of certain related diseases
16 499 in Chinese adults--study on optimal cut-off points of body mass index and waist
17 500 circumference in Chinese adults. *Biomed Environ Sci* 2002;**15**(1):83-96
- 18 501 20. Ya-qin LHJC-yZX-nZ. Height and weight standardized growth charts for Chinese children and
19 502 adolescents aged 0 to 18 years. *CHINESE JOURNAL OF PEDIATRICS* 2009;**47**(7)
- 20 503 21. Roy SK, Zeb I, Kadakia J, Li D, Budoff MJ. Body surface area is a predictor of coronary artery
21 504 calcium, whereas body mass index is not. *Coron Artery Dis* 2012;**23**(2):113-7 doi:
22 505 10.1097/MCA.0b013e32834f1b72[published Online First: Epub Date]].
- 23 506 22. Mickuviene N, Krasauskiene A, Kazanavicius G. [The results of thyroid ultrasound examination in
24 507 randomly selected schoolchildren]. *Medicina (Kaunas)* 2006;**42**(9):751-8
- 25 508 23. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer*
26 509 *Chemother Rep* 1970;**54**(4):225-35
- 27 510 24. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a
28 511 height-weight formula validated in infants, children, and adults. *J Pediatr* 1978;**93**(1):62-6
- 29 512 25. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;**317**(17):1098 doi:
30 513 10.1056/NEJM198710223171717[published Online First: Epub Date]].
- 31 514 26. Livingston EH, Lee S. Body surface area prediction in normal-weight and obese patients. *Am J*
32 515 *Physiol Endocrinol Metab* 2001;**281**(3):E586-91
- 33 516 27. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules
34 517 discovered incidentally on thyroid imaging. *Ann Intern Med* 1997;**126**(3):226-31
- 35 518 28. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an
36 519 epidemiological review focused on nutritional factors. *Cancer Causes Control*
37 520 2009;**20**(1):75-86 doi: 10.1007/s10552-008-9219-5[published Online First: Epub Date]].
- 38 521 29. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in
39 522 a cohort of Canadian women. *International Journal of Cancer* 2012:n/a-n/a doi:
40 523 10.1002/ijc.27704[published Online First: Epub Date]].
- 41 524 30. Rinaldi S, Lise M, Clavel-Chapelon F, et al. Body size and risk of differentiated thyroid carcinomas:
42 525 Findings from the EPIC study. *International Journal of Cancer* 2012;**131**(6):E1004-E14 doi:
43 526 10.1002/ijc.27601[published Online First: Epub Date]].
- 44 527 31. Dal Maso L, La Vecchia C, Franceschi S, et al. A pooled analysis of thyroid cancer studies. V.
45 528 Anthropometric factors. *Cancer Causes Control* 2000;**11**(2):137-44
- 46 529 32. Clavel-Chapelon F, Guillas G, Tondeur L, Kernaleguen C, Boutron-Ruault MC. Risk of

- 1
2
3 530 differentiated thyroid cancer in relation to adult weight, height and body shape over life: the
4 531 French E3N cohort. *Int J Cancer* 2010;**126**(12):2984-90 doi: 10.1002/ijc.25066[published
5 532 Online First: Epub Date]].
- 6
7 533 33. Gogakos AI, Duncan Bassett JH, Williams GR. Thyroid and bone. *Arch Biochem Biophys*
8 534 2010;**503**(1):129-36 doi: 10.1016/j.abb.2010.06.021[published Online First: Epub Date]].
- 9
10 535 34. Karger S, Schotz S, Stumvoll M, Berger F, Fuhrer D. Impact of pregnancy on prevalence of goitre
11 536 and nodular thyroid disease in women living in a region of borderline sufficient iodine supply.
12 537 *Horm Metab Res* 2010;**42**(2):137-42 doi: 10.1055/s-0029-1241861[published Online First:
13 538 Epub Date]].
- 14
15 539 35. Trimboli P, Rossi F, Thorel F, et al. One in five subjects with normal thyroid ultrasonography has
16 540 altered thyroid tests. *Endocr J* 2012;**59**(2):137-43
- 17
18 541 36. Engeland A, Trethi S, Akslen LA, Bjorge T. Body size and thyroid cancer in two million Norwegian
19 542 men and women. *Br J Cancer* 2006;**95**(3):366-70 doi: 10.1038/sj.bjc.6603249[published
20 543 Online First: Epub Date]].
- 21
22 544 37. Kitahara CM, Platz EA, Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and
23 545 women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev*
24 546 2011;**20**(3):464-72 doi: 10.1158/1055-9965.epi-10-1220[published Online First: Epub Date]].
- 25
26 547 38. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer: a
27 548 systematic review. *PLoS One* 2012;**7**(1):e29177 doi: 10.1371/journal.pone.0029177[published
28 549 Online First: Epub Date]].
- 29
30 550 39. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat
31 551 distribution, and insulin resistance. *Am J Clin Nutr* 2008;**87**(4):801-9
- 32
33 552 40. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking
34 553 cessation on the prevalence of overweight in the United States. *N Engl J Med*
35 554 1995;**333**(18):1165-70 doi: 10.1056/nejm199511023331801[published Online First: Epub
36 555 Date]].
- 37
38 556 41. Wannamethee SG, Shaper AG. Alcohol, body weight, and weight gain in middle-aged men. *Am J*
39 557 *Clin Nutr* 2003;**77**(5):1312-7
- 40
41 558 42. Hou X, Jia W, Bao Y, et al. Risk factors for overweight and obesity, and changes in body mass
42 559 index of Chinese adults in Shanghai. *BMC Public Health* 2008;**8**:389 doi:
43 560 10.1186/1471-2458-8-389[published Online First: Epub Date]].
- 44
45 561 43. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the
46 562 neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *J Clin Invest*
47 563 2003;**111**(9):1409-21 doi: 10.1172/jci17490[published Online First: Epub Date]].
- 48
49 564 44. LaMarca A, Volpe A. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl*
50 565 *J Med* 2004;**351**(22):2343; author reply 43 doi: 10.1056/nejm200411253512221[published
51 566 Online First: Epub Date]].
- 52
53 567 45. Astrup A, Buemann B, Christensen NJ, et al. The contribution of body composition, substrates, and
54 568 hormones to the variability in energy expenditure and substrate utilization in premenopausal
55 569 women. *J Clin Endocrinol Metab* 1992;**74**(2):279-86
- 56
57 570 46. Volzke H, Friedrich N, Schipf S, et al. Association between serum insulin-like growth factor-I
58 571 levels and thyroid disorders in a population-based study. *J Clin Endocrinol Metab*
59 572 2007;**92**(10):4039-45 doi: 10.1210/jc.2007-0816[published Online First: Epub Date]].
- 60
573 47. Vella V, Sciacca L, Pandini G, et al. The IGF system in thyroid cancer: new concepts. *Mol Pathol*

- 1
2
3 574 2001;**54**(3):121-4
4 575 48. Mazzaferri EL, de los Santos ET, Rofagha-Keyhani S. Solitary thyroid nodule: diagnosis and
5 576 management. *The Medical clinics of North America* 1988;**72**(5):1177-211
6
7 577 49. Mazzaferri EL. Management of a Solitary Thyroid Nodule. *New England Journal of Medicine*
8 578 1993;**328**(8):553-59 doi: doi:10.1056/NEJM199302253280807[published Online First: Epub
9 579 Date]].
10 580 50. Hurtado-Lopez LM, Basurto-Kuba E, Montes de Oca-Duran ER, Pulido-Cejudo A, Vazquez-Ortega
11 581 R, Athie-Gutierrez C. Prevalence of thyroid nodules in the Valley of Mexico. *Cir Cir*
12 582 2011;**79**(2):114-7
13 583 51. Yoon DY, Chang SK, Choi CS, et al. The prevalence and significance of incidental thyroid nodules
14 584 identified on computed tomography. *J Comput Assist Tomogr* 2008;**32**(5):810-5 doi:
15 585 10.1097/RCT.0b013e318157fd38[published Online First: Epub Date]].
16 586 52. Bartolotta TV, Midiri M, Runza G, et al. Incidentally discovered thyroid nodules: incidence, and
17 587 greyscale and colour Doppler pattern in an adult population screened by real-time compound
18 588 spatial sonography. *Radiol Med* 2006;**111**(7):989-98 doi:
19 589 10.1007/s11547-006-0097-1[published Online First: Epub Date]].
20 590 53. Guignard R, Truong T, Rougier Y, Baron-Dubourdiou D, Guenel P. Alcohol drinking, tobacco
21 591 smoking, and anthropometric characteristics as risk factors for thyroid cancer: a countrywide
22 592 case-control study in New Caledonia. *Am J Epidemiol* 2007;**166**(10):1140-9 doi:
23 593 10.1093/aje/kwm204[published Online First: Epub Date]].
24 594 54. Brindel P, Doyon F, Rachedi F, et al. Anthropometric factors in differentiated thyroid cancer in
25 595 French Polynesia: a case-control study. *Cancer Causes Control* 2009;**20**(5):581-90 doi:
26 596 10.1007/s10552-008-9266-y[published Online First: Epub Date]].
27 597 55. Negri E, Ron E, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer. I.
28 598 Methods. *Cancer Causes Control* 1999;**10**(2):131-42
29 599 56. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer:
30 600 a systematic review and meta-analysis of prospective observational studies. *Lancet*
31 601 2008;**371**(9612):569-78 doi: 10.1016/s0140-6736(08)60269-x[published Online First: Epub
32 602 Date]].
33 603 57. Clero E, Leux C, Brindel P, et al. Pooled analysis of two case-control studies in New Caledonia and
34 604 French Polynesia of body mass index and differentiated thyroid cancer: the importance of
35 605 body surface area. *Thyroid* 2010;**20**(11):1285-93 doi: 10.1089/thy.2009.0456[published
36 606 Online First: Epub Date]].
37 607 58. Suzuki T, Matsuo K, Hasegawa Y, et al. Anthropometric factors at age 20 years and risk of thyroid
38 608 cancer. *Cancer Causes Control* 2008;**19**(10):1233-42 doi:
39 609 10.1007/s10552-008-9194-x[published Online First: Epub Date]].
40 610 59. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and
41 611 subcutaneous fat. *Curr Diabetes Rev* 2006;**2**(4):367-73
42 612 60. Gunnell D, Berney L, Holland P, et al. How accurately are height, weight and leg length reported by
43 613 the elderly, and how closely are they related to measurements recorded in childhood? *Int J*
44 614 *Epidemiol* 2000;**29**(3):456-64
45 615 61. Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A. Validity of self-reported weight and
46 616 height in the French GAZEL cohort. *Int J Obes Relat Metab Disord* 2000;**24**(9):1111-8
47 617

618 TABLES

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

Variables	Nodule (n=2228)	Non-nodule (n=4565)	P
Age, year (Mean ± SD)	53.49±13.80	44.93±13.72	<0.001
Height, cm (Mean ± SD)	160.72±7.25	162.24±7.54	<0.001
Weight, kg (Mean ± SD)	59.30±8.12	59.10±8.33	0.177
BMI, kg/m² (Mean ± SD)	23.07±2.69	22.52±2.65	<0.001
Gender, n(%)			
male	646(28.99)	1870(40.96)	<0.001
female	1582(61.01)	2695(59.04)	
Education^a, n(%)			
primary school	922(42.10)	1317(29.15)	<0.001
Junior high school	647(29.54)	1440(31.87)	
senior high school	470(21.46)	1283(28.40)	
junior college and above	151(6.89)	478(10.58)	
Marriage, n(%)			
single	78(3.51)	378(8.29)	<0.001
married	1980(88.98)	3981(87.30)	
divorce	22(0.99)	47(1.03)	
widowed	139(6.25)	140(3.07)	
others	6(0.27)	14(0.31)	
Resident location, n(%)			
urban area	1214(54.49)	2125(46.55)	<0.001
rural area	1014(45.52)	2440(53.45)	
Cigarette smoking, n(%)			
Never	1825(82.65)	3508(77.46)	<0.001
Ever	69(3.13)	121(2.67)	
Current	314(14.22)	900(19.87)	
Alcohol drinking, n(%)			
No	1822(83.27)	3608(80.55)	0.027
Yes	366(16.73)	871(19.45)	
Salt appetite, n(%)			
moderate	1135(51.24)	2479(54.52)	0.036
salty	469(21.17)	916(20.15)	
light	611(27.58)	1152(25.34)	
Milk consuming, n(%)			
Yes	837(42.02)	1965(45.55)	0.009
No	1155(57.98)	2349(54.45)	
Diet patterns^b, n(%)			
balanced	1662(74.73)	3484(76.32)	0.043

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

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

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

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

619

620

621

622

623

624

625

626

627

628

629

630

631

632

633

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

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

^aVegetarian indicates that subjects consistently had vegetable diet; meat indicates that subjects consistently had meat diet; moderate indicates that subjects intermittently had vegetable diet or meat diet.

^bIodized salt indicates that subjects consistently consumed iodized salt; Non-iodized salt indicates that subjects intermittently consumed iodized salt or consistently consumed non-iodized salt.

634

635

636

637

638

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

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

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

^a: **Male**: high: height \geq 170cm, low: height $<$ 170cm; **female**: high: height \geq 160cm, low: height $<$ 160cm;

^b: **Male**: high: weight \geq 65kg, low: weight $<$ 65kg; **female**: high: weight \geq 60kg, low: weight $<$ 60kg;

^c: Low=BMI $<$ 24.0; high: BMI \geq 24;

^d: **Male**: high: BSA \geq 1.80m², low: BSA $<$ 1.80m²; **female**: high: BSA \geq 1.55m², low: BSA $<$ 1.55m²

639

640

641

642

643

644

645

646

647

648

649

650

651

652

653

654

655

656

657

658

659

660

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

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

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

^{a,b}:High: height or weight \geq reference standard, low: height or weight $<$ reference standard;

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

^d:**Male**: high: $BSA \geq 1.26 \text{ m}^2$, low: $BSA < 1.26 \text{ m}^2$; **female**: high: $BSA \geq 1.22 \text{ m}^2$, low: $BSA < 1.22 \text{ m}^2$;

Mean of male's $BSA = 1.26 \text{ m}^2$, Mean of female's $BSA = 1.22 \text{ m}^2$.

657

For peer review only

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

Variables	Adults	
	Males	Females
Height(cm)		
low	height<170cm	height<160cm
high	height≥170cm	height≥160cm
Weight(kg)		
low	weight<65kg	weight<60kg
high	weight≥65kg	weight≥60kg
BMI		
Low		BMI<24.0
High		BMI≥24
BSA(m²)		
low	BSA<1.80m ²	BSA<1.55m ²
high	BSA≥1.80m ²	BSA≥1.55m ²

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

Variables	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
	Pooled*		Female		Male	
Height(cm)^a						
<156	1.00		1.00		1.00	
156-<161	1.19(1.01,1.40)	0.0363	1.21(1.02,1.44)	0.0260	1.13(0.48,2.65)	0.7843
161-<168	1.34(1.11,1.60)	0.0019	1.35(1.11,1.65)	0.0031	1.22(0.55,2.73)	0.6262
≥168	1.38(1.09,1.75)	0.0075	1.83(1.25,2.70)	0.0021	1.10(0.50,2.46)	0.8084
Weight(kg)^a						
<54	1.00		1.00			
54-<60	1.20(1.02,1.43)	0.0330	1.13(0.94,1.35)	0.1936	1.00 ^{&}	
60-<65	1.63(1.36,1.95)	<0.001	1.62(1.33,1.98)	<0.001	1.03(0.75,1.41)	0.8556
≥65	1.73(1.44,2.08)	<0.001	1.97(1.58,2.45)	<0.001	1.00(0.75,1.34)	0.9924
BMI^b						
<18.5	1.00		1.00			
18.5-<24	1.50(1.09,2.04)	0.0116	1.41(1.02,1.93)	0.0350	/ [#]	/
≥24	1.88(1.37,2.60)	0.0001	2.01(1.45,2.79)	<0.001	/	/
BSA(m²)^a						
<1.53	1.00		1.00		1.00	
1.53-<1.63	1.30(1.10,1.53)	0.0023	1.27(1.07,1.50)	0.0072	0.69(0.06,7.96)	0.7664
1.63-<1.74	1.78(1.49,2.12)	<0.001	1.78(1.47,2.16)	<0.001	0.75(0.07,8.43)	0.8120
≥1.74	1.86(1.51,2.29)	<0.001	2.15(1.63,2.83)	<0.001	0.72(0.06,8.12)	0.7892

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

a: 4 categories by quartile;

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

&: No male's weight <54kg;

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

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

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

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

1
2
3
4 location, types of salt, salt appetite, diet patterns, milk consuming;

5 ^a: **Male**: high: height \geq 170cm, low: height $<$ 170cm; **female**: high: height \geq 160cm, low:
6 height $<$ 160cm;

7 ^b: **Male**: high: weight \geq 65kg, low: weight $<$ 65kg; **female**: high: weight \geq 60kg, low:
8 weight $<$ 60kg;

9 ^c: Low=BMI $<$ 24.0; high: BMI \geq 24;

10 ^d: **Male**: high: BSA \geq 1.80m², low: BSA $<$ 1.80m²; **female**: high: BSA \geq 1.55m², low:
11 BSA $<$ 1.55m²
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Variables	Nodule, n(%)	Non-nodule, n(%)	OR(95%CI)	P
Pooled*				
Height^a				
low	131(55.98)	1209(59.06)	1.00	
high	103(44.02)	838(40.94)	1.18(0.88,1.58)	0.2631
Weight^b				
low	111(47.44)	1130(55.20)	1.00	
high	123(52.56)	917(44.80)	1.36(1.02,1.81)	0.0335
BMI^c				
low	99(42.31)	993(48.51)	1.00	
high	135(57.69)	1054(51.49)	1.36(1.02,1.80)	0.0374
BSA^d				
low	68(29.06)	1098(53.64)	1.00	
high	166(70.94)	949(46.36)	3.13(1.94,5.04)	<0.0001
Girls				
Height^a				
low	73(53.68)	618(60.53)	1.00	
high	63(46.32)	403(39.47)	1.32(0.90,1.93)	0.1626
Weight^b				
low	58(42.65)	534(52.30)	1.00	
high	78(57.35)	487(47.70)	1.49(1.02,2.17)	0.0396
BMI^c				
low	59(43.38)	464(45.45)	1.00	
high	77(56.62)	557(54.55)	1.16(0.80,1.69)	0.4309
BSA(m²)^d				
low	39(28.68)	542(53.09)	1.00	
high	97(71.32)	479(46.91)	3.50(1.88,6.52)	<0.0001
Boys				
Height^a				
low	58(59.18)	591(57.60)	1.00	
high	40(40.82)	435(42.40)	1.02(0.66,1.57)	0.9390
Weight^b				
low	53(54.08)	596(58.09)	1.00	
high	45(45.92)	430(41.91)	1.21(0.78,1.85)	0.3948
BMI^c				
low	40(40.82)	529(51.56)	1.00	
high	58(59.18)	497(48.44)	1.67(1.08,2.59)	0.0219
BSA^d				
low	29(29.59)	556(54.19)	1.00	
high	69(70.41)	470(45.81)	2.74(1.34,5.64)	<0.0001

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

^{a,b}:High: height or weight \geq reference standard, low: height or weight <reference standard;

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

^d: **Male**: high: $BSA \geq 1.26 \text{ m}^2$, low: $BSA < 1.26 \text{ m}^2$; **female**: high: $BSA \geq 1.22 \text{ m}^2$, low: $BSA < 1.22 \text{ m}^2$;
Mean of male's $BSA = 1.26 \text{ m}^2$, Mean of female's $BSA = 1.22 \text{ m}^2$.

For peer review only

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

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

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (line 227-229) (b) Give reasons for non-participation at each stage (line 227) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (line 226-235) (b) Indicate number of participants with missing data for each variable of interest (Table 1) (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures (line 231-235)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (line -237-257) (b) Report category boundaries when continuous variables were categorized (line 218-219) (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (N/A)

Discussion

Key results	18	Summarise key results with reference to study objectives (line 260-264)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (line 397-403)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (line 265-385)
Generalisability	21	Discuss the generalisability (external validity) of the study results (line 260-262)

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (line 424-429)
---------	----	---

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

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