Thyroid stimulating hormone (TSH) is associated with general and abdominal obesity in girls during puberty

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Research article

Keywords: thyroid stimulating hormone, general obesity, central obesity, school-aged girls, puberty

Posted Date: November 8th, 2019

DOI: https://doi.org/10.21203/rs.2.17011/v1

Abstract

Background: Childhood obesity is an important public health issue. Although both thyroid hormone and menarche are known to play a role in body metabolism and energy expenditure, evidence for these associations in girls around puberty was limited. This study was aimed to investigate the association of TSH with general and abdominal obesity in girls during puberty.

Methods: A multi-stage cluster sampling method was used to select one junior middle school from each of 4 study areas: Minhang District in Shanghai, Haimen City in Jiangsu Province, Yuhuan City and Deqing County in Zhejiang Province. A total of 474 girls aged 11 to 14 years from 4 schools were enrolled. Information on demographic factors and puberty stage were collected, and anthropometric measurements and thyroid hormones were determined. Multivariate logistic regression models were used to assess the associations of Thyroid stimulating hormone (TSH) with the risk of obesity measured by body mess index (BMI) and waist circumference (WC).

Results: Of the 474 girls, the prevalences of BMI-based general obesity and WC-based abdominal obesity were 19.8% (94/474) and 21.7% (103/474), respectively. Compared with normal weight girls, the mean serum TSH concentration was significantly higher in BMI-based general overweight or obese girls (P=0.037), but not in WC-based central overweight or obese girls (P=0.173). In the multiple logistic regression models, for girls with highest tertile of serum TSH concentration relative to those in the lowest tertile, the odds ratios were 2.63 (95% CI 1.34 to 5.14) and 2.53(95% CI 1.31 to 4.88) for overweight or obesity based on BMI and WC after adjustment for puberty stage and other covariates.

Conclusions: Serum TSH concentration was positively associated with both general and abdominal obesity in school-age girls and the association was independent of puberty.

Background

Overweight and obesity are defined as abnormal and excess fat accumulation. The prevalence of overweight and obesity among children and adolescents aged 5–19 years has increased dramatically from 4% in 1975 to over 18% in 2016 globally.[1] Childhood obesity not only increases the risks of asthma and metabolic syndrome,[2 3] but also the risk of cardiovascular diseases (CVD) and premature death in adulthood.[4 5] Meanwhile, 30–50% of children with obesity tend to become obese adults.[6] Obesity is related to multiple endocrine alterations, where various hormones play a important role.{Beck, 1964 #344;Scacchi, 1999 #342}{Scacchi, 1999 #342;Mayes, 2004 #343}[7 8] However, the pathophysiology of obesity is not fully understood. Identifying hormonal targets involved in this process may contribute to prevent and manage obesity.

Thyroid hormone has a strong effect on body metabolism and energy expenditure,[9] and is usually reactivated during puberty.[10] Upon the onset of puberty, the incidence of thyroid disease increases in females only, and decreases after menopause. [11] Evidence suggested that thyroid dysfunction contributes to obesity, and conversely, obesity induces thyroidal alterations. [12] In our previous study, we observed a positive association between thyroid nodules and obesity in Chinese children. [13] Women with a history of earlier menarche have a higher risk of obesity than those with later menarche.[14] Studies of children and adolescents drawn from pediatric outpatient clinics reported an association between thyroid stimulating hormone (TSH) and obesity.[15] [16] In the current study, we assessed the associations of TSH with body mass index (BMI) and waist circumference (WC) in a girls aged 11–14 years in East China.

Methods

Study population

Four coastal cities in East China (Minhang District in Shanghai, Haimen City in Jiangsu Province, Yuhuan City and Deqing County in Zhejiang Province) were selected by purposive sampling. Previous studies have revealed an iodine-sufficient along with different iodized-salt consumption status among four sites.[17] [18] [19] [20] One junior middle school, where students were mainly local residents, was selected from each city. All girls of six classes (grade 6 in Minhang and grade 7 in Haimen, Yuhuan, and Deqing) were enrolled into this study. Ones who had thyroid or pituitary abnormalities, and other disorders which affect thyroid hormone levels were excluded.

Informed written consents were obtained from all the participants and their parents or guardian, and the study was approved by the ethical review board of the School of Public Health of Fudan University. A total of 474 girls participated in the study, with a response rate of 98.54%.

Information collection

Information on demographic and lifestyle factors were collected by a self-administrated questionnaire. Self-reported pubertal maturation level was assessed by using the Pubertal Development Scale (PDS).[21] Anthropometric measurements, including standing height (cm), weight (kg), and circumferences of the waist, hip and chest (cm) were taken by local health professionals according to a standard protocol. Height and weight were respectively measured to the nearest 0.1 cm and 0.1 kg with the subjects standing without shoes and wearing light clothing only. Waist circumference (WC) was measured to 0.1 cm at the midpoint between the lower rib and the upper iliac crest. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Determination of thyroid hormones

Blood samples of approximately 5 ml were collected through antecubital vein puncture after a 12-hour overnight fast from each panticipant. Serum and plasma samples were immediately separated, and then kept at −80°C freezer until transported to the DiAn medical laboratory center for analysis. Serum thyroid stimulating hormone (TSH) level and free thyroxine (FT4) level were measured by electrochemiluminescence immunoassay on ADVIA Centaur CP (Siemens Healthcare Diagnostics, USA). Coefficients of variation of the kits were 2.4% for TSH and 2.2% for FT4, respectively; and lower limits of detection were 0.005 mU/L for TSH and 1.3 pmol/L for FT4, respectively.

Urine and salt samples collection and iodine nutrition evaluation

First morning urine sample for each participant was collected and urine iodine concentration (UIC) was determined by inductively coupled plasma mass spectrometry method (ICP-MS) and evaluated according to WHO/ Unicef/ International Council for Control of Iodine deficiency Disorders (ICCIDD): insufficient (UIC<100μg/L), sufficient (100–199μg/L), more than adequate (200–299μg/L) and excessive (≥300μg/L). Each participant was also asked to bring a salt sample of more than 20 g from home and salt iodine concentration (SIC) was measured by using a national standard method with a proper quality control (GB/T 13025.7–2012).[22] Iodized salt consumption status was grouped into two categories: non-iodized-salt (SIC<5mg/kg) and iodized-salt (≥5mg/kg). [23]

Statistical analysis

Statistical analysis was based on data from 474 girls with complete information of thyroid hormones and anthropometric measurements. All participants were categorized into three groups of under / normal weight, overweight, and obesity status according to the BMI growth reference values for Chinese children suggested by Li H et.al.[24] The BMI (kg/m^2) cut-offs for overweight and obesity in girls were 19.6 and 22.7 for age 11, 20.5 and 23.9 for age 12, 21.4 and 25.0 for age 13, and 22.2 and 25.9 for age 14, respectively. Subjects were also divided into two groups of central obesity according to the cutoff values of 85th and 95th percentiles of WC data.[25]

Due to the lack of reference range of TSH for girls during puberty, the serum TSH concentration was categorized into three tertiles by corresponding cut-off values: tertile 1 (<1.53 mU/L), tertile 2 (1.53 mU/L≤TSH≤2.37 mU/L), and tertile 3 (>2.37 mU/L). Youth development assessment was according to the total scores of three items including menarche, breast development and body hair growth, and then converted into five stages. In the current analysis, we labelled “prepubertal” for stage 1, “pubertal” for stages 2, 3 and 4 combined and “postpubertal” for stage 5.[21 26] Wilcoxon test and χ^2 test were used to analyze continuous variables and categorical variables, respectively. Multivariate logistic regression models were utilized to estimate the odds ratios for BMI- or WC-based overweight and obesity in relation to TSH levels after adjustment for age, puberty stage, family history of thyroid disease, iodized-salt consumption, income, parents’ education, sleeping duration, physical activities, and serum FT4 concentrations. Potential effect modifications by age, puberty stage and iodized-salt consumption on the associations of interest were also examined by including associated interaction terms into the multivariable analysis. Due to a considerable day-to-day variation in urine iodine excretion, one-spot urinary iodine level was appropriate to evaluate the iodine status for population, but not for individuals. [27] Therefore, in above analysis, iodized-salt consumption instead of urine iodine concentration was considered as an adjustable variable into the models. Goiter (1.90%) was not common among these girls and were not included in the analysis. All analysis were performed by using SPSS software for Windows (version 24.0, IBM Crop., Armonk, New York, USA).

Results

The mean age was 12.48(±0.69) years for the study population. Of the 474 school-aged girls, 94 (19.8%) were overweight or obesity based on BMI, while 103 (21.7%) had central obesity based on WC (Table 1). The prevalence of central obesity measured by WC increased with age (P=0.023) and showed area disparity (P=0.001), while the prevalence of general obesity measured by BMI was similar across age and area groups. Girls of postpuberty were most likely to be overweight or obesity compared with other groups (P<0.001). The median serum TSH concentration in BMI-based overweight or obese girls (2.16mU/L) was higher than that in normal weight girls (1.85mU/L) (P=0.037), while TSH concentration was comparable between girls with /without central obesity (P=0.173).

Table1 Characteristics of normal weight and overweight or obesity in different subgroups for school-aged girls

	Total	Classified based on Body Mass Index (BMI)			Classified based on Waist Circumference (WC)		
		Normal Weight (N=380)	Overweight (N=74) or Obesity(N=20)	*P* value	Normal Weight (N=371)	Overweight (N=69) or Obesity(N=34)	*P* value
All	474	380(80.17)	94(19.83)		371(78.27)	103(21.73)	
Thyroid Hormone							
TSH(mU/L)	1.90(1.35-2.65)	1.85(1.33-2.61)	2.16(1.51-3.01)	0.037	1.85(1.34-2.62)	2.14(1.35-2.88)	0.173
FT4(pmol/L)	14.83(13.39-16.46)	14.79(13.27-16.45)	15.24(13.84-16.63)	0.280	14.68(13.07-16.42)	15.46(14.16-16.63)	0.004
Age (years)				0.994			0.023
11-12	217(45.78)	174(80.18)	43(19.82)		180(82.95)	37(17.05)	
13-14	257(54.22)	206(80.16)	51(19.84)		191(74.32)	66(25.68)	
Puberty status				<0.001			<0.001
Prepubertal	175(36.92)	158(90.29)	17(9.71)		155(88.57)	20(11.43)	
Pubertal	222(46.84)	180(81.08)	42(18.92)		171(77.03)	51(22.97)	
Postpubertal	77(16.24)	42(54.55)	35(45.45)		45(58.44)	32(41.56)	
Area				0.949			0.001
Minhang	128(27.00)	101(78.91)	27(21.09)		109(85.16)	19(14.84)	
Haimen	111(23.42)	89(80.18)	22(19.82)		76(68.47)	35(31.53)	
Yuhuan	116(24.47)	95(81.90)	21(18.10)		100(86.21)	16(1.43)	
Deqing	119(25.11)	95(79.83)	24(20.17)		86(72.27)	33(27.73)	
Goiter				0.062			0.971
No	465(98.10)	375(80.65)	90(19.35)		364(78.28)	101(21.72)	
Yes	9(1.90)	5(55.56)	4(44.44)		7(77.78)	2(22.22)	
Family history of thyroid disease				0.523			0.914
No	402(84.81)	323(80.35)	79(19.65)		313(77.86)	89(22.14)	
Yes	65(13.71)	50(76.92)	15(23.08)		51(78.46)	14(21.54)	
Salt iodine content(mg/kg)				0.286			0.306
< 5 (non-iodized-salt consumption)	40(10.70)	30(75.00)	10(25.00)		30(75.00)	10(25.00)	
≥5 (iodized-salt consumption)	398(83.97)	326(81.91)	72(18.09)		325(81.66)	73(18.34)	
Urine iodine concentration(μg/L)				0.065			0.003
<100 (insufficient)	83(17.51)	67(80.72)	16(19.28)		66(79.52)	17(20.48)	
100-199 (sufficient)	182(38.40)	154(84.62)	28(15.38)		154(84.62)	28(15.38)	
200-299 (more than adequate)	113(23.84)	89(78.76)	24(21.24)		88(77.88)	25(22.12)	
≥300 (excessive)	85(17.93)	60(70.59)	25(29.41)		55(64.71)	30(35.29)	
Income level (RMB)				0.640			0.264
≤3000	169(35.65)	137(81.07)	32(18.93)		127(75.15)	42(24.85)	
>3000	299(63.08)	237(79.26)	62(20.74)		238(79.60)	61(20.40)	
Parents education				0.278			0.148
Junior high school or below	205(43.25)	169(82.44)	36(17.56)		154(75.12)	51(24.88)	
Senior high school or above	264(55.70)	207(78.41)	57(21.59)		213(80.68)	51(19.32)	
Bedtime (hours)				0.743			0.781
≤8	251(52.95)	202(80.48)	49(19.52)		197(78.49)	54(21.51)	
>8	217(45.78)	172(79.26)	45(20.74)		168(77.42)	49(22.58)	
Activities time (hours)				0.241			0.181
≤1	320(67.51)	251(78.44)	69(21.56)		244(76.25)	76(23.75)	
>1	148(31.22)	123(83.11)	25(16.89)		121(81.76)	27(18.24)	

Multivariate logistic regression analysis showed that compared to girls with the lowest tertile of serum TSH concentration, girls in the highest tertile had a significantly higher risk of BMI-based overweight or obesity (OR=2.05, 95% CI 1.09 to 3.88), and the significant association remained after adjusted for puberty stage instead of age (OR=2.63, 95% CI 1.34 to 5.14) (Table 2). The results for central obesity based on WC were similar, and the corresponding ORs were 2.24 (95% CI 1.19 to 4.23) (model 2) and 2.53 (95% CI 1.31 to 4.88) (model 3) (Table 3). The association between TSH and the BMI-based risk of overweight or obesity was not significantly modified by age, puberty status and iodized salt consumption. In stratified analysis, the association tended to be stronger in girls aged 13 to 14 years, with consumption of iodized salt and during puberty.

Table 2 Associations of TSH with overweight or obesity risk based on Body Mass Index (BMI) by multinomial logistic regression in school-aged girls

	Total	Tertile1			Tertile2			Tertile3		
		N	%	OR(ref)	N	%	OR(95%CI)	N	%	OR(95%CI)
All subjects [a]	474	25	15.82		31	19.38		38	24.36	
Model 1				1.00			1.30(0.73-2.34)			1.76(0.99-3.12)
Model 2				1.00			1.33(0.69-2.54)			2.05(1.09-3.88)*
Model 3				1.00			1.44(0.73-2.83)			2.63(1.34-5.14)**
Age [b]										
11-12	217	9	17.65	1.00	12	16.22	0.83(0.31-2.22)	22	23.91	1.51(0.59-3.83)
13-14	257	16	14.95	1.00	19	22.09	1.80(0.75-4.35)	16	25.00	2.49(1.03-6.05)*
Puberty status [b]										
Prepubertal	175	3	5.77	1.00	4	6.67	1.33(0.26-6.75)	10	15.87	3.71(0.87-15.90)
Pubertal	222	9	11.84	1.00	13	18.84	3.12(0.96-10.11)	20	25.97	6.30(1.82-21.75)**
Postpubertal	77	13	43.33	1.00	14	45.16	0.71(0.20-2.52)	8	50.00	0.89(0.21-3.78)
Iodized salt consumption [c]										
No	40	4	26.67	1.00	2	14.29	0.60(0.08-4.73)	4	36.36	3.47(0.41-29.65)
Yes	398	16	12.70	1.00	25	18.38	1.54(0.76-3.11)	31	22.79	2.22(1.11-4.43)*

Tertile1：TSH<1.53 mU/L **Tertile2**：1.53 mU/L≤TSH≤2.37 mU/L **Tertile3**：TSH>2.37 mU/L

a Model 1 Adjusted for age alone

Model 2 Adjusted for age, family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

Model 3 Adjusted for puberty stage, family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

b Adjusted for family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

c Adjusted for age, family history of thyroid disease, income, parents education, bedtime, activities time, serum FT4 concentrations

*0.01<P<0.05, **P<0.01

Table 3 Associations of TSH with overweight or obesity risk based on Waist Circumstance (WC) by multinomial logistic regression in school-aged girls

	Total	Tertile1			Tertile2			Tertile3		
		N	%	OR(ref)	N	%	OR(95%CI)	N	%	OR(95%CI)
All subjects [a]	474	31	19.62		33	20.63		39	25.00	
Model 1				1.00			1.18(0.67-2.05)			1.57(0.91-2.72)
Model 2				1.00			1.49(0.78-2.85)			2.24(1.19-4.23)*
Model 3				1.00			1.52(0.78-2.95)			2.53(1.31-4.88)**
Age [b]										
11-12	217	7	13.73	1.00	11	14.86	0.94(0.33-2.72)	19	20.65	1.48(0.54-4.07)
13-14	257	24	22.43	1.00	22	25.58	1.57(0.69-3.60)	20	31.25	2.89(1.26-6.61)*
Puberty status [b]										
Prepubertal	175	3	5.77	1.00	6	10.00	1.55(0.34-7.13)	11	17.46	3.33(0.81-13.60)
Pubertal	222	18	23.68	1.00	15	21.74	2.08(0.77-5.58)	18	23.38	2.97(1.06-8.34)*
Postpubertal	77	10	33.33	1.00	12	38.71	0.93(0.27-3.25)	10	62.50	3.10(0.73-13.12)
Iodized salt consumption [c]										
No	40	5	33.33	1.00	2	14.29	0.46(0.06-3.88)	3	27.27	1.68(0.20-14.46)
Yes	398	15	11.90	1.00	26	19.12	1.88(0.92-3.84)	32	23.53	2.66(1.32-5.37)**

Tertile1：TSH<1.53 mU/L **Tertile2**：1.53 mU/L≤TSH≤2.37 mU/L **Tertile3**：TSH>2.37 mU/L

a Model 1 Adjusted for age alone

Model 2 Adjusted for age, family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

Model 3 Adjusted for puberty stage, family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

b Adjusted for family history of thyroid disease, iodized salt consumption, income, parents education, bedtime, activities time, serum FT4 concentrations

c Adjusted for age, family history of thyroid disease, income, parents education, bedtime, activities time, serum FT4 concentrations

*0.01<*P*<0.05, ***P*<0.01

Discussion

In this population-based study of pubertal girls in East China, we observed that girls with a higher serum TSH concentration had a higher risk of obesity or overweight measured by BMI or WC. Previous studies demonstrated that TSH was significantly positive related to obesity measured by BMI in pediatric outpatients,[16 28] and measured by WC in adolescents.[29] Increased WC, as a confirmed risk factor for many chronic conditions, is more prevalent in children with mild subclinical hypothyroidism (featured with higher serum TSH levels) than healthy euthyroid children.[30] Also, a significant relationship between TSH changes and alterations in WC was observed in Tehran women during long-term follow-up.[31]

TSH, also known as thyrotropin, is produced by the anterior pituitary. TSH secretion is regulated by the thyroid releasing hormone (TRH), and limited by negative feedback from the thyroid hormones (THs).[32] TH regulate basal metabolism, which constitutes approximately 66% of total daily energy expenditure.[33] In addition, THs are primarily involved in lipid and glucose metabolism with a mediator named sterol regulatory element-binding proteins (SREBP−2).[34 35] Nader et al. found that the increase in TSH level within the reference range was associated with an increase in insulin and an increase in homeostasis model assessment (HOMA) levels of insulin resistance(IR), [36] which may be caused by obesity, and may also contribute to the development of obesity in childhood.[37] Insulin is a critical regulator of adipoctye biology, and promotes adipocyte triglyceride storage by some mechanisms, including transportation of glucose, differentiation of preadipocytes to adipocytes, and synthesis of triglyceride (lipogenesis).[38] TSH was positively related to triglyceride and non-HDL lipoproteins in a large population-based study of children and adolescents.[39]Moreover, central depots of fat was much more sensitive to IR.[38]

On the other hand, obesity may be a cause of thyroid dysfunction and elevated TSH levels [12]. One plausible explanation is that adipose tissue secretes inflammatory cytokines into the general circulation, such as tumor necrosis factor (TNF-α) and interleukin (IL−1, IL−6). [40] These cytokines impede the expression of sodium iodine transporter mRNA and the activity of iodine uptake in human thyroid cells, which reduces the secretion of THs, and then leads a compensatory rise in TSH levels. Another hypothesis is that the production of leptin-mediated pro-thyrotropin-releasing hormone (pro-TRH) increases with weight gain.[41] Leptin is predominantly released by adipocytes and stimulates TSH secretion by hypothalamic-pituitary axis.[42] Non-synonymous mutations in thyroid stimulating hormone receptor (TSH-R) gene also plays a role in elevated TSH levels in relation to obesity.[43]

In stratified analysis, the positive association between TSH and obesity was only observed in girls aged 13 to 14 years. In general, timing of puberty in girls relies on age at menarche, and earlier menarche was related to an increased risk of adulthood obesity.[44] It seems that older girls were likely to be at the later stage of puberty. Aromatase activity increases with elevated adiposity in puberty, leading to increased conversion of androgens to estrogens,[45] which has a growth-promoting effect on thyroid hormones.[11]

The strengths of our study include population-based school-aged girls, directly-determined thyroid hormones and objectively anthropometric measurements following a standardized protocol. To our knowledge, this is the first study to observe the relationship of thyroid function with adiposity in girls around puberty. The study has several limitations. First, we did not have information on TPO-Ab (thyroid peroxidase antibody), which is better representative of thyroid function. In practice, determination of serum TSH level should be repeated within 3 months after the initial test. Moreover, we did not measure body composition, although BMI and WC are common indicators to define adiposity in population-based studies. In addition, cross-sectional design does not provide evidence for a causal association between TSH and obesity. In our study, But the changes of serum TSH level and body weight of these girls will be prospectively observed in the follow-up visit for three years, so the definite relationship between the above two variables will be further interpreted.

Conclusions

TSH level was positively associated with both general and abdominal obesity. Obesity was more prevalent in postpubertal than prepubertal. The association of TSH with obesity was independent of puberty.

Abbreviations

TSH, thyroid stimulating hormone; TRH, thyroid releasing hormone; THs, thyroid hormones; BMI, body mass index; WC, waist circumference.

Declarations

Acknowledgements

We gratefully acknowledge all the staff who participated in this project, including health workers in Deqing County Center for Disease Control and Prevention, Yuhuan City Center for Disease Control and Prevention, Minhang District Center for Disease Control and Prevention, and Haimen City Center for Disease Control and Prevention, and from Fudan School of Public Health, and from local community-based health facilities.

Author's Contributions

XLD, MFS, DLX, JHQ, NW and QWJ contributed to the study design; YYW, CWF, FJ, RL and NW contributed to data acquisition and collection; YYW, NW, and YC contributed to data analysis and interpretation; YYW, NW, and YC drafted the manuscript; all authors contributed to the preparation of the final document, read and approved the final manuscript.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81602806 to Na Wang) and Shanghai Leading Academic Discipline Project of Public Health (No. 15GWZK0801). None of the funders had any role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participant

The study was an non-interventional study and was approved by the ethical review board of the School of Public Health of Fudan University (#2012–03–0350S). Informed written consents for participation in the study were obtained from all the participants and their parents or guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing financial interests.

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References

1.World Health Organization. Obesity and overweight 2017. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 15 October 2018.

2.Lang JE. Obesity and childhood asthma. *Current opinion in pulmonary medicine.* 2019;25(1):34–43.

3.Kelishadi R. Childhood overweight, obesity, and the metabolic syndrome in developing countries. *Epidemiologic Reviews.* 2007;29:62–76.

4.Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and adult cardiovascular disease risk: a systematic review. *International Journal of Obesity.* 2010;34(1):18–28.

5.Park MH, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. *Obesity Reviews.* 2012;13(11):985–1000.

6.Angel Rivera J, Gonzalez de Cossio T, Susana Pedraza L, Cony Aburto T, Georgina Sanchez T, Martorell R. Childhood and adolescent overweight and obesity in Latin America: a systematic review. *Lancet Diabetes & Endocrinology.* 2014;2(4):321–332.

7.Scacchi M, Pincelli AL, Cavagnini F. Growth hormone in obesity. *International Journal of Obesity.* 1999;23(3):260–271.

8.Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. *Obesity reviews: an official journal of the International Association for the Study of Obesity.* 2004;5(4):197–216.

9.Mullur R, Liu YY, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiological Reviews.* 2014;94(2):355–382.

10.Peper JS, Brouwer RM, van Leeuwen M, et al. HPG-axis hormones during puberty: A study on the association with hypothalamic and pituitary volumes. *Psychoneuroendocrinology.* 2010;35(1):133–140.

11.Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. *Endocr-Relat Cancer.* 2014;21(5):T273-T283.

12.Garcia-Solis P, Garcia OP, Hernandez-Puga G, et al. Thyroid hormones and obesity: a known but poorly understood relationship. *Endokrynologia Polska.* 2018;69(3):292–303.

13.Wang N, Fang H, Fu CW, et al. Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficient areas: an observational study. *Bmj Open.* 2017;7(10).

14.Ong KK, Northstone K, Wells JCK. Earlier mother's age at menarche predicts rapid infancy growth and childhood obesity. *Plos Medicine.* 2007;4(4):737–742.

15.Ozer S, Butun I, Sonmezgoz E, Yilmaz R, Demir O. Relationships among thyroid hormones and obesity severity, metabolic syndrome and its components in Turkish children with obesity. *Nutricion Hospitalaria.* 2015;32(2):645–651.

16.Ekinci F, Uzuner A, Demet MC, Turgut B, Tosun N. Thyroid hormones and BMI in obese children: One year follow up results. *Marmara Medical Journal.* 2015;28(3):129–134.

17.Zhang Y, Wang Y, Wang X, et al. Iodine nutrition and thyroid abnormality in adolescent girls in Deqing County. *Chinese Journal of School Health.* 2018;39(11):1723–1725.

18.Su M, Wang C, Li S, et al. Repeated cross-sectional studies on urinary iodine and iodine content of salt among school-aged children from 2012 to 2014 in Yuhuan County, Zhejiang Province. *Journal of Hygiene Research.* 2016;45(1):14–18.

19.Liu P, Wang N, Fang H, et al. Alteration on household salt consumption status and urinary iodine concentration of a primary school children in Shanghai, 2012–2014. *Chinese Journal of Preventive Medicine.* 2016;50(3):282–284.

20.Huang P, Jiang F, Feng X, et al. A cross-sectional study of urinary iodine and salt iodine content among schoolchildren and their families in Haimen City, Jiangsu Province. *Chinese Journal of Endemiology.* 2014;33(6):654–656.

21.Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291–303.

22.Zhang Y, Huang Y. Discussion of “GB/T 13025.7–2012 general test method for the determination of iodine in salt industry”. *Chinese Journal of Endemiology.* 2014;33(3):346–348.

23.China MohotPsRo. Food safety national standard edible salt iodine content GB 26878–2011 [S]. In*.* Vol 1. Beijing: China standard publishing house; 2011.

24.Li H, Zhong X, Ji C, Mi J. Body mass index cut-offs for overweight and obesity in Chinese children and adolescents aged 2–18 years. *Chinese Journal of Endemiology.* 2010;31(6):616–620.

25.Yan WL, Yao H, Dai JH, et al. Waist circumference cutoff points in school-aged Chinese Han and Uygur children. *Obesity.* 2008;16(7):1687–1692.

26.Marwaha RK, Tandon N, Desai AK, et al. The evolution of thyroid function with puberty. *Clin Endocrinol (Oxf).* 2012;76(6):899–904.

27.Wang N, Fang H, Fu C, et al. Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficient areas: an observational study. *Bmj Open.* 2017;7(10).

28.Radhakishun NNE, van Vliet M, von Rosenstiel IA, et al. Increasing thyroid-stimulating hormone is associated with impaired glucose metabolism in euthyroid obese children and adolescents. *Journal of Pediatric Endocrinology & Metabolism.* 2013;26(5–6):531–537.

29.Zhang J, Jiang R, Li L, et al. Serum Thyrotropin Is Positively Correlated with the Metabolic Syndrome Components of Obesity and Dyslipidemia in Chinese Adolescents. *International Journal of Endocrinology.* 2014.

30.Cerbone M, Capalbo D, Wasniewska M, et al. Cardiovascular Risk Factors in Children With Long-Standing Untreated Idiopathic Subclinical Hypothyroidism. *Journal of Clinical Endocrinology & Metabolism.* 2014;99(8):2697–2703.

31.Motamed B, Eftekharzadeh A, Hosseinpanah F, Tohidi M, Hasheminia M, Azizi F. The relation between changes in thyroid function and anthropometric indices during long-term follow-up of euthyroid subjects: the Tehran Thyroid Study (TTS). *Eur J Endocrinol.* 2016;175(4):247–253. doi: 210.1530/EJE–1516–0414. Epub 2016 Jul 1511.

32.Amar AP, Weiss MH. Pituitary anatomy and physiology. *Neurosurgery Clinics of North America.* 2003;14(1):11-+.

33.Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid.* 2008;18(2):141–144.

34.Crunkhorn S, Patti ME. Links between thyroid hormone action, oxidative metabolism, and diabetes risk? *Thyroid.* 2008;18(2):227–237.

35.Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein–2 (SREBP–2). *Journal of Biological Chemistry.* 2003;278(36):34114–34118.

36.Nader NS, Bahn RS, Johnson MD, Weaver AL, Singh R, Kumar S. Relationships Between Thyroid Function and Lipid Status or Insulin Resistance in a Pediatric Population. *Thyroid.* 2010;20(12):1333–1339.

37.Chiarelli F, Marcovecchio ML. Insulin resistance and obesity in childhood. *Eur J Endocrinol.* 2008;159(Suppl 1):S67–74. doi: 10.1530/EJE–1508–0245. Epub 2008 Sep 1519.

38.Kahn BB, Flier JS. Obesity and insulin resistance. *Journal of Clinical Investigation.* 2000;106(4):473–481.

39.Witte T, Ittermann T, Thamm M, Riblet NBV, Voelzke H. Association Between Serum Thyroid-Stimulating Hormone Levels and Serum Lipids in Children and Adolescents: A Population-Based Study of German Youth. *Journal of Clinical Endocrinology & Metabolism.* 2015;100(5):2090–2097.

40.Reinehr T. Thyroid function in the nutritionally obese child and adolescent. *Curr Opin Pediatr.* 2011;23(4):415–420.

41.Mantzoros CS, Ozata M, Negrao AB, et al. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: Evidence for possible partial TSH regulation by leptin in humans. *Journal of Clinical Endocrinology & Metabolism.* 2001;86(7):3284–3291.

42.Betry C, Challan-Belval MA, Bernard A, et al. Increased TSH in obesity: Evidence for a BMI-independent association with leptin. *Diabetes & Metabolism.* 2015;41(3):248–251.

43.Weihrauch-Bluher S, Wiegand S. Risk Factors and Implications of Childhood Obesity. *Current Obesity Reports.* 2018;7(4):254–259.

44.Liu G, Yang Y, Huang W, et al. Association of age at menarche with obesity and hypertension among southwestern Chinese women: a new finding. *Menopause-the Journal of the North American Menopause Society.* 2018;25(5):546–553.

45.Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. *Trends Endocrinol Metab.* 2009;20(5):237–242.